The Health Consequences of Smoking—50 Years of Progress

A Report of the Surgeon General

U.S. Department of Health and Human Services

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U.S. Department of Health and Human Services
Centers for Disease Control and Prevention
National Center for Chronic Disease Prevention and Health Promotion
Office on Smoking and Health

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Message from Kathleen Sebelius
Secretary of Health and Human Services

Fifty years after the release of the first Surgeon General's report warning of the health hazards of smoking, we have learned how to end the tobacco epidemic. Over the past five decades, scientists, researchers and policy makers have determined what works, and what steps must be taken if we truly want to bring to a close one of our nation's most tragic battles—one that has killed ten times the number of Americans who died in all of our nation's wars combined.

In the United States, successes in tobacco control have more than halved smoking rates since the 1964 landmark Surgeon General's report came out. Americans' collective view of smoking has been transformed from an accepted national pastime to a discouraged threat to individual and public health. Strong policies have largely driven cigarette smoking out of public view and public air space. Thanks to smokefree laws, no longer is smoking allowed on airplanes or in a growing number of restaurants, bars, college campuses and government buildings.

Evidence in this new report shows tobacco's continued, immense burden to our nation—and how essential ending the tobacco epidemic is to our work to increase the life expectancy and quality of life of all Americans. This year alone, nearly one-half million adults will still die prematurely because of smoking. Annually, the total economic costs due to tobacco are now over $289 billion. And if we continue on our current trajectory, 5.6 million children alive today who are younger than 18 years of age will die prematurely as a result of smoking.

I believe that we can make the next generation tobacco-free. And I am extremely proud of the Obama Administration's tobacco-control record. For example, the 2009 *Children's Health Insurance Program Reauthorization Act* included an unprecedented $0.62 tax increase that raised the federal excise tax to $1.01 per pack of cigarettes; we know that increasing the cost of cigarettes is one of the most powerful interventions we can make to prevent smoking and reduce prevalence. Building on this knowledge, the President's Fiscal Year 2014 Budget includes a $0.94 per pack Federal tobacco tax increase. For the first time in history, the 2009 *Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) g*ave the U.S. Food and Drug Administration comprehensive authority to regulate tobacco products, which will play a critical role in reducing the harm caused by these products. The *Tobacco Control Act* also provided for user fees to be paid by tobacco manufacturers that can support sustained public education media campaigns targeting youth prevention and cessation. The 2010 *Affordable Care Act (ACA)* expands access to smoking cessation services and now requires most insurance companies to cover cessation treatments. The *Affordable Care Act's* Public Health and Prevention Fund is supporting innovative and effective community-based programs as well as public education campaigns promoting prevention and helping people to quit.

All of these tobacco control interventions are known to reduce tobacco use and, as a result, tobacco's extraordinary toll of death and disease. But in order to free the next generation from these burdens, we must redouble our tobacco control efforts and enlist nongovernmental partners—and society as a whole—to share in this responsibility. Ending the devastation of tobacco-related illness and death is not in the jurisdiction of any one entity. We must all share in this most worthwhile effort to end the tobacco epidemic.

Message from Howard Koh
Assistant Secretary for Health

The nation stands poised at the crossroads of tobacco control. On one hand, we can celebrate tremendous progress 50 years after the landmark 1964 Surgeon General's report: *Smoking and Health*. Adult smoking rates have fallen from about 43% (1965) to about 18% today. Mortality rates from lung cancer, the leading cause of cancer death in this country, are declining. Most smokers visiting health care settings are now routinely asked and advised about tobacco use. On the other hand, cigarette smoking remains the chief preventable killer in America, with more than 40 million Americans caught in a web of tobacco dependence. Each day, more than 3,200 youth (younger than 18 years of age) smoke their first cigarette and another 2,100 youth and young adults who are occasional smokers progress to become daily smokers. Furthermore, the range of emerging tobacco products complicates the current public health landscape.

In this context, the 50th Anniversary of the Surgeon General's report prompts us to pause and ask why this addiction persists when proven interventions can eliminate it. Of great concern, too many in our nation assume that past success in tobacco control guarantees future progress; nothing can be further from the truth. To rejuvenate and reinvigorate national efforts, in 2010, the U.S. Department of Health and Human Services unveiled its first ever strategic plan for tobacco control. *Ending the Tobacco Epidemic: A Tobacco Control Strategic Action Plan* provides a critical framework to guide efforts to rapidly drop prevalence rates of smoking among youth and adults. A major foundation and pillar of the plan is to encourage and promote leadership throughout all sectors of society. Now, this current 2014 Surgeon General's report can accelerate that leadership to fully implement the life-saving prevention that can make the next generation free of tobacco-related death and disease.

We have many tools that we know work. A comprehensive public policy approach emphasizing mass media campaigns to encourage prevention and quit attempts, smokefree policies, restrictions on youth access to tobacco products, and price increases can collectively drive further meaningful reductions in tobacco use. Furthermore, we can accelerate progress through full commitment to clinical and public health advances; including the widespread use of telephone quit lines and science-based counseling and medications for tobacco users. Promoting progress today also requires recognizing that tobacco use has evolved from being an equal-opportunity killer to one threatening the most vulnerable members of our society. We must confront, and reverse, the tragically higher tobacco use rates that threaten persons of low socioeconomic status, sexual minorities, high school dropouts, some racial/ethnic minority groups, and those living with mental illness and substance use disorders.

Of all the accomplishments of the 20th century, historians rank the 1964 Surgeon General's report as one of the seminal public health achievements of our time. Armed with both science and resolve, we can continue to honor the legacy of the report by completing the work it began in the last century. The current 2014 Surgeon General's report represents a national vision for getting the job done. With strategy, commitment, and action, our nation can leave the crossroads and move forward to end the tobacco epidemic once and for all.

Foreword

Fifty years have passed since publication of the landmark report of the Surgeon General's Advisory Committee on smoking and health. This report highlights both the dramatic progress our nation has made reducing tobacco use and the continuing burden of disease and death caused by smoking.

As a physician, when I think about smoking, I recall the patients I have cared for. The man who had a leg amputated. The woman who had to gasp for every single breath that she took. The man with heart disease who hoped to see his son graduate, but didn't live long enough to do so. That's the reality of smoking that health care providers see every day.

The prevalence of current cigarette smoking among adults has declined from 42% in 1965 to 18% in 2012. However, more than 42 million Americans still smoke. Tobacco has killed more than 20 million people prematurely since the first Surgeon General's report in 1964. The findings in this report show that the decline in the prevalence of smoking has slowed in recent years and that burden of smoking-attributable mortality is expected to remain at high and unacceptable levels for decades to come unless urgent action is taken.

Recent surveys monitoring trends in tobacco use indicate that more people are using multiple tobacco products, particularly youth and young adults. The percentage of U.S. middle and high school students who use electronic, or e-cigarettes, more than doubled between 2011 and 2012. We need to monitor patterns of use of an increasingly wide array of tobacco products across all of the diverse segments of our society, particularly because the tobacco industry continues to introduce and market new products that establish and maintain nicotine addiction.

Tobacco control efforts need to not only address the general population, but also to focus on populations with a higher prevalence of tobacco use and lower rates of quitting. These populations include people from some racial/ethnic minority groups, people with mental illness, lower educational levels and socioeconomic status, and certain regions of the country. We now have proven interventions and policies to reduce tobacco initiation and use among youth and adults.

With intense use of proven interventions, we can save lives and reduce health care costs. In 2012, the Centers for Disease Control and Prevention (CDC) launched the first-ever paid national tobacco education campaign — *Tips From Former Smokers* (*Tips*) — to raise awareness of the harms to health caused by smoking, encourage smokers to quit, and encourage nonsmokers to protect themselves and their families from exposure to secondhand smoke. It pulled back the curtain in a way that numbers alone cannot, and showed the tobacco-caused tragedies that we as health care professionals see and are saddened by every day. As a result of this campaign, an estimated 1.6 million smokers made an attempt to quit and, based on a conservative estimate, at least 100,000 smokers quit for good. Additionally, millions of nonsmokers talked with friends and family about the dangers of smoking and referred smokers to quit services. In 2013, CDC launched a new round of advertisements that helped even more people quit smoking by highlighting the toll that smoking-related illnesses take on smokers and their loved ones.

CDC has also established reducing tobacco use as one of its "Winnable Battles." These are public health priorities with large-scale impact on health that have proven effective strategies to address them. CDC believes that with additional effort and support for evidence-based, cost-effective policy and program strategies to reduce tobacco use, we can reduce smoking substantially, prevent millions of people from being killed by tobacco, and protect future generations from smoking.

While we have made tremendous progress over the past 50 years, sustained and comprehensive efforts are needed to prevent more people from having to suffer the pain, disability, disfigurement, and death that smoking causes. Most Americans who have ever smoked have already quit, and most smokers who still smoke want to quit. If we continue to implement tobacco prevention and cessation strategies that have proven effective in reducing tobacco use, people throughout our country will live longer, healthier, more productive lives.

Thomas R. Frieden, M.D., M.P.H.
Director
Centers for Disease Control and Prevention

Preface

from the Acting Surgeon General,
U.S. Department of Health and Human Services

On January 11, 1964, Luther L. Terry, M.D., the 9th Surgeon General of the United States, released the first report on the health consequences of smoking: *Smoking and Health: Report of the Advisory Committee of the Surgeon General of the Public Health Service*. That report marked a major step to reduce the adverse impact of tobacco use on health worldwide.

Over the past 50 years, 31 Surgeon General's reports have utilized the best available evidence to expand our understanding of the health consequences of smoking and involuntary exposure to tobacco smoke. The conclusions from these reports have evolved from a few causal associations in 1964 to a robust body of evidence documenting the health consequences from both active smoking and exposure to secondhand smoke across a range of diseases and organ systems.

The 2004 report concluded that smoking affects nearly every organ of the body, and the evidence in this report provides even more support for that finding. A half century after the release of the first report, we continue to add to the long list of diseases caused by tobacco use and exposure to tobacco smoke. This report finds that active smoking is now causally associated with age-related macular degeneration, diabetes, colorectal cancer, liver cancer, adverse health outcomes in cancer patients and survivors, tuberculosis, erectile dysfunction, orofacial clefts in infants, ectopic pregnancy, rheumatoid arthritis, inflammation, and impaired immune function. In addition, exposure to secondhand smoke has now been causally associated with an increased risk for stroke.

Smoking remains the leading preventable cause of premature disease and death in the United States. The science contained in this and prior Surgeon General's reports provide all the information we need to save future generations from the burden of premature disease caused by tobacco use. However, evidence-based interventions that encourage quitting and prevent youth smoking continue to be underutilized. This report strengthens our resolve to work together to accelerate and sustain what works—such as hard-hitting media campaigns, smokefree air policies, optimal tobacco excise taxes, barrier-free cessation treatment, and comprehensive statewide tobacco control programs funded at CDC-recommended levels. At the same time, we will explore "end game" strategies that support the goal of eliminating tobacco smoking, including greater restrictions on sales. It is my sincere hope that 50 years from now we won't need another Surgeon General's report on smoking and health, because tobacco-related disease and death will be a thing of the past. Working together, we can make that vision a reality.

Boris D. Lushniak, M.D., M.P.H.
Rear Admiral, U.S. Public Health Service
Acting Surgeon General
U.S. Department of Health and Human Services

Acknowledgments

Rebecca H. Bitsko, Ph.D., Health Scientist, Division of Human Development and Disability, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia.

Georgiy V. Bobashev, Ph.D., Senior Research Statistician, Research Triangle Institute, Durham, North Carolina.

Kari Bohlke, Sc.D., Consultant Epidemiologist, Alvin J. Siteman Cancer Center, Washington University School of Medicine in St. Louis, St. Louis, Missouri.

Ross C. Brownson, Ph.D., Professor and Co-Director, Prevention Research Center in St. Louis, Brown School; Division of Public Health Sciences and Alvin J. Siteman Cancer Center, School of Medicine, Washington University in St. Louis, St. Louis, Missouri.

Arthur L. Burnett, M.D., M.B.A., F.A.C.S., Patrick C. Walsh Distinguished Professor of Urology, Cellular and Molecular Medicine, Director, Sexual Medicine Division, Department of Urology, Johns Hopkins University, Baltimore, Maryland.

David M. Burns M.D., Professor Emeritus, Department of Family and Preventive Medicine, University of California San Diego, School of Medicine, San Diego, California.

Angelika H. Claussen, Ph.D., Research Psychologist, Division of Human Development and Disabilities, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia.

Graham A. Colditz, M.D., Dr. P.H., Fellow of the Australian Faculty of Public Health Medicine, Niess-Gain Professor and Chief, Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, and Associate Director, Prevention and Control, Siteman Cancer Center, St. Louis, Missouri.

David Coultas, M.D., Vice President for Clinical and Academic Affairs, Professor and Chair, Department of Medicine, The University of Texas Health Science Center, Tyler Texas.

James D. Crapo M.D., Professor of Medicine, National Jewish Health and University of Colorado, Denver, Colorado.

MeLisa R. Creamer, M.P.H., Ph.D. Candidate and Michael and Susan Dell Health Scholar, Division of Epidemiology, University of Texas School of Public Health, Austin Regional Campus, Michael and Susan Dell Center for Healthy Living, Austin, Texas.

Mary E. Cronin, M.D., Rheumatology Fellowship Program Director, Professor of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin.

K. Michael Cummings, Ph.D., M.P.H., Co-director, Tobacco Research Program, Hollings Cancer Center and Professor, Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, South Carolina.

Nancy E. Davidson, M.D., Director, University of Pittsburgh Cancer Institute and University of Pittsburgh Medical Center, Associate Vice Chancellor for Cancer Research, Hillman Professor of Oncology, Distinguished Professor of Medicine and Pharmacology and Chemical Biology, University of Pittsburgh, Pittsburgh, Pennsylvania.

Richard A. Daynard, J.D., Ph.D., President, Public Health Advocacy Institute, University Distinguished Professor of Law, Northeastern University, Boston, Massachusetts.

Cristine D. Delnevo, Ph.D., M.P.H., Director, Center for Tobacco Surveillance and Evaluation Research, Professor and Chair, Department of Health Education/Behavioral Science, Rutgers School of Public Health, New Brunswick, New Jersey.

Dawn L. DeMeo, M.D., M.P.H., Channing Division of Network Medicine, Associate Professor of Medicine, Harvard Medical School, Associate Physician, Division of Pulmonary and Critical Care, Brigham and Women's Hospital, Boston, Massachusetts.

Mark D. Eisner, M.D., M.P.H., Associate Professor of Medicine and Anesthesia, Division of Occupational and Environmental Medicine and Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of California, San Francisco, California.

Lucinda England, M.D., M.S.P.H., Medical Epidemiologist, Office on Smoking and Health, National Center for Chronic Disease and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Jonathan Golub, Ph.D, M.P.H., Associate Professor, Medicine, Epidemiology and International Health, Center for Tuberculosis Research, Johns Hopkins University, Baltimore, Maryland.

Mark Gottlieb, J.D., Executive Director, Public Health Advocacy Institute, Northeastern University School of Law, Boston, Massachusetts.

Stephen S. Hecht, Ph.D., Wallin Professor of Cancer Prevention, Masonic Cancer Center, University of Minnesota, Minneapolis, Minnesota.

Jack E. Henningfield, Ph.D., Vice President, Research and Health Policy, Pinney Associates, Bethesda, Maryland, and Professor, Adjunct, Behavioral Biology, Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, Baltimore, Maryland.

Theodore R. Holford, Ph.D., Professor, Department of Biostatistics, Yale School of Public Health, New Haven, Connecticut.

Stephen T. Holgate M.D., Professor, Fellow of the Academy of Medical Sciences, Medical Research Council, Clinical Professor of Immunopharmacology, University of Southampton, United Kingdom.

John W. Holloway, Ph.D., Professor of Allergy and Respiratory Genetics, Faculty of Medicine, University of Southampton, United Kingdom.

David M. Homa, Ph.D., M.P.H., Epidemiologist, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Margaret A. Honein, Ph.D., M.P.H., Chief, Birth Defects Branch, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia.

Frank B. Hu, M.D., Ph.D., Professor of Nutrition and Epidemiology, Harvard School of Public Health; Professor of Medicine, Harvard Medical School and Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts.

Susan Hutfless, Ph.D., Assistant Professor, Division of Gastroenterology and Hepatology, Department of Medicine, Johns Hopkins University, Baltimore, Maryland.

Rachel Kaufmann, M.P.H., Ph.D., Associate Director for Science, Center for Surveillance, Epidemiology, and Laboratory Services, Centers for Disease Control and Prevention, Atlanta, Georgia.

Brian A. King, Ph.D., M.P.H., Epidemiologist, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Gregory D. Kirk, M.D., M.P.H., Ph.D., Associate Professor of Epidemiology, Medicine and Oncology, Johns Hopkins University, Baltimore, Maryland.

Kim Klausner, Manager, Industry Documents Digital Libraries, University of California San Francisco, San Francisco, California.

Robert C. Klesges, Ph.D., Professor, Department of Preventive Medicine, The University of Tennessee Health Science Center, Memphis, Tennessee.

Darwin R. Labarthe, M.D., M.P.H., Ph.D., F.A.H.A., Professor of Preventive Medicine, Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois.

Anne Landman, B.A., Landman Research and Communications, Grand Junction, Colorado.

David T. Levy, Ph.D., Professor, Cancer Control, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, D.C.

Carolyn A. Lullo, Ph.D., M.S., Public Health Analyst, Division of Human Development and Disability, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia.

Patricia L. Mabry, Ph.D., Senior Advisor and Acting Deputy Director, Office of Behavioral and Social Sciences Research, Office of the Director, National Institutes of Health, Bethesda, Maryland.

David M. Mannino, M.D., Professor and Chair, Department of Preventive Medicine and Environmental Health, Director, Pulmonary Epidemiology Research Laboratory, University of Kentucky College of Public Health, Lexington, Kentucky.

Paul Melstrom, Phar.D., Ph.D., Toxicologist/Epidemiologist, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

David Méndez, Ph.D., Associate Professor, Health Management and Policy, School of Public Health, University of Michigan, Ann Arbor, Michigan.

Nathaniel D. Osgood, Ph.D., Director, Computational Epidemiology and Public Health Informatics Laboratory, Associate Professor, Department of Computer Science, Associate Faculty, Department of Community Health and Epidemiology, University of Saskatchewan, Saskatoon, Canada.

Mark Parascandola, Ph.D., M.P.H., Epidemiologist, Tobacco Control Research Branch, Behavioral Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, Maryland.

Terry F. Pechacek, Ph.D., Deputy Director for Research Translation, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Cheryl L. Perry, Ph.D., Professor and Regional Dean, University of Texas School of Public Health, Austin Regional Campus, Michael and Susan Dell Center for Healthy Living, Austin, Texas.

Keydra L. Phillips, M.Sc., Health Scientist, Division of Birth Defects and Developmental Disabilities, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia.

Elizabeth A. Platz, Sc.D., M.P.H., Professor, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health and the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, Maryland.

Jennita Reefhuis, Ph.D., Research Health Scientist, Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Nancy A. Rigotti, M.D., Director, Tobacco Research and Treatment Center and Associate Chief, General Medicine Division, Department of Medicine, Massachusetts General Hospital; Professor of Medicine, Harvard Medical School, Boston, Massachusetts.

Ann K. Rosenthal, M.D., Will and Cava Ross Professor of Medicine, Chief of Rheumatology and Vice Chair, Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin.

Hossein Sadeghi-Nejad, M.D., F.A.C.S., Professor of Surgery, Division of Urology, Rutgers New Jersey Medical School, Chief of Urology, Virginia-New Jersey Health Care System; Director, Center for Male Reproductive Medicine, Hackensack University Medical Center, Hackensack, New Jersey.

Jonathan M. Samet, M.D., M.S., Professor and Flora L. Thornton Chair, Department of Preventive Medicine, Keck School of Medicine; Director, Institute for Global Health, University of Southern California, Los Angeles, California.

Elizabeth Selvin, Ph.D., M.P.H., Associate Professor of Epidemiology and Medicine, Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland.

Steven D. Shapiro, M.D., Executive Vice President and Chief Medical and Scientific Officer, University of Pittsburgh Medical Center; President, Physician Services Division; Professor of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

Peter G. Shields, M.D., Deputy Director, Comprehensive Cancer Center, Professor, College of Medicine, James Cancer Hospital, The Ohio State University Wexner Medical Center, Columbus, Ohio.

Donald R. Shopland, U.S. Public Health Service (retired), Ringgold, Georgia.

David Sidransky, M.D., Director, Head and Neck Cancer Research Division, Professor in Otolaryngology, Cellular and Molecular Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland.

Edwin K. Silverman, M.D., Ph.D., Associate Professor of Medicine, Harvard Medical School, Associate Physician, Brigham and Women's Hospital, Boston, Massachusetts.

Martin R. Stampfli, Ph.D., Professor, Department of Pathology and Molecular Medicine, McMaster Immunology Research Centre, and Department of Medicine, Firestone Institute of Respiratory Health at St. Joseph's Healthcare, McMaster University, Hamilton, Ontario, Canada.

Melissa H. Stigler, Ph.D., M.P.H., Assistant Professor, The University of Texas Health Science Center at Houston, School of Public Health, Austin Regional Campus, Michael and Susan Dell Center for Healthy Living, Austin, Texas.

Edward L. Sweda, Jr., J.D., Senior Attorney, Public Health Advocacy Institute, Northeastern University School of Law, Boston, Massachusetts.

Rachel Taketa, Library Specialist, Industry Documents Digital Libraries, Library and Center for Knowledge Management, University of California, San Francisco, California.

Gerald W. Talcott, Ph.D., ABPP, Col USAF (ret), Director of Military Research, Associate Professor, Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis, Tennessee.

Leslie A. Thompson, M.D., Division of Rheumatology, Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin.

Michael J. Thun, M.D., Vice President Emeritus, Epidemiology and Surveillance Research, American Cancer Society, Atlanta, Georgia.

Hilary A. Tindle, M.D., M.P.H, Assistant Professor of Medicine, Epidemiology, and Clinical and Translational Science, University of Pittsburgh, Pittsburgh, Pennsylvania.

Scott L. Tomar, D.M.D., M.P.H., Dr. P.H., Professor, Department of Community Dentistry and Behavioral Science, University of Florida College of Dentistry, Gainesville, Florida.

Van T. Tong, M.P.H., Epidemiologist, Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Andrea C. Villanti, Ph.D., M.P.H., Associate Director for Regulatory Science and Policy, The Schroeder Institute for Tobacco Research and Policy Studies, American Legacy FoundationS, Washington, D.C.

Susanna N. Visser, M.S., Lead Epidemiologist, Division of Human Development and Disability, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia.

Kala Visvanathan, M.B.B.S., F.R.A.C.P., M.H.S., Associate Professor, Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland.

Kenneth E. Warner, Ph.D., Avedis Donabedian Distinguished University Professor of Public Health, Department of Health Management and Policy, School of Public Health, University of Michigan, Ann Arbor, Michigan.

Graham Warren M.D., Ph.D., Vice Chairman for Research in Radiation Oncology, Associate Professor, Department of Radiation Oncology, Department of Cell and Molecular Pharmacology, Hollings Cancer Center, Medical University of South Carolina, Charleston, South Carolina.

Sheila West, Ph.D., El Maghraby Professor, Vice Chair for Research, Wilmer Eye Institute, School of Medicine, Johns Hopkins University, Baltimore, Maryland.

Heather Wipfli, Ph.D., Associate Director, Institute for Global Health, Assistant Professor, Department of Preventive Medicine and School of International Relations, Keck School of Medicine, University of Southern California, Los Angeles, California.

Xin Xu, Ph.D., Senior Economist, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Mitchell Zeller, J.D., Senior Vice President, Pinney Associates, Bethesda, Maryland.

Reviewers were

David B. Abrams, Ph.D., Executive Director, The Schroeder Institute for Tobacco Research and Policy Studies, Professor, Department of Health, Behavior and Society, The Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, and Professor of Oncology (adjunct), Georgetown University Medical Center, Lombardi Comprehensive Cancer Center, Washington, D.C.

Anthony J. Alberg, Ph.D., M.P.H., Blatt Ness Professor, Department of Public Health Sciences, Associate Director of Cancer Prevention and Control, Hollings Cancer Center, Medical University of South Carolina, Charleston, South Carolina.

Ashwin N. Ananthakrishnan, M.D., M.P.H, Assistant Professor of Medicine, Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts.

Benjamin Apelberg, Ph.D., M.H.S., Chief, Epidemiology Branch, Division of Population Health Sciences, Office of Science, Center for Tobacco Products, U.S. Food and Drug Administration, Rockville, Maryland.

Erik M. Augustson, Ph.D., M.P.H., Behavioral Scientist, Tobacco Control Research Branch, Behavioral Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, Rockville, Maryland.

Olalekan A. Ayo-Yusuf, D.D.S., M.P.H., Ph.D., Head of Clinical Unit and Associate Professor, Department of Community Dentistry, University of Pretoria, Pretoria, South Africa.

Cathy L. Backinger, Ph.D., M.P.H., Deputy Director for Research, Office of Science, Center for Tobacco Products, U.S. Food and Drug Administration, Rockville, Maryland.

John A. Baron, M.D., Professor of Medicine, University of North Carolina, Chapel Hill, North Carolina.

Leslie Bernstein, Ph.D., Director and Professor, Division of Cancer Etiology, Department of Population Sciences, Beckman Research Institute, City of Hope, and Dean for Faculty Affairs, Office of Academic Affairs, City of Hope, Duarte, California.

Douglas W. Bettcher, M.D., M.P.H., Ph.D., Director, Prevention of Noncommunicable Diseases Department, Noncommunicable Diseases and Mental Health Cluster, World Health Organization, Geneva, Switzerland.

Mary Beth Bigley, Dr.P.H., M.S.N., A.N.P., Director, Division of Science and Communications, and Acting Editor, Public Health Reports, Office of the Surgeon General, Office of the Assistant Secretary for Health, Office of the Secretary, U.S. Department of Health and Human Services, Washington, D.C.

Michele Bloch, M.D., Ph.D., Chief, Tobacco Control Research Branch, Behavioral Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, Rockville, Maryland.

Ron Borland Ph.D., Nigel Gray Distinguished Fellow in Cancer Prevention, Research Division, Cancer Council Victoria, Australia.

Thomas H. Brandon, Ph.D., Director, Tobacco Research and Intervention Program, and Chair, Department of Health Outcomes and Behavior, Moffitt Cancer Center; Professor of Psychology and Oncologic Sciences, University of South Florida, Tampa, Florida.

Otis W. Brawley, M.D., Chief Medical and Scientific Officer, American Cancer Society; Professor, Departments of Hematology and Oncology, Medicine and Epidemiology, Emory University, Atlanta, Georgia.

Peter A. Briss, M.D., M.P.H., Medical Director, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Gerald Brock, M.D., Professor of Surgery, Urology Program Director, The University of Western Ontario, Vice President of Education, Canadian Urological Association, London, Ontario, Canada.

Paul A. Bunn, Jr., M.D., James Dudley Chair in Cancer Research, University of Colorado Cancer Center, Aurora, Colorado.

Gregory L. Burke, M.D., M.Sc., Professor and Chair, Division of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, North Carolina.

David M. Burns M.D., Professor Emeritus, Department of Family and Preventive Medicine, University of California San Diego School of Medicine, San Diego, California.

Tim Byers M.D., M.P.H., Associate Director for Cancer Prevention and Control, University of Colorado Cancer Center, Associate Dean for Public Health Practice at the Colorado School of Public Health, Aurora, Colorado.

Neil E. Caporaso, M.D., Chief, Genetic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland.

Richard Casaburi, Ph.D., M.D., Medical Director, Rehabilitation Clinical Trials Center, Los Angeles Biomedical Research Institute at Harbor-University of California Los Angeles Medical Center; Professor of Medicine, University of California Los Angeles, School of Medicine, Torrance, California.

Frank J. Chaloupka, Ph.D., Director, Health Policy Center, University of Illinois at Chicago, Distinguished Professor, Department of Economics, University of Illinois, Chicago, Illinois.

June M. Chan, Sc.D., Professor, Epidemiology and Biostatistics, and Urology, Steven and Christine Burd-Safeway Distinguished Professor, University of California, San Francisco, California.

Graham A. Colditz, M.D., Dr. P.H., Fellow of the Australian Faculty of Public Health Medicine, Niess-Gain Professor and Chief, Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, and Associate Director, Prevention and Control, Siteman Cancer Center, St. Louis, Missouri.

Gregory N. Connolly, D.M.D., M.P.H., Professor of Public Health Practice, Director, Center for Global Tobacco Control, School of Public Health, Harvard University, Boston, Massachusetts.

Karen H. Costenbader, M.D., M.P.H., Associate Professor of Medicine, Harvard Medical School; Associate Physician and Co-Director of Lupus Center, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, Massachusetts.

James D. Crapo, M.D., Professor of Medicine, National Jewish Health and University of Colorado Denver, Denver, Colorado.

Amanda J. Cross, Ph.D., Investigator, Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland.

K. Michael Cummings, Ph.D., M.P.H., Co-director, Tobacco Research Program, Hollings Cancer Center and Professor, Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, South Carolina.

Thomas Dietrich, D.M.D., M.D., M.P.H., Professor and Chair, Department of Oral Surgery, School of Dentistry, University of Birmingham, Birmingham, United Kingdom.

Carolyn Dresler, M.D., M.P.A., Associate Director of Medical and Health Sciences, Office of Science, Center for Tobacco Products, U.S. Food and Drug Administration, Rockville, Maryland.

Bruce A. Dye, D.D.S., M.P.H., U.S. Public Health Service, Dental Epidemiology Officer, Centers for Disease Control and Prevention, National Center for Health Statistics, Division of Health and Nutrition Examination Statistics, Hyattsville, Maryland.

Hashem B. El-Serag, M.D., M.P.H., Professor, Department of Medicine, Chief of Gastroenterology and Hepatology, Baylor College of Medicine, and Chief, Clinical Epidemiology and Outcomes, Michael E. DeBakey Department of Veterans Affairs Medical Center, Houston, Texas.

Michael Eriksen, Sc.D., Dean and Professor, School of Public Health, Georgia State University, Atlanta, Georgia.

Eric J. Feuer, Ph.D., Chief, Statistical Methodology and Applications Branch, Division of Cancer Control and Population Sciences, National Cancer Institute, Rockville, Maryland.

Lawrence J. Fine, M.D., Dr. P.H., Chief, Clinical Applications and Prevention Branch, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, Bethesda, Maryland.

David W. Fleming, M.D., Director and Health Officer for Public Health, Seattle and King County, Seattle, Washington.

Silvia Franceschi, M.D., Special Advisor, Head, Infections and Cancer Epidemiology Group, International Agency for Research on Cancer, Lyon, France.

Neal D. Freedman, Ph.D., M.P.H., Investigator, Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland.

Gary D. Friedman, M.D., M.S., Consulting Professor of Epidemiology, Department of Health Research and Policy, Stanford University School of Medicine; Adjunct Investigator (Former Director), Division of Research, Kaiser Permanente Medical Care Program of Northern California, Stanford, California.

Philip S. Gardiner, Dr. P.H., Program Officer, Policy and Regulatory Sciences, Nicotine Dependence and Neurosciences, Tobacco-Related Disease Research Program, Office of the President, University of California, Oakland, California.

Joseph Gfroerer, Chief, Population Survey Branch, Division of Surveillance and Data Collection, Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, Rockville, Maryland.

Gretchen Gierach, Ph.D., M.P.H., Investigator, Hormonal and Reproductive Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland.

Elizabeth Ginexi, Ph.D., Health Scientist/Program Director, Tobacco Control Research Branch, Behavioral Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, Rockville, Maryland.

Edward L. Giovannucci, M.D., Sc.D., Professor of Nutrition and Epidemiology, Harvard School of Public Health; Associate Professor of Medicine, Brigham and Women's Hospital, Harvard Medical School, Harvard University, Boston, Massachusetts.

Gary A. Giovino, Ph.D., M.S., Professor and Chair, Department of Community Health and Health Behavior, School of Public Health and Health Professions, The State University of New York at Buffalo, Buffalo, New York.

Stanton A. Glantz, Ph.D., Professor of Medicine and American Legacy Foundation Distinguished Professor in Tobacco Control; Director, Center for Tobacco Control Research and Education, University of California, San Francisco, California.

Thomas J. Glynn, Ph.D., Director, Cancer Science and Trends; Director, International Cancer Control, American Cancer Society, Washington, DC.

David C. Goff, Jr., M.D., Ph.D., Dean and Professor, Colorado School of Public Health, Aurora, Colorado.

Diane R. Gold, M.D., M.P.H., Professor of Medicine, Channing Laboratory, Department of Medicine, Brigham and Women's Hospital; Professor of Environmental Health, Department of Environmental Health, Harvard School of Public Health, Boston, Massachusetts.

Richard A. Goodman, M.D., M.P.H., Senior Medical Advisor, Office of the Medical Director, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Rebecca F. Gottesman, M.D., Ph.D., Associate Professor of Neurology and Epidemiology, Johns Hopkins University School of Medicine, Baltimore, Maryland.

Nigel Gray, AO, MBBS, FRACP, Honorary Senior Associate, Cancer Council Victoria, Carlton, Victoria, Australia.

Susan Marsiglia Gray, M.P.H., Coordinator, National Synar Program, Center for Substance Abuse Prevention, Substance Abuse and Mental Health Services Administration, Rockville, Maryland.

John D. Groopman, Ph.D., Anna M. Baetjer Professor of Environmental Health Sciences, Department of Environmental Health Sciences, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland.

Beth Han, M.D., Ph.D., M.P.H., Statistician, Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, U.S. Department of Health and Human Services, Rockville, Maryland.

Craig L. Hanis, Ph.D., Professor, Division of Epidemiology, Human Genetics and Environmental Sciences, University of Texas Health Science Center, Houston, Texas.

Curtis C. Harris, M.D., Chief, Laboratory of Human Carcinogenesis, Center of Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

Patricia Hartge, Sc.D., M.A., Deputy Director, Epidemiology and Biostatistics Program, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland.

Dorothy K. Hatsukami, Ph.D., Forster Family Professor in Cancer Prevention, Professor, Department of Psychiatry, University of Minnesota, Minneapolis, Minnesota.

Stephen S. Hecht, Ph.D., Wallin Professor of Cancer Prevention, Masonic Cancer Center, University of Minnesota, Minneapolis, Minnesota.

Jack E. Henningfield, Ph.D., Vice President, Research and Health Policy, Pinney Associates, Bethesda, Maryland, and Professor, Adjunct, Behavioral Biology, Department of Psychiatry and Behavioral Sciences, School of Medicine, The Johns Hopkins University, Baltimore, Maryland.

James C. Hogg, M.D., Ph.D., Emeritus Professor of Pathology, Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, British Columbia, Canada.

V. Michael Holers, M.D., Head, Division of Rheumatology; Professor of Medicine and Immunology, University of Colorado School of Medicine, Denver, Colorado.

Stephen T. Holgate M.D., Professor, Fellow of the Academy of Medical Sciences, Medical Research Council, Clinical Professor of Immunopharmacology, University of Southampton, United Kingdom.

Philip P. Huang, M.D., M.P.H., Medical Director, Health Authority, Austin, Travis County Health and Human Services Department, Austin, Texas.

Yvonne Hunt, Ph.D., M.P.H., Program Director, Tobacco Control Research Branch, Behavioral Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, Rockville, Maryland.

Richard D. Hurt, M.D., Professor of Medicine, College of Medicine, Director, Nicotine Dependence Center, Mayo Clinic, Rochester, Minnesota.

Corrine Husten, M.D., M.P.H., Senior Medical Advisor, Center for Tobacco Products, Food and Drug Administration, Rockville, Maryland.

Andrew Hyland, Ph.D., Chair, Department of Health Behavior, Roswell Park Cancer Institute, Buffalo, New York.

Eric J. Jacobs, Ph.D., Strategic Director of Pharmacoepidemiology, Epidemiology Research Program, American Cancer Society, Atlanta, Georgia.

Prabhat Jha, O.C., M.D., D.Phil., Professor and Chair in Disease Control, University of Toronto, Executive Director, Centre for Global Health Research, St. Michael's Hospital, University of Toronto, Ontario, Canada.

Kenneth C. Johnson, Ph.D., Senior Epidemiologist/Research Scientist, Centre for Chronic Disease, Prevention and Control, Public Health Agency of Canada, Ottawa, Ontario, Canada.

Ron Johnson, Ph.D., Program Director, Cancer Etiology Branch, Division of Cancer Biology, National Cancer Institute, Rockville, Maryland.

Amy E. Kalkbrenner, Ph.D., M.P.H., Assistant Professor, Zilber School of Public Health, University of Wisconsin-Milwaukee, Milwaukee, Wisconsin.

Gilaad G. Kaplan, M.D., M.P.H., Associate Professor, Departments of Medicine and Community Health Sciences, Division of Gastroenterology, University of Calgary, Calgary, Alberta, Canada.

Annette Kaufman, Ph.D., M.P.H., Health Scientist/Program Director, Tobacco Control Research Branch, Behavioral Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, Rockville, Maryland.

Talmadge E. King, Jr., M.D., Chair, Department of Medicine, Julius R. Krevans Distinguished Professorship in Internal Medicine, Department of Medicine, University of California, San Francisco, California.

Barbara B. E. Klein, M.D., M.P.H., Professor, School of Ophthalmology and Visual Sciences, University of Wisconsin, Madison, Wisconsin.

Ronald Klein, M.D., M.P.H., Professor, Department of Ophthalmology and Visual Sciences, School of Medicine and Public Health, University of Wisconsin, Madison, Wisconsin.

Jennie Kline, Ph.D., Senior Research Scientist, Imprints Center, New York State Psychiatric Institute, New York, New York; Adjunct Professor of Epidemiology, Department of Epidemiology at Mailman School of Public Health and the Sergievsky Center, Columbia University, New York, New York.

Nino Künzli, M.D., Ph.D., Deputy Director and Head of Department, Swiss Tropical and Public Health Institute, Basel, Switzerland; Professor, Department of Public Health, University of Basel, Basel, Switzerland.

Stephanie Land, Ph.D., Statistician, Tobacco Control Research Branch, Behavioral Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, Rockville, Maryland.

Kate Langley, Ph.D., Research Associate, The Medical Research Council Centre for Neuropsychiatric Genetics and Genomics, Neuroscience and Mental Health Research Institute, Cardiff University, Cardiff, United Kingdom.

Scott J. Leischow, Ph.D., Department of Health Sciences Research, Mayo Clinic, Scottsdale, Arizona.

Edward V. Loftus, Jr., M.D., Consultant, Division of Gastroenterology and Hepatology, Director of Inflammatory Bowel Disease Interest Group, Professor of Medicine, Mayo Clinic, Rochester, Minnesota.

David A. Lomas, Ph.D., Sc.D., F.R.C.P., FMedSci., Dean, Faculty of Medical Sciences, University College London, London, United Kingdom.

Jay H. Lubin, Ph.D., Special Volunteer, Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland.

Russell V. Luepker, M.D., M.S., Mayo Professor, Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota.

Jing Ma, M.D., Ph.D., Associate Professor, Channing Division of Network Medicine, Brigham and Women's Hospital, Harvard Medical School; Department of Epidemiology, Harvard School of Public Health, Harvard University, Boston, Massachusetts.

Patricia L. Mabry, Ph.D., Senior Advisor and Acting Deputy Director, Office of Behavioral and Social Sciences Research, Office of the Director, National Institutes of Health, Bethesda, Maryland.

Judith Mackay, F.R.C.P (Edin), F.R.C.P (Lon), Senior Advisor, World Lung Foundation, New York, USA; Director, Asian Consultancy on Tobacco Control, Hong Kong.

Ruth E. Malone, R.N., Ph.D., F.A.A.N., Professor and Chair, Department of Social and Behavioral Sciences, School of Nursing, University of California, San Francisco, Editor, *Tobacco Control,* San Francisco, California.

Stephen E. Marcus, Ph.D., Epidemiologist and Program Director, Social and Behavioral Modeling Research Program, Division of Biomedical Technology, Bioinformatics, and Computational Biology, National Institute of General Medical Sciences, National Institutes of Health, Bethesda, Maryland.

Joseph B. Margolick, M.D., Ph.D., Professor, Department of Molecular Microbiology and Immunology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland.

Fernando J. Martinez, M.D., M.S., Professor of Internal Medicine, Associate Division Chief of Clinical Research, Division of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor, Michigan.

Carol A. Mathews, M.D., Associate Professor, Department of Psychiatry, University of California, San Francisco; Co-Chair Tourette Syndrome Association International Consortium for Genetics, San Francisco, California.

J. Michael McGinnis, M.D., M.A., M.P.P., Executive Director, Value and Science-Driven Health Care; Senior Scholar, Institute of Medicine, The National Academies, Washington, D.C.

Paul Melstrom, Pharm.D., Ph.D., Toxicologist/Epidemiologist, Epidemiology Branch, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Martin M. Miner, M.D., Co-Director, Men's Health Center, The Miriam Hospital, Clinical Associate Professor of Family Medicine and Urology, Warren Alpert School of Medicine, Brown University, Providence, Rhode Island.

Glen Morgan, Ph.D., Psychologist, Tobacco Control Research Branch, Behavioral Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, Rockville, Maryland.

Matthew L. Myers, J.D., President, Campaign for Tobacco-Free Kids, Washington, D.C.

Thomas E. Novotny, M.D., M.P.H., Professor and Associate Director for Border and Global Health, Division of Epidemiology, Graduate School of Public Health, San Diego State University, San Diego, California.

Sarah Nyante, Ph.D., M.S.P.H, Postdoctoral Fellow, Hormonal and Reproductive Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland.

Andrew F. Olshan, Ph.D., Professor and Chair, Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, North Carolina.

Jamie S. Ostroff, Ph.D., Chief, Behavioral Sciences Service, Department of Psychiatry and Behavioral Sciences, Memorial Sloan-Kettering Cancer Center; Professor of Psychology and Public Health, Weill Cornell Medical College, New York, New York.

Yikyung Park, Sc.D., Staff Scientist, Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland.

John P. Pierce, Ph.D., Professor of Cancer Research, Department of Family and Preventive Medicine, Director of Population Research, Moores Cancer Center, University of California San Diego, La Jolla California.

Elizabeth A. Platz, Sc.D., M.P.H., Professor, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health and the Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, Maryland.

Robert N. Proctor, Ph.D., Professor of the History of Science and Professor, by courtesy, of Pulmonary and Critical Care, Stanford University, Stanford, California.

Stephen I. Rennard, M.D., Larson Professor, Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, University of Nebraska Medical Center, Omaha, Nebraska.

William N. Rom, M.D., M.P.H., Director, Division of Pulmonary, Critical Care, and Sleep Medicine, Sol and Judith Bergstein Professor of Medicine and Environmental Medicine, New York University School of Medicine, New York, New York.

Julia H. Rowland, Ph.D., Director, Office of Cancer Survivorship, Division of Cancer Control and Population Sciences, National Cancer Institute, Rockville, Maryland.

Marc B. Schenker, M.D., M.P.H., Director, Center for Occupational and Environmental Health; Professor, Department of Public Health Sciences, University of California, Davis, California.

Steven A. Schroeder, M.D., Distinguished Professor of Health and Healthcare and Director, Smoking Cessation Leadership Center, Department of Medicine, University of California-San Francisco, San Francisco, California.

David A. Schwartz, M.D., Professor of Medicine and Immunology, Chair, Department of Medicine, University of Colorado, Aurora, Colorado.

Donald W. Sexton, M.B.A., M.H.A., Doctoral Student, University of Michigan School of Public Health, and United States Army Medical Department, Ann Arbor, Michigan.

A. Richey Sharrett, M.D., Dr. P.H., Professor, Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland.

Peter G. Shields, M.D., Deputy Director, Comprehensive Cancer Center, Professor, College of Medicine, James Cancer Hospital, The Ohio State University Wexner Medical Center, Columbus, Ohio.

Donald R. Shopland, U.S. Public Health Service (retired), Ringgold, Georgia.

Alfred Sommer, M.D., M.H.S., Dean Emeritus, Bloomberg School of Public Health; Professor, Departments of Epidemiology, Ophthalmology and International Health, Johns Hopkins University, Baltimore, Maryland.

Frank E. Speizer, M.D., E. H. Kass Distinguished Professor of Medicine, Harvard Medical School, Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts.

Meir J. Stampfer, M.D., Dr.P.H., Head, Chronic Disease Epidemiology Unit, Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School; Professor of Epidemiology and Nutrition, Harvard School of Public Health; and Professor of Medicine, Harvard Medical School, Boston, Massachusetts.

Gary D. Stoner, Ph.D., Professor, Department of Medicine, Division of Hematology and Oncology, Medical College of Wisconsin, Milwaukee, Wisconsin.

Catherine M. Stoney, Ph.D., Program Director, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.

Ira B. Tager, M.D., M.P.H., Professor Emeritus of Epidemiology, School of Public Health, University of California, Berkeley, California.

Prue Talbot, Ph.D., Professor of Cell Biology, Director of the Stem Cell Center and Core, Department of Cell Biology and Neuroscience, University of California, Riverside, California.

Crystal E. Tan, M.D., M.S., Center for Tobacco Control Research and Education, University of California, San Francisco, California.

Michael J. Thun, M.D., M.S., Emeritus Vice President, Epidemiology and Surveillance Research, American Cancer Society, Atlanta, Georgia.

Douglas Tipperman, M.S.W., Lead Public Health Advisor, Center for Substance Abuse Prevention, Substance Abuse and Mental Health Services Administration, Rockville, Maryland.

Benjamin Toll, Ph.D., Program Director, Smoking Cessation Service at Smilow Cancer Hospital and Yale Cancer Center; Associate Professor, Department of Psychiatry, School of Medicine, Yale University, New Haven, Connecticut.

Edward J. Trapido, Sc.D., F.A.C.E., Associate Dean for Research, Professor and Wendell H. Gauthier Chair of Cancer Epidemiology, Louisiana State University School of Public Health; Deputy Director, Stanley S. Scott Cancer Center; Professor of Medicine and Senior Liaison to the Dean of the School of Medicine, Louisiana State University Health Sciences Center, New Orleans, Louisiana.

Bruce J. Trock, Ph.D., Professor, Departments of Urology, Oncology, Epidemiology, and Environmental Health Sciences, Director, Division of Epidemiology of the James Buchanan Brady Urological Institute, Johns Hopkins School of Medicine, Baltimore, Maryland.

Donna Vallone, Ph.D., M.P.H., Senior Vice President, American Legacy Foundation; Assistant Professor (Adjunct), Department of Health, Behavior and Society, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland.

Rohit Varma, M.D., M.P.H., Professor and Chair, Illinois Eye and Ear Infirmary, Department of Ophthalmology and Visual Sciences; Associate Dean for Strategic Planning, College of Medicine, Chicago, Illinois.

Robert E. Vollinger, M.S.P.H., Public Health Advisor, Tobacco Control Research Branch, Behavioral Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, Rockville, Maryland.

Melanie A. Wakefield, Ph.D., Director, Center for Behavioral Research in Cancer, Cancer Council Victoria, Melbourne, Australia.

Robert B. Wallace, M.D., M.Sc., Director, Center on Aging, Professor, Department of Epidemiology, College of Public Health, and Professor, Department of Internal Medicine, Carver College of Medicine, University of Iowa, Iowa City, Iowa.

Kenneth E. Warner, Ph.D., Avedis Donabedian Distinguished University Professor of Public Health, Department of Health Management and Policy, School of Public Health, University of Michigan, Ann Arbor, Michigan.

Walter C. Willett, M.D., Dr. P.H., Departments of Nutrition and Epidemiology, Harvard School of Public Health, Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.

Nick Wilson, M.B.Ch.B., M.P.H., Associate Professor of Public Health, Co-Director of the Burden of Disease Epidemiology, Equity and Cost-effectiveness Programme, University of Otago, Wellington, New Zealand.

Gayle C. Windham, Ph.D., M.S.P.H., Chief, Epidemiological Surveillance Unit, Division of Environmental and Occupational Disease, California Department of Public Health, Richmond, California.

Anna H. Wu, Ph.D., Professor, Keck School of Medicine, Department of Preventive Medicine, University of Southern California, Los Angeles, California.

Mandi Yu, Ph.D., M.S., Mathematical Statistician, Data Analysis and Interpretation Branch, Division of Cancer Control and Population Sciences, National Cancer Institute, Rockville, Maryland.

Other contributors were

Julie M. Carter, M.P.H., Public Health Analyst, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Stephanie Denkhoff Boone, Ph.D., M.P.H., Postdoctoral Associate, Department of Epidemiology and Population Health, School of Public Health and Information Sciences, James Graham Brown Cancer Center, University of Louisville, Louisville, Kentucky.

Athena Foong, M.S., Research Writer/Research Assistant to Jonathan M. Samet, M.D., M.S., Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California.

Earl S. Ford, M.D., M.P.H., Medical Officer, Epidemiology and Surveillance Branch, Division of Population Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Joseph Gfroerer, Chief, Population Survey Branch, Division of Surveillance and Data Collection, Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, U.S. Department of Health and Human Services, Rockville, Maryland.

Beth Han, M.D., Ph.D., M.P.H., Statistician, Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, U.S. Department of Health and Human Services, Rockville, Maryland.

S. Jane Henley, M.S.P.H., Epidemiologist, Division of Cancer Prevention and Control, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Carissa Baker Holmes, M.P.H., Public Health Analyst, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Lynn A. Hughley, Health Communications Specialist, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Joel London, M.P.H., C.H.E.S., Health Communications Specialist, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Kristy Marynak, M.P.P., Public Health Analyst, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Luz M. Moncayo, Executive Assistant to Jonathan M. Samet, M.D., M.S., Department of Preventive Medicine, Keck School of Medicine, Institute for Global Health, University of Southern California, Los Angeles, California.

Jake Nikota, Ph.D. Candidate, Department of Pathology and Molecular Medicine, McMaster Immunology Research Centre, McMaster University, Hamilton, Ontario, Canada.

Erin L. O'Connor, M.S., Data Analyst, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Alissa O'Halloran, M.S.P.H., Health Research Analyst, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Gabbi Promoff, M.A., Associate Director for Policy, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Hilda Razzaghi, Ph.D., M.S.P.H., Epidemiologist-ORISE Fellow, Birth Defects Branch, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia.

Lisa C. Richardson, M.D., M.P.H., Associate Director for Science, Division of Cancer Prevention and Control, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Emily Ridgway, M.P.H., ORISE Fellow, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Lauren K. Shaw, M.S., Statistician, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Dana Shelton, M.P.H., Deputy Director, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Kathryn E. Szynal, Editorial Assistant, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Cheryll C. Thomas, M.S.P.H., Deputy Associate Director for Science, Office of the Director, Division of Cancer Prevention and Control, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Dale J. Willett, J.D., Candidate Class of 2013, Legal Research and Writing Assistant, Northeastern University School of Law, Boston, Massachusetts.

Dongyan Yang, M.D., M.S., Assistant Professor, Department of Epidemiology and Population Health, School of Public Health, University of Louisville, Louisville, Kentucky.

The Health Consequences of Smoking—50 Years of Progress

Chapter 1
Introduction, Summary, and Conclusions

Introduction

On January 11, 1964, Luther L. Terry, M.D., Surgeon General of the United States, released *Smoking and Health: Report of the Advisory Committee of the Surgeon General of the Public Health Service*. This report, written at the request of President John F. Kennedy, was in response to the evidence on smoking and lung cancer that had been accumulating since the 1950s (see Chapter 2, "Fifty Years of Change 1964–2014"). This was the first in the series that is now generally referred to as the Surgeon General's reports. On the basis of more than 7,000 articles in the biomedical literature relating to smoking and disease that were available at the time, the Advisory Committee concluded that cigarette smoking is:

- Associated with 70% higher all-cause mortality rates among men

- A cause of lung cancer and laryngeal cancer in men

- A probable cause of lung cancer in women

- The most important cause of chronic bronchitis (U.S. Department of Health, Education, and Welfare [USDHEW] 1964).

For several days, the report was the topic of newspaper headlines across the country and lead stories on television newscasts (Parascandola 1997). Later, it was ranked among the top news stories of the 20th century (*USA Today* 1999). The release of that report was one of the first in a series of steps, still being taken 50 years later, to diminish the impact of tobacco use on the health of people worldwide. Ever since, individual citizens, private organizations, public agencies, and elected officials have pursued the Advisory Committee's call for "appropriate remedial action."

Early on, in response to the 1964 report, the U.S. Congress passed the *Federal Cigarette Labeling and Advertising Act of 1965* and the *Public Health Cigarette Smok-*

ing Act of 1969. These laws required a health warning on cigarette packages, banned cigarette advertising in the broadcasting media, and called for an annual report on the health consequences of smoking. Since then, there have been several actions at the federal level—the enactment of the *Family Smoking Prevention and Tobacco Control Act* in 2009, and the publication of *Ending the Tobacco Epidemic: A Tobacco Control Strategic Plan for the U.S. Department of Health and Human Services* (USDHHS 2010a).

Since that first report in 1964, knowledge of the health consequences of smoking and involuntary exposure to tobacco smoke has expanded dramatically (see Chapter 4, "Advances in Knowledge on the Health Consequences of Smoking: From 1964–2014"). This series of reports has provided definitive syntheses of the evolving evidence on smoking and health. The topics have ranged widely, including comprehensive coverage of the adverse health effects of active smoking and exposure to secondhand smoke (USDHEW 1979; U.S. Department of Health and Human Services [USDHHS] 1986, 2004, 2006), the impact of tobacco control policies (USDHHS 2000), and addiction (USDHHS 1988). A goal of these reports has been to synthesize available evidence to reach conclusions on causality that have public health implications. In reaching conclusions on causation, the reports have followed a model that originated with the 1964 report: compilation of all relevant lines of scientific evidence, critical assessment of the evidence, evaluation of the strength of evidence by using guidelines for evidence evaluation, and a summary conclusion on causation (USDHEW 1964; USDHHS 2004; Table 1.1; Chapter 3, "Producing the Surgeon General's Report from 1964–2014: Process and Purpose"). The Surgeon General's reports have established a long list of health consequences and diseases caused by tobacco use and exposure to tobacco smoke (see Chapter 4). Fifty years later, this report documents that our knowledge continues to expand as new causal conclusions are still being added to that long list (Figures 1.1A and 1.1B).

Table 1.1   Four-level hierarchy for classifying the strength of causal inferences from available evidence

Level 1	Evidence is **sufficient** to infer a causal relationship
Level 2	Evidence is **suggestive but not sufficient** to infer a causal relationship
Level 3	Evidence is **inadequate** to infer the presence or absence of a causal relationship (which encompasses evidence that is sparse, of poor quality, or conflicting)
Level 4	Evidence is **suggestive of no causal relationship**

Source: U.S. Department of Health and Human Services 2004.

Figure 1.1A   The health consequences causally linked to smoking

Cancers

Oropharynx

Larynx

Esophagus

Trachea, bronchus, and lung

Acute myeloid leukemia

Stomach

Liver*

Pancreas

Kidney
and ureter

Cervix

Bladder

Colorectal*

Chronic Diseases

Stroke

Blindness, cataracts, **age-related macular degeneration***

Congenital defects–maternal smoking: orofacial clefts*

Periodontitis

Aortic aneurysm, early abdominal aortic
atherosclerosis in young adults

Coronary heart disease

Pneumonia

Atherosclerotic peripheral vascular disease

Chronic obstructive pulmonary disease, **tuberculosis,***
asthma, and other respiratory effects

Diabetes*

Reproductive effects in women
(including reduced fertility)

Hip fractures

Ectopic pregnancy*

Male sexual function–erectile dysfunction*

Rheumatoid arthritis*

Immune function*

Overall diminished health

Source: USDHHS 2004, 2006, 2012.
Note: Each condition presented in bold text and followed by an asterisk (*) is a new disease that has been causally linked to smoking
in this report.

Organization of the Report

This report is divided into three sections. Section 1 "Historical perspective, overview, and conclusions" provides an overall summary of the report and its conclusions. It also provides a summary of the history of this series of reports, moving from their origins in 1964 to the present, contrasting what we knew in 1964 with what we know now in 2014. Section 2 "The Health Consequences of Active and Passive Smoking: The Evidence in 2014" provides a direct link to the 1964 report, which addressed the health effects of active smoking only. The first chapter

in this section gives a 50-year perspective on the identification of the health consequences of active smoking and exposure to secondhand smoke. The other chapters in this section provide updates on critical topics and on topics for which the evidence has advanced, since the previous reviews in the 2004 and 2006 Surgeon's reports, *The Health Consequences of Smoking: A Report of the Surgeon General* and *The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General,* including a brief review of the state of

Figure 1.1B   The health consequences causally linked to exposure to secondhand smoke

Children   **Adults**

Middle ear disease

Respiratory symptoms,
impaired lung function

Lower respiratory illness

Sudden infant death syndrome

Stroke*

Nasal irritation

Lung cancer

Coronary heart disease

Reproductive effects in women:
low birth weight
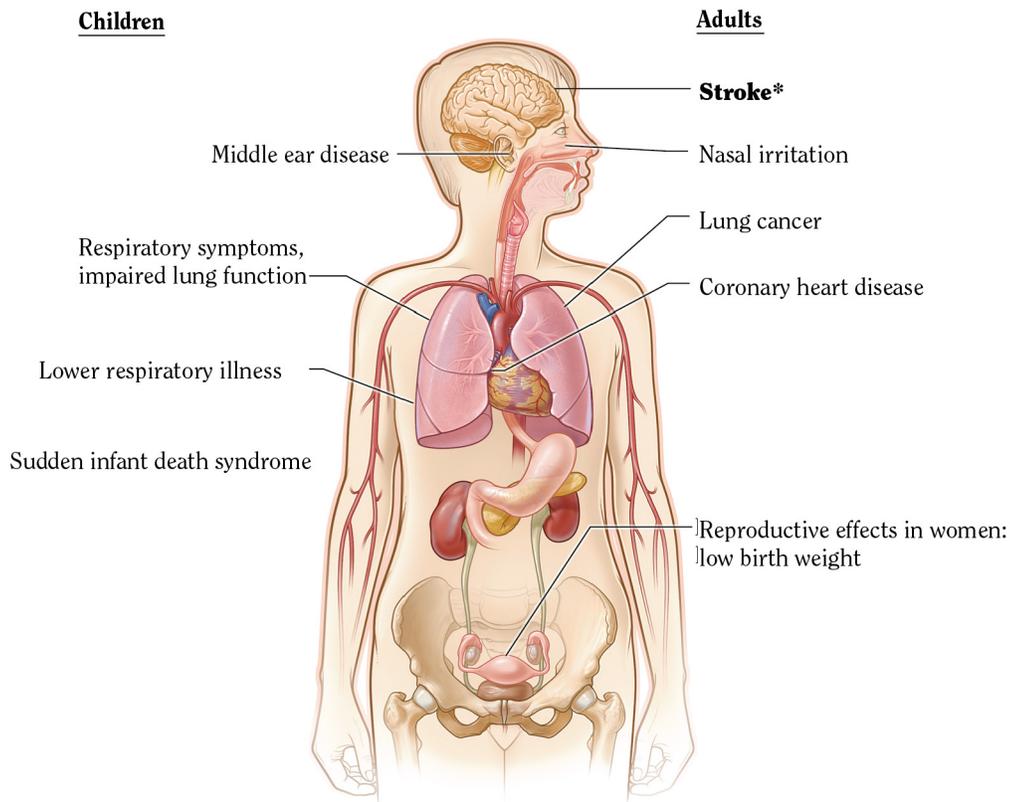
Source: USDHHS 2004, 2006.
Note: Each condition presented in bold text and followed by an asterisk (*) is a new disease that has been causally linked to exposure
to secondhand smoke in this report.

the evidence. Understanding of mechanisms, as laid out in the 2010 report, *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease,* is also (USDHHS 2010b). Active smoking and exposure to secondhand smoke are covered in the same chapters. Section 3 "Tracking and Ending the Epidemic" includes a descriptive chapter on the patterns of smoking, a chapter on the impact of the tobacco control environment on smoking since 1964, and additional chapters providing estimates of premature deaths that are avoidable.

The final chapter "A Vision for the Ending the Tobacco Epidemic" outlines broad strategies and potential courses of action for tobacco control in the future.

Each section within the chapters on the health consequences of smoking (Chapters 6 – 11) is accompanied by evidence tables detailing the studies that were used to evaluate the evidence to assess causality. A supplement to this report is provided that contains these tables. The tables included in the supplement are indicated with an "*S*" where they are called out in the text.

Development of the Report

The Surgeon General's reports on smoking and health were previously mandated by the Cigarette Smoking Act of 1969, Public Law 91-222, section 8 (a), which required that "The Secretary of Health, Education, and Welfare shall transmit a report to Congress not later than January 1, 1971, and annually thereafter, concerning (A) current information in the health consequences of smoking, and (B) such recommendations for legislation as he may deem appropriate." In addition, recent reports have also satisfied the statutory reporting required by the Comprehensive Smokeless Tobacco Health Education Act of 1986, Public Law 99-252, which required that "The Secretary of Health and Human Services shall transmit a report to Congress no later than January 11, 1987, and biennially thereafter, containing—(1) a description of the effects of health education efforts on the use of smokeless tobacco products, (2) a description of the use by the public of smokeless tobacco products, (3) an evaluation of the health effects of smokeless tobacco products and the identification of areas appropriate for further research, and (4) such recommendation for legislation and administrative action as the Secretary considers appropriate." These statutory requirements were sunsetted in 1999 and an annual report to Congress is no longer required by law.

Initially, the annual reports to Congress on the health consequences of smoking were prepared by the National Clearinghouse for Smoking and Health; however, in 1978 Secretary of Health, Education, and Welfare Joseph Califano established the Office on Smoking and Health in the Office of the Assistant Secretary of Health to coordinate the production of the annual report to Congress that would review not only the biomedical but also the behavioral and control data about smoking and its effects on health. The fifteenth anniversary report (USDHEW 1979) was the first report produced by the Office on Smoking and Health (see Table 3.1 for a full listing of reports from 1964–2012).

Beginning with Dr. Luther L. Terry, each Surgeon General has released the reports to the public and served as the primary spokesperson of the findings. However, the preparation of these reports, starting with the 1964 Advisory Committee, has been conducted with a high degree of independence, in order to protect their scientific integrity. Although the public may assume that the individual Surgeon Generals have been active in the authoring of the reports, their role has remained largely at the level of approving topics and reviewing drafts before the volume is published. Nevertheless, over time, the Office of the Surgeon General has increasingly become involved in developing the messaging for the public release of the reports. Consistent with a primary duty of the Surgeon General to "Protect and advance the health of the Nation through educating the public, advocating for effective disease prevention and health promotion programs and activities, and, providing a highly recognized symbol of national commitment to protecting and improving the public's health," the Office of the Surgeon General (n.d.) has expanded the range of educational materials supporting the release of the scientific report, particularly the development of a consumer summary which is produced in nontechnical but scientifically valid language.

As shown in Table 3.1, over time the size of the reports has grown, largely due to the increase in scientific literature on the topics reviewed, but also as the scope of topics has grown from those addressed in the initial charge provided by Secretary Califano in 1979 to address the behavioral and tobacco control aspects of the problem. This broader focus is reflected in the 2012 report which reviewed not only the epidemiology, causes, and health effects of tobacco use among youth and young adults, but also the interventions proven to prevent this problem (USDHHS 2012).

This report of the Surgeon General was prepared by the Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, USDHHS. Initial chapters were written between 2010–2011 by 75 experts selected because of their knowledge of, and familiarity with, the topics presented here. These contributions are summarized in 15 chapters, which were evaluated by more than 100 peer reviewers. The entire manuscript was then sent to more than 20 scientists and other experts, who examined it for scientific integrity. After each review cycle, the drafts were revised by the editors on the basis of the reviewers' comments. Subsequently, the report was reviewed by various institutes and agencies within USDHHS. Publication lags, even short ones, prevent an up-to-the-minute inclusion of all recently published articles and data. Therefore, by the time the public reads this report, additional studies or data may have been published.

The methodology for evidence compilation, review, and synthesis draws on the approach of the 1964 Surgeon General's report (USDHEW 1964), as further modified in the 2004 report (USDHHS 2004). That report also refined the methodology for causal inference and set out a classification of strength of evidence for causal inference.

Scientific Basis of the Report

The statements and conclusions throughout this report are documented by the citation of studies published in the scientific literature. For the most part, this report cites peer-reviewed journal articles, including reviews that integrate findings from numerous studies, and books by recognized experts. When a study has been accepted for publication, but the publication has not yet been issued, owing to the delay between acceptance and final publication, the study is referred to as "in press." This report also refers, on occasion, to unpublished research such as a presentation at a professional meeting or a personal communication from the researcher. These personal references are to acknowledge experts whose research is in progress.

Major Conclusions from the Report

1. The century-long epidemic of cigarette smoking has caused an enormous avoidable public health tragedy. Since the first Surgeon General's report in 1964 more than 20 million premature deaths can be attributed to cigarette smoking.

2. The tobacco epidemic was initiated and has been sustained by the aggressive strategies of the tobacco industry, which has deliberately misled the public on the risks of smoking cigarettes.

3. Since the 1964 Surgeon General's report, cigarette smoking has been causally linked to diseases of nearly all organs of the body, to diminished health status, and to harm to the fetus. Even 50 years after the first Surgeon General's report, research continues to newly identify diseases caused by smoking, including such common diseases as diabetes mellitus, rheumatoid arthritis, and colorectal cancer.

4. Exposure to secondhand tobacco smoke has been causally linked to cancer, respiratory, and cardiovascular diseases, and to adverse effects on the health of infants and children.

5. The disease risks from smoking by women have risen sharply over the last 50 years and are now equal to those for men for lung cancer, chronic obstructive pulmonary disease, and cardiovascular diseases.

6. In addition to causing multiple diseases, cigarette smoking has many other adverse effects on the body, such as causing inflammation and impairing immune function.

7. Although cigarette smoking has declined significantly since 1964, very large disparities in tobacco use remain across groups defined by race, ethnicity, educational level, and socioeconomic status and across regions of the country.

8. Since the 1964 Surgeon General's report, comprehensive tobacco control programs and policies have been proven effective for controlling tobacco use. Further gains can be made with the full, forceful, and sustained use of these measures.

9. The burden of death and disease from tobacco use in the United States is overwhelmingly caused by cigarettes and other combusted tobacco products; rapid elimination of their use will dramatically reduce this burden.

10. For 50 years the Surgeon General's reports on smoking and health have provided a critical scientific foundation for public health action directed at reducing tobacco use and preventing tobacco-related disease and premature death.

Chapter Conclusions

Note: Chapters 2-4 do not have conclusions.

Chapter 5: Nicotine

1. The evidence is sufficient to infer that at high-enough doses nicotine has acute toxicity.

2. The evidence is sufficient to infer that nicotine activates multiple biological pathways through which smoking increases risk for disease.

3. The evidence is sufficient to infer that nicotine exposure during fetal development, a critical window for brain development, has lasting adverse consequences for brain development.

4. The evidence is sufficient to infer that nicotine adversely affects maternal and fetal health during pregnancy, contributing to multiple adverse outcomes such as preterm delivery and stillbirth.

5. The evidence is suggestive that nicotine exposure during adolescence, a critical window for brain development, may have lasting adverse consequences for brain development.

6. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to nicotine and risk for cancer.

Chapter 6: Cancer

Lung Cancer

1. The evidence is sufficient to conclude that the risk of developing adenocarcinoma of the lung from cigarette smoking has increased since the 1960s.

2. The evidence is sufficient to conclude that the increased risk of adenocarcinoma of the lung in smokers results from changes in the design and composition of cigarettes since the 1950s.

3. The evidence is not sufficient to specify which design changes are responsible for the increased risk of adenocarcinoma, but there is suggestive evidence that ventilated filters and increased levels of tobacco-specific nitrosamines have played a role.

4. The evidence shows that the decline of squamous cell carcinoma follows the trend of declining smoking prevalence.

Liver Cancer

1. The evidence is sufficient to infer a causal relationship between smoking and hepatocellular carcinoma.

Colorectal Cancer

1. The evidence is sufficient to infer a causal relationship between smoking and colorectal adenomatous polyps and colorectal cancer.

Prostate Cancer

1. The evidence is suggestive of no causal relationship between smoking and the risk of incident prostate cancer.

2. The evidence is suggestive of a higher risk of death from prostate cancer in smokers than in nonsmokers.

3. In men who have prostate cancer, the evidence is suggestive of a higher risk of advanced-stage disease and less-well-differentiated cancer in smokers than in nonsmokers, and—independent of stage and histologic grade—a higher risk of disease progression.

Breast Cancer

1. The evidence is sufficient to identify mechanisms by which cigarette smoking may cause breast cancer.

2. The evidence is suggestive but not sufficient to infer a causal relationship between tobacco smoke and breast cancer.

3. The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and breast cancer.

4. The evidence is suggestive but not sufficient to infer a causal relationship between exposure to secondhand tobacco smoke and breast cancer.

Adverse Health Outcomes in Cancer Patients and Survivors

1. In cancer patients and survivors, the evidence is sufficient to infer a causal relationship between cigarette smoking and adverse health outcomes. Quitting smoking improves the prognosis of cancer patients.

2. In cancer patients and survivors, the evidence is sufficient to infer a causal relationship between cigarette smoking and increased all-cause mortality and cancer-specific mortality.

3. In cancer patients and survivors, the evidence is sufficient to infer a causal relationship between cigarette smoking and increased risk for second primary cancers known to be caused by cigarette smoking, such as lung cancer.

4. In cancer patients and survivors, the evidence is suggestive but not sufficient to infer a causal relationship between cigarette smoking and (1) the risk of recurrence, (2) poorer response to treatment, and (3) increased treatment-related toxicity.

Chapter 7: Respiratory Diseases

Chronic Obstructive Pulmonary Disease

1. The evidence is sufficient to infer that smoking is the dominant cause of chronic obstructive pulmonary disease (COPD) in men and women in the United States. Smoking causes all elements of the COPD phenotype, including emphysema and damage to the airways of the lung.

2. Chronic obstructive pulmonary disease (COPD) mortality has increased dramatically in men and women since the 1964 Surgeon General's report. The number of women dying from COPD now surpasses the number of men.

3. The evidence is suggestive but not sufficient to infer that women are more susceptible to develop severe chronic obstructive pulmonary disease at younger ages.

4. The evidence is sufficient to infer that severe α1-antitrypsin deficiency and cutis laxa are genetic causes of chronic obstructive pulmonary disease.

Asthma

1. The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and the incidence of asthma in adolescents.

2. The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and exacerbation of asthma among children and adolescents.

3. The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and the incidence of asthma in adults.

4. The evidence is sufficient to infer a causal relationship between active smoking and exacerbation of asthma in adults.

Tuberculosis

1. The evidence is sufficient to infer a causal relationship between smoking and an increased risk of *Mycobacterium tuberculosis* disease.

2. The evidence is sufficient to infer a causal relationship between smoking and mortality due to tuberculosis.

3. The evidence is suggestive of a causal relationship between smoking and the risk of recurrent tuberculosis disease.

4. The evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and the risk of tuberculosis infection.

5. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and the risk of tuberculosis infection.

6. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and the risk of tuberculosis disease.

Idiopathic Pulmonary Fibrosis

1. The evidence is suggestive but not sufficient to infer a causal relationship between cigarette smoking and idiopathic pulmonary fibrosis.

Chapter 8: Cardiovascular Disease

1. The evidence is sufficient to infer a causal relationship between exposure to secondhand smoke and increased risk of stroke.

2. The estimated increase in risk for stroke from exposure to secondhand smoke is about 20-30%.

3. The evidence is sufficient to infer a causal relationship between the implementation of a smokefree law or policy and a reduction in coronary events among people younger than 65 years of age.

4. The evidence is suggestive but not sufficient to infer a causal relationship between the implementation of a smokefree law or policy and a reduction in cerebrovascular events.

5. The evidence is suggestive but not sufficient to infer a causal relationship between the implementation of a smokefree law or policy and a reduction in other heart disease outcomes, including angina and out-of-hospital sudden coronary death.

Chapter 9: Reproductive Outcomes

Congenital Malformations

1. The evidence is sufficient to infer a causal relationship between maternal smoking in early pregnancy and orofacial clefts.

2. The evidence is suggestive but not sufficient to infer a causal relationship between maternal smoking in early pregnancy and clubfoot, gastroschisis, and atrial septal heart defects.

Neurobehavioral Disorders of Childhood

1. The evidence is suggestive but not sufficient to infer a causal relationship between maternal prenatal smoking and disruptive behavioral disorders, and attention deficit hyperactivity disorder in particular, among children.

2. The evidence is insufficient to infer the presence or absence of a causal relationship between maternal prenatal smoking and anxiety and depression in children.

3. The evidence is insufficient to infer the presence or absence of a causal relationship between maternal prenatal smoking and Tourette syndrome.

4. The evidence is insufficient to infer the presence or absence of a causal relationship between maternal prenatal smoking and schizophrenia in her offspring.

5. The evidence is insufficient to infer the presence or absence of a causal relationship between maternal prenatal smoking and intellectual disability.

Ectopic Pregnancy

1. The evidence is sufficient to infer a causal relationship between maternal active smoking and ectopic pregnancy.

Spontaneous Abortion

1. The evidence is suggestive but not sufficient to infer a causal relationship between maternal active smoking and spontaneous abortion.

Male Sexual Function

1. The evidence is sufficient to infer a causal relationship between smoking and erectile dysfunction.

Chapter 10: Other Specific Outcomes

Eye Disease: Age-Related Macular Degeneration

1. The evidence is sufficient to infer a causal relationship between cigarette smoking and neovascular and atrophic forms of age-related macular degeneration.

2. The evidence is suggestive but not sufficient to infer that smoking cessation reduces the risk of advanced age-related macular degeneration.

Dental Disease

1. The evidence is suggestive but not sufficient to infer a causal relationship between active cigarette smoking and dental caries.

2. The evidence is suggestive but not sufficient to infer a causal relationship between exposure to tobacco smoke and dental caries in children.

3. The evidence is suggestive but not sufficient to infer a causal relationship between cigarette smoking and failure of dental implants.

Diabetes

1. The evidence is sufficient to infer that cigarette smoking is a cause of diabetes.

2. The risk of developing diabetes is 30–40% higher for active smokers than nonsmokers.

3. There is a positive dose-response relationship between the number of cigarettes smoked and the risk of developing diabetes.

Immune Function and Autoimmune Disease

1. The evidence is sufficient to infer that components of cigarette smoke impact components of the immune system. Some of these effects are immune activating and others are immune-suppressive.

2. The evidence is sufficient to infer that cigarette smoking compromises the immune system and that altered immunity is associated with increased risk for pulmonary infections.

3. The evidence is sufficient to infer that cigarette smoke compromises immune homeostasis and that altered immunity is associated with an increased risk for several disorders with an underlying immune diathesis.

Rheumatoid Arthritis

1. The evidence is sufficient to infer a causal relationship between cigarette smoking and rheumatoid arthritis.

2. The evidence is sufficient to infer that cigarette smoking reduces the effectiveness of the tumor necrosis factor-alpha (TNF-α) inhibitors.

Systemic Lupus Erythematosus

1. The evidence is inadequate to infer the presence or absence of a causal relationship between cigarette smoking and systemic lupus erythematosus (SLE), the severity of SLE, or the response to therapy for SLE.

Inflammatory Bowel Disease

1. The evidence is suggestive but not sufficient to infer a causal relationship between cigarette smoking and Crohn's disease.

2. The evidence is suggestive but not sufficient to infer a causal relationship between cigarette smoking and a protective effect for ulcerative colitis.

Chapter 11: General Morbidity and All-Cause Mortality

1. The evidence is sufficient to infer a causal relationship between smoking and diminished overall health. Manifestations of diminished overall health among smokers include self-reported poor health, increased absenteeism from work, and increased health care utilization and cost.

2. The evidence is sufficient to infer that cigarette smoking increases risk for all-cause mortality in men and women.

3. The evidence is sufficient to infer that the relative risk of dying from cigarette smoking has increased over the last 50 years in men and women in the United States.

Chapter 12: Smoking-Attributable Morbidity, Mortality, and Economic Costs

1. Since the first Surgeon General's report on smoking and health in 1964, there have been more than 20 million premature deaths attributable to smoking and exposure to secondhand smoke. Smoking remains the leading preventable cause of premature death in the United States.

2. Despite declines in the prevalence of current smoking, the annual burden of smoking-attributable mortality in the United States has remained above 400,000 for more than a decade and currently is estimated to be about 480,000, with millions more living with smoking-related diseases.

3. Due to the slow decline in the prevalence of current smoking, the annual burden of smoking-attributable mortality can be expected to remain at high levels for decades into the future, with 5.6 million youth currently 0 to 17 years of age projected to die prematurely from a smoking-related illness.

4. Annual smoking-attributable economic costs in the United States estimated for the years 2009–2012 were between $289–332.5 billion, including $132.5–175.9 billion for direct medical care of adults, $151 billion for lost productivity due to premature death estimated from 2005–2009, and $5.6 billion (in 2006) for lost productivity due to exposure to secondhand smoke.

Chapter 13: Patterns of Tobacco Use Among U.S. Youth, Young Adults, and Adults

1. In the United States, the prevalence of current cigarette smoking among adults has declined from 42% in 1965 to 18% in 2012.

2. The prevalence of current cigarette smoking declined first among men (between 1965 and the 1990s), and then among women (since the 1980s). However, declines in the prevalence of smoking among adults (18 years of age and older) have slowed in recent years.

3. Most first use of cigarettes occurs by 18 years of age (87%), with nearly all first use by 26 years of age (98%).

4. Very large disparities in tobacco use remain across racial/ethnic groups and between groups defined by educational level, socioeconomic status, and region.

5. In the United States, there are now more former smokers than there are current smokers. More than half of all ever smokers have quit smoking.

6. The rate of quitting smoking among recent birth cohorts has been increasing, and interest in quitting is high across all segments of society.

7. Patterns of tobacco use are changing, with more intermittent use of cigarettes and an increase in use of other products.

Chapter 14: Current Status of Tobacco Control

1. The evidence is sufficient to conclude that there are diverse tobacco control measures of proven efficacy at the population and individual levels.

2. The evidence is sufficient to conclude that advertising and promotional activities by the tobacco companies cause the onset and continuation of smoking among adolescents and young adults.

3. Tobacco product regulation has the potential to contribute to public health through reductions in tobacco product addictiveness and harmfulness, and by preventing false or misleading claims by the tobacco industry of reduced risk.

4. The evidence is sufficient to conclude that litigation against tobacco companies has reduced tobacco use in the United States by leading to increased product prices, restrictions on marketing methods, and making available industry documents for scientific analysis and strategic awareness.

5. The evidence is sufficient to conclude that increases in the prices of tobacco products, including those resulting from excise tax increases, prevent initiation of tobacco use, promote cessation, and reduce the prevalence and intensity of tobacco use among youth and adults.

6. The evidence is sufficient to conclude that smokefree indoor air policies are effective in reducing exposure to secondhand smoke and lead to less smoking among covered individuals.

7. The evidence is sufficient to conclude that mass media campaigns, comprehensive community programs, and comprehensive statewide tobacco control programs prevent initiation of tobacco use and reduce the prevalence of tobacco use among youth and adults.

8. The evidence is sufficient to conclude that tobacco cessation treatments are effective across a wide population of smokers, including those with significant mental and physical comorbidity.

Chapter 15: The Changing Landscape of Tobacco Control— Current Status and Future Directions

1. Together, experience since 1964 and results from models exploring future scenarios of tobacco control indicate that the decline in tobacco use over coming decades will not be sufficiently rapid to meet targets. The goal of ending the tragic burden of avoidable disease and premature death will not be met quickly enough without additional action.

2. Evidence-based tobacco control interventions that are effective continue to be underutilized and implemented at far below funding levels recommended by the Centers for Disease Control and Prevention. Implementing tobacco control policies and programs as recommended by *Ending the Tobacco Epidemic: A Tobacco Control Strategic Plan* by the U.S. Department of Health and Human Services and the *Ending the Tobacco Problem: A Blueprint for the Nation* by the Institute of Medicine on a sustained basis at high intensity would accelerate the decline of tobacco use in youth and adults, and also accelerate progress toward the goal of ending the tobacco epidemic.

3. New "end game" strategies have been proposed with the goal of eliminating tobacco smoking. Some of these strategies may prove useful for the United States, particularly reduction of the nicotine content of tobacco products and greater restrictions on sales (including bans on entire categories of tobacco products).

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Chapter 2
Fifty Years of Change 1964–2014

Introduction

Tobacco, a New World plant, was used by the native peoples of the Americas for millennia. Brought to the Old World by Christopher Columbus, tobacco and tobacco products soon spread worldwide. The manufactured cigarette has been the dominant form of tobacco use in the United States for only a century (Figure 2.1), surpassing other forms of use as the modern tobacco industry was shaped by James B. Duke and his American Tobacco Company (Chandler 1977). During that century, referred to as "The Cigarette Century" (Brandt 2007), there was a sharp rise in tobacco consumption to a peak in the 1960s and then a decline that has continued over the last three decades. This chapter addresses why this rise and fall of cigarette smoking occurred, giving emphasis to the half-century since the 1964 report of the Advisory Committee to the Surgeon General, *Smoking and Health*, and to the impact of the reports of the Surgeon General on tobacco use in the United States.

This chapter provides a perspective on the tobacco epidemic, setting a context for this anniversary report by describing some of the most critical "lessons learned" with regard to the factors driving tobacco use and the strategies for ending it. The following chapter describes the Surgeon General's reports, including the approach used to compile and synthesize scientific evidence to reach conclusions that has been the foundation of these reports (see Chapter 3, "Producing the Surgeon General's Report From 1964–2014: Process and Purpose"). Two major sections follow: the first provides a comprehensive updating of the health consequences of active smoking and exposure to secondhand smoke, updating the many previous reviews; and the second details the current status of the epidemic, reviews the policy approaches that have proved effective for tobacco control, and offers a strategy and a vision for bringing this long-running epidemic to an end—the so-called "end game."

In offering a perspective on the long and complex story of the tobacco epidemic, this chapter is necessarily limited in its historical detail and does not follow the format of a detailed review of evidence that is typical of these reports. Lengthy and detailed historical accounts are available elsewhere (Kluger 1996; Brandt 2007; Proctor 2011). Americans' behaviors, perceptions, attitudes, and beliefs toward the cigarette have changed dramatically since 1964 when the first report of the Surgeon General on smoking and health was released. At the time, 40% of Americans were regular smokers, with the majority of men (53%) and about one-third of women being regular smokers (U.S. Department of Health, Education, and Welfare [USDHEW] 1979). The smoking habit crossed socioeco-

nomic, gender, race, and ethnicity boundaries. Cigarette smoking was widely accepted, highly prevalent, and not discouraged in homes, and it took place in public spaces of all kinds, including hospitals, restaurants, airplanes, and medical conferences (Brandt 1990). Today, the prevalence of smoking among U.S. adults is about 20% (see Chapter 13, "Patterns of Tobacco Use Among U.S. Youth, Young Adults, and Adults"), and state and local laws have prohibited smoking in workplaces, restaurants, and bars in many regions of the country (see Chapter 14, "Current Status of Tobacco Control"). The majority of households are smoke-free and smoking is banned on airplanes worldwide (U.S. Department of Health and Human Services [USDHHS] 2006). Moreover, the rise and fall of smoking-caused diseases and premature deaths during the twentieth century generally follow patterns of changing tobacco-use behavior, albeit several decades later.

Although there had been previous statements on the harms of using tobacco, the 1964 report was significant for providing the most thorough and comprehensive review up to that time. However, translating this knowledge into action to benefit public health was not a simple or direct process. At the time of release of the 1964 report, the tobacco industry had a powerful influence and attempted to minimize the impact of the report using a broad set of strategies (Kluger 1996; Brandt 2007; Proctor 2011). That influence has now greatly declined, diminished by many factors, including trends in American culture, politics, economics, health care, and social life. This chapter addresses how the evolving scientific evidence on tobacco has been a key driver of the changes that have led to a dramatic shift in social norms around cigarette smoking.

During this same time span, 1964–2014, there have been striking changes in mortality rates from major diseases and substantial improvements in life expectancy (see Chapter 4, "Advances in Knowledge of the Health Consequences of Smoking: From 1964–2014"). These changes have been driven by many factors, including patterns of tobacco use across the twentieth century to the present. Mortality from cardiovascular diseases (CVD) dropped sharply and progressively, and rates for a number of cancers peaked and began to decline, most notably in men. By contrast, mortality from chronic obstructive pulmonary disease steadily climbed. Changes in the prevalence of tobacco smoking contributed to these shifts, but patterns of other risk factors also changed over the last 50 years, as programs addressed hypertension and other risk factors for CVD, and medications became available that reduced CVD, such as statins (Feinlieb et al. 1979; Stern 1979; Jemal et al. 2005; Ford and Capewell 2011).

Figure 2.1   Adult* per capita cigarette consumption and major smoking and health events, United States, 1900–2012
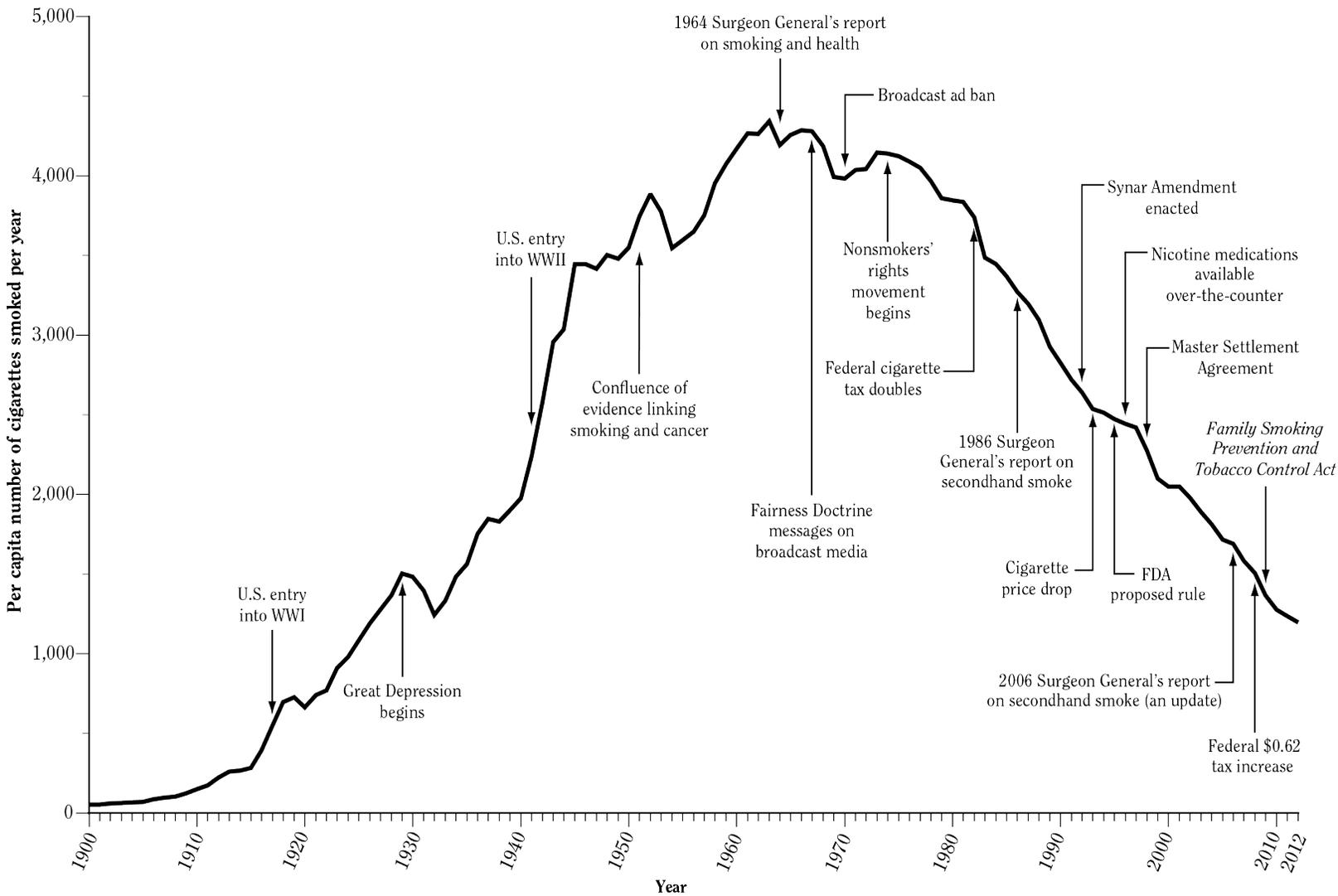
Adults ≥18 years of age as reported annually by the Census Bureau.

Tobacco Control: Before the 1964 Report

To understand the transformative consequences of the 1964 report for tobacco control, this chapter begins with a description of the developments in tobacco control before 1964. Cigarette smoking grew rapidly in early twentieth century America with the arrival of technology for mass production and the development of a consumer culture and effective advertising and promotion on an unprecedented national scale (Figure 2.1) (Kluger 1996). At the same time, there was strong opposition to this trend from some groups, but early condemnations were often based on concerns about adverse moral and social impact rather than specific health effects (Best 1979). Additionally, concerns focused on specific groups seen to be especially vulnerable to the social and psychological effects of chronic cigarette smoking, notably youth and women. And unrestricted tobacco advertising, often with health-related claims, was seen as taking unfair advantage of those who were most vulnerable. In the first two decades of the century, an organized antitobacco effort developed, composed of temperance advocates, religious leaders, and health reformers (Kluger 1996). They were alarmed by the increase in cigarette smoking among youth and believed it to be associated with the abuse of alcohol and narcotic drugs. During this period, a total of 15 states banned the sale, manufacture, possession, or use of cigarettes. Many other states considered such legislation, and municipalities imposed additional restrictions on advertising, smoking near school buildings, and women smoking in public (Tate 1999).

Warnings about tobacco were offered by the Surgeon General before 1964. In 1929, Surgeon General Hugh S. Cumming warned about the hazards of tobacco claiming that excessive smoking caused nervousness, insomnia, and other ill effects in young women (Burnham 1989). Cumming warned that smoking could lower the "physical tone" of the nation. Like many physicians at the time, he believed that women were more susceptible than men to certain injuries, especially of the nervous system. But Cumming, a smoker, distanced himself from the more extreme antitobacco and temperance reformers of the time (Parascandola 1997).

Although physicians generally did not see a significant health threat for most smokers, there was growing concern over cigarette advertising during the 1930s and 1940s that made a wide array of unfounded health claims. In the highly competitive branded cigarette market, prominent advertising campaigns included explicit health claims: "Not a cough in a carload" (Old Gold) (U.S. Federal Trade Commission [FTC] 1964, p. LBA-5); "we removed from the tobacco harmful corrosive acids (pungent irritants) present in cigarettes manufactured in the old fashioned way" (FTC, p. LBA-2); "Smoking Camels stimulates the natural flow of digestive fluids … increases alkalinity" (Camel, p. LBA-1a) (FTC 1964). Kool menthol cigarettes, characterized by the cooling effect of this additive, were offered to nose and throat specialists to hand out to their patients "suffering from colds and kindred disorders" (*Information* 1948, Bates No. 400566440/6490, p. 9). FTC brought legal action against each of the major cigarette companies during the 1940s in an effort to curb health claims in advertising, resulting in a series of cease-and-desist orders. However, the agency's power to control such advertising claims at the time was limited (FTC 1950a,b; *FTC v. P. Lorillard Co.,* 46 FTC 735 (1950); *FTC v. R.J. Reynolds Co.*, 46 FTC 706 (1950); *FTC v. American Tobacco Co.*, 47 FTC 1393 (1951); *FTC v. Philip Morris & Co.*, 49 FTC 703 (1952)).

By the 1930s, however, American scholars and activists had become aware of increasing cancer death rates. Statisticians in the insurance industry, such as Frederick L. Hoffman at Prudential Insurance Company, had amassed statistical data documenting the growing influence of cancer since the turn of the century, and voluntary organizations like the American Cancer Society had been using these data to bring public attention to the cancer problem (Patterson 1987). In the late 1930s, the government published cancer mortality statistics from 1900–1935 based on U.S. Census data and subsequently cause-specific mortality was tracked, providing an ongoing picture of mortality trends (Gover 1939).

Complementing these mortality statistics, some clinicians described a growing clinical experience with lung cancer patients and the surgical treatment of the disease by pneumonectomy, removal of a lung. Thoracic surgeon Alton Ochsner recounted being called as a medical student in 1910 to see an autopsy of a patient with lung cancer because such cases were so rare (Ochsner 1973). Several decades later, he began to see many such patients. Ochsner and DeBakey (1939) reported their experience with pneumonectomy for lung cancer and proposed that smoking contributed to the development of this malignancy: "In our opinion the increase in smoking with the universal custom of inhaling is probably a responsible factor, as the inhaled smoke, constantly repeated over a long period of time, undoubtedly is a source of chronic irritation to the bronchial mucosa" (p. 109). At the same time, smoking was clearly linked to decreased life expectancy by Pearl (1938), based on follow-up of adults in Baltimore.

Yet, there was also substantial skepticism within the medical community about whether the seeming increase in cancer deaths was real or an artifact of better diagnosis. The rise in lung cancer, a rare disease at the beginning of the twentieth century, drew particular scrutiny (Witschi 2001). However, the possibility of diagnostic bias was set aside through appropriate research and the continuing rise of lung cancer deaths made such diagnostic bias improbable (Macklin 1942; USDHEW 1964). A wide range of possible industrial and environmental causes were cited as possibly contributing to the increase, including road tars, vehicle exhaust, and air pollution, along with tobacco smoking (Witschi 2001).

Beginning as early as the 1920s, the rise of lung cancer prompted epidemiologic research on its causes that was carried out in the United States and Europe. These initial studies found an association between lung cancer and tobacco smoking that was repeatedly confirmed in a wave of research that began in the 1940s and continued in the 1950s (Witschi 2001). These studies were of the case-control design, involving comparison of the frequency and intensity of smoking by people with lung cancer to smoking among comparable people without lung cancer—the controls. By the early 1950s, in follow-up of the strong associations found in the case-control studies, cohort or follow-up studies were initiated that compared rates of lung cancer occurrence or death among smokers and nonsmokers. These epidemiologic studies provided the pivotal evidence on smoking and lung cancer for the 1964 report of the Surgeon General. The public responded to the new information on smoking and lung cancer with a slight decrease in consumption (from 1953–1954) that was quickly followed by a sharp rise (Figure 2.1).

The American tobacco industry's strategies for dealing with scientific evidence documenting the harms of its products also originated during the 1950s. By the early 1950s, the epidemiologic evidence on lung cancer and smoking was abundant and coherent, and Wynder and colleagues' (1953) mouse experiments had documented that cigarette smoke condensate caused tumors confirming earlier work by Angel H. Roffo (Proctor 2006). In a now well-documented effort to counter this evidence and to minimize risk to the industry, the executives of the major tobacco companies met in December 1953 and, with the guidance of the advertising firm Hill & Knowlton, devised a unified strategy that included the founding of an industry-funded research organization, initially the Tobacco Industry Research Committee (TIRC) and later the Council for Tobacco Research (DATTA Collection 1953), and the nationwide publication of the "Frank Statement," which publicly stated the industry's commitment to public health (Pollay Advertising Collection, n.d.). Clarence Cook Little, a leading researcher and academician, was hired in 1954 as the first head of TIRC; he assumed a public position of skepticism with regard to the evidence on smoking and health, seeking to create doubt about the harmful effects of smoking (Brandt 2007; Proctor 2011). For decades, the industry followed the strategies set out in the early 1950s: denying the harms of its products, discrediting the scientific evidence that showed these harms, funding research that was intended to divert attention from cigarettes, and marketing new products with implied lower risks than existing products (*United States v. Philip Morris Inc.* 2006; Brandt 2007; Proctor 2011).

Generally, there was little response in the medical community to the first wave of studies on the risks of smoking. In 1953, in the midst of early reports on cigarette smoking and lung cancer, the American Medical Association (AMA) did announce that it would stop accepting cigarette (and alcohol) advertising in its journal beginning January 1, 1954 (*Advertising Age* 1953). However, the move was not an indication that AMA accepted that smoking was hazardous, but was primarily a response to the medical claims increasingly seen in cigarette advertising; pharmaceutical companies had reportedly complained to AMA that while their claims were subject to thorough scrutiny, cigarette manufacturers' claims were not (*Advertising Age* 1953). Cigarette manufacturers were also starting to worry that overt medical claims could backfire, drawing attention to the growing evidence of harms.

In summary, in the first half century of the cigarette epidemic, concerns about cigarette smoking often focused on the habit's impact on the social and moral fabric of society. Additionally, broader fears about the booming consumer culture and the ubiquitous advertising associated with it led to attempts to control or warn the public about misleading advertising claims. As long as consumers were protected from misleading claims, the decision to smoke or not smoke was one that the medical community had little to say about. But the emergence of strong evidence related to cancer and other health risks from cigarette smoking during the 1950s shifted the focus to the scientific evidence on its health effects, setting the stage for evidence-based action.

Scientific Judgment and the 1964 Report

By the late 1950s, the amassing evidence on smoking and lung cancer called for public health action. The Surgeon General was among the first authoritative figures to address the public health implications of the rising evidence on the health risks of smoking. Before the 1964 report was released, there had been several previous statements from the Surgeon General, several consensus statements from groups of public health scientists, and a report from the Royal College of Physicians (1962), all identifying cigarette smoking as a cause of lung cancer (Cutler 1955; Study Group on Smoking and Health 1957). These reports were based largely on epidemiologic studies, both case-control and cohort; on findings from laboratory studies using animals and pathology studies; on chemical identification of known carcinogens in cigarette smoke; and on analyses of large-scale patterns of cigarette consumption and disease rates (Proctor 2011). Although the case-control studies were questioned on methodological grounds, evidence from several cohort studies was reported in the 1950s that confirmed the strong association between smoking and lung cancer. In June 1954, the results from the first cohort assembled by the American Cancer Society, which included 180,000 older men, were announced (Hammond and Horn 1958). The study showed that heavy smokers were dying of lung cancer at a rate 5 to 16 times higher than that of similar people who were not smokers. At the same time, similar findings were reported from studies of British physicians (Doll and Hill 1954) and U.S. veterans (Dorn 1958, 1959). By 1959, Surgeon General Leroy E. Burney declared cigarette smoking "the principal [sic] etiological factor in the increased incidence of lung cancer" (Burney 1959, p. 1835). The same year, a review by leading public health scientists assessed a range of potential criticisms of the research findings and concluded that the evidence was overwhelming: "if the findings had been made on a new agent, to which hundreds of millions of adults were not already addicted, and on one which did not support a large industry, skilled in the arts of mass persuasion, the evidence for the hazardous nature of the agent would generally be regarded as beyond dispute" (Cornfield et al. 1959, p. 198).

Thus, the 1964 report's most noteworthy finding—"Cigarette smoking is causally related to lung cancer in men; the magnitude of the effect of cigarette smoking far outweighs all other factors. The data for women, though less extensive, point in the same direction" (USDHEW 1964, p. 31)—had been anticipated in prior reviews. The report also concluded that "…cigarette smoking contributes substantially to mortality from certain specific diseases and to the overall death rate" (USDHEW 1964, p. 31). However, the 1964 report went beyond these earlier reviews in its transparent methodology and depth of analysis, including a systematic gathering and review of the data and a synthesis of the findings for causality based on prior criteria. The members of the Advisory Committee were carefully selected to identify a panel that would be considered as free of any bias as to the report's findings (Parascandola 1997). Its landmark status reflects this approach, which made it a model, not only for future reports of the Surgeon General, but for reviews in other fields.

The Surgeon General's emphasis on methodology merits highlighting (see Chapter 3). The report devoted two chapters to describing the working methods of the group, and the criteria they employed, in making inferences about cause and effect relationships. The Committee cited five criteria for making a determination of causation from an observed association: consistency, strength, specificity, temporal relationship, and coherence (USDHEW 1964). For lung cancer in particular, the Committee discussed a range of different types of evidence in great detail, responding to alternative explanations for the high risk of lung cancer in smokers, other than smoking, and addressing inconsistencies in the total body of evidence. Although previous reviews had covered some of the same material and employed similar criteria, the Advisory Committee did so in a way that was more explicit and formal than previous inquiries. In the end, it was no single study, but the mass of cumulative evidence from diverse sources that made the case for smoking as a cause of lung cancer irrefutable (Parascandola et al. 2006).

This approach successfully addressed the new problem in public health of interpreting observational findings. The 1950s and 1960s were a critical time for a new application of epidemiology with a focus on chronic rather than infectious diseases, an emphasis on identifying individual risk factors for disease, and the use of advanced quantitative methodology (Morris 1957; Lilienfeld 1978). Chronic diseases such as cancer and heart disease required a new approach to understanding their etiology. Unlike traditional infectious disease research, where a single necessary causal agent or organism could be identified and studied in the laboratory and in the population, cancer was associated with a wide range of exposures and agents and developed over decades. The picture was quite similar for cardiovascular diseases and chronic lung disease. Human experiments could not be carried out to determine if particular agents had causal effects; instead, risk factors were

identified through observational epidemiologic research which is inherently subject to various sources of bias.

As a result, there was substantial debate about what type of evidence was needed to declare cigarette smoking a cause of lung cancer (Brandt 1990; Parascandola 2004). Some advocated for a narrow view of cause and effect, insisting it must be demonstrated that cigarette smoking is uniquely linked to lung cancer, the link must be demonstrated in a randomized trial, or additional evidence demonstrating underlying biological mechanisms was required (Yerushalmy and Palmer 1959; Parascandola 2011). The tobacco industry took advantage of the methodologic divide, insisting that epidemiology and statistics alone could not prove cause and effect and that a detailed understanding of the mechanisms of cancer etiology was required to support such claims (Little 1961). The dismissal of epidemiologic evidence as imperfect was a strategy used repeatedly by the tobacco industry, particularly in attempting to thwart the consequences of the studies linking exposure to secondhand smoke to lung cancer and other diseases (Kluger 1996; Brandt 2007; Proctor 2011). However, as the evidence on smoking and disease accumulated throughout the 1950s, many public health scientists increasingly insisted that such "logically rigorous" proof of causation, requiring demonstration of a necessary and sufficient cause, was not required (Cornfield et al. 1959).

In the 1964 Surgeon General's report, the Advisory Committee endorsed this conceptual approach, explaining that, in the absence of experimentation, the "causal significance of an association is a matter of judgment" (USDHEW 1964, p. 20). Additionally, they employed a more flexible, pragmatic definition of "cause," which focused not on identifying a unique necessary and sufficient cause, as for infectious diseases, but on finding the modifiable multifactorial determinants of health outcomes with the ultimate aim of supporting prevention, an approach which was to be further developed by an emerging discipline of chronic disease epidemiology (MacMahon et al. 1960). The criteria for evidence evaluation offered flexibility for evidence interpretation that avoided the rigid requirements of the Henle-Koch postulates long used for infectious organisms (Evans 1976, 1978, 1993; Susser 1995).

The mechanism by which the report was produced gave it a status and authority beyond the previous reviews. When Surgeon General Luther Terry initiated the effort in 1962 at the request of President John F. Kennedy, he stated that the group would not conduct any new research or make any recommendations, but would provide an "objective assessment of the nature and magnitude of the health hazard" (USDHEW 1964, p. 8). The 10 Committee members were selected from a list of about 150 eminent physicians and biomedical scientists from a variety of different disciplines. Major medical associations, volunteer public health organizations, the Tobacco Institute, the Food and Drug Administration (FDA), FTC, and the President's Office of Science and Technology were all given the opportunity to remove a name from the list for any reason (Terry 1983). Anyone who had taken a prior public position on any question of smoking and health would be eliminated from the list (Terry 1983). The members of the Committee held their meetings at the National Library of Medicine in Bethesda, Maryland, with their deliberations under strict secrecy and documents under lock and key. Even the Surgeon General himself knew nothing of the details of their work until the final report was being printed (Terry 1983). This approach, which did not directly involve Terry, contrasted with Burney's statements during the 1950s, which had been presented as the "opinions" of the Surgeon General and senior U.S. Public Health Service (PHS) leaders (U.S. Congress 1957).

The process used for the report marks the beginning of a new role for scientific experts in the United States. Allan M. Brandt (2007) refers to the era of "procedural science" and Robert N. Proctor calls the report a product of an "administrative rather than a scientific consensus" (Proctor 2011, p. 236). That is, the crucial science relied upon by the Advisory Committee had been already published; the authority of the report also rested on the characteristics of the process used in reaching its conclusions, which assured that conclusions were reached by considering the full range of evidence available and judging the evidence in a transparent and consistent framework. The explicit appeal to the process and criteria for judgment was novel at the time, but has since come to be standard practice for evidence reviews in controversial areas of medicine and public health. The industry's documents provide insights into how the industry viewed the 1964 report from the planning process through the report's development and release (Allen 1962; Cullman 1962; Hockett and Thompson 1962; Bass 1963; Hill & Knowlton 1963; Council for Tobacco Research 1964; Cullman 1964; Haas 1964; Pacey 1964; Wakeham 1964; Weissman 1964). Notably, the industry was treated as a stakeholder and given the opportunity to make recommendations on members of the Advisory Committee and to provide research materials to the Committee (Terry 1983).

Remedial Action and Change Following the 1964 Report

The 1964 Surgeon General's report concluded that "Cigarette smoking is a health hazard of sufficient importance in the United States to warrant appropriate remedial action" (USDHEW 1964, p. 33). However, the report did not specifically state what actions should be taken and lacking any precedent at the time, it was not immediately clear what form this action should take. Surgeon General Luther Terry had initially outlined two distinct phases of inquiry. The first was an expert committee to provide an "objective assessment of the nature and magnitude of the health hazard" (USDHEW 1964, p. 8). The second phase, which would provide recommendations for action and require a different range of expertise, would follow, although this effort never fully materialized.

During the 1950s, federal public health officials saw their role as limited. Alexander Langmuir, who pioneered in disease surveillance at the Communicable Disease Center (now known as the Centers for Disease Control and Prevention [CDC]), viewed the role of public health researchers as generating evidence for others who make policy decisions: "When major health problems arise, someone must make decisions. This is not the primary responsibility of the epidemiologist. Administrative and political as well as technical considerations must also be brought to bear. It is the epidemiologists' function to get the facts to the decision makers" (Langmuir 1963, p. 191). Testifying before Congress in 1957, Surgeon General Leroy Burney insisted it was the role of PHS to present the facts as they became available to state health agencies, and sometimes the national media, but not to undertake an organized national educational campaign. He added, "We should not go all out on a campaign and put stickers on cigarettes and certain other things" (Burney 1957b, p. 24). When Burney released official statements on smoking and health in 1957 and 1959, they appeared in academic medical journals and were sent out to state public health officers and to AMA, but not to the general public. The statements received little public attention. Thus, although Burney (1957a) was unequivocal on the weight of the evidence, this judgment on the association of smoking with lung cancer did not necessarily translate into a call for action, even action to educate the public (*New York Times* 1957; Fritschler 1969). This approach contrasted sharply with Luther Terry's dramatic, nationally televised press conference in 1964. The 1964 report spoke with far more certainty than Burney's earlier publications, which were brief and had a more limited evidence base. Additionally, the 1964 report had been requested by President Kennedy and it was an unprecedented review of a public health

threat. Consequently, the release of the report was carefully managed with the media response in mind. The press conference was held on a Saturday to minimize the effects of the report on the stock market and to ensure coverage in the Sunday newspapers (Parascandola 1997). All of the approximately 200 reporters attending were required to remain for the entire session. Each was given a copy of the final report and allowed to study it for an hour. Reporters were then permitted to question the Surgeon General and the Administration. Finally, the doors were opened and reporters raced out to file their stories (Parascandola 1997). The report received enormous publicity. *Newsweek* lauded it as "monumental" and subsequently the report has been named by the New York Public Library as one of the top 100 books of the twentieth century (Diefendorf 1996). Terry made the Surgeon General into a public figure, no longer an anonymous government official; his use of the media to address national public health issues would be taken up and further developed by later Surgeons General.

Nevertheless, while the report was to lead to action, health officials and political leaders still saw a carefully circumscribed role for federal intervention on smoking and health. Secretary of Health, Education, and Welfare Anthony J. Celebrezze had already stated his views on the government's responsibilities even before the Committee began its work: "I firmly believe that it is not the proper role of the federal government to tell citizens to stop smoking" (Toth 1962, p. 20). The proposals that emerged were primarily aimed at ensuring that consumers had accurate information with which to make decisions about their own behavior. At the time, of course, the addictive potential of nicotine in tobacco smoke was not generally known. Government had a role in protecting consumers from industry abuses, such as fraudulent advertising, but not in intervening to change consumer behavior. For example, Senator Maurine Neuberger urged FTC to require cigarette manufacturers to state tar and nicotine yields on advertisements and cigarette packages to "stimulate the development of less hazardous cigarettes and facilitate intelligent choice between competing brands on the basis of relative safety" (Neuberger 1964, p. 1). But proposals to give FDA regulatory authority over tobacco products were rejected by federal public health officials as impractical and contrary to what the public would accept (U.S. Congress 1964, 1965).

Congress did enact legislation to educate consumers about the hazards of smoking. In 1965, the *Federal Cigarette Labeling and Advertising Act of 1965* mandated

the first Surgeon General's warning to appear on cigarette packages: "Caution: Cigarette Smoking May Be Hazardous to Your Health." It called for an annual report to Congress on the health consequences of smoking and for the Secretary of Health to make recommendations for needed legislation. In October 1965, PHS created the National Clearinghouse on Smoking and Health. This office was to play a key role in the development of the first 10 Surgeon General's reports (1967–1978) as well as development of national informational and educational programs about the risks of smoking. However, at the same time it prohibited FTC from taking any new regulatory action to control cigarette advertising for 4 years. Contemporary observers explained that the tobacco industry had decided it was in their interest to accept the warning label in exchange for halting any regulatory efforts (Drew 1965). However, subsequent analyses have shown how the tobacco industry used its connections within government to assure a weak bill and a weak warning label (Brandt 2007). The wording of the label, "Caution: Cigarette Smoking May Be Hazardous to Your Health," contrasts sharply with the certainty of the 1964 report's conclusion on smoking and lung cancer.

Subsequent government actions were largely focused around promoting public information about the risks of cigarette smoking and how they might be reduced. The Surgeon General convened another group of experts in 1966 to assess the importance of different constituents identified in cigarette smoke for disease risk; the group recommended that actions be encouraged to progressively reduce the tar and nicotine content of cigarette smoke (*Congressional Record* 1966). At the same time, FTC revised its advertising guidelines to permit manufacturers to include in advertisements "a factual statement of the tar and nicotine content (expressed in milligrams) of the mainstream smoke from a cigarette" (Shea 1966, Bates No. 00065004). Eventually, this disclosure became mandatory. In 1968, the National Clearinghouse for Smoking and Health, a government office, began a campaign "If You Must Smoke …" aimed at people who wanted to reduce their risk but did not want to quit smoking. The pamphlet provided five suggestions: (1) choose a cigarette with less tar and nicotine, (2) don't smoke the cigarette all the way down (the last few puffs have more tar and nicotine), (3) take fewer draws, (4) reduce inhaling, and (5) smoke fewer cigarettes (USDHEW 1968). In the absence of any authority to mandate changes in the product, public education became the primary tool to reduce risk.

However, one initiative that had a measurable impact on the prevalence of smoking was initiated by John F. Banzhaf III, a consumer lawyer. In 1967, Banzhaf successfully petitioned the Federal Communications Commission (FCC) to apply the Fairness Doctrine[1] to cigarette advertising to counter the tobacco industry's advertising messages (*Banzhaf v. FCC*, 405 F.2d 1082, 1086 [D.C. Cir. 1968], cert. denied, 396 U.S. 842, 90 S. Ct. 50 [1969]; USDHHS 2000). After a court struggle, the national networks were forced to air antismoking advertising spots in prime time, giving tens of millions of dollars' worth of free airtime to antismoking efforts. In 1968, 1,300 antitobacco messages were aired by the three major networks (Lewit et al. 1982). These public service announcements may have contributed to a reduction of overall consumption; per capita cigarette consumption fell from 4,197 in 1966 to 3,969 in 1970 (Figure 2.1). The effect was short-lived, however, as tobacco companies were mandated to take their ads off the airwaves in 1971 following the *Public Health Cigarette Smoking Act of 1969*, which included a prohibition on broadcast advertising of cigarettes. Consequently, the antismoking advertisements were no longer required under the Fairness Doctrine and cigarette consumption rose after they ended (Warner 1979).

From about the time of the 1964 report, per capita cigarette consumption began to decline in the United States (Figure 2.1), but not uniformly across the population. Physicians and other health professionals had begun to accept the evidence and to stop smoking even before the release of the 1964 report. While 60% of physicians smoked in 1949, this figure declined to 30% by 1964 (Garfinkel and Stellman 1976). Surveys of Massachusetts physicians during the 1950s found that by 1954 a majority of physicians (55% of smokers and 63% of nonsmokers) believed that "heavy smoking of cigarettes may lead to lung cancer" (Snegireff and Lombard 1954, p. 1042). Some had switched to smoking only a pipe or cigars, and many who continued to smoke had reduced the number of cigarettes they smoked. Ninety-three percent of the respondents supported antitobacco education efforts for youth, and those who did not said it was not because they doubted the harms of smoking, but because they doubted the effectiveness of educational efforts to change teenagers' behavior (Snegireff and Lombard 1959).

Surveys of physicians during the 1960s continued to show decreasing prevalence of smoking and acceptance of the hazards of cigarette smoking (Buechner et al. 1986). A 1965 survey of Oregon physicians found that more than one-third (36%) had modified their tobacco consumption in response to the 1964 report. Additionally, although many physicians had quit earlier, those who quit before 1964 were more likely to cite physical symptoms as

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[1]An FCC regulation that required broadcasters to allot time to contrasting points of view on controversial topics.

the reason while, after 1964, former smokers were more likely to cite scientific evidence of harm as their reason for quitting (Meighan and Weitman 1965). The prevalence of smoking was also dropping rapidly among medical trainees and younger physicians. The average prevalence of smoking among medical students at Johns Hopkins Medical School was 65% for the years 1948 through 1951, but by 1965 the prevalence had dropped below 40% (National Cancer Institute [NCI] 1994). Younger physicians were also more likely to report concern over the health effects of smoking on patients, to ask or advise patients about their smoking, and to agree that physicians should set an example by not smoking (Coe and Brehm 1971). By the early 1980s, surveys suggested that only 5–10% of physicians were smoking (Sachs 1983; Buechner et al. 1986). In 2006–2007, the prevalence of current smoking among physicians had reached about 2% (Sarna et al. 2010).

Appreciation of the health risks, and subsequent behavior change, was slow to follow among the general population. Gallup polls have surveyed Americans about their beliefs on the health effects of smoking since the 1950s (Gallup Organization 1964). In 1954, 70% of respondents believed that smoking was harmful to health. However, the question—"Do you think cigarette smoking is harmful, or not?"—was phrased in such a general way as to encompass a wide range of possible effects. Respondents were also specifically asked about lung cancer. Although 83% of respondents answered 'yes' to the question "Have you heard or read anything recently that cigarette smoking may be a cause of cancer of the lung," only 41% answered 'yes' to the next question "What is your opinion -- do you think cigarette smoking is one of the causes of lung cancer." When respondents were asked about specific health effects from smoking, only 7% mentioned cancer of any kind. Instead, most cited a variety of non-life-threatening problems such as coughing, sinus irritation, nervousness, and fatigue (Saad 2002).

Even after the 1964 report, there was not a dramatic change in public beliefs about smoking. In a 1966 Harris poll, only 40% recognized smoking as a major cause of lung cancer, 27% considered it a minor cause, and one-third were uncertain, saying that "science had not yet determined the relation between smoking and lung cancer" (Saad 1998, p. 3). In general, although there was widespread awareness of reports of findings on smoking and health, including lung cancer, people were unsure whether to believe the results were conclusive. This uncertainty may have reflected, at least in part, the doubt-creating strategies of the tobacco industry (Proctor 2011).

Some early studies hinted at the complexity of beliefs about health risks and the factors determining those beliefs. For example, having a higher education level among nonsmokers was associated with acceptance of statements that a link between smoking and health had been proven; but among smokers, the relationship was the opposite, and smokers with a higher education level were more likely to be skeptical of the evidence (Cannell and MacDonald 1956). In another study, a survey found that male smokers were relatively optimistic about their chances of contracting cancer, while female smokers were not (Toch et al. 1961). And a 1963 study found that awareness of science reporting had little impact on smoking behavior, as many smokers were prone to doubt the scientific claims or exhibit fatalistic attitudes about health risks (Robinson 1960). It was not until the 1970s that a majority of Americans said smoking was a cause of lung cancer. But the proportion with this view climbed steadily from about 70% during the 1970s to about 80% in the 1980s. By the 1990s, Gallup polls consistently showed 95% of Americans claiming to believe cigarette smoking to be harmful to health and 90% believing it to be a cause of lung cancer (Saad 1998; Moore 1999).

Cigarette consumption was similarly slow to change. Per capita consumption figures increased every year from 1950 to 1963, with the exception of 1953 and 1954, when there was the first widespread publicity on early laboratory animal and human cohort study findings (Figure 2.1). Consumption decreased in 1964 and during all of the Fairness Doctrine years of 1967–1970. Since 1973, every year for which data are available has seen declines in per capita adult cigarette consumption (U.S. Department of Agriculture 2007; U.S. Census Bureau 2013; U.S. Department of the Treasury 2013).

Although antismoking publicity and news reports did have an impact on beliefs and behavior over time, there were also forces working against this trend. In particular, the tobacco industry's marketing efforts and organized campaign to promote doubt around smoking and health surely slowed the pace of change. A 1966 PHS survey found that more than 60% of smokers agreed that the cancer link was "not yet proved" because it was "only based on statistics" (National Clearinghouse for Smoking and Health 1969, p. 743). Additionally, well over one-half of all smokers believed that most people would not be convinced smoking was harmful until "the tobacco industry itself" admitted the fact (USDHEW 1969). Even as public knowledge about the link between smoking and lung cancer became widespread during the 1970s and 1980s, a 1981 FTC review concluded that many Americans still had very limited knowledge of the nature and extent of the health risks or how those risks applied to their own behavior (FTC 1981).

The nature of cigarette advertising also changed, apparently in response to adverse publicity, to obscure the extent of the danger. During the 1970s, there was an increased emphasis on ads that featured claims about tar

and nicotine content, implying reduced exposures to cancer-causing agents (NCI 2001). Key words such as "light," "smooth," and "mild," were used to convey health-related messages (Kozlowski 2010). In the 1980s, these health messages became more subtle, relying on imagery of active, healthy models (Warner 1985b).

Additionally, the tobacco industry's power as a source of revenue for many print publications influenced the content of smoking and health media coverage (USDHHS 1989; NCI 2008). After the broadcast advertising ban, cigarette advertising and marketing continued to grow, but shifted to print publications, outdoor billboards, sponsorship of sports, placement of brand implants in movies, and a number of other methods. According to *Advertising Age*, the five major tobacco companies spent $62 million on magazine advertising in 1970, the year before the ban, but by 1976 they were spending $152 million (Smith 1978). Some publications became highly dependent on this revenue. An article in the *Columbia Journalism Review* noted a trend: "In magazines that accept cigarette advertising," Smith (1978) wrote, "I was unable to find a single article, in seven years of publication, that would have given readers any clear notion" of the nature and extent of the health effects of cigarette smoking, including news magazines like *Time* and *Newsweek*. As late as 1983, a *Newsweek* 16-page special supplement on "personal health care" prepared with AMA failed to explicitly identify cigarette smoking as a major health hazard. The same issue carried 12 pages of cigarette advertisements worth about $1 million in revenue for the magazine (Warner 1985a). An analysis of magazine coverage over a 22-year period found that a sample of major magazines reduced their coverage of smoking and health issues by 65% in the years after the broadcast advertising ban went into effect (Warner and Goldenhar 1989), and another study found that magazines which accepted an average amount of cigarette advertising were 38% less likely to carry stories on smoking and health than magazines that did not accept cigarette advertising (Warner et al. 1992).

Although many individual physicians rapidly accepted the smoking and health findings, AMA, the leading professional medical organization, took more than two decades to take a clear stand on the issue. In 1964, after the release of the report of the Surgeon General, AMA published a 7-page brochure for the general public titled "Smoking: Facts You Should Know," which described a range of "suspected health hazards" but portrayed experts as divided on the issue (AMA 1964). At the time, AMA officials also opposed federal efforts to mandate warning labels, advertising restrictions, or other public education efforts around smoking (Haseltine 1964). Historians have noted that AMA's position on smoking during the 1960s and 1970s was influenced by its need for support from congressional allies, particularly in southern tobacco-growing states, as well as its opposing Medicare and proposed national health insurance legislation during those years (Kluger 1996; Rothstein 2003; Proctor 2011).

Passive Smoking and Environmental Change

Surgeon General Jesse L. Steinfeld, appointed by President Richard M. Nixon in December 1969, helped to bring public attention to the effects of smoking on nonsmokers. Although he had more limited authority compared with his predecessors due to a reorganization within USDHEW, he made use of the public platform of the Office of the Surgeon General to advance public health. He reinvigorated the regular reports of the Surgeon General on smoking and health, involving dozens of outside experts as authors and peer reviewers to produce a 458-page report in 1971 and the first report to address passive smoking in 1972 (see Chapter 3).

In a 1971 address to the Interagency Council on Smoking and Health, Steinfeld asserted that "Nonsmokers have as much right to clean air and wholesome air as smokers have to their so-called right to smoke, which I would redefine as a 'right to pollute' " (Steinfeld 1971, Bates No. 91018247/8260, p. 14). He then went on to propose "It is high time to ban smoking from all confined public spaces such as restaurants, theaters, airplanes, trains, and buses. It is time that we interpret the Bill of Rights for the Non-smokers as well as the Smoker" (Steinfeld 1971, Bates No. 91018247/8260, p. 14). The subsequent 1972 report was the first in the series to identify the exposure of nonsmokers to cigarette smoke as a health hazard (USDHEW 1972). Dr. Steinfeld bluntly affirmed in his remarks when releasing the report "There is no disagreement – cigarette smoking is deadly" (Steinfeld 1972, Bates No. TITX0004900/4909, p. 2). In a chapter titled "Public Exposure to Air Pollution from Tobacco Smoke," the report summarized information on the contamination of indoor environments by tobacco smoke. The review showed that levels of carbon monoxide in a smoke-filled room could reach concentrations equal to and even above

standards for ambient air. The report also concluded the tobacco smoke was a source of discomfort for many people, but characterized the health risks of tobacco smoke in the air as unknown. Steinfeld continued to be outspoken and an advocate for smoking bans and, unlike his predecessors, he refused to meet with tobacco industry representatives (Kluger 1996).

A grassroots movement emerged in the early 1970s to promote the interests of nonsmokers. Influential early organizations included Group Against Smoking Pollution, with chapters in several states and Californians for Non-Smokers Rights (now known as Americans for Nonsmokers Rights) based in Berkeley, California. They drew explicitly on the rhetoric and discourse of the civil rights and environmental movements, referring to "the innocent victims of tobacco smoke" and a need to give the "right to breathe clean air" precedence over "the right of the smoker to enjoy a harmful habit" (Nathanson 1999). At the time, there was little data on the harms of exposure to secondhand smoke. However, an increasing number of nonsmokers viewed it as an annoyance in shared spaces, such as restaurants and airplane cabins. And the existence of a potential risk, however uncertain or small, was viewed in a fundamentally different way when it affected involuntarily exposed bystanders, some of whom might be susceptible to the effects (Bayer and Colgrove 2002).

A wave of new rules and legislation limiting smoking followed (USDHHS 2006). Several were at the federal level. In 1973, the Civil Aeronautics Board, which had jurisdiction, ordered domestic airlines to provide separate seating for smokers and nonsmokers. In 1974, the Interstate Commerce Commission ruled that smoking be restricted to the rear 20% of seats in interstate buses. Pioneering actions on indoor spaces were also taken at the local and state levels in the 1970s (USDHHS 2006). In 1973, Arizona became the first state to restrict smoking in some public spaces. In 1974, Connecticut enacted the first statute to restrict smoking in restaurants. Minnesota followed in 1975, requiring no-smoking zones in buildings open to the public. In 1977, Berkeley, California, became the first city to pass an ordinance limiting smoking in restaurants. At the same time, antismoking efforts in the United States began to develop into a more diverse movement, involving a broad constituency of volunteer health organizations, professional organizations, and newly created advocacy groups, such as Doctors Ought to Care created in 1977 (USDHHS 2006).

When lawyer Joseph A. Califano, Jr., became Secretary of the Department of Health, Education, and Welfare under the incoming Carter Administration, he made a strong antismoking campaign one of his first priorities. On January 11, 1978, Califano outlined his battle plan in a public speech in which he called cigarette smoking "Public Health Enemy Number One" and "slow motion suicide" and declared: "The first and most important element of this new program on smoking and health will be a major public information and education effort against smoking" (Califano 1978, p. 10). Califano's actions did not develop in a vacuum, however. They reflected a growing national agenda of public health advocacy against smoking (National Commission on Smoking and Public Policy 1978).

The 1979 Surgeon General's report, *Smoking and Health*, released under Califano, marked the 15-year anniversary of the original 1964 report. The report included more than 1,100 pages and presented an enormous amount of data from now decades-long epidemiologic cohort studies, studies of mechanisms of disease, studies of behavioral and psychosocial influences on tobacco use, and the effectiveness of education programs and interventions. It included a chapter titled "Involuntary Smoking" that summarized the data on contamination of indoor environments by tobacco smoke. The report also reviewed the initial evidence on the health consequences of involuntary smoking, but called for more research without reaching any conclusions as to risks (USDHEW 1979).

In the Secretary's Foreword to the volume, Califano wrote: "But why, the reader may nevertheless ask, should government involve itself in an effort to broadcast these facts and to discourage cigarette smoking? … Why, indeed? For one reason, because the consequences are not simply personal and private. Those consequences, economic and medical, affect not only the smoker, but every taxpayer" (USDHEW 1979, p. ii). That is, smoking went beyond being a private medical concern to being a major public health problem that affected smokers and nonsmokers. In particular, Califano cited two health policy challenges then facing the nation—the spiraling costs of health care, with a substantial portion borne by the federal government, and the fact that the health care system "overemphasizes expensive medical technology and institutional care, while it largely neglects preventive medicine and health promotion" (USDHEW 1979, p. ii). Smoking is, he noted, "the largest cause of preventable death in America" (USDHEW 1979, p. ii). At the same time, Califano acknowledged limits to government's role in regulating cigarette smoking in a free society and suggested that intervention would have to focus primarily on research, education, and persuasion. The report also brought a renewed focus to the need for understanding smoking behavior and how to help people who want to quit. Thirty million Americans, the report stated, had become former smokers since 1964, and this figure gave encouragement that persuasion and education could have population-level impacts (USDHEW 1979). The report also highlighted the effects of smoking for specific vulnerable or high-risk populations,

including women, youth, minorities, the developing fetus, and certain occupational groups. In this way, too, government intervention was seen as justified by the need to protect those who are most vulnerable or at increased risk. In his preface, Surgeon General Julius B. Richmond similarly highlighted the difficulty of seeing smoking as simply a personal choice, given the hundreds of millions of dollars spent each year in marketing and promotion of cigarettes and the possibility that "nicotine is a powerful addictive drug" (USDHEW 1979, p. xv).

At this time, the scientific evidence on the health effects of exposure to secondhand smoke was limited. Studies starting in the late 1960s had shown adverse effects of maternal smoking on the developing fetus and on children exposed to secondhand smoke in smoking households (Comstock and Lundin 1967; Colley et al. 1974). However, it was not until the following decade that a critical mass of scientific evidence emerged linking exposure to secondhand smoke with cancer and other chronic health effects among nonsmoking adults. In 1980 and 1981, scientific journals published epidemiologic research from Greece, Japan, and the United States finding that those who breathed "environmental tobacco smoke" suffered from decreased lung function (White and Froeb 1980) and increased risk of lung cancer (Hirayama 1981; Trichopoulos et al. 1981). Because the lung cancer investigations involved people who had experienced heavy exposure to smoke in the home over long periods of time, there were questions about whether, and to what extent, the data could be extrapolated to other enclosed public spaces. But over the next several years, additional studies gave weight to the argument that adult nonsmokers suffered harm by breathing the cigarette smoke of others and that smoking by parents adversely affected the respiratory health of their children. In 1986, two major scientific reviews were released in the United States—the U.S. Surgeon General's report, *The Health Consequences of Involuntary Smoking* (USDHHS 1986), and the National Academy of Science's report, *Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects* (National Research Council 1986)—both concluding that secondhand smoke could cause lung cancer in healthy adult nonsmokers and respiratory symptoms in children. In that same year, the World Health Organization's (WHO's) International Agency for Research on Cancer (IARC) concluded that "… passive smoking gives rise to some risk of cancer" (IARC 1986, p. 314).

The 1986 report of the Surgeon General on involuntary smoking represents another landmark in the series of reports. Following the approach of the 1964 report, it assembled the full body of evidence on exposure to secondhand smoke and health, reviewing the composition of tobacco smoke, dosimetry and toxicology, exposures, and the findings of epidemiologic studies (USDHHS 1986). It interpreted that evidence within the context of what was already known about active smoking, treating exposure to secondhand smoke as resulting in a lower dose of tobacco smoke, compared with active smoking, but to the same toxic mixture from a health perspective. The report had three overall conclusions, including its powerful first conclusion: "Involuntary smoking is a cause of disease, including lung cancer, in healthy nonsmokers" (USDHHS 1986, p. 7). Its second conclusion described the adverse effects of smoking by parents on the respiratory health of their children. Its third—"Simple separation of smokers and nonsmokers within the same air space may reduce, but does not eliminate, exposure of nonsmokers to environmental tobacco smoke" (USDHHS 1986, p. 7)—carried implications for controlling exposure to an agent identified as carcinogenic in the first conclusion.

Surgeon General C. Everett Koop, appointed by President Ronald W. Reagan in 1981, used the visibility of the position to a greater degree than any of his predecessors and used the findings of the report to call for smoke-free public places. He was an outspoken public foe of tobacco, advocating a smoke-free environment by the year 2000. Although he was aware of the controversy surrounding the scientific evidence on secondhand smoke, further fueled by the tobacco industry's efforts to focus attention on the limitations of the data, he insisted that the data were sufficient for public health intervention. Koop declared in his Preface to the 1986 report "Critics often express that more research is required, that certain studies are flawed, or that we should delay action until more conclusive proof is produced" (USDHHS 1986, p. xi). He went on to argue, based on the report's third overall conclusion, that many of the measures that had been put into place in many states and communities were inadequate, such as creating separate nonsmoking sections with a common ventilation system did not eliminate exposure for nonsmokers. Koop also asserted that "[t]he right of smokers to smoke ends where their behavior affects the health and well-being of others (USDHHS 1986, p. xii).

This report, along with the complementary findings of the reports from the National Academy of Science and IARC, provided the scientific foundation for policies and actions to protect nonsmokers from inhaling tobacco smoke (NRC 1986; USDHHS 1986). By the mid-1980s, almost all states had enacted some restrictions on where people could smoke in public; some 80% of the U.S. population lived in areas covered by such laws (USDHHS 2006). Between 1985–1988, the number of communities around the country that had enacted laws restricting public smoking almost quadrupled, to over 300 (USDHHS 1989).

In 1987, USDHHS established a smoke-free environment in all of its buildings nationwide, extending protection to more than 100,000 federal employees (USDHHS 2006). In 1988, Congress imposed a smoking ban on all U.S. domestic flights of 2 hours or less. Two years later, the ban was extended to flights of 6 hours or less, in effect banning smoking on all domestic flights.

Once these efforts gained momentum, new legislation spread rapidly. The recognition of exposure to secondhand smoke as a health risk to nonsmokers meant that the issue was no longer merely one of individual choice. People responded differently to risks that were imposed on them involuntarily. The existence of victims of cigarette smoking fundamentally altered the discussion about the right to smoke, and state and legal intervention was seen as entirely appropriate. There was also substantial public support for enacting restrictions on smoking in public spaces. As early as 1970 (before any Surgeon General had spoken out about harm to nonsmokers), 58% of men who had never smoked and 72% of women who had never smoked responded 'strongly agree' or 'agree' that smoking should be allowed in fewer public spaces than it was at the time (USDHEW 1973a, p. 11). More than three-quarters of those who had never smoked felt that it was "annoying to be near" someone who was smoking (USDHEW 1973a, p. 13). A 1983 Gallup poll found that 82% of nonsmokers believed that smokers should not smoke in their presence and that smoking posed a health hazard for them; 64% of smokers concurred (American Lung Association 1983). Additionally, the phenomenon may have been self-reinforcing, acting as a sort of contagion effect where actions on one locale influenced other locales (Asbridge 2004).The attention to secondhand smoke was also aided by the growth in public concern over environmental pollutants during the 1970s. In 1970, under the Nixon Administration, both the U.S. Environmental Protection Agency (EPA) and the Occupational Safety and Health Administration were created, and the *Clean Air Act Extension of 1970* established comprehensive regulatory control on outdoor air pollution. The following years saw a wide range of new environmental and safety laws aimed at protecting the public from involuntary risks, including, for example, the *Consumer Products Safety Act* (1972), the *Safe Drinking Water Act* (1974),

Amendments to the *Federal Food, Drug, and Cosmetic Act of 1938*, and the *Toxic Substances Control Act* (1976), creating new agencies and greatly expanding the regulatory authority of some existing agencies. In 1992, EPA carried out a risk assessment and classified environmental tobacco smoke as a human carcinogen, Group A under its carcinogen assessment guidelines (USEPA 1992).

The emerging evidence on exposure to secondhand smoke and disease, particularly lung cancer, sparked a vigorous response from the tobacco industry that is now well documented (Brandt 2007; Proctor 2011). The tobacco industry recognized the policy implications of evidence showing that exposure to secondhand smoke caused adverse effects among nonsmokers and initiated strategies to undermine the research findings, seeking to create doubt about the credibility of evidence that would drive policy-making (*United States v. Philip Morris Inc*. 2006; Brandt 2007; Proctor 2011). The first major study to link exposure to secondhand smoke to lung cancer, the cohort study carried out in Japan by Hirayama (1981), was the target of an orchestrated campaign to undermine its findings. The tactics included arranging critical letters to the editor of the *British Medical Journal*, which published the paper, commissioned research with the intent of obtaining findings that would point to bias in the study, and even newspaper advertisements discrediting the findings. Such strategies were directed at the wider body of evidence on secondhand smoke and health; the industry and its consultants raised methodologic problems, such as uncontrolled confounding and exposure measurement error, in order to sustain doubt about the findings (Kluger 1996; Proctor 2011).

These same tactics and others were used to try and diminish the impact of the 1986 Surgeon General's report. An attempt was made to engage some of the report's authors in a symposium that had undisclosed tobacco industry sponsorship. The report was characterized as political rather than scientific, and Surgeon General Koop's motives were questioned. The attack on the scientific foundation of the report intensified as well (Proctor 2011). Some of these same strategies were used subsequently in an attempt to derail EPA's risk assessment of environmental tobacco smoke.

Nicotine and Addiction

An estimated 30 million people quit smoking in the decade following the 1964 report. Organized programs to help people quit smoking, such as the Five-Day Plan, had gained popularity, and by 1970 there was a US$50 million a year industry of for-profit smoking cessation programs, including Smoke watchers, Quit Now, SmokeEnders, and Schick Centers for the Control of Smoking, but there was little rigorous testing of the effectiveness of these programs (Goodman 2005). Additionally, throughout the 1960s and 1970s, the general understanding of smoking behavior and nicotine addiction was very limited. At the time, health scientists viewed smoking as primarily psychological and social, rather than pharmacological or biological. The 1964 report concluded that tobacco dependence should be characterized as a form of habituation rather than addiction (USDHEW 1964), drawing on a distinction established by WHO in 1957. That definition emphasized the physical effects of the drug, the compulsion to obtain it at any cost, and the habit's detrimental effects on the individual and society (WHO 1957). The WHO Expert Committee on Addiction-Producing Drugs observed that for cigarette smoking, evidence was lacking at the time for a typical abstinence syndrome. "In contrast to drugs of addiction, withdrawal from tobacco never constitutes a threat to life," they wrote. "These facts indicate clearly the absence of physical dependence" (USDHEW 1964, p. 352). At the same time, because regular smoking was so widespread and socially accepted during the 1960s, scientists were reluctant to portray smokers as addicts or as presenting a threat to society. Maurice H. Seevers, the only pharmacologist on the Surgeon General's Advisory Committee, had served on WHO's expert committee that produced the 1957 definition of addiction and was a longtime proponent of the view that an observable physical abstinence syndrome was a crucial defining feature of addiction (Rasmussen and Seevers 2009). It would be another decade before federal research funders and public health scientists created an organized research program around smoking dependence and nicotine addiction. In the mid-1970s, scientists were beginning to compare tobacco smoking with other drug addictions. For example, Jerome H. Jaffe, who had promoted methadone treatment for heroin addicts as President Richard M. Nixon's drug czar from 1971–1973, began to argue in favor of treating cigarette smoking as an addiction in the mid-1970s, maintaining that it did meet the appropriate criteria, including the presence of a withdrawal syndrome. "The major difference between tobacco dependence and other drug addic-

tions," he stated, "is tobacco's social acceptability" (Jaffe 1977, p. 627).

By the late 1970s, as smoking behavior was increasingly recognized as resembling that of other drug addictions, an organized research effort began (Jarvik et al. 1977). A substantial portion of the 1979 Surgeon General's report was devoted to behavioral aspects of smoking (USDHEW 1979); indeed, of the 11 Surgeon General's smoking and health reports published between 1964–1980, it was the first to include any mention of smoking behavior or dependence. The authors of the report sought to avoid using the term addiction, not because they believed it to be scientifically inaccurate, but because of its loaded meaning related to illicit drug use (Henningfield and Zeller 2006). It was not until the 1988 report that the Surgeon General declared that cigarettes are addicting, similar to heroin and cocaine, and that nicotine is the primary agent of addiction (USDHHS 1988).

The focus on the behavioral and psychological aspects of cigarette smoking and addiction marked a substantial shift from the earlier science of smoking and health. Researchers studying the health effects of smoking during the 1960s and 1970s were primarily epidemiologists, statisticians, and pathologists without expertise in studying addictive behavior. These researchers were focused on the consequences of smoking and not on why people smoked. During the 1970s, scientists who had studied other drug addictions turned their attention to cigarette smoking, developing methods to measure nicotine intake and smoking behavior. A substantial body of evidence resulted.

The 1988 report of the Surgeon General, also released by Surgeon General Koop, reviewed this new evidence on smoking and addiction, concluding that: "Cigarettes and other forms of tobacco are addicting" (USDHHS 1988, p. 9) and "Nicotine is the drug in tobacco that causes addiction" (p. 9). The third overall conclusion compared nicotine addiction to other addicting drugs, including heroin and cocaine.

The report changed the view that smoking was just a habit. Cigarettes were now cast as addicting and as equally addictive as many illegal drugs. The findings also had implications for treatment, pointing to the possibility of using nicotine replacement therapy to increase successful quitting of nicotine (USDHHS 1988). For smoking initiation by youth, the finding that nicotine is addicting raised concern that adolescents and young adults might become addicted through experimentation; by 1988, the pattern

of initiation had moved to the teen years for both males and females (USDHHS 1988). The 1994 Surgeon General's report on *Preventing Tobacco Use Among Young People* emphasized that tobacco use and addiction almost always begins before 18 years of age and that most adolescent smokers face the same challenges as adults in quitting smoking (USDHHS 1994).

Like the 1986 report, the 1988 report had profound implications for the tobacco industry, and the report also received great attention from the industry and its consultants. The tobacco industry had information about the report when it was in development and was quick to criticize its findings after release. The finding that nicotine was addicting countered the argument that people became smokers by their own free choice. Efforts to discredit the report continued long after its publication, even though the industry's own documents show that it had long known that nicotine was addicting (Proctor 2011).

Denormalization and the Tobacco Industry

Beginning in the mid-1970s, per capita cigarette consumption began to decline more steeply than during the decade following the 1964 report (Figure 2.1). The scientific findings on tobacco smoke, summarized and transmitted to the health community and the population at large through the Surgeon Generals' reports and other channels, provided a basis for motivating effective action to control tobacco use. Underlying the decline was increasing public understanding of the dangers of cigarette smoking and increasing unacceptability of being a smoker; that is, the social norm around smoking changed from being completely acceptable and woven into day-to-day activities and interactions among people to becoming an increasingly unacceptable behavior. Many factors contributed to this change, including the evidence on the dangers of exposure to secondhand smoke and the ever-increasing reluctance of nonsmokers to inhale tobacco smoke in their workplaces, public places, and eventually their homes (USDHHS 1986).

Additionally, the tobacco control "toolbox" expanded with an increasing number of strategies: smoking bans, which both protected nonsmokers and encouraged cessation; educating youth and limiting their access to tobacco products with enforced laws; raising taxes to force the price of cigarettes upward; encouraging smoking cessation and using treatments that were shown to be effective; and using the media to counter the marketing of the tobacco industry (Kluger 1996; Proctor 2011). Advocacy at the local grassroots level played a critical role as nonsmokers demanded smoke-free environments. The need for using a battery of tobacco control measures was recognized and trials were carried out at the community level to assess the efficacy of combined approaches and their effectiveness in practice.

For example, during the 1990s, NCI conducted a large nationwide intervention study – American Stop Smoking Intervention Study, known as ASSIST. With a budget of approximately $117 million over 7 years, ASSIST provided funding to 17 states for the development of coalitions to pursue a range of interventions and policies at the state and local levels, including (1) promoting smoke-free environments; (2) countering tobacco advertising and promotion; (3) limiting youth access to tobacco products; and (4) raising excise taxes to increase the price of tobacco products (NCI 2005). The project was unique at the time for its scale and focus on studying the effectiveness of broad strategies for policy change. The intervention led to a greater reduction in the prevalence of smoking in states participating in the ASSIST program than in non-ASSIST states, although the effect was modest, likely because of the general trend of declining per capita cigarette consumption over the years of the study (Figure 2.1) (NCI 2005).

State tobacco control programs also took a more aggressive approach during the 1990s, moving beyond a focus on the harms of exposure to secondhand smoke to directly countering cigarette advertising efforts. As cigarette advertising linked smoking to glamour, vitality, and social success, some state programs, such as those in California, Florida, and Massachusetts, turned to explicit denormalization strategies (USDHHS 2000). They aimed "to push tobacco use out of the charmed circle of normal, desirable practice to being an abnormal practice" (California Department of Health Services 1998, p. 3). In the late 1990s, the states received substantial funding from the 1998 Master Settlement Agreement (MSA) between the tobacco companies and the attorneys general of 46 states (USDHHS 2000, 2012). Initially, some of the funds

from the MSA were directed to tobacco control, but the funding declined as states used the revenues for other purposes and only a few states ever reached the CDC's recommended funding levels (Sloan et al. 2005; CDC 2012).

Additionally, after decades of failed personal injury lawsuits against the tobacco industry for smoking-related harms, the climate for tobacco industry litigation transformed during the 1990s. There was one major development with *Cipollone v. Liggett Group, Inc.*, a personal injury case filed in 1983 on behalf of a New Jersey smoker and lung cancer victim (*Cippollone v. Liggett Group* 1988). The plaintiffs gained access to some internal tobacco company documents supporting claims that the industry had conspired to withhold information about harm from the public. But, it was during the 1990s that far more complete access was gained to the industry's internal documents. Two major events made this possible. First, an employee of a law firm that represented tobacco companies released documents to the public that exposed the tobacco companies' misconduct. Second, class-action litigation and litigation on behalf of state governments allowed plaintiffs to combine their resources and expertise on a scale not before realized (Miura et al. 2006). The litigation by the State of Minnesota and Blue Cross and Blue Shield of Minnesota resulted in the release of the industry's documents and their maintenance in two repositories, one in Minnesota for the U.S. industry and the other in Guildford, England, for British American Tobacco's documents. Under the MSA, the industry is required to continue to place its documents into a depository until 2021. The Legacy Tobacco Documents Library at the University of California at San Francisco (2013) was created to house these documents.

The MSA was the result of suits by state governments against tobacco companies to recover Medicaid expenses they had paid to care for sick smokers (USDHHS 2000). From 1993–1998, almost every state filed an action against the tobacco companies. The process ended with individual settlements with the states of Florida, Minnesota, Mississippi, and Texas, and the MSA with the remaining 46 states and the District of Columbia. The MSA required tobacco companies to pay $206 billion over the initial 25 years of the agreement. The MSA did not just provide monetary relief to the states, but also placed restrictions on the tobacco companies that included ending cigarette billboard advertising, banning the use of merchandise with cigarette brand names, and limiting sponsorships. Additionally, as a result of the Minnesota Settlement and the MSA, tens of millions of pages of internal memoranda, reports, and other tobacco company documents initially acquired through litigation were made available to the public (USDHHS 2000).

The tobacco industry was further discredited by congressional hearings and the litigation brought by the U.S. Department of Justice (DOJ) against the industry, *United States v. Philip Morris*, under the *Racketeer Influenced and Corrupt Organizations Act* (RICO 1970). FDA launched a large-scale investigation into the manipulation of nicotine levels in cigarettes and marketing to youth and, for the first time, asserted jurisdiction over cigarettes as drug delivery devices (see Chapter 14). At a 1994 hearing, seven tobacco company CEOs insisted that they believed nicotine was not addictive and not a cause of disease. Photographs of the group holding up their right hands and being sworn in at the hearing, while denying what most members of the public knew to be true about cigarettes, turned them into objects of ridicule and further diminished the public's view of the tobacco industry (Brandt 2007). In the DOJ litigation, the industry was found guilty of violating civil racketeering laws and lying to the public about the dangers of tobacco and its marketing to children. The opinion by Judge Gladys Kessler focused on the representation of cigarettes with reduced machine yields of tar and nicotine as conveying lower risks and the industry's denial of the health effects of exposure to secondhand smoke (*United States v. Philip Morris et al.* 2006).

Momentum from the states' lawsuits also turned the political tide against the tobacco industry in the mid-1990s, and their influence in Congress weakened (Sack 1997). Additionally, the characteristics of legislative debates on tobacco control measures at the state level changed from its prior focus (on the sufficiency of scientific evidence of health effects during the 1970s and early 1980s) to the impact of tobacco industry activities and marketing on children (Jacobsen and Wasserman 1997). Evidence compiled by FTC and researchers demonstrated that the RJ Reynolds' Joe Camel marketing campaign had a measurable impact on smokers below the legal age and was accompanied by an increase in smoking initiation among youth (DiFranza et al. 1991; Pierce et al. 1998). During this period, tobacco companies lost credibility in the eyes of the public. A Harris poll taken in March 1997 found that 92% of the respondents believed "tobacco companies know it causes cancer even if they do not admit it" and 80% believed that "some tobacco companies market their products deliberately to young people" (Sack 1997).

Attitudes around the engagement of scientists and physicians with the tobacco industry were also changing during the 1990s. The tobacco industry had long funded researchers through the Council for Tobacco Research and later through the Center for Indoor Air Research (Proctor 2011). Such funding became increasingly unacceptable, and universities began to implement policies that prohibited receipt of funding from the tobacco industry. It

had also recruited researchers as consultants, who were key in its doubt-creating initiatives. Engagement with the industry became increasingly unacceptable for researchers whose reputations were tarnished by their industry activities. At the same time, concerns about potential conflicts of interest among scientists increased, and disclosure of consulting activities to universities became the norm, making it more difficult for researchers to maintain secret ties to the tobacco industry. By contrast, when the 1964 report was released, there was little concern that scientists' results would be influenced by their funding source. During the 1990s, a number of tobacco control researchers and organizations began to speak out against tobacco industry funding of research at academic institutions. Some academic medical journals instituted policies refusing to accept papers for review if the research had been funded by the tobacco industry. In 1994, a number of academic medical centers, including Brigham and Women's Hospital, Massachusetts General Hospital, MD Anderson Cancer Center, Roswell Park Cancer Institute, and others, adopted policies barring their faculty and staff from accepting tobacco industry support. The bio-

medical research community was divided over the issue at the time, as some academic medical leaders objected that restrictions on funding from any particular industry would amount to a restriction on academic freedom. However, tobacco control advocates countered that the tobacco industry's well-documented record of manipulating scientific information and the extent of the harms from cigarette smoking distinguished them from other industries (Proctor 2011).

Under Commissioner David A. Kessler, who held the office from 1990–1997, FDA had attempted to regulate tobacco products (USDHHS 2000). This effort was ended by the Supreme Court, which found that Congress had not intended that FDA should regulate tobacco when it passed the *Food, Drug, and Cosmetic Act* (Bayer et al. 2013; Orentlicher 2013). With the passage of the *Family Smoking Prevention and Tobacco Control Act* (*Tobacco Control Act*) in 2009, FDA received authority to regulate tobacco products. FDA's Center for Tobacco Products is now proceeding with implementation of the provisions of the Act (see Chapter 14).

Summary

Over the "cigarette century," cigarette smoking prevalence has risen and fallen and moved from being widely accepted to socially unacceptable. In 1964, almost one-half of U.S. adults were cigarette smokers and smoking was ubiquitous in many public places, including restaurants, theaters, and airplane cabins. Today, the overall prevalence of U.S. adult smoking is around 20%, less than one-half of what it was in 1964 (see Chapter 13); as of April 2013, 81% of the U.S. population lives in municipalities covered by a smoke-free workplace law at the state or local level that includes at least nonhospitality workplaces (American Nonsmokers' Rights Foundation 2013). Twenty-four states and the District of Columbia have 100% smoke-free workplace laws that also cover bars and restaurants. In July 2011, a Gallup poll reported that for the first time, a majority of Americans (59%) supported a ban on smoking in all public places (Newport 2011). Opinions of the tobacco industry have fallen so low that it is now consistently ranked among the most distrusted of industries (Harris Poll 2012). The industry has been found guilty in the courts as well. Most notably, in 2006, U.S. District Judge Kessler ruled in the decade-long DOJ's lawsuit against the tobacco industry, finding "the industry had marketed and sold their lethal products with zeal,

with deception, with a single-minded focus on their financial success, and without regard for the human tragedy or social costs that success exacted" (*United States v. Phillip Morris* 2006, p. 28). The tobacco industry is the only legal industry to have been pursued and convicted under federal racketeering statutes.

The epidemic of smoking-caused disease in the twentieth century ranks among the greatest public health catastrophes of the century, while the decline of smoking consequent to tobacco control is surely one of public health's greatest successes. Many premature deaths have been avoided because of tobacco control programs, but many more could have been avoided if smoking prevalence had dropped more rapidly when the early warnings of lung cancer risk were widely reported in 1950. The 1964 Surgeon General's report gave momentum to tobacco control; the authority of the Surgeon General, and the approach of the Advisory Committee to developing the report, gave unimpeachable credibility to the conclusion that smoking caused lung cancer (in men). That same authority has empowered the conclusions of subsequent reports that have covered involuntary smoking, addiction to nicotine, tobacco control interventions, smoking by adolescents and young adults, and other topics.

Tobacco control programs proved more challenging than simply disseminating knowledge to the population of the dangers of smoking. Brandt notes that "Smoking is a complex behavior which has reflected deep social, cultural, and economic forces, as well as a powerful biological process of addiction. Simply identifying individual behavior as the primary vehicle of risk negates the fact that behavior itself is, at times, beyond the scope of individual agency" (Brandt 1990, p. 172). This complexity, the addicting nature of nicotine, and the dynamic efforts of the industry to maintain its market, challenged initial efforts to curb tobacco use. Over time, the need for broad interventions with multiple components was recognized, and cigarette consumption began to decline at a faster pace (Figure 2.1). Several factors were particularly crucial in altering social norms around cigarette smoking in the United States, making it increasingly less acceptable: (1) the emergence of a nonsmokers' rights movement and evidence linking exposure to secondhand smoke to disease; (2) an understanding of regular cigarette smoking as an addictive behavior and one that begins in adolescence; and (3) a focus on the tobacco industry itself as a key influence on smoking behavior and the importance of countering its actions. Other factors played a role in shaping attitudes and policies around cigarette smoking, including changes in political administrations, the development of a grassroots advocacy movement, the changing climate for litigation, and developments in the organization of public health research.

The production of the 1964 Surgeon General's report itself was a significant public health action, even if direct and immediate policy action seemed slow to follow. Additionally, the 1964 report was a pioneering step toward anticipating a much larger role for government, in collaboration with scientists, to use science to inform regulatory and other policies. This approach is embodied in the 2009 *Tobacco Control Act*. Although early twentieth century antitobacco reformers appealed to moral and social concerns to support their cause, the 1964 report reinforced the central role of science as the primary authority to inform public health policy. Subsequent reports have maintained that position.

Because of the complexity of the factors involved, it is difficult to measure the degree to which particular interventions, following the 1964 report, influenced patterns of tobacco use. However, it is clear that tobacco control policies and actions need to draw on the full suite of interventions of proven efficacy. Grassroots activities and coalitions have played a critical role, as they supported smoking bans and had substantial impact in changing the social norm around smoking.

The past half-century of public health experience with cigarette smoking, since the 1964 report, holds many important lessons for the future and for the actions that will follow from this report. Overall, this ongoing story illustrates the complexity of the factors involved and the need to consider cigarette smoking, not simply as an individual decision about behavior, but as a large-scale social and cultural phenomenon. Despite the conclusive evidence of the harms of cigarette smoking presented in the 1964 report, as evaluated by an objective group of experts, the process of changing public beliefs, attitudes, and behaviors took decades, and the implementation of effective policies involved a lengthy process of intervention, evaluation, and surveillance. The tobacco industry's extensive campaign to counteract these forces through marketing, public relations, political influence, and creation of doubt about the scientific evidence on tobacco is now well documented through the industry's internal documents. The industry used its influence to thwart public health action at all levels and fraudulently misled the public on many issues, including whether lower-yield cigarettes conveyed less risk to health and whether exposure to secondhand smoke harmed nonsmokers. Undoubtedly, these actions slowed progress in tobacco control.

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Chapter 3
Producing the Surgeon General's Report From 1964–2014: Process and Purpose

Introduction

In 1964, U.S. Surgeon General Luther L. Terry appointed an expert committee to submit a report to review and evaluate the current data on smoking and health. The publication of the committee's report, *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the United States* (U.S. Department of Health, Education, and Welfare [USDHEW] 1964), marked the first of a long series of reports issued by the Office of the Surgeon General to the American people on smoking and health (Table 3.1). This series of reports, released over a 50-year period, comprises a remarkable set of scientific documents that have provided internationally accepted consensus judgments on the scientific evidence implicating smoking in disease causation. In addition, the reports have built a scientific foundation to support tobacco control programs and interventions intended to control the epidemic of tobacco-caused disease (see Chapter 2, "Fifty Years of Change—1964–2014"). The reports have also been invaluable to the scientific community by highlighting what is known in this area and identifying the critical evidence gaps to be addressed with further research. Finally, the methods for reviewing evidence and causal inference have been widely applied in other contexts (Rothman and Greenland 1998).

The reports of the Surgeon General have developed a formal framework for assessing evidence on disease causation, and the formats of the reports have provided detailed presentations of the scientific evidence underlying each of their conclusions (USDHEW 1964; U.S. Department of Health and Human Services [USDHHS] 2004). The reports have been produced using a balanced and comprehensive review and editorial process to ensure that the evidence, rather than the authors' opinions, defines the conclusions. Across the five decades of reports, the emphasis has been on the evidence base and the scientific validity of the conclusions, and scientific conclusions have been clearly separated from any policy decisions that may result from the findings.

The result of the work undertaken over this 50-year period has been a series of reports that have maintained their utility and credibility despite marked shifts in governmental policies toward tobacco, powerful opposition from tobacco industry interests, and the sometimes heated debates on science and policy that have taken place within the tobacco control community. This chapter covers the production and evolution of the reports during the past 50 years, emphasizing the processes that have sustained their utility.

Development of a Scientific Consensus

Often considered the first report of the Surgeon General on the health consequences of smoking, the 1964 report on smoking and health was actually (as noted in the introduction above) a report of an expert Advisory Committee to the Surgeon General (USDHEW 1964). Although this report is widely viewed as pivotal in establishing with certainty that cigarette smoking causes lung cancer, a similar conclusion with regard to causation had been reached earlier by several scientific reviews and by Surgeon General Leroy E. Burney (see Chapter 2).

Given the rising evidence and to once again critically review the cumulative evidence, the Surgeon General in 1962 convened an independent group of scientists who had not up to that time publicly expressed an opinion on whether smoking caused lung cancer. This group of scientists was asked to review all of the available evidence on possible links between cigarette smoking and disease and to form a scientific judgment on this issue. In addition, the scientists were expected to report back to the Surgeon General with a solid evidence-based foundation for appropriate remedial action by the U.S. Public Health Service (PHS) responding to the emerging epidemic of lung cancer being caused by a highly profitable consumer product, the cigarette.

To ensure transparency, the committee codified the criteria used to reach the conclusion that smoking causes lung cancer. Both the resulting systematic, transparent review and the synthesis of evidence using those criteria were pioneering for the time.

Table 3.1   Surgeon General's reports on smoking and health, 1964–2012

Year	Title	Surgeon General	Subject/highlights	Number of pages
1964	*Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service*	Luther L. Terry, M.D.	First official report of the federal government on smoking and health. Concluded that "Cigarette smoking is a health hazard of sufficient importance in the United States to warrant appropriate remedial action" (p. 33). Also concluded that cigarette smoking is a cause of lung cancer in men and a suspected cause of lung cancer in women. The report was also responsible for the passage of the *Cigarette Labeling and Advertising Act of 1965,* which among other things, mandated the familiar Surgeon General's health warnings on cigarette packages (USDHEW 1964).	387
1967	*The Health Consequences of Smoking: A Public Health Service Review*	William H. Stewart, M.D.	Confirmed and strengthened conclusions of the 1964 report. Stated that "the case for cigarette smoking as the principal cause of lung cancer is overwhelming" (p. 16). Found that evidence "strongly suggests that cigarette smoking can cause death from coronary heart disease" (p. 26), which was upgraded from the 1964 conclusion of an "association." Also concluded that "Cigarette smoking is the most important of the causes of chronic non-neoplastic bronchopulmonary diseases in the United States" (p. 31) (USDHEW 1967).	199
1968	*The Health Consequences of Smoking: 1968 Supplement to the 1967 Public Health Service Review*	William H. Stewart, M.D.	Updated information that was presented in the 1967 report. Estimated that smoking-related loss of life expectancy among young men as 8 years for "heavy" smokers (more than 2 packs/day) and 4 years for "light" smokers (less than ½ pack/day) (USDHEW 1968).	117
1969	*The Health Consequences of Smoking: 1969 Supplement to the 1967 Public Health Service Review*	William H. Stewart, M.D.	Also supplemented 1967 report. Confirmed association between maternal smoking and infant low birthweight. Identified evidence of increased incidence of prematurity, spontaneous abortion, stillbirth, and neonatal death (USDHEW 1969).	98
1971	*The Health Consequences of Smoking*	Jesse L. Steinfeld, M.D.	Reviewed entire field of smoking and health with emphasis on most recent literature. Discussed new data indicating associations between smoking and peripheral vascular disease, atherosclerosis of the aorta and coronary arteries, increased incidence and severity of respiratory infections, and increased mortality from cerebrovascular disease and nonsyphilitic aortic aneurysm. Concluded that smoking is associated with cancers of the oral cavity and esophagus. Found that "Maternal smoking during pregnancy exerts a retarding influence on fetal growth" (p. 13) (USDHEW 1971).	458

Table 3.1   Continued

Year	Title	Surgeon General	Subject/highlights	Number of pages
1972	*The Health Consequences of Smoking*	Jesse L. Steinfeld, M.D.	Examined evidence on immunologic effects of tobacco and tobacco smoke, harmful constituents of tobacco smoke, and "public exposure to air pollution from tobacco smoke" (p. 121). Found tobacco and tobacco smoke antigenic in humans and animals; tobacco may impair protective mechanisms of immune system; nonsmokers' exposure to tobacco smoke may exacerbate allergic symptoms; carbon monoxide in smoke-filled rooms may harm health of persons with chronic lung or heart disease; tobacco smoke contains hundreds of compounds, several of which have been shown to act as carcinogens, tumor initiators, and tumor promoters. Identified carbon monoxide, nicotine, and tar as smoke constituents most likely to produce health hazards of smoking (USDHEW 1972).	158
1973	*The Health Consequences of Smoking*	Merlin K. DuVal, M.D.[a]	Presented evidence on health effects of smoking pipes, cigars, and "little cigars." Found mortality rates of pipe and cigar smokers higher than those of nonsmokers but lower than those of cigarette smokers. Found that cigarette smoking impairs exercise performance in healthy young men. Presented additional evidence on smoking as a risk factor in peripheral vascular disease and problems of pregnancy (USDHEW 1973).	249
1974	*The Health Consequences of Smoking*	Charles C. Edwards[a]	Tenth anniversary report. Reviewed and strengthened evidence on major hazards of smoking. Reviewed evidence on association between smoking and atherosclerotic brain infarction and on synergistic effect of smoking and asbestos exposure in causing lung cancer (USDHEW 1974).	124
1975	*The Health Consequences of Smoking*	Theodore Cooper, M.D.[a]	Updated information on health effects of involuntary (passive) smoking. Noted evidence linking parental smoking to bronchitis and pneumonia in children during the first year of life (USDHEW 1975).	235
1976	*The Health Consequences of Smoking: Selected Chapters from 1971 through 1975*	Theodore Cooper, M.D.[a]	Compiled selected chapters from 1971–1975 reports (USDHEW 1976).	657
1979	*The Health Consequences of Smoking, 1977–1978*	Julius B. Richmond, M.D.	Combined 2-year report focused on smoking-related health problems unique to women. Cited studies showing that use of oral contraceptives potentiates harmful effects of smoking on the cardiovascular system (USDHEW 1979b).	60

Table 3.1   Continued

Year	Title	Surgeon General	Subject/highlights	Number of pages
1979	*Smoking and Health*	Julius B. Richmond, M.D.	Fifteenth anniversary report. Presented most comprehensive review of health effects of smoking ever published, and first Surgeon General's report to carefully examine behavioral, pharmacologic, and social factors influencing smoking; to consider role of adult and youth education in promoting nonsmoking; and to review health consequences of smokeless tobacco. Many new sections, including one identifying smoking as "one of the primary sources of drug interactions in man" (p. 12-22) (USDHEW 1979a).	1,194
1980	*The Health Consequences of Smoking for Women*	Julius B. Richmond, M.D.	Devoted to health consequences of smoking for women. Reviewed evidence that strengthened previous findings and permitted new ones. Noted projections that lung cancer would surpass breast cancer as leading cause of cancer mortality in women. Identified trend toward increased smoking by adolescent females (USDHHS 1980).	359
1981	*The Health Consequences of Smoking–The Changing Cigarette*	Julius B. Richmond, M.D.	Examined health consequences of "the changing cigarette" (i.e., lower tar and nicotine cigarettes). Concluded that lower yield cigarettes reduced risk of lung cancer, but found no conclusive evidence that they reduced risk of cardiovascular disease, COPD, and fetal damage. Noted possible risks from additives and their products of combustion. Discussed compensatory smoking behaviors that might reduce potential risk of lower yield cigarettes. Emphasized that there is no safe cigarette and that any risk reduction associated with lower yield cigarettes would be small compared with benefits of quitting smoking (USDHHS 1981).	252
1982	*The Health Consequences of Smoking–Cancer*	C. Everett Koop, M.D.	Reviewed and extended understanding of the health consequences of smoking as a cause or contributory factor of numerous cancers. Included first Surgeon General's report consideration of emerging epidemiologic evidence of increased lung cancer risk in nonsmoking wives of smoking husbands. Did not find evidence at that time sufficient to conclude that relationship was causal, but labeled it "a possible serious public health problem" (p. 9). Discussed potential for low-cost smoking cessation interventions (USDHHS 1982).	322
1983	*The Health Consequences of Smoking–Cardiovascular Disease*	C. Everett Koop, M.D.	Examined health consequences of smoking for cardiovascular disease. Concluded that cigarette smoking is 1 of 3 major independent causes of CHD and, given its prevalence, "should be considered the most important of the known modifiable risk factors for CHD" (p. 6). Discussed relationships between smoking and other forms of cardiovascular disease (USDHHS 1983).	384

Table 3.1   Continued

Year	Title	Surgeon General	Subject/highlights	Number of pages
1984	*The Health Consequences of Smoking–Chronic Obstructive Lung Disease*	C. Everett Koop, M.D.	Reviewed evidence on smoking and COLD. Concluded that smoking is the major cause of COLD, accounting for 80–90% of COLD deaths in the United States. Noted that COLD morbidity has greater social impact than COLD mortality because of extended disability periods of COLD victims (USDHHS 1984).	545
1985	*The Health Consequences of Smoking–Cancer and Chronic Lung Disease in the Workplace*	C. Everett Koop, M.D.	Examined relationship between smoking and hazardous substances in the workplace. Found that for the majority of smokers, smoking is a greater cause of death and disability than their workplace environment. Risk of lung cancer from asbestos exposure characterized as multiplicative with smoking exposure. Observed special importance of smoking prevention among blue-collar workers because of their greater exposure to workplace hazards and their higher prevalence of smoking (USDHHS 1985).	542
1986	*The Health Consequences of Involuntary Smoking*	C. Everett Koop, M.D.	Focused on involuntary smoking, concluding that "Involuntary smoking is a cause of disease, including lung cancer, in healthy nonsmokers" (p. 7). Also found that, compared with children of nonsmokers, children of smokers have higher incidence of respiratory symptoms and infections and reduced rates of increase in lung function. Presented detailed examination of growth in restrictions on smoking in public places and workplaces. Concluded that simple separation of smokers and nonsmokers within same airspace reduces but does not eliminate exposure to environmental tobacco smoke (USDHHS 1986a).	359
1986	*The Health Consequences of Using Smokeless Tobacco*	C. Everett Koop, M.D.	Special report of advisory committee appointed by the Surgeon General to study the health consequences of smokeless tobacco. Concluded that use of smokeless tobacco can cause cancer in humans and can lead to nicotine addiction (USDHHS 1986b).	195
1988	*The Health Consequences of Smoking–Nicotine Addiction*	C. Everett Koop, M.D.	Established nicotine as a highly addictive substance, comparable in its physiological and psychological properties to other addictive substances of abuse (USDHHS 1988).	639
1989	*Reducing the Health Consequences of Smoking–25 Years of Progress*	C. Everett Koop, M.D.	Twenty-fifth anniversary report highlighted the dramatic progress that was achieved since the first report was issued in 1964. Highlighted important gains in preventing smoking and smoking-related disease, reviewed changes in programs and policies designed to reduce smoking, and emphasized remaining challenges (USDHHS 1989).	703

Table 3.1   Continued

Year	Title	Surgeon General	Subject/highlights	Number of pages
1990	*The Health Benefits of Smoking Cessation*	Antonia C. Novello, M.D., M.P.H.	Examined how an individual's risk of smoking-related diseases declines after quitting smoking (USDHHS 1990).	628
1992	*Smoking and Health in the Americas*	Antonia C. Novello, M.D., M.P.H.	Reviewed broad issues surrounding production and consumption of tobacco in the Americas (USDHHS 1992).	213
1994	*Preventing Tobacco Use Among Young People*	M. Joycelyn Elders, M.D.	Addressed the crucial problems of adolescent tobacco use by providing a detailed look at adolescence, the time of life when most tobacco users begin, develop, and establish their smoking behavior (USDHHS 1994).	314
1998	*Tobacco Use Among U.S. Racial/ Ethnic Minority Groups*	David Satcher, M.D., Ph.D.	Described the 4 major U.S. racial/ethnic minority groups—African Americans, American Indians and Alaska Natives, Asian Americans and Pacific Islanders, and Hispanics—patterns of tobacco use, adverse health effects, and the effectiveness of interventions in terms of tobacco's cultural and socioeconomic effects on the members of these groups. This report described the complex factors that play a part in the growing epidemic of diseases caused by tobacco use in these 4 groups (USDHHS 1998).	332
2000	*Reducing Tobacco Use*	David Satcher, M.D., Ph.D.	First report to offer a composite review of the various methods used to reduce and prevent tobacco use. This report evaluated each of the 5 major approaches to reducing tobacco use: educational, clinical, regulatory, economic, and comprehensive (USDHHS 2000).	462
2001	*Women and Smoking*	David Satcher, M.D., Ph.D.	Concluded that the increased likelihood of lung cancer, cardiovascular disease, and reproductive health problems among female smokers make tobacco use a serious women's health issue (USDHHS 2001).	675
2004	*The Health Consequences of Smoking*	Richard Carmona, M.D., M.P.H.	Concluded that smoking causes diseases in nearly every organ of the body. Also concluded that cigarette smoking is causally linked to leukemia, cataracts, pneumonia, and cancers of the cervix, kidney, pancreas, and stomach (USDHHS 2004).	941
2006	*The Health Consequences of Involuntary Exposure to Tobacco Smoke*	Richard Carmona, M.D., M.P.H.	Concluded that there is no risk-free level of exposure to secondhand smoke. Found that even brief secondhand smoke exposure can cause immediate harm. The report said the only way to protect nonsmokers from the dangerous chemicals in secondhand smoke is to eliminate smoking indoors (USDHHS 2006).	709
2010	*How Tobacco Smoke Causes Disease—The Biologic and Behavioral Basis for Smoking-Attributable Disease*	Regina Benjamin, M.D., M.B.A.	Described in detail the specific pathways by which tobacco smoke damages the human body (USDHHS 2010).	**704**

Table 3.1   Continued

Year	Title	Surgeon General	Subject/highlights	Number of pages
2012	Preventing Tobacco Use Among Youth and Young Adults	Regina Benjamin, M.D., M.B.A.	Updated the 1994 report on youth and described the epidemic of tobacco use among youth 12–17 years of age and young adults 18–25 years of age, including the epidemiology, causes, and health effects of this tobacco use and interventions proven to prevent it (USDHHS 2012).	899

Note: **CHD** = coronary heart disease; **COLD** = chronic obstructive lung disease; **COPD** = chronic obstructive pulmonary disease; **USDHEW** = U.S. Department of Health, Education and Welfare; **USDHHS** = U.S. Department Health and Human Services.
[a]Assistant Secretary for Health issued the report.

Development of the Criteria for Causation Used in the 1964 Report

The meaning of the word "cause" has a long and rich philosophical history; the term has been applied variably in different scientific contexts. Among these contexts have been the demonstration of causation experimentally in the laboratory, the causal attribution of a specific infectious disease to a specific microbiologic agent, and the understanding of the mechanism(s) leading to a disease. In the years before the creation of the Advisory Committee, the groups which considered the question of cigarette smoking as a cause of lung cancer recognized that these scientific contexts, and the resulting context-specific constructs of causation, could not be readily applied to the question of whether cigarette smoking caused human disease (Blackburn and Labarthe 2012; Glass et al. 2013). Obtaining direct experimental evidence in humans is an ethical impossibility and understanding the mechanisms of disease occurrence involves considering an ongoing, open-ended set of scientific questions. Furthermore, neither of these scientific contexts for defining causation is well suited to examining the effects of human behaviors and exposures on subsequent disease occurrence in populations.

The early scientific reviews that examined whether smoking causes human disease used the common, generally understood meaning of the term "cause": that the disease occurs as a result of exposure to the agent. This meaning was expressed in the 1964 report of the Surgeon General as follows: "The word *cause* is the one in general usage in connection with matters considered in this study, and it is capable of conveying the notion of a significant, effectual, relationship between an agent and an associated disorder or disease in the host" (USDHEW 1964, p. 21).

The 2004 Surgeon General's report, *The Health Consequences of Smoking*, described the subsequent refinement of the 1964 language for application in public health and epidemiologic considerations as "The qualitative judgment that an exposure causes a particular disease signifies that in the absence of exposure some fraction of cases or deaths would not occur or would occur at a later age" (USDHHS 2004, p. 10).

The 1964 report of the Advisory Committee clearly stated that the decision that cigarette smoking was a cause of lung cancer in men resulted from a judgment based on a synthesis of all of the available evidence, rather than the outcome of a single scientific study or a single line of evidence. Specifically, the report (USDHEW 1964, p. 20) noted:

Statistical methods cannot establish proof of a causal relationship in an association. The causal significance of an association is a matter of judgment which goes beyond any statement of statistical probability. To judge or evaluate the causal significance of the association between the attribute or agent and the disease, or effect upon health, a number of criteria must be utilized, no one of which is an all-sufficient basis for judgment.

Included in the evidence base for the 1964 report were observational data from epidemiologic studies of human populations. During the 1940s and 1950s, epidemiology was rapidly developing as a scientific discipline, but the observational, as opposed to experimental,

nature of epidemiologic approaches led some scientists to question whether such approaches could be used to determine causation scientifically. Others confused epidemiologic analyses with the statistical methods used to describe the data (Shimkin 1979). Cigarette manufacturers and their spokespersons capitalized on this confusion by claiming that only experimental approaches could lead to evidence establishing causation: the evidence used by public health authorities to conclude that smoking caused lung cancer was only "statistical" and therefore not scientific (Brandt 2007; Proctor 2011).

Given the ethical impossibility of conducting human experiments to establish causation and recognizing the validity of epidemiologic methods, the various groups (before the Advisory Committee's report) that examined the question of whether cigarette smoking caused lung cancer had relied heavily on epidemiologic studies as a key part of the evidence base establishing causation. Each review described how the epidemiologic data were examined and considered. The reviews acknowledged that epidemiologic studies lacked the methodologic reassurance and needed careful attention to identify potential methodologic flaws, various biases, and both measured and unrecognized confounding (e.g., lifestyle differences between never smokers and smokers) that might have resulted in the demonstrated association. Each of these reports explained how these factors were considered in assessing the evidence, but the Advisory Committee went further and defined the criteria by which epidemiologic evidence could be examined and synthesized to reach a causal judgment.

The Committee's process for using epidemiologic data in assessing causation included multiple steps. The process involved: (1) establishing that cigarette smoking was associated with lung cancer; (2) examining whether the association could be explained by other factors such as methodologic flaws, bias, or confounding; (3) examining whether there were plausible alternative explanations for the observed association; (4) considering the main points of criticisms raised about the association and its potential causal nature; and (5) ensuring all of the lines of evidence were generally consistent with a causal hypothesis (USDHEW 1964). A similar careful and extensive process for considering evidence of causality had been implemented earlier by Cornfield and colleagues (1959) in their review of smoking and lung cancer: their considerations provided guidance for the methodologic approach adopted by the Advisory Committee in 1964. Subsequent reports of the Surgeon General have used the same approach for examining questions of causality for smoking and specific diseases.

In its report, the Advisory Committee formally presented a set of criteria by which epidemiologic data could be used to define the causation of human disease: (1) the consistency of the association (replication of findings across different studies and populations), (2) the strength of the association (magnitude of the increased risk associated with exposure), (3) the specificity of the association (presence of a unique exposure-disease association), (4) the temporal relationship of the association (exposure comes before effect), and (5) the coherence of the association (support for the association from other lines of evidence) (USDHEW 1964).

These criteria were included in the widely recognized criteria for interpreting epidemiologic evidence in public health presented by Sir Austin Bradford Hill in 1965 (Hill 1965). The Bradford Hill criteria added four additional criteria, most notably the presence of a biologic gradient (dose-response relationship) in the evidence. The other three included plausibility (subsumed under coherence in the Surgeon General's criteria), experiment, and analogy.

Detailed discussions of these criteria, how they evolved, and how they are applied in reviewing epidemiologic evidence are presented in the 1964 report (USDHEW 1964) and the 2004 report (USDHHS 2004); that discussion will not be repeated here. Rather, the public health significance of formally expressed criteria for the use of epidemiologic evidence in defining causality is the focus of the present discussion. Historically, the articulation of these criteria marked a turning point in the utilization and acceptance of epidemiologic evidence. It laid the foundation for the current widespread use of epidemiologic evidence to define disease causation and identify methods for disease prevention and education of the public. These criteria, and their use by the Advisory Committee in reaching a judgment that smoking caused lung cancer in men, established an approach that remains in use for causal inference based around epidemiological and other evidence.

Evolution of the Application of the Criteria for Disease Causation in Subsequent Reports

As the evidence on smoking as a cause of disease expanded to include numerous disorders or problems (various cancers, multiple manifestations of atherosclerotic vascular disease, chronic obstructive pulmonary disease [COPD], complications of pregnancy, and a myriad of other diseases and conditions [USDHHS 2004]), a variety of terms were used to describe the established causal associations, including "cause," "causal factor," "risk factor," "contributing factor," and "causal association." Some of

these descriptor choices were stylistic, reflecting the preferences of authors and editors; others reflected differences in how causal associations were described for different disease processes, notably the use of risk factor in the literature on cardiovascular disease, where there are multiple causal factors. However, some uses of these terms were intended to convey different levels of certainty about the strength of the evidence establishing causation.

This use of multiple terms led to some ambiguity and confusion as to what was actually being said. Eventually, terms modifying the descriptors of causality were also introduced. These terms described the impact of smoking on the population in relation to either other causes of disease or the contribution of smoking for a specific disease. For example, the 1989 Surgeon General's report on smoking and health stated that "Smoking remains the single most important preventable cause of death in our society" (USDHHS 1989, p. 11). This modifier was intended to describe the magnitude of the effect of smoking on the population in contrast to other causes of premature death. Similarly, the relationship of cigarette smoking and lung cancer was described as "Cigarette smoking is the major cause of lung cancer in the United States" (USDHHS 1982, p. 5), which qualitatively characterized the fraction of lung cancer deaths in the population caused by smoking. This mixing of terms, which quantified the population disease burden with terms describing the strength of the evidence establishing disease causation, had the potential to create ambiguity about what was being concluded, particularly when the modifier was used for some diseases but not others, in the same report.

Importantly, the 2004 Surgeon General's report on smoking and health (USDHHS 2004) standardized the forms in which judgments on disease causation and statements about the population consequences of diseases caused by smoking were presented. For causation, the language, which defined the strength of the evidence establishing that smoking caused a specific disease, was made uniform to ensure clarity across the divergent disease processes, as illustrated by the following statement from the report:

> The first step in introducing this revised approach is to outline the language that will be used for summary conclusions regarding causality, which follows hierarchical language used by Institute of Medicine committees (Institute of Medicine 1999) to couch causal conclusions, and by IARC [International Agency for Research on Cancer] to classify carcinogenic substances (IARC 1986). These entities use a four-level hierarchy for classifying the strength of causal inferences based on available evidence as follows: (a) Evidence is **sufficient** to infer a causal relationship; (b) Evidence is **suggestive but not sufficient** to infer a causal relationship; (c) Evidence is **inadequate** to infer the presence or absence of a causal relationship (which encompasses evidence that is sparse, of poor quality, or conflicting); and (d) Evidence is **suggestive of no causal relationship** (USDHHS 2004, pp. 17–18).

The evidence on disease causation for each specific disease is synthesized, and a judgment on causation is made and expressed using the standardized language presented above. This format clearly defines both the evidence on which the judgment is based and the strength with which that conclusion can be expressed. As for the public health impact of smoking-caused disease for the population and the fraction of the disease caused by smoking, both are presented in these reports under a separate heading named "Implications" following the Conclusions section. It is in that section that the population-level impact of smoking and the fraction of the disease caused by smoking are examined.

Methods for Reviewing the Evidence and Developing Conclusions

The reports of the Surgeon General have continued to play a role in defining the science that underlies efforts in tobacco control by certifying the causation of various diseases and expressing the state of the science on the effectiveness of tobacco control interventions, approaches, and policies. The success of the series of reports reflects the processes used for reviewing and presenting the evidence and for the development of the conclusions. The processes used for subsequent reports evolved from the process used in the 1964 report of the Advisory Committee.

The 1964 report, at 387 pages, was substantively longer than the independent reviews that had preceded it. As

a consequence, it was able to offer a much more detailed presentation of the evidence in the text rather than simply providing references to the individual studies in support of the conclusions.

The depth of the evidence presentation in the Advisory Committee's report in 1964 can be seen readily in subsequent reports, and this comprehensive approach has been one reason for the reports' continuing credibility. An editorial standard evolved that required the conclusions of individual sections of the report to be based on discussions of the literature presented in the text that were coupled with relevant study results presented in the text, tables, and figures of those sections. This approach, of presenting the totality of evidence in sufficient detail to allow the reader to evaluate it, contrasted with the general approach of the time for written reviews, which relied heavily on syntheses of evidence by authors with literature citations for the publications reviewed. In the Surgeon General's reports, presentation of the critical findings from the relevant studies, coupled with discussion of the methods used to generate the evidence in the text of the report, has allowed readers to assess the validity of the conclusions directly rather than requiring them to conduct a time-consuming search of the cited publications. This transparency has strengthened the reports' findings in the face of the inevitable criticisms.

In synthesizing the evidence on exposure to secondhand smoke and disease, meta-analysis has been used, both in the Surgeon General's reports and in other evaluations. Generally, the term "meta-analysis" refers to the systematic analysis and quantitative summarization of the findings of multiple studies containing evidence to address the same question (Greenland 1987; Egger and Davey Smith 1997; Institute of Medicine 2011). In a meta-analysis, the data are the summary findings of the studies identified through a systematic review and not the data at the individual level. Meta-analysis has been used to summarize the evidence on exposure to secondhand smoke, primarily because the associations are generally much weaker than they are for active smoking. Meta-analysis was not used in the 1986 report, but it was applied to multiple outcomes in the 2006 report, *The Health Consequences of Involuntary Exposure to Tobacco Smoke*, and is used in this report.

Although meta-analysis has proven useful for summarizing the evidence and quantifying the risks of exposure to secondhand smoke as precisely as possible, the findings of meta-analyses and, particularly, information on whether an association found in the meta-analysis was statistically significant, have not figured directly in the causal inferences presented in the reports of the Surgeon General. The results are most useful for providing a single,

combined estimate of the risk for calculating the associated burden of disease and, potentially, for exploring why results vary from study to study.

The practice of presenting the relevant evidence needed to support the conclusions also has helped to ensure the validity of the conclusions as has the tiered approach and peer review process of the chapters. In the Surgeon General's reports, the initial author of an individual section is tasked with reviewing and assembling all of the relevant evidence available and presenting it in the text and related tables and figures with a level of detail sufficient to support the conclusions. Based on that presentation, the author then considers and discusses what conclusions the evidence supports. This comprehensive review process helps reduce inaccuracies that may occur when authors synthesize the evidence and reach conclusions based on their recall of what the literature shows, rather than on the evidence actually contained in that literature.

Passing the section on to the editors allows a different group of people to consider the evidence presented to evaluate the basis for the conclusions and to revise them, if appropriate. Similarly, as the chapters and reports proceed through the various review stages, the reviewers can independently consider the evidence presented as they consider the accuracy, completeness, balance, tone, and language of the conclusions. In providing their comments, the reviewers can focus on the evidence presented, consider whether the review of that evidence is complete, and judge whether the conclusions are supported by the evidence.

The intense criticisms of the reports by the cigarette manufacturers and their representatives prior to the late 1990s (see Chapter 2) helped to strengthen the process of developing conclusions for the reports. The anticipation of criticism motivated the development of conclusions that were firmly based on evidence without speculation. Before its elimination as a result of the 1998 Master Settlement Agreement, the Tobacco Institute (a representative of cigarette manufacturers) conducted a well-funded and highly visible public relations campaign to denigrate the quality of the science in each Surgeon General's report and question the validity of their conclusions (Kluger 1996; Brandt 2007; Proctor 2011). Based on the historical pattern of challenges to the Surgeon General's reports (see Chapter 14, "Current Status of Tobacco Control") the authors, editors, and reviewers of the reports assumed that every conclusion might be challenged and, therefore, each had to be solidly and fully supported by sufficient evidence. The result was that, as conclusions were drafted and reviewed, there was an intense focus on the quality and robustness of the evidence. Conclusions were structured to be unas-

sailably grounded in a foundation of evidence and the language of the conclusions was "conservative" such that the strength of evidence was not overstated. As the evidence foundation advanced, conclusions were strengthened.

This effort to achieve scientific transparency by laying out the evidence foundation for the conclusions has defined with clarity the state of the scientific evidence on disease causation, the effectiveness of efforts in tobacco control, and the consequences of changes in public policy. In addition, it has provided solid support for evidence-based public policy decisions on tobacco issues, has identified the areas where scientific certainty exists as separate from those areas where uncertainty remains, and has been a principal reason for the enduring credibility of this series of reports.

Process of Ensuring Consensus and Strength of the Peer Review

In a series of governmental reports, such as those of the Surgeon General which have both great visibility and a substantial impact on public policy, protections are needed to resist influences that could distort the process of forming a consensus and affect the conclusions.

As a report is in development, a myriad of factors may come into play: political pressures; pressures from a variety of individuals and groups to have the conclusions conform to their preexisting policy positions; the recognition that some conclusions can influence decisions on research funding; and even the well-intentioned belief of authors of sections of the report that the final conclusions should substantiate positions they have adopted based on their own research. Without a process to insulate the report's conclusions from such influences, the conclusions might be perceived as based on the politics and pressures of the moment rather than on a consensus of scientific opinion.

The National Clearinghouse for Smoking and Health prepared the initial series of reports (1967–1976) which followed the 1964 Surgeon General's report. The scientific and technical staff of the clearinghouse, a forerunner of the current Centers for Disease Control and Prevention's Office on Smoking and Health, was responsible for both drafting and editing the volume. The 1971 report, *The Health Consequences of Smoking*, was a comprehensive review of all of the available evidence, but the other reports in the 1967–1976 period were intended to review the evidence on the relationship of smoking to cancer, cardiovascular disease, and COPD that had been published since the previous report, with additional chapters focusing in more depth on specific topics. The "in-house" preparation of the volume was counterbalanced by a multilevel review process. Each draft chapter was reviewed by experts, external to the clearinghouse, from the academic community and select PHS agencies who were asked to evaluate the accuracy and completeness of the chapter. After the reviewers' comments were incorporated into the draft chapters, the chapters were assembled into a draft report. That version of the report was sent to a larger group of experts, broadly knowledgeable in smoking and health, who were asked to comment on the balance, tone, and accuracy of the volume and its conclusions. The draft report was also submitted for review to those agencies within PHS that were involved with tobacco issues. Revisions were made in response to these comments, and the volume was then submitted for formal clearance and release as the official position of PHS on the science of tobacco and health. As required by law, it was also transmitted to the U.S. Congress. This complex, multilayered peer review helped to ensure not only that the science in the volume was accurate but also that the positions expressed on the science were the prevailing view of the scientific community at the time and represented concurrence without being unduly influenced by any one individual or group.

Beginning with the 1979 Surgeon General's report on smoking and health and continuing to the present, an additional layer of insulation was added by selecting a set of editors for each volume who were drawn from the academic and scientific communities and, when selected, were not employees of the federal government. These editors have been tasked with ensuring the accuracy of the scientific content of the reports and providing additional independent oversight for the process of incorporating reviewers' comments. These independent editors, rather than the authors, have been responsible for making the final decisions on incorporating reviewers' comments into the text, thereby creating a layer of objectivity regarding reviewers' comments as they are considered and preventing the views of any single author from controlling the conclusions.

The evolution of this production process demonstrates that it is possible for a governmental review of a scientific topic of high societal interest and relevance to be conducted in a way that ensures independence and scientific accuracy for the resulting scientific conclusions.

Separation of Scientific Conclusions and the Formation of Policy

The findings of the reports of the Surgeons General have been the basis for a wide-ranging set of policy decisions and consequently some may consider the reports as offering policy recommendations. The overall intent of the reports, however, has been to provide a clear evidence foundation for scientific judgments on the diseases caused by smoking, the factors influencing smoking initiation and cessation, the effectiveness of smoking and tobacco control interventions, and the results of tobacco control programs and changes in public policy. The characterization of the state of the science on these issues remains the mission of the reports of the Surgeon General and is their principal enduring value. Although it is hoped that these scientific judgments will be used in the formation of public policy, and the reports have often examined the evidence on the effects of public policy decisions, the content of the reports has been limited to the state of the science on these issues. The reports have avoided defining or recommending specific public policies, leaving those decisions to the entities responsible for policy formation, including the Secretary of HHS and the various components of that department. The conclusions of the report have been intentionally framed to state what could be concluded scientifically from the evidence and to lay out the implications of those conclusions for the population.

The separation of scientific conclusions from policy recommendations, initially adopted because policy decisions and implementation occurred at organizational levels well above that of the National Clearinghouse for Smoking and Health, has helped to ensure the ongoing credibility of this series of reports. Public policy decisions are, and often must be, made before the evidence supporting them is complete. These reports have been the benchmark on the status of the evidence for decision-making.

By preserving its exclusive focus on the scientific foundation and avoiding the inclusion of policy recommendations by the scientists involved with the report, the reports of the Surgeon General have preserved their credibility and somewhat insulated the report development process from the need for scientific certainty among those responsible for forming public policy. Correspondingly, the recognized independence of the reports' conclusions has resulted in a solid and enduring foundation that supports those who are tasked with defining and implementing public policy.

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Chapter 4
# Advances in Knowledge of the Health Consequences of Smoking: From 1964–2014

Introduction

The 50-year span beginning in 1964 and ending in 2014 covers an era of remarkable advances in the understanding of disease etiology and opportunities for the prevention, diagnosis, and treatment of disease. There have also been striking changes seen in the incidence of disease, in mortality rates, and substantial gains in life expectancy. For example, in 1964 cancer was widely regarded as incurable and few causal agents had been identified, although tobacco smoke was already of concern because it had been identified as carcinogenic (Mukherjee 2010). Physicians and public health officials lacked today's preventive strategies for coronary heart disease and widely used drugs, such as statins, had not yet been developed. Coronary care units for managing acute myocardial infarctions and heart rhythm disturbances were not in

existence. Chronic obstructive pulmonary disease (COPD) was recognized, but it was referred to as "chronic bronchitis" or "emphysema," and the prevalence of what we now call COPD was far below the present level (Petty 2006; Kim and Criner 2013). Antibiotics were available for most bacterial infections, but not all infections could be cured with these drugs; antiviral agents, other than vaccines, were lacking altogether.

During the last half-century, major changes in disease occurrence have taken place that provide a critical context for the tobacco epidemic (Figure 4.1). The infectious diseases, particularly tuberculosis, declined as leading contributors to mortality to be replaced by the noncommunicable diseases: cardiovascular diseases, COPD, and cancer. Studies on the causes of these

Figure 4.1   Mortality rates for major diseases in the United States, 1900–2005
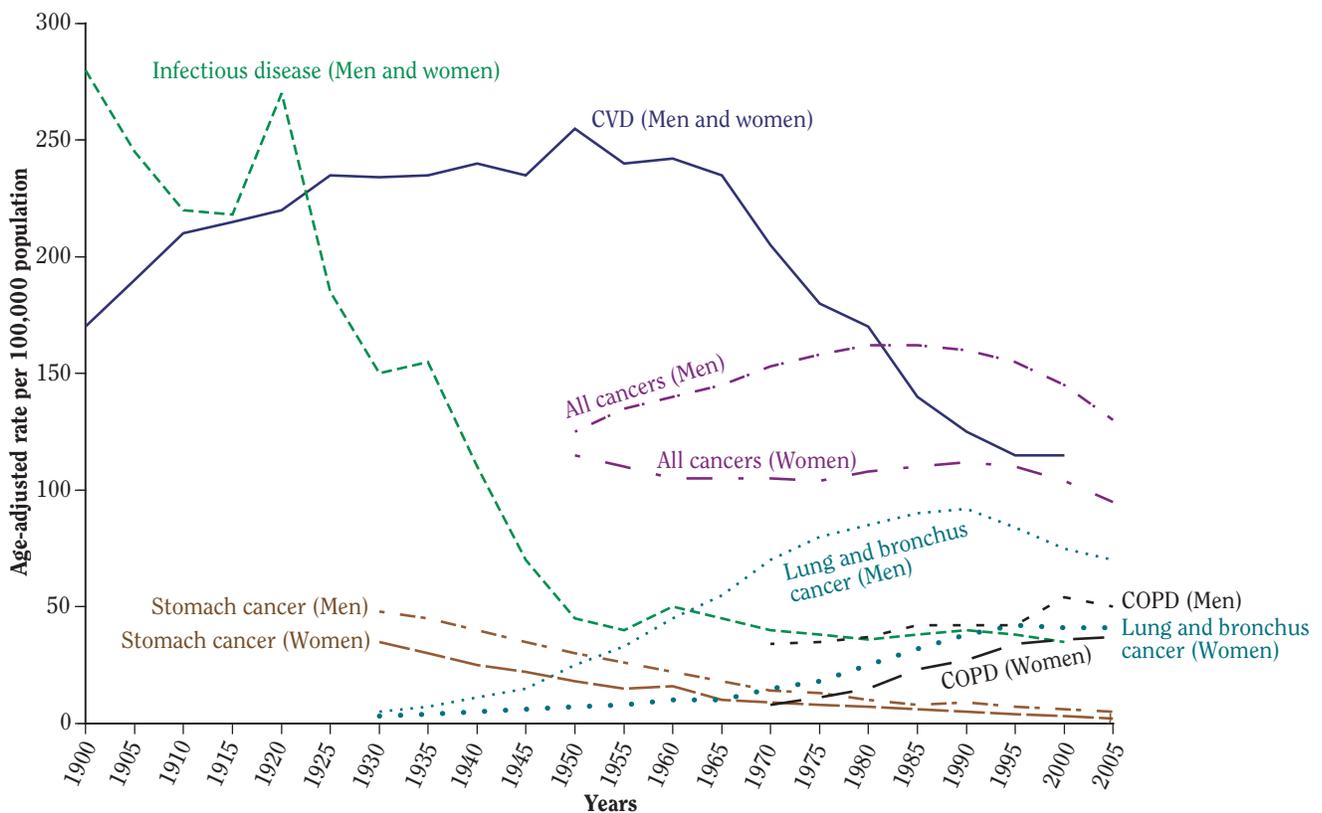
Source: Infectious disease and CVD rates from Cutler et al. 2006. Age-adjusted rates for stomach, lung, and bronchus cancer from American Cancer Society 2009. Age-standardized rate for all cancers from World Health Organization Mortality Database 2012. Age-adjusted rates for COPD from National Center for Health Statistics 2012.
*Note:* **COPD** = chronic obstructive pulmonary disease; **CVD** = cardiovascular disease.

noncommunicable diseases were motivated by their rising frequency. Observational epidemiologic studies had a critical role in the search for causes, while complementary laboratory research expanded the understanding of the biological mechanisms by which risk factors caused these diseases. But even before 1964, advances had been made in characterizing the etiology of noncommunicable diseases. These advances relied on case-control and landmark cohort studies started in the late 1940s and 1950s, such as the Framingham Heart Study (which identified multiple risk factors for noncommunicable diseases, and explored blood pressure, lipids, and smoking in relationship to risk for incident coronary heart disease) (Kannel et al. 1961), the British Doctors Study in the United Kingdom (Doll and Hill 1954), and studies carried out by the American Cancer Society in the United States (Hammond and Horn 1954) linking cigarette smoking to multiple diseases. Findings from these studies figured prominently in the 1964 report, *Smoking and Health: Report of the Advisory Committee of the Surgeon General of the Public*

Health Service, and in subsequent reports as follow-up of participants continued and risks were tracked over time.

During the 50 years since the first Surgeon General's report on smoking and health in 1964 to this anniversary report, the observational evidence on the causes of noncommunicable diseases has continued to advance as numerous case-control and cohort studies were carried out and our understanding of the mechanistic processes leading to these diseases was greatly enhanced. Numerous risk factors were identified that have been classified by the Global Burden of Disease project into broad groups, including air pollution, tobacco smoking including exposure to secondhand smoke, alcohol and drug use, dietary risk factors and physical inactivity, physiological risk factors, and occupational risk factors (Lim et al. 2012). Many of these risk factors, such as physical inactivity, unhealthy diet, and smoking, could be avoided, making primary prevention possible. Pharmacological therapies provided control for some risk factors, such as treatment of lipid abnormalities with statins and other medications.

Figure 4.2   Age-adjusted mortality rates for all causes[a], United States, selected years, 1900–2010
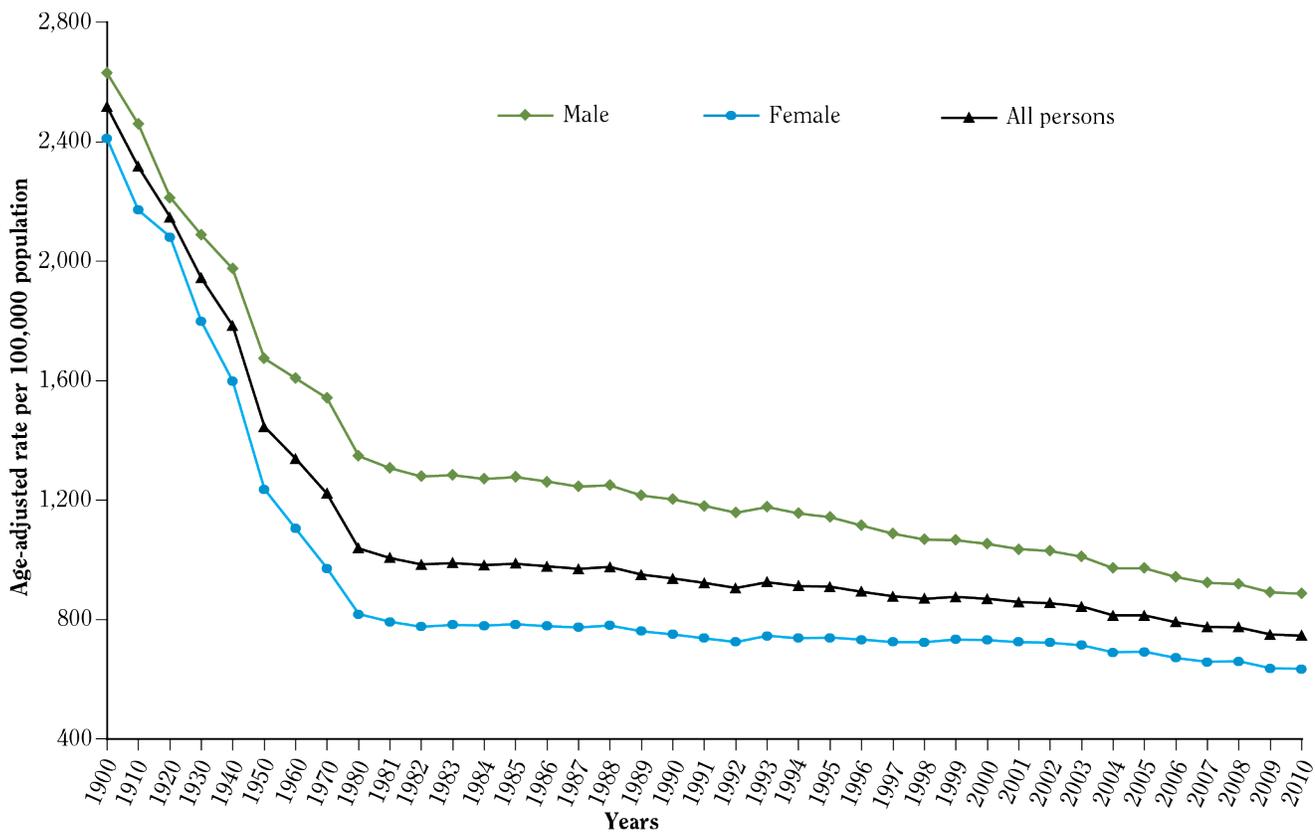
Source: Hoyert et al. 2001; National Center for Health Statistics 2013.
[a]All causes of deaths combined.

Figure 4.3   Mortality rates from selected cancers among men in the United States, 1930–2008[a]
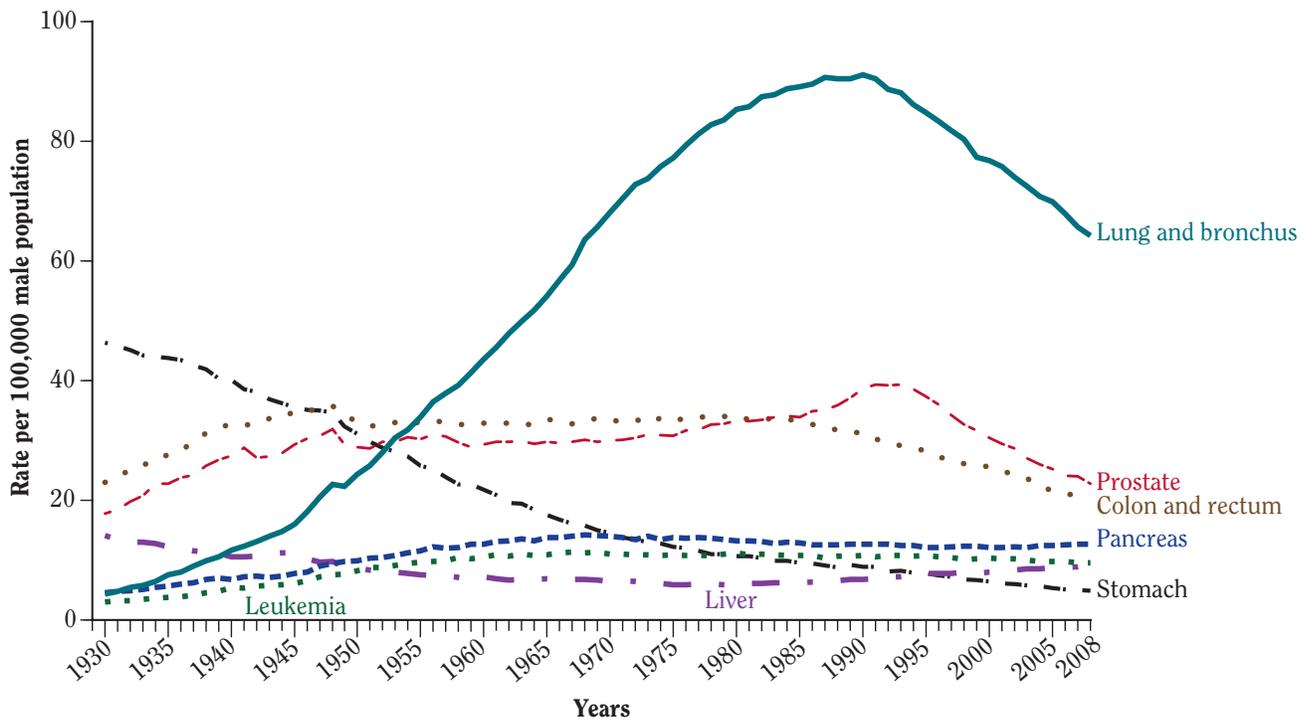
Source: Surveillance, Epidemiology, and End Results Program 2013.
*Note:* Due to changes in *International Classification of Diseases* coding, numerator information has changed over time. Rates for cancer of the liver, lung and bronchus, and colon and rectum are affected by these coding changes.
[a]Per 100,000, age-adjusted to the 2000 U.S. standard population.

Another important advance over the last several decades has been the incorporation of genetics into research on the etiology of noncommunicable diseases, especially in the use of genetics to identify those men and women who are particularly susceptible to certain extrinsic exposures, such as cigarette smoking. For the diseases caused by smoking, emphasis has been placed on understanding why some people who are exposed to tobacco smoke develop disease while others do not. Also in the last few decades, the approaches used to explore the genetic basis of disease have evolved from family and linkage studies to genome-wide association studies (GWAS) (Wellcome Trust Case Control Consortium 2007). The GWAS approach involves comparing the distribution of markers (single nucleotide polymorphisms) across the genome between (a) people affected by the disease of interest and (b) a control population. To date, however, even though hundreds of thousands of markers across the genome have been examined, few promising associations have been found (Visscher et al. 2012), but work is in progress to further explore the GWAS-identified markers in greater depth (U.S. Department of Health and Human Services [USDHHS] 2010).

During the 50-year period reviewed in this report, there have been substantial changes in disease patterns in the United States. Figure 4.1 shows the rates for mortality for selected major diseases across the twentieth century, and Figure 4.2 shows the rates for all-cause mortality. Although the time spans covered differ for the various causes of death because of changes in coding used in the *International Classification of Diseases* and in the availability of data, major patterns are evident. These include the substantial decline in all-cause mortality (Figure 4.2) and the sharp drop in infectious disease mortality (Figure 4.1), both long antedating the general availability of modern antibiotics at mid-century. The rising mortality from lung cancer and cardiovascular disease that triggered numerous epidemiologic inquiries is also evident in Figure 4.1. In the later decades of the time period, rates for coronary heart disease mortality declined sharply, while lung cancer mortality in men reached a plateau and then began to decline around 1990. In contrast, lung cancer mortality in women rose, reaching a plateau by the century's end. Mortality from COPD, variably described across the century with labels including chronic bronchitis and

Figure 4.4   Mortality rates from selected cancers among women in the United States, 1930–2008[a]
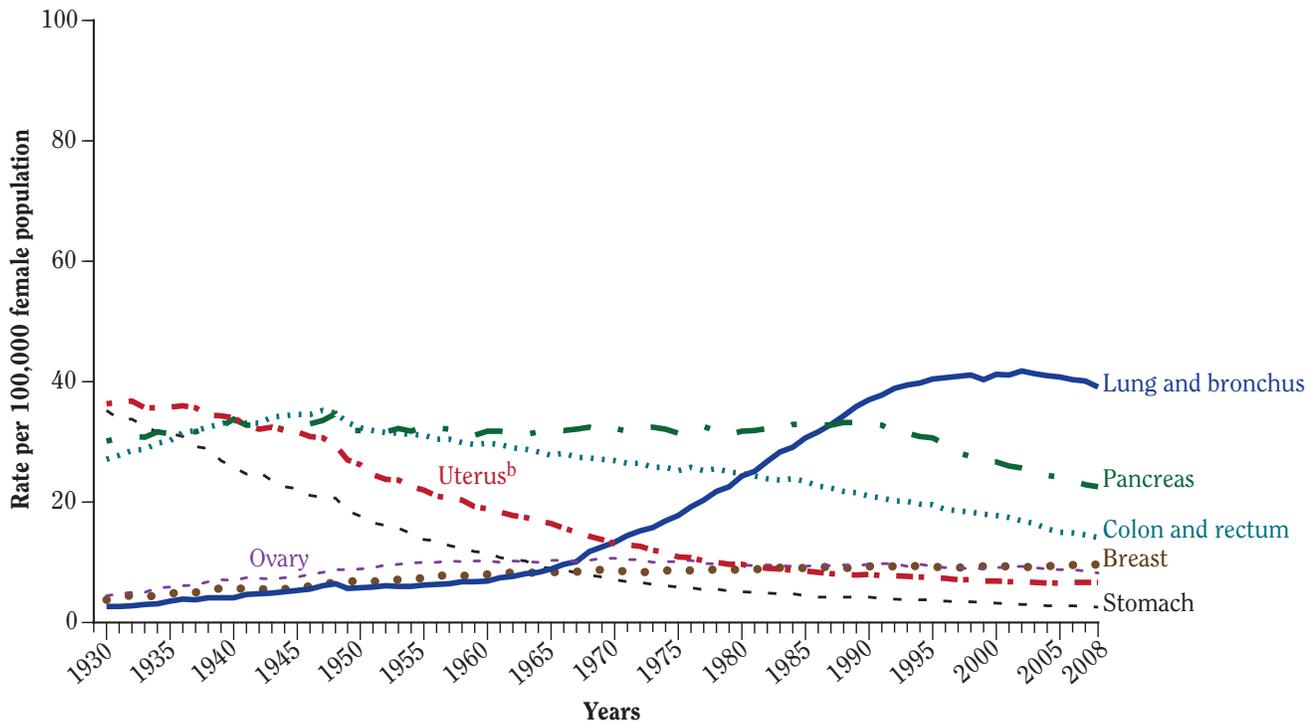
Source: Surveillance, Epidemiology, and End Results Program 2013.
Note: Due to changes in *International Classification of Diseases* coding, numerator information has changed over time. Rates for cancer of the liver, lung and bronchus, and colon and rectum are affected by these coding changes.
[a]Per 100,000, age-adjusted to the 2000 U.S. standard population.
[b]Uterus refers to uterine cervix and uterine corpus combined.

emphysema, has risen progressively, even as death rates for other major diseases, such as cardiovascular disease and lung cancer caused by smoking have declined (Petty 2006; Kim and Criner 2013).

Figures 4.3 and 4.4, spanning 1930–2008, provide further detail on mortality rates for cancer in men and women. For both genders, the rise of lung cancer to become the leading cause of cancer death is evident. Stomach cancer, once the leading cause of cancer death in men and second among women in 1930, dropped so far as to eventually rank last among the seven cancers portrayed in Figures 4.3 and 4.4. Also during the 1930–2008 period, the uterine cancer mortality rate for women declined steeply. In addition, among women the mortality rate for lung cancer surpassed that for breast cancer in the 1980s and continued to rise to a plateau as breast cancer mortality declined. The mortality rate for pancreatic cancer rose slowly between 1930–2008 for both men and women. Although many factors have driven these changing patterns of disease, the patterns reflect, in part, the rise and fall of the prevalence of cigarette smoking across the twentieth century (USDHHS 2004; U.S. Burden of Disease

Collaborators 2013). Tobacco control measures, driven by the emerging findings on the health consequences of tobacco smoking, have been a key determinant of changes in these rates.

This chapter reviews the evolution of the conclusions in the Surgeon General's reports with regard to the health consequences of smoking. The chapters following this one review the evidence for diseases and other adverse effects for which the evidence was previously found to be suggestive, including macular degeneration, colorectal cancer, breast cancer, prostate cancer, and male sexual dysfunction. Additionally, the chapters cover several health outcomes that have not been comprehensively addressed in previous Surgeon General's reports, including general effects on the immune system and the development of several diseases in which the immune system plays a key role, such as tuberculosis, diabetes, rheumatoid arthritis, and systemic lupus erythematosus. The reviews extend to active smoking and exposure to secondhand smoke, as appropriate. New reviews in Chapter 8 cover the relationship between exposure to secondhand smoke and stroke and the potential that smokefree policies will reduce

the incidence of cardiovascular events. For lung cancer, COPD, and cardiovascular diseases—well-established major consequences of cigarette smoking—perspectives are provided on the most critical issues relative to smoking in the etiology of these diseases. Several chapters address general and nonspecific consequences of smoking tobacco. The clinically significant topic of smoking and outcomes following the diagnosis of cancer is covered for

the first time, including the impact of smoking on treatment outcomes for cancer sites that have not been causally related to smoking. Chapter 11 addresses general morbidity and all-cause mortality, and updated estimates of the burden of smoking-attributable mortality and morbidity and of the direct and indirect costs of smoking are provided in Chapter 12.

Evolution of Conclusions on Cigarette Smoking and Exposure to Secondhand Smoke as a Cause of Disease

During the past 50 years, both the number and strength of the conclusions on active smoking and exposure to secondhand smoke as a cause of disease and other adverse health effects have increased markedly, moving from the two specific causal conclusions on lung cancer in males and on chronic bronchitis that were drawn in the 1964 report to numerous other conclusions that span most organs and now include exposure to secondhand smoke. Tables 4.1–4.5 address the evolution of the conclusions on active smoking, listing the report in which a particular health consequence was first mentioned; the strongest conclusion(s) reached before the 2004 report, *The Health Consequences of Smoking* (in which the classification of the strength of evidence was standardized); the conclusion(s) of the 2004 report; and any subsequent conclusions. The changes in the conclusions over time are characterized in this fashion because of the variable terminology used before the 2004 report (USDHHS 2004). Tables 4.6–4.10 provide a similar listing for exposure to secondhand smoke.

Although these conclusions relate primarily to specific diseases and other adverse health effects, the Surgeon General's reports have also tracked the evolution of the understanding of the pathogenesis and adverse health effects of these diseases and conditions. This deepening understanding has supported reaching stronger conclusions on causation. The 2010 report, *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease*, provides conclusions specific to this topic (USDHHS 2010).

Active Cigarette Smoking

Table 4.11 provides the conclusions formally adopted by the Advisory Committee to the Surgeon General in the

1964 report. The language ranges widely in describing the findings, from the clear conclusion that smoking causes lung cancer in men to the characterizations of the uncertainty and limitations of the evidence for some diseases. In most cases, the conclusions provide summary descriptions of the state of the evidence as well. The lack of knowledge of the mechanism(s) underlying the association of smoking with birth weight is mentioned.

In Table 4.1, which deals with active smoking and cancer, there has been consistency over time in the nomenclature so that interpretation of the changes in conclusions is not complicated by shifting terminology. With the exception of stomach cancer, causal conclusions were reached within the next two decades for cancer sites other than the lung that were mentioned in the 1964 report (i.e., oral cancer, laryngeal cancer, esophageal cancer, stomach cancer, and cancer of the urinary bladder) (U.S. Department of Health, Education, and Welfare [USDHEW] 1964). The 1982 report, *Health Consequences of Smoking – Cancer*, which focused on cancer, identified smoking as a contributory factor for pancreatic cancer and kidney cancer (USDHHS 1982). The list of cancers causally linked to active smoking lengthened with the 2004 report, which added cervical cancer and acute myeloid leukemia (USDHHS 2004). That report found the evidence on causation to be suggestive for breast cancer, colorectal cancer, and liver cancer. For prostate cancer, the evidence overall was not suggestive of a causal relationship.

For cardiovascular diseases (Table 4.2), the trends in the conclusions reflect the advancing understanding of the pathogenesis of these diseases and their common mechanistic basis (see Chapter 8 "Cardiovascular Diseases"). The 1964 report commented on the higher death rates from coronary artery disease among smokers compared with nonsmokers, but it expressed uncertainty with regard to the causal significance of the association

(USDHEW 1964). The conclusions on cardiovascular diseases strengthened throughout the next several decades. The 1979 report, *Smoking and Health*, offered a causal conclusion on coronary heart disease, but one that was introduced by the phrase "In summary, for the purposes of preventive medicine …" (USDHEW 1979, p. 1-15). This apparently cautious phrasing may have been reflective of the preventive implications of the causal conclusion, however, and not an indication that there was some doubt about the statement. Later, the 2004 report found the evidence to be sufficient to infer causation for abdominal aortic aneurysm, atherosclerosis and peripheral vascular disease, cerebrovascular disease, and coronary heart disease (Table 4.2) (USDHHS 2004).

The conclusions on respiratory diseases over the years (Table 4.3) have addressed COPD, variably designated, as well as the respiratory symptoms caused by smoking and its reduction of lung function which, if sustained, leads to COPD. The 1964 report concluded that "Cigarette smoking is the most important of the causes of chronic bronchitis in the United States, and increases the risk of dying from chronic bronchitis" (USDHEW 1964, p. 302). Although chronic bronchitis is the term long used for chronic cough and sputum production, at the time it was also used to refer to what is now called COPD. The 1984 report, *Health Consequences of Smoking: Chronic Obstructive Lung Disease*, which focused on the respiratory consequences of smoking, classified cigarette smoking as "… the major cause of COLD [chronic obstructive lung disease] morbidity in the United States…" (USDHHS 1984, p. 9). The 2004 report used the term COPD, finding the evidence to be sufficient to infer a causal relationship between smoking and both COPD morbidity and mortality (USDHHS 2004). The Surgeon General's reports have also addressed asthma, influenza, and pneumonia.

The effects of smoking on reproductive health (Table 4.4) have been addressed since the 1964 report, covering an increasing number and diversity of topics as the multiple adverse effects of smoking on reproductive health were identified. In fact, the 1964 report considered only birth weight and devoted just one page to the topic, citing just five retrospective and two prospective studies (USDHEW 1964). Over time, the effects of smoking have been found to extend from fertility to pregnancy and its outcome as well as the subsequent development of the child. There has also been substantial advancement in the understanding of how smoking affects reproductive health, the health of the fetus, and neurodevelopment as summarized in the 2010 report (USDHHS 2010). Male sexual functioning, not directly mentioned in the 1964 report, was covered extensively in the 2004 report (USDHHS 2004), and a causal conclusion on the relationship between smoking

and male sexual dysfunction has now been reached in this 2014 report.

Numerous other diseases and adverse consequences of smoking have been addressed in the reports of the Surgeon General (Table 4.5). These have included dental diseases, cataract and macular degeneration, peptic ulcer disease, fractures and osteoporosis, and diabetes. Nonspecific consequences of smoking have also been considered. All-cause mortality was covered in the 1964 report, but a specific conclusion was not offered. Several subsequent reports identified smoking as the leading cause of avoidable premature mortality (Table 4.12). The 2004 report assembled a wide range of evidence on nonspecific consequences of smoking, such as absenteeism and postoperative complications, with the report concluding that smoking caused "diminished health status" (Table 4.5), based on a review of a wide range of evidence (USDHHS 2004). The report's conclusion stated that diminished health status may manifest as "… increased absenteeism from work and increased use of medical care services" (USDHHS 2004, p. 29).

Exposure to Secondhand Smoke

The topic of secondhand smoke was first considered in the 1972 Surgeon General's report, *Health Consequences of Smoking*, in a chapter titled "Public Exposure to Air Pollution from Tobacco Smoke" (USDHEW 1972). The involuntary inhalation of tobacco smoke by nonsmokers has been referred to in the Surgeon General's reports as involuntary smoking or passive smoking. The smoke inhaled has been called secondhand smoke or environmental tobacco smoke. This chapter in the 1972 report reviewed the accumulating evidence on levels of air pollutants, such as carbon monoxide, in indoor environments where people were smoking. The report concluded that "An atmosphere contaminated with tobacco smoke can contribute to the discomfort of many individuals" (USDHEW 1972, p. 7). The 1982 report, which had a chapter on the relationship between exposure to secondhand smoke and lung cancer (USDHHS 1982), reviewed the findings of three epidemiologic studies, but it did not offer a conclusion, while noting the limited evidence available. The 1986 report, *The Health Consequences of Involuntary Smoking*, was the first to have involuntary smoking as its topic, and the 2006 report followed suit, as it was titled *The Health Consequences of Involuntary Exposure to Tobacco Smoke* (USDHHS 1986, 2006).

The 1984 Surgeon General's report addressed COPD, and the report's chapter on passive smoking addressed the

respiratory consequences, other than cancer, of exposure to secondhand smoke. By that time, a substantial body of literature had accumulated on the respiratory consequences of exposure to secondhand smoke in children, and there was a more limited body of evidence related to adults. Notably, the conclusions in the 1984 report were overall summaries of the evidence and not statements as to the strength of the evidence for causation.

Exposure to secondhand smoke and its effects was the sole topic of the 1986 report. With regard to the effects of parental smoking on child respiratory health, that report addressed the range of outcomes considered in the 1984 report, comprehensively reviewed the evidence, and offered summary conclusions, but it did not provide statements on the strength of evidence for causation. The 1986 report did, however, comprehensively cover the relationship of lung cancer to exposure to secondhand smoke and concluded that involuntary smoking caused lung cancer in never smokers. This causal conclusion was repeated in the 2006 report, which also addressed exposure to secondhand smoke. That report also found sufficient evidence to infer causation for the principal adverse effects considered in the earlier reports. The 2006 report covered childhood cancers as well, but the evidence was not judged to be sufficient to infer a causal relationship for any of the malignancies considered.

The 2001 report, *Women and Smoking,* had considered the relationship between exposure to secondhand smoke and breast cancer, and that topic was discussed in the 2006 report as well. Other cancers considered in relation to exposure to secondhand smoke included nasal sinus cavity and nasopharyngeal carcinoma (2006), and cervical cancer (2006); the conclusions drawn were that the evidence was either suggestive (breast cancer and nasal sinus cavity) or inadequate (nasopharyngeal carcinoma and cervical cancer). Reports after 2006 expanded the topics related to exposure to secondhand smoke and childhood health to include adverse effects on reproduction, risk for sudden infant death syndrome, and neurodevelopment.

The 1986 report did not cover exposure to secondhand smoke and cardiovascular diseases because only a few studies on that topic had been reported at that time. The 2001 report was the first to consider the topic, and found that the evidence did indicate a causal relationship. Finally, the 2006 report found that the evidence for a link between exposure to secondhand smoke and coronary heart disease was sufficient to infer a causal relationship, but it designated as suggestive the evidence for a similar link with atherosclerosis and cerebrovascular disease.

Summary

Over the 50 years that began with the seminal 1964 report, the conclusions of the Surgeon Generals' reports on smoking and health have evolved greatly, moving from the few causal associations set forth in the 1964 report to the inference of causal relationships between not only active smoking but also exposure to secondhand smoke and a wide range of diseases and other adverse health effects. The 2004 and 2006 reports provided comprehensive coverage of the evidence on active smoking and exposure to secondhand smoke, respectively, and the 2010 report addressed the mechanisms underlying the causal relationships described in these reports. The 2012 report, *Preventing Tobacco Use Among Youth and Young Adults*, provided additional coverage of the effects of smoking on the health of children, adolescents, and young adults, highlighting the linkages between early life events and subsequent risk for disease (USDHHS 2012).

Notably, this 2014 review extends the list of diseases and other adverse health effects caused by smoking and reaffirms the widespread consequences of smoking. In the 2004 report, it was noted that smoking affects nearly every organ of the body; the evidence in this report provides additional support for that finding.

Table 4.1   Conclusions from Surgeon General's report on active cigarette smoking and cancer

Disease	First mention and finding(s) in a Surgeon General's report (year)	Highest level conclusion(s) from subsequent Surgeon General's reports before 2004 (year)	Conclusion(s) from the 2004 Surgeon General's report	Additional or updated conclusion(s) from the 2014 Surgeon General's report
Bladder	"Available data suggest an association between cigarette smoking and urinary bladder cancer in the male but are not sufficient to support a judgment on the causal significance of this association." (1964, p. 225)	"Smoking is a cause of bladder cancer; cessation reduces risk by about 50 percent after only a few years, in comparison with continued smoking." (1990, p. 10)	"The evidence is sufficient to infer a causal relationship between smoking and … bladder cancer." (p. 26)	— —
Brain (adult)	____	— —	"The evidence is suggestive of no causal relationship between smoking cigarettes and brain cancer in men and women." (p. 26)	— —
Breast	"Thus, active smoking does not appear to appreciably affect breast cancer risk overall. However, several issues were not entirely resolved, including whether starting to smoke at an early age increases risk, whether certain subgroups defined by genetic polymorphisms are differentially affected by smoking, and whether ETS exposure affects risk." (2001, p. 217) "The totality of the evidence does not support an association between smoking and risk for breast cancer." (2001, p. 224)[a]	— —	"The evidence is suggestive of no causal relationship between active smoking and breast cancer." (p. 26)	"The evidence is sufficient to identify mechanisms by which cigarette smoking may cause breast cancer." "The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and breast cancer." (Chapter 6)
Cervical	"There are conflicting results in studies published to date on the existenc of a relationship between smoking and cervical cancer; further research is necessary to define whether an association exists and, if so, whether that association is direct or indirect." (1982, p. 8)	"Smoking has been consistently associated with an increased risk for cervical cancer. The extent to which this association is independent of human papillomavirus infection is uncertain." (2001, p. 224) "Smoking may be associated with an increased risk for vulvar cancer, but the extent to which the association is independent of human papillomavirus infection is uncertain." (2001, p. 224)	"The evidence is sufficient to infer a causal relationship between smoking and cervical cancer." (p. 26)	— —

Table 4.1   Continued

Disease	First mention and finding(s) in a Surgeon General's report (year)	Highest level conclusion(s) from subsequent Surgeon General's reports before 2004 (year)	Conclusion(s) from the 2004 Surgeon General's report	Additional or updated conclusion(s) from the 2014 Surgeon General's report
Colorectal	"Women who smoke may have increased risks for…colorectal cancer." (2001, p. 231	—	"The evidence is suggestive but not sufficient to infer a causal relationship between smoking and colorectal adenomatous polyps and colorectal cancer." (p. 26)	"The evidence is sufficient to infer a causal relationship between smoking and colorectal adenomatous polyps and colorectal cancer." (Chapter 6)
Endometrial	"Several studies have reported that endometrial cancer is less frequent among women who smoke cigarettes than among nonsmokers (Baron et al. 1986). Cigarette smoking exerts an antiestrogenic effect that may explain this inverse association. The public health significance of this association is limited because of the overall adverse impact of cigarette smoking on morbidity and mortality." (1989, p. 58)	"Current smoking is associated with a reduced risk for endometrial cancer, but the effect is probably limited to postmenopausal disease. The risk for this cancer among former smokers generally appears more similar to that of women who have never smoked." (2001, p. 224)	"The evidence is sufficient to infer that current smoking reduces the risk of endometrial cancer in postmenopausal women." (p. 26)	——
Esophageal	"The evidence on the tobacco-esophageal cancer relationship supports the belief that an association exists. However, the data are not adequate to decide whether the relationship is causal." (1964, p. 218)	"Cigarette smoking is a major cause of esophageal cancer in the United States." (1982, p. 7)	"The evidence is sufficient to infer a causal relationship between smoking and cancers of the esophagus." (p. 26)	——
Kidney	"Cigarette smoking is a contributory factor in the development of kidney cancer in the United States. The term 'contributory factor' by no means excludes the possibility of a causal role for smoking in cancers of this site." (1982, p. 7)	"There is a positive association between smoking and kidney cancer, with relative risks ranging from 1 to more than 5. The increased risk of kidney cancer due to cigarette smoking is found for both males and females, and there is a dose-response relationship as measured by the number of cigarettes smoked per day." (1989, p. 56)	"The evidence is sufficient to infer a causal relationship between smoking and renal cell, [and] renal pelvis… cancers." (p. 26)	——

Table 4.1   Continued

Disease	First mention and finding(s) in a Surgeon General's report (year)	Highest level conclusion(s) from subsequent Surgeon General's reports before 2004 (year)	Conclusion(s) from the 2004 Surgeon General's report	Additional or updated conclusion(s) from the 2014 Surgeon General's report
Laryngeal	"Evaluation of the evidence leads to the judgment that cigarette smoking is a significant factor in the causation of laryngeal cancer in the male." (1964, p.212)	"Cigarette smoking is causally associated with cancer of the lung, larynx, oral cavity, and esophagus in women as well as in men…." (1980, p.126)	"The evidence is sufficient to infer a causal relationship between smoking and cancer of the larynx." (p. 25)	— —
Leukemia (acute)	"Leukemia has recently been implicated as a smoking-related disease … but this observation has not been consistent." (1990, p. 176)	"Smoking may be associated with an increased risk for acute myeloid leukemia among women but does not appear to be associated with other lymphoproliferative or hematologic cancers." (2001, p. 231)	"The evidence is sufficient to infer a causal relationship between smoking and acute myeloid leukemia." (p. 26)	— —
Liver	"Primary hepatocellular cancer has been associated with smoking in a number of recent studies."(1990,p. 176)	"Women who smoke may have increased risks for liver cancer…." (2001, p. 231)	"The evidence is suggestive but not sufficient to infer a causal relationship between smoking and liver cancer." (p. 26)	"The evidence is sufficient to infer a causal relationship between smoking and hepatocellular carcinoma." (Chapter 6)

Table 4.1   Continued

Disease	First mention and finding(s) in a Surgeon General's report (year)	Highest level conclusion(s) from subsequent Surgeon General's reports before 2004 (year)	Conclusion(s) from the 2004 Surgeon General's report	Additional or updated conclusion(s) from the 2014 Surgeon General's report
Lung	"Cigarette smoking is causally related to lung cancer in men; the magnitude of the effect of cigarette smoking far outweighs all other factors. The data for women, though less extensive, point in the same direction." (1964, p. 196)	"Additional epidemiological, pathological, and experimental data not only confirm the conclusion of the Surgeon General's 1964 Report regarding lung cancer in men but strengthen the causal relationship of smoking to lung cancer in women." (1967, p. 36) "Cigarette smoking is causally related to lung cancer in both men and women." (1979, p. 1-16) "Cigarette smoking is the major cause of lung cancer in the United States." (1982, p. 5) "Cigarette smoking is the major cause of lung cancer among women. About 90 percent of all lung cancer deaths among U.S. women smokers are attributable to smoking." (2001, p. 13)	"The evidence is sufficient to infer a causal relationship between smoking and lung cancer." (p. 25)	"The evidence is sufficient to conclude that the risk of developing adenocarcinoma of the lung from cigarette smoking has increased since the 1960s." "The evidence is sufficient to conclude that the increased risk of adenocarcinoma of the lung in smokers results from changes in the design and composition of cigarettes since the 1950s." "The evidence is not sufficient to specify which design changes are responsible for the increased risk of adenocarcinoma, but there is suggestive evidence that ventilated filters and increased levels of tobacco-specific nitrosamines have played a role." "The evidence shows that the decline of squamous carcinoma follows the trend of declining smoking prevalence." (Chapter 6)

Table 4.1   **Continued**

Disease	First mention and finding(s) in a Surgeon General's report (year)	Highest level conclusion(s) from subsequent Surgeon General's reports before 2004 (year)	Conclusion(s) from the 2004 Surgeon General's report	Additional or updated conclusion(s) from the 2014 Surgeon General's report
Oral cavity and pharyngeal	"The causal relationship of the smoking of pipes to the development of cancer of the lip appears to be established." (1964, p. 204) "Although there are suggestions of relationships between cancer of other specific sites of the oral cavity and the several forms of tobacco use, their causal implications cannot at present be stated." (1964, p. 205)	"Epidemiological studies indicate that smoking is a significant causal factor in the development of oral cancer. The risk increases with the number of cigarettes smoked per day." (1979, p. 1-17) "Cigarette smoking is a major cause of cancers of the oral cavity in the United States." (1982, p. 6)	"The evidence is sufficient to infer a causal relationship between smoking and cancers of the oral cavity and pharynx." (p. 25)	— —
Ovarian	"Smoking does not appear to be associated with risk for ovarian cancer." (2001, p. 224)	— —	"The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and ovarian cancer." (p. 26)	— —
Pancreatic	"Cigarette smoking is a contributory factor in the development of pancreatic cancer in the United States. This relationship is not as strong as that noted for the association between smoking and cancers of the lung, larynx, oral cavity, and esophagus. The term 'contributory factor' by no means excludes the possibility of a causal role for smoking in cancers of this site." (1982, p. 7)	"Smoking cessation reduces the risk of pancreatic cancer, compared with continued smoking, although this reduction in risk may only be measurable after 10 years of abstinence." (1990, p. 10)	"The evidence is sufficient to infer a causal relationship between smoking and pancreatic cancer." (p. 26)	— —

Table 4.1 **Continued**

Disease	First mention and finding(s) in a Surgeon General's report (year)	Highest level conclusion(s) from subsequent Surgeon General's reports before 2004 (year)	Conclusion(s) from the 2004 Surgeon General's report	Additional or updated conclusion(s) from the 2014 Surgeon General's report
Prostate cancer	— —	— —	"The evidence is suggestive of no causal relationship between smoking and risk for prostate cancer." (p. 26)	"The evidence is suggestive of no causal relationship between smoking and the risk of incident prostate cancer." "The evidence is suggestive of a higher risk of death from prostate cancer in smokers than in nonsmokers." "In men who have prostate cancer, the evidence is suggestive of a higher risk of advanced-stage disease and less well-differentiated cancer in smokers than in nonsmokers, and—independent of stage and histologic grade—a higher risk of disease progression." (Chapter 6)
Stomach	"No relationship has been established between tobacco use and stomach cancer." (1964, p. 229)	"Data on smoking and cancer of the stomach … are unclear." (2001, p. 231)	"The evidence is sufficient to infer a causal relationship between smoking and gastric cancers." (p. 26)	— —

Note: **ETS** = environmental tobacco smoke.
[a]Refers to a general conclusion that was reached for breast cancer.

Table 4.2 **Conclusions from Surgeon General's report on active cigarette smoking and cardiovascular diseases**

Disease	First mention and finding(s) in a Surgeon General's report (year)	Highest level conclusion(s) from subsequent Surgeon General's reports before 2004 (year)	Conclusion(s) from the 2004 Surgeon General's report	Additional or updated conclusion(s) from the 2012/2014 Surgeon General's report
Abdominal aortic aneurysm	"Cigarette smoking is a strong risk factor for atherosclerotic aortic aneurysm." (1979, p. 4-56)	"Death from rupture of an atherosclerotic abdominal aneurysm is more common in cigarette smokers than in nonsmokers." (1983, p. 195)	"The evidence is sufficient to infer a causal relationship between smoking and abdominal aortic aneurysm." (p. 27)	"The evidence is sufficient to conclude that there is a causal relationship between active smoking in adolescence and young adulthood and early abdominal aortic atherosclerosis in young adults." (2012, p. 111)
Atherosclerosis/ peripheral vascular disease	"Autopsy studies suggest that cigarette smoking is associated with a significant increase in the atherosclerosis of the aorta and coronary arteries." (1969, p. 4)	"Cigarette smoking is the most powerful risk factor predisposing to atherosclerotic peripheral vascular disease." (1983, p. 8)	"The evidence is sufficient to infer a causal relationship between smoking and subclinical atherosclerosis." (p. 26)	"The evidence is suggestive but not sufficient to conclude that there is a causal relationship between smoking in adolescence and young adulthood and coronary artery atherosclerosis in adulthood." (2012, p. 111)
Cerebrovascular disease	"Additional evidence strengthens the association between cigarette smoking and cerebrovascular disease, and suggests that some of the pathogenetic [*sic*] considerations pertinent to coronary heart disease may also apply to cerebrovascular disease." (1967, p. 28)	"Cigarette smoking is a major cause of cerebrovascular disease (stroke), the third leading cause of death in the United States." (1989, p. 12)	"The evidence is sufficient to infer a causal relationship between smoking and stroke." (p. 27)	— —
Coronary heart disease	"Male cigarette smokers have a higher death rate from coronary artery disease than non-smoking males, but it is not clear that the association has causal significance." (1964, p. 327)	"In summary, for the purposes of preventive medicine, it can be concluded that smoking is causally related to coronary heart disease for both men and women in the United States." (1979, p. 1-15)	"The evidence is sufficient to infer a causal relationship between smoking and coronary heart disease." (p. 27)	— —

Table 4.3 **Conclusions from Surgeon General's report on active cigarette smoking and respiratory diseases**

Disease	First mention and finding(s) in a Surgeon General's report (year)	Highest level conclusion(s) from subsequent Surgeon General's reports before 2004 (year)	Conclusion(s) from the 2004 Surgeon General's report	Additional or updated conclusion(s) from the 2012/2014 Surgeon General's report
Asthma	"Cigarette smoking does not appear to cause asthma." (1964 p.302)	— —	"The evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and asthma in adults." (p. 28)	"The evidence is sufficient to conclude that there is a causal relationship between active smoking and wheezing severe enough to be diagnosed as asthma in susceptible child and adolescent populations." (2012, p. 111)
			"The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and increased nonspecific bronchial hyperresponsiveness." (p. 28)	"The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and incidence of asthma in adolescents." (2014, Chapter 7)
				"The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and exacerbation of asthma among children and adolescents." (2014, Chapter 7)
				"The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and the incidence of asthma in adults." (2014, Chapter 7)
			"The evidence is sufficient to infer a causal relationship between active smoking and poor asthma control." (p. 28)	"The evidence is sufficient to infer a causal relationship between active smoking and exacerbation of asthma in adults." (2014, Chapter 7)

Table 4.3   Continued

Disease	First mention and finding(s) in a Surgeon General's report (year)	Highest level conclusion(s) from subsequent Surgeon General's reports before 2004 (year)	Conclusion(s) from the 2004 Surgeon General's report	Additional or updated conclusion(s) from the 2012/2014 Surgeon General's report
COPD (Formerly designated as chronic bronchitis; emphysema; COLD; chronic obstructive bronchopulmonary disease)	"Cigarette smoking is the most important of the causes of chronic bronchitis in the United States, and increases the risk of dying from chronic bronchitis." (1964, p. 302) "A relationship exists between pulmonary emphysema and cigarette smoking but it has not been established that the relationship is causal. The smoking of cigarettes is associated with an increased risk of dying from pulmonary emphysema." (1964, p. 302)	"Cigarette smoking is the major cause of COLD … morbidity in the United States; 80 to 90 percent of COLD in the United States is attributable to cigarette smoking." (1984, p. 9) "Cigarette smoking is a primary cause of COPD among women, and the risk increases with the amount and duration of smoking. Approximately 90 percent of mortality from COPD among women in the United States can be attributed to cigarette smoking." (2001, p. 14)	"The evidence is sufficient to infer a causal relationship between active smoking and chronic obstructive pulmonary disease morbidity and mortality." (p. 28)	"The evidence is sufficient to infer that smoking is the dominant cause of chronic obstructive pulmonary disease (COPD) in men and women in the United States. Smoking causes all elements of the COPD phenotype, including emphysema and damage to the airways of the lung." (2014, Chapter 7) "Chronic obstructive pulmonary disease mortality has increased dramatically in men and women since the 1964 Surgeon General's report. The number of women dying from COPD now surpasses the number of men." (2014, Chapter 7) "The evidence is suggestive but not sufficient to infer that women are more susceptible to develop severe chronic obstructive pulmonary disease at younger ages." (2014, Chapter 7) "The evidence is sufficient to infer that severe α-1-antitrypsin deficiency and cutis laxa are genetic causes of chronic obstructive pulmonary disease." (2014, Chapter 7)

Table 4.3   **Continued**

Disease	First mention and finding(s) in a Surgeon General's report (year)	Highest level conclusion(s) from subsequent Surgeon General's reports before 2004 (year)	Conclusion(s) from the 2004 Surgeon General's report	Additional or updated conclusion(s) from the 2012/2014 Surgeon General's report
Chronic respiratory symptoms (cough, phlegm, wheeze, dyspnea, etc.)	"Cough, sputum production, or the two combined are consistently more frequent among cigarette smokers than among non smokers." (1964, p. 302)	"Cigarette smokers have an increased frequency of respiratory symptoms, and at least two of them, cough and sputum production, are dose-related." (1979, p. 1-18)	"The evidence is sufficient to infer a causal relationship between active smoking and all major respiratory symptoms among adults, including coughing, phlegm, wheezing, and dyspnea." (p. 28)	____
Influenza, pneumonia, infections, and acute respiratory illnesses	"Although death certification shows that cigarette smokers have a moderately increased risk of death from influenza and pneumonia, an association of cigarette smoking and infectious diseases is not otherwise substantiated." (1964, p. 302)	"Smoking cessation reduces rates of respiratory symptoms such as cough, sputum production, and wheezing,and respiratory infections such as bronchitis and pneumonia, compared with continued smoking." (1990, p. 11)	"The evidence is sufficient to infer a causal relationship between smoking and acute respiratory illnesses, including pneumonia, in persons without underlying smoking-related chronic obstructive lung disease." (p. 27) "The evidence is suggestive but not sufficent to infer a causal relationship between smoking and acute respiratory infections among persons with preexisting chronic obstructie pulmonary disease." (p. 27)	____

Table 4.3 **Continued**

Disease	First mention and finding(s) in a Surgeon General's report (year)	Highest level conclusion(s) from subsequent Surgeon General's reports before 2004 (year)	Conclusion(s) from the 2004 Surgeon General's report	Additional or updated conclusion(s) from the 2012/2014 Surgeon General's report
Tuberculosis	— —	— —	— —	"The evidence is sufficient to infer a causal relationship between smoking and an increased risk of *Mycobacterium tuberculosis* disease." (2014, Chapter 7)

"The evidence is sufficient to infer a causal relationship between smoking and mortality due to tuberculosis." (2014, Chapter 7)

"The evidence is suggestive of a causal relationship between smoking and the risk of recurrent tuberculosis disease." (2014, Chapter 7)

"The evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and the risk of tuberculosis infection." (2014, Chapter 7) |
| Lung function level | "Cigarette smoking is associated with a reduction in ventilatory function. Among males, cigarette smokers have a greater prevalence of breathlessness than non-smokers." (1964, p. 302) | "Cigarette smoking accelerates the age-related decline in lung function that occurs among never smokers. With sustained abstinence from smoking, the rate of decline in pulmonary function among former smokers returns to that of never smokers." (1990, p. 11) | "The evidence is sufficient to infer a causal relationship between active smoking in adulthood and a premature onset of and an accelerated age-related decline in lung function." (p. 27)

"The evidence is sufficient to infer a causal relationship between sustained cessation from smoking and a return of the rate of decline in pulmonary function to that of persons who had never smoked." (p. 27) | "The evidence is sufficient to conclude that there is a causal relationship between active smoking and both reduced lung function and impaired lung growth during childhood and adolescence." (2012, p. 111) |

Table 4.3   Continued

Disease	First mention and finding(s) in a Surgeon General's report (year)	Highest level conclusion(s) from subsequent Surgeon General's reports before 2004 (year)	Conclusion(s) from the 2004 Surgeon General's report	Additional or updated conclusion(s) from the 2012/2014 Surgeon General's report
Respiratory effects due to active smoking during childhood and adolescence	— —	"Cigarette smoking during childhood and adolescence produces significant health problems among young people, including cough and phlegm production, an increased number and severity of respiratory illnesses, decreased physical fitness, an unfavorable lipid profile, and potential retardation in the rate of lung growth and the level of maximum lung function." (1994, p. 41)	"The evidence is sufficient to infer a causal relationship between active smoking and impaired lung growth during childhood and adolescence." (p. 27) "The evidence is sufficient to infer a causal relationship between active smoking and the early onset of lung function decline during late adolescence and early adulthood." (p. 27) "The evidence is sufficient to infer a causal relationship between active smoking and respiratory symptoms in children and adolescents, including coughing, phlegm, wheezing, and dyspnea." (p. 27) "The evidence is sufficient to infer a causal relationship between active smoking and asthma-related symptoms (i.e., wheezing) in childhood and adolescence." (p. 27)	— —

Note: **COLD** = chronic obstuctive lung disease; **COPD** = chronic obstructive pulmonary disease.

Table 4.4 **Conclusions from Surgeon General's report on active cigarette smoking and adverse reproductive outcomes or childhood neurobehavioral disorders**

Disease	First mention and finding(s) in a Surgeon General's report (year)	Highest level conclusion(s) from subsequent Surgeon General's reports before 2004 (year)	Conclusion(s) from the 2004 Surgeon General's report	Additional or updated conclusion(s) from the 2014 Surgeon General's report
Child physical, behavioral, and cognitive development	"According to studies of long-term growth and development, smoking during pregnancy may affect physical growth, mental development, and behavioral characteristics of children at least up to the age of 11." (1979, p. 1-21)	"Maternal smoking during pregnancy may adversely affect the child's long-term growth, intellectual development, and behavioral characteristics." (1980, p. 11)	"The evidence is inadequate to infer the presence or absence of a causal relationship between maternal smoking and physical growth and neurocognitive development of children." (p. 28)	"The evidence is suggestive but not sufficient to infer a causal relationship between maternal prenatal smoking and disruptive behavioral disorders, and ADHD in particular, among children." "The evidence is insufficient to infer the presence or absence of a causal relationship between maternal prenatal smoking and anxiety and depression in children." "The evidence is insufficient to infer the presence or absence of a causal relationship between maternal prenatal smoking and Tourette syndrome." "The evidence is insufficient to infer the presence or absence of a causal relationship between maternal prenatal smoking and schizophrenia in her offspring." "The evidence is insufficient to infer the presence or absence of a causal relationship between maternal prenatal smoking and intellectual disability." (Chapter 9)

Table 4.4   Continued

Disease	First mention and finding(s) in a Surgeon General's report (year)	Highest level conclusion(s) from subsequent Surgeon General's reports before 2004 (year)	Conclusion(s) from the 2004 Surgeon General's report	Additional or updated conclusion(s) from the 2014 Surgeon General's report
Congenital malformations	"…no conclusions can be drawn about any relationship between maternal cigarette smoking and congenital malformations at the present time." (1973, p. 137)	"The accumulated evidence does not support a conclusion that maternal smoking increases the incidence of congenital malformations." (1979, p. 1-22) "There are insufficient data to support a judgment on whether maternal and/or paternal cigarette smoking increases the risk of congenital malformations." (1980, p. 11) "Smoking does not appear to affect the overall risk for congenital malformations." (2001, p. 307)	"The evidence is inadequate to infer the presence or absence of a causal relationship between maternal smoking and congenital malformations in general." (p. 28) "The evidence is suggestive but not sufficient to infer a causal relationship between maternal smoking and oral clefts." (p. 28)	"The evidence is sufficient to infer a causal relationship between maternal smoking in early pregnancy and orofacial clefts." "The evidence is suggestive but not sufficient to infer a causal relationship between maternal smoking in early pregnancy and clubfoot, gastroschisis, and atrial septal heart defects." (Chapter 9)
Fertility	"Studies in women and men suggest that cigarette smoking may impair fertility." (1980, p. 12)	"The available information suggests that current smoking is related to low sperm density. However, these data are limited." (1990, p. 405) "Women who smoke have increased risks for conception delay and for both primary and secondary infertility." (2001, p. 307)	"The evidence is sufficient to infer a causal relationship between smoking and reduced fertility in women." (p. 28) "The evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and sperm quality." (p. 28)	— —
Fetal death, stillbirths, and infant mortality	"…it appears that maternal smoking during pregnancy may be associated with an increased incidence of spontaneous abortion, stillbirth, and neonatal death and that this relationship may be most marked in the presence of other risk factors." (1969, p. 5)	"Cigarette smoking is now considered to be a probable cause of …increased infant mortality." (1989, p. 20) "The risk for perinatal mortality—both stillbirth and neonatal deaths—and the risk for sudden infant death syndrome (SIDS) are increased among the offspring of women who smoke during pregnancy." (2001, p. 307) "Women who smoke may have a modest increase in risks for… spontaneous abortion."(2001, p. 307)	— —	"The evidence is suggestive but not sufficient to infer a causal relationship between maternal active smoking and spontaneous abortion." (Chapter 9)

Table 4.4   **Continued**

Disease	First mention and finding(s) in a Surgeon General's report (year)	Highest level conclusion(s) from subsequent Surgeon General's reports before 2004 (year)	Conclusion(s) from the 2004 Surgeon General's report	Additional or updated conclusion(s) from the 2014 Surgeon General's report
Infant birth weight	"Women who smoke cigarettes during pregnancy tend to have babies of lower birth weight." (1964, p. 343)	"Infants born to women who smoke during pregnancy have a lower average birth weight…than infants born to women who do not smoke." (2001, p. 307) "Infants born to women who smoke during pregnancy …are more likely to be small for gestational age than are infants born to women who do not smoke." (2001, p. 307)	"The evidence is sufficient to infer a causal relationship between maternal active smoking and fetal growth restriction and low birth weight." (p. 28)	— —
Male sexual function	"…element of masculinity as indicated by external morphologic features"… "weakness of the masculine component is significantly more frequent in smokers than in nonsmokers, and most frequent in heavy smokers." (1964, pp. 383–4)	"In summary, the level of sexual activity does not appear to be affected by cigarette smoking. Cigarette smoking may be associated with impaired male sexual performance. …Because of limited and uncontrolled data, no conclusions can be drawn regarding sexual performance or PBI among former smokers." (1990, pp. 403–4)	"The evidence is suggestive but not sufficient to infer a causal relationship between smoking and erectile dysfunction." (p. 29)	"The evidence is sufficient to infer a causal relationship between smoking and erectile dysfunction." (Chapter 9)

Table 4.4   Continued

Disease	First mention and finding(s) in a Surgeon General's report (year)	Highest level conclusion(s) from subsequent Surgeon General's reports before 2004 (year)	Conclusion(s) from the 2004 Surgeon General's report	Additional or updated conclusion(s) from the 2014 Surgeon General's report
Pregnancy complications	"Maternal smoking increases the risk of fetal death through maternal complications such as abruptio placenta, placenta previa, antepartum hemorrhage, and prolonged rupture of membranes." (1979, p. 1-22)	"Smoking during pregnancy is associated with increased risks for preterm premature rupture of membranes, abrupio placentae, and placenta previa, and with a modest increase in risk for preterm delivery." (2001, p. 14) "Women who smoke may have a modest increase in risks for ectopic pregnancy and spontaneous abortion." (2001, p. 14) "Women who smoke during pregnancy have a decreased risk for preeclampsia." (2001, p. 14)	"The evidence is sufficient to infer a causal relationship between maternal active smoking and premature rupture of the membranes, placenta previa, and placental abruption." (p. 28) "The evidence is sufficient to infer a causal relationship between maternal active smoking and preterm delivery and shortened gestation." (p. 28) "The evidence is sufficient to infer a causal relationship between maternal active smoking and a reduced risk for preeclampsia." (p. 28) "The evidence is suggestive but not sufficient to infer a causal relationship between maternal active smoking and ectopic pregnancy." (p. 28) "The evidence is suggestive but not sufficient to infer a causal relationship between maternal active smoking and spontaneous abortion." (p. 28)	"The evidence is sufficient to infer a causal relationship between maternal active smoking and ectopic pregnancy." (Chapter 9)

Table 4.4   Continued

Disease	First mention and finding(s) in a Surgeon General's report (year)	Highest level conclusion(s) from subsequent Surgeon General's reports before 2004 (year)	Conclusion(s) from the 2004 Surgeon General's report	Additional or updated conclusion(s) from the 2014 Surgeon General's report
Respiratory effects in infants and children due to maternal active smoking	— —	"In utero exposure to maternal smoking is associated with reduced lung function among infants…." (2001, p. 14)	"The evidence is sufficient to infer a causal relationship between maternal smoking during pregnancy and a reduction of lung function in infants." (p. 27) "The evidence is suggestive but not sufficient to infer a causal relationship between maternal smoking during pregnancy and an increase in the frequency of lower respiratory tract illnesses during infancy." (p. 27) "The evidence is suggestive but not sufficient to infer a causal relationship between maternal smoking during pregnancy and an increased risk for impaired lung function in childhood and adulthood." (p. 27)	— —
Sudden infant death syndrome (SIDS)	"Smoking by pregnant women contributes to the risk of their infants being victims of the "sudden infant death syndrome." (1979, p. 1-22)	"… the risk for sudden infant death syndrome (SIDS) are increased among the offspring of women who smoke during pregnancy." (2001, p. 307)	"The evidence is sufficient to infer a causal relationship between sudden infant death syndrome and maternal smoking during and after pregnancy." (p. 28)	— —

Note: **ADHD** = attention deficit hyperactivity disorder; **PBI** = penile-brachial index.

Table 4.5	**Conclusions from Surgeon General's report on active cigarette smoking and other adverse health effects**			
Disease	**First mention and finding(s) in a Surgeon General's report (year)**	**Highest level conclusion(s) from subsequent Surgeon General's reports before 2004 (year)**	**Conclusion(s) from the 2004 Surgeon General's report**	**Additional or updated conclusion(s) from the 2014 Surgeon General's report**
Accidents	"Smoking is associated with accidental deaths from fires in the home." (1964, p. 39) "No conclusive information is available on the effects of smoking on traffic accidents." (1964, p. 39)	— —	— —	— —
Dental diseases	"Tobacco use, excessive alcohol use, and inappropriate dietary practices contribute to many diseases and disorders. In particular, tobacco use is a risk factor for oral cavity and pharyngeal cancers, periodontal diseases, candidiasis, and dental caries, among other diseases." (2000, p. 6)[a]	— —	"The evidence is sufficient to infer a causal relationship between smoking and periodontitis." (p. 29) "The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and coronal dental caries." (p. 29) "The evidence is suggestive but not sufficient to infer a causal relationship between smoking and root-surface caries." (p. 29)	"The evidence is suggestive but not sufficient to infer a causal relationship between active cigarette smoking and dental caries." "The evidence is suggestive but not sufficient to infer a causal relationship between cigarette smoking and failure of dental implants." (Chapter 10)
Diabetes mellitus	— —	"Smoking appears to affect glucose regulation and related metabolic processes, but conflicting data exist on the relationship of smoking and the development of type 2 diabetes mellitus and gestational diabetes among women." (2001, p. 14)	— —	"The evidence is sufficient to infer that cigarette smoking is a cause of diabetes." "The risk of developing diabetes is 30–40% higher for active smokers than nonsmokers." "There is a positive dose-response relationship between the number of cigarettes smoked and the risk of developing diabetes." (Chapter 10)

Table 4.5   Continued

Disease	First mention and finding(s) in a Surgeon General's report (year)	Highest level conclusion(s) from subsequent Surgeon General's reports before 2004 (year)	Conclusion(s) from the 2004 Surgeon General's report	Additional or updated conclusion(s) from the 2014 Surgeon General's report
Diminished health status	— —	— —	"The evidence is sufficient to infer a causal relationship between smoking and diminished health status that may manifest as increased absenteeism from work and increased use of medical care services." (p. 29) "The evidence is sufficient to infer a causal relationship between smoking and increased risks for adverse surgical outcomes related to wound healing and respiratory complications." (p. 29)	— —
Eye diseases	"Tobacco amblyopia had been related to pipe and cigar smoking by clinical impressions. The association has not been substantiated by epidemiological or experimental studies." (1964, p. 342)	"Women who smoke have an increased risk for cataract." (2001, p. 15) "Women who smoke may have an increased risk for age-related macular degeneration." (2001, p. 15) "Studies show no consistent association between smoking and open-angle glaucoma." (2001, p. 15)	"The evidence is sufficient to infer a causal relationship between smoking and nuclear cataract." (p. 29)	"The evidence is sufficient to infer a causal relationship between cigarette smoking and neovascular and atrophic forms of age-related macular degeneration." "The evidence is suggestive but not sufficient to infer that smoking cessation reduces the risk of advanced age-related macular degeneration." (Chapter 10).
Hip fractures	— —	"Women who currently smoke have an increased risk for hip fracture compared with women who do not smoke." (2001, p. 321)	"The evidence is sufficient to infer a causal relationship between smoking and hip fractures." (p. 29)	— —
Liver cirrhosis	"Increased mortality of smokers from cirrhosis of the liver has been shown in the prospective studies. The data are not sufficient to support a direct or causal association." (1964, p. 342)	— —	— —	— —

Table 4.5   Continued

Disease	First mention and finding(s) in a Surgeon General's report (year)	Highest level conclusion(s) from subsequent Surgeon General's reports before 2004 (year)	Conclusion(s) from the 2004 Surgeon General's report	Additional or updated conclusion(s) from the 2014 Surgeon General's report
Low bone density	— —	"Postmenopausal women who currently smoke have lower bone density than do women who do not smoke." (2001, p. 321)	"In postmenopausal women, the evidence is sufficient to infer a causal relationship between smoking and low bone density." (p. 29)	— —
Peptic ulcer	"Epidemiological studies indicate an association between cigarette smoking and peptic ulcer which is greater for gastric than for duodenal ulcer." (1964, p. 340)	"The relationship between cigarette smoking and death rates from peptic ulcer, especially gastric ulcer, is confirmed. In addition, morbidity data suggest a similar relationship exists with the prevalence of reported disease from this cause." (1967, p. 40)	"The evidence is sufficient to infer a causal relationship between smoking and peptic ulcer disease in persons who are *Helicobacter pylori* positive." (p. 29)	— —

[a]U.S. Department of Health and Human Services 2000. *Oral Health in America: A Report of the Surgeon General.*

Table 4.6 **Conclusions from Surgeon General's report on exposure to secondhand smoke and cancer[a]**

Disease	First mention and finding(s) in a Surgeon General's report (year)	Highest level conclusion(s) from subsequent Surgeon General's reports before 2006 (year)	Conclusion(s) from the 2006 Surgeon General's report	Additional or updated conclusion(s) from the 2014 Surgeon General's report
Breast	— —	"Several studies suggest that exposure to environmental tobacco smoke is associated with an increased risk of breast cancer, but this association remains uncertain." (2001, p. 13)	"The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke and breast cancer." (p. 15)	"The evidence is suggestive but not sufficient to infer a causal relationship between exposure to secondhand tobacco smoke and breast cancer." (Chapter 6)
Cervical	— —	— —	"The evidence is inadequate to infer the presence or absence of a causal relationship between secondhand smoke exposure and the risk of cervical cancer among lifetime nonsmokers." (p. 15)	— —
Lung	"Although the currently available evidence is not sufficient to conclude that passive or involuntary smoking causes lung cancer in nonsmokers, the evidence does raise concern about a possible serious public health problem." (1982, p. 9)	"Involuntary smoking can cause lung cancer in nonsmokers." (1986, p. 13) "Exposure to ETS is a cause of lung cancer among women who have never smoked." (2001,	"The evidence is sufficient to infer a causal relationship between secondhand smoke exposure and lung cancer among lifetime nonsmokers. This conclusion extends to all secondhand smoke exposure, regardless of location." (p. 15)	— —
Nasal sinus cavity and nasopharyngeal carcinoma	— —	p 350 .) — —	"The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and a risk of nasal sinus cancer among nonsmokers." (p. 15) "The evidence is inadequate to infer the presence or absence of a causal relationship between secondhand smoke exposure and a risk of nasopharyngeal carcinoma among nonsmokers." (p. 15)	— —

Note: **ETS** = environmental tobacco smoke.

[a]General conclusion on cancers other than lung: "The associations between cancers, other than cancer of the lung, and involuntary smoking require further investigation before a determination can be made about the relationship of involuntary smoking to these cancers." (1986, p. 14)

Table 4.7 **Conclusions from Surgeon General's report on exposure to secondhand smoke and cardiovascular diseases[a]**

Disease	First mention and finding(s) in a Surgeon General's report (year)	Highest level conclusion(s) from subsequent Surgeon General's reports before 2006 (year)	Conclusion(s) from the 2006 Surgeon General's report	Additional or updated conclusion(s) from the 2014 Surgeon General's report
Atherosclerosis/ subclinical vascular disease	— —	— —	"Studies of secondhand smoke and subclinical vascular disease, particularly carotid arterial wall thickening, are suggestive but not sufficient to infer a causal relationship between exposure to secondhand smoke and atherosclerosis." (p. 15)	— —
Cerebrovascular disease	— —	— —	"The evidence is suggestive but not sufficient to infer a causal relationship between exposure to secondhand smoke and an increased risk of stroke." (p. 15)	"The evidence is sufficient to infer a causal relationship between exposure to secondhand smoke and increased risk of stroke." "The estimated increase in risk for stroke from exposure to secondhand smoke is about 20–30%." (Chapter 8)
Coronary heart disease	"The presence of such levels" as found in cigarettes "indicates that the effect of exposure to carbon monoxide may on occasion, depending upon the length of exposure, be sufficient to be harmful to the health of an exposed person. This would be particularly significant for people who are already suffering from...coronary heart disease." (1972, p. 7)	"Epidemiologic and other data support a causal relationship between ETS exposure from the spouse and coronary heart disease mortality among women nonsmokers." (2001, p.356)	"The evidence is sufficient to infer a causal relationship between exposure to secondhand smoke and increased risks of coronary heart disease morbidity and mortality among both men and women." (p. 15)	— —

Note: **ETS** = environmental tobacco smoke.

[a]General conclusion on cardiovascular disease: "Further studies on the relationship between involuntary smoking and cardiovascular disease are needed in order to determine whether involuntary smoking increases the risk of cardiovascular disease." (1986, p. 14). ["The evidence is sufficient to infer that smoking is the dominant cause of chronic obstructive pulmonary disease (COPD) in men and women in the United States. Smoking causes all elements of the COPD phenotype, including emphysema and damage to the airways of the lung" (2014)].

Table 4.8 **Conclusions from Surgeon General's report on exposure to secondhand smoke and respiratory effects in children**

Disease	First mention and finding(s) in a Surgeon General's report (year)	Highest level conclusion(s) from subsequent Surgeon General's reports before 2006 (year)	Conclusion(s) from the 2006 Surgeon General's report	Additional or updated conclusion(s) from the 2012/2014 Surgeon General's report
Asthma	"The limited existing data yield conflicting results concerning the relationship between passive smoke exposure and pulmonary function changes in patients with asthma." (1984, p. 13)[a]	— —	"The evidence is sufficient to infer a causal relationship between parental smoking and ever having asthma among children of school age." (p. 14) "The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure from parental smoking and the onset of childhood asthma." (p. 14)	— —
Chronic respiratory symptoms (cough, phlegm, wheeze, dyspnea, etc.)	"Chronic cough and phlegm are more frequent in children whose parents smoke compared with children of nonsmokers. The implications of chronic respiratory symptoms for respiratory health as an adult are unknown and deserve further study." (1986, p. 13)	— —	"The evidence is sufficient to infer a causal relationship between parental smoking and cough, phlegm, wheeze, and breathlessness among children of school age." (p. 14) "The evidence is sufficient to infer a causal relationship between secondhand smoke exposure from parental smoking and the onset of wheeze illnesses in early childhood." (p. 14)	— —

Table 4.8   Continued

Disease	First mention and finding(s) in a Surgeon General's report (year)	Highest level conclusion(s) from subsequent Surgeon General's reports before 2006 (year)	Conclusion(s) from the 2006 Surgeon General's report	Additional or updated conclusion(s) from the 2012/2014 Surgeon General's report
Influenza, pneumonia, infections, and acute respiratory illnesses	"The children of smoking parents have an increased prevalence of reported respiratory symptoms, and have an increased frequency of bronchitis and pneumonia early in life." (1984, p. 13)	"The children of parents who smoke have an increased frequency of a variety of acute respiratory illnesses and infections, including chest illnesses before 2 years of age and physician-diagnosed bronchitis, tracheitis, and laryngitis, when compared with the children of nonsmokers." (1986, p. 13) "The children of parents who smoke have an increased frequency of hospitalization for bronchitis and pneumonia during the first year of life when compared with the children of nonsmokers." (1986, p. 13)	"The evidence is sufficient to infer a causal relationship between secondhand smoke exposure from parental smoking and lower respiratory illnesses in infants and children." (p. 14)	— —
Lung growth and pulmonary function	"The children of smoking parents appear to have measurable but small differences in tests of pulmonary function when compared with children of nonsmoking parents. The significance of this finding to the future development of lung disease is unknown." (1984, p. 13)	"The children of parents who smoke have small differences in tests of pulmonary function when compared with the children of nonsmokers. Although this decrement is insufficient to cause symptoms, the possibility that it may increase susceptibility to chronic obstructive pulmonary disease with exposure to other agents in adult life, e.g., [*sic*] active smoking or occupational exposures, needs investigation." (1986, p. 13)	"The evidence is sufficient to infer a causal relationship between maternal smoking during pregnancy and persistent adverse effects on lung function across childhood." (p. 14) "The evidence is sufficient to infer a causal relationship between exposure to secondhand smoke after birth and a lower level of lung function during childhood." (p. 14)	— —

Table 4.8 **Continued**

Disease	First mention and finding(s) in a Surgeon General's report (year)	Highest level conclusion(s) from subsequent Surgeon General's reports before 2006 (year)	Conclusion(s) from the 2006 Surgeon General's report	Additional or updated conclusion(s) from the 2012/2014 Surgeon General's report
Middle ear disease and adenotonsillectomy	"A number of studies report that chronic middle ear effusions are more common in young children whose parents smoke than in children of nonsmoking parents." (1986, p. 14)	— —	"The evidence is sufficient to infer a causal relationship between parental smoking and middle ear disease in children, including acute and recurrent otitis media and chronic middle ear effusion." (p. 14) "The evidence is suggestive but not sufficient to infer a causal relationship between parental smoking and the natural history of middle ear effusion." (p. 14) "The evidence is inadequate to infer the presence or absence of a causal relationship between parental smoking and an increase in the risk of adenoidectomy or tonsillectomy among children." (p. 14)	— —
Atopy	—	— —	"The evidence is inadequate to infer the presence or absence of a causal relationship between parental smoking and the risk of immunoglobulin E-mediated allergy in their children." (p. 14)	— —

Note: **TB** = tuberculosis.

[a]General conclusion without specification of outcome in children or adults.

Table 4.9	**Conclusions from Surgeon General's report on exposure to secondhand smoke and respiratory effects in adults**			
Disease	**First mention and finding(s) in a Surgeon General's report (year)**	**Highest level conclusion(s) from subsequent Surgeon General's reports before 2006 (year)**	**Conclusion(s) from the 2006 Surgeon General's report**	**Additional or updated conclusion(s) from the 2012/2014 Surgeon General's report**
Asthma	"The limited existing data yield conflicting results concerning the relationship between passive smoke exposure and pulmonary function changes in patients with asthma." (1984, p. 13)[a]	— —	"The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and adult-onset asthma." (p. 16) "The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and a worsening of asthma control." (p. 16)	— —
Chronic respiratory symptoms (cough, phlegm, wheeze, dyspnea, etc.)	— —	— —	"The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and acute respiratory symptoms including cough, wheeze, chest tightness, and difficulty breathing among persons with asthma." (p. 15) "The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and acute respiratory symptoms including cough, wheeze, chest tightness, and difficulty breathing among healthy persons." (p. 15) "The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and chronic respiratory symptoms." (p. 15)	— —

Table 4.9   **Continued**

Disease	First mention and finding(s) in a Surgeon General's report (year)	Highest level conclusion(s) from subsequent Surgeon General's reports before 2006 (year)	Conclusion(s) from the 2006 Surgeon General's report	Additional or updated conclusion(s) from the 2012/2014 Surgeon General's report
Chronic obstructive pulmonary disease	"Healthy adults exposed to environmental tobacco smoke may have small changes on pulmonary function testing, but are unlikely to experience clinically significant deficits in pulmonary function as a result of exposure to environmental tobacco smoke alone." (1986, pp. 13–14)	— —	"The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and risk for chronic obstructive pulmonary disease." (p. 16) "The evidence is inadequate to infer the presence or absence of a causal relationship between secondhand smoke exposure and morbidity in persons with chronic obstructive pulmonary disease." (p. 16)	— —
Lung function (Formerly designated as chronic bronchitis; emphysema; chronic obstructive lung disease; chronic obstructive bronchopulmonary disease)	"Other components of tobacco smoke, such as particulate matter and the oxides of nitrogen, have been shown in various concentrations to affect adversely animal pulmonary...function. The extent of the contributions of these substances to illness in humans exposed to the concentrations present in an atmosphere contaminated with tobacco smoke is not presently known." (1972, pp. 7–8)	"...some studies suggest that high levels of involuntary [tobacco] smoke exposure might produce small changes in pulmonary function in normal subjects. … Two studies have reported differences in measures of lung function in older populations between subjects chronically exposed to involuntary smoking and those who were not. This difference was not found in a younger and possibly less exposed population." (1984, p. 13)	"The evidence is suggestive but not sufficient to infer a causal relationship between short-term secondhand smoke exposure and an acute decline in lung function in persons with asthma." (p. 16) "The evidence is inadequate to infer the presence or absence of a causal relationship between short-term secondhand smoke exposure and an acute decline in lung function in healthy persons." (p. 16) "The evidence is suggestive but not sufficient to infer a causal relationship between chronic secondhand smoke exposure and a small decrement in lung function in the general population." (p. 16) "The evidence is inadequate to infer the presence or absence of a causal relationship between chronic secondhand smoke exposure and an accelerated decline in lung function." (p. 16)	— —

Table 4.9   Continued

Disease	First mention and finding(s) in a Surgeon General's report (year)	Highest level conclusion(s) from subsequent Surgeon General's reports before 2006 (year)	Conclusion(s) from the 2006 Surgeon General's report	Additional or updated conclusion(s) from the 2012/2014 Surgeon General's report
Odor and irritation	"An atmosphere contaminated with tobacco smoke can contribute to the discomfort of many individuals." (1972, p. 7) "Cigarette smoke in the air can produce an increase in both subjective and objective measures of eye irritation." (1984, p. 13)	"The main effects of the irritants present in ETS occur in the conjunctiva of the eyes and the mucous membranes of the nose, throat, and lower respiratory tract. These irritant effects are a frequent cause of complaints about poor air quality due to environmental tobacco smoke." (1986, p. 252)	"The evidence is sufficient to infer a causal relationship between secondhand smoke exposure and odor annoyance." (p. 15) "The evidence is sufficient to infer a causal relationship between secondhand smoke exposure and nasal irritation." (p. 15) "The evidence is suggestive but not sufficient to conclude that persons with nasal allergies or a history of respiratory illnesses are more susceptible to developing nasal irritation from secondhand smoke exposure." (p. 15)	— —
Tuberculosis	— —	— —	— —	"The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and the risk of tuberculosis infection." (2014, Chapter 7) "The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and the risk of tuberculosis disease." (2014, Chapter 7)

Note: **ETS** = environmental tobacco smoke.

[a]General conclusion without specification of outcome in children or adults.

Table 4.10   Conclusions from Surgeon General's report on exposure to secondhand smoke amd reproductive and developmental effects

Disease	First mention and finding(s) in a Surgeon General's report (year)	Highest level conclusion(s) from subsequent Surgeon General's reports before 2006 (year)	Conclusion(s) from the 2006 Surgeon General's report	Additional or updated conclusion(s) from the 2012/2014 Surgeon General's report
Child physical and cognitive development	— —	— —	"The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and cognitive functioning among children." (p. 13) "The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and behavioral problems among children." (p. 13) "The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and children's height/growth." (p. 13)	— —
Congenital malformations	— —	— —	"The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and congenital malformations." (p. 13)	— —
Fertility	— —	— —	"The evidence is inadequate to infer the presence or absence of a causal relationship between maternal exposure to secondhand smoke and female fertility or fecundability. No data were found on paternal exposure to secondhand smoke and male fertility or fecundability." (p. 13)	— —
Fetal death, stillbirths, and infant mortality	"Studies of ETS exposure and the risks for delay in conception, spontaneous abortion, and perinatal mortality are few, and the results are inconsistent." (2001, p. 372)	— —	"The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and neonatal mortality." (p. 13)	— —
Sudden infant death syndrome (SIDS)	— —	— —	"The evidence is sufficient to infer a causal relationship between exposure to secondhand smoke and sudden infant death syndrome." (p. 13)	— —

Table 4.10 Continued

Disease	First mention and finding(s) in a Surgeon General's report (year)	Highest level conclusion(s) from subsequent Surgeon General's reports before 2006 (year)	Conclusion(s) from the 2006 Surgeon General's report	Additional or updated conclusion(s) from the 2012/2014 Surgeon General's report
Infant birth weight	"…maternal exposure to ETS appears to be causally associated with detrimental effects on fetal growth." (2001, p. 364)	— —	"The evidence is sufficient to infer a causal relationship between maternal exposure to secondhand smoke during pregnancy and a small reduction in birth weight." (p. 13)	— —
Pregnancy complications	— —	— —	"The evidence is inadequate to infer the presence or absence of a causal relationship between maternal exposure to secondhand smoke during pregnancy and spontaneous abortion." (p. 13) "The evidence is suggestive but not sufficient to infer a causal relationship between maternal exposure to secondhand smoke during pregnancy and preterm delivery." (p. 13)	— —

Note: **ETS** = environmental tobacco smoke.

Table 4.11   Conclusions reached by the Advisory Committee to the Surgeon General in 1964

Lung Cancer

"Cigarette smoking is causally related to lung cancer in men; the magnitude of the effect of cigarette smoking far outweighs all other factors. The data for women, though less extensive, point in the same direction.

The risk of developing lung cancer increases with duration of smoking and the number of cigarettes smoked per day, and is diminished by discontinuing smoking.

The risk of developing cancer of the lung for the combined group of pipe smokers, cigar smokers, and pipe and cigar smokers, is greater than for nonsmokers, but much less than for cigarette smokers. The data are insufficient to warrant a conclusion for each group individually." (p. 196)

Oral Cancer

"The causal relationship of the smoking of pipes to the development of cancer of the lip appears to be established. Although there are suggestions of relationships between cancer of other specific sites of the oral cavity and the several forms of tobacco use, their causal implications cannot at present be stated." (pp. 204–5)

Cancer of the Larynx

"Evaluation of the evidence leads to the judgment that cigarette smoking is a significant factor in the causation of laryngeal cancer in the male." (p. 212)

Cancer of the Esophagus

"The evidence on the tobacco-esophageal cancer relationship supports the belief that an association exists. However, the data are not adequate to decide whether the relationship is causal." (p. 218)

Cancer of the Urinary Bladder

"Available data suggest an association between cigarette smoking and urinary bladder cancer in the male but are not sufficient to support a judgment on the causal significance of this association." (p. 225)

Stomach Cancer

"No relationship has been established between tobacco use and stomach cancer." (p. 229)

Non-Neoplastic Respiratory Diseases, Particularly Chronic Bronchitis and Pulmonary Emphysema

"Cigarette smoking is the most important of the causes of chronic bronchitis in the United States, and increases the risk of dying from chronic bronchitis.

A relationship exists between pulmonary emphysema and cigarette smoking but it has not been established that the relationship is causal. The smoking of cigarettes is associated with an increased risk of dying from pulmonary emphysema.

For the bulk of the population of the United States, the importance of cigarette smoking as a cause of chronic bronchopulmonary disease is much greater than that of atmospheric pollution or occupational exposures.

Cough, sputum production, or the two combined are consistently more frequent among cigarette smokers than among non-smokers. Cigarette smoking is associated with a reduction in ventilatory function. Among males, cigarette smokers have a greater prevalence of breathlessness than non-smokers.

Cigarette smoking does not appear to cause asthma.

Although death certification shows that cigarette smokers have a moderately increased risk of death from influenza and pneumonia, an association of cigarette smoking and infectious diseases is not otherwise substantiated." (p. 302)

Table 4.11   Continued

Cardiovascular Disease

"Male cigarette smokers have a higher death rate from coronary artery disease than non-smoking males, but it is not clear that the association has causal significance." (p. 327)

Peptic Ulcer

"Epidemiological studies indicate an association between cigarette smoking and peptic ulcer which is greater for gastric than for duodenal ulcer." (p. 340)

Tobacco Amblyopia

"Tobacco amblyopia (dimness of vision unexplained by an organic lesion) has been related to pipe and cigar smoking by clinical impressions. The association has not been substantiated by epidemiological or experimental studies." (p. 342)

Cirrhosis of the Liver

"Increased mortality of smokers from cirrhosis of the liver has been shown in the prospective studies. The data are not sufficient to support a direct or causal association." (p. 342)

Maternal Smoking and Infant Birth Weight

"Women who smoke cigarettes during pregnancy tend to have babies of lower birth weight. Information is lacking on the mechanism by which this decrease in birth weight is produced. It is not known whether this decrease in birth weight has any influence on the biological fitness of the newborn." (p. 343)

Smoking and Accidents

"Smoking is associated with accidental deaths from fires in the home. No conclusive information is available on the effects of smoking on traffic accidents." (p. 345)

Morphological Constitution of Smokers

"The available evidence suggests the existence of some morphological differences between smokers and non-smokers, but is too meager to permit a conclusion." (p. 387)

"The overwhelming evidence points to the conclusion that smoking—its beginning, habituation, and occasional discontinuation—is to a large extent psychologically and socially determined. This does not rule out physiological factors, especially in respect to habituation, nor the existence of predisposing constitutional or hereditary factors." (p. 377)

Source: U.S. Department of Health, Education, and Welfare 1964.

Table 4.12   Conclusions from previous Surgeon General's reports related to smoking and all-cause mortality

Year	Conclusion
1964	"Cigarette smoking is associated with a 70 percent increase in the age specific death rates of males, and to a lesser extent with increased death rates of females. The total number of excess deaths causally related to cigarette smoking in the U.S. population cannot be accurately estimated. In view of the continuing and mounting evidence from many sources, it is the judgment of the Committee that cigarette smoking contributes substantially to mortality from certain specific diseases and to the overall death rate." (p. 31)
1967	"1. Cigarette smokers have substantially higher rates of death and disability than their nonsmoking counterparts in the population. This means that cigarette smokers tend to die at earlier ages and experience more days of disability than comparable nonsmokers. 2. A substantial portion of earlier deaths and excess disability would not have occurred if those affected had never smoked." (p. 3)
1968 (supplement to 1967)	"Previous findings reported in 1967 indicate that cigarette smoking is associated with an increase in overall mortality and morbidity and leads to a substantial excess of deaths in those people who smoke." (p. 3)
1978	"1. Overall mortality rates for cigarette smokers are about 70 percent higher than those for nonsmokers. 2. Overall mortality risk increases with the amount smoked. For the two-pack-a-day cigarette smoker, the risk of premature death is approximately twice that of the nonsmoker. 3. Overall mortality ratios of smokers compared to nonsmokers are highest at earlier ages and decline with increasing age. For cigarette smokers, the risk of premature death is twice that of nonsmokers at age 40. 4. Overall mortality ratios are higher for those who begin smoking at a young age compared to those who begin later. For those who begin smoking before the age of 15, the risk of premature death is about 86 percent higher than that for nonsmokers." (pp. 44–5)
1979	"1. The overall mortality ratio for all male current cigarette smokers, irrespective of quantity, is about 1.7 (70 percent excess) compared to nonsmokers. 2. Mortality ratios increase with amount smoked. The two-pack-a-day male smoker has a mortality ratio of 2.0 compared to nonsmokers. 3. Overall mortality ratios are directly proportional to the duration of cigarette smoking. The longer one smokes, the greater the risk of dying. 4. Overall mortality ratios are higher for those who initiated their cigarette smoking at younger ages compared to those who began smoking later. 5. Overall mortality ratios are higher among cigarette smokers who inhale than among those who do not." (p. 1-10)
1980	"1. The mortality ratio for women who smoke cigarettes is about 1.2 or 1.3. 2. Mortality ratios for women increase with the amount smoked. In the largest prospective study the mortality ratio was 1.63 for the two-pack-a-day smoker as compared to nonsmokers. 3. Mortality ratios are generally proportional to the duration of cigarette smoking; the longer a woman smokes, the greater the excess risk of dying. 4. Mortality ratios tend to be higher for those women who begin smoking at a young age as compared to those who begin smoking later." (p. 6)
1989	"Smoking is responsible for more than one of every six deaths in the United States. Smoking remains the single most important preventable cause of death in our society." (p. 11)

Table 4.12   Continued

Year	Conclusion
2001	"1. Cigarette smoking plays a major role in the mortality of U.S. women. 2. The excess risk for death from all causes among current smokers compared with persons who have never smoked increases with both the number of years of smoking and the number of cigarettes smoked per day." (p. 12)
2004	"There have been more than 12 million premature deaths attributable to smoking since the first published Surgeon General's report on smoking and health in 1964. Smoking remains the leading preventable cause of premature death in the United States." (p. 30)
2006[a]	"Secondhand smoke causes premature death and disease in children and in adults who do not smoke." (p. 11)

[a]Exposure to secondhand smoke.

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Chapter 5
Nicotine

Introduction

Nicotine has been addressed in multiple previous reports of the Surgeon General. Most notably, the 1988 Surgeon General's report, *The Health Consequences of Smoking: Nicotine Addiction,* concluded that cigarettes and tobacco products are addicting and that "Nicotine is the drug in tobacco that causes addiction" (U.S. Department of Health and Human Services [USDHHS] 1988, p. 9). The 2010 report, *How Tobacco Smoke Causes Disease,* addressed the mechanisms by which nicotine leads to addiction, providing full coverage of pharmacology, genetic factors, manifestations of addiction, and epidemiologic aspects (USDHHS 2010). The topic of trajectories of addiction and relapse was also addressed and further covered in regard to adolescents and young adults in the 2012 report, *Preventing Tobacco Use Among Youth and Young Adults* (USDHHS 2012).

This chapter addresses the acute toxicity of nicotine and the effects of longer-term exposure on reproductive outcomes, lung growth and development, neurocognitive function and cognitive decline, psychiatric morbidity, immune function, cancer risk, and cardiovascular disease. A number of new noncombustible products (e.g., electronic cigarettes) have been marketed by the tobacco industry and other manufacturers that provide nicotine through the oral and inhaled routes. Use of such products is projected by some to take an increasing market share over the next decade (Citigroup Global Markets 2011). Additionally, nicotine replacement therapy (NRT) remains a mainstay of cessation aids and many former smokers may remain on such therapy for periods of time longer than recommended and approved by the U.S. Food and Drug Administration (West and Russell 1985; Hajek et al. 1988; Hughes et al. 1991; Hughes 1998).

Given the possibility of increasing exposure of the population to nicotine obtained from products other than conventional cigarettes, this chapter considers the acute and longer-term adverse consequences of nicotine. The chapter also provides background for the consideration of future policy directions in Chapter 16, "A Vision for Ending the Epidemic: A Society Free of Tobacco-Related Death and Disease."

Toxicokinetics and Acute Toxicity of Nicotine

Nicotine is the major chemical component responsible for addiction in tobacco products (USDHHS 1988; Stolerman and Jarvis 1995; Royal College of Physicians of London 2000; Balfour 2004). The risk for nicotine addiction depends on the dose of nicotine delivered and the way it is delivered; the potential for addiction increases with the dose delivery rate, the rate of absorption, and the attained concentration of nicotine (Henningfield and Keenan 1993; de Wit and Zacny 1995; Stitzer and de Wit 1998). For an in-depth discussion of the pharmacokinetics of nicotine as related to addiction, see the pharmacokinetics section of Chapter 4 in the 2010 Surgeon General's report (USDHHS 2010). Similarly, the toxicity caused by nicotine is dependent on dose, dose duration and frequency, route of exposure, formulation of the nicotine product, and interpersonal variability as addressed in the 2010 report. This section discusses the toxicokinetics and the acute toxicity of nicotine.

Toxicokinetics

Nicotine, 3-(1-methyl-2-pyrrolidinyl) pyridine, is a volatile alkaloid with a molecular weight of 162.23. The absorption and elimination via renal excretion of nicotine are highly dependent on pH. At a high (alkaline) pH, nicotine (pKa[1] = 8.5) is in the non-ionized state, which passes more easily through lipoprotein membranes than the ionized (charged) state (Stratton et al. 2001). Nicotine in its un-ionized state can be readily absorbed across the epithelium of the lung, the oral mucosa, and the nose, and through the skin. Nicotine in tobacco smoke inhaled into the lung is rapidly absorbed because of the large surface area of the alveoli and small airways and the dissolution of nicotine in the fluid coating the lung's epithelial layer, which has a physiological pH that facilitates absorption. Similarly, nicotine from oral tobacco products that

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[1]The logarithmic measure of the acid disassociation constant, which represents the pH of a solution in which half of the acid molecules are ionized.

have an alkaline pH is readily absorbed through the oral mucosa, but more gradually than via the lungs. Nicotine can be well absorbed in the small intestine, because of its more alkaline pH and large surface area. However, nicotine is poorly absorbed from the stomach, because its acidic environment results in greater ionized nicotine. In addition, unlike ingestion, nicotine's bioavailability is greater through the lung or through the oral mucosa, because nicotine reaches the systemic circulation before passing through the liver where it is metabolized (first-pass metabolism). Arterial concentrations of nicotine from smoking are higher than venous concentrations (Figure 5.1). Across studies, the ratios of arterial to venous concentration range from 2.3–10 (Henningfield et al. 1993; Gourlay and Benowitz 1997; Rose et al. 1999). Less than 5% of nicotine is protein-bound in the plasma (Benowitz et al. 1982). It distributes extensively to body tissues, including the liver, kidney, spleen, lung, and brain and also accumulates in gastric juice and saliva, breast milk, skeletal muscle, and fetal serum and amniotic fluid (Dahlstrom et al. 1990; Breese et al. 1997; Perry et al. 1999; Dempsey and Ben-

owitz 2001). The time course of nicotine accumulation in the brain and other body organs, and the resultant pharmacologic effects, are highly dependent on route and rate of dosing. The lag time between a puff on a cigarette until nicotine reaches the brain is 10–20 seconds (Henningfield and Keenan 1993; de Wit and Zachy 1995; Stitzer and de Wit 1998; Rose et al. 1999).

More than 80% of nicotine absorbed into the body undergoes metabolism in the liver, principally by CYP2A6, UDP-glucuronosyltransferase, and flavin-containing monooxygenase (Cashman et al. 1992; Park et al. 1993; Benowitz and Jacob 1994; Benowitz et al. 2009). Several metabolites of nicotine reach the central nervous system (CNS) after acute administration of nicotine (Crooks and Dwoskin 1997). Nornicotine is both a metabolite of nicotine and a minor tobacco alkaloid. Researchers have observed similar behavioral effects from nicotine and nornicotine. However, because nornicotine is present only as a minor metabolite, it is unclear whether it has significant pharmacologic or toxicologic effects in nicotine users. Less data are available on cotinine, a major metabolite of

Figure 5.1   Venous blood concentrations of nicotine over time for various nicotine delivery systems
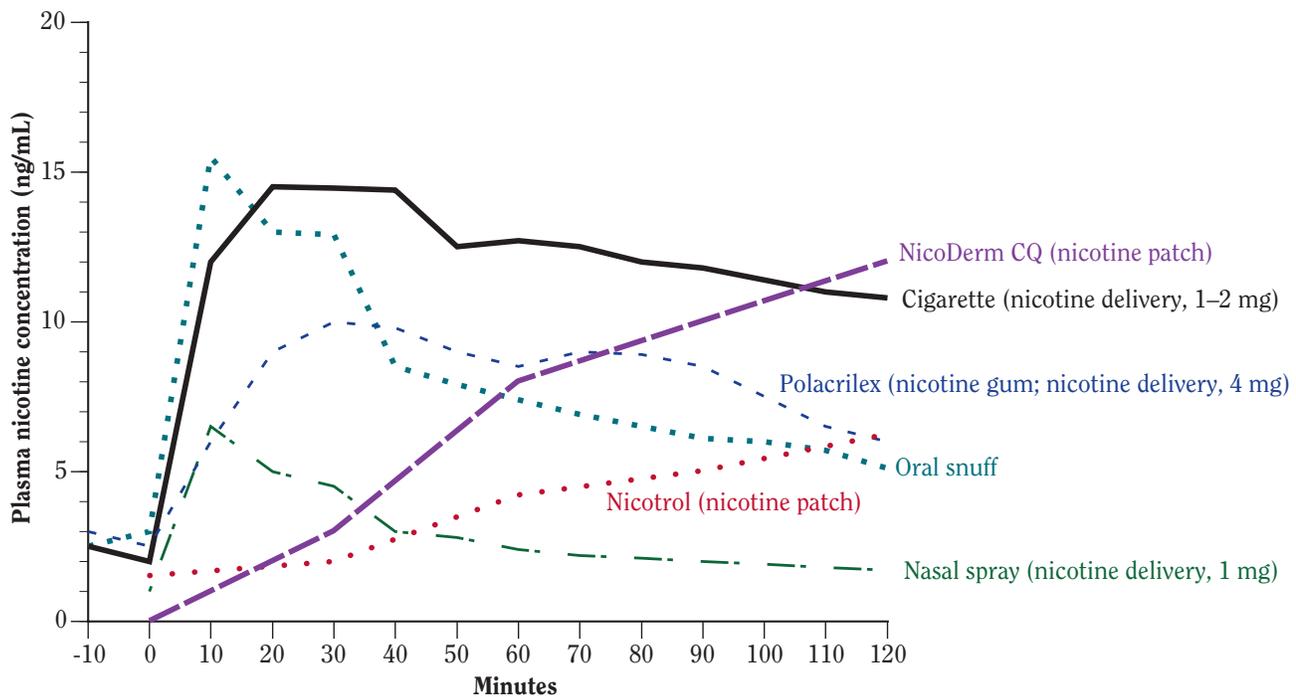
Source: Adapted from Fant et al. 1999 with permission from Elsevier, ©1999.
Note: **mg** = milligrams; **ng/mL** = nanograms per milliliter.

Table 5.1   **Animal studies on acute toxicity of nicotine**

Study	Species tested	Route of exposure	Study objective/endpoint
Larson et al. 1945	Mice, rabbits	i.p.	Determine LD50
Hicks and Sinclair, 1947	Rats	i.p.	Determine LD50
Yamamoto et al. 1966	Rats	i.p.	Determine LD50
Lazutka et al. 1969	Mice, rats	Oral, inhalation	Determine LD16, LD50, LD100
Stalhandske and Slanina 1970	Mice	i.p.	Determine difference in response to LD50 between young and old rats
Tepper et al. 1979	Mice	i.p.	Determine LD50 by mouse strain, age, gender; ED50 of onset of tremor
Okamoto et al. 1992	Rats	i.p.	Determine time to convulsions
Okamoto et al. 1994	Rats	i.p.	Determine difference in response to LD50 between young and old rats
Yuen et al. 1995	Rats	Oral (water)	Examine acute hepatotoxicity

Note: **ED50** = median dose where 50% of sample subjects achieve a predefined endpoint; **i.p.** = intraperitoneal; **LD16** = dosage of a given drug required to kill 16% of a test population; **LD50** = dosage of a given drug required to kill 50% of a test population; **LD100** = dosage of a given drug required to kill 100% of a test population.

nicotine (Benowitz and Jacob 1994; Keenan et al. 1994). For discussion of the pharmacodynamics of nicotine in the brain, see the section on "Pathophysiology of Nicotine Addiction" in Chapter 4 of the 2010 Surgeon General's report (USDHHS 2010).

Acute Toxicity of Nicotine

Nicotine exerts its effects via stimulation of the nicotinic acetylcholine receptors (nAChRs), which are located in the CNS, at interganglionic junctions of the autonomic nervous system, and on target organs throughout the body as part of the parasympathetic autonomic nervous system (USDHHS 2010). As a result of the global expression of these receptors, their stimulation causes broad physiologic effects. Although the nicotine intoxication syndrome is not fully characterized, symptoms of mild acute toxicity might include nausea and vomiting, progressing with increased exposure to cholinergic syndrome, which includes diarrhea, increased salivation, increased respiratory secretions, and bradycardia. Severe poisonings can progress further to seizures and respiratory depression. Countering the development of acute toxicity is the relatively rapid development of tolerance with repeated exposure (Benowitz et al. 1987; Okamoto et al. 1992).

Acute toxicologic data on nicotine is limited. Such information comes from three sources: (1) animal studies, (2) studies investigating nicotine as a therapeutic agent (including NRT), and (3) poisonings involving nicotine. A few acute toxicological studies performed on animals are available (Table 5.1). These studies contribute basic LD50 (dose causing 50% lethality) values primarily in rats and mice (Larson et al. 1945; Hicks and Sinclair 1947; Yamamoto et al. 1966; Lazutka et al. 1969; Tepper et al. 1979), as well as examining the effects of age and gender, and endpoints other than lethality, such as hepatotoxicity and time to convulsions. However, the studies available do not adequately characterize acute toxicity. Studies investigating nicotine as a therapeutic agent in humans are limited in predicting the acute toxicity of nicotine. These studies are better at documenting adverse effects rather than overt toxicity, as the doses administered are chosen, in part, because they are considered subtoxic. Mild adverse effects, as defined by the World Health Organization's (WHO's) Collaborating Center for International Drug Monitoring (WHO 1972), of nicotine given as pharmacologic treatment for nicotine addiction have been commonly reported (Barrueco et al. 2005). Studies examining nicotine's potential role to treat ulcerative colitis using nicotine patches or enemas provide similar findings with regard to adverse effects (Nikfar et al. 2010; Lunney and Leong 2012).

Numerous poisonings have been documented in the literature since the use of nicotine as a pesticide became widespread in the early part of the twentieth century. These studies describe patients exposed to doses associated with toxicity via one or more routes of exposure, and a resulting predicted clinical course of acute toxicity as noted previously in this section. However, the literature also notes exceptions, including a rapid progression to near fatal symptoms after a relatively low exposure to a piece of 2 milligrams (mg) nicotine gum that was chewed briefly and discarded – never swallowed (Mensch and Holden 1984), as well as a patient receiving a relatively large dose, 240 mg nicotine, in an accidental subcutaneous administration that proved to be nonfatal (Brady et al. 1979). In both instances, the affected persons were active cigarette smokers. The case report involving the 2 mg gum did not specifically document nicotine intoxication; rather, a clinical diagnosis was made. Yet, despite the abundance of case reports, it appears that there has not been a systematic assessment of the literature to characterize the dose-response relationship. Finally, the human oral fatal dose is commonly reported to be between 50–60 mg for adults, with the fatal dose for youth expected to be lower, but not determined specifically. A study by Lazutka and colleagues (1969), in a Russian language publication, is commonly cited in support of these figures. However, Lazutka and colleagues make no such estimation. Further, a systematic literature search was performed using OVID MEDLINE for nicotine (focusing on 'toxicity' n = 744 and 'poisonings' n = 134), as well as a search of databases such as the Hazardous Substances Data Bank and Haz-Map using Toxnet; however, no study was located as a source for an estimate of the dose that is fatal to humans and the figure of 50–60 mg is poorly documented.

Summary

In its un-ionized state, nicotine readily enters the body, regardless of the mode of administration. It has known acute toxicity, reflecting its pharmacologic activity. There is a potential for poisoning from ingestion of nicotine-containing products.

Pathophysiology of Nicotine Addiction

Summary of Evidence from the 2010 Surgeon General's Report

Dependence on nicotine is characterized by both the persistence of a drug-taking behavior and the emergence of withdrawal symptoms upon the abrupt cessation of nicotine administration (Wikler 1973; Levine 1974; Stewart et al. 1984; Ludwig 1986; O'Brien et al. 1990; Hughes and Hatsukami 1992; Koob et al. 1993; Markou et al. 1993, 1998; American Psychiatric Association 1994; Kenny and Markou 2001; USDHHS 2010). Therefore, both the neurosubstrates (brain structures, pathways, and systems) mediating the reinforcing effects of acute administration of nicotine and those mediating the nicotine withdrawal syndrome are relevant to nicotine addiction. The physiological systems that develop adaptations to repeated nicotine administration, and lead to the emergence of withdrawal signs on cessation of nicotine administration, are likely to intersect with systems that mediate the acute effects of nicotine (Markou et al. 1998; Kenny and Markou 2001). That is, nicotine addiction develops as a neurobiologic adaptation to chronic nicotine exposure. However, all forms of nicotine delivery do not pose an equal risk in establishing or maintaining nicotine addiction. NRT medicines, which are designed to minimize addiction risk, carry a low risk of establishing addiction and are generally substantially easier to discontinue than tobacco products (Henningfield et al. 2011; WHO 2012). Conversely, cigarettes have been researched, designed, and manufactured to increase the likelihood that initiation will lead to dependence and difficulty achieving cessation due to contents and emissions in addition to nicotine (e.g., acetaldehyde, ammonia compounds, and menthol); design features that may increase free-base nicotine and produce larger puffs (filter-tip ventilation); and other factors that reduce the concerns for smokers and increase the attractiveness of the products (USDHHS 2010, 2012).

nAChRs are ligand-gated ion channels composed of five membrane-spanning subunits that combine to form a functional receptor (Lindstrom et al. 1996; Role and Berg 1996; Albuquerque et al. 1997; Lèna and Changeux 1998, 1999; Dani 2000; Gotti et al. 2006). As a result of actions at the nAChR sites, nicotine stimulates the release of most neurotransmitters throughout the brain (Araujo et al. 1988; Toide and Arima 1989; McGehee and Role 1995; Gray et al. 1996; Role and Berg 1996; Wilkie et al. 1996; Albuquerque et al. 1997; Alkondon et al. 1997; Kenny et al. 2000; Grady et al. 2001). Therefore, various transmitter systems are likely to be involved in the rewarding effects of nicotine and in the adaptations that occur in response

to chronic exposure to nicotine, which give rise to dependence and to withdrawal responses.

The positive reinforcing aspects of nicotine addiction primarily results from the release of dopamine in the ventral tegmental area region of the brain (Grenhoff et al. 1986; Nisell et al. 1994a,b, 1997; Pidoplichko et al. 1997; Watkins et al. 2000; Picciotto and Corrigall 2002; Balfour 2004). Nicotine stimulates nAChRs on glutamatergic terminals that release glutamate, an excitatory neurotransmitter, which results in an increased release of dopamine in the nucleus accumbens and the frontal cortex (Gray et al. 1996; Gioanni et al. 1999; Fu et al. 2000; Grillner and Svensson 2000; Mansvelder and McGehee 2000; Reid et al. 2000). Nicotine also excites nAChRs on gamma-aminobutyric acid (GABA)-releasing terminals (Schilström et al. 1998; Mansvelder and McGehee 2000). Thus, levels of GABA, an inhibitory neurotransmitter, are also increased by nicotine. However, the interplay between the quick desensitization of nAChRs on the GABA neuron and the higher doses of nicotine required to desensitize nAChRs on the glutamate neuron results in an increase in dopamine levels (Schilström et al. 1998; Mansvelder and McGehee 2000). A critical role may also be played by nicotine-induced increases in norepinephrine transmission, although the role of this transmitter system in nicotine dependence has not been investigated as extensively as that of the dopamine, glutamate, and GABA systems. The roles of endocannabinoids, serotonin, and endogenous opiates in nicotine addiction are less certain. For further discussion of neurosubstrates, see 'Neurosubstrates of Nicotine Reinforcement' in the "Pathophysiology of Nicotine Addiction" section of Chapter 4 in the 2010 Surgeon General's report.

The neurophysiological mechanisms associated with withdrawal symptoms may vary with the type of symptoms experienced (e.g., somatic vs. affective). The nAChRs appear to be involved in both the somatic and affective components of nicotine withdrawal. Decreased mesolimbic dopaminergic transmission seems to mediate various aspects of the withdrawal syndrome (Fung et al. 1996; Hildebrand et al. 1998, 1999; Carboni et al. 2000). Noradrenergic and serotonergic systems may also play a role in withdrawal. Decreased glutamate transmission appears to mediate the affective aspects of withdrawal, but GABA transmission does not appear to change with withdrawal.

Trajectory of Addiction

The addiction caused by the nicotine in tobacco smoke is critical in the transition of smokers from experimentation to sustained smoking and, subsequently, in the maintenance of smoking for the majority of smokers who want to quit (USDHHS 2010, 2012). Substantial longitudinal research has shown that smoking typically begins with experimental use of cigarettes and that the transition to regular smoking can occur relatively quickly, with the smoking of as few as 100 cigarettes (USDHHS 2012). Longitudinal studies show that there are individual trajectories of smoking as tracked by the index of numbers of cigarettes smoked daily. These trajectories are variable, with some smokers quickly progressing to regular smoking and others doing so more slowly (USDHHS 2010, 2012). Research is in progress on the possible role of genetic factors in determining the trajectory of nicotine use.

The 2012 Surgeon General's report makes clear that addiction can begin in people who begin experimenting with tobacco use during their teenage years (USDHHS 2012). Although the phenotype of addiction is not so well defined as with adults, symptoms of withdrawal occur among youth who become regular smokers. As documented in that report, the longitudinal studies show several different patterns of smoking uptake, with some young people rapidly escalating their use to a typical pattern of regular use and others doing so more slowly. Some adolescents may be able to smoke on an experimental or intermittent basis without becoming addicted (USDHHS 2012).

Health Consequences of Nicotine Exposure

Cancer

Nicotine is a highly bioactive compound with effects ranging from being a natural pesticide in tobacco leaves to causing addiction in tobacco users. For cancer, there is some biological basis for proposing that nicotine may promote cancer based on experimental studies that have limitations in replicating human exposure and on mechanistic studies, but human evidence is lacking (Lee et al. 2005, 2012; Dasgupta and Chellappan 2006; Zheng et al. 2007; Catassi et al. 2008; Chen et al. 2008b, 2010; Egleton et al. 2008). Nicotinic receptors are found not only in the

brain but throughout the body; for example, in muscle, lung, endothelia, kidney, and skin (Improgo et al. 2011; Cardinale et al. 2012; Hurst et al. 2013). These receptors trigger a number of cellular pathways involved in carcinogenesis. The presence of nicotinic cholinergic receptors throughout the normal lung and in lung tumors has been well documented (Schuller 2009; Improgo et al. 2011). This section reviews the current literature that relates to the hypothesis that nicotine may contribute to the carcinogenic process. The evidence comes from experimental cell culture and animal studies, and from human studies including epidemiologic.

The potential for nicotine to contribute to the risk of incident cancer or cancer recurrence is important due to the number of smokers who have quit by using NRT, some of whom use NRT for long durations to remain smoking abstinent, and other smokers who switch to alternate sources of nicotine (e.g., e-cigarettes or smokeless tobacco products). Although using NRT or other noncombusted sources of nicotine is different than smoking in evident ways, the possibility of increased risk in long-term users compared to those who use such products only briefly for cessation merits consideration. Thus, when contemplating the available evidence, coming largely from laboratory experiments, the following questions need to be addressed: (1) What is the cancer risk for those who quit smoking but use long-term NRT or other sources of nicotine compared with those who continue to smoke? (2) What is the cancer risk of a lifetime pattern of repeatedly quitting with NRT and relapsing, but smoking fewer lifetime cigarettes overall? (3) What is the cancer risk of long-term NRT use without relapse to smoking or sustained switching to a noncombusted nicotine source compared with long-term abstinence without NRT or other source of nicotine or relapse to smoking? This section will address these questions.

Genotoxicity

There are mixed data for a genotoxic effect of nicotine. Most studies were negative that used the Ames assay (including urine of rats exposed to nicotine), chromosomal aberration and sister chromatid exchange (SCE) assays in Chinese hamster ovary cells, and the bacterial genotoxicity luminescence test (Mizusaki et al. 1977; Riebe et al. 1982; Doolittle et al. 1991, 1995; Yim and Hee 1995). In contrast, two studies were positive for chromosomal aberration and SCEs (Riebe and Westphal 1983; Trivedi et al. 1990), one was positive for micronuclei formation that was inhibited with antioxidants (Argentin and Cicchetti 2004), one was positive for an *Escherichia coli POLA*+/*POLA*− mutation assay (Riebe et al. 1982), and another using nasal mucosal cells was positive by the Comet assay, which is inhibited by

antioxidants or nicotinic receptor inhibitors (Ginzkey et al. 2012). One study found that cotinine, and not nicotine, was genotoxic by the bacterial genotoxicity luminescence test, but another was null for the Ames assay and SCE induction (Doolittle et al. 1995; Yim and Hee 1995). Some reports indicate that nicotine can lead to the formation of DNA adducts using the ultrasensitive technique accelerator mass spectroscopy (Cheng et al. 2003). Although cigarette smoke is highly genotoxic, a comparison of Ames mutagenicity for cigarette smoke from cigarettes with differing nicotine yields did not indicate different mutagenic potential, suggesting that there was no additional contribution by nicotine (Chen et al. 2008a).

Effects of Nicotine on Carcinogenic Pathways

There are numerous studies that focus on lung cells and cells from other organs relating to nicotine exposure. A wide range of effects has been reported in cellular systems, including at doses similar to those in the blood of smokers (Cardinale et al. 2012). The presence of nAChRs throughout the lung has been well documented via protein studies and demonstration of the presence of transcripts for both normal tissues and lung tumors (Improgo et al. 2011). These receptors are important for triggering many signaling pathways in lung cells (Schuller 2009). In lung cells, nicotine has been shown to: (1) inhibit apoptosis including apoptosis induced by chemotherapy (Maneckjee and Minna 1990, 1994; Cardinale et al. 2012), which involves the PI3-K-Akt pathway and attendant positive effects on Bcl-2 and negative effects on BAD and BAX (West et al. 2003; Jin et al. 2004; Xin and Deng 2005); (2) affect proliferation by stimulating the release of epidermal growth factor and, therefore, activation of the Ras-Raf-ERK cascade (Dasgupta and Chellappan 2006; Carlisle et al. 2007; Paleari et al. 2008); and (3) stimulating fibronectin production activating ERK, PI3-K, mTOR, and the expression of PPAR-β/δ (Dasgupta et al. 2006). Also, there is evidence that nicotine may promote metastases because of stimulation of cell motility and migration, loss of adhesion, and inducing the transition of a well-differentiated epithelial cell to a highly invasive carcinoma via epithelial-mesenchymal transition (Catassi et al. 2008; Egleton et al. 2008; Cardinale et al. 2012).

An important consideration for cancer survival and metastasis is angiogenesis. A variety of mechanisms are stimulated by nicotine to promote angiogenesis; for example, promoting endothelial cell migration, proliferation, survival, and tube formation (Cardinale et al. 2012; Lee and Cooke 2012). Nicotine directly binding to nicotinic receptors in endothelial cells induced endothelial cell tube migration by stimulating VEGF in lung cancer cells (Conklin et al. 2002; Heeschen et al. 2002; Li and Wang

2006; Ng et al. 2007). Lower doses of nicotine in vitro induce endothelial cell proliferation, while higher doses induce cytotoxicity (Villablanca 1998). These effects also occur via stimulation of nicotinic receptors in the endothelia. The angiogenic effect of nicotine involves MAPK, PI3K/Akt, and NF-κB activation (Heeschen et al. 2002). Angiogenesis has been shown in a variety of tumor cells, such as breast, colon, and lung, implanted in a chick chorioallantoic membrane, and other systems (Heeschen et al. 2002; Mousa and Mousa 2006).

Limited research has addressed whether the nicotine in tobacco smoke somehow alters the toxicity of tobacco smoke. Chen and colleagues (2008a) conducted various in vitro studies comparing cigarettes with differing amounts of nicotine, and where nicotine was added back to the condensate. They found that nicotine attenuated the cytotoxicity of cigarette smoke through inhibition of apoptotic pathways, increased proliferative activity, and increased cell survival. There was no evidence of an effect on the gap junction intracellular communication, which is considered to be a marker of tumor promotion effects.

Experimental Animal Studies for Carcinogenicity

Several studies in experimental animals also did not indicate that nicotine alone is tumorigenic (Martin et al. 1979; Waldum et al. 1996; Hecht 2003; Murphy et al. 2011). These studies have included the inhalational route of exposure, fetal exposure, and exposure through maternal milk. The only exception to the null findings is the report of nicotine inducing sarcomas in the muscle or uterus of exposed A/J mice; other tumors, including those in the lung, were not observed in that same study (Galitovskiy et al. 2012). The A/J mouse model is used for assessing the carcinogenic effects of cigarette smoke in inducing lung tumors. However, the lack of nicotine induction of lung tumors may be related to the dose and route of exposure.

As a tumor promoter, nicotine has been reported to increase the frequency of tumors induced by agents such as nicotine-derived nitrosamine ketone, and 7,12-dimethylbenz(a)anthracene (Chen and Squier 1990), *N*-methyl-N´-nitro-*N*-nitrosoguanidine (Gurkalo and Volfson 1982), and *N*-[4-(5-nitro-2-furyl)-2-thiazolyl] formamide (LaVoie et al. 1985). Other studies showed that nicotine had no effect in promoting tumors related to other *N*-nitrosamines (Habs and Schmahl 1984) and had an antitumor effect in some cases (Zeller and Berger 1989). In a different tumor promotion model, nicotine induced lung tumors in hamsters in the presence of hyperoxia (Schuller et al. 1995). In addition, studies using cancer xenograft models have shown that nicotine promotes tumor growth

and metastases (Heeschen et al. 2001; Jarzynka et al. 2006; Al-Wadei et al. 2009; Davis et al. 2009).

Other studies have investigated the potential for nicotine to promote the carcinogenic effects of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). Maier and colleagues (2011) conducted a series of studies to determine if nicotine would promote the carcinogenesis induced by NNK. The results were null. The investigators used several models, including a crossed A/J and C57BL/6 mouse, a mutant *k-Ras* animal model prone to develop lung tumors, and a syngeneic lung-cancer graft model with NNK-transformed lung cancer cells. The dosing of nicotine, albeit by drinking water, was specifically intended to be similar to the levels human smokers receive when using NRT. In a separate study, Murphy and colleagues (2011) studied the A/J mouse and did not find a difference in tumorigenesis whether the nicotine was given before or after NNK, compared to NNK alone.

In summary, the findings of animal studies do not support the hypothesis that nicotine is a complete carcinogen. It is a tumor promoter in some experimental models, although not for tobacco-specific nitrosamines. Studies examining other classes of tobacco smoke carcinogens (e.g., polycyclic aromatic hydrocarbons) would need to be performed to better define the potential cancer risk inferred from animal studies.

Human Studies

Very little human data are on human cancer risk relating to nicotine. The Lung Health Study is the only study that provides information about long-term users of NRT (Murray et al. 2009). This study was not designed to directly examine nicotine's potential cancer risk. It was a 5-year randomized trial to assess the effects of smoking cessation and reduction on chronic lung disease and lung function. Among 5,887 persons initially enrolled, the researchers continued to follow them for an additional 7 years (n = 3,220). Study participants were offered NRT without consideration of randomization or study design. Although they were encouraged to use NRT for only 6 months, many continued to use it long term. A total of 75 lung cancers were diagnosed among smokers and quitters of the extended surveillance group, but the use of NRT was not associated with lung cancer (or other cancers). A major limitation was the short follow-up period of only 7 additional years. Notwithstanding the limitations, this study at least does not indicate a strong role for nicotine in promoting carcinogenesis in humans, and clearly the risk, if any, is less than continued smoking.

Another approach to examining whether nicotine could contribute to carcinogenesis would be to consider its delivery in the context of long-term smokeless tobacco

use. Smokeless tobacco products used in northern European countries appear to result in a substantially reduced exposure to many tobacco smoke carcinogens, because smokeless tobacco does not undergo combustion. Epidemiologic studies of smokeless tobacco indicate that it increases the risk of oral cavity, esophageal and pancreatic cancers, (IARC 2012) at least for some forms of smokeless tobacco. The associated risks for these sites are less than the risk of these cancers from smoking; however, high rates of oral cancers in India and Sudan are attributable to the use of smokeless tobacco products (Accortt et al. 2005; Boffetta et al. 2005, 2008; Luo et al. 2007). The risks for many cancers commonly associated with smoking are not elevated by long-term smokeless tobacco use. This pattern of risk suggests that in humans nicotine may not have a strong tumor promoting effect. Further, although levels of nicotine are similar for smokers and smokeless tobacco users, the risk of cancer of the oral cavity, esophagus, and pancreas is less for the smokeless tobacco users, indicating that exposures other than nicotine contribute to the cancer process. This conclusion, however, needs to be tempered by the possibility that there may be a different risk due to route of exposure, because smokeless tobacco use leads to nicotine exposure via the oral mucosa and ingestion, while smoking results in inhalation exposure. Risks inferred from smokeless tobacco studies may not extend directly to inhalation exposures.

There is some evidence that NRT can endogenously lead to the formation of the carcinogenic tobacco-specific nitrosamines, NNK and N-nitrosonornicotine (NNN), at least in rats (Carmella et al. 1997), which conceptually would increase cancer risk if the resultant dose was similar to those which result from smoking or the use of smokeless tobacco. A smoking cessation study by Stepanov and colleagues (2009b) demonstrated that NNK metabolites were not detectable in persons using NRT (Hecht et al. 1999). However, they did find intermittently high levels of NNN similar to baseline smoking levels in 13 of 34 participants using NRT gum or lozenges, and in only 1 of 9 persons using the patch (Stepanov et al. 2009a). Although these data indicate a potential cancer risk to NRT users, especially oral users, it is important to realize that NNN is only one of the tobacco-specific nitrosamines in cigarette smoke. Thus, it will be important to quantify the level of risk from long-term use of NRT or other noncombusted sources of nicotine, particularly if long-term nicotine use from sources other than smoking becomes more prevalent. Although there is a variety of evidence that nicotinic receptor polymorphisms play a role in lung cancer risk and in determining the amount of tobacco use, the genes on chromosome 15 (i.e., *CHRNA3, CHRNA4, CHRNA5, CHRNA6, CHRNB2, CHRNB3*, and *CHRNB4*),

chromosome 1 (i.e., *CHRNB2*), chromosome 8 (*CHRNB3*), and chromosome 20 (*CHRNA4*), it is not known how much of an effect there is, if any, by these genes on carcinogenesis independently of an effect on tobacco use (Thorgeirsson et al. 2008; Bierut 2009, 2010; Johnson et al. 2010; Li et al. 2011; Russo et al. 2011; Sarginson et al. 2011; Sorice et al. 2011; Timofeeva et al. 2011; Wassenaar et al. 2011; Broms et al. 2012; Budulac et al. 2012; Kapoor et al. 2012). Separately, there are data on CYP2A6 genetics and nicotine metabolism that show associations with smoking behavior, nicotine levels, and lung cancer risk (Wassenaar et al. 2011; Gold and Lerman 2012; Liu et al. 2013; Zhu et al. 2013).

Summary

There is insufficient data to conclude that nicotine causes or contributes to cancer in humans, but there is evidence showing possible oral, esophageal, or pancreatic cancer risks. Additionally, there is substantial experimental evidence indicating that nicotine is bioactive for a number of carcinogenic mechanisms in experimental systems. Although in vitro data are suggestive of relevant biological activity, this is not supported overall by the most recent experimental animal studies. In humans, there has been limited research and only one relatively short–term follow-up study on nicotine and cancer.

Cardiovascular Diseases

The potential role of nicotine in atherogenesis and in triggering acute coronary events has been discussed extensively in the medical literature (USDHHS 2010) and reviewed in Chapter 8, "Cardiovascular Diseases," of this volume. It is likely that the sympathomimetic effects of nicotine increase heart rate and myocardial contractility, increase coronary vascular resistance, and reduce insulin sensitivity, contributing to some extent to increasing cardiovascular risk in smokers. However, other mechanisms by which nicotine might contribute to atherogenesis have also been proposed (Lee and Cooke 2011). nAChRs are found not only in neuronal and muscle cells but also in endothelial cells and immune cells. Nicotine has been reported to induce the proliferation of vascular smooth muscle cells and migration of cells into blood vessels (Lee and Cooke 2012). In apoE*deficient mouse models of atherosclerosis, oral nicotine was shown to promote plaque progression and neovascularization. The primary nicotine receptor in endothelial cells is the alpha 7 homomeric nicotine receptor. In mice deficient in this receptor subtype, the effect of nicotine in augmenting angiogenesis

is blunted. Tolerance develops to many of the effects of nicotine with prolonged exposure, both in people and animals. Chronic oral administration of nicotine was shown to abolish the augmenting effect of nicotine on angiogenic responses to limb ischemia (Konishi et al. 2010). Thus, it is unclear whether the short-term effects of nicotine in enhancing angiogenesis persist with long-term exposure, as seen with users of tobacco or other nicotine-delivering products.

A genomewide association study found an association between a gene cluster on chromosome 15 and an increased risk of peripheral arterial obstructive disease (Thorgeirsson et al. 2008). Since this gene cluster is strongly associated with the level of nicotine dependence, it is not clear whether the association indicates a direct role of nicotine in atherosclerosis.

Immune Function and Related Disorders

Nicotine has both stimulatory and suppressive effects on the immune system, and levels of nicotine, inferred from urine markers, have been linked with both induction of and protection from immunologically mediated disease (Cloëz-Tayarani and Changeux 2007). Nicotine exerts its effects via pentameric nicotinic cholinoceptors that vary in their alpha and beta subunit composition (USDHHS 2010). Nicotine can act directly on cells, but in vivo it is also a direct activator of the sympathetic nervous system, which itself can have strong immune-regulatory effects. Aged-smoke extracts that still contain all of the nicotine of fresh smoke but lack reactive intermediates are much less active in immune assays than freshly prepared, oxidant-rich extracts (Laan et al. 2004; Bauer et al. 2008). Nicotine patches or mecamylamine (a full antagonist) or nicotine partial antagonists (e.g., varenicline), which are used as adjuncts in smoking cessation, are not immune-modulatory in humans (Cahill et al. 2008), and snus (the nicotine-rich low nitrosamine smokeless tobacco product that is used widely in Sweden) does not replicate the effects of smoking. This interpretation is consistent with research with macrophages where the effects of smoking on immunity were linked to oxidation (McMaster et al. 2008).

This highly contradictory literature is further reinforced by studies on human immune effector cells linked to atherosclerosis where nicotine was found to stimulate, not suppress, dendritic cells as part of adaptive immune responses (Aicher et al. 2003). However, a large body of evidence suggests that nicotine acting via the alpha 7 subunit that contains neuronal nicotinic cholinoceptors

can suppress cellular immunity both in vivo and in vitro. Nicotine suppresses the production of antibodies in B cells, reduces the proliferation of T cells, and induces an anergy-like state where signaling via the T cell receptor is attenuated (Geng et al. 1995, 1996). These effects have been linked to the impaired host defense response to bacteria and viruses in nicotine-treated animals.

In summary, as reviewed here and discussed in more detail in Chapter 10, "Other Specific Outcomes," there is compelling evidence that nicotine affects cellular immunity, either directly by interacting with nicotinic cholinoceptors or indirectly via its effects on the nervous system. Whether these effects contribute to the overall adverse effects of cigarette smoke on immunity is less well-understood.

Reproductive Health Outcomes

Pregnancy is accompanied by a complex series of maternal physiological adjustments to support fetal growth and homeostasis. Basic characteristics of embryologic and fetal development include cell growth, differentiation, interaction, and migration. Teratogenic factors can disturb one or more of these processes, resulting in abnormalities in fetal structure or function, including growth retardation, malformations due to abnormal growth or morphogenesis, and altered CNS performance (Hacker et al. 2010). In addition, there is a growing appreciation that teratogenic substances can have effects throughout the duration of pregnancy, and that those effects can be more subtle than gross anatomic anomalies (Yaffe and Aranda 2011). Thus, for women of reproductive age, a comprehensive exploration of the known and potential harms of the range of available tobacco products, all of which contain nicotine, is needed. The health effects of smoking and of components in tobacco smoke, including nicotine, on reproduction are reviewed in Chapter 9, "Reproductive Outcomes." A focused review of what is known about the effects of nicotine on maternal and fetal health outcomes is presented here.

Cigarette use before and/or during pregnancy remains a major cause of reduced fertility as well as maternal, fetal, and infant morbidity and mortality (see Chapter 9) and over 400,000 live-born infants in the United States are exposed in utero to tobacco from maternal smoking annually (Hamilton et al. 2012; Tong et al. in press). Conditions causally associated with maternal prenatal smoking include preterm delivery and fetal growth restriction, placenta previa, placental abruption, sudden infant death syndrome (SIDS), some congenital anomalies, ectopic

pregnancy, and reduced preeclampsia risk. Maternal prenatal smoking has also been associated with stillbirth and spontaneous abortion (USDHHS 2004).

Much of what can currently be inferred about nicotine and reproductive health comes from studies comparing the effects of prenatal smokeless tobacco use with the effects of prenatal smoking because smokeless tobacco products do not expose users to products of combustion, but all contain nicotine. In addition, some smokeless products such as Swedish snus contain lower levels of certain toxicants when compared with conventional smokeless tobacco products (Stepanov et al. 2008). This differential exposure between snus and other smokeless products allows researchers to study the health effects of smokeless tobacco while reducing the likelihood that adverse outcomes will mistakenly be attributed to nicotine. Studies of health outcomes in randomized trials of nicotine therapy in pregnant women offer additional insights.

Fetal Growth Restriction

It has been believed for decades that in utero exposure to cigarette smoke causes fetal growth restriction through nicotine-mediated vasoconstriction of uteroplacental vessels (Lambers and Clark 1996). However, this hypothesis has been questioned because it is not likely that nicotine's vasoconstrictive effects are sufficient to overcome placental circulatory reserve (Benowitz and Dempsey 2004). Further evidence against a vasoconstrictive mechanism comes from studies of pregnancy outcomes in smokeless tobacco users. These studies have consistently demonstrated only modest contributions of smokeless tobacco to reduced infant birth weight (England et al. 2003, 2012; Gupta and Sreevidya 2004; Juarez and Merlo 2013). Results from a population-based study in Sweden conducted from 1999–2010 suggest that smokeless tobacco (snus) use increases the risk for delivering a small-for-gestational-age infant (for term births, adjusted odds ratio [AOR] = 1.21; 95% confidence interval [CI], 1.02–1.43). The effect was smaller in magnitude for smokeless tobacco than for cigarette smoking (AOR = 2.27; 95% CI, 2.62–2.91) (Baba et al. 2013). In a trial of 250 women randomized to a nicotine patch (15 mg) or to placebo for 11 weeks, the researchers found that there was no difference between the two arms in quit rates or in saliva cotinine, but birth weight was significantly higher in the NRT group (186g [95% CI, 35–336g]), possibly due to reduced cigarette smoking and exposure to products of combustion. Taken together, these studies support a modest role for nicotine in fetal growth restriction.

Preterm Delivery

Maternal smoking is associated with a 27% increase in the risk of preterm delivery (Shah and Bracken 2000) and several studies have also found an increased risk of preterm delivery in smokeless tobacco users (Gupta and Sreevidya 2004; Baba et al. 2012; England et al. 2013). In Sweden, snus use and smoking during pregnancy were both associated with increased risks of preterm birth, and the magnitudes of the associations were similar (Baba et al. 2012). Together, these studies provide evidence that nicotine increases the risk of preterm delivery. The potential roles of nicotine and products of combustion in preterm delivery are discussed in detail in Chapter 9.

Stillbirth, Perinatal Mortality, and Sudden Infant Death Syndrome

Studies of stillbirth have also been conducted among smokeless tobacco users. Studies in India and Sweden showed an increased risk of stillbirth in women using smokeless tobacco (Krishna 1978; Gupta and Subramoney 2006; Wikström et al. 2010). In the study conducted in Sweden, when antenatal bleeding and small-for-gestational-age deliveries were excluded, the smoking-related risk of stillbirth was markedly reduced although the elevated risk for snus users remained the same. These findings suggest that the mechanisms underlying the associations between smoking and stillbirth and between smokeless tobacco use and stillbirth both involve nicotine, but other factors may also contribute to increased risk in smokers (Wikström et al. 2010).

The effects of nicotine on the brainstem, cardiopulmonary integration, fetal and neonatal responses to hypoxic stress, and arousal in early infancy are reviewed in Chapter 9. For example, it has been hypothesized that tobacco-related changes in autonomic function and/or arousal could increase the risk of SIDS, although a mechanistic pathway has not been established (American Academy of Pediatrics Task Force on Sudden Infant Death Syndrome 2011). Studies of human infants have shown an association between prenatal exposure to cigarette smoke and impaired recovery from hypoxia in preterm infants (Schneider et al. 2008) and an association with impaired arousal patterns that correlates with cotinine levels (Richardson et al. 2009). Maternal prenatal cigarette use has also been associated with increased obstructive apnea and decreased arousal in response to apnea events in infants (Sawnani et al. 2004). Additional data suggest that maternal prenatal smokeless tobacco use also increases infants' risk of apnea, of a similar magnitude to that seen with maternal smoking (Gunnerbeck et al. 2011).

Extensive animal research has generated plausible and generalizable models to explain how nicotine could increase the risk of SIDS and perinatal mortality (Slotkin and Seidler 1988); these models are reviewed in Chapter 9. In one such model, the fetal/infant protective response to hypoxia is impaired. During parturition, the fetus normally experiences significant hypoxia, but is able to respond with a massive release of catecholamines from the adrenal medulla (Lagercrantz and Bistolelli 1977; Lagercrantz and Slotkin 1986) in order to maintain blood flow to the brain and heart. In the fetus and neonate, the adrenal gland responds directly to hypoxia, independent of central reflexes, and this direct mechanism persists until chromaffin cells differentiate after the development of splanchnic nerve function (Slotkin 1998). However, prenatal nicotine exposure in rat models causes immature chromaffin cells in the adrenal gland to differentiate prematurely, resulting in loss of the normal direct stimulation of the adrenal gland by hypoxia, complete absence of catecholamine release, and impaired cardiac response in the presence of hypoxia (Slotkin 1998). The effect is a temporary loss of a critical protective response to hypoxia and, theoretically, is accompanied by a temporary increased mortality risk (Slotkin 1998).

Congenital Malformations

In this report, the evidence was determined to be sufficient to support a causal relationship between maternal smoking and orofacial clefts, and to be suggestive of a causal relationship for clubfoot, cryptorchidism, gastroschisis, and some types of congenital heart defects (see Chapter 9). The 2010 Surgeon General's report examined the biological basis for increased risk of congenital defects in infants of mothers who smoke and specifically considered the potential role of nicotine (USDHHS 2010); this report updates that review. A number of potential mechanisms were cited by which nicotine having crossed the placenta, could contribute to defects.

Summary

The evidence supports the hypothesis that nicotine plays a key role in mediating adverse effects of smoking on reproductive health, including preterm delivery and stillbirth. Smoking has been linked to diverse adverse health outcomes for the developing fetus and experimental research and pharmacologic understanding indicate that nicotine specifically has a role in causing them.

Lung Development

The 2004 Surgeon General's report concluded that "the evidence is sufficient to infer a causal relationship between maternal smoking during pregnancy and a reduction of lung function in infants" (p. 27). This conclusion was based on epidemiologic studies that consistently demonstrated an inverse dose-response relationship between the number of cigarettes smoked per day during pregnancy by the mother and the level of lung function and pulmonary compliance in the newborn. The 2006 Surgeon General's report expanded the conclusions of the 2004 report to address the duration of effects after infancy: "The evidence is sufficient to infer a causal relationship between maternal smoking during pregnancy and persistent adverse effects on lung function across childhood" (p. 399). The report further concluded that the "evidence shows that parental smoking *(referring to secondhand smoke exposure and maternal smoking during pregnancy)* reduces the maximum achieved level *(of lung growth),* although not to a degree (on average) that would impair individuals" (p. 400). "Nonetheless, a reduced peak level increases the risk for future chronic lung disease, and there is heterogeneity of the effect so that some exposed children may have a much greater reduction than the mean" (p. 400). This section considers studies on the mechanisms underlying the relationship between maternal smoking and the infant or child's lung development and function and the potential role of nicotine in these mechanisms.

Human lung development begins in the embryonic stage and extends through early adulthood. During fetal lung growth, structural and vascular development take place and major airway branching and mesenchymal proliferation are complete by the end of the second trimester. Alveolarization (marked by septation and multiplication of alveoli) begins in the third trimester of pregnancy and multiplication of alveolar number continues to 2–3 years of age, when lungs reach the full adult quantity of approximately 300 million alveoli. Alveolar size and surface, however, increase until after adolescence as the lungs grow (Joshi and Kotecha 2007). Lung development is tightly regulated, and intrauterine and postnatal environmental factors can interfere with this complicated set of processes. The alveolar phase of development is particularly sensitive to late-pregnancy and postnatal insults (Harding and Maritz 2012).

As reviewed in previous Surgeon General's reports, the clinical and epidemiologic data strongly support that maternal smoking in pregnancy has lasting effects on lung development. Studies of infants exposed in utero to tobacco smoke show evidence of impaired lung function with reduced respiratory compliance, forced expiratory flow, and tidal breathing ratio, consistent with impaired airways development (Hanrahan et al. 1992; Tager et al. 1995; Lødrup Carlsen et al. 1997; Stocks and Dezateux 2003). Maternal prenatal smoking has also been associated with impaired lung function with reduced small airway flow rates in school-age offspring (Cunningham et al. 1994, 1995), even after adjustment for the offspring's current and past exposure to secondhand smoke (Gilliland et al. 2000), and with deficits in measures of airflow among adolescents, especially among those with a history of early-onset asthma (Gilliland et al. 2003). There is also evidence to suggest that exposure to prenatal tobacco smoke could result in an acceleration of lung aging and an increased susceptibility to obstructive lung disease, lasting beyond childhood (Maritz and Harding 2011).

Numerous studies using animal models have been conducted to develop a better understanding of the mechanisms through which maternal smoking affects fetal and infant lungs. These studies are summarized in several review articles (Stocks and Dezateux 2003; Maritz 2008; Maritz and Harding 2011). Studies in primates specifically examining nicotine exposure have demonstrated decreased lung size and volume, increased type I and type III collagens, decreased elastin in the lung parenchyma, increased alveolar volume, and increased airway wall area (Sekhon et al. 1999, 2001, 2002). Animal studies have also demonstrated decreased expiratory flow rates and increased pulmonary resistance with nicotine exposure, similar to findings in human studies (Hanrahan et al. 1992; Cunningham et al. 1995; Tager et al. 1995; Dezateux et al. 1999). Primate studies further suggest that nicotine-induced changes in airway wall thickness or stiffness could be an underlying cause of altered lung function (Pierce and Nguyen 2002; Sekhon et al. 2002). Finally, nicotine exposure in fetal lambs has been associated with accelerated maturation of lung acini and reduced proximal airway conductance (Sandberg et al. 2004), hyperreactive proximal airways, and changes in proximal airway wall composition with associated defects in airflow (Sandberg et al. 2011).

At the molecular level, nicotine crosses the placenta and binds nAChRs in numerous locations in the lung, including bronchial epithelial cells, alveolar epithelial cells, neuroendocrine cells, submucosal glands, airway and vascular smooth muscle cells, fibroblasts, and pulmonary macrophages (Pierce and Nguyen 2002). Nicotine administration to pregnant rhesus monkeys is associated with an increase in nAChRs in the lungs (Sekhon et al. 1999; Fu et al. 2009), increased collagen deposition in airway walls, and increases in the numbers of alveolar type II and neuroendocrine cells (Sekhon et al. 1999, 2002). Coinciding with these changes are alterations in smooth muscle and vascular tension, perhaps explaining the effects of maternal smoking on infant lung function (Stocks and Dezateux 2003). Other hypothesized mechanisms through which nicotine could affect lung development include premature onset of cell differentiation and decreased replication and impaired alveolar development—resulting from altered expression or deposition of elastin (Pierce and Nguyen 2002; Stocks and Dezateux 2003).

Together, these findings indicate that nicotine is a primary mediator of many of the adverse effects of maternal smoking on fetal lung development. However, the mechanisms involved remain incompletely understood.

Summary

Studies reviewed in the 2004 and 2006 Surgeon General's reports and subsequently published data collectively show that prenatal tobacco exposure affects the structure and function of the lung; these effects may have consequences that last into childhood beyond, as lung development and growth are completed. Studies in rhesus monkeys, which have lung development similar to that of humans, and in other animal models consistently show that nicotine may be the primary mediator of many of the adverse effects of maternal smoking on fetal lung development.

Cognitive Function

Researchers have suggested that smoking may have cognition-enhancing properties (West 1993; Heishman et al. 2010), such as improvements in sustained attention, reaction time, and memory (Evans and Drobes 2008; Poorthuis et al. 2009; Heishman et al. 2010). Initial reports of improved cognitive function were based on empirical evidence from smokers (Bell et al. 1999); thus, these observations could reflect the mitigation of cognitive impairment from nicotine withdrawal, enhancement of smokers' cognitive function independent of nicotine's effects on withdrawal symptoms, or both. Interest in the effects of nicotine on cognition has since expanded to include healthy nonsmokers and individuals with underlying neuropsychiatric conditions accompanied by cognitive deficits. Concurrently, there is a growing awareness of the potential harms of nicotine exposure during certain vulnerable stages of brain development, such as during fetal and adolescent growth (Dwyer et al. 2008; Duncan et

al. 2009; Poorthuis et al. 2009; Bublitz and Stroud 2012; Goriounova and Mansvelder 2012). This section reviews the evidence on the effects of nicotine on cognitive function in general (in smokers and nonsmokers), and in potentially vulnerable populations.

Cognitive Function and the Nicotinic Acetylcholine Receptor System

Underlying the purported connection between nicotine and cognitive enhancement is the role of nAChRs in attention, learning, memory, and cortical plasticity (Wallace and Bertrand 2013). nAChRs are receptors that normally bind endogenous neurotransmitter acetylcholine, but are also particularly responsive to nicotine. nAChRs are abundant in brain regions associated with learning and memory, including the prefrontal cortex (Poorthuis et al. 2009), and in primate and rodent models, depletion of acetylcholine in the prefrontal cortex results in impaired attentional performance (Poorthuis et al. 2009; Wallace and Bertrand 2013). β2 nAChRs are especially abundant in the brain and have a high affinity for nicotine (Evans and Drobes 2008; Poorthuis et al. 2009; Herman and Sofuoglu 2010). Recent evidence from animal studies suggests that β2 nAChRs play a critical role in regulating attention (Howe et al. 2010; Poorthuis et al. 2013a). Additional research has demonstrated that nicotine interferes with cholinergic control of β2 nAChRs in the prefrontal cortex in mice, which could result in acute impairment of attention and alterations of the prefrontal cortex network, and lead to long-term effects on attention (Poorthuis et al. 2013a). Mice lacking the β2 nAChR subunit demonstrate deficits in executive function (Granon et al. 2003).

Effects of Nicotine on Cognitive Function in Healthy Adult Smokers and Nonsmokers

In adults, the negative effects of nicotine withdrawal on cognitive function have been documented in both humans and animals, and the administration of nicotine during withdrawal mitigates cognitive impairment (Evans and Drobes 2008). In dependent smokers, abstinence from smoking is associated with reductions in working memory and sustained attention (Evans and Drobes 2008), and adverse effects on attention can be seen as early as 30 minutes after smoking the last cigarette (Hendricks et al. 2006). Nicotine withdrawal is also commonly accompanied by symptoms of negative affect (anxiety and depression) (Edwards and Kendler 2011) and relief of this symptom may be an important element of addiction in smokers (Baker et al. 2004). Because negative affect and attentional control are related, the effects of smoking on these two domains could be interrelated (Evans and Drobes 2008).

Whether there are direct effects of nicotine on cognitive function (positive or negative) in nonabstinent smokers and in healthy nonsmoking adults is less clear. In a recent meta-analysis of double-blind, placebo-controlled studies examining the acute effects of nicotine (administered mainly as nicotine replacement product) on cognitive function in nonsmokers and smokers abstinent for 2 hours or less, nicotine was found to result in cognitive enhancement in six of nine performance domains: fine motor, alerting attention-accuracy and response time (RT), orienting attention and RT, short-term episodic memory accuracy, and working memory RT (Heishman et al. 2010). To separate the effects of nicotine on symptoms of withdrawal versus its direct effects, the results were stratified by smoking status. The effects on alerting attention accuracy and short-term episodic memory accuracy were significant in smokers but not in nonsmokers; effects on alerting attention RT were significant in nonsmokers but not in smokers; effects on working memory RT were significant in both smokers and nonsmokers, and in the remaining outcomes there were insufficient numbers of studies on smokers to conduct stratified analysis. Thus, nicotine may have some positive effects on cognitive performance that are unique to nonsmokers. No studies meeting the inclusion criteria for the review addressed learning or executive function.

Critical Periods of Exposure in the Nervous System

Across the lifespan, there are several developmental windows during which exposure to nicotine may have adverse consequences. In the fetus, nicotine targets neurotransmitter receptors in the brain, potentially resulting in abnormalities in cell proliferation and altering synaptic activity (Slotkin 1998). The effects of prenatal exposure to nicotine on the fetal nervous system are summarized earlier in this chapter and elsewhere in this report (see Chapter 9).

Human brain development continues far longer than was previously realized. In particular, areas involved in higher cognitive function such as the prefrontal cortex continue to develop throughout adolescence (the period during which individuals are most likely to begin smoking) and into adulthood (Poorthuis et al. 2009; Goriounova and Mansvelder 2012). During this extended period of maturation, substantial neural remodeling occurs, including synaptic pruning and changes in dopaminergic input, as well as changes in gray and white matter volume. The density of projections from the amygdala to the prefrontal cortex increases, suggesting that there is substantial development of the connectivity between the emotional and cognitive areas of the brain (Durston et al. 2001; Ernst and Fudge 2009). The cholinergic system, which matures

in adolescence, plays a central role in maturation of cognitive function and reward (Poorthuis et al. 2009).

Smoking during adolescence has been associated with lasting cognitive and behavioral impairments, including effects on working memory and attention, although causal relationships are difficult to establish in the presence of potential confounding factors (Goriunova and Mansvelder 2012). In addition, functional magnetic resonance imaging in humans showed that young adult smokers had reduced prefrontal cortex activation during attentional tasks when compared with nonsmoking controls. Diminished prefrontal cortex activity correlated with duration of smoking, supporting the hypothesis that smoking could have long-lasting effects on cognition (Musso et al. 2007).

Animal studies provide evidence that nicotine exposure during adolescence has effects on the brain that differ from exposure during other periods of development. Studies in rodents show that nicotine induces changes in gene expression in the brain to a greater degree with adolescent exposure than during other periods of development (Schochet et al. 2005; Polesskaya et al. 2007). DNA microarrays in female rats demonstrated that gene expression in response to nicotine was most pronounced around the age of puberty and the effects of nicotine on gene expression were most dramatic in the hippocampus, with upregulation of growth factors and cyclic AMP signaling pathways (Polesskaya et al. 2007). Expression of the *Arc* gene (implicated in synaptic plasticity, learning, memory, and addiction) was upregulated in the prefrontal cortex in adolescent rats exposed to nicotine, and to a much greater extent than in adult rats (Schochet et al. 2005).

Nicotine exposure during adolescence also appears to cause long-term structural and functional changes in the brain (Dwyer et al. 2009). Exposure of adolescent rats to nicotine resulted in upregulation of nAChRs in the midbrain, cerebral cortex, and hippocampus that was still present 4 weeks after the end of the exposure, in contrast to adult rats in which upregulation had disappeared by 4 weeks. Receptor upregulation was more pronounced in male adolescent rats than females (Trauth et al. 1999). Indices of cell damage and size in rats with adolescent nicotine exposure indicate reduced cell number and size in the cerebral cortex, midbrain, and hippocampus (Trauth et al. 2000). Structural changes in prefrontal cortex neurons have also been described, including increased dendritic length and spine density (Brown and Kolb 2001).

Some effects of nicotine exposure appear to be gender-selective. For example, adolescent nicotine exposure resulted in increased membrane protein concentration in the hippocampus, consistent with cell damage and/or cell loss, in female rats, but not in males (Trauth et al. 1999). Male rats with nicotine exposure demonstrated a loss of a dopaminergic response to nicotine more than a month after exposure ended, while females exhibited deficits in hippocampal norepinephrine content and turnover during the month after nicotine exposure (Trauth et al. 2001). Because estrogen regulates hippocampal cell proliferation in an adult rat, there may be interactions between the effects of nicotine and the hormonal milieu in the adolescent (Trauth et al. 1999).

Corresponding behavioral studies of adolescent rats have also shown effects of nicotine exposure. Exposed females exhibited reduced grooming during exposure and reduced locomotion and rearing after cessation of exposure; these results were not seen in exposed adult rats, which show increased grooming in both genders and no decrease in locomotion (Trauth et al. 2000). Adolescent rats, tested 5 weeks after nicotine exposure ended, demonstrated an increase in premature responses and a reduction in correct responses when given a serial reaction time test; this effect was not seen with adult exposure (Counotte et al. 2009).

Thus, adolescents appear to be particularly vulnerable to the adverse effects of nicotine on the CNS. Based on existing knowledge of adolescent brain development, results of animal studies, and limited data from studies of adolescent and young adult smokers, it is likely that nicotine exposure during adolescence adversely affects cognitive function and development. Therefore, the potential long-term cognitive effects of exposure to nicotine in this age group are of great concern.

The effects of nicotine exposure on cognitive function after adolescence and young adulthood are unknown. There are data to suggest that smoking accelerates some aspects of cognitive decline in adults, and that these effects appear to be mediated by an increased risk of respiratory and cardiovascular disease (Swan and Lessov-Schlaggar 2007; Almeida et al. 2011). However, in a cohort study of more than 7,000 men and women, the authors found that current male smokers and recent former smokers had a greater 10-year decline in global cognition and executive function than never smokers (with the greatest adverse effect on executive function); these differences were not explained by other health behaviors or measures, including heart disease and stroke, and measures of lung function. An analysis using pack-years[2] as the exposure measure provided evidence of a dose-response relation-

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[2]Pack-years: the number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

ship. The results of the latter study suggest that there may be mechanisms contributing to cognitive decline in addition to and independent of respiratory and cardiovascular disease; however, whether nicotine plays a role in accelerating cognitive decline is unknown.

Other Vulnerable Populations

Although the contribution of nicotine to the effects of smoking on cognitive decline is unclear, there has been a great deal of interest in applications of nicotine as a treatment for several conditions characterized by cognitive deficits, including Alzheimer's disease and Parkinson's disease. These disorders have underlying deficits in the cholinergic system, and it has been hypothesized that nicotine and/or nicotine analogs may be effective in attenuating symptoms or slowing disease progression. This hypothesis is further supported by research (reviewed earlier in this chapter) suggesting that acute administration of nicotine has cognitive-enhancing properties. In addition, some early observational studies showed evidence for a reduced risk of Alzheimer's in smokers, suggesting that components in tobacco smoke, such as nicotine, may have protective properties. A growing body of evidence now links smoking to an increased risk for Alzheimer's disease (Almeida et al. 2002; Anstey et al. 2007; Hernán et al. 2008; Purnell et al. 2009) rather than a reduced risk; however, research on nicotine as a treatment for this condition (and for Parkinson's disease) continues.

Other disorders associated with cognitive and attentional impairment, such as schizophrenia and attention deficit hyperactivity disorder (ADHD), are characterized by a very high prevalence of smoking among those affected. It has been proposed that individuals with these disorders smoke in order to alleviate the symptoms of their disease, and a number of clinical trials using nicotine as a therapeutic agent have been conducted.

Alzheimer's Disease

Alzheimer's disease is a common form of dementia in which individuals experience ongoing deterioration of cognitive abilities. Although smoking is recognized as a risk factor for Alzheimer's disease (Peters et al. 2008; Cataldo et al. 2010), acute nicotine administration has been reported to improve some Alzheimer's symptoms, such as recall, visual attention, and mood (Lopez-Arrieta and Sanz 2001). The plausibility of this effect is supported by studies of Alzheimer's disease patients showing deficits in cholinergic systems and a loss of nicotinic binding sites (Whitehouse et al. 1982). However, evidence from randomized trials to support improvement of Alzheimer's symptoms from nicotine treatment is sparse. In a 2001 Cochrane review updated in 2010, the authors found no double-blind, placebo-controlled, randomized trials of treatment for Alzheimer's disease with nicotine and concluded that there is no evidence to recommend nicotine as a treatment for Alzheimer's disease (Lopez-Arrieta and Sanz 2001).

Parkinson's Disease

Parkinson's disease is a degenerative hypokinetic movement disorder. Most patients with Parkinson's disease will also eventually develop cognitive impairment—with deficits in attention, executive and visual-spatial functions, and memory—and subsequent dementia. In Parkinson's disease, both the dopaminergic and cholinergic systems undergo degeneration, which leads to deficits in dopamine and acetylcholine at synapses; thus, nicotinic mechanisms may play a role in cognitive deficits. In contrast to Alzheimer's, data consistently support that smokers are at reduced risk for developing Parkinson's disease (Ritz et al. 2007; Wirdefeldt et al. 2011), and twin studies have reported a 20–30% reduction of Parkinson's disease risk for ever smoking or regular smoking in monozygotic and dizygotic, same-gender male twin pairs who were discordant for Parkinson's disease (Tanner et al. 2002; Wirdefeldt et al. 2005). This suggests that genetic factors contributing to both Parkinson's disease and smoking are not responsible for the apparent smoking and Parkinson's disease association.

Two studies have examined the association between smokeless tobacco use and risk of Parkinson's disease: a case-control study found a significant inverse association (odds ratio [OR] 0.18; 95% CI, 0.04–0.82, in ever users vs. never users of smokeless tobacco) (Benedetti et al. 2000) and a prospective cohort study that assessed Parkinson's disease mortality as the outcome found a relative risk of 0.22 (95% CI, 0.07–0.67) for current users of smokeless tobacco versus never users (O'Reilly et al. 2005). These studies add support for a protective role for nicotine. However, there are few controlled trials of the effects of nicotine on cognitive function in patients with Parkinson's disease, and results have been inconsistent (Kelton et al. 2000; Vieregge et al. 2001; Lemay et al. 2004; Holmes et al. 2011).

ADHD and Schizophrenia

Several neuropsychiatric disorders characterized by attention-related cognitive defects are characterized by high prevalence of smoking, including ADHD and schizophrenia. It has been suggested that smoking may be particularly reinforcing for individuals with these conditions because of the cognitive-enhancing effects of nicotine. Because cholinergic systems play an important role in functional impairments in certain neurodegenerative

diseases, it also has been suggested that individuals with attention-related cognitive defects may benefit from treatment with nicotine through nicotine's role as a cholinergic agonist (Singh et al. 2004; Kumari and Postma 2005; Evans and Drobes 2008). Some research suggests that nicotine may improve attention performance in individuals with ADHD and schizophrenia (Evans and Drobes 2008).

ADHD is a common disorder of childhood with symptoms of inattention and hyperactivity/impulsivity. Behavioral inhibition and delay aversion deficits are believed to be factors contributing to impulsive behavior. Other features, such as poor planning, and deficits in working memory and cognitive flexibility, are more recently recognized traits. Limited research suggests that nicotine might improve the symptoms and measures of behavioral inhibition, delay aversion, and recognition memory in individuals with ADHD (Gehricke et al. 2006, 2009).

Schizophrenia is a chronic disorder marked by delusions, hallucinations, thought disorder, and negative symptoms such as flattening of affect. The evidence suggests that dysregulation of cholinergic systems is involved in altered sensory physiology and individuals with schizophrenia have decreased dopaminergic activity in the prefrontal cortex (Punnoose and Belgamwar 2006). The prevalence of smoking in individuals with schizophrenia is high, perhaps as the result of an effort of patients to relieve symptoms associated with the disorder (Kumari and Postma 2005). Specifically, it has been suggested that nicotine-induced release of dopamine could improve attention and processing symptoms and sensory-gating deficits in schizophrenia, and that nicotine treatment could attenuate antipsychotic-induced cognitive impairment and extrapyramidal symptoms, through nicotine's effects on dopamine release (Alder et al. 1993; Newhouse et al. 2004; Birkett et al. 2007; Evans and Drobes 2008). However, in a 2012 Cochrane Review update, the authors reviewed all randomized controlled trials in which nicotine or tobacco and placebo were administered to patients with schizophrenia or schizophrenia-like illness and found no studies that met the inclusion criteria. A number of studies were excluded because they were a crossover design, which was determined to be inappropriate because schizophrenia is an unstable condition and nicotine may have carryover effects (Punnoose and Belgamwar 2006).

Tobacco Industry Influence

The tobacco industry has a long-standing interest in nicotine and neurocognitive functioning and psychiatric disease. The tobacco industry has invested in pharmaceutical applications of nicotine and nicotine analogs for decades (Vagg and Chapman 2005). Philip Morris and R.J. Reynolds both developed research programs to explore the potential uses of nicotine and analogs in the treatment of neurological disorders (R.J. Reynolds 1993). In the early 1990s, R.J. Reynolds established both its "Nicotine Pharmacology and Neurodegenerative Disease Program" and later Targacept, a pharmaceutical company, for the purpose of discovering therapeutic uses of nicotinic compounds. Tobacco industry documents indicate that diversification into the pharmaceutical industry was seen not only as potentially profitable but also as a strategy to improve the tobacco industry's corporate image (Vagg and Chapman 2005).

Data from observational studies describing the protective effects of smoking on the risk of Parkinson's disease and Alzheimer's disease and the high prevalence of smoking among individuals with ADHD and schizophrenia are often cited in industry-sponsored and non-industry-sponsored literature as evidence to support the therapeutic applications of nicotine. However, there is evidence that the tobacco industry influenced many of these epidemiologic studies of smoking and psychiatric disorders. For example, an analysis of publications on the relationship between smoking and Alzheimer's disease that controlled for authors' industry affiliation revealed that pooled ORs for studies without industry funding were neutral or indicated an increased risk with smoking, depending on study design, while industry-affiliated studies indicated a reduced risk (Cataldo et al. 2010). Studies of tobacco industry documents have also revealed that the industry sought to influence scientific attitudes regarding the role of smoking in schizophrenia (Prochaska et al. 2008). Tobacco industry documents indicate that the industry funded research for the specific purpose of perpetuating the belief that smoking improves symptoms in schizophrenic patients, advocated for exceptions for smoking in hospitalized psychiatric patients, and funded studies of medicinal uses of nicotine analogs to treat mental illnesses (Prochaska et al. 2008).

Evidence of the tobacco industry's interest in the cognitive-enhancing properties of nicotine comes from a 1997 review of publications investigating the effects of tobacco and nicotine on cognitive performance. Turner and Spilich (1997) found that authors acknowledging tobacco industry funding were much less likely than nonindustry-funded authors to report a negative effect of nicotine on cognitive performance. Nonindustry-funded authors reported both positive and negative findings, while industry-funded authors reported positive findings almost exclusively (Turner and Spilich 1997). Studies of this type using more recent published articles are needed to better understand current industry influences on the scientific literature.

It is difficult to estimate the extent to which industry-generated research activities have influenced scientific thinking regarding the effects of nicotine on cognitive performance and on nicotine's therapeutic applications. Authors' industry affiliations and potential conflicts of interest reported in publications may go unnoticed by readers, may be difficult to identify, or may not be disclosed at all. Reviews and other articles citing industry-affiliated studies generally did not include author affiliations or potential conflicts of interest at all, leaving the readers unaware of possible industry influences. A growing concern about conflicts of interest resulting from funding through the tobacco industry is reflected in the National Institute on Drug Abuse (NIDA) advice to its grantees that "Receiving funding from the tobacco industry may compromise the perceived objectivity of their research results, which in turn could impact the overall credibility of their research findings, including its interpretation, acceptance and implementation" (NIDA n.d.).

Summary

Evidence shows that acute nicotine administration has some modest cognition-enhancing effects in adult smokers during withdrawal. However, less is known about the acute effects in nonabstinent smokers and in nonsmokers, and about the effects of long-term nicotine exposure on cognitive performance. Human and animal evidence show detrimental effects on cognition from smoking during aging. Evidence also shows that exposure to cigarette smoke and to nicotine has adverse effects on fetal and adolescent brain development, which could result in lasting deficits in cognitive function. Furthermore, withdrawal from tobacco in dependent-users results in cognitive impairment. Among individuals with attention-related cognitive defects, nicotine has been proposed as a potential treatment because of its effect as a cholinergic agonist. However, randomized controlled trials to demonstrate safety and efficacy of nicotine treatment in individuals with these disorders are lacking, and the long-term effects of low-dose, chronic nicotine exposure on individuals with neuropsychiatric disorders are unknown. Because nAChRs are distributed extensively across the central and peripheral nervous systems, studying the effects of nicotine across the behavioral spectrum, rather than on isolated domains, may reveal adverse effects and may help establish whether the potential benefits of nicotine are clinically meaningful (Heishman 1998).

Evidence Summary

This chapter complements reviews in prior reports and in other sections of this report on the potential toxicity of nicotine, a pharmacologically active agent that readily enters the body and is distributed throughout. Nicotine activates multiple biological pathways that are relevant to fetal growth and development, immune function, the cardiovascular system, the CNS, and carcinogenesis. Experimental research documents that nicotine plays a key role in several adverse consequences of maternal smoking for the fetus, including altered lung development, and has effects on the developing brain. Evidence supports that acute nicotine administration has modest cognition-enhancing properties in adult smokers during withdrawal and in adult nonsmokers. However, little is known about the effects of long-term nicotine exposure on cognitive performance and how nicotine withdrawal impairs cognition. Previous reports have reached causal conclusions related to nicotine and addiction (USDHHS 1988, 2010, 2012). Evidence in this chapter considers the particular vulnerability of adolescents and other groups to nicotine. Beyond the use of NRT cessation aids, the therapeutic roles for nicotine have not been established, in spite of clinical research, some carried out by the tobacco industry.

Acute toxicity of nicotine, reflecting its pharmacologic activity, is well established. There is a potential for poisoning from ingestion of nicotine-containing products.

Conclusions

1. The evidence is sufficient to infer that at high-enough doses nicotine has acute toxicity.

2. The evidence is sufficient to infer that nicotine activates multiple biological pathways through which smoking increases risk for disease.

3. The evidence is sufficient to infer that nicotine exposure during fetal development, a critical window for brain development, has lasting adverse consequences for brain development.

4. The evidence is sufficient to infer that nicotine adversely affects maternal and fetal health during pregnancy, contributing to multiple adverse outcomes such as preterm delivery and stillbirth.

5. The evidence is suggestive that nicotine exposure during adolescence, a critical window for brain development, may have lasting adverse consequences for brain development.

6. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to nicotine and risk for cancer.

Implications

Large numbers of people are exposed to nicotine through products other than conventional cigarettes, including NRT, smokeless tobacco, and new nicotine-containing noncombustible products. The fetus will be exposed to nicotine without other smoke components if the mother uses these products. The number of people exposed to nicotine long-term may grow under a number of potential future scenarios; for example, expanding use of multiple products or the replacement of conventional combustible cigarettes with other nicotine delivery systems (see Chapter 15, "The Changing Landscape of Tobacco Control: Current Status and Future Directions"), or increased appeal and uptake of nicotine product use because of their apparent relative safety in comparison to cigarettes. In considering such scenarios, information will be needed on the risks of long-term exposure to nicotine, including the consequences for reproductive health and adolescent cognitive development, compared with cigarette smoking, and no tobacco products use at all. The evidence reviewed in this chapter, in other chapters in this report, and in previous reports shows that long-term nicotine use may have adverse consequences for those exposed and it clearly harms the developing fetus. The latest U.S. Public Health Service guidelines acknowledge this risk and have not made a specific recommendation on the use of NRT during pregnancy. Pregnant women who smoke should consider and discuss with their health care providers the potential risk to the fetus from continuing to smoke and from using NRT. There is a strong recommendation from the U.S. Preventive Services Task Force for health care providers to ask pregnant women about tobacco use and provide the appropriate counseling.

The possibility of increasing chronic nicotine exposure in the population from various nicotine-containing products for the long-term merits further research. Cancer, cardiovascular, and neurocognitive outcomes are of concern. The evidence is already sufficient to provide appropriately cautious messages to pregnant women and women of reproductive age as well as adolescents about the use of nicotine-containing products such as smokeless tobacco and electronic cigarettes, and newer forms of nicotine-containing tobacco products, as alternatives to smoking.

All tobacco products contain toxicants, so all tobacco product use poses some health risks. Because of the potential for fetal and adolescent nicotine exposure to have long-term detrimental effects on brain development, measures should be taken to ensure that nicotine is not perceived by the public as a cognitive-enhancing substance. It also does not have an established role in the management of people with a severe mental illness.

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Chapter 6
Cancer

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Sections of this chapter on the health consequences of smoking are accompanied by evidence tables detailing the studies that were used to evaluate the evidence to assess causality. A supplement to this report is provided that contains these tables. The tables included in the supplement are indicated with an "*S*" where they are called out in the text.

Introduction

The signature finding of the landmark 1964 Surgeon General's report, *Smoking and Health*, was the conclusion that cigarette smoking was a cause of lung cancer in men (U.S. Department of Health, Education, and Welfare [USDHEW] 1964). At that time, cancer was a highly feared disease with limited therapeutic options (Mukherjee 2010). Surgery and radiation therapy were essentially the only treatment options, as chemotherapy was in its infancy. The efficacy of chemotherapy for childhood acute lymphoblastic leukemia and for testicular cancer had not yet been established (Proctor 1995). Chemoprevention, as now used for breast cancer, for example, had not been implemented. Screening was employed for only one disease, cervical cancer, using the Papanicolaou (Pap) smear. The first trial of mammographic screening for breast cancer, the Health Insurance Plan (HIP) study, had just been launched (Mukherjee 2010). Many of the most critical advances in mechanistic understanding that are relevant to prevention and treatment today had yet to arrive (Table 6.1) (DeVita and Rosenberg 2012).

From the perspective of 2014, the understanding 50 years ago of the pathogenesis and etiology of cancer was also quite limited (Figure 6.1) (DeVita and Rosenberg 2012). Radiation was a long-established cause of multiple types of cancer; the increased risk of lung cancer in radon-exposed uranium miners was established; and follow-up of the atomic bomb survivors had documented their increased risk of acute leukemia. Clinical experience and epidemiologic studies were documenting links between occupational exposures, including asbestos and nickel oxides, and cancer. The wave of epidemiologic studies that focused on lifestyle and risk of cancer was just starting, and relatively little attention was given to viruses and bacteria as causes of cancer.

The process of carcinogenesis was commonly understood as prolonged and involving multiple stages, leading to uncontrolled cell replication (Armitage and Doll 1954; Shimkin 1977). The 1964 Surgeon General report's discussion of carcinogenesis referred to "…a slow multi-stage process" (p. 142) and pointed out that some chemicals are "initiators," causing permanent changes in cells, while others are "promoters" of the carcinogenic process. The structure of DNA and the genetic code were identified, but research on DNA, mutations, and cancer was just starting (Table 6.1). Of course, many processes now considered to be critical in carcinogenesis (e.g., those involving oncogenes, tumor suppressor genes, and epigenetics) had not yet been discovered.

Figures 4.3 and 4.4 document trends in cancer mortality among men and women for the period 1930–2010 (American Cancer Society [ACS] 2013). However, mortality does not capture the full picture of cancer occurrence, since it matches incidence (i.e., the occurrence of new cases) for only those malignancies for which survival is very poor. For lung cancer, given a 5-year survival rate of around 15%, incidence and death rates are close. In 1964, lung cancer was the leading cause of cancer deaths in men, having passed colorectal cancer about a decade previously. Death rates for stomach cancer had declined steadily in men and women, as had the uterine (corpus and cervix) cancer mortality rate for women. The lung cancer mortality rate in 1964 for women was just starting its upward trajectory. Figure 4.3 charts the continuing course of lung cancer death rates, showing an eventual plateau and decline in men. Figure 4.4 shows a long upward course and then the beginning of a decline in women.

Overall, cancer survival has also improved in the United States. In 1953, relative 5-year survival for people with cancer was only 35% (DeVita and Rosenberg 2012). By 1977, the figure was 49% and the most recent data from the National Cancer Institute's (NCI's) Surveillance, Epidemiology, and End Results (SEER) Program for cases diagnosed between 2003–2009 and followed through 2010 was 68% (NCI 2013).

Since 1973, the incidence of cancer has been tracked in some states and metropolitan areas through the SEER Program. Figures 6.2 and 6.3 show trends for age-adjusted incidence of cigarette-caused cancers across the span covered by the SEER data among men and women. Among men, incidence rates of lung, colorectal, oropharyngeal,

Table 6.1   **Singular discoveries and major events in the cancer field and changing relative survival rates for persons with cancer in the United States, 1863–2006**

Year	Discovery or event	Relative 5-year survival rate
1863	Cellular origin of cancer (Virchow)	
1889	Seed-and-soil hypothesis (Paget)	
1914	Chromosomal mutations in cancer (Boveri)	
1937	Founding of the National Cancer Institute	
1944	Transmission of cellular information by DNA (Avery)	
1950	Availability of cancer drugs through CCNSC	
1953	Report on structure of DNA	35%
1961	Breaking of the genetic code	
1970	Reverse transcriptase	
1971	Restriction enzymes Passage of *National Cancer Act of 1971*	
1975	Hybridomas and monoclonal antibodies Tracking of cancer statistics by SEER Program	50%
1976	Cellular origin of retroviral oncogenes	
1979	Epidermal growth factor and receptor	
1981	Suppression of tumor growth by *P53*	
1982	Discovery of *RAS* oncogenes	
1984	G proteins and cell signaling	
1986	Retinoblastoma gene	
1990	First decrease in cancer incidence and mortality	
1991	Association between mutation in *APC* gene and colorectal cancer	
1994	Genetic cancer syndromes Association between *BRCA1* and breast cancer	
2000	Sequencing of the human genome	
2002	Epigenetics in cancer Micro-RNAs in cancer	
2005	First decrease in total number of deaths from cancer	68%
2006	Tumor stromal interaction	

Source: Adapted from DeVita and Rosenberg 2012 using data from Chang et al. 1982. Reprinted with permission from Massachusetts Medical Society, © 2012.
Note: **CCNSC** = Cancer Chemotherapy National Service Center; **SEER** = Surveillance, Epidemiology, and End Results Program of the National Cancer Institute.

Figure 6.1   Timeline of pivotal events in cancer prevention

Viruses and cancer ....
Chemoprevention ——————
Tobacco and cancer — — — —

HPV vaccine developed, 1985

Vaccine prevents hepatitis and hepatoma, 1981

Tamoxifen prevention trials, 1989

Link discovered between HPV and cervical cancer, 1976

Proof of principle: chemoprevention works, 1990

Hepatitis linked to hepatoma, 1974

Lung-cancer incidence and mortality begin to fall, 1990–1991

First vaccine against hepatitis B, 1974

BCG prevents bladder cancer, 1991

Tobacco advertising on radio and television banned in U.S., 1970

Antiestrogen drugs prevent DCIS, 1995

Hepatitis B discovered, 1967

Tamoxifen discovered, 1967

Tamoxifen reduces breast cancer incidence, 1998

Hypothesis that tobacco is linked to lung cancer, 1912

Warning labels on cigarette packages, 1965

FDA approves HPV vaccine to prevent cervical cancer, 2000

Surgeon General's report on risks of smoking, 1964

Finasteride reduces prostate cancer incidence, 2003

HPV discovered, 1907

Experimental evidence links lung cancer to smoking, 1950

Aspirin prevents colon cancer, 2003

	1890	1900	1910	1920	1930	1940	1950	1960	1970	1980	1990	2000	2010	2020
Incidence per 100,000 (age adjusted)									400		511		473	444
Mortality per 100,000 (age adjusted)									200		215		178	151

Source: DeVita and Rosenberg 2012. Reprinted with permission from Massachusetts Medical Society, © 2012.
Notes: **BCG** = bacille Calmette-Guérin; **DCIS** = ductal carcinoma in situ; **FDA** = U.S. Food and Drug Administration; **HPV** = human papilloma virus.

stomach, and laryngeal cancers have declined over time, but rates for kidney and liver cancers continue to rise. The trend is similar among women, with the exception of lung cancer for which incidence rates increased in the two decades since 1975, and reached a plateau since the mid-1990s, before declining in 2007 (Howlader et al. 2013). In addition to the SEER areas, the rest of the nation and the District of Columbia are covered by the National Program of Cancer Registries (NPCR) of the Centers for Disease Control and Prevention (CDC). The *Annual Report to the Nation on the Status of Cancer*, a collaborative publication by the ACS, the North American Association of Central Cancer Registries, CDC, and NCI, provides an

ongoing assessment of progress in cancer control. The most recent report reveals a decline in the incidence of lung cancer for both men and women in the first decade of the twenty-first century (Jemal et al. 2013). For men, the rate declined by 2.0% annually during this decade, while the annual decline was 0.2% for women.

This chapter reviews the evidence on smoking and cancer for malignancies for which the evidence was previously found to be inadequate or was insufficient to reach a causal conclusion. Specifically, four cancer sites are covered—breast, colon and rectum, liver, and prostate—and also the changing cigarette and risk for lung cancer over time. The chapter also covers the rela-

Figure 6.2   Surveillance, Epidemiology, and End Results (SEER) age-adjusted incidence, selected sites, males, 1975–2010
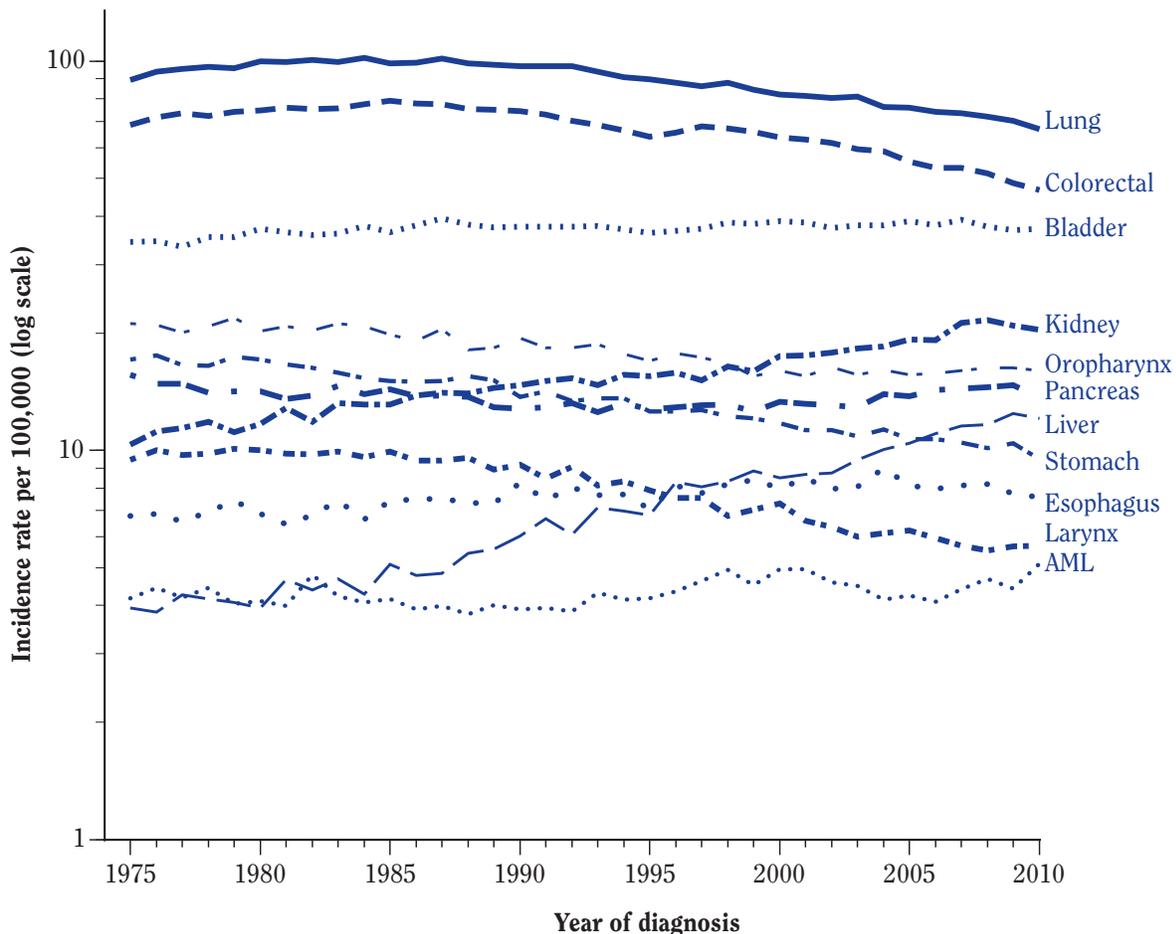
Source: Howlader et al. 2013.
Note: The data are for nine SEER areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta). Rates are per 100,000 and are age-adjusted to the 2000 U.S. standard population (19 age groups – Census P25-1130). **AML** = acute myeloid leukemia.

Figure 6.3   Surveillance, Epidemiology, and End Results (SEER) age-adjusted incidence, selected sites, females, 1975–2010
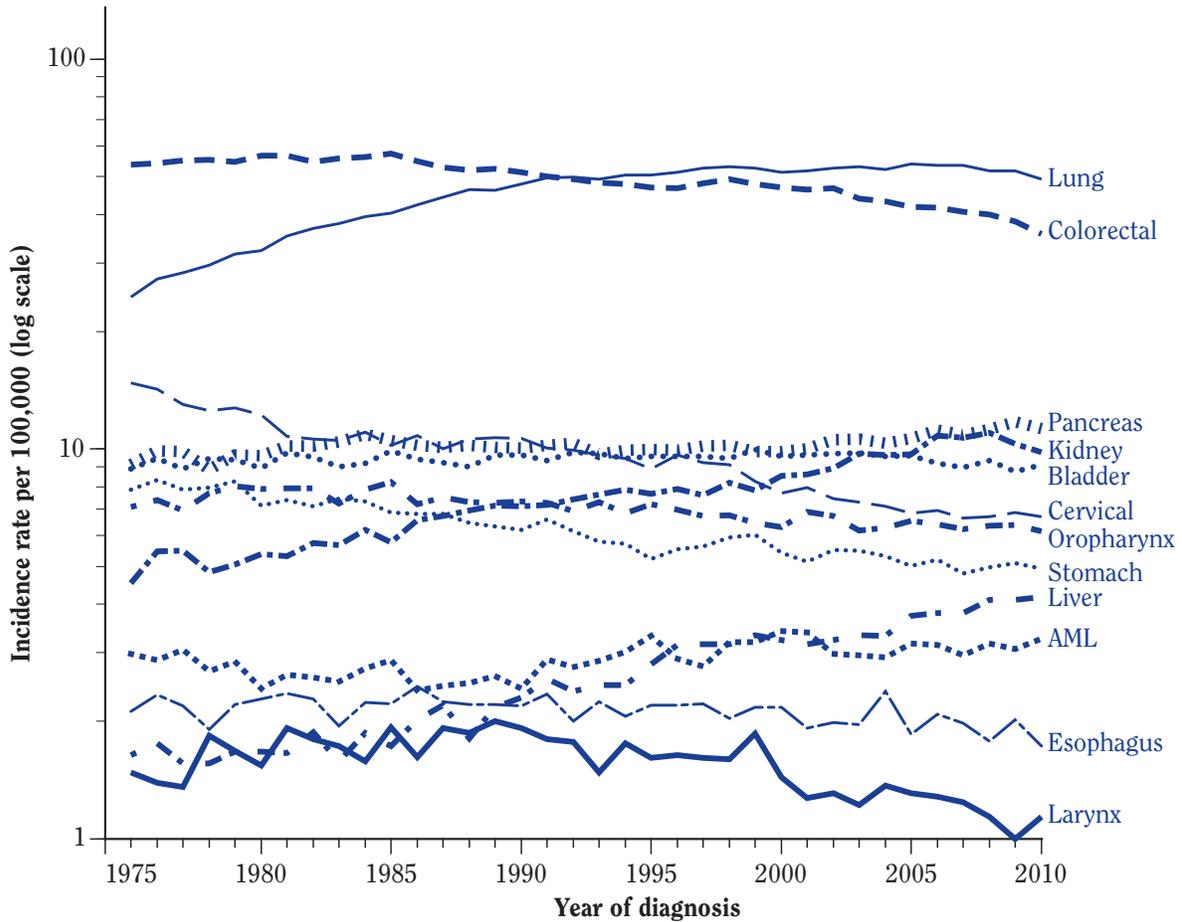
Source: Howlader et al. 2013.
Note: The data are for nine SEER areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta). Rates are per 100,000 and are age-adjusted to the 2000 U.S. standard population (19 age groups – Census P25-1130). **AML** = acute myeloid leukemia.

tionship between smoking and the outcome of cancer, a topic not previously addressed in the reports of the Surgeon General on smoking and health. Previous reviews related to cancer were included in the 2004 Surgeon General's report on active smoking (U.S. Department of Health and Human Services [USDHHS] 2004) and in the 2006 report on exposure to secondhand smoke (USDHHS

2006). Figure 1.1A shows those malignancies for which the Surgeon General's reports classified the relationship with smoking as causal. The chapter begins with an overview of the mechanisms by which smoking causes cancer, based on the indepth coverage of this topic in the 2010 Surgeon General's report *How Tobacco Smoke Causes Disease* (USDHHS 2010).

Mechanisms of Cancer Induction by Tobacco Smoke

Classic studies demonstrating the covalent binding of carcinogens, or their reactive electrophilic metabolites, to cellular macromolecules (including DNA) were published at about the same time as the 1964 Surgeon General's report on smoking and health (USDHEW 1964; Miller and Miller 1976). Building on these seminal observations, many researchers explored this mechanistic concept in detail and confirmed it for different classes of chemical carcinogens; that line of research continues even today (Searle 1984; Loebe and Harris 2008; Penning 2011). Tobacco smoke, with its multiple carcinogens, recapitulates the classic mechanisms established in these studies. The general concept of exposure to carcinogens, metabolism to reactive intermediates, and DNA damage leading to mutations in critical genes has been established as one major mechanism by which tobacco smoke causes cancer. This topic was discussed in some detail in Chapter 5 of the 2010 Surgeon General's report. A mechanistic framework encompassing these steps and related phenomena was presented in that report and in related publications, and

it is reproduced here as Figure 6.4 (Hecht 1999, 2012a). This section will present a brief overview of the relevant steps in Figure 6.4 and a more detailed discussion of some recent findings pertinent to this overall mechanism.

People begin to smoke cigarettes at a relatively young age, typically have difficulty stopping, and may continue to smoke for decades. Nicotine is addictive, but is not a direct chemical carcinogen (see Chapter 5, "Nicotine") (Maier et al. 2011; Murphy et al. 2011). However, by creating and sustaining addiction, it leads to the prolonged exposure to tobacco smoke that increases cancer risk for smokers. When smokers inhale smoke, each cigarette puff delivers a mixture of carcinogens and toxicants. Tobacco smoke contains more than 7,000 chemicals, and at least 69 of these can cause cancer (USDHHS 2010). These include polycyclic aromatic hydrocarbons (PAHs); tobacco-specific nitrosamines; aromatic amines; and volatile carcinogens such as formaldehyde, acetaldehyde, 1,3-butadiene, and benzene (as well as various metals).

Figure 6.4   Pathway for causation of cancer by carcinogens in tobacco smoke
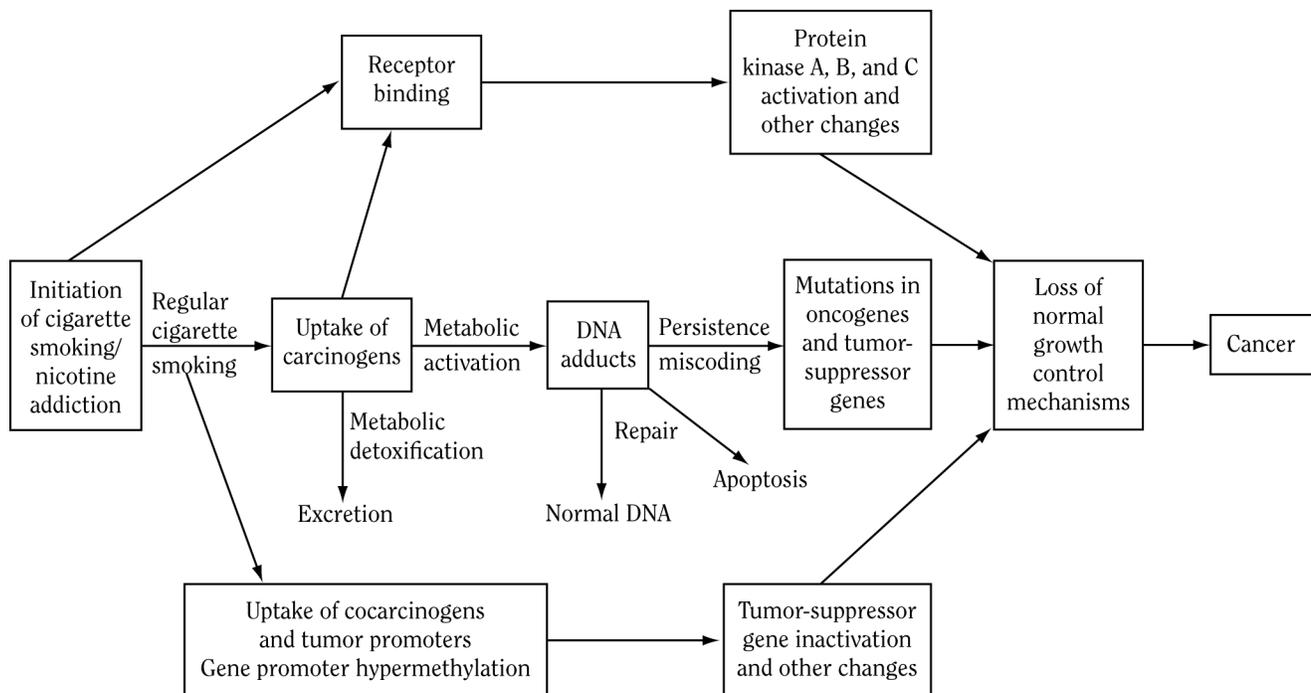
Source: Modified from U.S. Department of Health and Human Services 2010.

Most constituents of cigarette smoke, including the carcinogens, are compounds foreign to the human body and, consequently, are acted upon by metabolizing enzymes designed to detoxify them. These enzymes, including cytochrome P-450, glutathione *S*-transferases, and UDP-glucuronosyl transferases and sulfotranferases, catalyze the conversion of these foreign compounds to more water-soluble products that can be easily excreted from the body. But during this process, certain reactive compounds may be formed as intermediates. Examples of these reactive intermediates include electrophilic carbocations or epoxides that can bind covalently to nucleophilic sites in DNA, including the nitrogen and oxygen atoms of DNA nucleobases. These binding products are known as DNA adducts and are critical in carcinogenesis if they are not fixed by DNA repair enzymes. Persons with rare syndromes in which DNA repair is deficient, such as *Xeroderma pigmentosum*, are highly prone to cancer development; people with this syndrome develop skin cancer because of the multiple types of DNA damage that result from exposure to sunlight (Weinberg 2007).

There is convincing evidence for the presence of DNA adducts in the lungs and other tissues of smokers in amounts generally higher than those found in nonsmokers. While many of these adducts remain unidentified, a number of studies have characterized specific carcinogen-DNA adducts in the tissues of smokers (Phillips and Venitt 2012).

If the DNA adducts produced by tobacco smoke carcinogens and their metabolites evade repair systems and remain, they can cause miscoding during DNA replication when bypass DNA polymerase enzymes direct the placement of an incorrect nucleobase opposite the adduct (USDHHS 2010). This can result in a permanent mutation in the DNA sequence. If this mutation occurs in an important section of a cellular oncogene such as *KRAS*, or in a tumor suppressor gene such as *TP53*, the result can be an alteration of the normal growth control mechanisms, leading to uncontrolled proliferation, further mutations, and cancer. Multiple studies, using state-of-the-art methods, have shown that thousands of mutations are present in the DNA of lung tumors from smokers, including in critical growth regulatory genes, most frequently *KRAS* and *TP53*. These genes are discussed in more detail below (Greenman et al. 2007; Ding et al. 2008a; Lee et al. 2010c; Pleasance et al. 2010).

Some constituents of tobacco smoke or their metabolites may bind directly to cellular receptors, leading to activation of protein kinases, growth receptors, and other pathways, which can contribute to carcinogenesis (Chen et al. 2011b). Cigarette smoke contains substances that can induce inflammation resulting in enhanced pneumocyte proliferation, activation of nuclear factor-kappa B (NF-κB), and tumor promotion (Takahashi et al. 2010). Cigarette smoke also has cocarcinogens which, while not carcinogenic themselves, enhance the smoke's carcinogenic effects. Further, cigarette smoke induces oxidative damage and gene promoter methylation, processes that also likely contribute to cancer development.

In the last few years, there have been some developments that were not fully covered in the 2010 Surgeon General's report, but are pertinent to a fuller understanding of the mechanisms of carcinogenesis by cigarette smoke. They are discussed briefly here.

Addiction to nicotine results from its binding to nicotinic acetylcholine receptors (nAChRs). An association between common variants in the *CHRNA5-CHRNA3-CHRNB4* nAChRs subunit gene cluster on chromosome 15q25 and the risk of lung cancer was reported in three genome-wide association studies (Amos et al. 2008; Hung et al. 2008; Thorgeirsson et al. 2008). These genes are strongly associated with nicotine dependence (Saccone et al. 2007), and multiple studies have confirmed and amplified these observations (Saccone et al. 2009, 2010; Timofeeva et al. 2011; Wang et al. 2011; Ware et al. 2011; Wassenaar et al. 2011). These results are likely due to changes in smoking behavior causing an increased uptake of nicotine as well as a greater presence of lung carcinogens, such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), in carriers of the gene variants described above (Le Marchand et al. 2008). The increased uptake of nicotine, which was confirmed by measurement of its metabolite cotinine in a similar study based on the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, is a surrogate for the uptake of carcinogens and toxicants in cigarette smoke (Timofeeva et al. 2011; Yuan et al. 2011a, 2012). Thus, carriers of the gene variants smoke their cigarettes more intensely and are exposed to higher levels of NNK and other carcinogens in smoke, thereby increasing their risk of lung cancer.

Modern DNA-sequencing methods allow scientists to carry out detailed investigations of mutations in human cancers. Because there are multiple carcinogens in cigarette smoke and multiple DNA adducts in the lungs of smokers, one would expect to find many mutations within critical genes in the lung tumors from smokers. Sequencing studies are consistent with this expectation. For example, when Greenman and colleagues (2007) investigated mutations in the coding exons of more than 500 protein kinase genes, they found that lung cancers were among those with the most somatic mutations (4.21 per megabase). The authors attributed this finding to

recurrent exposure to exogenous mutagens (Greenman et al. 2007). Another investigation sequenced 188 primary lung adenocarcinomas; altogether, 247 megabases of tumor DNA sequence were analyzed and 1,013 nonsynonymous somatic mutations in 163 of the 188 tumors were identified, including 915 point mutations, 12 dinucleotide mutations, 29 insertions, and 57 deletions (Ding et al. 2008a). Twenty-six significantly mutated genes were identified, including oncogenes and tumor suppressor genes commonly found to be mutated in lung cancer, such as *TP53*, *KRAS*, *CDKN2A*, *STK11*, and others. Mutations were most common in *TP53* and *KRAS*.

More recently, a report on complete exome and genome sequences of 183 lung adenocarcinomas revealed a mean exonic somatic mutation rate of 12.0 events per megabase (Imielinski et al. 2012). Analysis of nucleotide context-specific mutation signatures grouped the sample set into distinct clusters that correlated with smoking history and alterations of reported lung adenocarcinoma genes. Elsewhere, Pleasance and colleagues (2010) sequenced a small-cell lung cancer cell line; these investigators identified 22,190 somatic substitutions, including 134 in coding exons. They found that $G{\rightarrow}T$ transversions were the most common (34%), followed by $G{\rightarrow}A$ transitions (21%) and $A{\rightarrow}G$ transitions (19%). These results are similar to data that have been obtained by analysis of the *TP53* gene, which is discussed later in this overview. Elsewhere, a case report focused on a non-small-cell lung cancer (NSCLC) from a 51-year-old patient who had smoked 25 cigarettes per day for 15 years prior to excision of the tumor, which yielded a poorly differentiated sample with 95% tumor content, most likely an adenocarcinoma (Lee et al. 2010c). In this patient, single nucleotide variants were common, mostly at $G{\rightarrow}C$ base pairs, frequently $G{\rightarrow}T$ transversions; these were statistically distinct from germline mutations. More than 50,000 single nucleotide variants were observed, approximately 17.7 mutations per megabase. At least eight genes in the EGFR-RAS-RAF-MEK-ERK pathway were either mutated or amplified.

In another investigation, whole-exome sequencing and gene copy number analyses were used to study 32 primary head and neck squamous cell carcinomas (Agrawal et al. 2011). Tumors from patients with a history of tobacco use had more mutations than did tumors from patients who did not use tobacco, and tumors that were negative for human papilloma virus (HPV) had more mutations than did HPV-positive tumors. Six of the genes that were mutated in multiple tumors were assessed in up to 88 additional head and neck squamous cell carcinomas. In addition to previously described mutations in

TP53, *CDKN2A*, *PIK3CA*, and *HRAS*, new frequent mutations were found in *FBXW7* and *NOTCH1*. In all, 11 of the 28 mutations (39%) identified in *NOTCH1* were predicted to truncate the gene product, suggesting that *NOTCH1* may function as a tumor suppressor gene rather than as an oncogene in this tumor type. Moreover, a similar study of 78 additional tumors reported that 30% of the cases harbored mutations in genes that regulate squamous differentiation (including *NOTCH1*, *IRF6*, and *TP63*), implicating such dysregulation as a major driver of carcinogenesis in head and neck squamous cell carcinoma (Stransky et al. 2011).

The results of these studies are consistent with those reported in the 2010 Surgeon General's report and with information found in the COSMIC (Catalogue of Somatic Mutations in Cancer) database (Wellcome Trust anger Institute 2012), which stores and displays somatic mutations in genes associated with cancer, such as *TP53* and *KRAS*. Collectively, the available results of late-generation sequencing studies, as well as the extensive databases on *TP53* and *KRAS* mutations, are completely consistent with the induction of multiple mutations in critical growth control genes by metabolically activated carcinogens of cigarette smoke, although other processes downstream from exposure to carcinogens could also contribute.

Epigenetic changes, defined as nonsequence DNA changes, are also an integral part of cancer progression. Gene promoter hypermethylation is an epigenetic change, involving extensive methylation at the 5-position of C in CpG islands within the promoter region, and, often, extending into exon 1 of regulatory genes (Jones and Baylin 2002). In lung cancer, more than 750 genes are inactivated by gene promoter hypermethylation, and new genes are still being identified through genomewide screening approaches (Selemat 2012). The end result of this process can be the loss of gene transcription and, therefore, the silencing of gene function. Comparison of DNA methylation profiles between lung adenocarcinomas of current and never smokers, using a genome-wide platform, showed only modest differences between the groups, and it identified only *LGALS4* as significantly hypermethylated and downregulated in smokers (Selemat et al. 2012). Analysis of the DNA methylation data identified two tumor subgroups, one of which showed increased DNA methylation and was significantly associated with *KRAS* mutation and, to a lesser extent, with smoking. Promoter methylation of several genes, including *P16,* occurs early in tumor formation. One study of head and neck cancer found that *P16* methylation was significantly and positively associated with pack-years[1] of smoking and was an independent risk factor for overall survival, being

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[1]Pack-years = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

significantly associated with shorter survival in patients with early resectable adenocarcinomas (Ai et al. 2003). In that study, *P16* promoter hypermethylation also correlated significantly with a history of alcohol consumption or tobacco use in head and neck cancer. Other genes, such as *BRMS1* and *RASSF1A,* may be more frequently methylated in various tumor types from smokers. In a study by Tessema and colleagues (2009), the frequency of methylation of *TNFRSF10C*, *BHLHB5*, and *BOLL* was significantly higher in adenocarcinomas from never smokers than in those from smokers. Methylation of genes, such as *MGMT* and *AGT* promoter hypermethylation, may increase $G{\rightarrow}A$ transition mutations at CpG sites within the *TP53* gene in NSCLC.

These data in aggregate support the pathways illustrated in Figure 6.4. The contribution of specific tobacco smoke carcinogens to lung cancer (and also to esophageal cancer) has been investigated in several nested case-control studies as well. In these studies, the carcinogens or their metabolites were quantified in stored urine samples that were collected from smokers years or decades before cancer developed. For example, using frozen urine samples collected during the 1980s from more than 18,000 smokers in Shanghai, China, scientists have found that specific metabolite levels were associated with an increased risk of lung or esophageal cancer, even after correction for the number of years of smoking and number of cigarettes smoked per day (Yuan et al. 2009, 2011a,b). Thus, significantly elevated risks for lung cancer were associated with increased levels of the NNK metabolites' total NNAL [4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides] and the PAH metabolite phenanthrene tetraol. The strongest elevated risk was for esophageal cancer in individuals with the highest levels of the tobacco-specific carcinogen *N′*-nitrosonornicotine and its glucuronides in their urine.

This carcinogen induces a high incidence of esophageal tumors in rats (Yuan et al. 2009, 2011a,b).

Smokers experience proinflammatory changes in their lungs. Inflammation is intimately associated with activation of NF-κB and tumor promotion (Malkinson 2005; Smith et al. 2006; Lee et al. 2008), and many studies in laboratory animals demonstrate that anti-inflammatory agents can decrease tobacco carcinogen-induced lung tumorigenesis (Hecht et al. 2009). In addition, chronic obstructive pulmonary disease, particularly emphysema, is an independent risk factor for lung cancer in smokers. This association further implicates a strong role for inflammation in lung cancer (Turner et al. 2007). In one study, the tumor-promoting activity of cigarette smoke was examined in mouse models of lung tumorigenesis (Takahashi et al. 2010); here, exposure to smoke after treatment of A/J mice with NNK increased the multiplicity of lung tumors. Similar results were obtained in *KRAS^{LA2}* mice harboring a mutation in *KRAS* codon 12 identical to that caused by NNK. IκB kinase β (IKKβ) was required for NF-κB activation and played a critical role in tumor promotion in this system, most likely through the induction of inflammation and related phenomena (Takahashi et al. 2010). These studies amplify and extend earlier observations demonstrating the tumor-promoting activity of cigarette smoke.

Summary

Understanding of the mechanisms by which smoking causes cancer continues to advance. An overall framework for the causation of cancer by tobacco smoking was set out in the 2010 Surgeon General's report. The utility of that framework is supported by new experimental findings as well as by ongoing studies of smokers in the population.

Changing Cigarettes and Risk for Lung Cancer Over Time

Cigarette smoking is the predominant cause of lung cancer in the United States, and lung cancer is the country's leading cause of cancer death (USDHHS 2004). Cigarette smoke, which contains multiple carcinogens (Hoffmann and Hoffmann 1997; IARC 2004; USDHHS 2004; Rodgman and Perfetti 2009), is composed of gases and particles with a distribution of size that result in substantial deposition in the lung when the smoke is inhaled (Stratton et al. 2001; Gower and Hammond 2007). The composition of tobacco smoke varies with cigarette

type (e.g., filtered or unfiltered) and across brands of the same type (IARC 2004; Burns et al. 2008; World Health Organization [WHO] 2008b). Over past decades, multiple substantive changes in the design and composition of cigarettes have altered the chemistry of tobacco smoke raising the question as to whether lung cancer risks have changed in response (Hoffmann and Hoffmann 1997; Rodgman and Perfetti 2009). This section reviews evidence relevant to this question.

This section focuses on lung cancer because it is the cancer most related to cigarette smoking (USDHHS 2004). Substantial data are available, both over time and from many countries, on the occurrence of lung cancer, both generally and by histologic type. The topic of lung cancer in relation to smoking has been addressed in depth in several past reports of the Surgeon General. These reports have focused on levels of machine-measured tar and nicotine in relation to risk and have considered whether changes in design and characteristics that have lowered the tar yield of cigarettes have also reduced the risk of diseases caused by smoking (USDHHS 1981, 2004). The 2004 Surgeon General's report on the health consequences of smoking concluded that no substantive reduction in the risk of disease was associated with using cigarettes with low levels of tar, as measured by machine. This and earlier reports clearly document that machine-measured tar yields have little relationship to the doses actually received by smokers because of the phenomenon of compensation. This section focuses mainly on whether the changes in the design and composition of cigarettes over time that paralleled the reduction in tar yields (by machine measurement) may have altered—and possibly even increased—the risk of lung cancer associated with cigarette smoking. The analysis is limited to cigarette design issues and does not consider other issues, such as changing nicotine yields and the marketing of various types of cigarettes. This section does not explore the implications of these changes for diseases other than lung cancer.

Changes in Cigarettes Over the Past Several Decades

Since the 1950s, cigarettes have undergone changes in their design and composition (Hoffmann and Hoffmann 1997; NCI 2001). The most prominent changes have been the addition of filters and the use of ventilation holes in the filters to lower machine-measured tar and nicotine yields. Figure 6.5 shows the rapid rise in the use of filtered cigarettes that followed the heavy marketing of such cigarettes in the mid-1950s. The marketing effort promised a lower risk product to smokers who had become concerned about the disease risks of smoking (Brandt 2007). This shift to filters continued and today almost all manufactured cigarettes currently consumed in the United States are filtered (Hoffmann and Hoffmann 1997; NCI 2001). Figure 6.6 shows the move to cigarettes with lower tar yields, beginning with a shift from brands with more than 20 milligrams (mg) of machine-measured tar

Figure 6.5   Market share and total annual cigarette sales of filtered and unfiltered cigarettes in the United States, 1925–1993
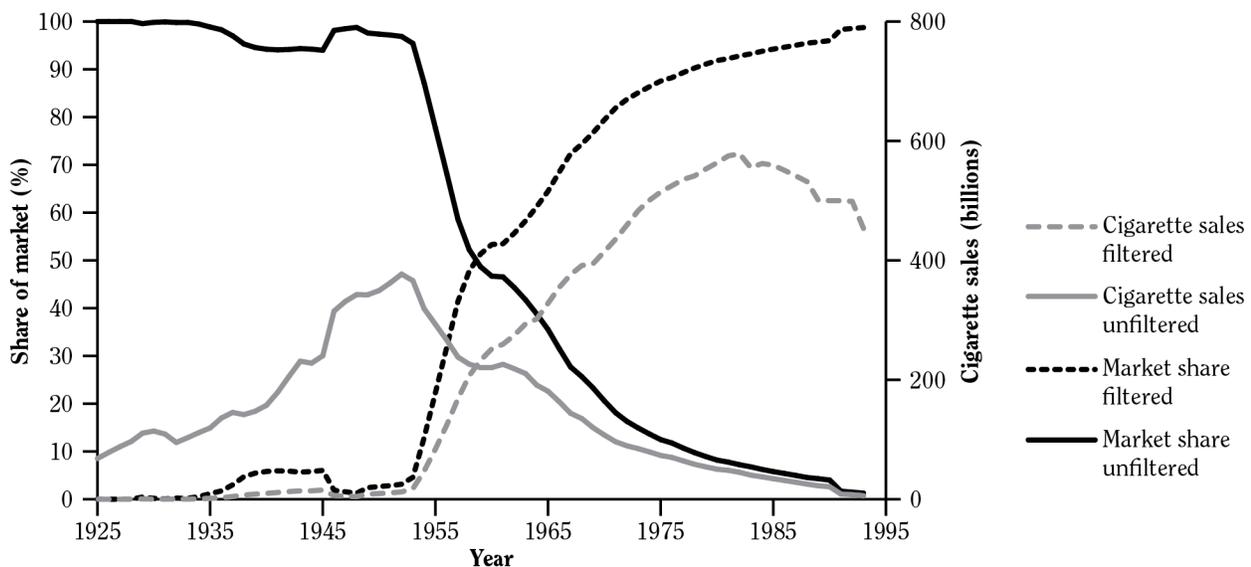
Source: National Cancer Institute 2001; data from Maxwell 1994.

Figure 6.6   Market share of total cigarettes sold per year, by tar yield (milligrams [mgs] of tar by Federal Trade Commission method), United States, 1967–1990
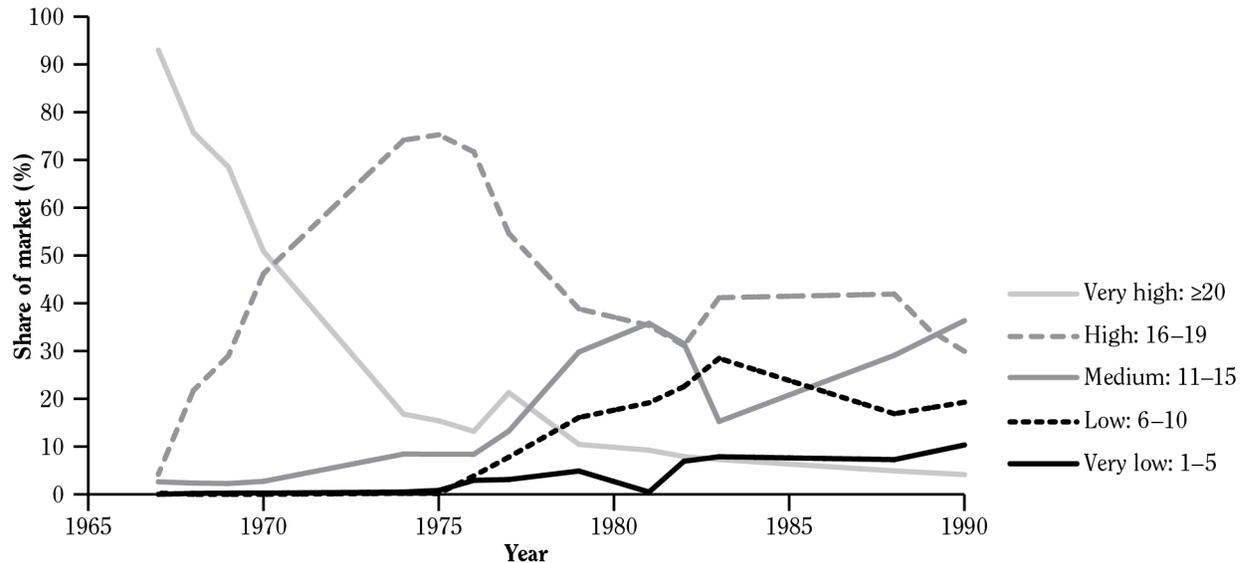
Source: National Cancer Institute 2001; data from Maxwell 1994.
Note: Tar levels for given years are derived from Federal Trade Commission reports (for years 1967–1990). Sales data by brand are from Maxwell (1994). Brand-specific market shares are summed by tar level of the brand in the given year to generate the market share for cigarettes with given tar yields.

to lower tar-yielding brands in the late 1960s and early 1970s (NCI 2001). By 1990, about two-thirds of cigarettes sold had either medium (11–15 mg), low (6–10 mg), or very low (1–5 mg) yields of tar. The principal mechanism underlying the lower yields of machine-measured tar was the increase in the number and the size of ventilation holes in the filter, thereby diluting the smoke entering the machine (Hoffmann and Hoffmann 1997; NCI 2001). Although these changes reduced tar delivery as measured by the U.S. Federal Trade Commission's (FTC's) protocol, which did not reflect how smokers actually smoke; they did not reduce the risks of disease and premature mortality in smokers (NCI 2001; USDHHS 2004).

Epidemiologic evaluations of risk and assessments of smoke chemistry during the decades in which these substantial changes occurred tended to treat all cigarettes as if they were equivalent, both over time and across brands. The exception was that these evaluations did consider the machine-measured tar and nicotine yields and whether they were filtered. However, the design and composition of cigarettes changed substantially in other ways, even as they were continuously redesigned to deliver ever lower machine-measured yields of substances. Unfortunately,

researchers in the past did not have access to information about the nature and extent of these and other changes in cigarettes because they were handled as trade secrets and, therefore, not disclosed by the industry.

Changes in Design, Curing, and Composition

Although smokers may perceive cigarettes as very simple devices: chopped-up tobacco rolled in paper, perhaps with a filter attached to the end, the reality, however, is that cigarettes are highly engineered products (Hoffmann and Hoffmann 1997; Rodgman and Perfetti 2009; Proctor 2011). The design features of cigarettes can have significant effects on the composition of the tobacco smoke and perhaps its toxicity. Over time, changes to cigarettes have become progressively more extensive and more complex, further complicating the efforts of researchers to understand their health implications (Hoffmann and Hoffmann 1997; NCI 2001; O'Connor et al. 2008; O'Connor and Hurley 2008; WHO 2008b). Many factors can influence the chemistry of tobacco smoke: (1) the geographic location where the tobacco is grown (which can alter the heavy metal content of smoke, for example) (IARC 2004,

2007); (2) agricultural practices (which can influence levels of nitrates and pesticides, but also polonium and heavy metal content as well) (Hoffmann and Hoffmann 1997; Rodgman and Perfetti 2009); (3) how the tobacco is cured and processed (which can influence tobacco-specific nitrosamine levels and other factors) (Hoffmann and Hoffmann 1997; NCI 2001; Peele et al. 2001; O'Connor et al. 2008; O'Connor and Hurley 2008); (4) the blend of tobacco used; (5) the use of reconstituted tobacco sheet and puffed tobacco (tobacco expanded through an industrial process) (Hoffmann and Hoffmann 1997; IARC 2004, 2007; O'Connor et al. 2008; O'Connor and Hurley 2008; Rodgman and Perfetti 2009); (6) the engineering characteristics of the manufacturing process (Hoffmann and Hoffmann 1997; O'Connor et al. 2008; O'Connor and Hurley 2008; Rodgman and Perfetti 2009); (7) the additives used in tobacco; and (8) the pattern of puffing the smoker uses to generate the smoke (which can alter the quantity of smoke generated and the relative composition of its constituents) (WHO 2007, 2008b; Burns et al. 2008).

Cigarettes in Australia, Canada, and the United Kingdom are made primarily of flue-cured tobacco, but most brands sold in the United States use a blend of air-cured tobaccos (Hoffmann and Hoffmann 1997; IARC 2004; WHO 2008b; Rodgman and Perfetti 2009). In addition, substantial amounts of reconstituted tobacco sheet and puffed tobacco are added to the blend. The soil in which the tobacco is grown, the agricultural practices used, and the methods of curing and processing the tobacco also differ across brands and have changed over time (Hoffmann and Hoffmann 1997; Peele et al. 2001; IARC 2004; Rodgman and Perfetti 2009). Flavoring agents; processing aids, such as humectants; chemicals intended to alter the pH of the smoke; and other agents are added to tobacco as part of the manufacturing process.

Approaches used to alter the processes of generating smoke may involve the cut size of the reconstituted tobacco sheet, filter ventilation, the density of the tobacco in the rod, the composition and design of the filter material, the porosity of the cigarette paper, and other factors (Hoffmann and Hoffmann 1997; O'Connor et al. 2008; O'Connor and Hurley 2008; Rodgman and Perfetti 2009). The pattern the smoker uses to puff the cigarette is superimposed on all of its intrinsic characteristics. This pattern varies among smokers and can change with different types of cigarettes smoked by the same smoker; it can also change systematically across smokers in response to certain design features, most notably filters and ventilation (NCI 2001; WHO 2008b). Rodgman and Perfetti (2009), O'Connor and colleagues (2008), and O'Connor and Hurley (2008) have reviewed the impact of many of these factors on the composition of tobacco smoke, but a detailed review of the extensive literature describing the effect of isolated changes on smoke composition is beyond the scope of this section.

Beyond the data held by the manufacturers, the details on differences in the design and composition of cigarettes across U.S. brands are not available in a systematic form. Complete and representative information is also not available over time on the composition of smoke generated by individual brands or on the changes in manufacturing practices for different brands. Longitudinal data on brands marketed in the United States are limited to data—using FTC's protocol—on machine-measured yields of the tar, nicotine, and carbon monoxide produced. Without this information, the research and public health communities have been unable to fully assess the potential effects of changes in the design and composition of cigarettes on smokers' exposures over time to toxicants in cigarette smoke. Nevertheless, the limited data that exist allow for some assessment of likely changes in smoke toxicity following changes that have been made in cigarettes.

Differences Across Brands in Toxicant Yields

Of the 7,000 or more constituents in tobacco and tobacco smoke, 69 have been identified as carcinogens (USDHHS 2010). The complexity and expense of measuring multiple constituents for all the different brands under multiple sets of machine parameters have led tobacco industry scientists to suggest that constituent yields can be benchmarked and reliably predicted from machine-measured tar yields (Counts et al. 2004, 2005, 2006; Morton and Laffoon 2008). This concept is based on the assumed relationship between the total mass of smoke and its nicotine content, as measured by a smoking machine. However, the mass of smoke generated by a smoking machine using any fixed protocol bears little relationship to the amount of smoke inhaled by a smoker or to the differences between brands in smoke exposure (Jarvis et al. 2001; NCI 2001). A more appropriate method for examining the variation in constituent yields across brands is to examine these yields after they have been normalized per mg of tar or per mg of nicotine to characterize the variation that might be experienced for a given level of nicotine intake.

Nicotine is the principal addictive constituent sought by the smoker and the ratio of tar to nicotine is relatively constant across brands. When the Massachusetts Benchmark Study data on yields for a 1999 sample of U.S. brands of cigarettes are normalized per mg of tar or per mg of nicotine, the ability of tar yields to predict the variation in yields of other constituents is poor (Harris 2001, 2004). In fact, the normalized yields of several

constituents are higher for cigarettes with low machine-measured tar yields than for those whose machine-measured tar yields are high (Harris 2004).

Table 6.2 presents the variability in the yields of a variety of constituents across brands, normalized per mg of tar or per mg of nicotine, from the Massachusetts Benchmark Study sample of U.S. cigarettes in 1999. In this table, the coefficient of variation across brands (which represents the standard deviation of the measurements across brands normalized to the mean value of that constituent for all brands) is divided by the mean standard deviation of replicate measurements for that constituent. This formulation expresses the variation of constituents across brands in relation to the precision with which the constituent can be measured. Table 6.2 demonstrates that for many of the toxicants measured, the variation in constituents across brands, normalized per mg of tar or per mg of nicotine, is many times higher than can be explained by the variability of the measurement. Clearly, at least in terms of constituent yields from machine-generated cigarette smoke, smoke from all cigarettes is not uniform in composition. This variability is likely not limited to 1999, when the cigarettes were sampled, or to have remained constant over time. Furthermore, normalized constituent yields in Canadian and Australian cigarette brands and a sample of international blended cigarette brands manufactured by Philip Morris International have demonstrated similar variability (WHO 2008b). In addition, when biomarkers of exposure to specific toxicants are assessed, the data show considerable variability in their levels among smokers, particularly in heavy smokers (Joseph et al. 2005); this finding is consistent with variation in exposure due to differences in smoke composition across brands and to inherent variability among smokers.

Changes in Tobacco-Specific Nitrosamine and Benzo[*a*]pyrene Levels Over Time

Because only limited longitudinal data are available for toxicant yields, changes in these yields over time are difficult to characterize accurately for all brands. However, for one major U.S. brand, some data are available for two of the major toxicants: benzo[*a*]pyrene (B[*a*]P) and the tobacco-specific nitrosamines (*N*´-nitrosonornicotine [NNN] and NNK).

B[*a*]P, one of the earliest identified carcinogens in cigarette smoke, is a typical carcinogenic PAH and is often used as a surrogate index for the PAHs as a group. Efforts to reduce the levels of this carcinogen in smoke have included increasing the proportion of tobacco in the cigarette rod that is made up of reconstituted sheet, changing the tobacco blend, increasing the porosity of the

paper, and using other techniques (O'Connor et al. 2008; O'Connor and Hurley 2008; WHO 2008b; Rodgman and Perfetti 2009). Data are not available for all U.S. brands over time, but Hoffmann and Hoffmann (1997) published data for a prominent cigarette brand, measured repeatedly from 1959–1995, that showed a modest decline in B[*a*]P levels in smoke over that period.

In contrast to the decline in levels of B[*a*]P, levels of tobacco-specific nitrosamines, specifically NNK, increased dramatically in the previously referenced brand from 1978–1995 (Hoffmann and Hoffmann 1997). This increase was due in part to the increased nitrate levels in the tobacco used in cigarettes even before the curing (Hoffmann and Hoffmann 1997; Ding et al. 2008b; O'Connor et al. 2008; O'Connor and Hurley 2008; Rodgman and Perfetti 2009) and to changes in curing practices that have increased the presence of oxides of nitrogen and nitrate ion and the latter's reaction products during curing, with the resultant formation of tobacco-specific nitrosamines from the nicotine in the leaf (Hoffmann and Hoffmann 1997; NCI 2001; Peele et al. 2001; IARC 2004; Ding et al. 2008b; O'Connor et al. 2008; O'Connor and Hurley 2008).

Differences in Toxicant Yields Across Countries

Relatively more evidence is available for differences in toxicant yields from comparisons of international brands of cigarettes. Of particular note, the use of burley tobacco in U.S.-style blended cigarettes contributes substantially to the differences in tobacco-specific nitrosamines between U.S.-style cigarettes and those of Canada and Australia (Burns et al. 2008; Ding et al. 2008b; WHO 2008b), where most brands contain mainly unblended, flue-cured tobacco. Datasets are available for some smoke constituents that have been measured for major brands in the Canadian and Australian markets (WHO 2008b) and for a selection of international brands of blended cigarettes manufactured by Philip Morris (Counts et al. 2004, 2005).

Several other differences between Canadian and Australian brands were found, although cigarettes in both countries are made with unblended, flue-cured tobacco. Differences in the levels of cadmium and lead between the brands are notable. Figure 6.7 presents the mean yields of some toxic constituents for the major Canadian and Australian brands sampled in late 2000 to early 2001. The yields are normalized per mg of nicotine and expressed as a ratio to the mean yields for an international sample of brands manufactured by Philip Morris. The data for the Canadian brands are presented for all brands and for brands other than those with high NNN levels (U.S.-style and Gauloise cigarettes). The expected differences between flue-cured

Table 6.2   **Ratio of brand coefficient of variation to replicate measurement coefficient of nicotine and tar variation per milligram (mg), per Massachusetts Machine Smoking Protocol, in rank order**

Per mg nicotine	Constituent	Per mg tar	Constituent
6.84	NNN	8.85	NNN
6.18	NAT	8.18	NAT
5.25	NAB	7.45	NAB
5.00	Mercury	6.28	Isoprene
4.79	Isoprene	6.07	Mercury
4.10	Benzene	4.86	Benzene
3.72	Acetone	4.36	Toluene
3.64	Toluene	4.33	Acetone
3.63	Propionaldehyde	4.30	HCN
3.59	HCN	4.21	Nitric oxide
3.59	Methyl ethyl ketone	4.19	1,3-Butadiene
3.47	Acetaldehyde	4.12	Propionaldehyde
3.43	1,3-Butadiene	4.11	Acetaldehyde
3.35	Acrolein	4.11	NNK
3.34	Nitric oxide	3.97	Methyl ethyl ketone
3.30	Phenol	3.78	Acrylonitrile
3.18	m + p-Cresol	3.76	3-Aminobiphenyl
3.12	NNK	3.49	Acrolein
2.91	Acrylonitrile	3.40	4-Aminobiphenyl
2.86	B[a]P	3.35	m + p-Cresol
2.79	Ammonia	3.23	2-Aminonaphthalene
2.45	3-Aminobiphenyl	3.18	Phenol
2.45	Hydroquinone	3.14	1-Aminonaphthalene
2.32	4-Aminobiphenyl	2.77	Styrene
2.27	2-Aminonaphthalene	2.59	Hydroquinone
2.24	Styrene	2.09	Ammonia
2.03	Crotonaldehyde	2.03	Cadmium
1.93	1-Aminonaphthalene	1.80	Butyraldehyde
1.93	Formaldehyde	1.78	Crotonaldehyde
1.90	Pyridine	1.75	Catechol
1.67	Butyraldehyde	1.73	Formaldehyde
1.46	Cadmium	1.66	B[a]P
1.44	Catechol	1.62	Pyridine
1.42	Lead	1.61	Lead
1.29	Arsenic	1.46	Quinoline
1.28	Quinoline	1.45	Arsenic

Source: Unpublished data from the 1999 Massachusetts Benchmark Study as provided by Greg Connolly, Massachusetts Department of Health.

Note: **B[a]P =** benzo[a]pyrene; **HCN** = hydrogen cyanide; **NAB** = *N'*-nitrosoanabasine; **NAT** = *N*-nitrosoanatabine; **NNK** = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; **NNN** = *N'*-nitrosonornicotine.

Figure 6.7   **Ratio of the means of constituents in cigarette brands from Canada and Australia to the mean for an international sample of U.S.-style blended cigarettes manufactured by Philip Morris and sampled from late 2000 to early 2001**
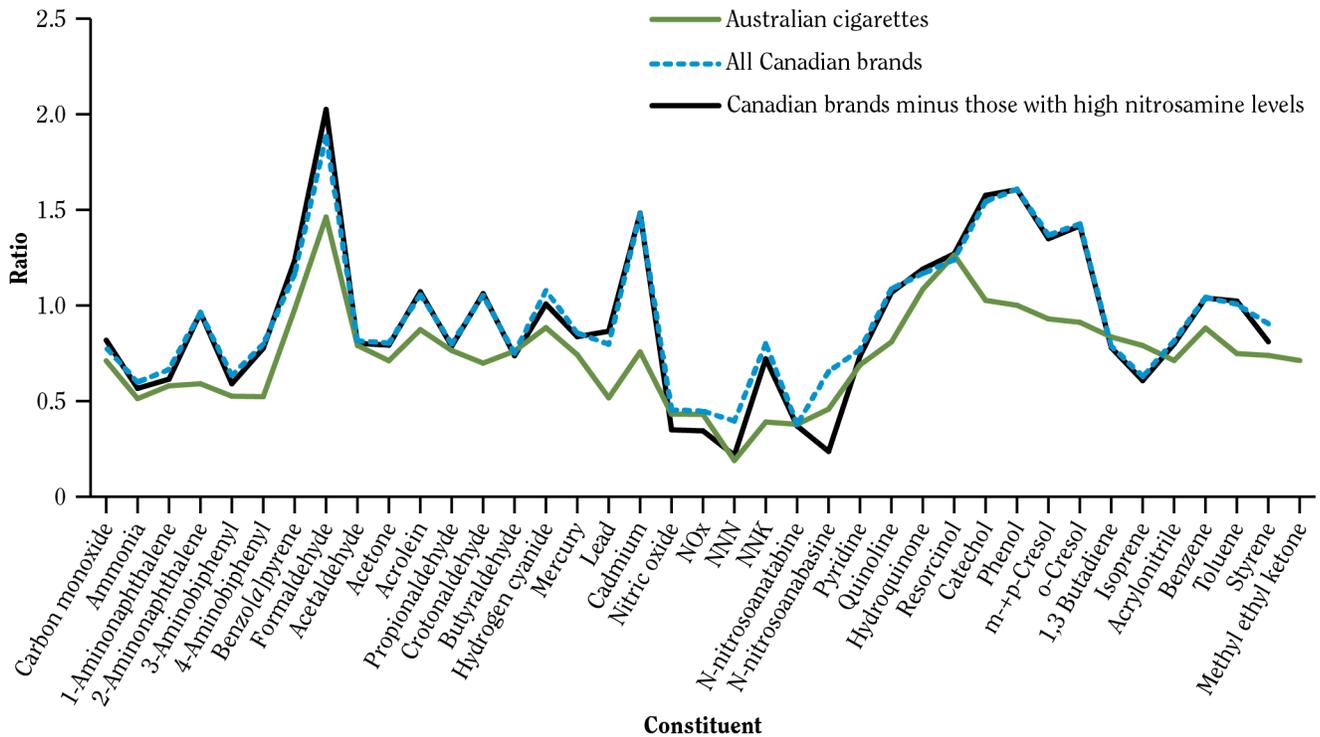
Source: Counts et al. 2005; World Health Organization 2008. Reprinted with permission from World Health Organization, © 2008.
Note: **NNK** = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; **NNN** = *N'*-nitrosonornicotine; **NOx** = nitrogen oxides.

and blended cigarettes are evident (Ding et al. 2008b); the flue-cured cigarettes from Australia and Canada have much lower levels of tobacco-specific nitrosamines (notably NNN and NNK) and substantially higher levels of B[*a*]P. Australian and Canadian brands, however, differ markedly from blended cigarettes in a number of other toxicants, with lower levels of oxides of nitrogen; 1-aminonapthalene; 1,3-butadiene; and isoprene. Canadian, but not Australian, cigarettes have higher levels of catechol, phenol, and cresols. These differences may reflect the use of tobacco grown for use in cigarettes in different regions of Canada and Australia.

Figure 6.8 shows the differences in NNN and NNK between Australian brands and a blended version of the Marlboro brand designed for the Australian market (Burns et al. 2008; WHO 2008b). The levels of NNN and NNK in the blended-tobacco cigarette from Marlboro are much higher than those for even the highest level brand reported to the Australian regulatory authorities.

These differences in tobacco-specific nitrosamine levels in smoke translate to different exposures among smokers. Mouth-level exposures to NNN and NNK and urinary measures of NNAL—a metabolite of NNK—are higher among smokers in the United States than in smokers in Australia and Canada (Ashley et al. 2010), demonstrating that the observed differences in the composition of smoke result in substantive differences in exposure to tobacco-specific nitrosamines.

Low-Tar Cigarettes Do Not Reduce Risk of Lung Cancer

Early efforts to alter the risks of cigarettes focused on reducing the yields of tar and nicotine as measured by machine-smoking methods. As a result, machine-measured yields of tar and nicotine declined by more than 60% from the 1960s to 1990 (Hoffmann and Hoffmann 1997; NCI 2001). Much of that reduction was accomplished initially by adding filters and later by ventilating

Figure 6.8 **Mean and range of *N*´-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) yields per milligram [mg] of nicotine for brands reported to the Australian government, contrasted with the levels of NNN and NNK reported for a Philip Morris Marlboro brand cigarette identified as an Australian brand, in 1999**
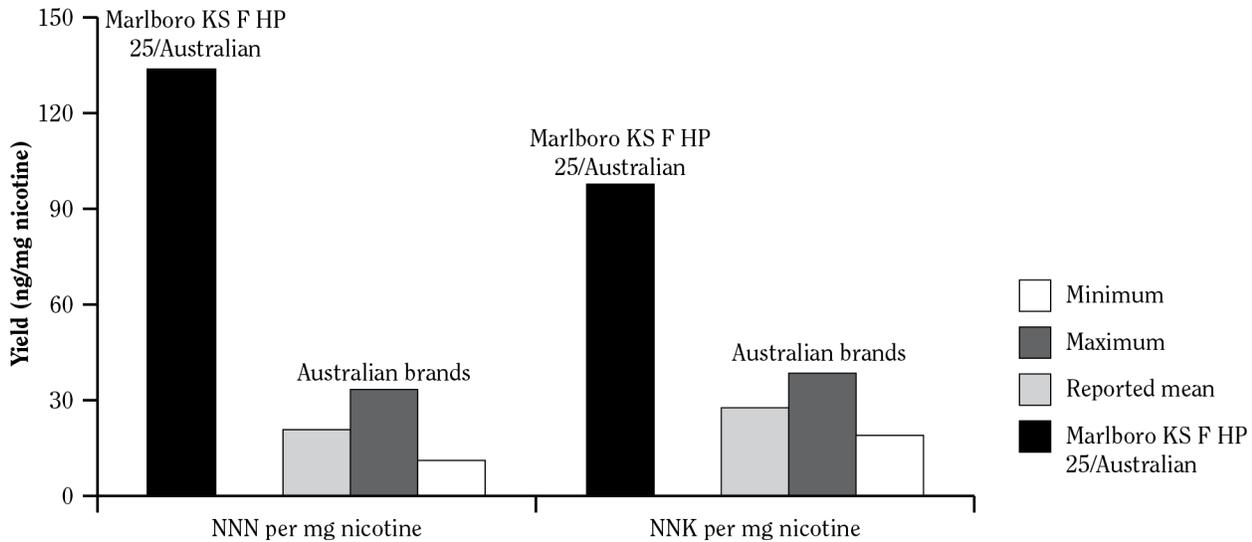
Source: World Health Organization 2008b. Reprinted with permission from World Health Organization, © 2008.
Note: **F** = filter; **HP** = hard pack; **KS** = king size; **ng** = nanogram.

the filter to dilute the smoke coming through it, thus lowering the machine-measured yields of tar and nicotine so the newer products could be marketed as being less risky to health (NCI 2001). But to compensate for the reduced yields, smokers changed the way they smoked these cigarettes, resulting in no meaningful reduction in either the total dose of smoke received or in the risks of diseases caused by smoking (NCI 2001; USDHHS 2004). Changes in patterns included increasing the volume and velocity of puffs, increasing the duration of puffing, and shortening the intervals between puffs (NCI 2001). However, the protocol for smoking by machines was not changed.

Overall Death Rates for Lung Cancer Indicate Increased Risk of Smoking in Recent Decades

In the United States, the prevalence of smoking among males has declined since at least the 1950s, but age-adjusted death rates for lung cancer among men did not begin to decline until approximately 1990 (Wingo et al. 1999). Among women, the comparable death rates peaked around 2003 and significantly declined (Jemal et al. 2013), likely due to considerable success in reducing the prevalence of smoking among women. The long delay between decreases in the prevalence of smoking and changes in death rates for lung cancer raises the question

as to whether there might have been an increasing risk of lung cancer over time from smoking cigarettes that could have contributed to this delay.

Epidemiologic studies are a key source of evidence for assessing whether the risk of lung cancer associated with smoking has changed over time. Particularly informative is the comparison by Thun and Heath (1997) of two prospective cohort studies of the risk of smoking conducted by the ACS. Each study, conducted more than 20 years apart, followed more than 1 million men and women. The Cancer Prevention Study I (CPS-I) began in 1959, and the Cancer Prevention Study II (CPS-II) began in 1982. The more than two decades between the studies saw substantial changes in the design and composition of cigarettes and in the brands of cigarettes that Americans smoked. The decline in machine-measured yields of toxicants in cigarettes between these two studies led to an expectation that the risk of lung cancer death for smokers would likely be lower in the CPS-II. The authors compared death rates from lung cancer in the first 6 years of follow-up for each study among the subsamples of never and current smokers at enrollment. The risks were found to be higher in CPS-II (Thun and Heath 1997). Figure 6.9 presents the results from these analyses for men and women current smokers and never smokers based on 786,387

CPS-I and 711,363 CPS-II participants. The risk for never smokers (as measured by the death rate from lung cancer) went essentially unchanged during the interval between the two studies, but the risk for smokers increased dramatically, with a proportionately greater increase among women smokers. The increase in risk of death from lung cancer remained after controlling for measured differences in duration and intensity (number of cigarettes smoked per day) between the smokers in the two studies.

The 40-year follow-up of the British Doctors' Study from 1951–1991 presents similar evidence. During the second 20 years of follow-up, the risk of death from lung cancer was greater than during the first 20 years (Doll et al. 1994); this increase over time was limited to smokers and former smokers. Among never smokers, rates of lung cancer mortality were relatively constant across calendar years (Thun et al. 2006, 2008), suggesting that the changes observed in the relative risk (RR) of smoking were unlikely to have resulted from changes in population demographics or in other risk factors for lung cancer in the general population.

Models of risk based on smoking patterns have been applied to data on smoking prevalence for birth cohorts (i.e., sets of individuals born during specified calendar years and for whom rates can be examined as the cohorts advance in age and calendar year) to estimate the expected occurrence of death from lung cancer in the absence of any change in the risk imposed by smoking. Using birth-cohort-specific data on smoking developed by Harris (1983) and a multistage carcinogenesis model similar to that developed by Whittemore (1988), Swartz (1992) predicted overall age-adjusted trends in lung cancer mortality for White men from 1970–1985. The author estimated that a 12% decline in rates should have occurred during this interval, based on the assumption of a constant effect over time. However, this estimated decline contrasted sharply with the observed 26% increase in lung cancer death rates during the interval (Swartz 1992). To predict death rates for lung cancer over time by birth cohort, Tolley and colleagues (1991) used an updated set of birth-cohort-specific estimates for smoking prevalence and a risk model developed by Peto (1986) that was based on data from the British Doctors' Study (Doll et al. 1994). These authors estimated that overall lung cancer mortality should have started to decline in the early 1980s for White men and in the mid-1990s for White women. Instead, observed lung cancer mortality continued to rise throughout the 1980s, peaking in the early 1990s for White men (Wingo et al. 1999) and 2003 for women generally (Jemal et al. 2013). A similar approach, using risk models developed from

Figure 6.9   Death rates from all lung cancers, by smoking status, Cancer Prevention Study I (CPS-I) and Cancer Prevention Study II (CPS-II), 1959–1965 and 1982–1988
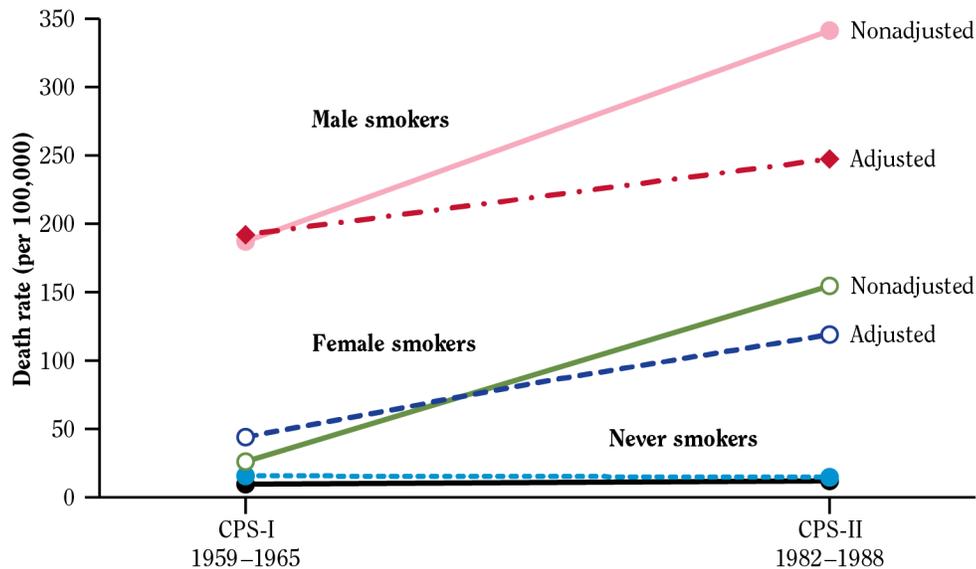
Source: Thun and Heath 1997. Reprinted with permission from Elsevier, © 1997.
Note: All data are age adjusted. Data for male and female smokers are also adjusted for duration of smoking and number of cigarettes smoked per day. Each data point represents the mortality from the 6-year interval specified by the study.

the CPS-I data and birth-cohort-specific data on smoking prevalence from the National Health Interview Survey, demonstrated a systematic trend of increasing underestimation of observed death rates for lung cancer across all birth cohorts with advancing calendar years (NCI 2001).

Estimates of smoking behaviors for birth cohorts that incorporate changes in the number of cigarettes smoked per day were developed for NCI's Cancer Intervention and Surveillance Modeling Network (CISNET) (Anderson et al. 2012). These estimates are more detailed than previous data on smoking behaviors for birth cohorts and include estimates of the intensity and duration of smoking for 5-year birth cohorts from 1900–1984. For each calendar year, these estimates provide rates of smoking initiation; prevalence of current and former smoking; and distributions of the duration of smoking, the duration of abstinence, and the number of cigarettes smoked per day for current and former smokers. These estimates for smoking behavior were combined with risk models for current, former, and never smokers derived from 12-year follow-up data from the CPS-I (Knoke et al. 2004, 2008) to estimate birth-cohort-specific lung cancer death rates from 1960–2000 (Burns et al. 2011b). The resulting estimates were compared with observed U.S. national lung cancer death rates for the same birth cohorts. The comparison showed a progressively increasing underestimation of U.S. national lung cancer death rates across all birth cohorts as calendar years advanced from the 1960s to 2000 (Burns et al. 2011b). This underestimation was eliminated when a term that increased the risk of smoking, based on the estimated duration of smoking after 1972, was added to the risk model. These analyses suggest that estimates of smoking-related lung cancer deaths that are based on observations in the 1960s underestimate the current risks of smoking, implying that the risk of death from lung cancer associated with smoking may have increased over the past several decades—that is, during the same decades in which changes in the design of cigarettes were made.

Considering the increase in risk of death from lung cancer seen from CPS-I to CPS-II, Thun and Heath (1997) recognized the possibility that the risk of death from lung cancer observed in CPS-I might underestimate the contributions of (a) amount smoked and (b) duration of smoking due to overreporting in the CPS-I data of the duration of smoking and the number of cigarettes smoked early in life. Among White men, the transition from other forms of tobacco use (e.g., cigars and pipes) to cigarettes began largely after 1914, because cigarette smoking was uncommon before that year (Burns et al. 1997). Because lung cancer is a disease of older ages, much of the lung cancer mortality experience in CPS-I occurred among men who were well past their adolescence by 1914, and yet many of them reported initiating smoking at early ages.

Some participants in CPS-I may have reported initiating cigarette smoking at the time at which they first used tobacco of any type, or they may have otherwise overestimated their duration of cigarette smoking, leading to a longer reported duration of cigarette smoking than actually occurred. The resulting misclassification, with a bias toward reporting a longer duration of smoking, could lead to a reduced magnitude of the estimated effect of duration of smoking on risk of lung cancer death in risk models based on CPS I data. Because a much larger fraction of those who developed lung cancer in CPS-II took up smoking after 1914, the effect of overreporting the duration of smoking would be lower in CPS-II, the magnitude of the estimated duration effect would increase, and the risk of smoking would appear to have increased between the two studies, with adjustment for differences in reported duration of smoking.

The study used the CISNET smoking rates and risk models based on CPS-I (Burns et al. 2011b) and attempted to minimize the contribution of overreporting of smoking duration and early smoking by eliminating birth cohorts born before 1915—the period during which overreporting was most likely. In addition, the potential for underestimation of the increase in duration over time to produce the observed progressive underestimation of the U.S. birth-cohort-specific death rates for lung cancer with advancing calendar time was examined by iteratively increasing the duration term and examining the fit of the resulting estimates to the observed U.S. death rates. Although increasing the duration term increased the estimated rates as anticipated, the pattern of a progressive change in risk remained even as calendar years advanced, with an overestimated actual risk giving way to an underestimated risk as calendar years advanced. Thus, an increasing effect of duration on risk of death from lung cancer did not explain the progressive underestimation of mortality from lung cancer, whereas a term increasing the risk of cigarette smoking over time did.

Overreporting in CPS-I also may have resulted in an overestimation of the number of cigarettes smoked early in life, but the contribution of cigarettes smoked per day to risk of lung cancer is much smaller than the contribution of duration (Flanders et al. 2003; Knoke et al. 2004), and the exponent for the cigarettes-per-day term in the CPS-I risk equations is close to one (Knoke et al. 2004, 2008). As a result, any underestimation of lifetime number of cigarettes smoked per day due to overreporting of smoking early in life is expected to be modest and could be approximated by a constant that would be incorporated in the risk equations when they are adjusted for the healthy population selection bias (Pinsky et al. 2007) required for such estimates (Tolley et al. 1991; Burns et al. 2011b).

To further assess changes in the risk of lung cancer from smoking over time, Thun and colleagues (2013) extended their analyses by comparing the lung cancer risk associated with smoking observed in five contemporary cohorts (2000–2010) with risks observed in CPS-I (1959–1965) and CPS-II (1982–1988). For never smokers, rates of death from lung cancer remained constant across time among men and increased only slightly among women. Among females 55 years of age and older at baseline, the RR for lung cancer comparing current smokers to never smokers progressively increased from 2.73 in CPS-I to 12.65 in CPS-II to 25.66 for the 2000–2010 cohorts. Corresponding RRs for current male smokers were 12.22, 23.81, and 24.97, respectively. Compared with their counterparts in CPS-I and CPS-II, both men and women in the contemporary cohorts were at greater risk for lung cancer despite smoking fewer cigarettes per day. Duration of smoking increased substantially across the study time periods for women. In comparison, duration of smoking changed only modestly for men across the studies and actually declined slightly between CPS-II and the 2000–2010 cohorts.

Thun and colleagues (2013) also stratified their analyses by smoking intensity (i.e., number of cigarettes smoked per day) and duration of smoking for all three study periods. Within each stratum of smoking intensity and duration of smoking, the RR estimates increased over time for women. For men, RR estimates increased over time within each stratum of smoking intensity, but a consistent pattern was not evident for each stratum of smoking duration. The authors concluded that the risk of lung cancer from smoking has continued to increase among women but among men has plateaued at the very high levels observed in the 1980s.

Trends in most other tobacco-related cancers have not been examined in detail, although Baris and colleagues (2009) reported an increase in the incidence of bladder cancer over the past several decades.

Changes Over Time in the Types of Lung Cancer Associated With Smoking

Adenocarcinoma of the lung has been increasing in the United States since the 1970s (Travis et al. 1996; Wingo et al. 1999), as manifested in rising incidence rates and an increasing proportion of all lung cancers that are adenocarcinomas (Wingo et al. 1999; Devesa et al. 2005). Theoretically, this increase could be due to changes over time in the classification of tumors, but an analysis by Charloux and colleagues (1997) found the increase to be real and not a consequence of changing diagnostic practices.

Notably, the increase in adenocarcinoma of the lung has been accompanied by an increase in the estimated RR for this type of lung cancer associated with cigarette smoking. Early in the investigation of the lung cancer epidemic, the most common histologic type of lung cancer in men was squamous cell carcinoma, and the RR of squamous cell carcinoma associated with smoking was substantially higher than that for adenocarcinoma (Wu-Williams and Samet 1994; USDHHS 2004). Kreyberg (1962) even debated whether adenocarcinoma was associated with cigarette smoking, because of the low RR and because adenocarcinoma is the most common type of lung cancer among women who have never smoked. As the incidence of lung adenocarcinoma increased over time, the RRs of this type of lung cancer associated with smoking also increased (USDHHS 2001), suggesting that a new, or at least a substantially enhanced, risk of developing adenocarcinoma of the lung occurred in smokers. In a comparison of data from CPS-I and CPS-II, Thun and colleagues (1997) found that the RR for adenocarcinoma increased in smokers from 4.6 for men and 1.5 for women (per data from CPS-I, conducted 1959–1965) to 19.0 for men and 8.1 for women (per data from CPS-II, conducted 1982–1988), but that the age-adjusted death rates for adenocarcinoma of the lung among never smokers were essentially unchanged over the period. Furthermore, risk for lung cancer of all tissue types among never smokers remained constant over the same interval (Thun et al. 2006, 2008).

Trends across calendar years in age-standardized incidence rates of lung cancer have also varied by tumor type. Figure 6.10 presents trends in age-standardized incidence rates in the United States from 1973–2010 for lung cancer by gender and histologic type using data from NCI's SEER Program. Among men, the decline in the incidence rate of squamous cell carcinoma started well ahead of the decline for incidence rates for adenocarcinoma; similar trends are seen for women. Rates of squamous cell and small cell carcinoma have been declining in men since the early- to mid-1980s, but rates of adenocarcinoma did not peak until the 1990s (Travis et al. 1996; Wingo et al. 1999; Devesa et al. 2005). Age-standardized rates in women reflect their later uptake of smoking, resulting in a later year of peak smoking-induced rates of lung cancer, and the patterns are more difficult to interpret. However, rates of squamous cell carcinoma leveled off among women around 1990, but their rates of adenocarcinoma continued to increase through the 1990s (Wingo et al. 1999; Devesa et al. 2005). The recent trends in rates for the NSCLCs have been affected by trends in diagnostic practice,

Figure 6.10   Standardized incidence of lung cancer, by gender and histology (age adjusted to 2000 U.S. population), 1973–2010

A. Males

B. Females
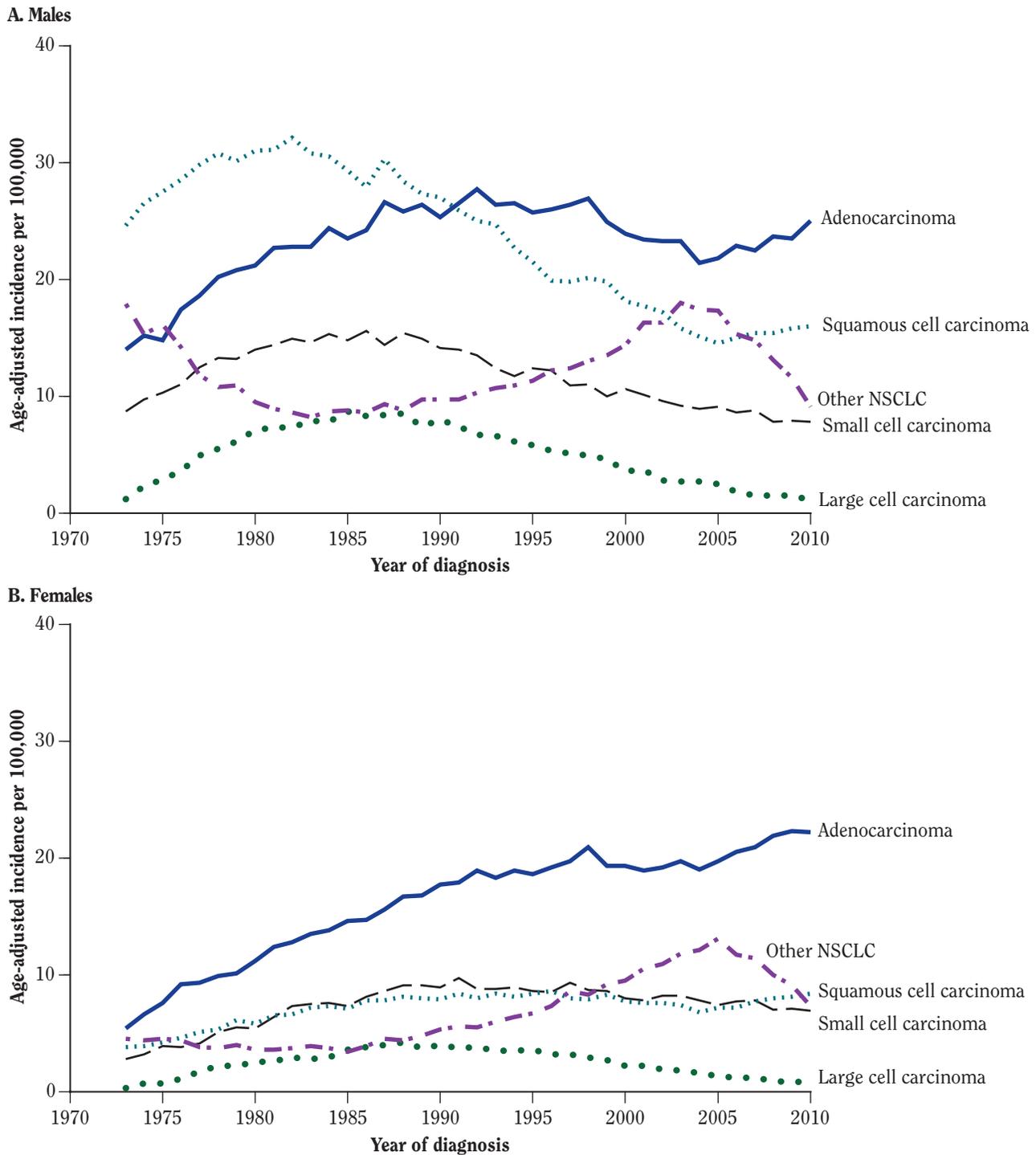
Source: Surveillance, Epidemiology, and End Results (SEER) Program, public use data.
Note: Other non-small-cell-lung carcinoma (NSCLC) includes code 8046 from the SEER Registry, as well as others. In the most recent years (2001–2010), most of the "Other NSCLC" were 8046. Before 2001, most "Other NSCLC" were coded as 8010 "Carcinoma, NOS." Around 2004 there were changes in how lung cancers were coded in the SEER Registry data (Travis et al. 2004, 2011; Johnson et al. 2007). There were also advances in diagnosis and treatment around 2004 (erlotinib or gefitinib for patients with *EGFR* mutations, bevacizumab for patients with non-squamous NSCLC) that make accurate histologic classification important (Langer et al. 2010; Kulesza et al. 2011; Conde et al. 2013).

reflecting treatment approaches that are targeted by histologic type. There has been a trend to avoid nonspecific classification and to designate lung cancers as adenocarcinoma and squamous cell carcinoma (Langer et al. 2010; Travis et al. 2011; Conde et al. 2013).

Interpreting age-standardized rates of lung cancer is difficult because of variations in the prevalence of smoking, in the distribution of duration of smoking, and in the distribution of the duration of abstinence in the U.S. population over the past several decades. For that reason, rates of lung cancer by histologic type have also been examined by birth cohorts. This approach examines outcomes as the population born during the selected calendar years initiates and quits smoking over time (and ages, as well). These two smoking behaviors have been found to differ substantially across sequential birth cohorts for the U.S. population (Burns et al. 1997, 2011b).

Zheng and colleagues (1994) found that birth-cohort-specific rates of lung cancer by histologic type across calendar years in the Connecticut Tumor Registry data demonstrated a clear birth-cohort pattern for increased rates of adenocarcinoma; that is, there were identifiable differences in rates by cohort. These changes paralleled gender and generational changes in smoking rather than advances in diagnostic procedures (Thun et al. 1997a). In this Connecticut study, the birth-cohort trends for squamous cell carcinoma were consistent with changes in smoking prevalence by birth cohort over time, but rates of adenocarcinoma by birth cohort progressively increased for both men and women in a manner that was not consistent with changes in smoking prevalence by birth cohort (Zheng et al. 1994). This increase was consistent with an increase over time in the risk of adenocarcinoma associated with smoking due to changes in the design of cigarettes, including the introduction of filters and low-tar cigarettes (Zheng et al. 1994; Thun et al. 1997a).

Figures 6.11 and 6.12 present incidence rates for lung cancer by histologic type based on 5-year birth cohort data from the SEER Program. Although the proportion of lung cancer that is adenocarcinoma is somewhat higher for women across all birth cohorts, a trend is found in which adenocarcinoma represents an increasing proportion of lung cancer when sequential cohorts are examined for both men and women. Data in Figures 6.11 and 6.12 are combined in Figure 6.13 to present mean values for the proportions of all lung cancers with a designated histologic type that were adenocarcinoma for those cohorts with data available. The mean values demonstrate a substantial increase in the proportion of lung cancer that is adenocarcinoma when moving from the earliest to the more recent cohorts. An important caveat in interpreting these means is that the age range for each cohort is different, as it must be, with the earliest cohorts having only the older age ranges and the more recent cohorts only the younger age ranges.

Data from the SEER Program do not contain information about smoking status at the individual level, but the birth-cohort rates for the different histologic types presented in the figures result from a steadily progressing mixture of current, former, and never-smoking behaviors that are specific for each cohort as it moves forward in time. Therefore, differences in the proportion of lung cancers due to a specific histologic type are not due to differences by histology in overall smoking behaviors, given that these behaviors are the same for all of the histologic types in any given calendar year. Differences by histologic type within a cohort can reflect differences in the relationship of age to histologic type, differences in the rate of decline in risk after smoking cessation for the different histologies, or variation in the exposures over time in the agents causing the different types of lung cancer.

Effects due to aging, such as those that might be manifested if the durations of smoking required to produce squamous cell carcinoma and adenocarcinoma are different, would likely reveal themselves in a similar fashion across all cohorts as those cohorts reach the appropriate ages, but Figures 6.11 and 6.12 do not indicate a consistent pattern with age.

The time course of reduction in excess risk of lung cancer after cessation of smoking likely differs for the different histologic types. For example, some data suggest that excess risks for squamous cell and small cell lung cancers may decline more rapidly after cessation than do excess risks for adenocarcinoma (Kenfield et al. 2008). As calendar years have advanced, the U.S. population in the age groups at substantial risk for lung cancer (i.e., those over 50 years of age) is composed of an increasing fraction of former smokers, and those former smokers have had longer durations of abstinence. The potential effect of a slower decline in risk for adenocarcinoma raises the possibility that the decline in squamous cell carcinoma and the increase in adenocarcinoma over time may be a result of a relatively more rapid decline in risk for squamous cell carcinoma, leaving an increasing fraction of lung cancer as adenocarcinoma. However, if the increasing proportion of lung cancer that is adenocarcinoma was in fact due to this effect (of a less rapid decline in the excess risk for adenocarcinoma following cessation), then the greatest shift would be in the earliest birth cohorts, among whom the effects of differences in risk with abstinence would be most evident. Figures 6.11 and 6.12 show the opposite pattern—the greatest increase in the proportion of lung cancer that is adenocarcinoma occurs in the more recent birth cohorts who are younger in age and have less cumulative abstinence.

Figure 6.11 **Incidence of lung cancer among U.S. men from various birth cohorts, by histologic type (adenocarcinoma, squamous cell carcinoma, and small and large cell carcinoma) and year of diagnosis, 1975–2000**
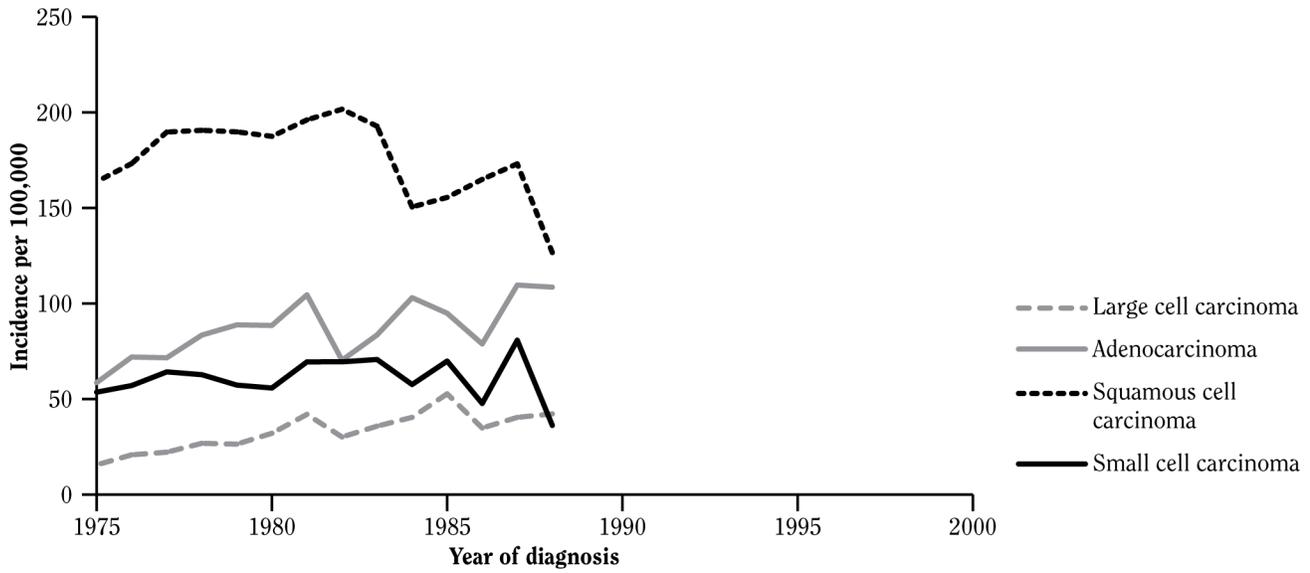
A. Birth cohort: 1900

B. Birth cohort: 1905
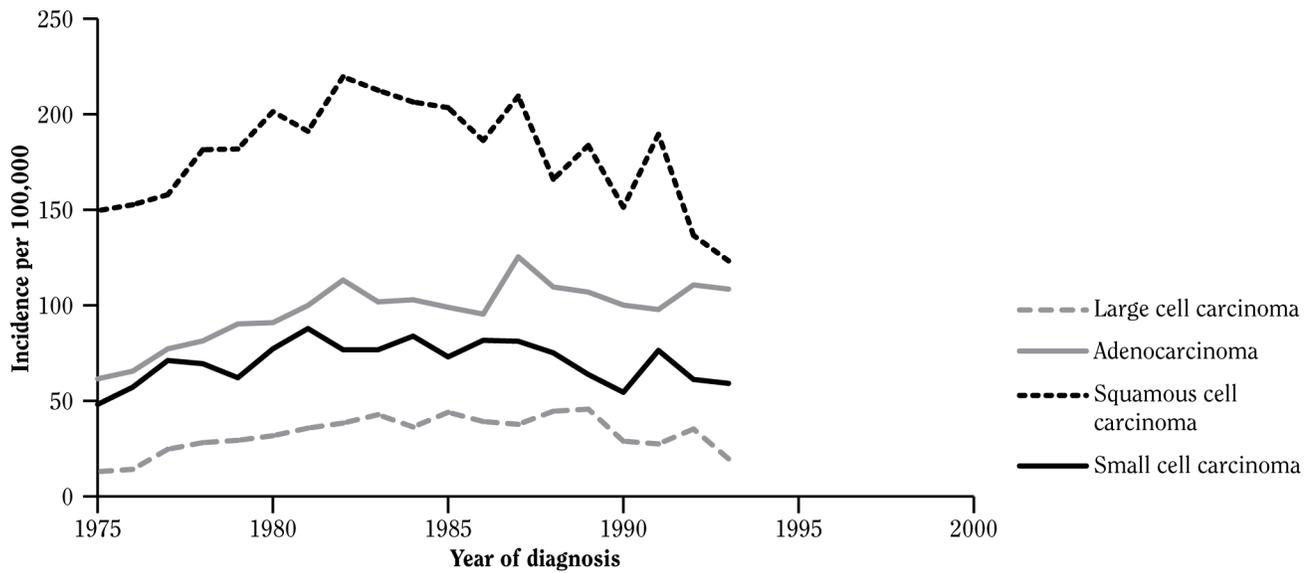
Figure 6.11   Continued

C. Birth cohort: 1910
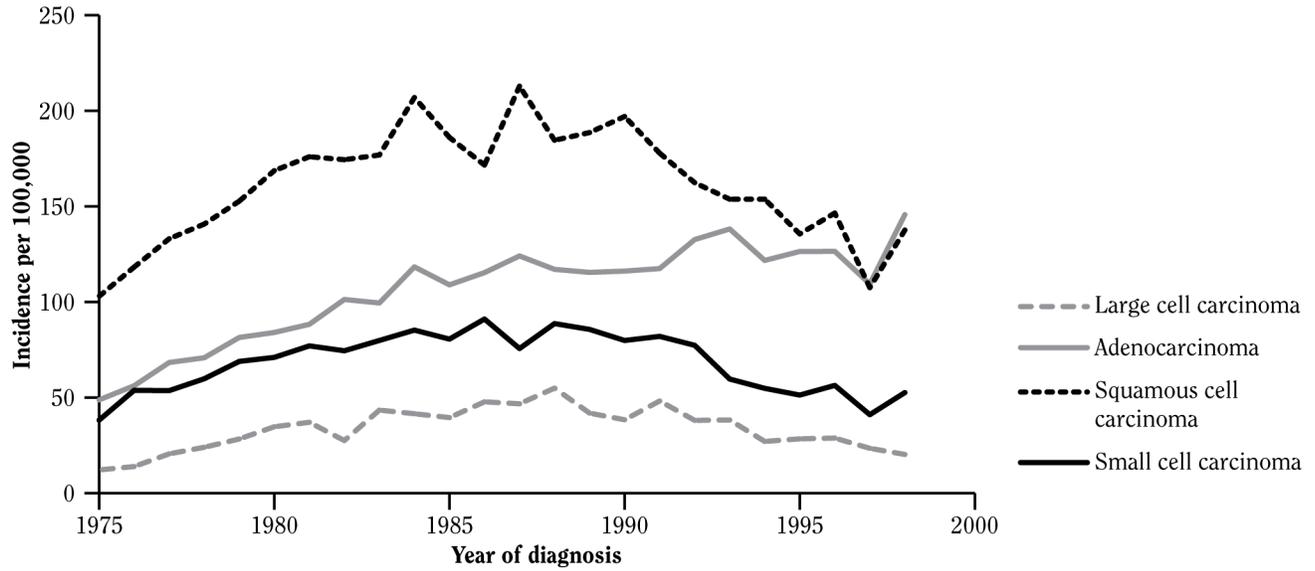
D. Birth cohort: 1915
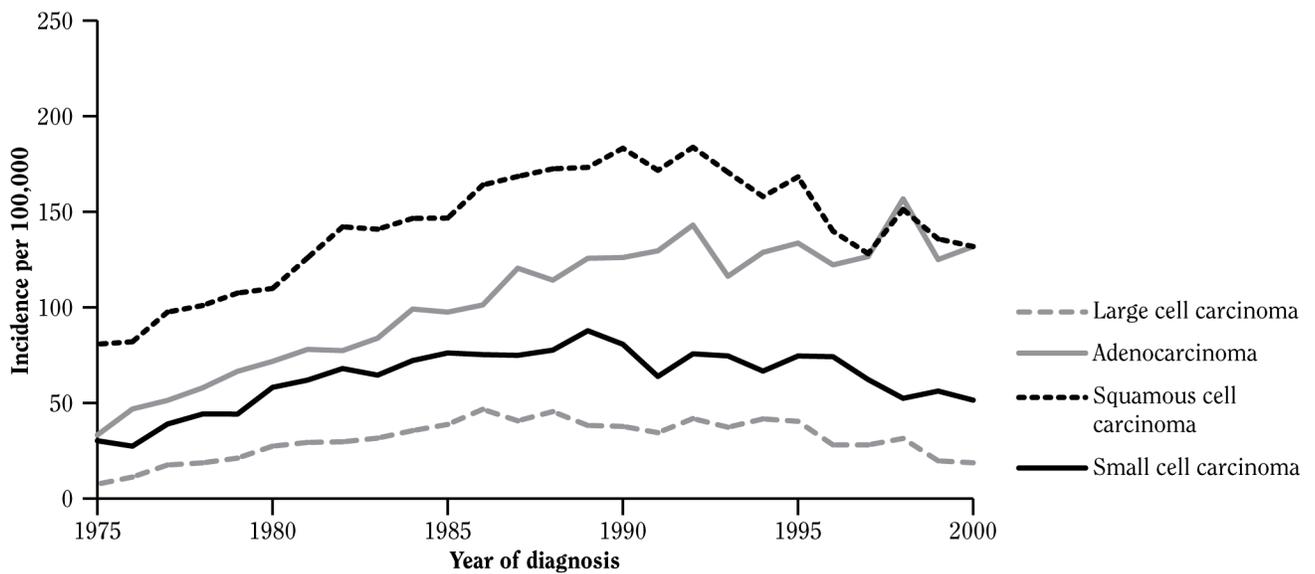
Figure 6.11   Continued

E. Birth cohort: 1920
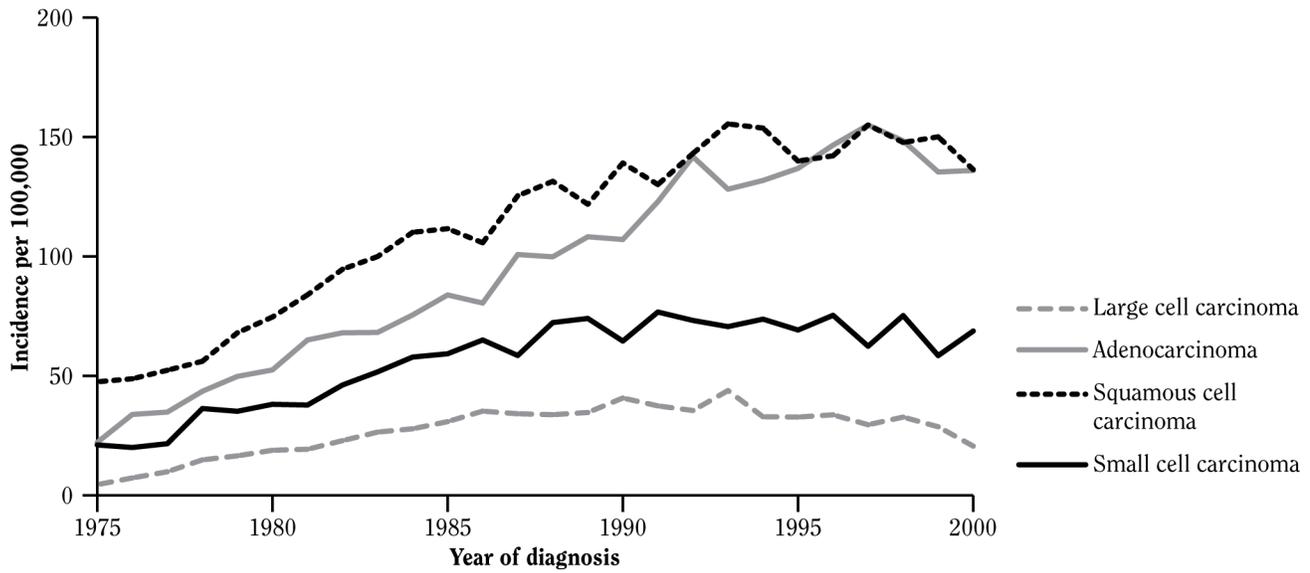
F. Birth cohort: 1925
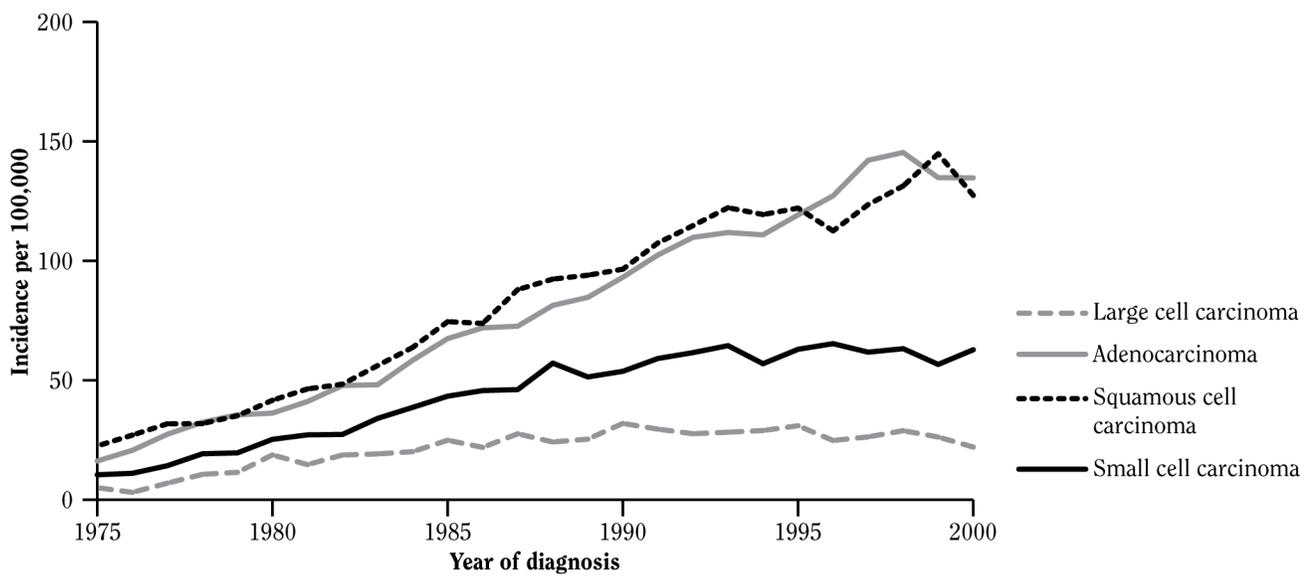
Figure 6.11   Continued

G. Birth cohort: 1930
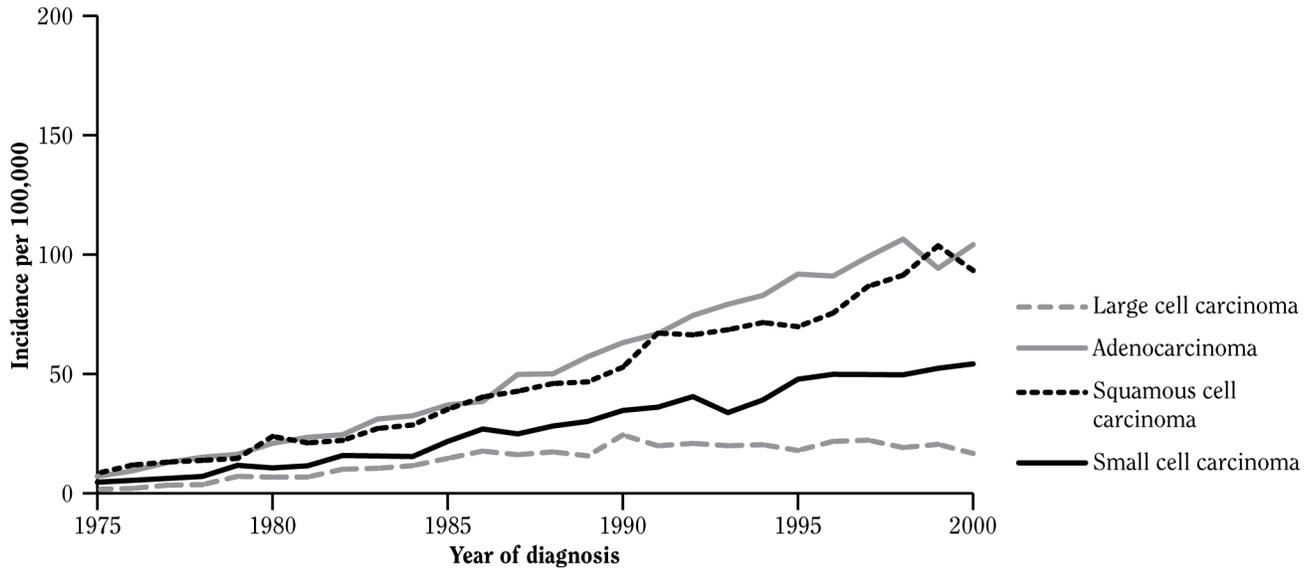
H. Birth cohort: 1935
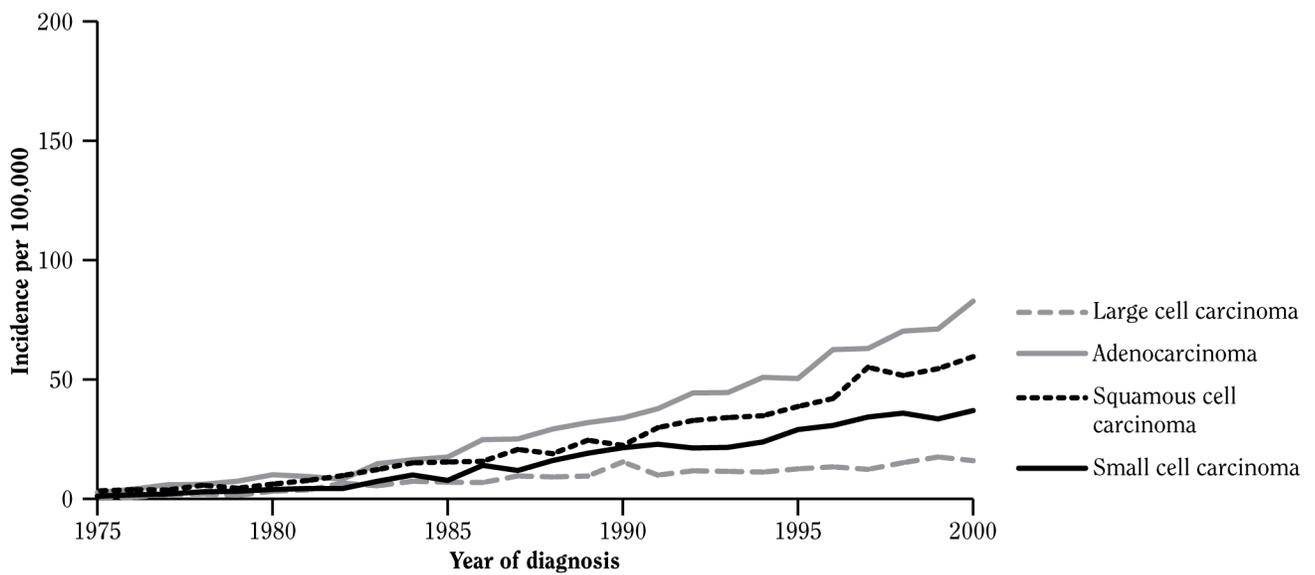
Figure 6.11   Continued

I. Birth cohort: 1940
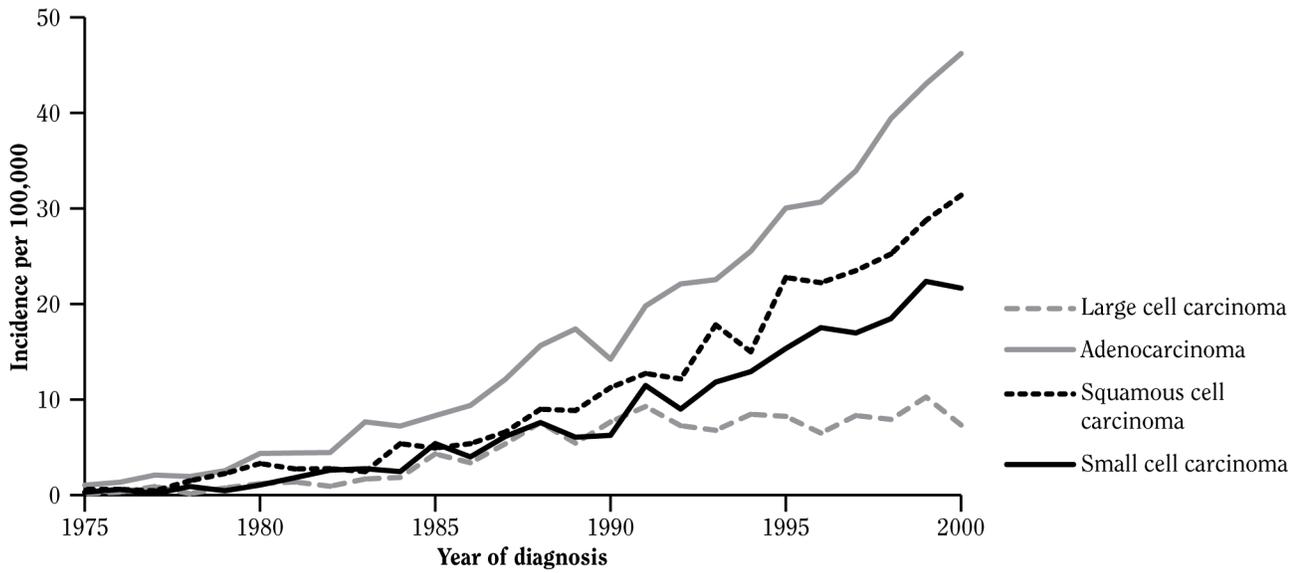
J. Birth cohort: 1945
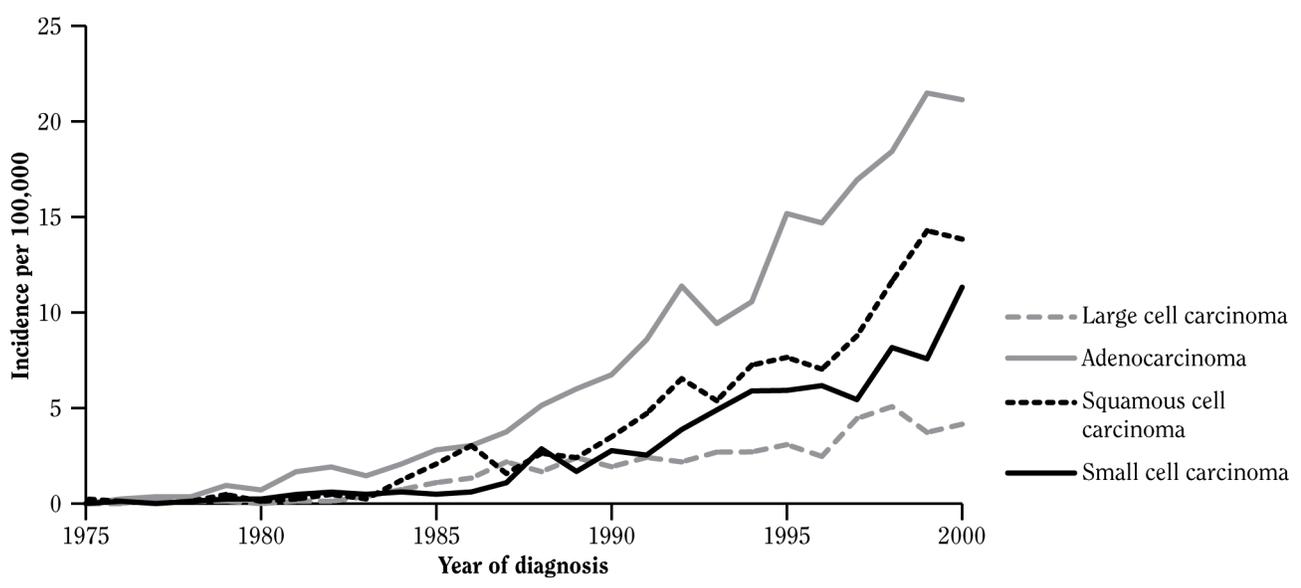
Figure 6.11   Continued

K. Birth cohort: 1950
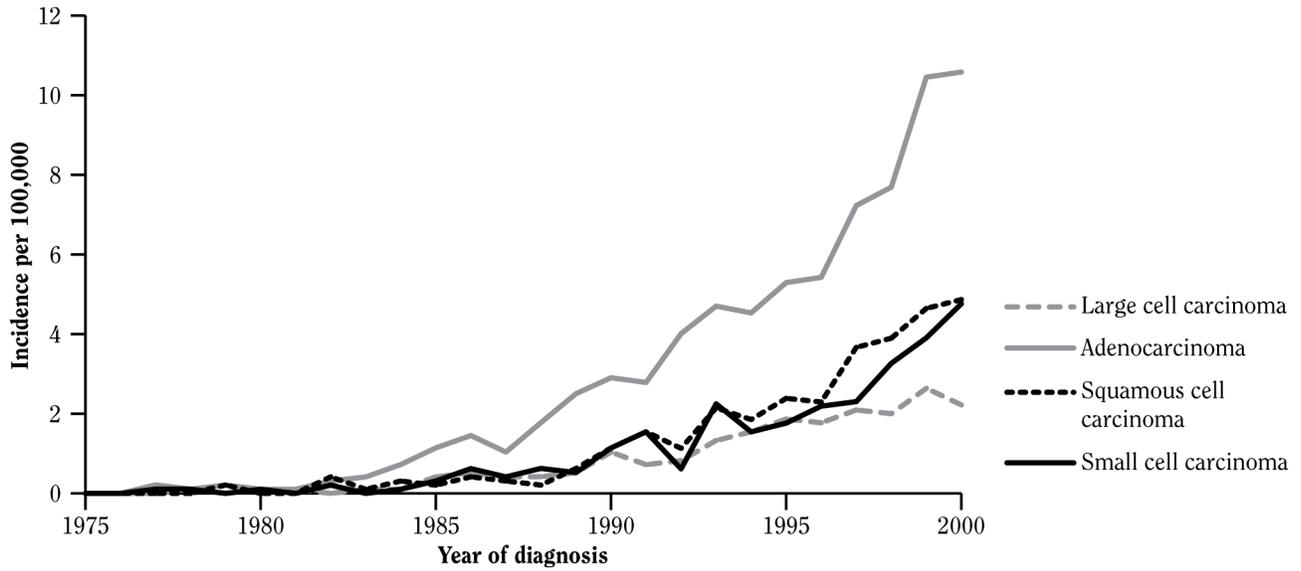
L. Birth cohort: 1955
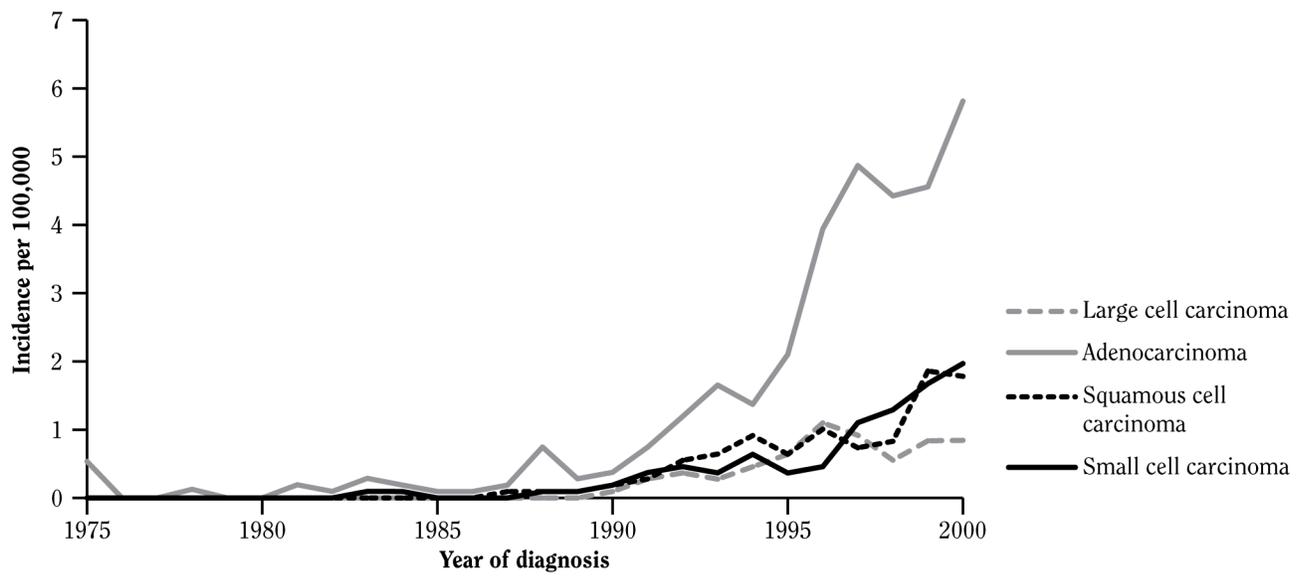
Source: Surveillance, Epidemiology, and End Results Program, public use data.

Figure 6.12   Incidence of lung cancer among U.S. women from various birth cohorts, by histologic type (adenocarci-noma, squamous cell carcinoma, and small and large cell carcinoma) and year of diagnosis, 1975–2000
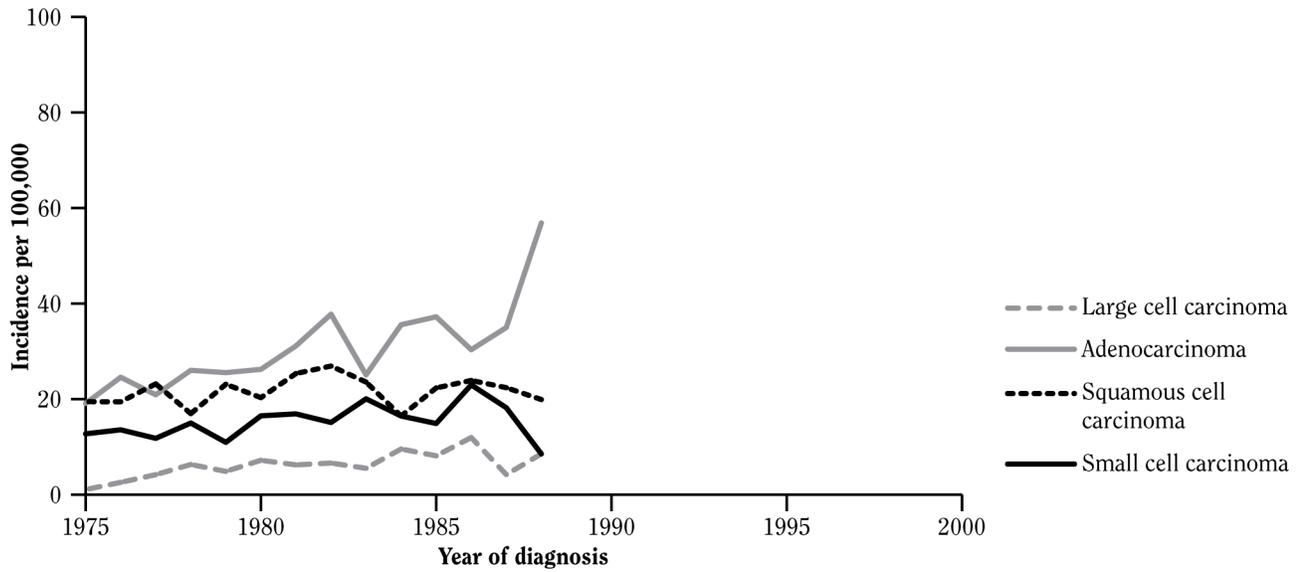
A. Birth cohort: 1900

B. Birth cohort: 1910
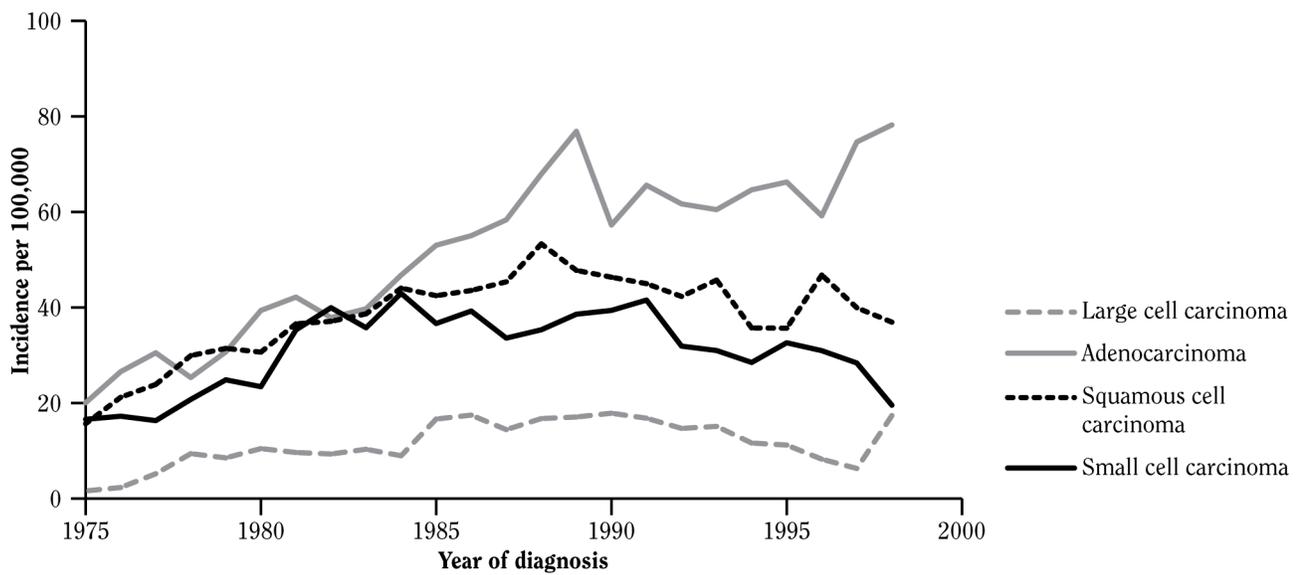
Figure 6.12   Continued

C. Birth cohort: 1920
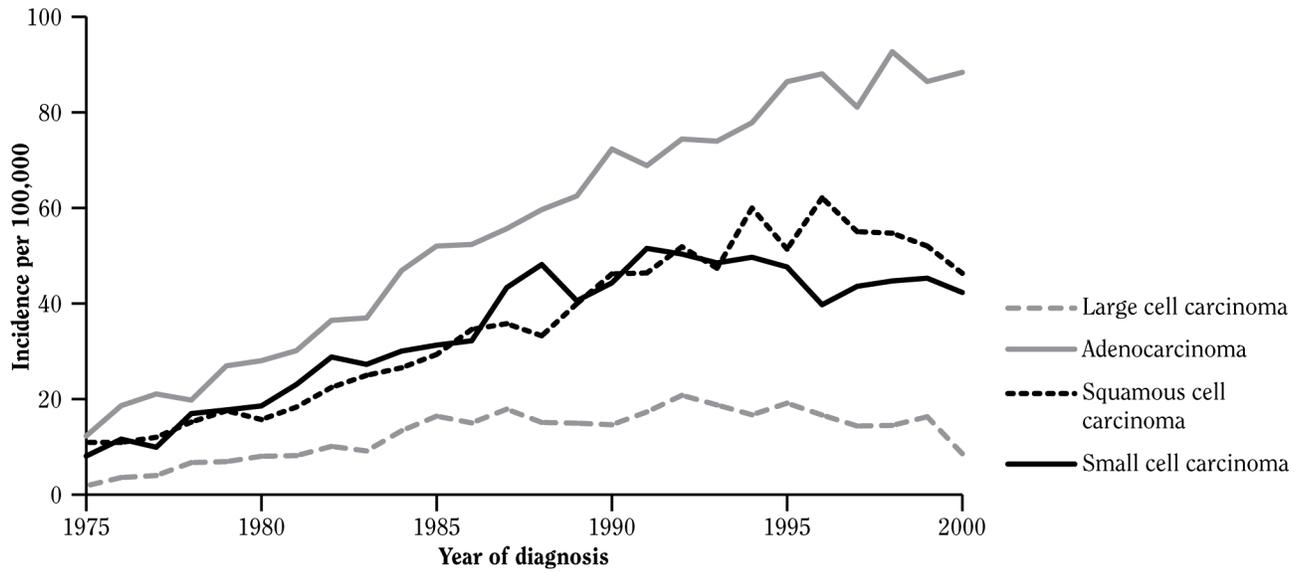
D. Birth cohort: 1925
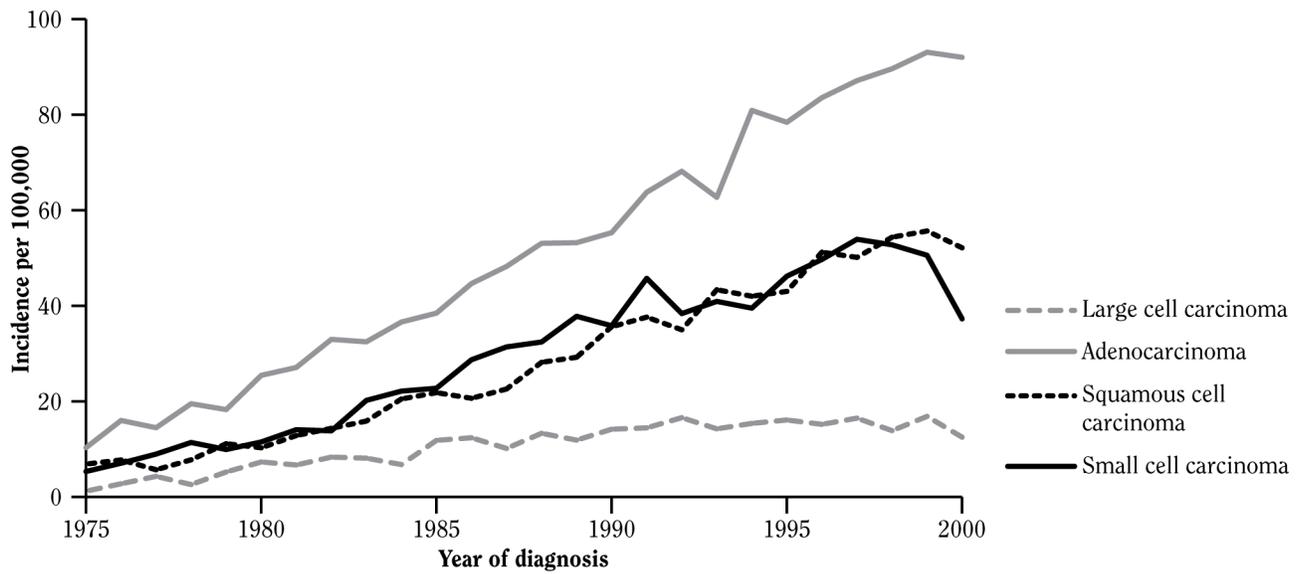
Figure 6.12   Continued

E. Birth cohort: 1930
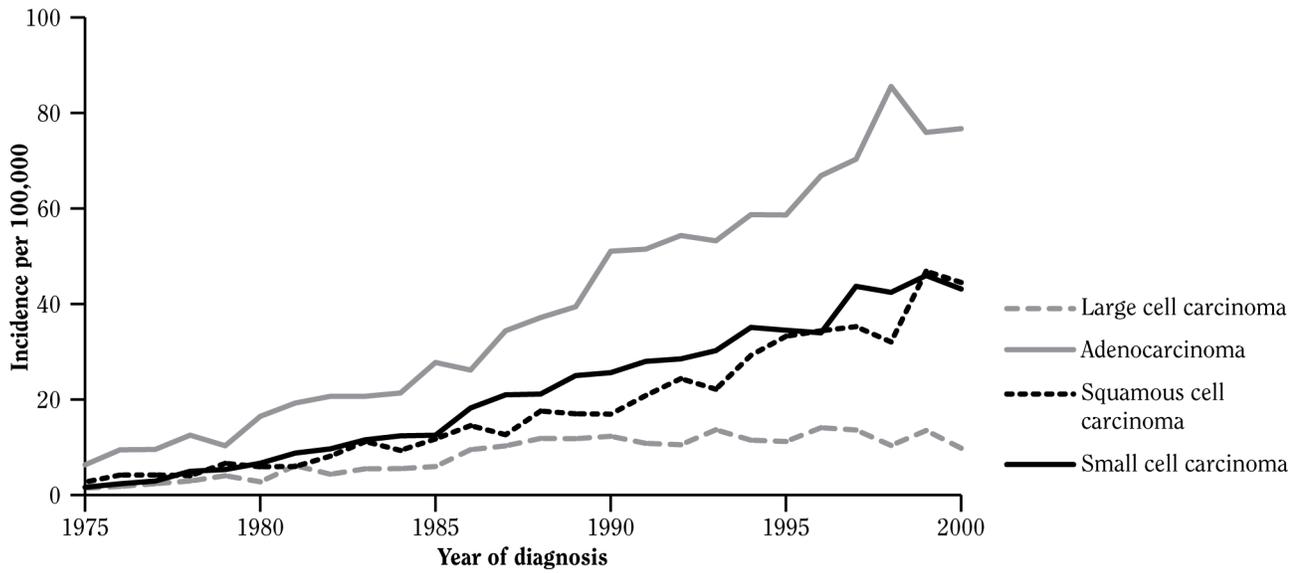
F. Birth cohort: 1935
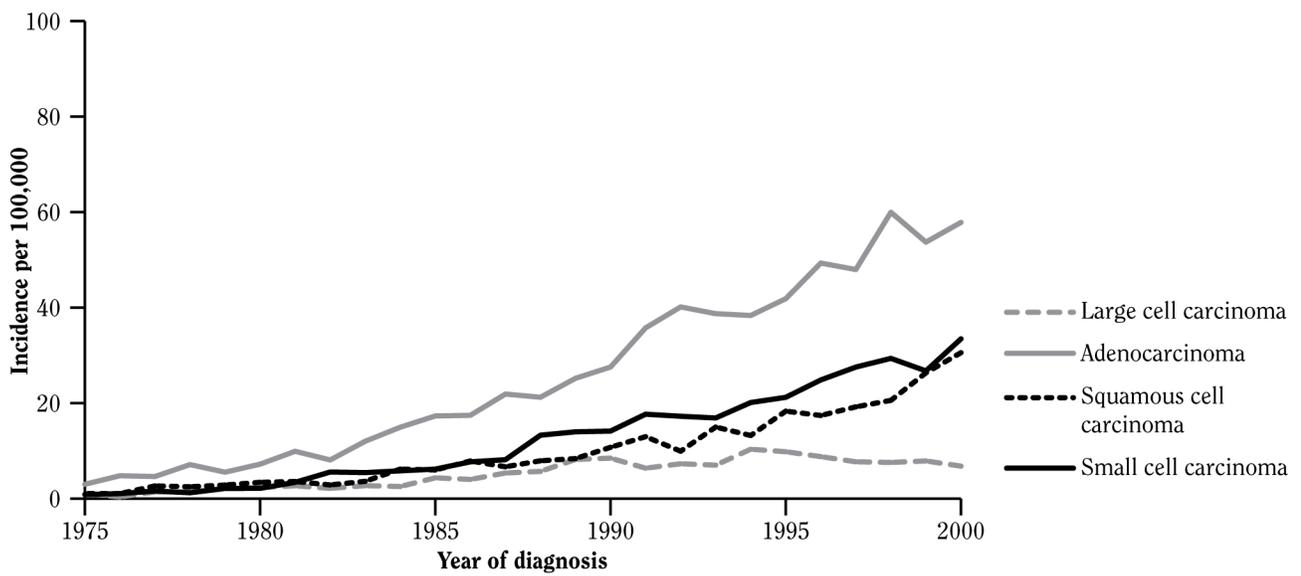
Figure 6.12   Continued

G. Birth cohort: 1940
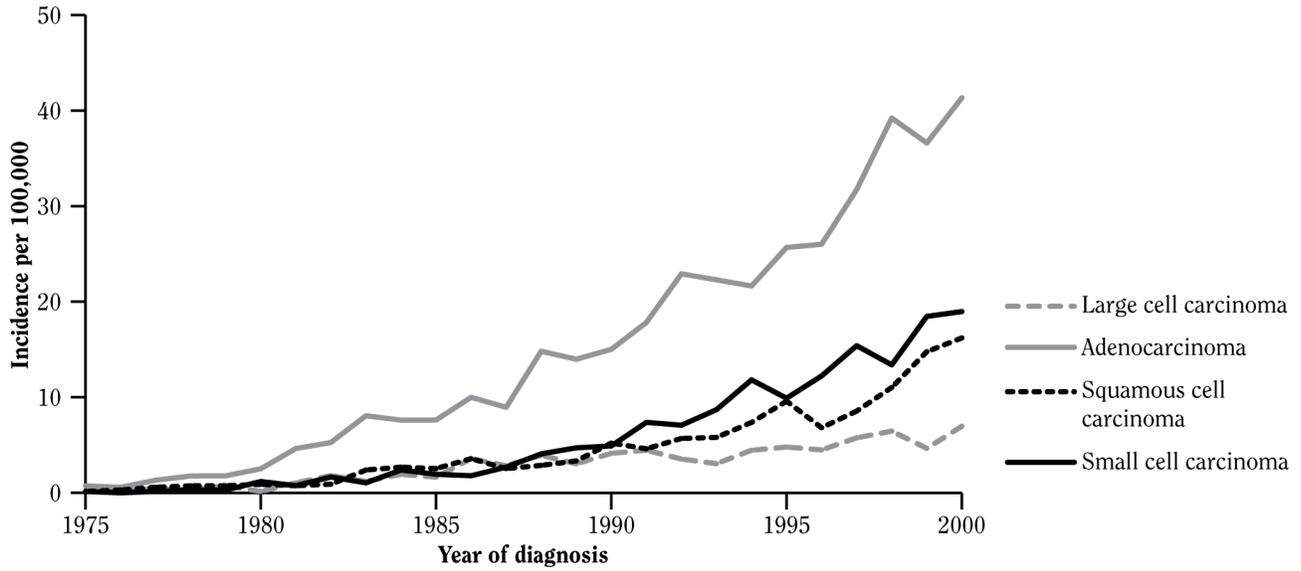
H. Birth cohort: 1945
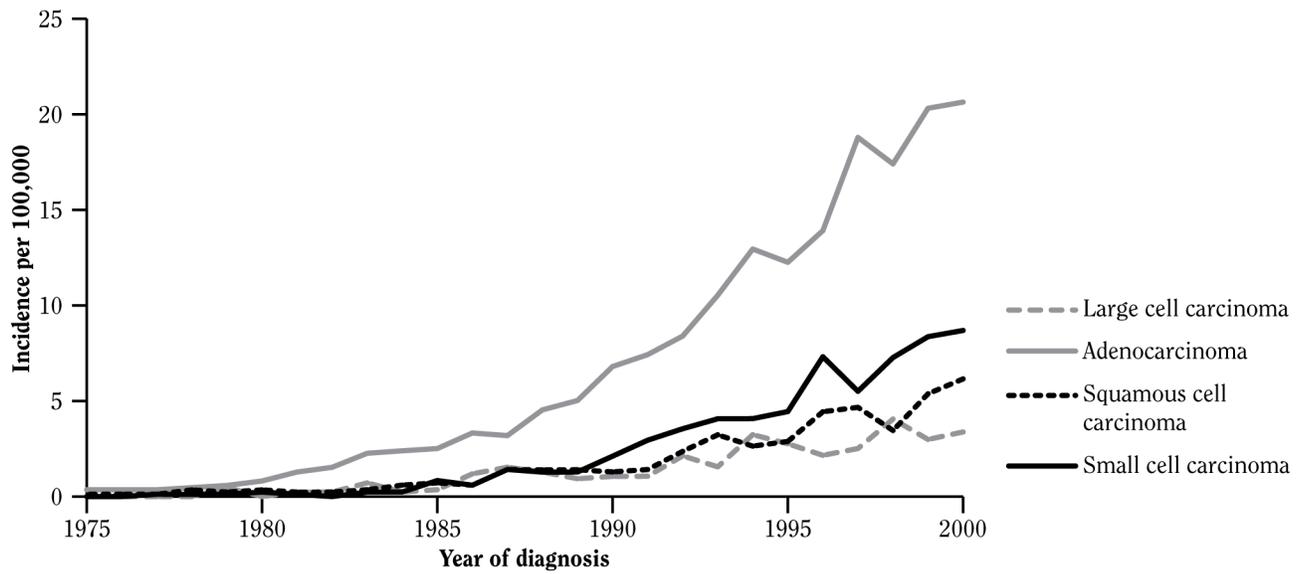
Figure 6.12   Continued

I. Birth cohort: 1950
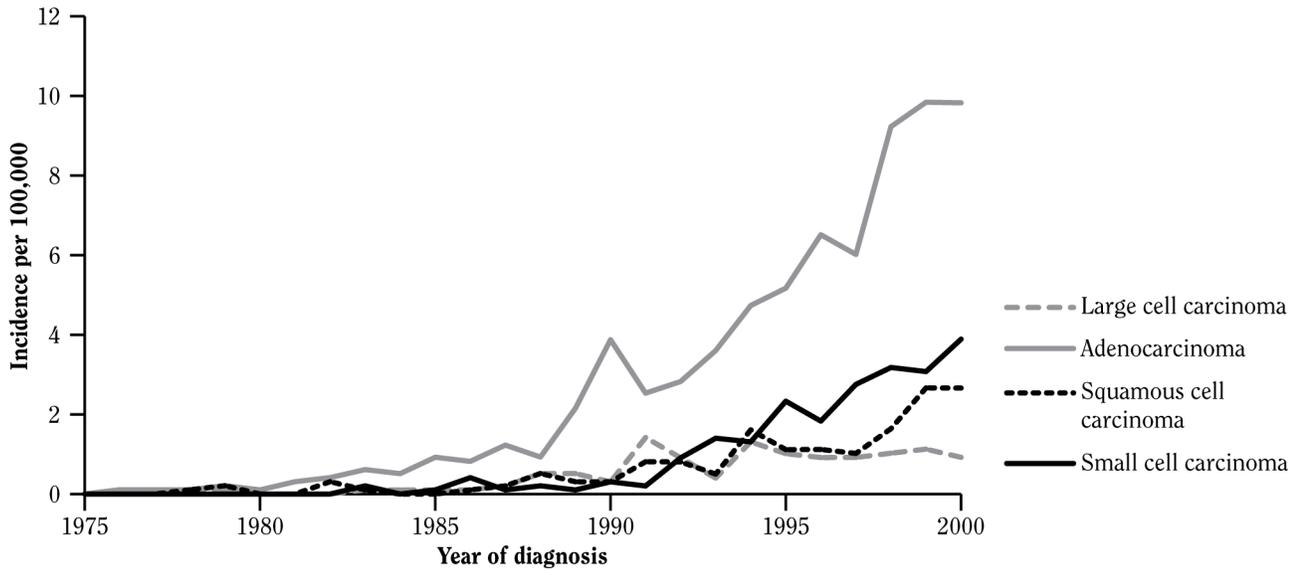
J. Birth cohort: 1955
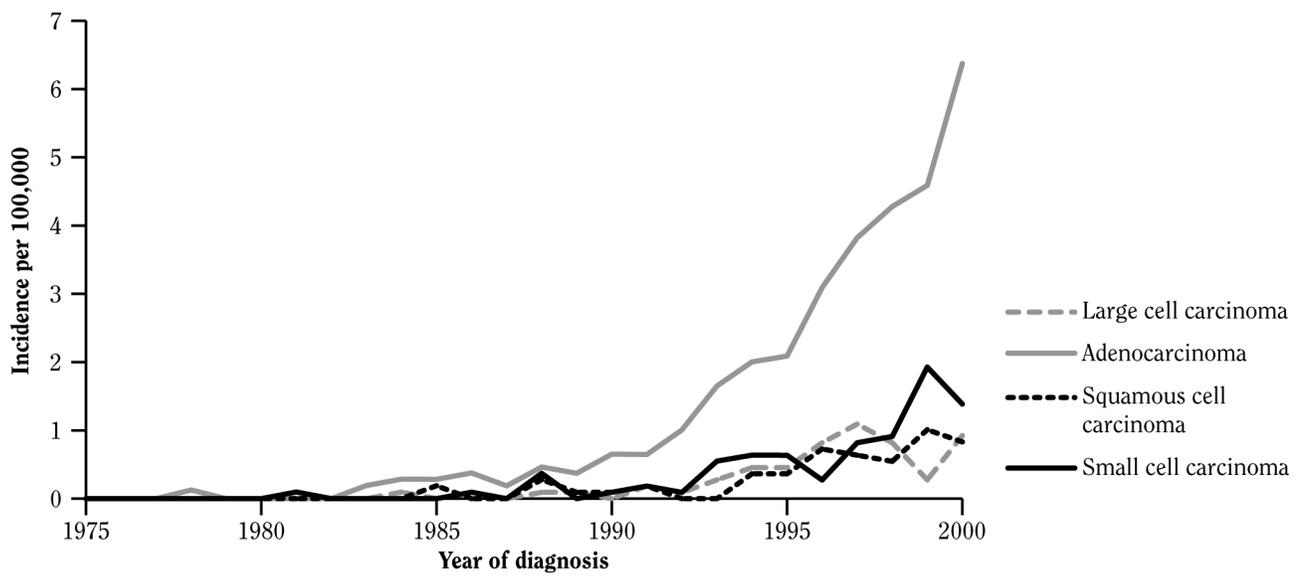
Source: Surveillance, Epidemiology, and End Results Program, public use data.

Figure 6.13 **Unweighted mean percentage of all lung cancers that were adenocarcinoma, by gender and birth cohort for the available calendar years, United States, 1890–1955**

A. Males
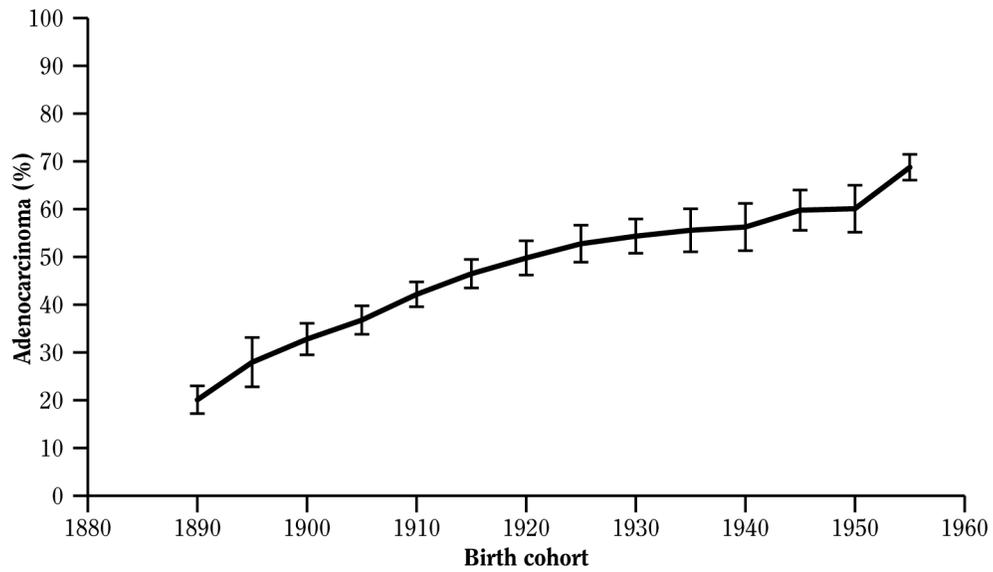
B. Females
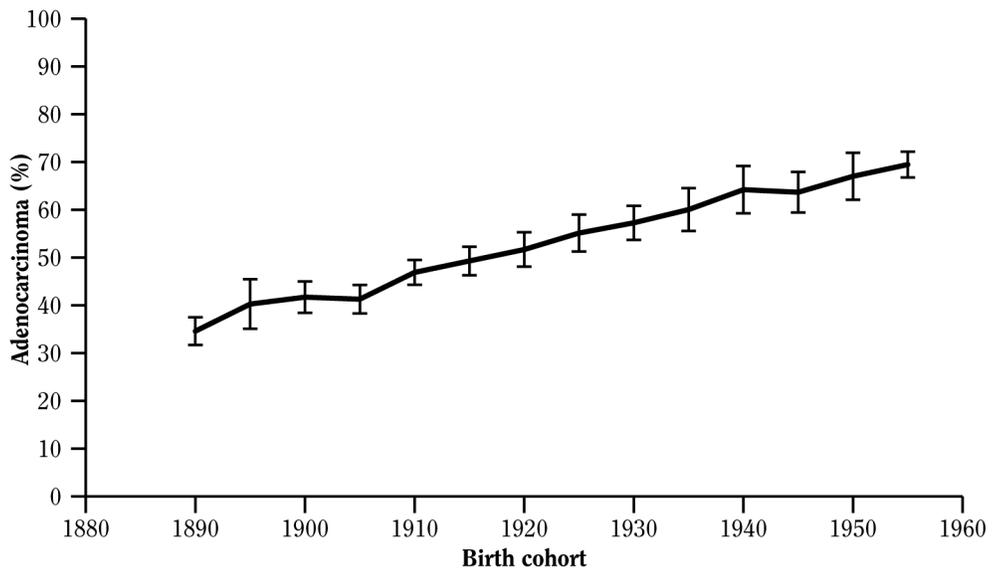
Source: Surveillance, Epidemiology, and End Results Program, public use data.

The birth-cohort pattern observed in Figures 6.11 and 6.12 suggests that changes in the design and composition of cigarettes may be a factor that is driving the increase in rates of adenocarcinoma (Charloux et al. 1997; Thun et al. 1997a; NCI 2001). Risk of lung cancer reflects cumulative exposure to cigarette smoke, and if a change in the design or composition of cigarettes increases the risk of lung cancer from smoking, then the onset of increasing risk begins at the time when the change is made. Each succeeding cohort would have a larger fraction of its cumulative smoking exposure from the new cigarettes, as existing brands are refashioned and smokers switch to brands with greater risk characteristics. This increased risk becomes stronger in successive birth cohorts, particularly if use of the newer, more hazardous product is more common among younger than older smokers. Among older individuals from the earlier birth cohorts, rates of lung cancer will continue to be dominated by the substantial contribution of their past smoking, and an increase in risk resulting from a more recently changed cigarette product will make a relatively modest proportional contribution to the pre-existing and already substantial risk for these cohorts. As more recent birth cohorts are examined, the onset of increasing risk due to a change in product design will begin at an earlier age because members of the cohort will begin smoking the newer products at a younger age. The increment in risk with the use of the newer products reflects a larger proportion of the total risk for the cohort, simply because the duration of smoking preceding the shift to a more dangerous type of cigarette is shorter and thus the risk for that earlier period as a fraction of total risk is smaller. Such an effect could explain the progressive increase in the proportion of lung cancers that are adenocarcinomas across sequential cohorts, as shown in Figure 6.13.

Differences in the prevalence of current and former smoking and differences in the distribution of the duration of smoking and the duration of abstinence from smoking vary markedly across birth cohorts and contribute to differences in risks of lung cancer. To account for these differences in the examination of rising rates of adenocarcinoma, birth-cohort-specific smoking behaviors have been used to model changes in the rates of lung cancer of different histologic types (Burns et al. 2011a), as was done for overall lung cancer mortality and incidence rates. Risk models derived from CPS-I were applied to the smoking behaviors of birth cohorts. These behaviors include rates of smoking initiation, prevalence of current and former smoking, and distributions of the duration of smoking, duration of abstinence, and number of cigarettes smoked per day for current and former smokers (Burns et al. 2011a). The resulting rates were adjusted for a healthy

population selection bias and differences between rates of incidence and mortality and then were scaled, based on the fraction of lung cancers of the appropriate histologic type in the SEER Program data for the first years available (1973–1975).

The predicted rates for squamous cell carcinoma and adenocarcinoma by 5-year birth cohort were compared with the rates observed in data from the SEER Program for the same cohorts during the calendar years 1973–2000. For squamous cell carcinoma, the predicted rates closely matched the rates from the SEER Program, suggesting that much of the variability in the incidence rates of squamous cell carcinoma over the past several decades can be explained by changes in the rates of smoking prevalence and cessation. In contrast, the predicted rates for adenocarcinoma did not match data in the SEER Program, and the differences between predicted rates and those of the SEER Program varied systematically by birth cohort. When a term increasing the risk for adenocarcinoma with duration of smoking after 1950 was added to the risk model for current and former smokers (to simulate an increasing risk over time associated with a change in the design of cigarettes), the predicted rates matched the rates from the SEER Program. Thus, these analyses suggest that increasing risk of lung cancer over time may be associated with changes in the design or composition of cigarettes. The analyses also raise the possibility that the increase in overall lung cancer mortality from smoking may reflect an increase in the risk of developing adenocarcinoma from smoking, with little change in the risk of developing squamous cell carcinoma.

Some researchers have suggested alternative explanations for the increase in lung adenocarcinoma. Based on birth-cohort analyses of data from the SEER Program and differences in the temporal trends in the incidence of squamous cell lung cancer and adenocarcinoma of the lung, Chen and colleagues (2007b,c, 2009) suggested an effect of air pollution, and specifically nitrogen oxides, as the cause for the trends in adenocarcinoma. However, because among never smokers both lung cancer mortality and the incidence of adenocarcinoma do not seem to have changed over time and because the risk of adenocarcinoma among smokers has increased, changes in cigarette smoking are a more likely cause of the temporal trends than air pollution.

Changes in the demographics of smokers are another potential explanation. Over time, the poorer and less-educated segments of the population have become a progressively greater fraction of U.S. smokers (see Chapter 13, "Patterns of Tobacco Use Among U.S. Youth, Young Adults, and Adults"). Within birth cohorts, an increasing proportion of smokers come from population groups

characterized by less education and lower income and cessation rates are lower in these groups as well, compared with those having more education and higher incomes. Occupational and environmental exposures associated with increased lung cancer risk are also more common among those with less education and lower income. As a result, the effects of this demographic shift should be relatively uniform across cohorts, unlike the pattern observed in the figures. In addition, a demographic shift of this type in the characteristics of smokers would not affect rates of adenocarcinoma or squamous cell carcinoma or would not affect rates of adenocarcinoma or influence rates of squamous cell carcinoma.

In summary, adenocarcinoma has been increasing in the United States as a fraction of all lung cancers, becoming the most common histologic type of lung cancer. Despite decreases in smoking prevalence and concomitant decreases in squamous cell carcinoma, the incidence of lung adenocarcinoma among smokers has increased since the 1960s. Changes in the design and/or composition of cigarettes during the 1960s have increased the levels of tobacco-specific nitrosamines and other carcinogens in cigarette smoke. Evidence from birth-cohort models and epidemiologic studies are sufficient to conclude that the increased risk of lung adenocarcinoma among smokers is due to changes in the design and/or composition of cigarettes which increased the carcinogenicity of cigarette smoke.

Evidence for a Rising Risk of Adenocarcinoma of the Lung in the United States

Differences Across Time in Rates of Adenocarcinoma Within the United States and Across Countries

In a population, the principal determinants of risk for lung cancer are the prevalence of current smoking and the distribution of the duration of smoking among current and former smokers. As described previously, assessing the impact of differences in population-based smoking behaviors on rates of lung cancer is a complex undertaking. Even so, some understanding can be gained by comparing rates of lung cancer in countries where smokers have similar behaviors but smoke different types of cigarettes.

Incidence rates of adenocarcinoma of the lung and the proportions of adenocarcinoma in relation to all lung cancers increased in most countries through 1995–1997 (Devesa et al. 2005). These trends were particularly evident among women and reflected the higher risk of lung cancer accompanying their increasing smoking prevalence and a

rising proportion of lung cancer that was adenocarcinoma (Devesa et al. 2005). When examined at the national level, however, the rates of increase of adenocarcinoma and the patterns of the shift to adenocarcinoma as the most common form of lung cancer varied among countries (Devesa et al. 2005). In many countries—such as European countries (Devesa et al. 2005), including Italy (Russo et al. 1997); Japan (Yoshimi et al. 2003); and Hong Kong (Tse et al. 2009)—the patterns among men have roughly mimicked those of U.S. men, with falling rates of squamous cell carcinoma and initially rising but then falling rates of adenocarcinoma. Among women, interpretations of changes in rates of cancer by histologic type need to consider the rising rates of smoking prevalence for women. Regardless, rates of adenocarcinoma rose faster than rates of squamous cell carcinoma in most countries for which data were available (Devesa et al. 2005).

As described previously, flue-cured cigarettes of the type preferred in Australia, Canada, and the United Kingdom have substantially lower levels of tobacco-specific nitrosamines than do U.S.-style blended cigarettes and have higher levels of B[a]P (WHO 2008b). Tobacco-specific nitrosamines, specifically NNN and NNK, are organ-specific carcinogens for adenocarcinoma of the lung in animal models (IARC 2007; USDHHS 2010); NNK selectively induces adenocarcinoma of the lung in rats, mice, and hamsters. The level of NNAL, a metabolite of NNK, in the urine of smokers has been shown to be an independent predictor of risk for lung cancer even when the analysis controls for intensity (by cotinine concentration) and duration of smoking (Church et al. 2009; Yuan et al. 2009).

In terms of PAHs, one prospective cohort study found that a biomarker (phenanthrene tetraol) for PAH exposure was not an independent predictor of risk for lung cancer (Church et al. 2009). When the risk for lung cancer was examined by histologic type in this study, however, a significant association was found between NNAL in the urine and adenocarcinoma of the lung. The relationship between NNAL and risk for lung cancer was not significant for all other types of lung cancer combined, and the odds ratios for adenocarcinoma and other lung cancers did not differ significantly from each other (Church et al. 2009).

Mouth-level exposure to tobacco-specific nitrosamines in smoke has been examined among smokers in countries with high use of blended cigarettes (United States) and flue-cured unblended cigarettes (Australia, Canada, and the United Kingdom) (Ashley et al. 2010). Levels of NNK exposure among Australian and Canadian smokers were approximately one-third that of U.S. smokers, and levels of NNN exposure were 85–90% lower than the U.S. experience. Among smokers in the United

Kingdom, levels of NNK exposure were 20% lower than those of smokers in the United States, and levels of NNN were approximately 50% lower (Ashley et al. 2010).

In England and Scotland, flue-cured cigarettes remain popular, but measures of the level of exposure to tobacco-specific nitrosamines fall between those observed in smokers in the United States and in smokers in other countries where unblended cigarettes are common (Canada and Australia) (Ashley et al. 2010). In England (Bennett et al. 2008) and Scotland (Harkness et al. 2002), incidence rates of adenocarcinoma of the lung for men have increased only slightly, and squamous cell carcinoma remains the predominant lung cancer. Rates of squamous cell carcinoma among men in those countries are declining consistently as smoking prevalence drops.

In Canada, the incidence rate of adenocarcinoma among men in 1995–1997 remained lower than that of squamous cell carcinoma and well below the rate for White men in the United States (Figure 6.14) (Devesa et al. 2005). In contrast, rates for squamous cell carcinoma were similar for men in the United States and Canada in this period and in women as well (Devesa et al. 2005). Based on data up to 1997, the incidence of adenocarcinoma of the lung did not appear to be increasing over time in Canada. Instead, the data suggest that squamous cell carcinoma was decreasing so that adenocarcinoma represented an increasing fraction of lung cancers over time (Devesa et al. 2005).

In Australia, where flue-cured, unblended cigarettes with low tobacco-specific nitrosamine levels are also prominent, the rate of adenocarcinoma among men rose across birth cohorts and over time and exceeded the rates of squamous cell carcinoma for the most recent cohorts (Blizzard and Dwyer 2002). In contrast, the rate of adenocarcinoma among men in New South Wales, Australia, remained essentially constant between 1985 and 1997 (Figure 6.14) (Devesa et al. 2005) or rose only slightly over time. However, the rate for squamous cell carcinoma in 1995–1997 among New South Wales men declined to a level approximating that of adenocarcinoma (Figure 6.14) (Joshua et al. 2005). Similarly in South Australia, the rate of adenocarcinoma among men through 2000 was also relatively consistent over time, and the rate of squamous cell carcinoma fell to the same level as adenocarcinoma (Nguyen et al. 2003). However, in South Australia, the rate of adenocarcinoma increased among younger age groups.

When comparing the United States and Australia, the different patterns of cigarettes smoked may contribute to different patterns of lung cancer. Figure 6.15 presents gender- and age-specific rates of lung cancer mortality for the United States and Australia for 2000 (Peto et al. 2006). Lung cancer death rates were lower in all age groups for men and women in Australia compared with the United States. Detailed comparisons of smoking behaviors similar to those used to model U.S. death rates are not available for Australia, but estimates of the prevalence of smoking show a general similarity for Australia and the United States, particularly during the 1990s (White et al. 2003).

Figure 6.16 presents information on adenocarcinoma as a proportion of all lung cancers with a designated histologic type, by birth cohort and gender for the United States and Australia (Burns et al. 2011a). In Australia, a modest rise occurs in the proportion of lung cancers that are adenocarcinoma across the birth cohorts for both genders, but the fraction remains well below 50% for men and only slightly above 50% for women. Data for the United States show a much more dramatic increase in the proportion of lung cancer that is adenocarcinoma, with the proportion exceeding 60% in the most recent cohorts for White men and women. Notably, the earliest birth cohorts for the U.S. population, those born from 1880–1900, have proportions similar to those found in Australia.

In summary, rates for squamous cell carcinoma of the lung have been decreasing in most countries in which the prevalence of smoking has been declining. In contrast, the incidence rate of adenocarcinoma has been rising in the United States and has been level or increasing in other countries, with the general result that adenocarcinoma has increased as a proportion of lung cancer in most countries. The magnitude of that increase has differed between the United States, where the predominant type of cigarette is made of blended tobacco with relatively high levels of tobacco-specific nitrosamines, and Canada and Australia, where flue-cured cigarettes with lower levels of tobacco-specific nitrosamines predominate. Incidence rates of adenocarcinoma and the proportion of lung cancer that is adenocarcinoma are substantially higher in the United States than in Canada and Australia.

Effects of Filter Ventilation on Deposition of Smoke in the Lung and the Toxicity of This Smoke

One potential explanation for the rise in adenocarcinoma of the lung in the United States is a change in the pattern of smoking after ventilated filters were introduced to lower the machine-measured yields of tar and nicotine (Zheng et al. 1994; Thun et al. 1997a; Wingo et al. 1999). Smokers who shift to brands with nominally lower machine-measured yields with ventilated filters change their smoking pattern to restore their nicotine delivery to the level needed to sustain their addiction. As described previously, changes include increasing puff volume and velocity, greater duration of puffing, and shortening the

Figure 6.14   Trends in incidence rates for lung cancer (age adjusted, world standard), by histologic type (squamous cell carcinoma, small cell carcinoma, and adenocarcinoma) and geographic area, 1980–1982 to 1995–1997

A. Squamous cell carcinoma of the lung

North America and Oceania
- U.S. Blacks
- U.S. Whites
- Canada
- New South Wales, Australia

Nordic Countries
- Denmark
- Iceland
- Norway
- Sweden

Other Europe
- Eindhoven, The Netherlands
- Varese, Italy
- Slovenia
- France
- Spain
- Switzerland
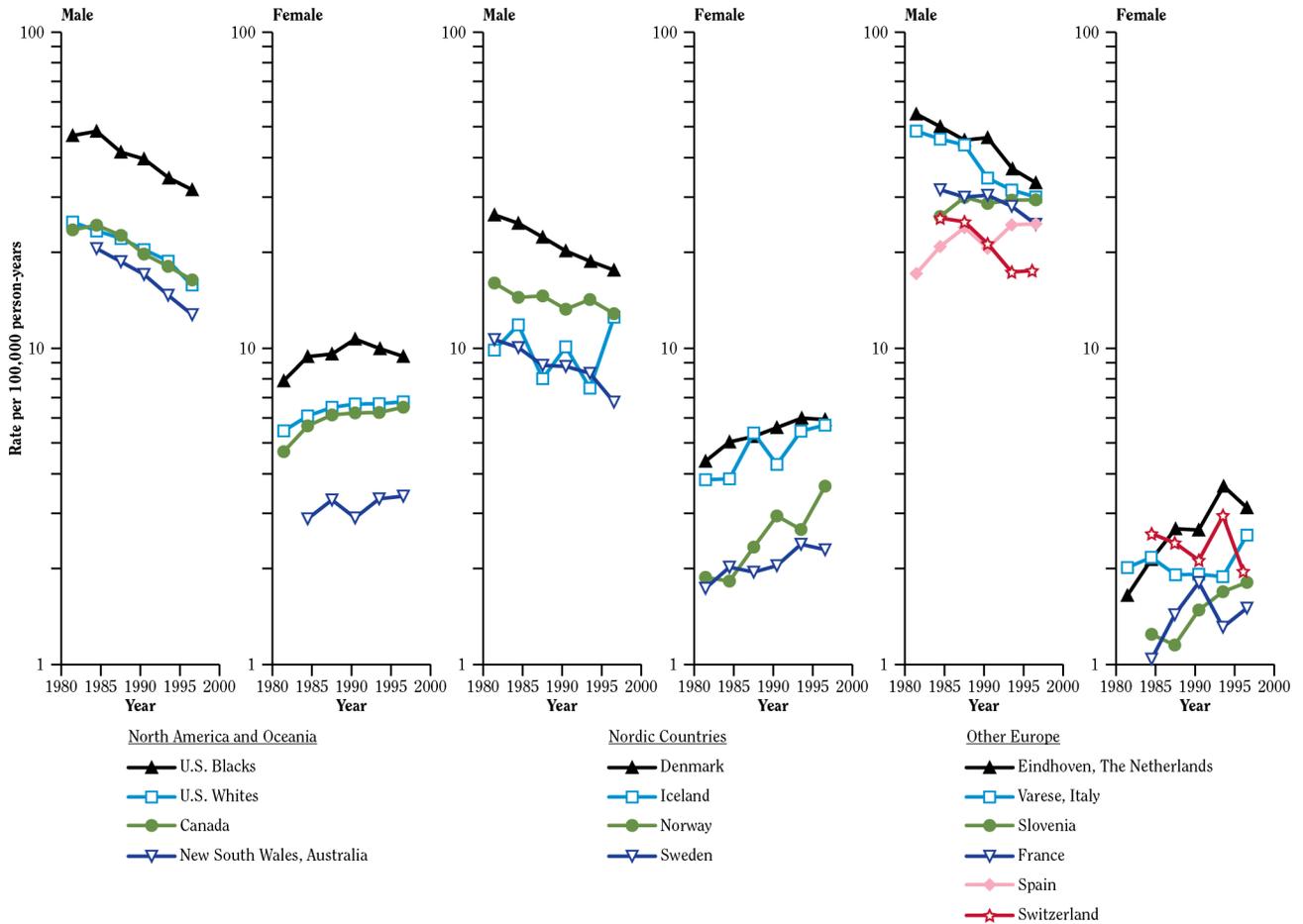
Figure 6.14   Continued

B. Small cell carcinoma of the lung

North America and Oceania
- U.S. Blacks
- U.S. Whites
- Canada
- New South Wales, Australia

Nordic Countries
- Denmark
- Iceland
- Norway
- Sweden

Other Europe
- Eindhoven, The Netherlands
- Varese, Italy
- Slovenia
- France
- Spain
- Switzerland
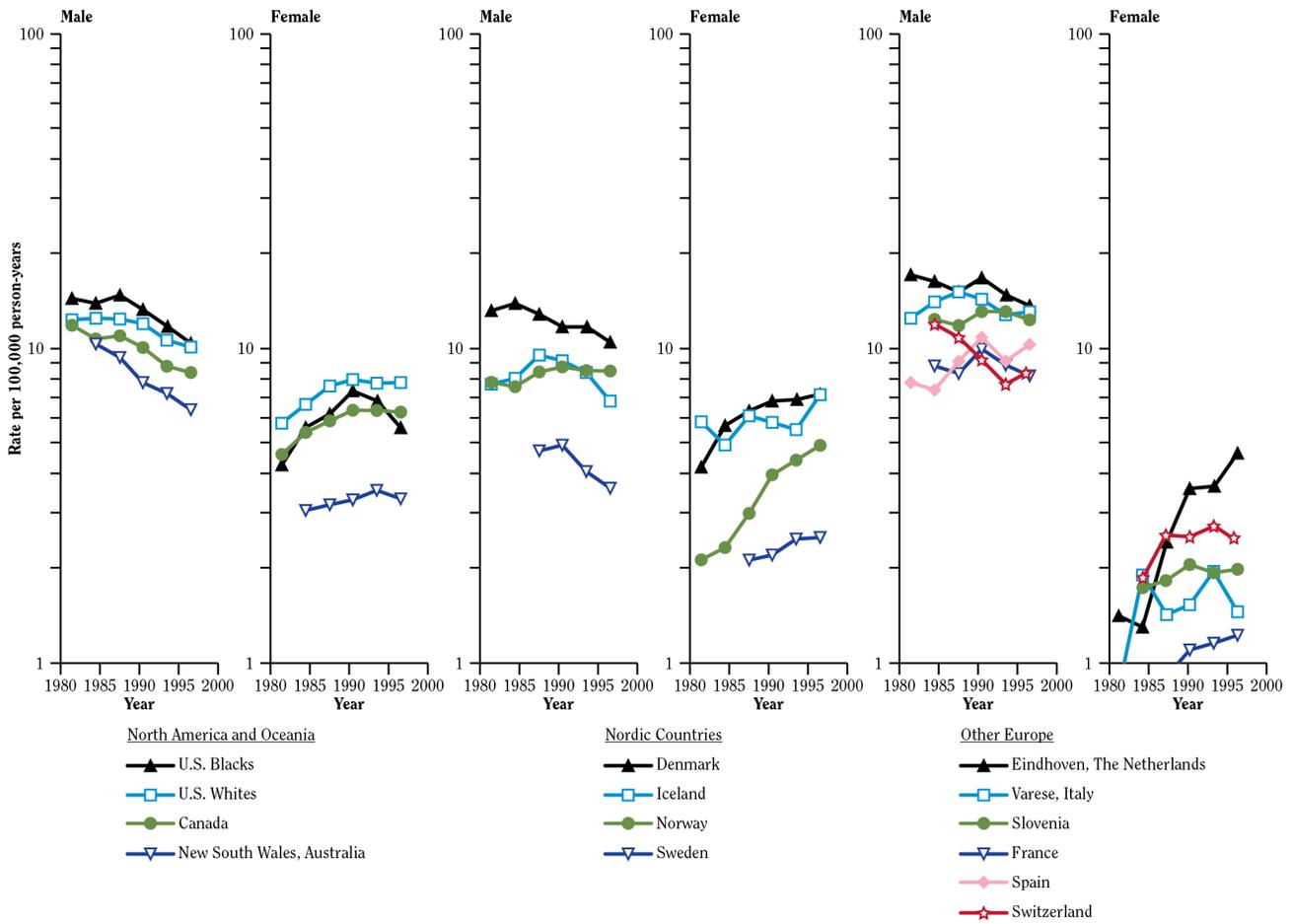
Figure 6.14   Continued

C. Adenocarcinoma of the lung
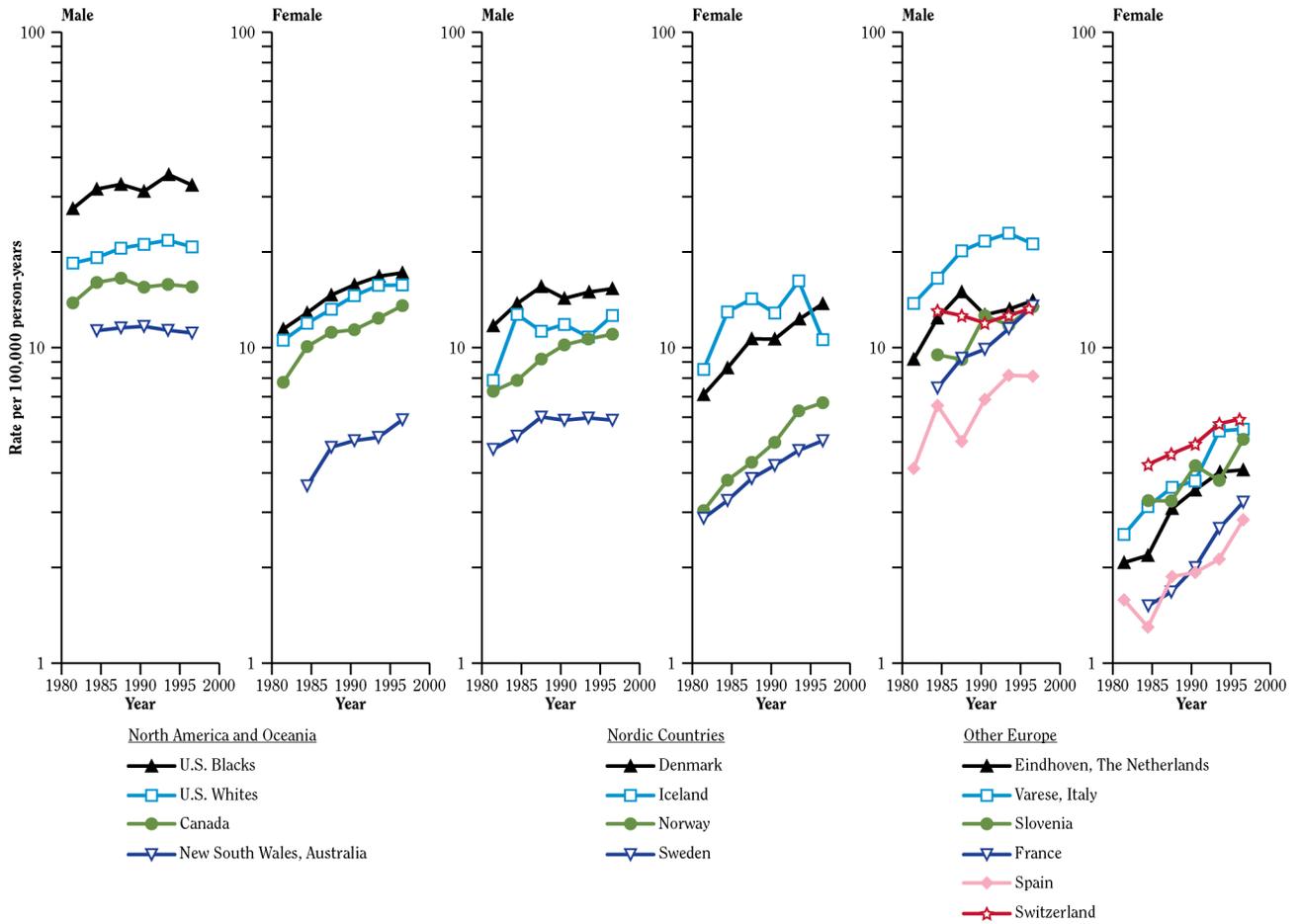
Source: Devesa et al. 2005. Reprinted with permission from John Wiley & Sons, Inc., © 2005.
Note: Incidence rates were calculated for 3-year time periods: 1980–1982 (plotted at 1981.5), 1983–1985 (plotted at 1984.5), 1986–1988 (plotted at 1987.5), 1989–1991 (plotted at 1990.5), 1992–1994 (plotted at 1993.5), 1996 (Switzerland only; plotted at 1996), and 1995–1997 (plotted at 1996.5). Incidence rates were age-adjusted by the direct method, using the Segi world standard (Bray et al. 2002), and expressed per 100,000 person-years.

Figure 6.15 Age-specific rates of lung cancer death, by gender and age group, in the United States and Australia, 2000

A. Men
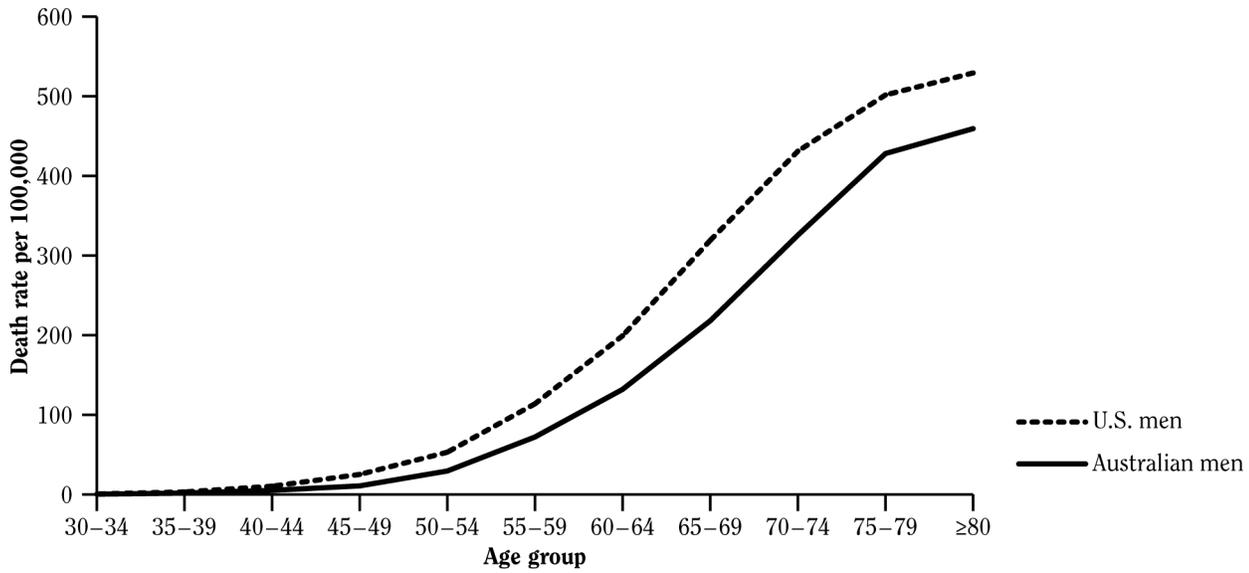
B. Women
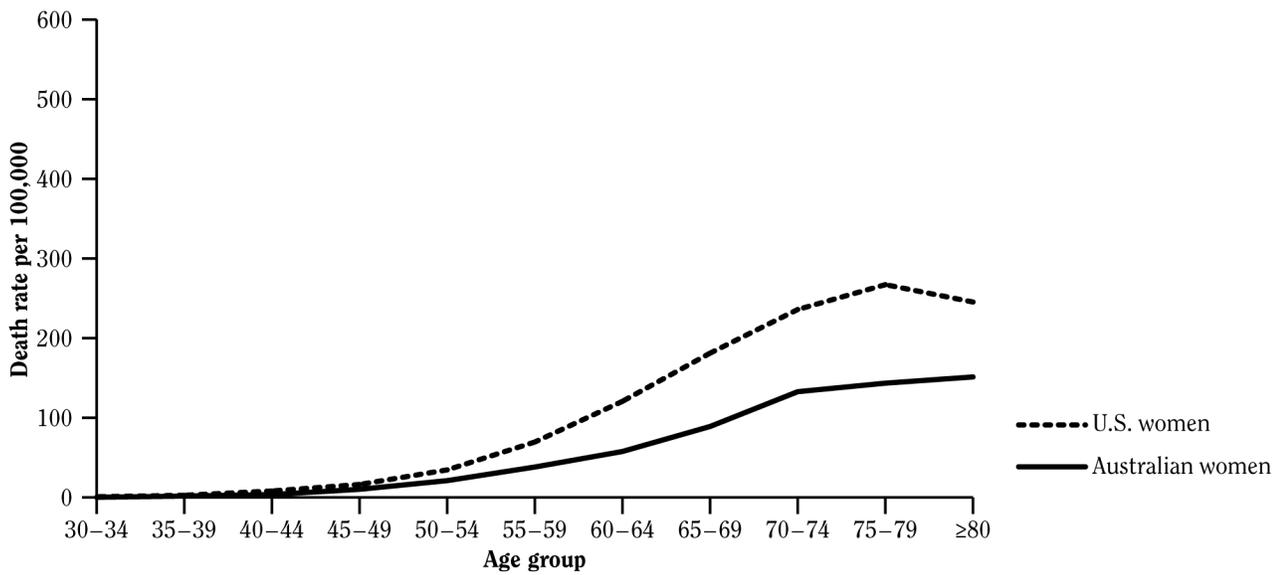
Source: Peto et al. 2006.

Figure 6.16   Adenocarcinoma as a percentage of designated lung cancers in U.S. White men and women and Australian men and women, by various birth cohorts, 1890–1955

A. U.S. White men and women
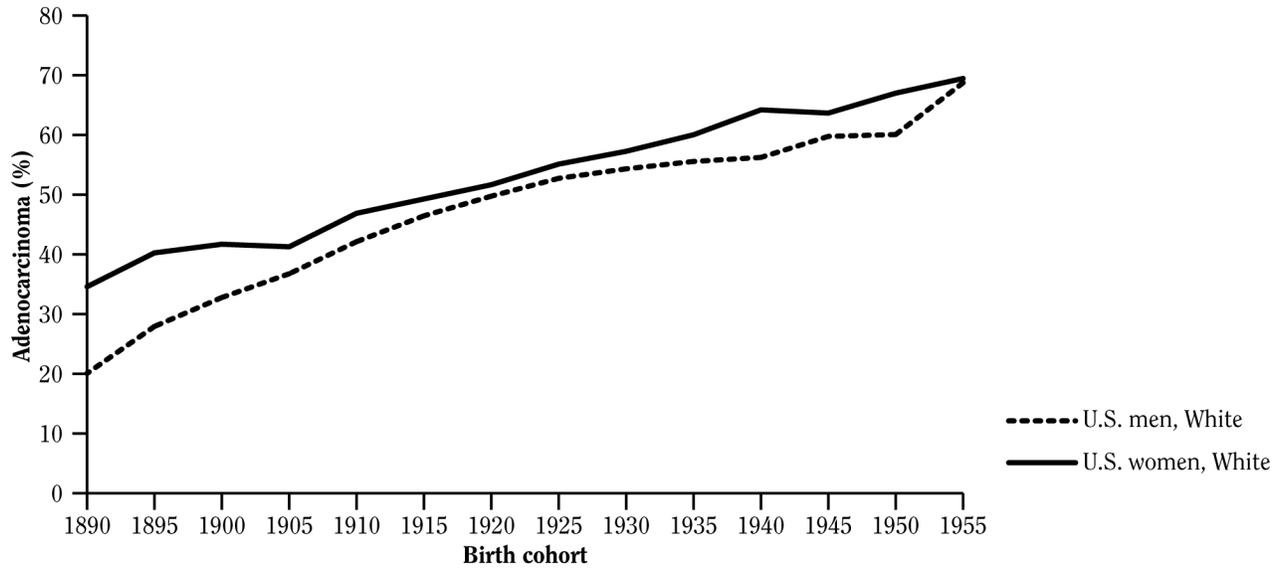
B. Australian men and women
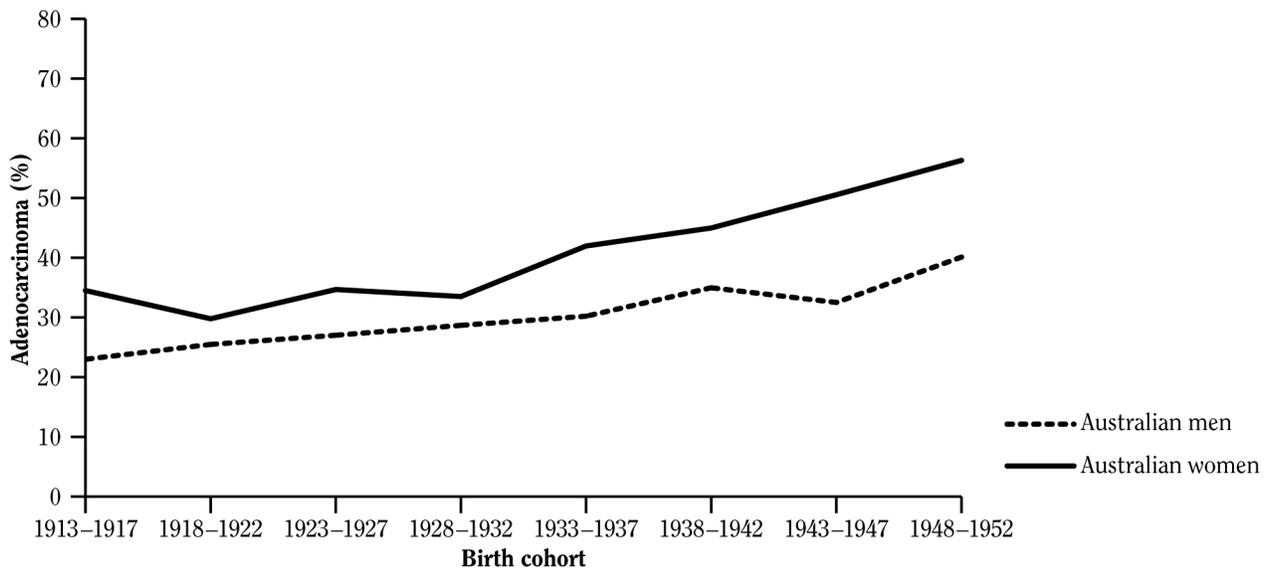
Source: Burns et al. 2011a. Reprinted with permission from Science & Business Media B.V., © 2011.
Note: Data for the Australian national cancer registry provided by Helen Farrugia, Director Information Systems, Cancer Epidemiology Centre, The Cancer Council Victoria.

intervals between puffs (NCI 2001). In addition, smokers may increase the depth of inhalation and hold the smoke in their lungs longer to increase nicotine uptake. Notably, there is little difference in markers of nicotine ingestion between smokers of brands of cigarettes with substantially different machine yields (Jarvis et al. 2001; NCI 2001). Increasing depth of inhalation and other more intense smoking patterns likely increase the deposition of smoke in the alveolar region of the lung.

Most physical models of particles disseminating in the lung incorporate the size-dependence of particle deposition in the lung, but do not fully reflect the complexity of smoking behavior. As a consequence, the models may underestimate the fraction of smoke particles retained in the lung (Stratton et al. 2001; Gower and Hammond 2007; Rostami 2009), raising questions about their validity in characterizing the distribution and deposition of particles in different regions of the lung with different tobacco products. An analysis by Gower and Hammond (2007) of models of cigarette smoke deposition that examined the effects of the changes in pattern of smoking after a shift to brands with lower machine-measured yields showed that puff time, inhalation depth, time holding one's breath, and exhalation time may affect total smoke deposition. While a shift in deposition to the alveolar level remains a possibility, the researchers could not determine whether the changes in patterns of smoking resulting from the use of more highly ventilated cigarettes could produce a large enough shift in the location of deposition to change the pattern of incidence of a specific histologic type of lung cancer. Although the magnitude of the potential change in regional deposition in the lung remains uncertain, existing evidence suggests that changes in the pattern of smoking, with a shift to lower tar-yield cigarettes, will likely increase the fraction of cigarette smoke particles deposited in the alveolar region of the lung. This shift may also have played a role in increasing the risk of adenocarcinoma of the lung over time.

The introduction of ventilated filters, or changes in the design and composition of cigarettes that accompanied their introduction, may have increased the carcinogenicity of cigarette smoke. Given the dilution of smoke by filter ventilation and the compensation for that dilution by smokers when these cigarettes are used, comparisons of the toxicity of cigarettes on a per-cigarette basis can be misleading, making comparisons on the basis of "per mg tar" or "per mg total particulate matter" more useful.

The level of filter ventilation alters the composition of tobacco smoke. In general, based on the International Organization for Standardization protocol and under more intense smoking parameters, higher levels of ventilation result in more complete combustion in flue-cured, unblended cigarettes smoked by a machine (Adam et al. 2010). When experimental (Rickert et al. 2007) or commercial (Roemer et al. 2004) U.S.-blended cigarettes were compared with experimental, unblended, flue-cured cigarettes (Monitor-7 Canadian reference cigarette) in mutagenicity testing, the level of revertants per mg (the indicator of mutational strength) of the total particulate matter was lower for the unblended Canadian reference cigarette. For Kentucky reference cigarettes, mutagenicity per mg of total particulate matter was 30–40% lower for unfiltered cigarettes than for the same cigarette with a filter added (Shin et al. 2009).

Tobacco industry documents show internal company research demonstrating that increasing filter ventilation increases the mutagenicity of the resultant tar on a per-mg of tar basis (Johnson et al. 2009). The published evidence produced by the industry is less clear. In a study from R.J. Reynolds, Chepiga and colleagues (2000) compared full-flavor, full-flavor low-tar, and ultralow-tar cigarettes and reported a nonsignificant trend of increased revertants per mg of tar in mutagenicity studies as the level of machine-measured tar decreased. In a study from Philip Morris, Roemer and colleagues (2004) reported that higher total yields of particulate matter were associated with a trend toward less mutagenic activity per mg of total particulate matter. In another study from Philip Morris, Patskan and colleagues (2008) compared the mutagenic activity of Marlboro full flavor, Marlboro Lights, and Marlboro Ultra Lights, finding that mutagenic activity was higher per mg of total particulate matter for Marlboro Ultra Lights, but this was for only some *Salmonella* strains used in the mutagenicity testing and for only some runs. Thus, the evidence supports a modest increase in the mutagenicity of tobacco tar as the level of machine-measured tar falls; this effect may result from increased ventilation.

These data should be interpreted with caution for several reasons. Mutagenicity is generally used as only a screening test, is often poorly associated with carcinogenicity in humans, and has not been quantitatively associated with differences in human risk. In addition, most of the studies described previously compared smoke generated under standardized machine-testing protocols. In actual use, smokers change their patterns of smoking, compensating for the design changes that result in lower yields of machine-measured tar and nicotine. This compensatory smoking behavior makes comparisons of cigarettes with very different machine-tested yields difficult to interpret relative to carcinogenicity in humans when the smoke for the different cigarettes is generated using a single, standardized, machine-smoking protocol.

Existing evidence about changes in the patterns of smoking cigarettes with low yields of tar and high ventilation supports a shift in the deposition of smoke in the lung toward the alveolar region; this shift likely contributes to the observed increase in adenocarcinoma of the lung. Research has not clarified whether the magnitude of this shift in lung deposition, by itself, is great enough to explain the dramatic increase in adenocarcinoma observed in the United States. The mutagenicity of tobacco tar from cigarettes with lower yields of machine-measured tar is trending upward. However, the trend is modest in size, and difficulties in extrapolating results from mutagenicity testing to risk for humans make it difficult to know whether these changes contribute to increasing the risk of lung cancer.

Evidence Synthesis

The design and composition of cigarettes have changed substantively since the first major wave of evidence linking smoking to lung cancer in the 1950s. Although the details of these changes are only partially understood, changes in design—notably the addition of ventilated filters—have clearly changed the pattern of smoking, including more intense puffing. In addition, changes in the composition of cigarettes have resulted in incompletely characterized alterations in the chemical composition of cigarette smoke. Documented changes include increases in tobacco-specific nitrosamines and decreases in PAHs in the smoke of U.S. cigarettes. Substantial differences between U.S. cigarettes and those of many other nations include the use of blended tobacco in U.S. cigarettes and the use of unblended, flue-cured tobacco in cigarettes in Australia, Canada, and the United Kingdom. The United States has somewhat preceded most other developed countries in the adoption of filtered and low-yield, machine-tested cigarettes, but U.S. products are also used widely in most countries. These changes raise a question of whether rates of lung cancer have been altered by the changes in the design and composition of cigarettes—changes that were accompanied by an initial belief that lower yields of machine-tested tar might signal a lower risk for lung cancer. In fact, the risk of lung cancer in the United States may have increased as a result of such changes.

Comparison of results of CPS-I and CPS-II—two large epidemiologic studies conducted 20 years apart by ACS—demonstrated an increased risk of death from lung cancer from smoking across the 20-year interval between the studies. For female smokers, the results from the contemporary cohorts show that lung cancer risk continued to rise through 2000–2010. Modeling of risks of lung cancer from smoking behaviors suggests that risk estimates based on the smoking experience in the 1960s underestimated the current incidence of lung cancer. In addition, the incidence of adenocarcinoma of the lung and the proportion of lung cancer that is adenocarcinoma has increased dramatically during the past several decades. This shift from squamous cell carcinoma to adenocarcinoma is confined to smokers, because neither the overall risk of lung cancer nor the risk of adenocarcinoma has changed over time among never smokers. The rate of squamous cell carcinoma of the lung has declined in the United States since the 1980s and is well-predicted by declines in smoking behaviors, but the rate of adenocarcinoma continued to rise for an additional 10–15 years before either leveling off or beginning to decline. Birth-cohort-specific analyses of trends in overall mortality from lung cancer and the incidence of type-specific lung cancer suggest that increases in diagnostic accuracy, differences by tumor type in the time course of excess risk reduction with cessation, and underestimation of the effect of intensity and duration of smoking in the studies that defined risk in the 1960s do not explain the observed trends. In contrast, a change in the risk of the cigarettes smoked over time does explain the increase in risk. A shift in the demographic composition of smokers toward those groups with less income and education may contribute to the increased risk of lung cancer among smokers, but this shift does not likely explain the increase in adenocarcinoma or the difference in the rates of incidence of squamous cell carcinoma and adenocarcinoma.

Most countries have experienced increases in the proportion of all lung cancer that is adenocarcinoma, but substantial differences are found in the extent of this increase when comparing the United States, where blended cigarettes are used, with Australia and Canada, where unblended cigarettes are used. Adenocarcinoma in the United States has increased more steeply, represents a much higher fraction of lung cancer, and has higher absolute incidence rates than those of Australia or Canada. Compared with unblended cigarettes, U.S.-style blended cigarettes have dramatically higher levels of tobacco-specific nitrosamines—an organ-specific carcinogen of adenocarcinoma of the lung in animals. Exposure to tobacco-specific nitrosamines is also much higher among U.S. smokers than among their counterparts in Australia and Canada. Levels of a metabolite of NNK, a tobacco-specific nitrosamine, are an independent risk predictor for the occurrence of lung cancer after controlling for the intensity and duration of smoking.

Compensatory changes in the patterns of puffing and inhaling smoke by smokers switching to cigarettes with low yields of toxicants may increase the deposition of smoke particles in the alveolar region of the lung. This is supported by modeling of particle deposition in the lung that suggests this effect likely increases the deposition of particles in the alveolar region. Increased alveolar deposition and increasing tobacco-specific nitrosamine levels over time may have combined to increase the risk for adenocarcinoma.

Conclusions

1. The evidence is sufficient to conclude that the risk of developing adenocarcinoma of the lung from cigarette smoking has increased since the 1960s.

2. The evidence is sufficient to conclude that the increased risk of adenocarcinoma of the lung in smokers results from changes in the design and composition of cigarettes since the 1950s.

3. The evidence is not sufficient to specify which design changes are responsible for the increased risk of adenocarcinoma, but there is suggestive evidence that ventilated filters and increased levels of tobacco-specific nitrosamines have played a role.

4. The evidence shows that the decline of squamous cell carcinoma follows the trend of declining smoking prevalence.

Implications

The evidence presented has multiple implications. Above all, if the risk of lung cancer has increased with changes in the design and composition of cigarettes, then the potential exists to reverse that increase in risk through changes in design and composition. Even a mod-est reduction in the large burden of mortality from lung cancer would result in saving substantial numbers of lives over time.

The evidence reviewed suggests that differences in the design and composition of cigarettes may contribute to differences in smoking-related risks of lung cancer in different populations and different geographic locations. Data also suggest that epidemiologic studies treating all cigarettes as having identical risks, or using single biomarkers of exposure to quantify actual exposure to the multiple carcinogens in cigarette smoke, should be undertaken with some caution. The number of cigarettes smoked per day, measures of cotinine in biologic samples, and other measures of total smoke exposure will remain useful for estimating total smoke exposure and population risk. However, the potential for differences in products to yield differences in risk suggests that a broader array of biomarkers of exposure should be used to examine whether differences in the toxicity and composition of a given total exposure to smoke may also play an important role in determining differences in risks.

The changing risk for lung cancer associated with cigarettes over time also has implications for the surveillance of tobacco products. Monitoring tobacco products needs to go beyond tracking the most obvious changes, such as the addition of a filter, to assess the characteristics of the tobacco in the cigarette, how the product is manufactured, how it is likely to be smoked, the design of the cigarette, and its performance under a variety of smoking patterns. The absence of such information for past and current tobacco products limits the ability to more fully study the effects of changes in the design and composition of cigarettes on risks of disease. The availability of such information could help in the assessment of potential differences in risks going forward.

Finally, the rise in the risk of adenocarcinoma of the lung from smoking was unanticipated. This experience, like that of cigarettes with purportedly low yields of toxicants, indicates that changes to cigarettes should undergo careful, evidence-based assessments as such changes are being considered.

Liver Cancer

In many parts of the world, liver cancer remains a leading cause of cancer mortality. Primary liver cancer, the great majority of which is hepatocellular carcinoma (HCC), generally presents at an advanced stage with limited treatment options and a poor prognosis. Although worldwide liver cancer is the sixth most common cancer in terms of incidence, it represents the third most common cause of cancer-related death (Ferlay et al. 2010).

A number of strong risk factors for HCC have been identified, including infection with the hepatitis B or C viruses (HBV, HCV), exposure to aflatoxins, and alcohol-associated cirrhosis (London and McGlynn 2006). The incidence of liver cancer varies geographically worldwide, with rates generally consistent with the regional prevalence of the primary viral etiologic factors (Nordenstedt et al. 2010). Globally, Asia and sub-Saharan Africa—with endemic HBV infection and common dietary exposure to aflatoxins—have the highest incidence of HCC. Rates of HCC appear to have stabilized or started to decline in several Asian countries, where widespread vaccination against HBV and reduction of HBV cofactors have occurred during the past few decades (Yuen et al. 2009). HCV infection has been the primary etiologic agent for HCC in various countries having substantial incidence of HCC (London and McGlynn 2006).

Historically, the United States has had a low incidence of liver cancer and low death rates for the disease. However, rates of HCC have been increasing in the United States over the last two decades (Altekruse et al. 2009; El-Serag 2011). In recent years, Whites and Blacks, particularly those 50–59 years of age, have experienced the largest annual percentage increases in rates of HCC; rates of HCC among Asians/Pacific Islanders have been stable (O'Connor et al. 2010). The increased rates of HCC in the United States appear to be largely a consequence of chronic HCV infection (El-Serag 2004). However, obesity, diabetes, and associated nonalcoholic fatty liver disease, and the substantial burden of chronic HBV infection among foreign-born Asians may also be potential contributors to the increasing incidence of HCC (Larsson and Wolk 2007; Starley et al. 2010). In addition to viral hepatitis, cirrhosis from consumption of alcohol represents an important cause of HCC worldwide (London and McGlynn 2006). HCC is more common among men than women, which likely reflects gender differences in exposure to viral hepatitis and rates of progression of that disease, differences in smoking and in consumption of alcohol, and perhaps hormonal differences.

The association between smoking and HCC is complicated by the potential for confounding with the causal factors of consumption of alcohol and HBV and HCV infection. For example, people who drink alcohol are more likely to be smokers than people who do not drink alcohol (Dawson 2000). In addition, most HCV infections worldwide are acquired by injecting drugs, and the prevalence of smoking is very high among injection drug users (Marshall et al. 2011). In regions of the world with a high incidence of HCC, HBV infection is generally acquired perinatally or during early childhood. However, in other regions, HBV may be more commonly acquired through parenteral or sexual transmission; these behaviors may also be associated with smoking. Hence, the potential confounders must be examined carefully when assessing the association between smoking and HCC. However, considerable epidemiologic evidence, including data from studies in which measures have been taken to address potential confounding, indicates that smokers are at an increased risk for liver cancer (IARC 2004).

Conclusions of Previous Surgeon General's Reports

The Surgeon General's report on smoking cessation (USDHHS 1990) noted an association between smoking and HCC that persisted after controlling for potentially confounding lifestyle factors, including consumption of alcohol. The report also noted that HBV infections may modify the effects of smoking on the risk of liver cancer. The Surgeon General's report on women and smoking (USDHHS 2001) concluded that smoking may be a contributing factor to the development of liver cancer. The Surgeon General's report on the health consequences of smoking (USDHHS 2004) noted a consistent association between smoking and HCC after controlling for potentially confounding factors, but it called for further consideration of the history of viral hepatitis and consumption of alcohol. Overall, the 2004 report concluded that although the data were suggestive of an association between smoking and liver cancer, further evidence was required to classify smoking as a cause of liver cancer.

Biologic Basis

Circulating carcinogens from tobacco smoke are metabolized in the liver, exposing the liver to many absorbed carcinogens. Experimental studies have identified several constituents of tobacco smoke (e.g., *N*-nitrosodimethylamine, 4-aminobiphenyl) as liver carcinogens (IARC 2004). Limited human data on smoke-related carcinogens have suggested increased levels of 4-aminobiphenyl and PAH adducts in HCC tissues compared with normal liver tissues (Wang et al. 1998; Chen et al. 2002). Therefore, long-term exposure to carcinogens in smoke may lead to cellular damage in the liver and contribute to the development of cancer. Cigarette smoking may also contribute to liver carcinogenesis through the development of liver fibrosis (Dev et al. 2006; Mallat et al. 2008; Altamirano and Bataller 2010). Similar to their effects on other fibrogenic conditions (e.g., cardiac, renal, or pancreatic diseases), components of smoke may induce pro-inflammatory cytokines, oxidative stress pathways, and direct fibrogenic mediators (e.g., transforming growth factor-β1, angiotensin II) (Altamirano and Bataller 2010). Smoking has also been recognized as a risk factor for primary biliary cirrhosis, which itself can progress to HCC (Zein et al. 2006; Corpechot et al. 2012; Smyk et al. 2012). Although their results have been inconsistent, several epidemiologic studies have demonstrated that smoking substantially increases the risk for progression from chronic liver disease to HCC (Tsukuma et al. 1993; Marrero et al. 2005; Fujita et al. 2006). Further clarification is needed of the mechanistic and epidemiologic effects of smoking in relation to potential etiologic agents that can influence these pathways (chronic inflammation and/or oxidative stress associated with HCV infection, obesity, or diabetes).

Epidemiologic Evidence

Since the 2004 report of the Surgeon General, 90 additional studies have been published or identified that report on the association between smoking and liver cancer. IARC (2004) concluded that there was sufficient evidence of a causal association between cigarette smoking and liver cancer. Subsequently, Lee and colleagues (2009) published a meta-analysis that was based on the studies considered in the 2004 IARC report.

Studies for the current review were compiled by searching the MEDLINE database (from January 1966 to December 2012) using the medical subject headings "tobacco," "smoking," "liver neoplasms," or "hepatocellular carcinoma" and by examining references cited in the previous Surgeon General's reports, the IARC (2004) monograph on smoking and liver cancer, and the associated meta-analysis (Lee et al. 2009). The epidemiologic data came from a wide range of studies in both low- and high-incidence countries (Tables 6.3S and 6.4S). For many studies, the outcome was defined as HCC and was based on clinical, radiographic, laboratory (alpha-fetoprotein levels), or pathologic criteria. A minority of studies relied on linkage to cancer or mortality registries, often using primary liver cancer as the outcome defined by the coding of cancer diagnoses from the *International Classification of Disease for Oncology* or causes of death from the *International Classification of Diseases*. Some studies were unable to distinguish between HCC and intrahepatic cholangiocarcinoma; however, none of these studies were from geographic regions where intrahepatic cholangiocarcinoma would likely represent a substantial portion of primary liver cancers. Studies that did not explicitly differentiate between primary and secondary liver cancer (and therefore may have included cancers with a different primary site that had metastasized to the liver) were excluded from the analysis. Quantitative analyses included all studies that reported sufficient information to abstract or calculate an effect estimate and 95% confidence interval (CI); these analyses were stratified by study design (case-control or cohort).

This review focused on evaluations of the separate effects observed in current smokers, ever smokers, and former smokers in comparisons with never smokers or nonsmokers; studies with a reference group other than never smokers or nonsmokers were excluded (e.g., those comparing heavy smokers with light smokers). The quantitative analyses excluded all studies that compared liver cancer cases with controls who had chronic viral hepatitis, cirrhosis, or other chronic liver disease. Finally, the review separately examined the effects of smoking on HCC in studies that controlled for confounding by the main etiologic factors (HBV, HCV, and consumption of alcohol) for HCC in the region under study. Assessment of viral hepatitis status was considered adequate for inclusion in the quantitative analysis if the study reported on serological measurement of HBV surface antigen (HBsAg) or antibodies to HCV (anti-HCV) as indicators of chronic HBV or HCV infection, respectively.

Overall, 113 studies—including 59 case-control (Table 6.3S) and 54 cohort studies (Table 6.4S)—provided data on smoking and primary liver cancer. These studies, taken together, offered substantial heterogeneity in design, study population, assessment of smoking exposure, and the reporting of risk estimates. Many studies, however, were limited by having few HCC cases and reported nonsignificant increases in risk associated with

various measures of smoking. Furthermore, many studies did not adequately control for potential confounding by major causal factors such as consumption of alcohol or HBV or HCV infection.

In an analysis combining data from 31 studies (12 case-control and 19 cohort) that reported sufficient information to estimate risk for HCC in current smokers compared with nonsmokers (Figure 6.17), the overall estimate for RR was 1.7 (95% CI, 1.5–1.9). The relationship between current smoking and HCC was similar in cohort studies (overall RR = 1.7; 95% CI, 1.5–1.9) and case-control studies (RR = 1.6; 95% CI, 1.2–2.1). When 11 studies (6 case-control and 5 cohort) that controlled for confounding by the primary etiologic factors (e.g., HBV, HCV, consumption of alcohol) were analyzed (Figure 6.18), the RR (1.6; 95% CI, 1.2–2.0) was similar to that in the overall analysis. Among these studies that directly addressed confounding, the relationship between current smoking and HCC was stronger in cohort studies (RR = 2.2; 95% CI, 1.4–3.3) than in case-control studies (odds ratio [OR] = 1.2; 95% CI, 0.9–1.5). Overall, these findings are similar to those in the meta-analysis performed by Lee and colleagues (2009) in association with the 2004 IARC report, which reported a 51% increased risk for liver cancer for current smokers compared with never smokers (meta-RR = 1.51; 95% CI, 1.37–1.67). The findings of the IARC (2004) review and the current review are similar, except that the present review includes a greater number of studies (31 vs. 20) and includes studies that reported results for only one gender. Both the present review and the IARC analysis defined current smoking as reported at entry into the cohort or at the time of diagnosis of liver cancer.

Among 26 studies (18 case-control and 8 cohort) with evaluable comparisons between ever smokers and never smokers (Figure 6.19), the risk for HCC was increased among ever smokers (RR = 1.4; 95% CI, 1.3–1.6), with comparable estimates of the magnitude of effect observed in case-control studies (RR = 1.4; 95% CI, 1.1–1.7) and cohort studies (RR = 1.5; 95% CI, 1.3–1.7). In the 4 studies that adjusted for exposure to the primary etiologic agents (Figure 6.20), the magnitude of risk was notably higher among ever smokers (RR = 1.7; 95% CI, 1.4–2.2) compared to the magnitude of risk among ever smokers in studies (Figure 6.19).

Among 33 case-control studies that evaluated dose-response relationships between smoking (e.g., increasing intensity, pack-years, or duration) and HCC, only 6 (18%) reported a statistically significant trend. Among 26 cohort studies that evaluated these relationships, 10 (38%) reported a significant dose-response effect of smoking intensity on increased risk for HCC, and 2 (8%) reported an inverse dose-response relationship. Many studies that

evaluated dose response did not formally test for trends; however, a substantial proportion of these studies were not adequately powered to address such relationships. In their meta-analysis, Lee and colleagues (2009) summarized data from 7 studies with evaluable estimates and reported a significant dose-response trend showing increased risk for liver cancer with higher number of cigarettes smoked. However, this effect was notably less apparent among case-control studies that used hospital-based instead of population-based control groups.

Because of concern for residual confounding of smoking effects by coinfection with viral hepatitis, the association between smoking and HCC was evaluated in the present review among persons who did not have evidence for chronic viral hepatitis. In an analysis combining data from 13 studies (9 case-control and 4 cohort) that estimated risk among persons who were negative for markers of chronic HBV or HCV infection (Figure 6.21), the risk of HCC among current or ever smokers was significantly increased (RR = 1.8; 95% CI, 1.2–2.7) in a comparison with never smokers. After excluding a study that reported markedly increased risk among persons who were negative for HBV and HCV (Jeng et al. 2009), the estimated risk was attenuated but still significant (RR = 1.3; 95% CI, 1.0–1.8). Finally, when the analysis was restricted to the 3 studies that included only persons negative for both HBsAg and anti-HCV and also adjusted for consumption of alcohol (Kuper et al. 2000; Yuan et al. 2004; Koh et al. 2011), the RR was 1.7 (95% CI, 1.2–2.5).

The present review did not identify any studies that directly evaluated the effects of interventions aimed at smoking cessation on subsequent risk for liver cancer. Among 23 studies with the requisite data available from the publication (11 case-control and 12 cohort) (Figure 6.22), the risk for liver cancer among persons identified as former smokers relative to never smokers was lower (RR = 1.4; 95% CI, 1.1–1.7) than for current smokers (RR = 1.7, 95% CI 1.5–1.9).

Despite substantial geographic variation in the incidence of HCC and the distribution of etiologic factors, smoking was consistently related to increased risk for HCC in all geographic regions, although the magnitude of the association was not as strong in studies conducted in European countries. Among 35 studies conducted in Asian countries (Table 6.3*S*), the RR for HCC among current or ever smokers was 1.5 (95% CI, 1.4–1.6).

In countries in sub-Saharan Africa, the present data analysis was limited to case-control studies that evaluated ever smoking. The number of cases of HCC in these studies ranged from 46–240, and all of them adjusted for HBV or HCV infection and consumption of alcohol. Each study suggested an association between smoking and HCC, but

Figure 6.17   Estimated risk for liver cancer in current smokers compared with nonsmokers

Study	Country	Population		ES (95% CI)
Case-control				
Austin and Cole 1986	United States	All		1.6 (0.7–3.7)
La Vecchia et al. 1988	Italy	All		0.9 (0.6–1.5)
Tsukuma et al. 1990	Japan	All		2.5 (1.4–4.5)
Choi and Kahyo 1991	Korea	Males		1.0 (0.7–1.6)
Tanaka et al. 1992	Japan	All		1.5 (0.8–2.7)
Takeshita et al. 2000	Japan	Males		1.6 (0.7–3.5)
Hassan et al. 2002	United States	All		1.2 (0.6–2.4)
Farker et al. 2003	Germany	All		2.4 (0.9–6.4)
Marrero et al. 2005	United States	All		10.9 (3.5–34.0)
Franceschi et al. 2006	Italy	All		1.1 (0.6–2.2)
Zhu et al. 2007	United States	Males		1.5 (0.8–2.7)
Hara et al. 2008	Japan	All		1.8 (0.6–5.1)
Subtotal (I-squared = 53.0%, p = 0.015)				1.6 (1.2–2.1)
Cohort				
Hirayama 1989	Japan	Males		3.1 (1.8–5.4)
Akiba and Hirayama 1990	Japan	Males		1.5 (1.2–1.9)
Akiba and Hirayama 1990	Japan	Females		1.6 (1.2–2.0)
Hsing et al. 1990a	United States	Males		2.4 (1.6–3.5)
Shibata et al. 1990	Japan	Males–Cohort I		1.1 (0.2–4.7)
Shibata et al. 1990	Japan	Males–Cohort II		3.6 (0.6–22.3)
Goodman et al. 1995	Japan	All		2.2 (1.5–3.2)
McLaughlin et al. 1995	United States	Males		1.8 (1.4–2.3)
Nordlund et al. 1997	Sweden	Females		0.7 (0.2–2.0)
Mizoue et al. 2000	Japan	Males		3.3 (1.2–9.5)
Evans et al. 2002	China	Males		0.9 (0.8–1.1)
Evans et al. 2002	China	Females		2.0 (0.9–4.2)
Jee et al. 2004a	Korea	Males		1.5 (1.3–1.7)
Jee et al. 2004a	Korea	Females		1.1 (0.8–1.7)
Ogimoto et al. 2004	Japan	Males, age 40–59		2.0 (0.8–5.1)
Ogimoto et al. 2004	Japan	Males, age 60–69		2.6 (1.2–5.8)
Ogimoto et al. 2004	Japan	Females, age 40–59		2.8 (0.6–13.1)
Ogimoto et al. 2004	Japan	Females, age 60–69		1.5 (0.5–4.9)
Wen et al. 2004	China	Males		1.5 (1.2–1.8)
Wen et al. 2004	China	Females		5.0 (2.4–10.7)
Yun et al. 2005	Korea	Males		1.5 (1.3–1.7)
Fujita et al. 2006	Japan	Anti-HCV+		9.6 (1.5–61.4)
Fujita et al. 2006	Japan	Anti-HCV–		1.7 (0.6–5.1)
Chen et al. 2008	China	HBV– and HCV–		2.4 (1.2–5.0)
Chen et al. 2008	China	HBV+ and HCV–		1.1 (0.8–1.5)
Chen et al. 2008	China	HBV– and HCV+		1.4 (0.6–3.3)
Ohishi et al. 2008	Japan	All		2.0 (0.8–5.0)
Koh et al. 2011	Singapore	All		1.6 (1.3–2.1)
Trichopoulos et al. 2011	Europe	All		4.6 (1.9–10.9)
Oh et al. 2012	Korea	All		1.3 (0.6–2.6)
Subtotal (I-squared = 69.6%, p = 0.000)				1.7 (1.5–1.9)
Overall (I-squared = 65.5%, p = 0.000)				1.7 (1.5–1.9)

0.2   0.5   1   2   5   10   20

Note: Weights are from random effects analysis. **CI** = confidence interval; **ES** = effect size; **HBV** = 675 hepatitis B virus; **HCV** = hepatitis C virus.

Figure 6.18   Estimated risk for hepatocellular carcinoma in current smokers compared with nonsmokers among studies that controlled for confounding by primary etiological factors (viral hepatitis, consumption of alcohol)

Study	Country	Population	ES (95% CI)
Case-control			
La Vecchia et al. 1988	Italy	All	0.9 (0.6–1.5)
Choi and Kahyo 1991	Korea	Males	1.0 (0.7–1.6)
Tanaka et al. 1992	Japan	All	1.5 (0.8–2.7)
Hassan et al. 2002	United States	All	1.2 (0.6–2.4)
Hara et al. 2008	Japan	All	1.8 (0.6–5.1)
Ohishi et al. 2008	Japan	All	2.0 (0.8–5.0)
Subtotal (I-squared = 0.0%, p = 0.549)			1.2 (0.9–1.5)
Cohort			
Liaw and Chen 1998	China	Males	2.2 (1.4–3.6)
Jee et al. 2004a	Korea	Males	1.5 (1.3–1.7)
Fujita et al. 2006	Japan	Anti-HCV+	9.6 (1.5–61.4)
Fujita et al. 2006	Japan	Anti-HCV–	1.7 (0.6–5.1)
Koh et al. 2011	Singapore	HBV– and HCV–	1.8 (0.6–5.7)
Trichopoulos et al. 2011	Europe	All	4.6 (1.9–10.9)
Subtotal (I-squared = 57.5%, p = 0.038)			2.2 (1.4–3.3)
Overall (I-squared = 47.1%, p = 0.036)			1.6 (1.2–2.0)

0.2   0.5   1   2   5   10   20

Note: Weights are from random effects analysis. **CI** = confidence interval; **ES** = effect size; **HBV** = 683 hepatitis B virus; **HCV** = hepatitis C virus 684.

Figure 6.19   Estimated risk for hepatocellular carcinoma in ever smokers compared with never smokers

Study	Country	Population		ES (95% CI)
Case-control				
Lam et al. 1982	China	All		1.3 (0.7–2.4)
Stemhagan et al. 1983	United States	Males		0.7 (0.5–1.1)
Stemhagan et al. 1983	United States	Females		1.0 (0.6–1.7)
Austin et al. 1986	United States	All		1.1 (0.5–2.4)
Lu et al. 1988	China	All		1.1 (0.7–1.8)
Kew et al. 1990	South Africa	Black females		2.2 (0.8–6.1)
Olubuyide and Bamgboye 1990	Nigeria	All		1.7 (0.9–3.1)
Lin et al. 1991	China	Males, HBsAg–, alcoholic cirrhosis		0.6 (0.4–1.0)
Ross et al. 1992	China	Males		1.8 (0.6–5.6)
Goritsas et al. 1995	Greece	All		1.6 (0.9–2.0)
Siemiatycki et al. 1995	Canada	Males, age 35–70		0.9 (0.4–2.1)
Koide et al. 2000	Japan	All		5.4 (1.1–26.7)
Lam et al. 2001	China	Males, age 35–69		1.6 (1.3–1.9)
Lam et al. 2001	China	Males, age ≥70		1.2 (0.9–1.5)
Lam et al. 2001	China	Females, age 35–69		1.4 (0.8–2.4)
Lam et al. 2001	China	Females, age ≥70		1.4 (0.9–2.0)
Yu et al. 2002	China	All		0.7 (0.3–1.7)
Munaka et al. 2003	Japan	All		1.2 (0.6–2.7)
Marrero et al. 2005	United States	All		12.3 (4.4–34.2)
Hassan et al. 2009	United States	All		1.8 (1.3–2.4)
Jeng et al. 2009	China	All		2.3 (1.5–3.5)
Soliman et al. 2010	Egypt	All		1.4 (0.7–2.8)
Subtotal (I-squared = 66.6%, p = 0.000)				1.4 (1.1–1.7)
Cohort				
Yu and Chen 1993	China	Males		1.2 (0.4–3.1)
Goodman et al. 1995	Japan	All		2.2 (1.5–3.2)
McLaughlin et al. 1995	United States	Males		1.7 (1.3–2.2)
Chen et al. 1996	China	All		3.6 (1.3–10.6)
Lam et al. 1997	China	Males		1.1 (0.4–2.9)
Liu et al. 1998	China	Males, age 35–69		1.4 (1.3–1.5)
Liu et al. 1998	China	Females, age 35–69		1.2 (1.1–1.3)
Mori et al. 2000	Japan	All		2.1 (0.6–7.2)
Wang et al. 2003	China	Males		1.5 (1.1–2.3)
Subtotal (I-squared = 58.9%, p = 0.013)				1.5 (1.3–1.7)
Overall (I-squared = 63.7%, p = 0.000)				1.4 (1.3–1.6)

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        0.2      0.5    1    2      5    10   20
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Note: Weights are from random effects analysis. **CI** = confidence interval; **ES** = effect size; **HBsAg** = 690 hepatitis B surface antigen.

Figure 6.20   Estimated risk for hepatocellular carcinoma in ever smokers compared with never smokers among studies that controlled for confounding by primary etiological factors (viral hepatitis, consumption of alcohol)

Study	Country	Population		ES (95% CI)
Ross et al. 1992	China	Males		1.8 (0.6–5.6)
Yu and Chen 1993	China	Males		1.2 (0.4–3.1)
Goritsas et al. 1995	Greece	All		1.6 (0.9–2.0)
Hassan et al. 2009	United States	All		1.8 (1.3–2.4)
Subtotal (I-squared = 0.0%, p = 0.89)				1.7 (1.4–2.2)
Overall (I-squared = 0.0%, p = 0.89)				1.7 (1.4–2.2)

0.2   0.5   1   2   5   10   20
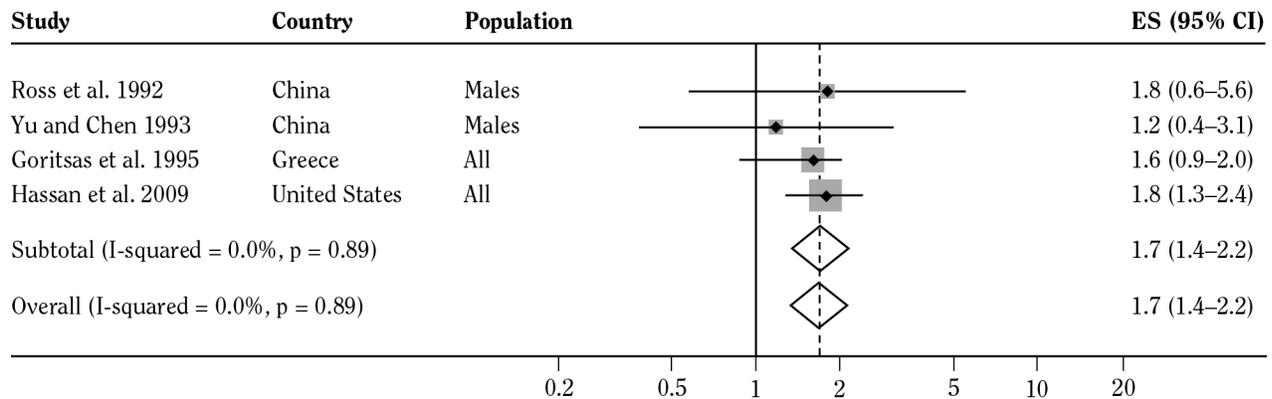
Note: Weights are from random effects analysis. **CI** = confidence interval; **ES** = effect size.

none of them were statistically significant—likely because of the limited number of cases. Overall, the RR from the three studies with data available (Kew et al. 1990; Olubuyide and Bamgboye 1990; Soliman et al. 2010) for countries in Africa was 1.7 (95% CI, 1.1–2.5).

Eight studies evaluated current or ever smoking and risk for HCC in the United States (Stemhagen et al. 1983; Austin and Cole 1986; Hsing et al. 1990; McLaughlin et al. 1995; Hassan et al. 2002, 2009; Marrero et al. 2005; Zhu et al. 2007). Veterans of the armed services were substantially overrepresented in these studies. The overall RR estimate in an analysis that combined current and ever smoking was 1.8 (95% CI, 1.3–2.5), and substantial heterogeneity in estimated risk was not found by study design.

Among the 14 studies reviewed from countries in Europe, 11 were case-control studies, largely from southern Europe, and 3 were cohort studies. Substantial heterogeneity was observed in these studies. In a series of case-control studies from Greece, smoking was consistently associated with HCC, but the associations were more pronounced (and statistically significant) among HBV-negative persons (Trichopoulos et al. 1980, 1987b; Tzonou et al. 1991; Goritsas et al. 1995). After adjusting for HBV and HCV infection, a study from Greece by Kuper and colleagues (2000) demonstrated a 1.5- and 1.6-fold nonsignificant increase in risk of HCC among persons smoking fewer than or at least 40 cigarettes per day, respectively. Elsewhere, 4 case-control studies from Italy reported null findings (Filippazzo et al. 1985; La Vecchia

et al. 1988; Gelatti et al. 2005; Franceschi et al. 2006). In 2 cohort studies from Sweden, the risk estimate in 1 study among females was less than 1.0 (RR = 0.7; 95% CI, 0.2–2.0) (Nordlund et al. 1997). But, the other study observed increased rates of mortality from liver cancer among a cohort of men and a significant dose-response association with increased smoking (Carstensen et al. 1987). In a Europe-wide cohort study, Trichopoulos and colleagues (2011) rigorously characterized the smoking behavior, alcohol consumption, diet, and viral hepatitis status of a half-million people. Overall, the RR for HCC among current smokers compared to never smokers was 4.6 (95% CI, 1.9–10.9), and the RR was notably higher among males (5.4; 95% CI, 1.7–16.8) than among females (1.7; 95% CI, 0.3–8.5). In addition, the authors estimated that smoking contributed to nearly one-half of the number of cases of HCC, exceeding the proportion of HCC attributable to HBV, HCV, or consumption of alcohol. Finally, in a quantitative analysis for the present review from 5 evaluable studies in Europe, the RR for HCC among current or ever smokers (La Vecchia et al. 1988; Goritsas et al. 1995; Nordlund et al. 1997; Farker et al. 2003; Franceschi et al. 2006) was 1.4 (95% CI, 1.0–2.3).

Similar to the experience in Greece, several studies from other regions suggested a higher risk of liver cancer with smoking among HBV-negative persons than among those who were HBV positive (Lam et al. 1982; Yu et al. 1991a; Chen et al. 2008). Some other studies, however, failed to find any difference in this risk by HBV status (Kew

Figure 6.21   Estimated risk for hepatocellular carcinoma among persons without evidence for chronic viral hepatitis infection for current or ever smokers compared with never smokers

Study	Country	Population		ES (95% CI)
Case-control				
Lam et al. 1982	China	HBsAg–		2.9 (0.8–10.7)
Austin and Cole 1986	United States	HBsAg–		1.1 (0.5–2.4)
Lin et al. 1991	China	Males, HBsAg–, alcoholic cirrhosis–		0.6 (0.4–1.0)
Goritsas et al. 1995	Greece	HBsAg–		6.1 (1.5–25.5)
Yuan et al. 2004	United States	Blacks and Whites, HBV– and HCV–		1.7 (1.0–3.0)
Franceschi et al. 2006	Italy	HBsAg– and anti-HCV–		1.0 (0.5–2.0)
Hassan et al. 2008	United States	Males, HBsAg1– and anti-HBc13–		2.0 (1.2–3.3)
Hassan et al. 2008	United States	Females, HBsAg1– and anti-HBc13–		1.1 (0.6–1.9)
Jeng et al. 2009	China	HBsAg– and anti-HCV–		44.4 (17.8–116.1)
Soliman et al. 2010	Egypt	HCV–		0.5 (0.1–1.8)
Subtotal (I-squared = 88.6%, p = 0.000)				1.9 (1.0–3.7)
Cohort				
Jee et al. 2004a	Korea	Males, HBsAg–		1.1 (0.9–1.4)
Fujita et al. 2006	Japan	Anti-HCV–		1.7 (0.6–5.1)
Chen et al. 2008	China	HBV– and HCV–		2.4 (1.2–5.0)
Koh et al. 2011	China	HBsAg–, anti-HBc–, anti-HBs–, and anti-HCV–		1.6 (0.6–4.2)
Subtotal (I-squared = 40.1%, p = 0.171)				1.5 (1.0–2.2)
Overall (I-squared = 84.7%, p = 0.000)				1.8 (1.2–2.7)

0.2   0.5   1   2   5   10   20   60

Notes: Weights are from random effects analysis. **CI** = confidence interval; **ES** = effect size; **HBc13** = hepatitis B virus core 13; **HBsAg** = hepatitis B surface antigen; **HBV** = hepatitis B virus; **HCV** = hepatitis C virus.

Figure 6.22   Estimated risk for hepatocellular carcinoma in former smokers compared with never smokers

Study	Country	Population		ES (95% CI)
Case-control				
La Vecchia et al. 1988	Italy	All		0.6 (0.4–1.0)
Tsukuma et al. 1990	Japan	All		0.7 (0.3–1.9)
Choi and Kahyo 1991	Korea	Males		0.6 (0.4–1.2)
Tanaka et al. 1992	Japan	All		1.5 (0.8–2.8)
Takeshita et al. 2000	Japan	Males		0.7 (0.3–1.5)
Farker et al. 2003	Germany	All		2.5 (1.2–5.0)
Marrero et al. 2005	United States	All		13.3 (4.5–38.9)
Franceschi et al. 2006	Italy	All		0.8 (0.4–1.5)
Zhu et al. 2007	United States	Males		1.9 (1.0–3.3)
Hara et al. 2008	Japan	All		0.8 (0.3–2.3)
Hassan et al. 2008	United States	All		1.4 (0.9–2.1)
Subtotal (I-squared = 76.4%, p = 0.000)				1.2 (0.8–1.9)
Cohort				
Shibata et al. 1990	Japan	Males, Cohort II		2.9 (0.3–29.0)
Goodman et al. 1995	Japan	All		2.3 (1.5–3.6)
McLaughlin et al. 1995	United States	Males		1.5 (1.2–2.0)
Mizoue et al. 2000	Japan	All		2.9 (1.0–8.4)
Jee et al. 2004a	Korea	Males		1.1 (1.0–1.3)
Jee et al. 2004a	Korea	Females		1.3 (0.8–2.1)
Ogimoto et al. 2004	Japan	Males, age 40–59		2.4 (0.8–6.8)
Ogimoto et al. 2004	Japan	Males, age 60–69		2.7 (1.2–6.1)
Ogimoto et al. 2004	Japan	Females, age 60–69		1.2 (0.2–8.7)
Fujita et al. 2006	Japan	Anti-HCV+		7.8 (1.1–56.0)
Fujita et al. 2006	Japan	Anti-HCV–		0.3 (0.0–1.7)
Chen et al. 2008	China	HBV– and HCV–		1.0 (0.2–4.6)
Chen et al. 2008	China	HBV+ and HCV–		1.0 (0.5–2.0)
Chen et al. 2008	China	HBV– and HCV+		2.9 (0.9–9.1)
Ohishi et al. 2008	Japan	All		1.1 (0.3–5.1)
Koh et al. 2011	Singapore	All		1.1 (0.8–1.5)
Trichopoulos et al. 2011	Europe	All		2.0 (0.9–4.4)
Oh et al. 2012	Korea	All		1.2 (0.4–3.3)
Subtotal (I-squared = 46.9%, p = 0.015)				1.5 (1.2–1.8)
Overall (I-squared = 62.7%, p = 0.000)				1.4 (1.1–1.7)

0.2   0.5   1   2   5   10   20

Notes: Weights are from random effects analysis. **CI** = confidence interval; **ES** = effect size; **HBV** = hepatitis B virus; **HCV** = hepatitis C virus.

et al. 1985; Mohamed et al. 1992; Evans et al. 2002). And yet, according to eight studies published in 2000 or later, smokers with chronic HBV or HCV infection have a substantially higher risk for HCC than those who do not have chronic hepatitis infection (Mori et al. 2000; Wang et al. 2003; Jee et al. 2004a; Franceschi et al. 2006; Fujita et al. 2006; Hassan et al. 2008; Jeng et al. 2009; Soliman et al. 2010). Formal evaluations of interactions between smoking and HBV or HCV infections have been reported infrequently from these studies.

Although the present review focuses on HCC, which represents a substantial majority of primary liver cancer, a meta-analysis by Wenbin and colleagues (2013) reported on the association between smoking with gallbladder cancer. In an analysis of data from 1,158 cases across 11 studies (all but 1 were case-control), smokers had a significantly increased risk for gallbladder cancer (RR = 1.5; 95% CI, 1.1–1.9) compared with nonsmokers.

Evidence Synthesis

Overall, a substantial body of evidence documents the association between smoking and primary liver cancer. The role of the liver as a primary site for metabolism of several recognized carcinogens provides strong biologic plausibility for a causal association between smoking and HCC. In epidemiologic studies from various geographic regions and with different designs, findings demonstrate a consistent but nonuniform association between smoking and primary liver cancer. In 2004, IARC classified smoking as a cause of HCC. In the meta-analysis by Lee and colleagues (2009), which updated the evidence considered in the 2004 IARC report, the overall OR showed a moderate association, with an estimated 50% increased risk of liver cancer associated with current smoking.

In the expanded meta-analysis included in this report, 113 studies were identified that reported data on the risk of liver cancer from smoking. In the primary analysis, which focused on studies of HCC that compared current and never smokers, the overall estimate from 31 studies with evaluable data indicated that current smoking increases risk for HCC by approximately 70% (Figure 6.17). Although confounding by consumption of alcohol and HBV or HCV infection status may bias the findings of some studies, controlling for these risk factors does not fully account for the effects seen. In 11 higher quality studies that adjusted adequately for potential confounding factors, risk of HCC from smoking was moderated only slightly (60% increased risk) (Figure 6.18). Importantly, when analyses of data were restricted to persons without chronic HBV or HCV infection, the risk for HCC from smoking remained significantly increased.

Data combined from 26 studies indicated a 40% increased risk of HCC from ever smoking (Figure 6.19). Furthermore, the effect of ever smoking on risk of liver cancer was strengthened in the studies that addressed primary confounding factors. Risk for liver cancer was significantly increased in former smokers compared with never smokers, although risk for former smokers was attenuated relative to risk for current smokers. While heterogeneity was observed in studies that evaluated dose-response associations, meta-analysis of a limited number of studies with data that could be combined suggested that increased smoking intensity increases the risk for liver cancer.

The finding of increased risk for liver cancer from smoking was generally consistent regardless of geography or study design. The greatest number of studies originated from Asia, and quantitative analysis from this region indicated a 50% increased risk of liver cancer from smoking. The estimated risk for liver cancer associated with smoking increased to 70–80% in studies from Africa and the United States. Greater heterogeneity was observed in studies from Europe than elsewhere. Several hospital-based case-control studies from southern Europe reported null or nonsignificant associations and the overall relationship between smoking and liver cancer was thus notably smaller in Europe.

Modification of the effect of smoking on risk for liver cancer by viral hepatitis has been suggested, although formal statistical evaluation remains limited. Stronger associations between smoking and HCC among persons who are negative for HBV infection have been observed in studies conducted on selected populations in Europe and China. In contrast, most studies from diverse regions—such as Asia, Egypt, Europe, and the United States—have found greater risks for liver cancer from smoking among persons with chronic HBV or HCV infections.

Conclusion

1. The evidence is sufficient to infer a causal relationship between smoking and hepatocellular carcinoma.

Implications

The burden of liver cancer is increasing in many regions of the world, notably due to HCV-related cases of HCC occurring in more developed countries. Among such persons, smoking also increases risk and consequently

incidence and death rates related to liver cancer may continue to grow substantially in the more developed countries with rising HCC. In high-burden regions of the world where vaccination against HBV or reductions in exposure to aflatoxin are being achieved, rates of liver cancer are expected to decline. However, if smoking increases in these low- and middle-income countries, then the potential for reducing liver cancer from these preventive interventions will not be fully realized.

Colorectal Cancer

Colorectal cancer—that is, cancer of the colon or rectum—is the third most common type of cancer in the United States and also ranks third as a cause of cancer deaths among men and women in the United States (Siegel et al. 2013). For 2013, the ACS projected 102,480 new cases of cancer of the colon and 40,340 new cases of cancer of the rectum as well as 51,710 deaths from the two cancers combined (Siegel et al. 2013). In the mid-1990s, the lifetime probability of developing colorectal cancer was estimated to be 5.6% in the United States (Howlader et al. 2013).

Worldwide, incidence and death rates for colorectal cancer vary more than 10-fold among countries. The highest rates occur in Australia/New Zealand, Japan, North America, and Western Europe, and the lowest rates are seen in countries with developing economies, particularly in Africa and Asia (Parkin et al. 1999). Studies show that among immigrants moving from low- to high-incidence countries, rates increase within one generation to the approximate rates of the new country, suggesting a strong role for environmental agents (Thomas and Karagas 1987). Risk also varies substantially even within countries. For example, in a study by Wei and colleagues (2009) of a middle-aged cohort of U.S. women, risk to age 70 varied up to 10-fold based on lifestyle factors.

An increased risk of colorectal cancer has been linked to a variety of risk factors, including physical inactivity (Wolin et al. 2009); obesity (Renehan et al. 2008); low calcium levels (Cho et al. 2004); and alcohol intake (Thun et al. 1997). Risk for colorectal cancer also increases for persons with a family history of colorectal cancer or polyps (Fuchs et al. 1994). Finally, a high-meat diet and a diet low in vegetables, fruits, or folate (World Cancer Research Fund/American Institute for Cancer Research 2007) have been implicated.

Conversely, several factors are consistently associated with a reduced risk of colorectal cancer, including the use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs). Aspirin use of 10–20 years is associated with a decreased risk of colorectal cancer mortality (Flossmann and Rothwell 2007), and short-term or current use of hormone replacement therapy (HRT) reduces risk in women (Rossouw et al. 2002). In addition, higher levels of vitamin D may protect against adenomatous polyps and incidence, recurrence, and death from colorectal cancer (Ng et al. 2009; Giovannucci 2010). Calcium supplementation reduces the risk of recurrent polyps (Baron et al. 1999).

The hypothesis that prolonged cigarette smoking may increase the risk of colorectal cancer gained support in the mid-1990s when epidemiologic studies, particularly cohort studies, showed a high incidence of adenomatous polyps and/or colorectal cancer in long-term smokers (Giovannucci et al. 1994a,b). Initially, there was concern that this observed association reflected uncontrolled confounding factors, such as lifestyle characteristics, as well as differences in risk between colon and rectal cancer, which are often combined in epidemiologic studies. Subsequent studies suggested a stronger relationship between smoking and rectal cancer than between smoking and colon cancer (Terry et al. 2002b; Wei et al. 2004). This difference was confirmed in two meta-analyses that were limited to prospective cohort studies (Liang et al. 2009; Tsoi et al. 2009) and one that included both case-control and cohort study data (Botteri et al. 2008a). In the latter systematic review, Botteri and colleagues searched the literature through May 2008 and evaluated data from six studies that compared the association of smoking and colon cancer separately from smoking and rectal cancer mortality. The RRs of ever smokers and current smokers were significantly higher for rectal cancer mortality than for colon cancer (rectal cancer: ever vs. never smoker, RR = 1.4 [1.2–1.7], current vs. never smoker, RR 1.6 = [1.3–1.8], colon cancer: ever vs. never smoker, RR = 1.2 [1.0–1.4], current vs. never smoker, RR = 1.2 [1.1–1.3]) (Botteri et al. 2008a).

Conclusions from Previous Surgeon General's Reports

Until the 2001 Surgeon General's report on women and smoking (USDHHS 2001), the reports of the Surgeon General on smoking had not considered the relationship of smoking with cancers of the colon and rectum. The 2001 Surgeon General's report concluded that "Women who smoke may have increased risk for … colorectal cancer" (p. 231). IARC reported in 2004 that "There is some evidence from prospective cohort studies and case-control studies that the risk of colorectal cancer is increased among tobacco smokers," but noted that "Inadequate adjustment for various potential confounders could account for some of the small increase in risk that appears to be associated with smoking" (p. 1183). The 2004 Surgeon General's report, after reviewing extensive evidence, concluded that the evidence is suggestive but not sufficient to infer a causal relationship between smoking and colorectal adenomatous polyps and colorectal cancer.

Biologic Basis

Most cancers of the colon and rectum are adenocarcinomas. These tumors typically develop from clonal expansions of mutated cells through a series of histopathologic stages—from single crypt lesions to benign tumors (adenomatous polyps) to metastatic carcinomas—that take place over a span of 20–40 years (Fearon and Vogelstein 1990). The number and order of genetic and epigenetic changes in tumor suppressor genes (such as *APC*, *P53*, and *DCC*) and oncogenes (such as *RAS*) determine the probability of tumor progression (Fearon and Vogelstein 1990). On the basis of the observation that mutations of the *APC* gene on chromosome 5q are found as frequently in small adenomatous polyps as in cancers, the loss of normal APC function is considered an early (and possibly initiating) event in colorectal tumorigenesis (Powell et al. 1992; Morin et al. 1997). Products of the *APC* gene influence cell proliferation, adhesion, migration, and apoptosis. Activating mutations in codons 12 and 13 of the *RAS* oncogene are important in the progression of adenomas but are not directly involved in malignant transformations in the bowel (Bos 1989; Ohnishi et al. 1997). However, *KRAS* does have a role in advanced colorectal cancer (Fearon 2011). In addition, some studies suggest that smokers develop adenomas without *KRAS* mutations (Wark et al. 2006). Slattery and colleagues (2000) related smoking to microsatellite instability (a genetic marker) in colon tumors, and Curtin and colleagues (2009a) showed microsatellite instability in rectal tumors that were

diagnosed in current smokers. Approximately 85% of colorectal cancers show inactivating mutations of the *p53* tumor suppressor gene on chromosome 17p, resulting in loss of the ability to arrest cell growth and/or produce apoptosis; these mutations are important at a late stage in malignant transformation (Hollstein et al. 1991). Clonal expansion of colorectal tumors containing mutant *p53* genes gains a selective survival advantage for these tumors and they become increasingly invasive and metastatic.

Cigarette smoke contains many carcinogens, PAHs, heterocyclic aromatic amines, and *N*-nitrosamines (Hoffmann and Hoffmann 1997) that can reach the large bowel via the circulatory system (Giovannucci and Martinez 1996). One study documented that DNA adducts to metabolites of B[*a*]P, a potent PAH, in colonic mucosa occur more frequently and at higher concentrations in smokers than in nonsmokers (Alexandrov et al. 1996); this study provides direct evidence that tobacco carcinogens bind to DNA in the human colonic epithelium. Moreover, DNA adduction levels in the colonic epithelium were found in one study to be higher in tumor tissue from persons with colorectal cancer than from control subjects (Pfohl-Leszkowicz et al. 1995).

Other genes known to be important in colorectal cancer include mismatch repair genes associated with the hereditary familial syndrome, nonpolyposis colorectal cancer, or sporadic cases of colorectal cancer (Liu et al. 1995; Thibodeau et al. 1998). One study associated cigarette smoking with a mismatch repair deficiency in colorectal cancer, as reflected by a sixfold increase in the risk of microsatellite instability in tumors in current smokers compared with nonsmokers (Yang et al. 2000). Elsewhere, in a large case-control study of incident colon cancer, Curtin and colleagues (2009b) evaluated base excision repair and observed a twofold increase in the risk of tumor mutations in current and former smokers. More generally, research continues to provide insight into pathways by which smoking could increase risk for colorectal cancer (Campbell et al. 2009).

To date, the association between cigarette smoking and colorectal cancer has not been found to be modified by polymorphisms of genes that are important in the detoxification of carcinogens found in tobacco smoke, including *GSTM1*, *GSTT1*, and *NAT2* (Gertig et al. 1998; Slattery et al. 1998). Studies of colorectal adenomas have found no modification of the risk of cigarette smoking by polymorphisms of *GSTM1*, *NAT2*, or cytochrome P4501A1, an enzyme important in the activation of PAHs (Lin et al. 1995; Potter et al. 1999). However, when researchers examined only adenomas that were 1 centimeter (cm) or larger, current smokers with the *GSTM1 null* genotype were at a higher risk than those without the *null* genotype (Lin et al. 1995). Furthermore, some evidence

suggests an increased risk of colorectal cancer and advanced polyps in smokers with *GST1 null* genotype (Ates et al. 2005). Overall, a meta-analysis of 12 studies that evaluated polymorphisms in *GSTM1* did not show any significant interaction with smoking and risk (Raimondi et al. 2009). Combined data from 7 of the 12 studies indicated that smokers with *mEH3 low-* or *medium-metabolizer* genotypes had a slightly lower risk of colorectal adenoma than smokers with *mEH3 high-metabolizer* genotypes. None of the other common genetic polymorphisms involved in metabolizing tobacco carcinogens modified the risk of colorectal adenoma or cancer.

Animal models of the carcinogenicity of tobacco in the colon and rectum have been limited to date and have not included studies in which the route of exposure was inhalation. In inbred male Syrian hamsters, adenocarcinomas of the colon have been produced by intrarectal instillation of B[*a*]P (Wang et al. 1985), and in vivo mutational assay studies found that oral administration of B[*a*]P to the *lacZ* transgenic mouse (Muta Mouse) induced a higher frequency of mutation in the colon than in the other organs tested (Autrup et al. 1978; Hakura et al. 1998, 1999; Kosinska et al. 1999). Finally, in vitro studies have shown that both rat and human colonic epithelium in cell cultures can enzymatically activate B[*a*]P (Autrup et al. 1978).

Description of the Literature Review

The published studies on cigarette smoking and colorectal adenomatous polyps and cancer cited in this section were identified by updating through December 2009 the search of the MEDLINE database from 1966 through July 2000 that was used in the 2004 Surgeon General's report. The headings "tobacco," "smoking," "colorectal adenomas," "colorectal neoplasms," "colonic neoplasms," and "rectal neoplasms" were used in the newer search. In addition, this more recent search included examination of the Web of Science and Embase, also through December 2009. Since the 1960s, the association between cigarette smoking and colorectal adenomas and cancer has been evaluated in many prospective and case-control studies; the present review extends work summarized in the 2004 Surgeon General's report and focuses on published studies that excluded cigar and pipe smokers, identified lifetime nonsmokers, and distinguished current smokers from former smokers. If multiple reports resulted from the same prospective cohort, then the results from the longest follow-up are used unless otherwise stated.

Epidemiologic Evidence

Adenomatous Polyps

Botteri and colleagues (2008b) used rigorous search and data extraction techniques to synthesize the evidence for an association between smoking and the risk of adenomatous polyps. Among articles published from 1988–2007, they evaluated 125 in detail; these studies were conducted in countries around the world. Combined data from 33 studies found that current smokers had a significantly increased risk of adenomas (RR = 2.14; 95% CI, 1.86–2.46) (Figure 6.23). Among current smokers, the pooled RR estimates were somewhat greater (RR = 2.02; 95% CI, 0.62–6.56) for larger adenomas (≥10 millimeters [mm]) and those classified as high risk (RR = 2.04; 95% CI, 1.56–2.66). In addition, in a comparison with never smokers in 27 studies, former smokers had a significantly increased risk of adenomas (RR = 1.47; 95% CI, 1.29–1.67) (Figure 6.24). Finally, for every additional 10 pack-years of smoking, ever smokers had a 13% increase in risk of adenomatous polyps (95% CI, 9–18%). An evaluation for publication bias by Botteri and colleagues (2008b) showed no indication of such bias for the reporting of results about current smokers, but there was evidence for reports related to former and ever smokers.

Colon and Rectal Cancer

Table 2.27 of the 2004 Surgeon General's report presented data from cohort studies of incidence and mortality for colon and rectal cancer among men and women in the United States (USDHHS 2004). Data published through 2000 and summarized in the 2004 Surgeon General's report consistently indicated that current smokers had an increased risk of colon cancer (the RRs ranged from 1.2–1.4) and of rectal cancer (RRs ranged from 1.4–2.0), regardless of the number or types of covariates for which there was adjustment.

Table 6.5*S* summarizes the 19 prospective cohort studies on smoking and the incidence of colorectal cancer that were published from 2002–2009. In the first study listed, Terry and colleagues (2002b) followed 89,835 Canadian women for a mean of 10.6 years and confirmed 363 cases of colon cancer and 164 of rectal cancer. The RR for rectal cancer for women with a smoking duration of 30–39 years was 1.52 (95% CI, 1.01–1.26)[2]; for women

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[2]The RR does not fall within the CI. The information presented here appears just as it does on page 481 of Terry and colleagues (2002b).

Figure 6.23   Forest plot of relative risk for colorectal adenoma for current smokers versus never smokers
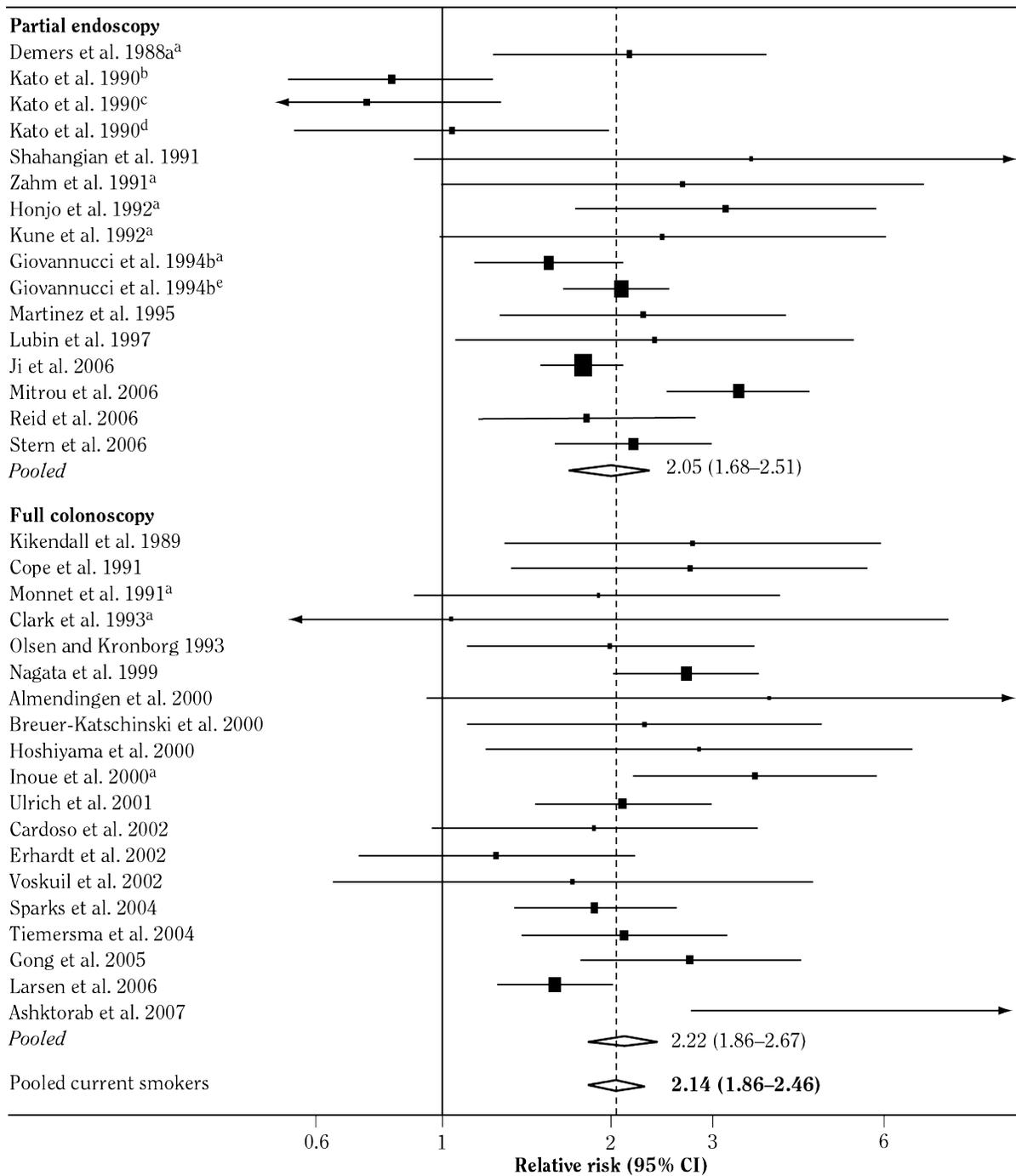
Source: Adapted from Botteri et al. 2008b, with permission from Elsevier, © 2008.
Note: Partial endoscopy group is composed of studies in which some or all controls underwent partial colon examination. Full colonoscopy group is composed of studies in which all controls underwent complete colon examination. **CI** = confidence interval.
[a]Estimates for males only.
[b]Estimates for distal colon.
[c]Estimates for proximal colon.
[d]Estimates for rectum.
[e]Estimates for women only.

Figure 6.24   Forest plot of relative risk for adenomatous polyps for former smokers versus never smokers
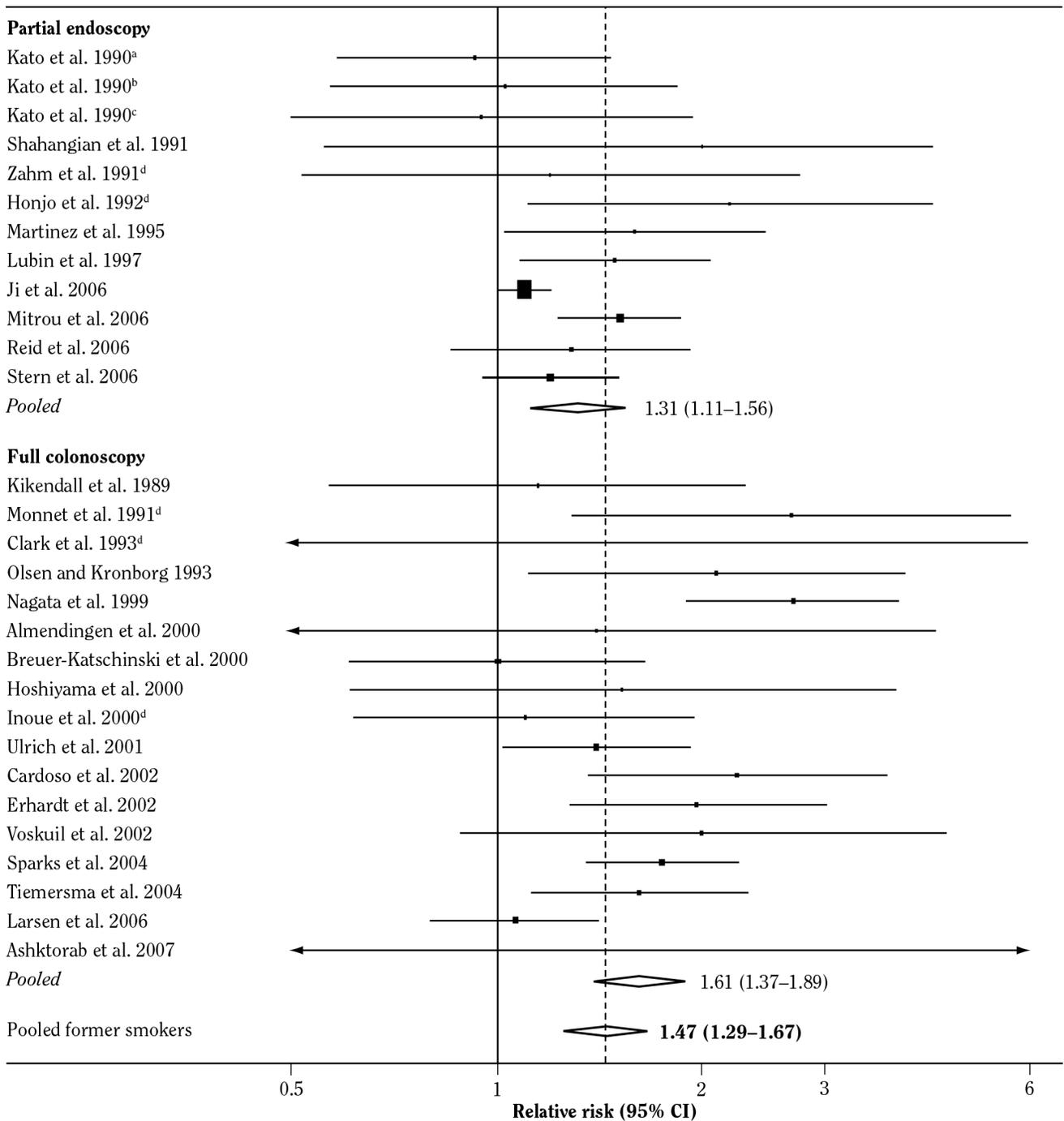
Partial endoscopy
Kato et al. 1990[a]
Kato et al. 1990[b]
Kato et al. 1990[c]
Shahangian et al. 1991
Zahm et al. 1991[d]
Honjo et al. 1992[d]
Martinez et al. 1995
Lubin et al. 1997
Ji et al. 2006
Mitrou et al. 2006
Reid et al. 2006
Stern et al. 2006
Pooled   1.31 (1.11–1.56)

Full colonoscopy
Kikendall et al. 1989
Monnet et al. 1991[d]
Clark et al. 1993[d]
Olsen and Kronborg 1993
Nagata et al. 1999
Almendingen et al. 2000
Breuer-Katschinski et al. 2000
Hoshiyama et al. 2000
Inoue et al. 2000[d]
Ulrich et al. 2001
Cardoso et al. 2002
Erhardt et al. 2002
Voskuil et al. 2002
Sparks et al. 2004
Tiemersma et al. 2004
Larsen et al. 2006
Ashktorab et al. 2007
Pooled   1.61 (1.37–1.89)

Pooled former smokers   **1.47 (1.29–1.67)**

0.5   1   2   3   6
Relative risk (95% CI)

Source: Adapted from Botteri et al. 2008b, with permission from Elsevier, © 2008.
Note: Partial endoscopy group is composed of studies in which some or all controls underwent partial colon examination. Full colonoscopy group is composed of studies in which all controls underwent complete colon examination. **CI** = confidence interval.
[a]Estimates for distal colon.
[b]Estimates for proximal colon.
[c]Estimates for rectum.
[d]Estimates for males only.

with duration of 40 or more years, the RR was 2.27 (95% CI, 1.06–4.87).

Tiemersma and colleagues (2002) followed 36,000 Dutch men and women who were 20–59 years of age at enrollment. At the end of follow-up (8.5 years), the investigators confirmed 102 cases of colorectal cancer. The relationship between smoking and risk for colorectal cancer was null among current smokers but significant among two groups of former smokers (durations of 16–30 and >30 years). In a U.S.-based study, Limburg and colleagues (2003) followed 34,467 women who were 55–69 years of age at baseline. The study confirmed 869 cases of colorectal cancer; duration of smoking was significantly related to risk of colorectal cancer incidence.

Per Table 6.5*S*, Otani and colleagues (2003) followed 90,004 Japanese men and women who were 40–69 years of age at enrollment. When the analysis was limited to invasive cases, there was a significant increase in risk among current smokers (RR = 1.6; 95% CI, 1.1–2.1) that was comparable to results when the analysis included all cases of invasive and noninvasive colon and rectal cancers.

In Japan, Shimizu and colleagues (2003), who followed 29,051 men and women for 8 years, confirmed 181 cases of colon cancer and 95 of rectal cancer. Among men, no trend was revealed between the risk of colon cancer and lifetime smoking (in pack-years), but for rectal cancer, the risk was significantly greater with more than 20 pack-years (RR = 2.44; 95% CI, 1.12–5.30) than it was for nonsmokers. In The Netherlands, a study by van der Hel and colleagues (2003a), which followed a cohort of 27,222 women, identified 249 cases of colorectal cancer. Ever smoking was similarly related (but not significantly) to colon cancer (RR = 1.36; 95% CI, 0.97–1.92) and to rectal cancer (RR = 1.31; 95% CI, 0.76–2.25).

Wakai and colleagues (2003), who followed a Japanese cohort of 25,260 men and 34,619 women for an average of 7.6 years, confirmed 408 cases of colon cancer and 204 cases of rectal cancer. Among both men and women, there was no relationship between years of smoking and risk of colon cancer or rectal cancer. In the United Kingdom, the Oxford Vegetarian Study, which followed a cohort of 11,140 vegetarians (Sanjoaquin et al. 2004), confirmed 95 cases of colorectal cancer and found that risk was elevated among both former and current smokers. In Europe, The Netherlands Cohort Study on Diet and Cancer followed 58,279 men and 62,573 women (Lüchtenborg et al. 2005); during the last 5.0 years of the 7.3-year follow-up, the study identified 661 cases of colorectal cancer. The risk of colorectal cancer was elevated among former smokers (RR = 1.30; 95% CI, 1.03–1.65) but not current smokers. In Asia, Yun and colleagues (2005) followed the Korean National Health Insurance Corporation cohort of 733,134 men and identified 417 cases of colon cancer and

453 cases of rectal cancer. The risk of colon cancer was elevated among former smokers but not current smokers, while there were no significant findings for rectal cancer. In the United States, Berndt and colleagues (2006) followed 22,887 participants in the Campaign Against Cancer and Heart Disease (CLUE II) cohort from Washington County, Maryland, and confirmed 250 cases of colorectal cancer. Compared with never smokers, ever smokers in the CLUE II cohort had an increased risk of colorectal cancer that failed to reach statistical significance (RR = 1.23; 95% CI, 0.91–1.66). This analysis adjusted for age and gender but not for other risk factors for colorectal cancer.

In Korea, Kim and colleagues (2006), who followed a cohort of 14,103 men and women, confirmed 100 cases of colorectal cancer. These investigators found that duration of smoking was significantly related to risk of colorectal cancer: for those who had smoked more than 45 years, the RR was 2.35 (95% CI, 1.16–4.74) in a comparison with never smokers. Also in Asia, Akhter and colleagues (2007) followed a cohort of 25,279 Japanese men (40–64 years of age at baseline) for a mean of 7 years and identified 188 cases of colorectal cancer. These researchers observed a significant increase in risk among former smokers and a statistically insignificant, modestly increased risk among current smokers. Both age at initiation and duration of smoking were related to risk. In the United States, Paskett and colleagues (2007) analyzed data from 146,877 participants in the Women's Health Initiative (WHI). After nearly 8 years of follow-up, the study confirmed 1,075 cases of colon cancer and 176 cases of rectal cancer. The study did not find a significant relationship between smoking and risk of colon cancer, but current smokers had a significantly elevated risk of rectal cancer (RR = 1.95; 95% CI, 1.10–3.47). Duration of smoking was associated with risk of colon cancer (p-trend = 0.03) and rectal cancer (p-trend = 0.05).

Among a cohort of Chinese men and women in Singapore, Tsong and colleagues (2007) confirmed 516 cases of colon cancer and 329 cases of rectal cancer during a mean follow-up of 11 years. In this cohort, both current and former smoking were related to risk of rectal cancer but not to risk of colon cancer. Similarly, age at initiation and duration of smoking were related to risk of rectal cancer but not to risk of colon cancer. In the United States, a study by Driver and colleagues (2007) reported on follow-up results for male physicians in the Physicians' Health Study; after 20 years of follow-up, there were 381 confirmed cases of colon cancer and 104 confirmed cases of rectal cancer. Overall, ever smoking was related to risk of colorectal cancer (RR = 1.42; 95% CI, 1.17–1.72). In addition, current smokers who smoked two packs per day had an increased risk of colon cancer (RR = 1.53; 95% CI, 1.02–2.29) and rectal cancer (RR = 1.92; 95% CI, 1.01–

3.66). In Maryland, Hooker and colleagues (2008) evaluated incidence of rectal cancer in two cohorts of residents from that state's Washington County. In the cohort that was followed from 1963 to 1978, there was a significant increase in risk of rectal cancer among current male smokers but not among their female counterparts. The RR for rectal cancer in the cohort followed from 1975 to 1994 ranged from 1.57 to 1.92 for current and former smokers, but only the RR for former female smokers (1.87; 95% CI, 1.02–3.45) reached significance.

Also in the United States, Hannan and colleagues (2009) studied 184,187 men and women as part of the Nutrition cohort of the CPS-II. After 13 years of follow-up, the study confirmed 1,962 cases of colorectal cancer. Current smokers had an increased risk of colorectal cancer (RR = 1.27; 95% CI, 1.06–1.52), as did former smokers (RR = 1.23; 95% CI, 1.11–1.36). Among current smokers, the RR was greatest for those with a long duration of smoking. RR was comparable between men and women. Finally, a study by Gram and colleagues (2009) followed 68,160 women in Norway and confirmed 425 cases of colorectal cancer. Duration of smoking was significantly related to overall risk of colorectal cancer, but when individual sites were evaluated, sparse data limited the power to find significant associations. Increasing pack-years smoked was related to increased risk of colorectal cancer.

Table 6.6S summarizes 16 case-control studies published from 2001–2008; here the findings are mixed, with only a few studies reporting significant increases in risk associated with various measures of smoking. The studies were carried out in diverse locations, including Asia, North America, and Europe. Sample sizes ranged up to 2,000 cases and adjustments were made for a variety of risk factors.

Table 6.7S presents details on nine cohort studies that reported mortality data for either colorectal cancer overall or separately for colon and rectal cancer. The cohort studies of mortality also came from North America, Asia, and Europe. In several studies, risk for death from colorectal cancer was significantly increased; for example, in two studies among women in the United States—the Nurses' Health Study (NHS) (Kenfield et al. 2008) and the Iowa Women's Health Study (Limburg et al. 2003)—current smokers have an approximate 60% increased risk of colorectal cancer mortality. Several of these studies summarized in Table 6.7S also observed significant increases in risk based on number of cigarettes smoked per day or total pack-years.

Most of these studies were summarized in the three separate meta-analyses referenced earlier in this chapter (Botteri et al. 2008a; Liang et al. 2009; Tsoi et al. 2009). Notably, the meta-analysis by Botteri and colleagues (2008a) combined data from 53 studies (33 prospective cohort and 20 case-control) that were published from 1980–2008 and further characterized the association of smoking with colorectal cancer. Drawing on 47 of those studies, the authors found that former smokers had an increased risk of colorectal cancer (RR = 1.17; 95% CI, 1.11–1.22) in comparison with never smokers. In addition, based on 25 of the studies, ever smokers had an increased risk of colorectal cancer (RR = 1.18; 95% CI, 1.11–1.25) compared with never smokers. This meta-analysis also evaluated risk for colorectal cancer mortality; based on 14 and 12 studies, respectively, current smokers (RR = 1.28; 95% CI, 1.15–1.42) and former smokers (RR = 1.23; 95% CI, 1.14–1.32) had an increased risk of mortality from colorectal cancer in a comparison with never smokers (Botteri et al. 2008a). The increased mortality could reflect a higher incidence of colorectal cancer in smokers or an unfavorable effect on the disease's natural history.

Evidence Synthesis

Taken as a whole, the results of the studies summarized in Tables 6.5S–6.7S, which come from millions of person-years of follow-up, confirm the findings of three meta-analyses for colorectal cancer (Botteri et al. 2008a; Liang et al. 2009; Tsoi et al. 2009). The individual studies have addressed cancers of the colon and rectum separately, as well as the combined outcome of colorectal cancer. Mechanistic understanding at present supports the handling of the combined outcome in synthesizing the evidence.

Although adjustments for covariates differed to some extent across the studies included in the meta-analyses, longer duration of smoking was consistently associated with increased risk of colorectal cancer. In addition, there was no evidence of heterogeneity of effect when the prospective cohort studies were combined in the three separate meta-analyses (Botteri et al. 2008a; Liang et al. 2009; Tsoi et al. 2009).

These epidemiologic data must be placed in the context of our growing understanding of the biologic etiology of colorectal cancers; researchers now have excellent insights into the sequence of genetic changes taking place from normal cells to a polyp to malignancy. The evidence now points strongly to an effect of smoking in increasing the formation of polyps, the precursor of colorectal cancer, and possibly on the development of malignancy (Botteri et al. 2008a,b; Liang et al. 2009; Tsoi et al. 2009). Furthermore, for colorectal cancer, recent findings from prospective cohort studies suggest that long-term cigarette smoking is associated with increased risk of both incidence and mortality in men as well as women. In

some studies, the risk of incidence and mortality tended to increase with longer duration of smoking and younger age at smoking initiation and to decrease with a younger age at successful cessation and a greater number of years since that took place, but the effects of these factors (age at starting or quitting and duration of smoking or time since cessation) cannot be readily separated because of their inherent correlation.

The aggregate epidemiologic evidence supports the hypothesis of Giovannucci and colleagues (1994a,b) and of Giovannucci and Martínez (1996) that a latent period of several decades is necessary for cigarette smoking to increase either the incidence of colorectal cancer or mortality from that disease and that cigarette smoking likely plays a role in early carcinogenesis in both the colon and rectum. This combined hypothesis is further supported by the consistent association between smoking and adenomas, which represents the starting point for colorectal cancer, with a doubling of risk among current smokers (Botteri et al. 2008b). Studies with null findings but only limited follow-up of long-term smokers are not informative for testing the hypothesis that a lengthy duration of smoking is needed to increase the risk of colorectal cancer. Analyses of available studies show little indication of publication bias. There is also no indication of significant heterogeneity of effect among study results.

In assessing whether cigarette smoking plays a causal role in colorectal cancer, nutrition and other factors such as physical activity and screening histories for colorectal cancer must be considered because they may confound the association. Not all of the studies to date have controlled for risk factors for colorectal cancer that may also be associated with smoking, such as physical inactivity. However, indirect evidence against confounding comes from the consistent finding of a small but statistically significant increase in risk for colon or rectal cancer associated with smoking, regardless of the set of covariates for which there was adjustment. Furthermore, among the prospective cohort studies, many controlled for physical activity, use of alcohol, and other potential risk factors.

Cumulative findings from large prospective cohort studies show an increased risk of colon and rectal cancer after smoking for two or more decades. The evidence suggests that smoking acts in the early stages of carcinogenesis, as shown by its association with adenoma, the elevated risk for most smokers, and the associated risk with duration of smoking. The temporal pattern of the effects of smoking, with continuing increase in risk, particularly for rectal cancer and for mortality among current smokers, suggests that smoking may also act in the later stages of carcinogenesis.

Conclusion

1. The evidence is sufficient to infer a causal relationship between smoking and colorectal adenomatous polyps and colorectal cancer.

Implications

The aggregate evidence indicates that cigarette smoking may be a modifiable factor that can cause colorectal cancer. Accordingly, clinicians and public health personnel should include both current and former smoking as potential risk factors for this disease.

Prostate Cancer

Among American men, prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer death. In 2013, 238,590 American men were expected to be diagnosed with prostate cancer and 29,720 were expected to die from this disease (Siegel et al. 2013). Since the mid-1990s, death rates for prostate cancer have been declining, but incidence rates have fluctuated (Siegel et al. 2013). The decline in death rates has been attributed to the combination of earlier detection and advances in the treatment of men who are in advanced stages of the disease (Etzioni et al. 2008); the fluctuation in inci-dence may be due to trends in prostate-specific antigen (PSA) testing.

To date, several risk factors for prostate cancer have been identified with certainty; these risk factors cannot be modified:

- *Age*. The risk of prostate cancer increases with age.

- *Race*. Prostate cancer incidence and death rates are highest among African American men and lowest among Asian men.

- *Family history*. Men who have a father or brother diagnosed with prostate cancer are twice as likely to be diagnosed with prostate cancer as those with unaffected fathers and brothers.

Unlike the case in breast and colon cancer, research has not yet identified the inherited mutations in genes that consistently explain the strong family associations found in prostate cancer, but some studies have discovered a small number of common variants across the genome that are associated with the risk for this disease (Eeles et al. 2008, 2009; Thomas et al. 2008).

Biologic pathways influencing prostate cancer involve hormones and growth factors. Androgens and their signaling pathways are necessary for the development of prostate cancer. Support for the role of these pathways is based on results of two trials showing that drugs inhibiting 5-α-reductases, the enzymes that convert testosterone to the more androgenic dihydrotestosterone, reduce the risk of prostate cancer (Thompson et al. 2003; Andriole et al. 2010). In epidemiologic studies, however, circulating levels of androgens have not been associated with the risk of prostate cancer (Roddam et al. 2008a). Growth factors are also important: for example, results from cohort studies have consistently associated circulating levels of insulin-like growth factor-1 with increased risk for prostate cancer (Roddam et al. 2008b). Research on pathways may provide insights into etiologic factors.

In terms of modifiable risk factors, obesity is associated with an increased risk of death from prostate cancer (Calle et al. 2003), but evidence for an association between risk for incident prostate cancer and physical inactivity is not consistent (Friedenreich and Thune 2001). Drinking alcohol does not appear to be an important factor for prostate cancer incidence or mortality (Velicer et al. 2006; Gong et al. 2009; Chao et al. 2010). Some studies have found a higher risk of prostate cancer or advanced disease with a higher intake of energy (calories), processed meat, dairy foods, and calcium, as well as lower intake of tomatoes and cruciferous vegetables (Giovannucci et al. 2007; World Cancer Research Fund 2007). Regarding prevention, two studies found reduced risk of prostate cancer as a secondary endpoint. In one study, persons who had skin cancer and lived in areas with low levels of selenium in the soil received selenium supplements (Clark et al. 1998); in the other study, men who were current or former smokers received vitamin E (Alpha-Tocopherol 1994). However, in a subsequent trial designed to test the hypothesis that supplementation with these agents would reduce the risk of prostate cancer, Lippman and colleagues (2009) found that supplementation with selenium or with vitamin E did not reduce risk in men who were not selected for exposure to selenium or smoking status.

Conclusions from Previous Surgeon General's Reports

The relationship between smoking and risk for prostate cancer was first addressed in the 2004 Surgeon General's report on the health consequences of smoking. That report drew two conclusions: (1) the evidence is suggestive of no causal relationship between smoking and risk for prostate cancer; and (2) the evidence for mortality, although not consistent across all studies, suggests a higher mortality rate from prostate cancer in smokers than in nonsmokers (USDHHS 2004, p. 26).

Biologic Basis

Zu and Giovannucci (2009) outlined several possibilities for increased mortality from prostate cancer, including mutations in genes associated with the cancer's progression caused by carcinogenic constituents of cigarette smoke and the effects of smoking on levels of sex steroid hormones, angiogenesis, and DNA methylation. Regarding carcinogenicity and methylation, for example, loss of glutathione *S*-transferase pi expression, via hypermethylation of its gene promoter region early in the natural history of prostate cancer (Nakayama et al. 2003) may render prostate cancer cells susceptible to DNA damage as well as other kinds of damage caused by electrophiles from cigarette smoke (e.g., PAHs) (Roberts et al. 2003). In terms of hormones, compared with men who do not smoke, men who currently smoke have higher circulating levels of androstenedione—a weak androgen that is a precursor to testosterone and estradiol—and higher levels of total and free testosterone (Dai et al. 1988; Field et al. 1994; Muller et al. 2003; Shiels et al. 2009). On the other hand, former and never smokers have similar levels of total and free testosterone (Shiels et al. 2009). Because androgens are necessary for the development of prostate cancer, this pattern is consistent with the observation in some epidemiologic studies that current but not former smoking is associated with risk of death from prostate cancer. As for estradiols, some studies have found that men who smoke have higher total and free levels of this hormone than men who do not smoke (Barrett-Connor and Khaw 1987; Shiels et al. 2009). The role of estrogens in human prostate carcinogenesis is not clear.

Description of the Literature Review

To further examine the association between cigarette smoking and the risk for prostate cancer incidence, case fatality (prostate-cancer-specific mortality), and mortality from all other causes, epidemiologic studies were identified through reviews of the reference lists in the 2004 Surgeon General's report on the health consequences of smoking; published meta-analyses, expert reviews, and research articles; and through searches of the National Library of Medicine's PubMed service for research articles published after the 2004 report. The PubMed search terms used were "smoking," "cigarettes," "tobacco," "prostate cancer," "prostate neoplasms," "prostatic neoplasia," and "prostate tumor." The last PubMed search was performed April 15, 2010, for studies dating back to 2000. Case-control studies were not considered because they do not directly address factors determining incidence or provide data about mortality.

Epidemiologic Evidence

Incidence and Mortality

More than 30 prospective studies have investigated the link between smoking and incidence of prostate cancer or death from that disease; Table 6.8*S* summarizes the findings from studies that reported rates, risks, or RRs of prostate cancer associated with cigarette smoking. Of note, Table 6.8*S* presents updated findings from 8 studies that have examined five cohorts over time (see notes a–f in Table 6.8*S*). Epidemiologic studies of the association between cigarette smoking and prostate cancer incidence and mortality have been reviewed previously (Colditz 1996; Lumey 1996; Hickey et al. 2001; Levi and La 2001; Zu and Giovannucci 2009), including an Australian consensus conference report (Colditz 1996). To date, the association between cigarette smoking and prostate cancer has not been found to be modified by polymorphisms of genes that are important in the detoxification of carcinogens found in tobacco smoke, including *GSTM1, GSTT1,* and *NAT2* (Gertig et al. 1998; Slattery et al. 1998). However, some studies indicate association of xenobiotic metabolism gene SNPs with colorectal cancer and smoking (Nisa et al. 2010; Koh et al. 2011; Osawa et al. 2012; Fu et al. 2013). Meta-analyses of prospective studies (Huncharek et al. 2010) and case-control studies (Lumey 1996) have also been conducted. In the pooled analysis of data from 24 cohort studies, Huncharek and colleagues (2010) reported some evidence of increased risk for incident prostate

cancer (RR = 1.04; 95% CI, 0.87–1.24) among current smokers. The elevated risk was significant in data stratified by amount smoked (cigarettes per day: RR = 1.22; 95% CI, 1.01–1.46; pack-years of smoking: RR = 1.11; 95% CI, 1.01–1.22). Increased risk of deaths from prostate cancer was also found among current smokers (RR = 1.14; 95% CI, 1.06–1.19) (Huncharek et al. 2010).

Twenty-one of the 35 prospective studies reviewed in Table 6.8*S* did not support a positive association between cigarette smoking and risk (incidence) of prostate cancer. Four of the 35 studies supported positive associations (Whittemore et al. 1984; Hiatt et al. 1994; Adami et al. 1996; Cerhan et al. 1997), and 10 produced either null associations or findings that appeared to indicate inverse associations. Beyond the studies summarized in Table 6.8*S*, a nested case-control study by Heikkilä and colleagues (1999) did not reveal a baseline difference in the prevalence of current smoking between incident prostate cancer cases and controls. In another study, in a comparison with the general population, Malila and colleagues (2006) found a higher than expected incidence rate of prostate cancer in the placebo arm of the Alpha-Tocopherol, Beta-Carotene Trial of male smokers (median level of smoking at randomization: 20 cigarettes/day for 36 years): the standardized incidence ratio here was 1.20 (95% CI, 1.06–1.35) (Malila et al. 2006).

In contrast to the lack of a consistent association described above between smoking and incidence of prostate cancer, 12 prospective studies (Hammond and Horn 1958; Akiba and Hirayama 1990; Hsing et al. 1991; Tverdal et al. 1993; Adami et al. 1996; Coughlin et al. 1996; Rodriguez et al. 1997; Giovannucci et al. 2007; Rohrmann et al. 2007; Batty et al. 2008; Watters et al. 2009; Weinmann et al. 2010) of the 20 such studies that evaluated prostate cancer mortality in Table 6.8*S* supported a modest-to-moderate positive association with smoking. In an investigation not included in Table 6.8*S*, a prospective cohort study by Eichholzer and colleagues (1999) that used non-smokers with normal levels of vitamin E as a comparison group reported a higher risk of prostate cancer death among men who smoked and had a low plasma concentration of vitamin E (RR = 3.26; 95% CI, 1.27–8.35). In contrast, no difference in risk was found among male smokers who had a normal level of vitamin E.

Unlike associations between smoking and other types of cancer such as neoplasms of the lung, the risk of prostate cancer death does not appear to rise with an increasing number of cigarettes smoked per day, duration of smoking, or total pack-years. However, current or recent smoking (Figure 6.25), rather than smoking in the distant past or a cumulative smoking history, may influence prostate cancer mortality. For example, among

Figure 6.25   Prospective cohort studies on the association between current cigarette smoking and prostate cancer mortality
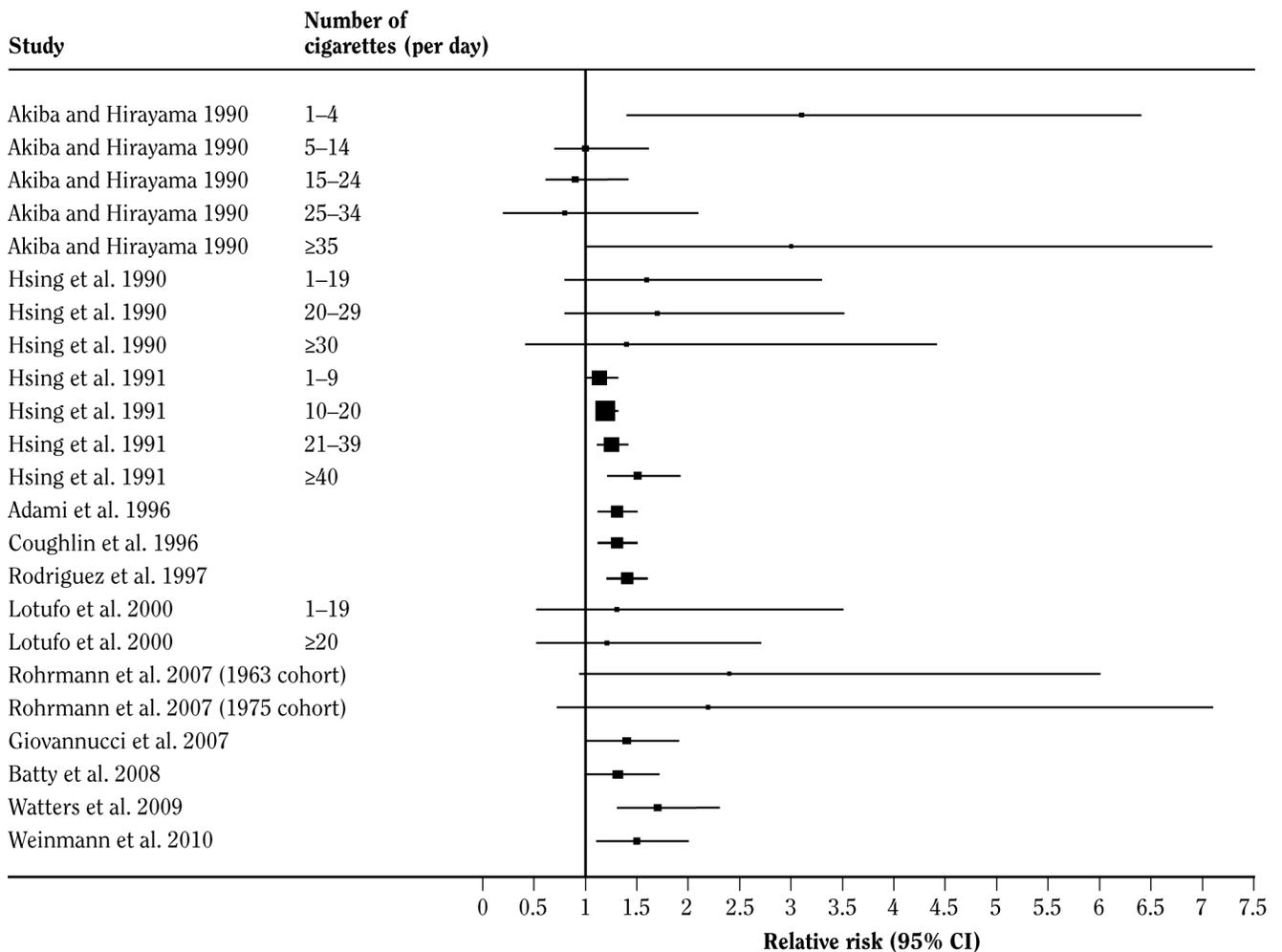
Note: Includes studies reporting a relative risk and 95% confidence interval for current smoking or current number of cigarettes smoked per day. See Table 6.8*S* for additional studies for which confidence intervals were not reported. **CI** = confidence interval.

studies in Table 6.8*S* reporting a positive association for smoking, the RR was larger for current smokers than for former smokers (Hsing et al. 1991; Adami et al. 1996; Rodriguez et al. 1997; Giovannucci et al. 2007; Batty et al. 2008; Watters et al. 2009; Weinmann et al. 2010) or was stronger when considering smoking status closer to the time of death from prostate cancer (Hsing et al. 1991; Rohrmann et al. 2007).

Two reports from Giovannucci and colleagues (1999, 2007) provide further evidence for the importance of relatively recent smoking. In an earlier report from the Health Professionals Follow-up Study (not shown in Table 6.8*S*), Giovannucci and coworkers (1999) followed participants

from 1986 to 1994 and noted 177 prostate cancer deaths in 351,261 person-years. Compared with never smokers, the RR was 1.58 for current smokers at baseline, 1.73 for men who had quit smoking within 10 years of baseline, and 1.04 for those who had quit 10 or more years before baseline. In a later report from the same study, Giovannucci and associates (1999) followed participants from 1986–2002 and noted 312 prostate cancer deaths in 673,706 person-years. Using simple updating of biennially assessed smoking status (rather than baseline smoking status, as in their 1999 report), the authors found that the RR among current smokers, in a comparison with smokers who had quit within 10 years, was 1.41 (95% CI, 1.04–1.91).

Data from some studies do not support the hypothesis that the association between prostate cancer mortality is stronger for current smoking than for former smoking (Doll et al. 2005). Their British Doctors Study, which followed physicians from 1951–2001, noted 878 prostate cancer deaths in 34,439 male physicians. The study recorded updated smoking status in 1957, 1966, 1971, 1978, and 1991. The prostate cancer mortality rate (indirectly standardized for age and study year) did not differ (Table 6.8*S*) between never smokers (89.4/100,000 men per year), former smokers (80.9), and current smokers (90.0). Despite the overall lack of association among smokers, however, the prostate cancer mortality rate (per 100,000 men per year) increased with the number of cigarettes smoked per day by current smokers (1–14/day = 66.7; 15–24 = 99.6; ≥25 = 113.3), but the p for trend was not significant (0.52) (Table 6.8*S*).

Ten of the studies in Table 6.8*S* were not cited in the 2004 Surgeon General's report (Lotufo et al. 2000; Lund Nilsen et al. 2000; Putnam et al. 2000; Allen et al. 2004; Doll et al. 2005; Giovannucci et al. 2007; Rohrmann et al. 2007; Batty et al. 2008; Watters et al. 2009; Weinmann et al. 2010). Of these, 7 reported on cigarette smoking and prostate cancer mortality (Lotufo et al. 2000; Doll et al. 2005; Giovannucci et al. 2007; Rohrmann et al. 2007; Batty et al. 2008; Watters et al. 2009; Weinmann et al. 2010); 4 of the 7 gave quantitative support for a positive association between smoking (3 implicated current smoking) and death from prostate cancer (Rohrmann et al. 2007; Batty et al. 2008; Watters et al. 2009; Weinmann et al. 2010). Two of the 10 studies not cited in the 2004 Surgeon General's report but shown in Table 6.8*S* (Doll et al. 2005; Giovannucci et al. 2007) were updates of studies included in the 2004 report (Doll et al. 1994; Giovannucci et al. 1999). The findings in the 2004 report of no association with prostate cancer mortality in the British Doctors Study (Doll et al. 1994) and of a positive association in the Health Professionals Study (Giovannucci et al. 1999) were unchanged with additional follow-up.

Stage and Histologic Grade

As shown in Table 6.9*S*, three studies (Hussain et al. 1992; Roberts et al. 2003; Moreira et al. 2010) investigated the association between smoking and both disease stage and histologic grade at the time of diagnosis or surgical treatment, while two (Daniell 1995; Kobrinsky et al. 2003) looked at smoking and disease stage but not histologic grade. Advanced stage (e.g., local invasion, metastasis to a regional lymph node, metastasis to bone) and high grade (e.g., a high sum of the two Gleason scores given by the pathologist or poorly differentiated cancer at pathologic examination) are indicators of a poor prognosis. Thus, studies about smoking and stage or grade of the cancer are relevant for interpreting the findings of higher mortality in the prospective studies. Cases were ascertained from a clinical setting in three studies (Hussain et al. 1992; Daniell 1995; Roberts et al. 2003), from a regional cancer registry in one (Kobrinsky et al. 2003), and from the SEARCH cohort in the fifth (Moreira et al. 2010). All five studies support the hypothesis that smokers diagnosed with prostate cancer are more likely to have advanced-stage disease or less-well-differentiated disease than men who have prostate cancer and do not smoke. In the only study that evaluated intensity of smoking, risk of extraprostatic disease or high-grade disease increased with number of pack-years of smoking (Roberts et al. 2003).

Progression, Case Fatality, and All-Cause Mortality

Nine studies have investigated the association between smoking and the progression of prostate cancer after diagnosis, death from the disease, or death from all causes in men who have prostate cancer (Table 6.10*S*). Eight of the studies used a retrospective cohort design, while one (Gong et al. 2008) was a prospective study. Five studies reported on progression, defined as biochemical recurrence/progression/failure, local recurrence/failure, distant failure, or development of hormone-refractory disease (Merrick et al. 2004; Oefelein and Resnick 2004; Pickles et al. 2004; Pantarotto et al. 2007; Moreira et al. 2010). Five studies reported on case fatality (Daniell 1995; Pickles et al. 2004; Jager et al. 2007; Pantarotto et al. 2007; Gong et al. 2008), and five reported on all-cause mortality (Yu et al. 1997; Oefelein and Resnick 2004; Pickles et al. 2004; Jager et al. 2007; Pantarotto et al. 2007). One study reported on death from all causes *other* than prostate cancer (Gong et al. 2008).

Of the nine studies reported in Table 6.10*S*, six suggest that in men who have prostate cancer, smoking is associated with a higher risk of progression or death from the disease; these findings were independent of smoking's possible influence on stage or grade. Among men diagnosed with prostate cancer, all-cause mortality appears to be higher in smokers than in nonsmokers. In some studies, many of these deaths were due to prostate cancer because the majority of men had advanced-stage disease (Oefelein and Resnick 2004). In other studies, deaths were more likely due to other causes because the majority of men had localized disease (Pickles et al. 2004; Gong et al. 2008).

Evidence Synthesis

The published literature suggests that smoking, especially current or recent smoking, is a risk factor for prostate cancer mortality but not for incidence of the disease. Findings of a positive association with prostate cancer mortality and null associations with incidence are somewhat consistent across a set of prospective cohort studies (in which temporality is clear) that have been conducted in a number of settings and across several decades. The strength of the association between current smoking and prostate cancer mortality is modest to moderate, and unlike the case with some other cancers, the strength of the association does not appear to depend on the number of cigarettes smoked per day or pack-years of smoking.

The published literature also consistently shows that in men who have prostate cancer, smoking is a risk factor for being diagnosed with disease that is already of advanced stage or of high grade, and—independent of stage and grade—is a risk factor for progression of the disease, including progression to death. Although these patterns of association are biologically plausible, the specific biologic basis is unknown at this point. Alternative explanations to a causal association cannot be completely excluded with confidence (Zu and Giovannucci 2009).

Conclusions

1. The evidence is suggestive of no causal relationship between smoking and the risk of incident prostate cancer.

2. The evidence is suggestive of a higher risk of death from prostate cancer in smokers than in nonsmokers.

3. In men who have prostate cancer, the evidence is suggestive of a higher risk of advanced-stage disease and less-well-differentiated cancer in smokers than in nonsmokers, and—independent of stage and histologic grade—a higher risk of disease progression.

Implications

The biologic processes underlying the suggestive association between cigarette smoking and prostate cancer mortality, case fatality, and more seriously unfavorable pathologic characteristics of the tumor require further investigation, particularly because incidence is not associated with smoking. Further research on the association between smoking and the incidence of prostate cancer is warranted because the mortality rate indicates an effect of public health significance. Additional epidemiologic studies should address the timing of cigarette smoking relative to mortality and case fatality, and laboratory-based studies should address the biologic mechanisms underlying the apparently worse phenotype of prostate cancer in smokers. The finding that the risk of prostate cancer mortality is not elevated in former smokers who quit years in the past suggests that quitting smoking may reduce prostate cancer mortality. Further research is needed to refine this temporal relationship and to quantify the benefits of cessation after a diagnosis of prostate cancer.

Breast Cancer

Breast cancer is the most frequently diagnosed type of cancer, other than nonmelanoma skin cancers, and the second leading cause of cancer death among women (Siegel et al. 2013). Despite an approximate 2% decrease in incidence since 1999 and a 28% decline in breast cancer mortality since 1991 (Jemal et al. 2010a,b), about 211,000 new cases of invasive breast cancer were diagnosed and approximately 40,000 deaths resulted from breast cancer among U.S. women in 2009 (Howlader et al. 2013). The age adjusted incidence and death rates for 2004–2008 were 124/100,000 and 23.5/100,000 women per year, respectively, based on the 17 geographic areas covered by the SEER Program of NCI (Howlader et al.

2013). Average annual incidence rates per 100,000 women varied substantially by race/ethnicity in 2004–2008: 77.9 for American Indians/Alaska Natives, 92.1 for Hispanics, 93.7 for Asians/Native Hawaiian or Other Pacific Islanders, 119.9 for Blacks, and 127.3 for non-Hispanic Whites. Death rates per 100,000 women also varied by race/ethnicity during this period: 12.2 for Asians/Native Hawaiian or Other Pacific Islanders, 15.1 for Hispanics, 17.2 for American Indians/Alaska Natives, 22.8 for non-Hispanic Whites, and 32.0 for Blacks.

The burden of breast cancer morbidity and mortality is high. Thus, researchers have long sought to identify modifiable etiologic factors to prevent and

control this disease. Active cigarette smoking and exposure to secondhand smoke have received increasing attention over the past two decades, as clinical studies have detected nicotine and its metabolite cotinine in the breast fluid of nonlactating women (Petrakis et al. 1978; Hill and Wynder 1979), and data from rodent studies have indicated that genotoxic carcinogens in cigarette smoke can induce mammary tumors (el-Bayoumy 1992). Sixty-nine known carcinogens are detectable among the myriad chemicals in tobacco smoke (USDHHS 2004). Adipose tissue of the breast can store lipophilic carcinogens, and these can be locally activated by breast epithelial cells to form DNA adducts (Phillips et al. 2002). The prevalence of carcinogen DNA adducts is reported to be increased in smokers and in women with breast cancer (see "DNA Adducts"). A recent report suggests that nicotine leads to overexpression of cyclin D3 and induces neoplastic transformation and proliferation of breast epithelial cells in vitro (Lee et al. 2010a). Thus, evidence is accumulating for several plausible mechanisms by which smoking may induce breast cancer; this evidence is reviewed in greater detail below.

Historically, the epidemiologic evidence for an association between breast cancer and active cigarette smoking and between breast cancer and exposure to secondhand smoke has been inconsistent, leading to conclusions in the past that smoking is not a risk factor for this type of cancer (Palmer and Rosenberg 1993; Terry and Rohan 2002). However, some recent reviews have concluded that both active and passive smoking may increase the risk of breast cancer, although there is continuing disagreement as to the magnitude of effect (California Environmental Protection Agency [Cal/EPA] 2005; Collishaw et al. 2009 for the Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk; Institute of Medicine 2012).

Biologic Basis—Evidence for Potential Etiologic Mechanisms

Breast cancer is the end result of a multistep process in which some epithelial cells in the breast undergo a series of mutations. In doing so, these cells escape from programmed cell death and then proliferate and invade surrounding tissue (Armitage and Doll 1957; Fisher 1958; Cairns 1975; Tomlinson et al. 1996). Genetic and epigenetic mutations in critical genes in cells—such as tumor suppressor genes, DNA replication and repair genes, and proto-oncogenes—can lead to the initiation of tumorigenesis. Clones from these mutated cells continue to expand and proliferate, rendering them susceptible to further

cancer-causing mutations. For hereditary cancers, as proposed in the Knudson (1996) model, at least two allelic mutations are necessary, one of which might be inherited. Endogenous and exogenous exposures can potentially affect the development and proliferation of mutant cells in both inherited and sporadic breast cancer and thereby affect breast carcinogenesis.

The following section addresses biologic mechanisms by which tobacco smoke, an exogenous exposure, can potentially contribute to the causation of breast cancer. The review in this section addresses the plausibility of a causal association between risk of breast cancer and active or passive smoking. The studies were identified through literature searches using the following key words: smoking and breast cancer, carcinogenesis, DNA adducts, epigenetic, hormones (androgens, progesterones, and estrogens), anti-estrogen hypothesis, and ovarian function. Past Surgeon General's reports were also reviewed: those published in 2004 and 2006, which addressed active and passive smoking, respectively (USDHHS 2004, 2006), and the one in 2010, which focused on mechanisms by which tobacco smoke contributes to disease (USDHHS 2010).

DNA Adducts

Cigarette smoke contains thousands of compounds including 69 known to be carcinogens (USDHHS 2010). Some of these compounds have been shown to cause mammary tumors in rodents (Hecht 2002). Nicotine, one of the major constituents of tobacco smoke, has been measured in the nipple aspirate of female smokers (Petrakis et al. 1978) and smoking-related DNA adducts have been found in the DNA of epithelial cells within breast milk (Thompson et al. 2002), documenting that components of smoke reach breast tissue. Carcinogens in tobacco smoke cause cancer by damaging DNA; this is the initiating event in tumorigenesis (Figure 6.4). Many carcinogens from tobacco smoke are metabolically activated by the cytochrome P-450 (CYP) enzymes, including CYP1A1 and CYP1B1, and by NAT2, all of which are present in breast tissue. These activated metabolites bind to DNA to form DNA adducts that in turn can damage DNA (USDHHS 2010). Elevated levels of DNA adducts have been associated with certain types of cancer, supporting a positive association between increasing levels of DNA adducts and risk of cancer (Phillips 2005). The degree of activation of detoxification enzymes—such as glutathione S-transferases (GSTs), uridine-5'-disphosphate-glucuronosyltransferases (UGTs), epoxide hydrolases, and sulfatases, which are also present in the breast—is important because these enzymes catalyze the excretion of the toxic metabolites, thereby potentially decreasing the formation of DNA adducts.

Smoking induces activity of some of these enzymes (USDHHS 2010).

As a biomarker, smoking-related DNA adducts are an integrated measure of exposure to tobacco smoke, metabolic activation, and delivery of the metabolite to DNA in the target tissue (Groopman et al. 1995). Smoking-related DNA adducts can be quantified in breast fluid, tissue, and peripheral blood cells. However, an increase in the levels of DNA adducts does not directly correspond to a similar increase in cancer risk because other processes are involved (Phillips 2005). To causally link the presence of smoking-related DNA adducts to risk of breast cancer, elevated levels ideally need to be detected in breast epithelial cells before the onset of the cancer and at higher levels in those individuals going on to develop cancer than in those who do not. Levels of DNA adducts measured at the time of diagnosis or after diagnosis (e.g., in case-control or cross-sectional studies) may not reflect the etiologically relevant time window of tumor initiation. Similarly, levels of DNA adducts in peripheral cells may not reflect what is happening locally at a specific target site: circulating levels of biomarkers have not always been correlated with levels at the tissue site.

Several studies have evaluated the relationship between smoking and the prevalence of smoking-related DNA adducts in breast tissue (Perera et al. 1995; Li et al. 1996; Rundle et al. 2000). These studies have confirmed the presence of smoking-related DNA adducts in breast tumor cells and adjacent normal epithelial cells in some, but not all, current and former smokers (Perera et al. 1995; Li et al. 1996; Rundle et al. 2000; Faraglia et al. 2003). Some case-control studies have reported high levels of DNA adducts in smokers compared with nonsmokers (Perera et al. 1995; Li et al. 1999; Conway et al. 2002; Li et al. 2002; Rundle et al. 2002). Faraglia and colleagues (2003) conducted a large, comprehensive case-control study that included 148 breast tumor tissues and adjacent normal samples from the Long Island Breast Cancer Study Project. The arylamine 4-aminobiphenyl (4-ABP) DNA adduct was measured using an immunoperoxidase method that had been validated by mass spectrometry. The study's authors observed a significant trend between levels of 4-ABP DNA adducts in normal breast tissue and smoking status, and they measured higher levels of DNA adducts in active and passive smokers than in never smokers. Interestingly, mean levels of DNA adducts were significantly lower in tumor tissue than in adjacent normal tissue.

Elsewhere, circulating levels of PAH-DNA adducts in peripheral blood mononuclear cells were assessed in two sample sets taken 4.5 years apart from the same case-control study (Gammon et al. 2004b). The authors observed a modest association in both sets of samples between the highest PAH-DNA adduct levels and the risk of breast cancer, but they did not observe a dose-response relationship with increasing adduct levels. Furthermore, the strength of the association did not differ between active and passive smokers. To date, no prospective cohort study has incorporated these markers.

Polymorphisms in genes encoding enzymes involved in the metabolic activation and detoxification of toxins, such as those from exposure to cigarette smoke, could also affect breast carcinogenesis by either promoting or preventing the formation of DNA adducts. Firozi and colleagues (2002) observed a significant interaction between levels of DNA adducts in breast tissue and *CYP1A1, GSTM1,* and *NAT2* polymorphisms among ever smokers. These authors also observed higher levels of DNA adducts among smokers with combined *CYP1A1*1/*2* or **2/*2* and *GSTM1 null* genotypes than among smokers with polymorphisms in either genes. In addition, the frequency of smoking-related DNA adducts was higher in those with slow acetylator alleles of the *NAT2* gene than in those having rapid acetylator alleles.

Several studies have examined the association between smoking, *p53* mutations, and/or protein expression in breast tumors; results have been mixed (Conway et al. 2002; Furberg et al. 2002; Gaudet et al. 2008; Van Emburgh et al. 2008a). Mordukhovich and colleagues (2010), who conducted a large case-control study of 859 cases and 1,556 controls from the Long Island Breast Cancer Study Project, found that women in the study with p53-positive tumors were less likely to have been exposed to cigarette smoke than women without *p53* mutations. This finding suggests that smoking may not significantly affect the p53 pathway. In this study, *p53* mutations were identified from DNA extracted from paraffin blocks and p53 protein expression was evaluated using immunohistochemistry.

Other Cellular Mechanisms

In addition to forming DNA adducts, constituents of tobacco smoke may contribute to carcinogenesis by promoting cell growth and proliferation through the activation of a number of receptors, such as cyclooxygenase II and prostaglandin E2, and signaling pathways, including Akt and epidermal growth factor receptor (Narayan et al. 2004; Miller et al. 2005; Kundu et al. 2007; Botlagunta et al. 2008; Guo et al. 2008; Connors et al. 2009; Dasgupta et al. 2009). Constituents of tobacco smoke may also cause cells to evade apoptosis after DNA damage by altering cellular response at the mRNA and protein levels (Connors et al. 2009). In addition, cigarette smoke can inactivate tumor suppressor genes via genetic and epigenetic changes (Liu et al. 2010a). Narayan and colleagues (2004)

found that cigarette smoke condensate increases levels of *GADD45*—a gene whose expression is upregulated in response to DNA damage and/or growth arrest in a dose-dependent manner—to increase proliferation of epithelial cells and to induce cell cycle arrest at the synthesis/gap$_2$/mitosis (S/G$_2$/M) phase. Furthermore, Dasgupta and colleagues (2009) found that the exposure of human breast cancer cells to nicotine can contribute to epithelial-mesenchymal transition, a collection of changes seen in more advanced cancers that is characterized by loss of cell adhesion, increased cell mobility, and repression of E-cadherin. These mechanistic studies were conducted in cell culture experiments using normal and malignant breast epithelial cell lines, but they have yet to be replicated in an in vivo model.

Hormones

Estrogen's role in the initiation, promotion, and progression of breast cancer is well established through preclinical data, observational studies, and clinical trials (Yager and Davidson 2006). Studies in experimental animal models and cultured human cells demonstrate that estradiol (E2) and estrone (E1) are carcinogenic (Yager and Davidson 2006). Estrogen is thought to exert its carcinogenic effects primarily through two complementary pathways (Figure 6.26). The first pathway involves the

activation of signaling pathways via the estrogen receptor (ER), which leads to altered gene expression and increased proliferation and, in turn, the opportunity for more mutations. The second pathway involves the oxidative metabolism of estrogen (E2/E1) to catechol estrogens and then to reactive quinone metabolites. The quinone metabolites have the ability to form depurinating DNA adducts or to form catechols through the oxidation-reduction cycle that produce reactive oxygen species causing oxidative damage to DNA (Lavigne et al. 2001). The catechols can be inactivated by methylation mediated by catechol-*O*-methyltransferase, glucuronidation, and sulfation. In women, blocking the action of the ER by such agents as tamoxifen, a selective estrogen receptor modulator, or by decreasing estrogen production (e.g., by removing the ovaries in premenopausal women) has been shown to decrease the incidence of breast cancer up to 50% (Fisher et al. 1998; Parker et al. 2009). Estrogen metabolism, which occurs in the liver, kidney, and other organs, including the breast, involves a complex set of pathways (Figure 6.27). Various CYP isoforms, which are often tissue specific, are responsible for the oxidation and conjugation of estrogen metabolites. One of the first steps in estrogen metabolism is the oxidation of the parent estrogens (E2/E1) at the 2, 4, and 16 positions of the carbon skeleton to the 2, 4, and 16 hydroxylated metabolites (Yager and Liehr 1996).

Figure 6.26   Pathways to estrogen carcinogenesis
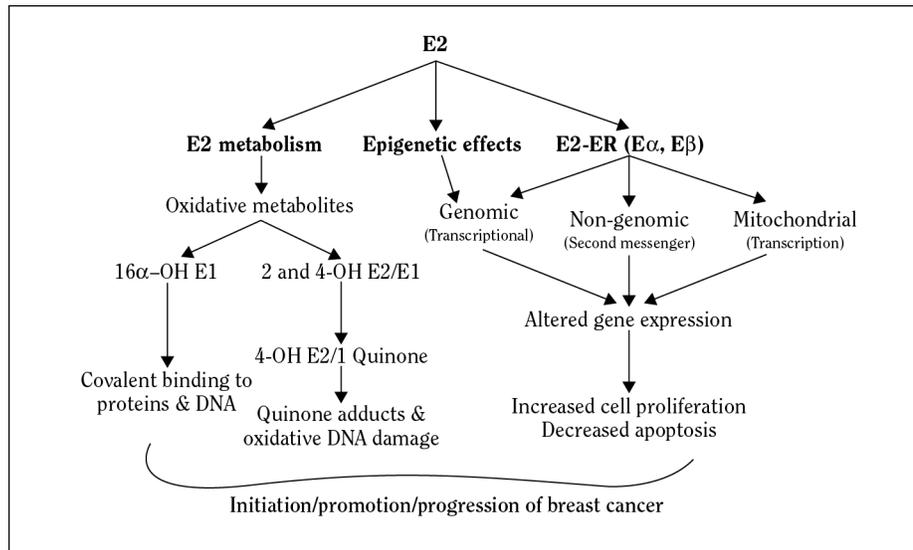
Source: Adapted from Yager and Davidson 2006, updated for Surgeon General's Report.
Note: **4-OH E1** = 4-hydroxyestrone; **4-OH E2** = 4-hydroxyestradiol; **16α-OH E1** = 16α-hydroxyestrone; **E1** = estrone; **E2** = estradiol; **ER** = estrogen receptor.

Figure 6.27   Pathways involved in estrogen metabolism
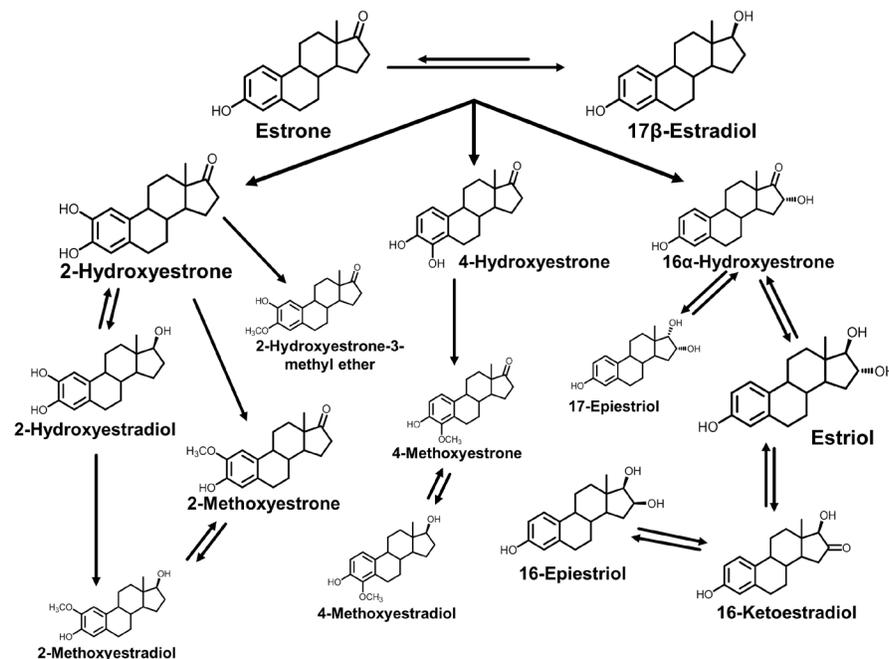
Source: Adapted from Ziegler et al. 2010.

Davis and colleagues (1993) showed that the 16 hydroxy estrogens exhibit strong estrogenic and mitogenic activities and hypothesized that higher levels of such activities increase the risk for breast cancer by uncontrolled cellular proliferation and by binding to the ER, thereby damaging DNA. The 2- and 4-hydroxy metabolites also exhibit estrogenic activity and can stimulate cellular proliferation. Despite being more abundant than the 4-hydroxy metabolite, the 2-hydroxy metabolite is much less potent and shorter acting. Both the 2- and 4-hydroxy estrogen metabolites can go on to form genotoxic reactive quinone metabolites.

In cell culture studies of granulosa cells, choriocarcinoma cells, and placental microsomes, nicotine was shown to directly inhibit the aromatase enzyme, resulting in reduced conversion of androgens to estrogen in a dose-dependent manner (Barbieri et al. 1986a,b). This is an important pathway, particularly in postmenopausal women among whom estrogen is generated primarily in peripheral tissues. In animal studies, cigarette smoke reduced the number of oocytes, caused toxicity to ovarian follicles, and led to ovarian atresia (Mattison 1982; Blackburn et al. 1994; Miceli et al. 2005), which could affect estrogen production in premenopausal women.

Observational studies have linked cigarette smoking to earlier age at menopause (Baron et al. 1990; Bromberger et al. 1997) and reduced bone density in postmenopausal women (Daniell 1976; Baron et al. 2001); both conditions are associated with relative estrogen deficiency and a reduction in the risk for breast cancer. Smoking is also associated with decreased fertility (USDHHS 2004, 2010) and with earlier menarche in children whose mothers were heavy smokers during pregnancy (Windham et al. 2004); both conditions are known risk factors for breast cancer. However, as noted in the 2001, 2004, and 2010 Surgeon General's reports, the majority of epidemiologic studies comparing circulating endogenous estrogen levels in premenopausal (Table 6.11*S*) and postmenopausal women (Table 6.12*S*) have not found differences between smokers and nonsmokers. In several small studies, premenopausal women who smoked were found to have significantly elevated urinary levels of 2-hydroxy E1 or reduced levels of E1, E2, or estriol (E3) during the luteal phase of the menstrual cycle compared with nonsmokers (MacMahon et al. 1982; Michnovicz et al. 1986, 1988; Westhoff et al. 1996). The clinical implications of these findings and any associated changes in breast tissue have not been investigated.

Studies that compared the effect of HRT, an exogenous hormonal exposure, in smokers and nonsmokers did observe differences by smoking status in circulating levels of estrogen and its metabolites, supporting the hypothesis that smoking increases hepatic metabolism of estrogens (Jensen et al. 1985; Jensen and Christiansen 1988; Cassidenti et al. 1990; Geisler et al. 1999). Among postmenopausal women who were using orally administered HRT, circulating estrogen metabolites—including E1, E2, and estrone sulfate—were 40–70% lower in smokers than in nonsmokers (Jensen et al. 1985; Jensen and Christiansen 1988; Cassidenti et al. 1990; Geisler et al. 1999). A dose-dependent, reciprocal increase in the binding capacity of sex-hormone-binding globulin was observed by Cassidenti and colleagues (1990) and, importantly, differences in levels of estrogen and its metabolites were not evident before treatment with HRT in these same women (Jensen et al. 1985; Cassidenti et al. 1990). Furthermore, significant changes in circulating hormone levels between smokers and nonsmokers were not observed after transdermal administration of HRT, a method that bypasses estrogen metabolism in the liver (Geisler et al. 1999; Mueck and Seeger 2005).

Alterations in estrogen metabolism pathways have also been observed in pregnant women who smoked (USDHHS 2001). Several studies have found that pregnant women who smoked had lower levels of circulating E2 and E3 than pregnant women who did not smoke (Targett et al. 1973; Mochizuki et al. 1984; Bernstein et al. 1989; Petridou et al. 1990; Kaijser et al. 2000). However, compared with their nonsmoking pregnant counterparts, rates of 4-hydroxylation were increased in pregnant smokers in samples of placental tissue (Chao et al. 1981; Juchau et al. 1982), and rates of 2-hydroxylation were nonsignificantly increased (Juchau et al. 1982). Smoking did not alter E2 metabolism or the formation of E1, 2-hydroxyestradiol, and other estrogen metabolites, but 15α-hydroxyestradiol, 4-hydroxyestradiol, and 7α-hydroxyestradiol were significantly elevated (Zhu et al. 2002). Finally, Piasek and colleagues (2001) found that levels of progesterone were lower in pregnant women who smoked than in those who did not smoke. If the rate of 4-hydroxylation continues to be higher after pregnancy in smokers than in nonsmokers, then smoking may increase risk for breast cancer rather than having a protective effect, as suggested by the anti-estrogenic hypothesis proposed by Michnovicz and colleagues (1986).

Several other circulating hormones have also been compared between smokers and nonsmokers. In premenopausal women, Cramer and colleagues (1994) and Windham and colleagues (2005) did observe higher levels of circulating follicle-stimulating hormone in smokers than in nonsmokers (Table 6.11*S*). Last, circulating levels of androgens (e.g., androstenedione, dihydroepiandrosterone sulfate, and testosterone), progesterone, and cortisol have been found to be higher in smokers than in nonsmokers. In postmenopausal women, these elevated levels may affect breast carcinogenesis. Missmer and colleagues (2004) associated increased levels of circulating androgens with increased risk for breast cancer among postmenopausal women. A meta-analysis by Law and colleagues (1997) found that levels of dihydroandroepiandosterone sulfate and androstenedione were significantly higher in postmenopausal smokers than in nonsmokers but that levels of estrogens did not differ. Finally, cigarette smoking has been shown to directly affect adrenal cortical hormone levels (Baron et al. 1995). The effects of these hormonal changes on breast tissue are not known.

Summary

The available evidence supports biologically plausible mechanisms, particularly for DNA adduct formation and unrepaired DNA mutations, by which exposure to tobacco smoke could cause breast cancer. However, data are limited and a detailed mechanistic model of how exposure to tobacco smoke may affect risk for breast cancer cannot yet be assembled.

Epidemiologic Evidence—Overview

The following sections update and expand the reviews in previous Surgeon General's reports on the associations between cigarette smoking and breast cancer and between exposure to secondhand smoke and breast cancer. Conclusions from previous reports and recent epidemiologic evidence are summarized with reference to the criteria for the assessment of causation used in this series of reports (Hill 1965; USDHHS 2004). The studies reviewed cover a lengthy period of time and include a variety of study designs and inclusion criteria, data collection techniques, exposure measurements, and study endpoints. Reports based on cohort studies prior to 2012 and case-control studies published between 2000–2011 were identified in MEDLINE using key words and extended terms. All studies that evaluated the association between smoking and breast cancer risk and mortality were eligible for review. Combinations of the following key words were used, depending on the evidence sought: breast cancer, breast neoplasms, tobacco smoke, cigarette smoking, active smoking, passive smoke, secondhand smoke, involuntary smoke exposure, case-control study, cohort study, risk, survival, mortality, prognosis, recurrence, second primary, genotype, polymorphism, single nucleotide polymorphisms (SNPs), NAT1, NAT2, CYP1A1 and CYP1B1,

GST, GSTM1, GSTT1, GSTP1, GSTA1, SULT1A1*, MnSOD2,* XRCC1, XPD or ERCC2, MGMT, and *BRCA1,* and *BRCA2.* Additional studies were identified from reference lists in pertinent papers. The search focused on English-language studies that evaluated either (a) the main effects of cigarette smoking or passive exposure to smoke on breast cancer risk or mortality, or (b) the interaction of cigarette smoking or passive exposure to smoke with such risk factors as menopausal status, hormone receptor status, family history, and susceptibility genotypes. All studies that reported a main effect for smoking are identified in the sections below on active smoking (see "Active Cigarette Smoking and Risk for Breast Cancer") and exposure to secondhand smoke (see "Exposure to Secondhand Smoke and Risk for Breast Cancer"), regardless of whether they were one of multiple studies on the same population. However, when multiple studies were reported for the same population, only the most recent findings, with a few exceptions noted in the analytical sections, were included in the meta-analyses presented later.

Active Cigarette Smoking and Risk for Breast Cancer

Individual authors and various review panels have evaluated the evidence for an association between active and passive cigarette smoking and breast cancer. The first systematic review of such an association was included in IARC Monograph 38 (1986). Based on a review of 10 case-control and 8 cohort studies published between 1959 and 1983, the 1986 IARC monograph found "no consistent effect of smoking on the risk of breast cancer" (p. 298). The literature at the time was limited, however. Only 2 of the case-control studies (CDC 1983; Janerich et al. 1983) were population-based, rather than hospital-based, and few studies adjusted for potential confounders. All but 1 cohort study (Hiatt et al. 1982) mixed incident and decedent cases and few adequately adjusted for relevant confounders. Palmer and Rosenberg (1993) reviewed 5 cohort and 16 case-control studies (9 with population controls, 3 with participants in a screening program, and 4 with hospital controls), finding "little evidence to suggest that cigarette smoking materially increases risk" (p. 154). However, the authors noted that future investigations should consider age at initiation of smoking because of evidence that women were beginning to smoke at earlier ages. Terry and Rohan (2002) published a comprehensive literature review on cigarette smoking and breast cancer, concluding that "the association between cigarette smoking and breast cancer risk remains unclear" and that the observed "increased risk

with smoking of long duration, smoking before a first full-term pregnancy, and passive smoking require (sic) confirmation in future epidemiological studies" (p. 965). They suggested that future studies and meta-analyses consider timing of exposure (e.g., age at initiation of smoking and smoking before first pregnancy), duration and dose (years of exposure and pack-years of smoking), sources of passive exposure, the overlap of active and passive exposures, potential confounders, and modification by menopausal status and genetic susceptibility.

IARC (2004) summarized results from 36 case-control studies, 8 cohort studies, and a large pooled analysis of data from 10 cohort and 43 case-control studies, the pooled analysis having been conducted by the Collaborative Group on Hormonal Factors in Breast Cancer and colleagues (2002) and based on studies having at least 100 women with incident invasive breast cancer. The pooled analysis was restricted to nondrinkers (38% of cases and 43% of controls), because alcohol was considered a potentially significant confounder of the effects of smoking. Sufficient data were available to consider a wide variety of other potential confounders, including age at diagnosis, parity, age at birth of first child, breastfeeding, race, country, education, family history, age at menarche, height, weight, body mass index (BMI), use of hormonal contraceptives, and menopausal status. Study site, age, parity, and age at first birth were included as covariates in the final analysis of the effect of smoking on risk of breast cancer among nondrinkers. However, the analysis did not consider duration or amount of smoking or exposure to secondhand smoke. Results indicated no association between active smoking and risk for breast cancer (RR = 1.03; 95% CI, 0.98–1.07) in women who did not drink alcohol. The Collaborative Group (2002) also contrasted this result with those for all women regardless of alcohol intake (RR = 1.09) and statistically adjusted for alcohol intake (RR = 1.05). The 2004 IARC report concluded that: (a) the majority of epidemiologic studies "found no association with active smoking, after controlling for established risk factors"; and (b) the Collaborative Group analysis of women who reported themselves to be nondrinkers "confirms the lack of an increased risk of breast cancer associated with smoking" (p. 1183). The Cal/EPA reviewed many of the same studies in 2005 and came to a different conclusion: "Considering the epidemiological studies, the biology of the breast and the toxicology of tobacco smoke constituents together, the data provide support for a causal association between active smoking and elevated breast cancer risk" (p. 7-79).

In April 2009, the Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk conducted an extensive descriptive evaluation of active cigarette smoking and exposure to secondhand smoke, paying particular

attention to the timing of these exposures (age at initial exposure and before or during first full-term pregnancy), duration and dose (years of exposure and number of pack-years of smoking), modification by menopausal status, and genetic susceptibility (Collishaw et al. 2009). The panel's approach, to some extent, followed the suggestions of Terry and Rohan (2002) that future studies and meta-analyses focus more carefully on the issues of duration, timing, genetic susceptibility, source of passive exposure, the overlap of passive and active exposure, and potential confounders. The evaluation included summative reviews, meta-analyses, and the most recently published studies through November 2008. Pooled analyses and meta-analyses were not performed. The evaluation paid particular attention to results from the 2002 analysis by the Collaborative Group on Hormonal Factors in Breast Cancer, the 2005 Cal/EPA report, and the 2004 and 2006 Surgeon General's reports.

The Canadian Expert Panel evaluated results from more recent, updated analyses published for four of the cohort studies and nine of the case-control studies that were included in the 2002 Collaborative Report in which duration of smoking was reported. Unlike the 2002 report, which excluded women who consumed alcohol, the Canadian panel reported risk estimates adjusted for alcohol intake. The four cohort studies included the NHS-I (Egan et al. 2002), the Canadian National Breast Screening Study (Cui et al. 2006), the CPS-II (Calle et al. 1994), and the Iowa Women's Health Study (Olson et al. 2005). Three of these (Calle et al. 1994; Olson et al. 2005; Cui et al. 2006) reported significantly increased RRs, ranging from 1.18–1.50, for the longest duration of smoking (≥40 years). Among the nine case-control studies (Rohan and Baron 1989; Palmer et al. 1991; Smith et al. 1994; Baron et al. 1996; Johnson et al. 2000; Kropp and Chang-Claude 2002; Alberg et al. 2004; Magnusson et al. 2007; Prescott et al. 2007), five reported an increase in risk of greater than 45% for smoking durations ranging from 11 to more than 50 years and for high cumulative levels of pack-years or cigarette-years[3] (Rohan and Baron 1989; Palmer et al. 1991; Johnson et al. 2000; Kropp and Chang-Claude 2002; Alberg et al. 2004). However, results were statistically significant only for postmenopausal women who reported more than 35 years of active smoking (OR = 1.7; 95% CI, 1.1–2.7) in one study (Johnson et al. 2000).

The Canadian Expert Panel also evaluated three cohort studies published after 2002 in which the risk of breast cancer was significantly increased for the longest

durations of active smoking, ranging from 20 or more years to 31 or more years (Al-Delaimy et al. 2004; Reynolds et al. 2004b; Gram et al. 2005). According to the Canadian Expert Panel, when these studies were considered along with three of the four older cohort studies (Egan et al. 2002; Olson et al. 2005; Cui et al. 2006) (Calle et al. 1994 was excluded because it was a mortality study), five reported an increased risk for the highest duration category of smoking: two with borderline significance (RR = 1.15 [95% CI, 1.00–1.33]; 1.18 [95% CI, 1.00–1.38]) (Reynolds et al. 2004b; Olson et al. 2005, respectively) and three with statistical significance (RR = 1.21 [95% CI, 1.01–1.45]; 1.36 [95% CI, 1.1–1.7]; and 1.50 [95% CI, 1.19–1.89]) (Al-Delaimy et al. 2004; Gram et al. 2005; Cui et al. 2006, respectively). However, it should be noted that the result used for the Gram study is based on a subgroup of women who reported ever smoking for at least 20 years. The result for all current smokers with 25 or more years of smoking was increased but not statistically significant (RR = 1.26; 95% CI, 0.98–1.63). Although four of these five studies reported statistically significant trends across levels of duration (Olson did not calculate a p for trend), only three (Gram et al. 2005; Olson et al. 2005; Cui et al. 2006) actually showed unambiguous evidence of an increasing trend with duration of active smoking. The panel also reviewed four cohort studies published after 2002 that reported risk estimates by pack-years of smoking (Reynolds et al. 2004b; Gram et al. 2005; Olson et al. 2005; Cui et al. 2006). Among these studies, three had statistically significant RRs ranging from 1.17–1.48 for the highest category of pack-years (Reynolds et al. 2004b; Gram et al. 2005; Cui et al. 2006). Additionally, the panel reviewed 32 case-control studies in which ORs were reported for duration of active smoking and 27 in which estimates were reported for pack-years. The results from these case-control studies were found to be inconsistent, regardless of menopausal status. The Canadian Expert Panel concluded that the results from the cohort studies for increased risk with longer duration and higher pack-years were more "persuasive" than those from the case-control studies and "that the relationship between active smoking and breast cancer is consistent with causality" (Collishaw et al. 2009, p. 49). Johnson and colleagues (2011) summarized the results from the Canadian Expert Panel in a brief report.

In November 2009, IARC issued a special report on human carcinogens, including tobacco, that encompassed more than 150 epidemiologic studies about the association between tobacco smoke and breast cancer (Secretan

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[3]Cigarette-years: the number of years of smoking multiplied by the number of cigarettes smoked per day.

et al. 2009). This report updated findings and conclusions from the 2004 IARC report and noted that two large cohort studies conducted after 2002 showed positive, but small, statistically significant associations. These studies included the California Teachers Study (hazard ratio [HR] = 1.13; 95% CI, 1.0–1.28) (Reynolds et al. 2004b), which was also reviewed in the 2006 Surgeon General's report, and the Canadian National Breast Screening Study (HR = 1.18; 95% CI, 1.09–1.27) (Cui et al. 2006). Based on these findings and those from previous reports, as well as evidence from studies of animal and human tissues, the IARC panel concluded that "there is limited evidence that tobacco smoking causes breast cancer" (Secretan et al. 2009, p. 1033) and added the female breast as a new cancerous tumor site associated with exposure to tobacco smoking.

In addition to these extensive reports, several reviews and meta-analyses have addressed active cigarette smoking alone (Khuder and Simon 2000; Khuder et al. 2001; Nagata et al. 2006; Ren et al. 2007), exposure to secondhand smoke but not active smoking (Lee and Hamling 2006; Pirie et al. 2008), both active and passive smoking (Morabia 2002b; Johnson 2005; Sadri and Mahjub 2007; Iwasaki and Tsugane 2011), smoking-genotype interactions (Vogl et al. 2004; Masson et al. 2005; Terry and Goodman 2006; Ochs-Balcom et al. 2007; Ambrosone et al. 2008; Zhang et al. 2010), smoking-DNA repair marker interactions (Neumann et al. 2005), timing in relation to first pregnancy or birth of first child (Lawlor et al. 2004; DeRoo et al. 2011b), and intrauterine exposure (Park et al. 2008).

Conclusions from Previous Surgeon General's Reports

The 2001 Surgeon General's report on women and smoking concluded that "active smoking does not appear to appreciably affect breast cancer risk overall," but it suggested that future research address both age at initiation of smoking and potential susceptibility associated with specific genetic polymorphisms (p. 217). The 2004 Surgeon General's report on the health consequences of smoking evaluated: (a) the influence that cigarette smoking has on endogenous estrogen levels due to changes in metabolism and lowered body weight; (b) the effects of early age at smoking initiation, smoking-genotype interactions, and exposure to secondhand smoke; and (c) carcinogenic and anti-estrogenic effects of smoking on breast tissues. The 2004 Surgeon General's report concluded that "evidence is suggestive of no causal relationship between active smoking and breast cancer," that subgroups of women at high risk because of smoking could not be "reli-

ably identified," and that the previous finding of a lower risk for breast cancer among women with *BRCA1* or *BRCA2* mutations in one study (Brunet et al. 1998) "was not replicated" in a later study (Couch et al. 2001) and therefore not established (USDHHS 2004, p. 312).

The sections below review and quantitatively summarize studies of cigarette smoking by study design (cohort, case-control), and by geographic regions (North America, Europe, Asia) that differ for smoking prevalence, as well as breast cancer incidence and mortality. Table 6.13 shows selected estimates of the prevalence of smoking from the WHO Reports on the Global Tobacco Epidemic (2008a, 2011) for countries represented in these reports. Although there is considerable variation, the prevalence of smoking in women is generally similar in North America and Europe but substantially lower in Asia.

The following sections include reports on the association between smoking and breast cancer risk based on cohort studies published up to 2012 (Table 6.14*S*) and case-control studies published from 2000–2011 (Table 6.15*S*). A list of studies by category of exposure is provided in Table 6.16*S*. Studies based on incident cases that estimate risk of breast cancer are emphasized because studies that focus on mortality may include a different mix of correlates and etiologic pathways affecting survival that alter the association with smoking (Al-Delaimy et al. 2004). As a result, studies of smoking and breast cancer mortality are evaluated in a separate section (see "Exposure to Tobacco Smoke and Breast Cancer Mortality"). Some studies or reviews that mix prevalent with incident cases, however, are included (Lawlor et al. 2004; Hanaoka et al. 2005; Ha et al. 2007).

Cohort Studies

Table 6.14*S* presents an overview of 15 publications from the 12 cohort studies on breast cancer and active smoking published since 2000 (Manjer et al. 2000b, 2001; Egan et al. 2002; Terry et al. 2002a; Al-Delaimy et al. 2004; Lawlor et al. 2004; Reynolds et al. 2004b; Gram et al. 2005; Hanaoka et al. 2005; Olson et al. 2005; Cui et al. 2006; Ha et al. 2007; Lin et al. 2008; Xue et al. 2011; Luo et al. 2011b). The study by Lawlor and colleagues (2004) was restricted to parous women in the United Kingdom and combined prevalent and incident cases. The report by Manjer and colleagues (2001) was based on the same cohort as used in an earlier report by Manjer and colleagues (2000b), but was restricted to women with tumor tissue available for analysis. Consequently, Lawlor and colleagues (2004) and Manjer and colleagues (2001) are excluded from the meta-analyses and forest plots. Additionally, reports by Terry and colleagues (2002a) and Cui

Table 6.13   Age-standardized estimates of the prevalence of current cigarette smoking for selected member states of the World Health Organization (WHO), 2009

WHO region	Member states	Males (%)	Females (%)
North America	United States	28	24
	Canada	19	16
Europe	Denmark	30	28
	Finland	28	22
	France	36	27
	Germany	33	25
	Italy	33	19
	Netherlands	28	22
	Norway	31	28
	Poland	36	25
	Slovenia	30	22
	Sweden	20	25
	Switzerland	31	21
	United Kingdom	25	23
Western Pacific	Australia	22	19
	China	50	2
	India	11	1
	Japan	42	12
	Republic of Korea	53	6
	Philippines	47	10

Source: Data for Republic of Korea and Sweden are from WHO 2008a (Appendix III, Tables 3.4b and 3.6b). Data for the other member states presented in this table are from WHO 2011 (Appendix VII, Table 7.1.0). Reprinted with permission from World Health Organization, © 2008, 2011.

Note: Prevalence estimates are standardized to age distributions of the country's current smoking. Estimates of current smoking are calculated based on cigarette smoking at the time of survey, daily or nondaily. Estimates rounded to nearest whole number.

and colleagues (2006) were based on the same cohort, the Canadian National Breast Screening Study. Although Table 6.14*S* summarizes both studies, estimates only from Cui and colleagues (2006) are used in the meta-analyses to avoid duplication. Two reports stem from the NHS-I (baseline year 1976) (Egan et al. 2002; Xue et al. 2011); data from the more recent report are used in the majority of the meta-analyses. Data from the NHS-II are included because it is a separate premenopausal-women-only cohort with a different baseline year (1989) (Al-Delaimy et al. 2004). All three of these studies are summarized in Table 6.14*S*.

North American Studies

The U.S. Radiologic Technologists Study (USRTS) (Ha et al. 2007) reported nonsignificantly increased RRs for breast cancer among former smokers (RR = 1.17; 95% CI, 0.99–1.38) and current smokers (RR = 1.13; 95% CI, 0.96–1.32). Although the study adjusted for the first year in which an individual worked as a radiologic technician, either residual confounding or synergy may have occurred between smoking and exposure to radiation at work, because previous analyses showed an increased risk (RR =

2.41; 95% CI, 1.32–4.41) associated with exposure to radiation at work among women who were employed before 1940, when exposure to occupational radiation was potentially higher for this group (Mohan et al. 2003; Sigurdson et al. 2003). Eighty-six percent of cases (781 out of 906) were ascertained by self-report, of which 20% (155 out of 781) could not be verified against medical records (Ha et al. 2007), but a previous report from the USRTC indicated 99.4% agreement between self-report and breast cancers ascertained from medical records (Sigurdson et al. 2003). In addition, 14% (125) of the cases were ascertained from death certificates, and date of diagnosis was imputed using the average survival time between 1973 and 2000 based on SEER data.

Several reports from the NHS-I cohort on smoking and breast cancer are based on both premenopausal and postmenopausal women (Willett et al. 1987; London et al. 1989; Hunter et al. 1997; Collaborative Group on Hormonal Factors in Breast Cancer et al. 2002; Egan et al. 2002; Xue et al. 2011). All but two (Egan et al. 2002; Xue et al. 2011) have been incorporated in previous reviews or meta-analyses. The report by Xue and colleagues (2011) analyzed data for 8,772 incident cases of breast cancer in 111,440 women followed for up to 30 years (1976 baseline). The RR was 1.09 (95% CI, 1.02–1.17) for current smokers and 1.06 (95% CI, 1.01–1.11) for former smokers in comparisons with never smokers. These estimates were adjusted for age, family history of breast cancer, age at menarche, height, BMI at 18 years of age, use of oral contraceptives, history of benign breast disease, physical activity, alcohol use, age at first birth, parity, passive smoking at home and at work, current BMI, age at menopause, menopausal status, and use of HRT. Risk was significantly and positively associated with increasing pack-years of smoking (p trend = 0.001), number of cigarettes smoked per day (p trend = 0.02), and duration of smoking (p trend = 0.01), particularly in the intervals between menarche and menopause and menarche and first birth (RR = 1.11; 95% CI, 1.07–1.15; and 1.18; 95% CI, 1.10–1.27 for every 20 pack-years, respectively). The authors also reported a significant trend (p = 0.02) toward decreasing risk with increasing pack-years of smoking after menopause.

In an earlier report from the NHS-I, Egan and colleagues (2002) reported results for a subset of 78,206 premenopausal or postmenopausal women that was restricted to those for whom data on both active and passive smoking were collected and based on an average of 14 years of follow-up (1982 baseline). The RR, based on a reference group of women who reported no history of active or passive smoking, was 1.15 (95% CI, 0.98–1.34) and 1.17 (95% CI, 1.01–1.34) for current and former smokers, respectively. Last, Al-Delaimy and colleagues (2004) analyzed

data from the NHS-II cohort (1989 baseline), based predominantly on premenopausal women, and reported a significantly increased risk for breast cancer among former smokers (RR = 1.18; 95% CI, 1.02–1.36) but not current smokers (RR = 1.12; 95% CI, 0.92–1.37) in comparisons with never smokers over an average of 10 years of follow-up. This study also reported a positive association between risk for breast cancer and increasing duration of smoking (p trend = 0.04) and a significantly increased risk for smoking 20 years or more (RR = 1.21; 95% CI, 1.01–1.45).

Cui and colleagues (2006), using data from the Canadian Breast Screening Study (1980–1985 baseline, 40–59 years of age) reported an increased risk for breast cancer among current smokers (RR = 1.18; 95% CI, 1.09–1.27) but not former smokers (RR = 1.00; 95% CI, 0.93–1.08). This report was an update of the same cohort from an analysis by Terry and colleagues (2002a), but at an average of 16 years of follow up for 4,445 cases rather than an average of 10.6 years for 2,552 cases. Overall, few differences can be found between these two reports. The 16-year follow-up study, using never smokers as the referent, found significant associations between risk for breast cancer and the highest categories of cigarettes smoked per day (RR = 1.20; 95% CI, 1.00–1.44), duration of smoking (RR = 1.50; 95% CI, 1.19–1.89), and pack-years of smoking (RR = 1.17; 95% CI, 1.02–1.34), as well as for smoking for more than 5 years before first pregnancy (RR = 1.13; 95% CI, 1.01–1.25) and for initiation of smoking between 16 and 19 years of age (RR = 1.10; 95% CI, 1.01–1.21). Effect modification by menopausal status was not found, but positive associations were stronger in women who did not report vigorous physical activity.

In the Iowa Women's Health Study cohort, Olson and colleagues (2005) reported a significantly increased risk (vs. never smokers) for breast cancer among postmenopausal current smokers (RR = 1.19; 95% CI, 1.03–1.37) but not former smokers. Increased risks were also detected for age at smoking initiation (older than 18 years of age: RR = 1.11; 95% CI, 1.00–1.24), smoking duration (≥40 years: RR = 1.18; 95% CI, 1.00–1.38), and smoking before first pregnancy (RR = 1.21; 95% CI, 1.07–1.37).

Reynolds and colleagues (2004b) used data from the California Teachers Study to evaluate the association of smoking with breast cancer. The authors detected significantly increased risks for breast cancer among current smokers in comparisons with two reference groups: never smokers (RR = 1.32; 95% CI, 1.10–1.57) and women who reported no active or passive exposure to smoking (RR = 1.25; 95% CI, 1.02–1.53). Results for former smokers, when compared with women who reported no active or passive exposure to smoking or with never smokers, were attenuated and not significant, regardless of

reference group. This study reported significant trends toward increasing risk of breast cancer with longer duration and greater pack-years of smoking and more cigarettes smoked per day. In addition, risk of breast cancer was increased in women who initiated smoking before 20 years of age (RR = 1.17; 95% CI, 1.05–1.30) and who smoked for 5 or more years before first pregnancy (RR = 1.13; 95% CI, 1.00–1.28). In response to a letter by Johnson (2004), Reynolds and colleagues (2004a) conducted additional analyses to evaluate the associations for smoking duration, pack-years of smoking, and average number of cigarettes smoked per day with risk of breast cancer stratified by nulliparous women only, parous women who smoked less than 5 years prepartum, and parous women who smoked for 5 or more years prepartum. These analyses suggested a stronger risk effect among parous women who smoked for 5 or more years before first pregnancy for duration, pack-years, and cigarettes smoked per day (RR = 1.12, 1.28, and 1.25, respectively, for highest levels) than for women who smoked for less than 5 years before first pregnancy (RR = 1.18, 1.12, and 1.11, respectively, for highest levels) compared with their nonsmoking counterparts. Results were significant for the highest levels for pack-years and cigarettes smoked per day for parous women who had smoked for 5 or more years prior to pregnancy. Risk of breast cancer was increased among nulliparous women (RR = 1.13, 1.33, and 1.37, respectively, for highest levels), but significant for only those women who reported smoking 20 or more cigarettes per day compared with nonsmoking nulliparous women.

Luo and colleagues (2011b) reported results for 3,520 cases among 79,990 postmenopausal women followed for an average of 10.3 years in the Women's Health Initiative Observational Study cohort. The RRs for former and current smokers were 1.09 (95% CI, 1.02–1.17) and 1.16 (95% CI, 1.00–1.34), respectively, when based on a reference group of never smokers. These risks increased about 7–8% when based on a no active/no passive exposure reference group (RR = 1.16; 95% CI, 0.98–1.38 and RR = 1.24; 95% CI, 1.00–1.54, respectively). Risk was significantly (p <0.05) and inversely associated with age at initiation of smoking, and it was positively associated with cigarettes per day, duration, and pack-years of smoking. The RR for 50 or more pack-years of smoking was 1.18 (95% CI, 1.02–1.37), very similar to the estimate of 1.19 (95% CI, 1.07–1.33) for 51 or more pack-years reported by Xue and colleagues (2011) for the NHS-I. It is important to note, however, that the estimate for the Women's Health Initiative (Luo et al. 2011b) is for postmenopausal women only; the NHS-I (Xue et al. 2011) reported a significant (p = 0.02) inverse association with pack-years of smoking after menopause but a strong (p <0.001) positive association before menopause. Thus, these two large cohort studies provide contradictory results for the effect of smoking on risk of breast cancer in postmenopausal women.

Last, in a companion report from the Women's Health Initiative, Luo and colleagues (2011a) provided results suggesting that the risk of breast cancer is greater in nonobese women who smoke. The RR for current smoking was 1.25 (95% CI, 1.05–1.47) in nonobese women (BMI <30) versus 0.96 (95% CI, 0.69–1.34) in obese women. Significant trends in risk were found for age at initiation, duration and pack-years of smoking, and cigarettes per day in nonobese but not in obese women. The RR for 50 or more years of smoking was 1.62 (95% CI, 1.22–2.17) in nonobese women but only 0.62 (95% CI, 0.28–1.40) in obese women. This is one of three studies to date that have examined the interaction of smoking and body size on risk of breast cancer and the only one to formally test for statistical interaction; the other studies have been case-control. Gammon and colleagues (2004a) also reported an increased risk of breast cancer in lean women (BMI <22.3) exposed to both active and passive smoking (OR = 1.76; 95% CI, 1.06–2.92) but no association for obese women (BMI >29.2) in their case-control Long Island Breast Cancer Study Project. In contrast, Band and colleagues (2002) found a nonsignificant inverse association in ever smokers with a BMI less than 21 (RR = 0.75; 95% CI, 0.29–1.94) but an increased risk in those with a BMI 21 or greater (RR = 1.13; 95% CI, 0.63–2.04); however, the latter result is for lean, normal, overweight, and obese women combined and therefore cannot be compared with the other studies. Luo and colleagues (2011a) speculated as to whether this interaction could be associated with either an anti-estrogenic effect of smoking or with different distributions of genetic susceptibility polymorphisms in obese versus nonobese postmenopausal women.

European Studies

Since 2000, three European cohort reports have been published for findings on two studies of smoking and risk for breast cancer. Gram and colleagues (2005) studied the Norwegian-Swedish Cohort, a large population-based cohort (n = 102,098) in Scandinavia with up to 9 years of follow-up. Although the study detected nonsignificant increased risks for breast cancer among former smokers (RR = 1.15; 95% CI, 0.94–1.41) and current smokers (RR = 1.17; 95% CI, 0.95–1.40), it found some strong associations with timing of smoking initiation, duration of smoking, and smoking dose. Risk estimates for initiation of smoking before 15 years of age (RR = 1.48; 95% CI, 1.03–2.13), "before/around menarche" (RR = 1.39; 95% CI, 1.03–1.87), and before first pregnancy (RR = 1.27; 95% CI, 1.00–1.62) were all significantly associated with breast cancer among women who reported smoking for at least 20

years in comparisons with never smokers. Among women with 20 or more years of smoking, significant increased risks were also reported for smoking at least 10 cigarettes per day (RR = 1.34; 95% CI, 1.06–1.70), accumulating 20 or more pack-years of smoking (RR = 1.46; 95% CI, 1.11–1.93), and smoking for at least 25 years (RR = 1.36; 95% CI, 1.06–1.74) in comparison with never smokers. These results were attenuated on the order of 1–7% when analyzed for current smokers and were no longer significant except for pack-years of smoking and number of cigarettes smoked per day, as shown in Table 6.14*S*. Earlier, Manjer and colleagues (2000b) reported results from a smaller cohort study (n = 10,902) conducted in Malmö, Sweden. In premenopausal and postmenopausal women combined, former smoking—but not current smoking or number of cigarettes smoked per day—was significantly associated with risk for breast cancer (RR = 1.31; 95% CI, 1.02–1.69).

Asian Studies

Since 2000, studies published have included a systematic review of three cohort and eight hospital-based case-control studies by Nagata and colleagues (2006) and a single cohort study by Lin and colleagues (2008). The three cohort studies in the review by Nagata and colleagues (2006) included the study by Hanaoka and colleagues (2005) of middle-aged Japanese women, a study of atomic bomb survivors by Goodman and colleagues (1997), and a study of breast cancer mortality by Hirayama (1984, 1990). All eight case-control studies were conducted before 2000. In addition to multiple problems with the design of these studies, their results are difficult to interpret and have poor generalizability because of the low incidence of breast cancer and very low prevalence of smoking among Asian women (Table 6.13). Although the prevalence of smoking is very low among Chinese women (2%) and low among Japanese (12%) women, it is high among Chinese (50%) and Japanese (42%) men (Table 6.13, based on WHO 2011). Thus, women in Asia are exposed to secondhand smoke more so than to active cigarette smoking.

The study by Lin and colleagues (2008) included approximately 12 years of follow-up of 34,401 women (Table 6.14*S*). However, the study had limited power to detect an association between smoking and breast cancer because of a small number of cases (n = 208) and the low prevalence of current smoking (1.6%) and former smoking (5.3%). The RRs for breast cancer were 0.67 (95% CI, 0.32–1.38) for current smokers and 1.27 (95% CI, 0.46–3.48) for former smokers. However, when the analysis was restricted to postmenopausal women, current smokers had an elevated, albeit not significant, risk (RR = 1.20; 95% CI, 0.52–2.80). The study included too few premeno-

pausal women to conduct a formal test of interaction, but the results suggest the possibility of effect modification by menopausal status. The Japan Public Health Center-based prospective cohort study by Hanaoka and colleagues (2005) also lacked statistical power, with only 180 incident cases among 21,805 women and a smoking prevalence of 5.7%. Moreover, the analyses appeared to mix incident morbidity data with mortality data. The RRs were 1.7 (95% CI, 1.0–3.1) for current smokers and 1.1 (95% CI, 0.4–3.5) for former smokers, using a no active/no passive reference group. Among premenopausal women, the RR was significantly increased, but imprecisely estimated for ever smokers (RR = 3.9; 95% CI, 1.5–9.9); the study found no increased risk among postmenopausal women (RR = 1.1; 95% CI, 0.5–2.5).

Case-Control Studies

Since 2000, there have been 34 reports based on 30 case-control studies on smoking and breast cancer (Table 6.15*S*). The reports provided by Metsola and colleagues (2005) and Sillanpaa and colleagues (2005a) were based on the same study group, and both used a no active/no passive exposure reference group. Because the report by Sillanpaa and colleagues (2005a) adjusted for a number of potential confounders and these adjustments made a difference in the reported estimates, this report is used in the meta-analyses and forest plots. Table 6.15*S* presents an overview of these studies. Seven studies are limited by either a small sample (<200 cases) with low statistical power (Delfino et al. 2000; Morabia et al. 2000; Alberg et al. 2004; Gibson et al. 2010; Kaushal et al. 2010) or by other design features that limit interpretation, such as clinic-based controls (Delfino et al. 2000; Kruk 2007; Cerne et al. 2011) or benign breast disease controls (Delfino et al. 2000). These studies vary considerably in reporting type and detail for measures of smoking and whether results are stratified by ethnicity, menopausal status, or genetic biomarkers.

North American Studies

Since 2000, findings on smoking and risk for breast cancer have been reported across seven large population-based case-control studies with at least 1,000 cases (Johnson et al. 2000; Innes and Byers 2001; Band et al. 2002; Gammon et al. 2004a; Mechanic et al. 2006; Prescott et al. 2007; Slattery et al. 2008; Young et al. 2009). The reports by Fink and Lash (2003) and DeRoo and colleagues (2011a) are not included in this section because they dealt exclusively with smoke exposure during pregnancy. Young and colleagues (2009) conducted the largest case-control study to date, with 6,235 cases and 6,533 controls (Table

6.15*S*). The study was based on pooled data from two case-control studies in Ontario, Canada: the Ontario Women's Health Study and the Ontario Women's Diet and Health Study. The designs of the two studies were similar, with cases ascertained through the provincial cancer registry and controls randomly selected from a population-based listing or by random-digit dialing. A risk estimate of 1.10 (95% CI, 0.98–1.23) was reported for current smokers versus women with no history of active or passive smoking. A significantly increased risk was found for older age at smoking initiation (≥26 years vs. a no active/no passive group) (OR = 1.26; 95% CI, 1.03–1.55), but there were no associations at younger ages of initiation (<12 years: OR = 0.88; 95% CI, 0.59–1.31; 12–15 years: OR = 1.02; 95% CI, 0.90–1.16; 16–20 years: OR = 1.12; 95% CI, 1.01–1.24). There was a significant risk of breast cancer for smoking initiated more than 5 years before first birth (OR = 1.16; 95% CI, 1.04–1.31), and for smoking initiated after first birth (OR = 1.24; 95% CI, 1.02–1.52). These results do not support the hypothesis that early initiation of smoking and smoking before first birth are more strongly associated with risk of breast cancer than are later initiation and initiation of smoking after first birth.

Johnson and colleagues (2000), in a study in eight Canadian provinces, ascertained 2,317 cases through the provincial tumor registries in the mid-1990s. Controls (2,438) were randomly sampled from health plan listings, a property assessment database, or by random-digit dialing. Extensive data were collected via a mailed questionnaire on active smoking and exposure to secondhand smoke. The analyses of cigarette smoking status used two reference groups: never smoker and no active/no passive exposure. Only the no active/no passive exposure referent was used for age at smoking initiation, number of cigarettes smoked per day, duration of smoking, pack-years of smoking, and number of years since quitting smoking. In general, risk estimates were higher when using the no active/no passive referent group than when using the never smoker referent group. Among premenopausal women, adjusted estimates (using no active/no passive as the referent) were higher for former smokers (OR = 2.6; 95% CI, 1.3–5.3) than for current smokers (OR = 1.9; 95% CI, 0.9–3.8); estimates for postmenopausal women were marginally higher for current smokers (OR = 1.6; 95% CI, 1.0–2.5) than for former smokers (OR = 1.4; 95% CI, 0.9–2.1). As for other measures of smoking (using no active/no passive exposure as the referent), premenopausal women had risk estimates at least 20% higher than postmenopausal women for current and former smoking status, age at smoking initiation, number of cigarettes smoked per day, duration of smoking, and number of years since quitting smoking. The study oversampled women younger than 55 years of age, so it is one of only a few with sufficient statistical power to detect associations among premenopausal women.

Only two studies reported results that were stratified by race/ethnicity. In one, Mechanic and colleagues (2006) provided data from Phases I and II of the Carolina Breast Cancer Study, a study that examined former and current smoking among 894 African American and 1,414 non-Hispanic White women. These cases were ascertained through the North Carolina Central Cancer Registry, and population-based controls (n = 2,022) were selected from motor vehicle and Health Care Financing Administration (now the Centers for Medicare & Medicaid Services) listings. This report serves as an update to the study by Marcus and colleagues (2000), which provided age and race-adjusted estimates from Phase I. In the study by Mechanic and colleagues (2006), risk for breast cancer was significantly increased in African American women who were former smokers (OR = 1.80; 95% CI, 1.30–2.50) or who had smoked more than 20 years (OR = 1.80; 95% CI, 1.20–2.60). In contrast, risk was not significantly elevated for White women who were former smokers (OR = 1.20; 95% CI, 0.90–1.50) or who had smoked for more than 20 years (OR = 1.10; 95% CI, 0.90–1.50). Increased risk was not significantly associated with current smoking for either racial group.

Slattery and colleagues (2008) conducted a population-based case-control study in Arizona, Colorado, New Mexico, and Utah. This study provided data on the risk of breast cancer associated with smoking status, pack-years of smoking, age at smoking initiation, and smoking before first pregnancy. Among women with a first primary breast cancer who had data for smoking, 798 were Hispanic/American Indian and 1,527 were non-Hispanic White. Cases were ascertained from state or national cancer registries (e.g., NCI's SEER Program). Population-based controls were randomly sampled, of which 924 Hispanics/American Indians and 1,601 non-Hispanic Whites had data for smoking. Among premenopausal non-Hispanic White women, risk for breast cancer was significantly increased among ever smokers (OR = 1.3; 95% CI, 1.0–1.7), those who smoked before first pregnancy (OR = 1.4; 95% CI, 1.0–1.9), and those who accumulated more than 15 pack-years of smoking (OR = 1.6; 95% CI, 1.1–2.4). The study did not find any significant associations with breast cancer in premenopausal Hispanic and American Indian women or in postmenopausal non-Hispanic White or Hispanic/American Indian women.

Results from the three remaining large case-control studies are inconsistent. Gammon and colleagues (2004a), who reported results from the Long Island Breast Cancer Study Project for 1,356 cases and 1,383 population-based controls, found that risk for breast cancer was not significantly increased among active/current smokers using a

no active/no passive exposure referent regardless of the number of cigarettes per day, pack-years of smoking, age at smoking initiation, or smoking before first pregnancy. Significant associations were not found in a variety of subgroups, even after stratifying by menopausal status, BMI, alcohol use, use of HRT, use of oral contraceptives, family history, and age at reference date. In Los Angeles, Prescott and colleagues (2007), who conducted a case-control study of 1,728 cases and 441 controls, did not find significant associations between risk for breast cancer and smoking status, duration of smoking, age at smoking initiation, or smoking before first pregnancy. In contrast, Band and colleagues (2002) reported significant associations between risk for breast cancer and ever smoking (OR = 1.50; 95% CI, 1.09–2.07) and smoking for at least 20 years or more (OR = 1.60; 95% CI, 1.08–2.37) in premenopausal but not postmenopausal women based on responses from 1,018 cases and 1,025 controls who participated in a study conducted in British Columbia, Canada. There were no significant associations between risk and age at smoking initiation, but smoking before first pregnancy was significant for premenopausal women (OR = 1.51; 95% CI, 1.07–2.13) but not for postmenopausal women.

Six additional but smaller studies (<1,000 cases) that were conducted in the United States are notable for their findings (Lash and Aschengrau 2002; Egan et al. 2003; Li et al. 2005; Rollison et al. 2008; Ahern et al. 2009; Brown et al. 2010). In one, Li and colleagues (2005) examined a sample of 975 cases and 1,007 controls in Washington state and found a significantly increased risk (30% in each instance) for breast cancer among ever smokers, those who smoked, those 20–39 years of age, those who started smoking before age 20, and those who smoked before their first full-term birth. In addition, women who reported 20 or more pack-years of smoking and a history of HRT involving both estrogen and progestin had increased risk for breast cancer. The study by Lash and Aschengrau (2002) stands out because it found a significant inverse association for ever smoking (OR = 0.72; 95% CI, 0.55–0.95). That 2002 study conflicts, however, with a 1999 study (OR = 2.0; 95% CI, 1.1–3.6) in the same geographic area of Cape Cod, Massachusetts, carried out by the same team (Lash and Aschengrau 1999). Both studies included deceased cases and controls for which information about smoking was collected from proxies. However, the 2002 study, unlike the 1999 study, did not provide information about the fraction of data collected from proxy respondents. Thus, the results of the 2002 study could have been affected by information bias.

In a report from the Collaborative Breast Cancer Study, a population-based study conducted in Maine, Massachusetts, New Hampshire, and Wisconsin between 1988–1991 (Baron et al. 1996), Egan and colleagues (2003)

analyzed data from the Massachusetts and Wisconsin sites (791 cases, 797 controls) for effect modification of smoking risk by *NAT2* genotype. Not accounting for genotype, this study found a significantly increased risk for ever smokers (OR = 1.37; 95% CI, 1.12–1.69) and for women with more than 25 pack-years of smoking (OR = 1.54; 95% CI, 0.87–2.71). Results for the latter variable were OR = 1.54 (95% CI, 0.87–2.71) for premenopausal women and OR = 1.53 (95% CI, 1.10–2.13) for postmenopausal women. In a subsequent report, Ahern and colleagues (2009) analyzed data from only the Massachusetts site in the Collaborative Breast Cancer Study (557 cases, 432 controls) but did not find an association between pack-years of active smoking (OR = 0.90; 95% CI, 0.7–1.3 for >23 pack-years) and risk of breast cancer. However, this report was focused mainly on effects or associations with passive smoking.

The study by Rollison and colleagues (2008) reported an increased risk for breast cancer among ever smokers (OR = 1.43, 95% CI, 1.03–1.99). The authors attempted to compare results based on a no active/no passive to a no active-only reference group but the sample size was too small to provide sufficient statistical power to make an evaluation. Brown and colleagues (2010) conducted a case-control study of risk factors for breast cancer among Asians (Chinese, Filipino, Japanese) who immigrated to San Francisco-Oakland, California; Los Angeles, California; or Oahu, Hawaii. Just over one-half of the women in the study (54% of cases; 58% of controls) were born in Asia (China, Taiwan, Hong Kong, Macau, Japan, the Philippines, Southeast Asia, the Malaysian Peninsula, Singapore, or India) as opposed to Western or Western-style countries (such as those in North America or Europe or the nations of Australia and New Zealand). Women born in Asia and more recent migrants (<8 years) to the West had a lower risk of breast cancer regardless of smoking history than women born and raised in the West or a Western-style country. The overall OR for ever smoking was 1.2 (95% CI, 0.9–1.6). The only significant association between smoking and breast cancer was for age at initiation of younger than 16 years of age (OR = 2.92; 95% CI, 1.1–7.9), but this was based on a very small stratum (11 cases, 9 controls).

European Studies

Since 2000, three large (>1,000 cases) population based case-control studies have been conducted in Europe: one each in Germany (Andonova et al. 2010; Rabstein et al. 2010), Sweden (Magnusson et al. 2007), and Poland (Lissowska et al. 2006). Andonova and colleagues (2010) reported results from the Gene Environment Interaction and Breast Cancer in Germany (GENICA) study that included estimates of risk for breast cancer for former (OR = 0.95; 95% CI, 0.75–1.19) and current (OR =

0.84; 95% CI, 0.66–1.06) smoking using data for 1,021 cases and 1,015 controls in the greater Bonn region. This report and a companion report (Rabstein et al. 2010) were restricted to those subjects with available DNA and are further described in the section on genetic susceptibility.

Magnusson and colleagues (2007) ascertained 3,345 cases from six regional cancer registries and randomly selected 3,454 controls from a governmental population listing in Sweden. The study found few significant or consistent associations between risk of breast cancer and current or former smoking, duration of smoking, pack-years of smoking, age at initiation of smoking, or smoking before first full-term birth. However, data were missing for nearly 17% of cases and 25% of controls. The higher rate of missing data in controls was due partly to the use of a telephone interview that did not collect data for alcohol consumption and perhaps other covariates. In the Polish study, Lissowska and colleagues (2006) did not obtain significant results for all women considered together. However, among women younger than 45 years of age (n = 511), significantly increased risks were observed for current smoking (OR = 2.03; 95% CI, 1.40–2.95), the highest level of duration of smoking (>20 years: OR = 2.33; 95% CI, 1.32–4.13), smoking before first pregnancy (OR = 2.03; 95% CI, 1.40–2.94), and ever smoking approached statistical significance (OR = 2.40; 95% CI, 1.00–5.72). It is difficult to interpret some of these associations due to conflicting findings across levels of these exposures; for example, risks were also increased for duration of smoking less than 10 years (OR = 1.57; 95% CI, 1.01–2.44) and for smoking after first pregnancy (OR = 2.40; 95% CI, 1.27–4.53). Kruk (2007) also conducted a clinic-based study in Poland in which the control group was characterized by a higher prevalence of smoking than those in the general population. This study found some of the highest significant risks to date among women who smoked 10 or more cigarettes per day. Here, the ORs were 2.55 (95% CI, 1.81–3.60) for premenopausal women and 1.78 (95% CI, 1.33–2.37) for postmenopausal women.

In England, Roddam and colleagues (2007) conducted a population-based study of 639 cases, 36–45 years of age, with 640 age-matched controls. Significant associations were not detected for former smokers (OR = 1.15; 95% CI, 0.87–1.53) or current smokers (OR = 1.04; 95% CI, 0.79–1.36), age at initiation of smoking, duration of smoking, or number of cigarettes smoked per day. Data for duration of smoking and age at smoking initiation were analyzed as continuous variables. Thus, the results were not combined with those from other studies in generating summary estimates. The OR for former smokers, when calculated using a no passive/no active exposure reference group, was slightly lower (OR = 1.12; 95% CI, 0.72–1.73)

for women with no passive exposure, and it decreased a bit more for women reporting passive exposure (OR = 1.09; 95% CI, 0.75–1.56). Interpreting the importance of the differences among the various estimates is difficult because none are statistically significant and the CIs overlap. Kropp and Chang-Claude (2002) evaluated the same smoking measures with a no active/no passive reference group. Their estimate for former smokers was comparable to that of Roddam and colleagues (2007) but was considerably higher for current smokers (OR = 1.47; 95% CI, 0.99–2.20). Last, Cerne and colleagues (2011) reported results from a clinic-based case-control study of breast cancer among 784 cases and 709 controls among postmenopausal Slovenian women. This report was focused on the effects of HRT, but an estimate was provided for smoking at least 10 cigarettes per day, adjusting for age and education only (OR = 1.70; 95% CI, 1.20–2.43). Notably, the reference group of nonsmokers included former smokers.

Asian Studies

Two small case-control studies from Asia were published between 2000 and 2011. For ever smoking, the study conducted in Manila, the Philippines (Gibson et al. 2010), reported an RR of 1.3 (95% CI, 0.6–2.9), and a study in northeast India (Kaushal et al. 2010) reported an RR of 1.15 (95% CI, 0.62–2.13).

Adjustment for Selected Covariates

Breast cancer is recognized as a heterogeneous disease with many associated risk factors (Hankinson and Hunter 2001; Brinton et al. 2002; Spicer and Pike 2005; Hortobagyi et al. 2006). Some of these risk factors have complex relationships with cancer of the breast, and the direction of their associations may differ according to characteristics such as breast cancer phenotype, age, menopausal status, and race/ethnicity. Established risk factors include:

- increasing age;

- family history of breast cancer in first-degree relatives;

- increased levels of endogenous estrogen;

- history of benign breast disease;

- mammographically dense breasts;

- less frequent screening;

- history of ionizing radiation exposure to the chest;

- various reproduction-related factors—increased risk with younger age at menarche (<12 years of age), older age at menopause (>54 years of age), older age at first pregnancy or live birth (>30 years of age), no history of breast feeding or a short duration of lactation, nulliparity, and decreased risk with increased number of pregnancies;

- higher socioeconomic status (e.g. higher level of education and/or family income);

- use of exogenous hormones (HRT, combined estrogen/progesterone oral contraceptives); and

- increased body size among postmenopausal women (as determined by height, weight, BMI, waist circumference, waist/hip ratio).

Studies have also demonstrated a modestly increased risk for breast cancer, on the order of 25–30%, associated with low level of physical activity (Friedenreich and Cust 2008) and on the order of nearly 50% with intake of 45 or more grams of alcohol per day (Collaborative Group on Hormonal Factors in Breast Cancer et al. 2002; Baan et al. 2007). IARC (2002) has concluded that alcohol consumption is a causal risk factor for breast cancer; additionally, Volume 6 of the *IARC Handbook on Cancer Prevention* concluded that regular physical activity reduces the risk of breast cancer. Many of these factors show a complex pattern of association that depends on timing in relation to other exposures, specifically increased estrogen levels, duration of exposure, and menopause. Differences in the distributions of these factors between women who smoke and those with no history of active smoking are likely to vary across populations; to the extent possible, the potential for confounding has been considered in individual studies and in the meta-analyses.

The great majority of cohort and case-control studies published since 2000 and described in this report (Tables 6.14*S* and 6.15*S*) either adjusted for, or evaluated the need for adjustment of, relevant confounders. Reproductive factors and family history are well-established, strong risk factors for breast cancer (Spicer and Pike 2005). In addition, since 2000 an increasing number of studies have demonstrated that alcohol use and obesity are important risk factors for breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer et al. 2002). In a review by Kendall and colleagues (2007), the authors found that higher BMI is associated with increased endogenous estradiol levels among postmenopausal women. Although they did not find a clear relationship between alcohol use and estrogen levels, there was an apparent positive trend with increasing alcohol consumption (Kendall et al. 2007). All cohort studies described in this report adjusted for at least one reproductive factor and BMI; most of them either adjusted for or stratified on menopausal status; and all but one adjusted for alcohol consumption (Lawlor et al. 2004). Three cohort studies (Table 6.14*S*) did not adjust for family history (Manjer et al. 2000b; Lawlor et al. 2004; Gram et al. 2005).

The selection of covariates for adjustment varied across case-control studies (Table 6.15*S*). Some studies did not adjust for reproductive factors (Delfino et al. 2000; Alberg et al. 2004; Li et al. 2005; Metsola et al. 2005), alcohol intake (Delfino et al. 2000; Zheng et al. 2002b; van der Hel et al. 2003b; Alberg et al. 2004; Metsola et al. 2005), body size (Delfino et al. 2000; van der Hel et al. 2003b; Alberg et al. 2004; Metsola et al. 2005; Mechanic et al. 2006; Prescott et al. 2007), or family history (Johnson et al. 2000; van der Hel et al. 2003b; Alberg et al. 2004; Li et al. 2005; Metsola et al. 2005; Slattery et al. 2008). Five case-control studies did not adjust, stratify, or match on menopausal status, but in these studies the age range included both premenopausal and postmenopausal women (Marcus et al. 2000; Lash and Aschengrau 2002; Alberg et al. 2004; Metsola et al. 2005; Magnusson et al. 2007). Several studies explored models that adjusted for multiple covariates but reported results for only the most parsimonious models, adjusting for covariates that changed point estimates on the order of 5–15% (Marcus et al. 2000; van der Hel et al. 2003b; Gammon et al. 2004a; Li et al. 2005; Lissowska et al. 2006; Mechanic et al. 2006; Kruk 2007; Magnusson et al. 2007; Rollison et al. 2008; Young et al. 2009). Most studies with findings that were considered for inclusion in the meta-analyses made an effort to statistically detect and adjust for confounders within the data. However, the methods for considering potential confounders varied across studies and the basis for selecting the final, adjusted model was not always explicit.

Meta-Analysis of Breast Cancer Risk Associated with Measures of Active Smoking

All available non-overlapping cohort study reports published prior to 2012 and case-control study reports published from 2000–2011 were included in meta-analyses for this report. These timeframes were selected to identify the most recent evidence that was specifically relevant to associations between risk for breast cancer and active and passive smoking. The older literature has been repeatedly reviewed; the majority of studies published before 2000

were either cross-sectional or case-control in design and were not considered for inclusion in the meta-analysis. Reports from cohort studies published prior to 2000 were evaluated for inclusion; most of these have been superseded by subsequent reports. Table 6.16*S* provides a listing of the 65 reports from case-control and cohort studies. Twenty-six reports overlapped with results on the same study population, and of these, 11 were included in the meta-analyses because they were either the most recent or complete reports from their study. In the case of 1 cohort study (NHS-I) and 1 case-control study (Collaborative Breast Cancer Study), 2 reports contributed to separate meta-analyses because they offered different measures (NHS-I: Egan et al. 2002 and Xue et al. 2011; Collaborative Breast Cancer Study: Egan et al. 2003 and Ahern et al. 2009). Three cohort studies (Mills et al. 1989b; Land et al. 1994; Thomas et al. 1997), which were included in the report by the Collaborative Group on Hormonal Factors in Breast Cancer and colleagues (2002), were excluded from the present report because the individual estimates were not published in the original reports and they were combined into an 'other' category for the Collaborative Report. Four studies (1 cohort, 3 case-control) were included in only the meta-analysis of smoking before a first full-term pregnancy or first birth (Innes and Byers 2001; Fink and Lash 2003; Lawlor et al. 2004; DeRoo et al. 2011a). Thus, a total of 46 separate reports were included in the initial analysis of ever smoking. The total number included in each subsequent meta-analysis depended on whether a risk estimate was reported in a study for the measure of smoking. RR estimates were pooled across categories of exposure to fit common definitions of ever smoking, smoking status (former or current), duration of smoking, cigarettes smoked per day, pack-years of smoking, age at smoking initiation, and smoking before first pregnancy. Data are provided in Table 6.16*S* on studies affected by design and analysis issues, including small sample size, a mixed reference group (former smokers and nonsmokers combined), inadequate covariate adjustment, use of proxy subject reports, issues associated with exposure category cutpoints, and the presence of extreme outliers.

The DerSimonian and Laird (1986) procedure for random-effects meta-analysis was used to calculate summary estimates. The random-effects model was selected because the studies included in the meta-analysis showed substantial variation in type and quality of design, time period, geographic setting, composition of population, ascertainment of cases, selection of controls for case-control studies, and definition and measurement of smoking exposure. Whereas a fixed-effects model assumes that all studies are estimating the same true effect and that

differences between studies are the result of random variation (precision) within studies, a random-effects model assumes that between-study variation is partly due to factors that influence the magnitude of the *true* effect within each study, resulting in a distribution of true effects across studies. The fixed-effects model gives greater weight to larger, more precise studies, whereas the random-effects model dampens to some degree the influence of these larger studies relative to smaller ones. Additionally, the summary estimates from random-effects models generally have broader CIs than those from fixed-effects models, making the former method intrinsically more conservative (Borenstein et al. 2009). The random-effects model accounts for heterogeneity among studies, which can be quantified, for example, in the Q-test statistic. When heterogeneity is low, the random-effects model converges with the fixed-effects model.

Meta-analyses were conducted in STATA 11.0 (STATA Corp., College Station, TX, USA) using the meta STATA command (Sterne 2009). The meta-funnel STATA command was used to create funnel plots for visual assessment of publication bias and outliers. Between-study heterogeneity was assessed with Cochran's $\chi 2$ test, reported as the Q-test statistic, and bias was assessed formally using Egger's statistical test (Egger et al. 1997) and Begg's rank correlation test (Begg and Mazumdar 1994), with the latter calculated via the metabias STATA command. The Begg test is reported to have low power when the number of studies is small. The Egger test is more powerful but also biased and can produce false-positive results (Deeks et al. 2005). Sensitivity analyses considered study design, prevalence of exposure, sample size, and measurement of exposure effect. Results for the Begg and Egger tests are included as a note in figures as appropriate. Summary estimates from random effects models are reported for all meta-analyses.

Ever Smoking

If not reported, a measure for ever smoking was calculated for all 46 studies by pooling available data on smoking status, smoking duration, cigarettes smoked per day, or pack-years of smoking, with the exception of four studies that provided data only for exposure before or during first pregnancy (Table 6.16*S*). A meta-analysis was conducted of nonoverlapping reports from all cohort studies through 2011, as well as case-control studies published from 2000–2011, for ever smoking, resulting in a summary estimate with significant heterogeneity (p_h <0.001): RR = 1.12 (95% CI, 1.07–1.17; n = 46) (Table 6.17*S*, Figure 6.28). From visual inspection, the funnel plot in Figure 6.29 shows no sign of skewness, indicating that publica-

Figure 6.28   Forest plot showing association between ever smoking and risk for breast cancer, based on cohort studies published before 2012 and case-control studies published from 2000 to 2011 (n = 46)

Study	Year
Lash & Aschengrau	2002 ^
Lin et al.	2008 *
Delfino et al.	2000 ^
Hiatt et al.	1988 *
Alberg et al.	2004 ^
van den Brandt et al.	1995 *
Andonova et al.	2010 ^
Prescott et al.	2007 ^
Magnusson et al.	2007 ^
Gram et al.	2005 *
Engeland et al.	1996 *
Schatzkin et al.	1989 *
Nordlund et al.	1997 *
Vatten & Kvinnsland	1990 *
Ahern et al.	2009 ^
Slattery et al.	2008 ^
Gammon et al.	2004a^
Xue et al.	2011 *
Sillanpaa et al.	2005a^
Cui et al.	2006 *
Roddam et al.	2007 ^
Zheng et al.	2002a^
Lissowska et al.	2006 ^
Young et al.	2009 ^
Luo et al.	2011b*
Johnson et al.	2000 ^
Olson et al.	2005 *
Hiatt & Fireman	1986 *
Ha et al.	2007 *
Kaushal et al.	2010 ^
Al-Delaimy et al.	2004b*
Reynolds et al.	2004b*
Manjer et al.	2000b*
Band et al.	2002 ^
Mechanic et al.	2006 ^
Brown et al.	2010 ^
MWSCG	1999 *
Gibson et al.	2010 ^
Li et al.	2005 ^
Kropp & Chang-Claude	2002 ^
van der Hel et al.	2003b^
Rollison et al.	2008 ^
Hanaoka et al.	2005 *
Cerne et al.	2011 ^
Kruk	2007 ^
Morabia et al.	2000a^
Overall	

RR axis: .5   .7   1   1.4   2   3.5

RR

Note: * = cohort study; ^ = case-control study. Meta-analysis RR = 1.12 (95% CI, 1.07–1.17); Begg z = 0.48, p = 0.63; Egger bias = 0.44, p = 0.25. See Table 6.17S (*note a*) for studies excluded. Size of square is proportional to the weights used in the meta-analysis; error bars show the associated 95% CI. Solid vertical line represents the null value. Diamond represents the summary estimate and associated 95% CI. **MWSCG** = Million Women Study Collaborative Group; **RR** = relative risk.

Figure 6.29   Funnel plot for estimates in meta-analysis of ever smoking with risk for breast cancer, based on cohort studies published before 2012 and case-control studies published from 2000 to 2011 (n = 46)
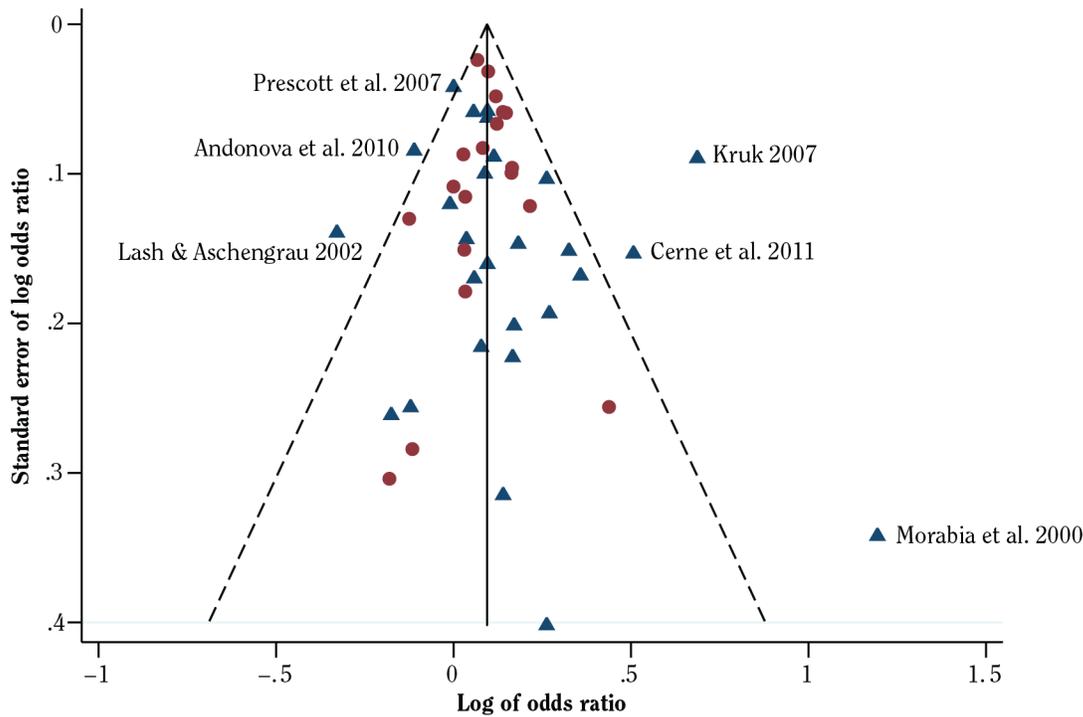
*Note:* ▎ = cohort study; ● = case-control study. Includes the same studies reported in Figure 6.28.

tion bias was not a significant issue. This finding was further confirmed by Begg's rank correlation test (z = 0.48, p = 0.63) and the Egger test (bias = 0.44, p = 0.25). Stratification by study design revealed that the heterogeneity was due primarily to variation among the 27 case-control studies (RR = 1.15; 95% CI, 1.06–1.25; p_h <0.001) than to variation among the 19 cohort studies (RR = 1.10; 95% CI, 1.07–1.13; p_h = 0.793).

Thirteen studies were excluded in the following sequence (some studies fell into more than one category).

1. Six cohort studies reported in the pooled analysis restricted to nondrinkers conducted by the Collaborative Group on Hormonal Factors in Breast Cancer and colleagues (2002) and for which there were no data available on smoking in the original report (van den Brandt et al. 1995; Engeland et al. 1996; Million Women Study Collaborative Group 1999).

2. Eight additional studies, three cohort (Schatzkin et al. 1989; Hanaoka et al. 2005; Lin et al. 2008) and five case-control (Delfino et al. 2000; Morabia et al.

2000; Alberg et al. 2004; Gibson et al. 2010; Kaushal et al. 2010), with less than 210 cases.

3. Two additional studies, one cohort (Vatten and Kvinnsland 1990) and one case-control (Cerne et al. 2011), with an estimate reported for only current smokers and for which the reference group appeared to mix never smokers with former smokers.

The summary estimate for the 12 cohort studies remaining (Table 6.17S) after the exclusion of the 7 studies that were restricted to nondrinkers had a small sample, or a mixed reference group did not change meaningfully from the overall estimate (RR = 1.10; 95% CI, 1.07–1.13; p_h = 0.717). For case-control studies, the RR was attenuated slightly (RR = 1.13; 95% CI, 1.04–1.23; p_h <0.001) when 6 were excluded that were either small (<210 cases), from Asia, or had a mixed reference group (Table 6.16S). The additional exclusion of a cohort study (Nordlund et al. 1997) that adjusted only for age and place of residence did not alter the summary RR for cohort studies. The funnel plot in Figure 6.29 indicates that the studies by Kruk

(2007) and Lash and Aschengrau (2002) are outliers. The case-control study by Lash and Aschengrau (2002) relied on proxy interviews for deceased cases. Kruk (2007), which was conducted in Poland, used clinic-based controls that were reported to have a higher percentage of smoking (33%) than in the general population (23%). However, a comparison of self-reported prevalence of cigarette smoking and cotinine saliva samples (cutpoint for active smoking—1.5 nanogram [ng]/milliliter [mL]) indicated that true prevalence may be underestimated in Poland by 4.4% (West et al. 2007). The removal of Kruk (2007) and Lash and Aschengrau (2002) resulted in a summary risk estimate of 1.08 (95% CI, 1.03–1.13) and decreased heterogeneity (p_h = 0.340) for case-control studies, without adding significant bias according to the Begg (z = 0.73, p = 0.46) and Egger (bias = 0.43, p = 0.19) tests (see notes for Figure 6.30). The RR for the combined case-control and cohort studies (n = 30) decreased to 1.09 (95% CI, 1.06–1.12; p_h = 0.500). In summary, the significant heterogeneity among studies for the association between ever smoking and breast cancer is attributable mainly to the study by Kruk (2007), which is the more extreme of the two outliers. Excluding this study substantially reduces heterogeneity and results in an attenuated summary estimate. When taken together, these 30 studies suggest that ever smoking increases the RR for breast cancer by a statistically significant average of 9% (Table 6.17*S*, Figure 6.30). These 30 reports remained as the baseline to be considered for the remaining meta-analyses.

No Active-Only Versus No Active/No Passive Exposure Referent Group

Wells (1991) first suggested that the most appropriate reference group would exclude women who were exposed to passive smoke because their inclusion would attenuate the association with active smoking. Morabia and colleagues (1996) first used this criterion in an analysis of data from a case-control study in Switzerland. Since then, other investigators have narrowed the definition of the reference group to women who report no active or passive smoking exposure. In this report, 5 cohort studies (Egan et al. 2002; Reynolds et al. 2004b; Gram et al. 2005; Hanaoka et al. 2005; Luo et al. 2011b) and 14 case-control studies (Morabia et al. 2000; Delfino et al. 2000; Johnson et al. 2000; Kropp and Chang-Claude 2002; Lash and Aschengrau 2002; Alberg et al. 2004; Gammon et al. 2004a; Sillanpaa et al. 2005a; Lissowska et al. 2006; Mechanic et al. 2006; Roddam et al. 2007; Rollison et al. 2008; Ahern et al. 2009; Young et al. 2009) included results based on a no active/no passive exposure reference group. Ten studies reported results for both reference groups that can be compared for ever smoking (Johnson

et al. 2000; Egan et al. 2002; Reynolds et al. 2004b; Gram et al. 2005; Hanaoka et al. 2005; Lissowska et al. 2006; Roddam et al. 2007; Rollison et al. 2008; Ahern et al. 2009; Luo et al. 2011b). Six compared estimates using the two referent groups by smoking status (Johnson et al. 2000; Egan et al. 2002; Reynolds et al. 2004b; Hanaoka et al. 2005; Roddam et al. 2007; Luo et al. 2011b), 1 did so by pack-years (Ahern et al. 2009), and 2 provided comparisons by duration, dose, and timing (Rollison et al. 2008; Luo et al. 2011b). Nine studies used only a no active/no passive reference group (Delfino et al. 2000; Morabia et al. 2000; Kropp and Chang-Claude 2002; Lash and Aschengrau 2002; Alberg et al. 2004; Gammon et al. 2004a; Sillanpaa et al. 2005a; Mechanic et al. 2006; Young et al. 2009). As noted previously, estimates for ever smoking were derived for some studies by pooling other exposure measures, such as former and current smoking. Additionally, the terminology for defining these reference groups (no active-only, no active/no passive) varies among studies, although the definitions are common.

The size of the reference group is greatly decreased when restricted to no active/no passive exposure because of the high prevalence of passive smoking exposure: most studies indicate that only about 10–20% of never smokers report no passive exposure. In a study by Arheart and colleagues (2008), an estimated 28% of people who reported no passive exposure were actually exposed based on serum cotinine levels, suggesting that the true no active/no passive group may be even smaller, particularly if considered in a lifetime context. No systematic analyses have been conducted to determine whether using only a small no active/no passive referent produces selection bias or sparse data bias (Greenland et al. 2000) as well as loss of statistical power, or whether statistical adjustment for passive smoking exposure in assessing active smoking is as efficient as having a no active/no passive referent. One exception may be Ahern and colleagues (2009), who estimated associations of active smoking with breast cancer using a restricted no active/no passive exposure reference group while also employing statistical adjustment for passive smoking exposure. Unfortunately, it is difficult to interpret the differences between the two approaches because only 30% of participants in that study had data for both active and passive smoking.

In the California Teachers Study cohort (Table 6.14*S*), the RRs for breast cancer in current smokers overall were both significant and quite similar with the two reference groups used: no active-only ("never") (RR = 1.32; 95% CI, 1.10–1.57) and no active/no passive (RR = 1.25; 95% CI, 1.02–1.53) (Reynolds et al. 2004b). In contrast, ORs for ever smokers (i.e., former or current) in Johnson and colleagues' (2000) population-based

Figure 6.30   Forest plot showing association between ever smoking and risk for breast cancer, based on cohort studies published before 2012 and case-control studies published from 2000 to 2011, excluding studies with design or analysis issues (n = 30)
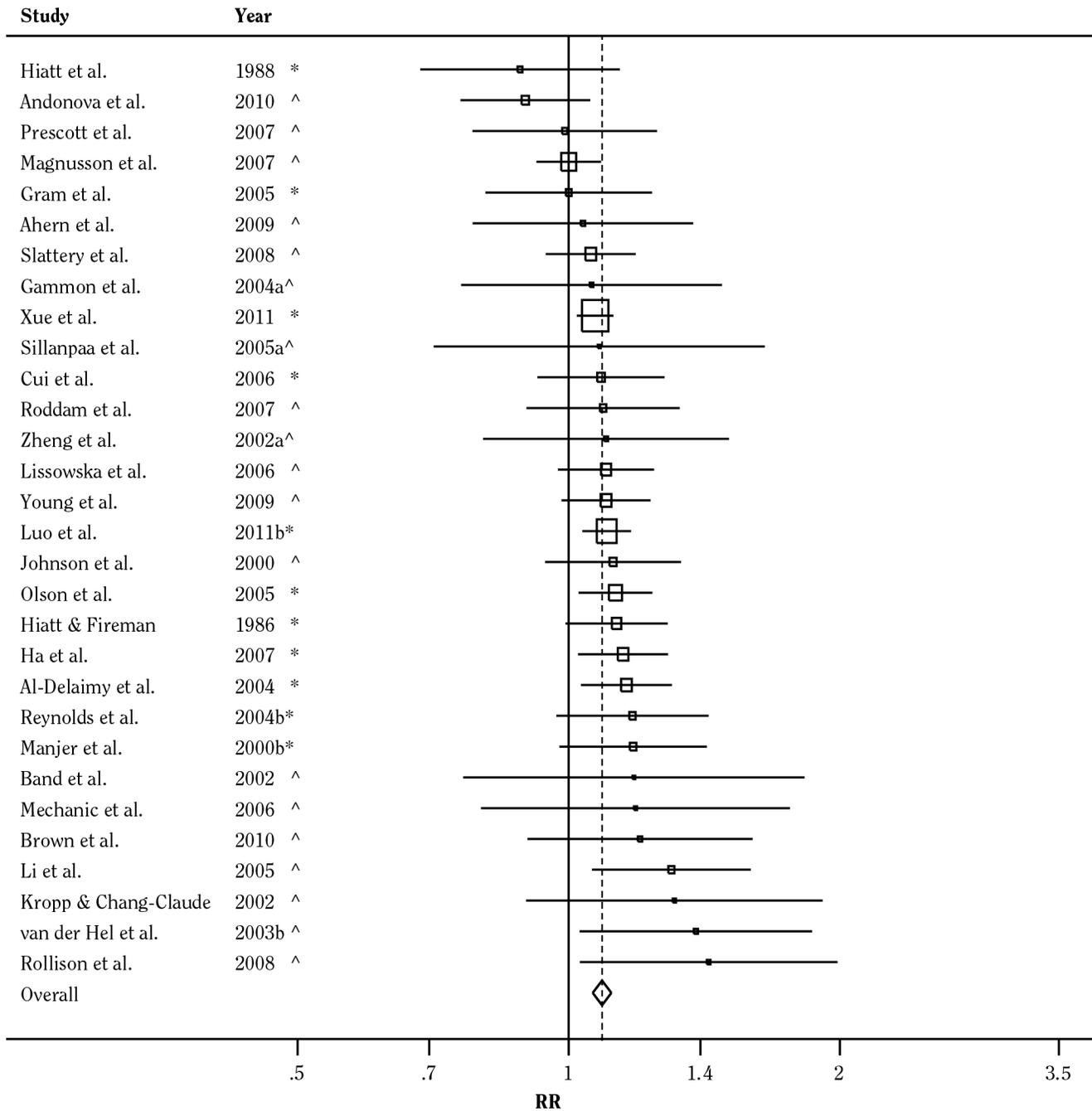
Note: * = cohort study; ^ = case-control study. Meta-analysis RR = 1.09 (95% CI, 1.06–1.12); Begg z = 0.73, p = 0.46; Egger bias = 0.43, p = 0.19. See Table 6.17S (*note c*) for studies excluded. Size of square is proportional to the weights used in the meta-analysis; error bars show the associated 95% CI. Solid vertical line represents the null value. Diamond represents the summary estimate and associated 95% CI. **CI** = confidence interval; **RR** = relative risk.

Canadian case-control study were 1.0 (95% CI, 0.8–1.3) for premenopausal women and 1.2 (95% CI, 1.0–1.4) for postmenopausal women when based on the no active-only ("never") reference group, versus 2.3 (95% CI, 1.2–4.5) for premenopausal women and 1.5 (95% CI, 1.0–2.3) for postmenopausal women when based on the no active/no passive exposure reference group. Although these results seem to suggest a strong effect when using a no active/ no passive exposure reference group, the estimates were based on a restricted subgroup of women (62% of the reference group) who were able to account for and report data for more than 90% of their lifetime residential passive smoking exposure. In addition, the no active/no passive reference group consisted of only 193 women (49 premenopausal and 144 postmenopausal women), compared with 2,292 women in the no active-only reference group.

Only two case-control studies have compared results for measures of smoking other than ever smoking or smoking status, but the results are difficult to interpret because of small samples and low statistical power (Rollison et al. 2008; Ahern et al. 2009). For cohort studies, Lin and colleagues (2008) compared results using the two different definitions of reference groups (no active/no passive, no active-only) in the Japan Collaborative Cohort Study for Evaluation of Cancer Risk and stated there was no difference in the estimates, but they did not provide numerical evidence. Luo and colleagues (2011b) reported findings for the only cohort study to date with parallel, multivariable adjusted analyses contrasting no active/no passive exposure with no active-only reference groups for multiple measures. The use of a no active/no passive exposure reference group resulted in a small but consistent increase in RR ranging from 2–10% for most measures of active smoking (ever, status, age at initiation, duration, cigarettes smoked per day, pack-years). The strongest effect of active smoking was for duration greater than 50 years, where the RR was 1.45 (95% CI, 1.06–1.98) using a no active/no passive exposure group compared with 1.35 (95% CI, 1.03–1.77) using a no active-only ("never") reference group. The analysis suggests that the use of a no active/no passive exposure reference group may provide a small benefit in control for confounding between active and passive smoking effects. However, this small gain in control of confounding is at the cost of statistical power. It has not been established whether statistical adjustment for passive exposure of estimates for the risk of active smoking adequately controls for this confounding. Additionally, the small, restricted subgroup with no active/no passive exposure could differ systematically for other confounders or modifiers that are not measured or adequately controlled. Luo and colleagues (2011b) did not systematically compare the subgroup of no active/no passive smokers with the rest of the

study population to determine whether there were any differences for other potential confounders such as race/ethnicity, education, alcohol consumption, or reproductive variables. This comparison, in fact, was not made in any of the studies that used a no active/no passive exposure reference group.

Meta-analyses were conducted to compare 27 studies reporting results based on a no active-only reference group with 15 studies reporting estimates based on a no active/no passive exposure reference group (Table 6.16*S*), after the 13 exclusions cited previously. The number of studies was further reduced to 25 for the no active-only and 14 for the no active/no passive exposure analyses with the exclusion of 3 studies (Nordlund et al. 1997; Lash and Aschengrau 2002; Kruk 2007) for reasons given above. The report by Egan and colleagues (2002) was used because the more recent report by Xue and colleagues (2011) did not report results using a no active/no passive exposure reference group. The RR for the no active-only exposure reference group was 1.09 (95% CI, 1.06–1.13; $p_h = 0.308$) (Table 6.17*S*, Figure 6.31). This estimate is slightly lower than that calculated for 14 studies using a no active/no passive exposure reference group (RR = 1.15; 95% CI, 1.09–1.21; $p_h = 0.572$) (Table 6.17*S*, Figure 6.32). Nine of the studies—4 of which were large cohort studies (Egan et al. 2002; Reynolds et al. 2004b; Gram et al. 2005; Luo et al. 2011b)—calculated estimates using both reference groups. These 9 studies were included in the two meta-analyses. Neither of these analyses was significantly affected by publication or small-study bias, according to Begg or Egger statistics (see notes for Figures 6.31 and 6.32; funnel plots not shown). These analyses suggest that the use of a restricted no active/no passive exposure reference group results in a small increase in estimates of the association between ever smoking and breast cancer.

Cigarette Smoking Status

A total of 25 studies reported estimates for current and former smoking; 20 used a no active-only and 5 a no active/no passive exposure reference group (Table 6.16*S*, Figures 6.33 and 6.34). The summary estimates were similar for current smokers (RR = 1.12; 95% CI, 1.08–1.16; $p_h = 0.347$) and former smokers (RR = 1.09; 95% CI, 1.05–1.13; $p_h = 0.062$) (Table 6.17*S*). Results for former smokers were virtually identical for the two study designs: cohort (RR = 1.09; 95% CI, 1.03–1.14; $p_h = 0.021$) and case-control (RR = 1.09; 95% CI, 1.03–1.16; $p_h = 0.354$). The summary estimate for current smokers in the 11 cohort studies (OR = 1.14; 95% CI, 1.10–1.18; $p_h = 0.746$) was higher than the estimate for those in the 14 case-control studies (OR = 1.07; 95% CI, 1.00–1.16; $p_h = 0.209$). Sensitivity analyses were conducted that excluded the 4 case-control studies (Kropp and Chang-Claude 2002; Gammon

Figure 6.31   Forest plot showing association between ever smoking and risk for breast cancer, based on the subset of cohort studies published before 2012 and case-control studies published from 2000 to 2011 with a no active-only referent group (n = 25)
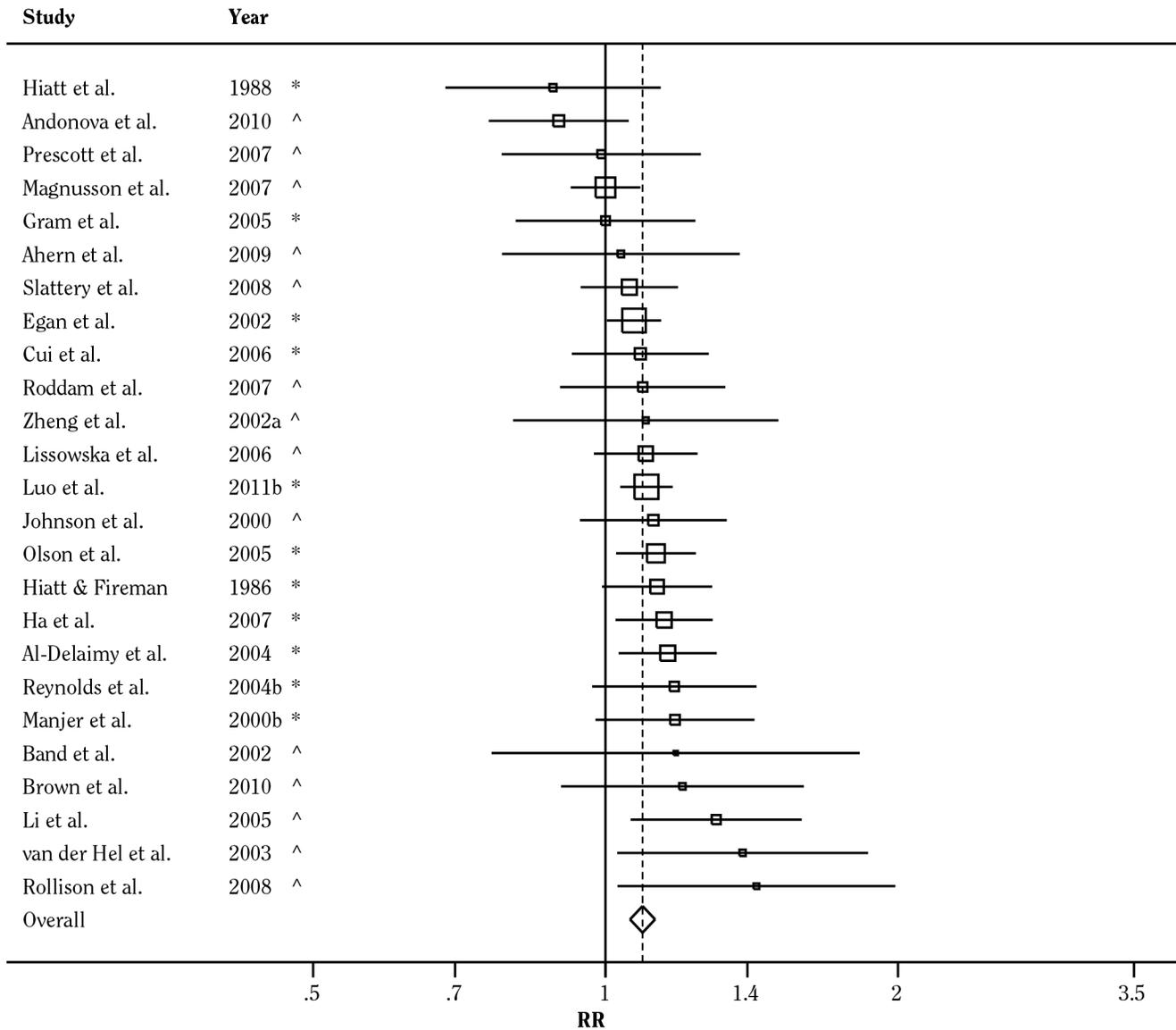
Note: * = cohort study; ^ = case-control study. Meta-analysis RR = 1.09 (95% CI, 1.06–1.13); Begg z = 0.70, p = 0.48; Egger bias = 0.43, p = 0.34. See Table 6.17S (*note d*) for studies excluded. Size of square is proportional to the weights used in the meta-analysis; error bars show the associated 95% CI. Solid vertical line represents the null value. Diamond represents the summary estimate and associated 95% CI. **CI** = confidence interval; **RR** = relative risk.

Figure 6.32   Forest plot showing association between ever smoking and risk for breast cancer, based on the subset of cohort studies published before 2012 and case-control studies published from 2000 to 2011 with a no active/no passive exposure referent group (n = 14)
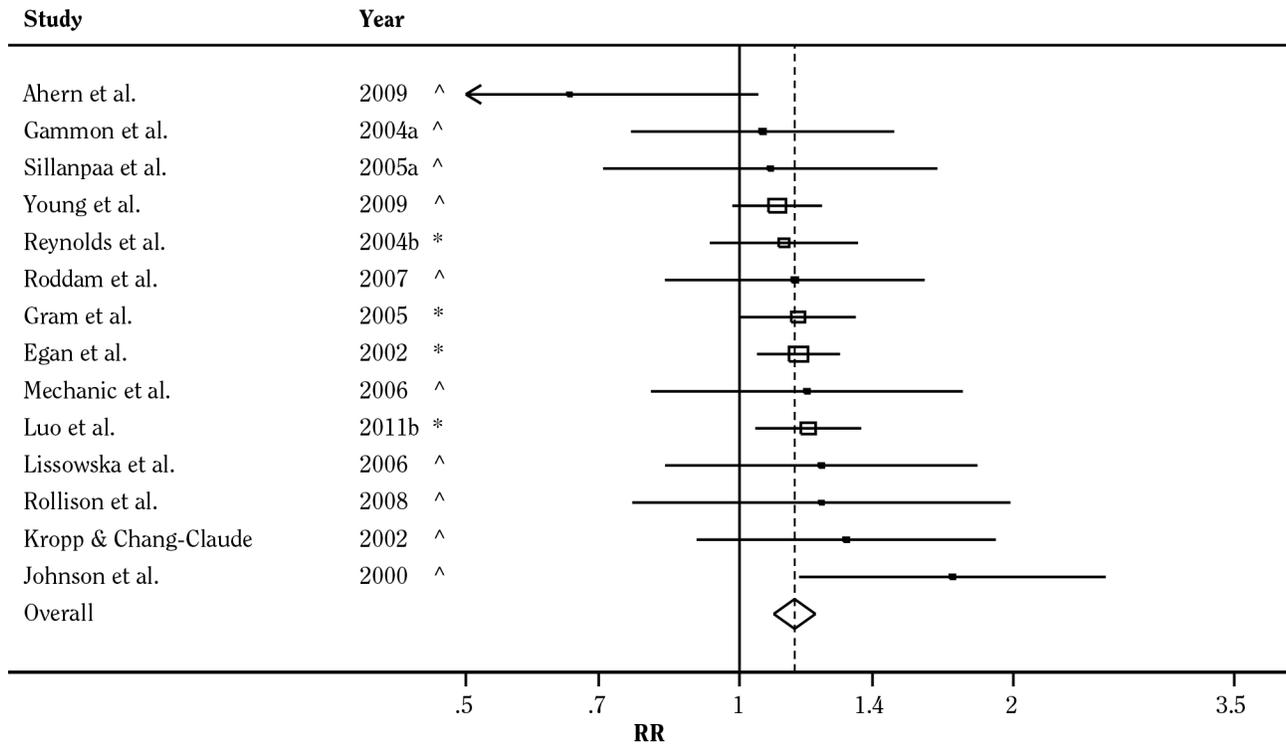
Note: * = cohort study; ^ = case-control study. Meta-analysis RR = 1.15 (95% CI, 1.09–1.21); Begg z = 0.05, p = 0.96; Egger bias = 0.04, p = 0.94. See Table 6.17*S* (*note e*) for studies excluded. There were nine studies with estimates reported for both a no active-only and a no active/no passive reference group (also shown in Figure 6.31). Size of square is proportional to the weights used in the meta-analysis; error bars show the associated 95% CI. Solid vertical line represents the null value. Diamond represents the summary estimate and associated 95% CI. **CI** = confidence interval; **RR** = relative risk.

et al. 2004a; Sillanpaa et al. 2005a; Mechanic et al. 2006) and 1 cohort study (Gram et al. 2005) with estimates based on only a no active/no passive exposure reference group. Excluding these studies did not meaningfully alter the overall results for either current smokers (RR = 1.11; 95% CI, 1.07–1.16) or former smokers (RR = 1.09; 95% CI, 1.04–1.13). There was significant heterogeneity among the cohort studies for the association with former smoking because of 1 study (Hiatt et al. 1988) with an outlying estimate (RR = 0.65; 95% CI, 0.47–0.89). The exclusion of this study, as well as the other 5 that were excluded, eliminated the heterogeneity (p_h = 0.220) but did not change the point estimate. The association between risk for breast cancer and former smoking may be attenuated relative to current smoking because the former association includes women with variable lengths of time since cessation. These results suggest that current smoking is associated with an increase in the RR for breast cancer by an average of 12%, and former smoking with an increase by an average of 9%. These results are similar to those for ever smoking. Neither of these analyses was significantly affected by publication or small-study bias according to Begg or Egger statistics (see notes for Figures 6.33 and 6.34).

Duration of Cigarette Smoking

Several cohort studies support an association between risk for breast cancer and long duration of smoking exposure (Table 6.14*S*). The Canadian National Breast Screening Study (RR = 1.50; 95% CI, 1.19–1.89; p trend = 0.0003 for ≥40 years) (Cui et al. 2006) and the NHS-II (RR = 1.21; 95% CI, 1.01–1.45; p trend = 0.04 for ≥20 years) (Al-Delaimy et al. 2004) both showed

Figure 6.33   Forest plot showing association between current smoking and risk for breast cancer, based on the subset of cohort studies published before 2012 and case-control studies published from 2000 to 2011 (n = 25)
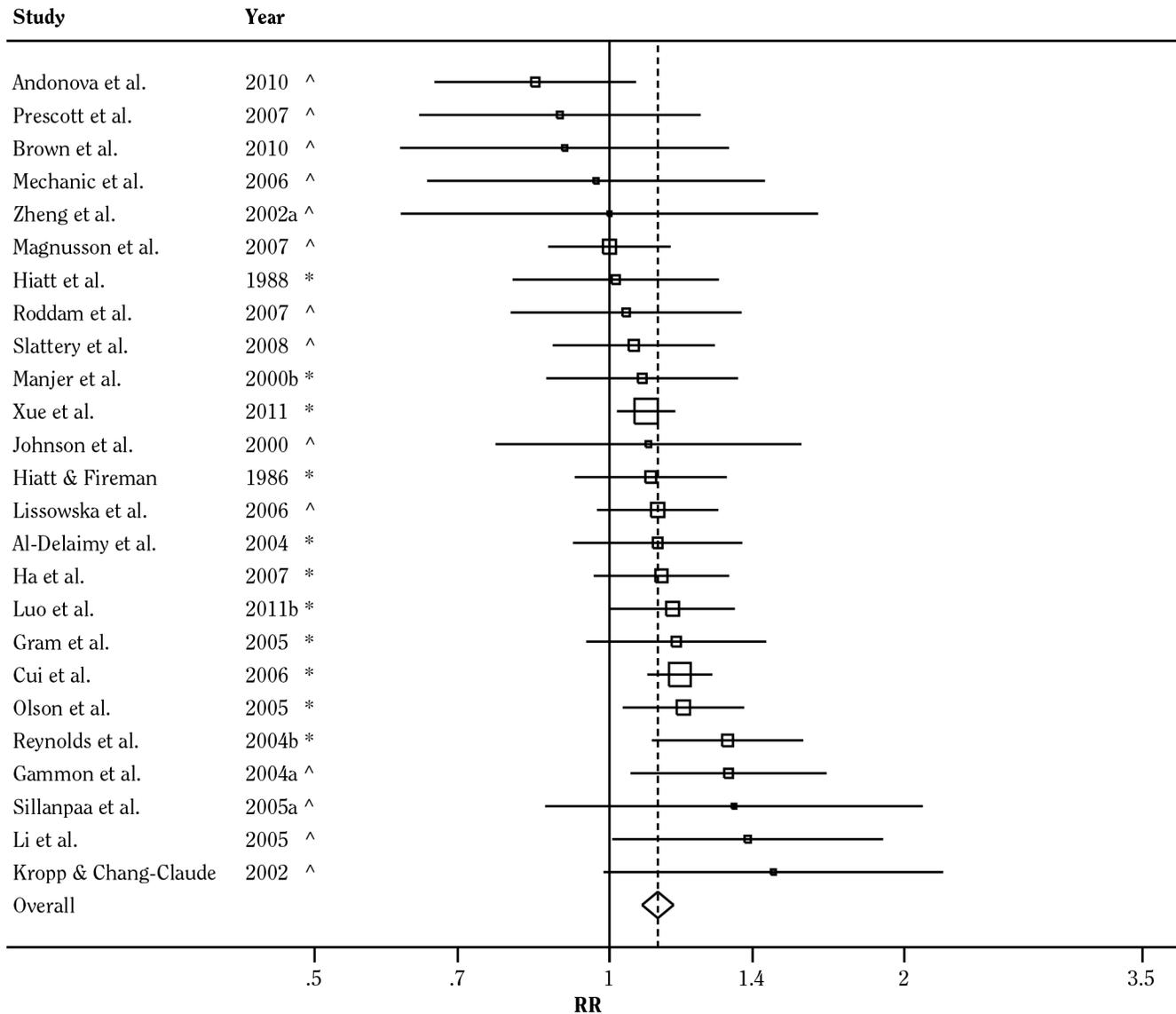
Note: * = cohort study; ^ = case-control study. Meta-analysis RR = 1.12 (95% CI, 1.08–1.16); Begg z = -0.75, p = 0.46; Egger bias = -0.21, p = 0.62. See Table 6.17S (*note f*) for studies excluded. Size of square is proportional to the weights used in the meta-analysis; error bars show the associated 95% CI. Solid vertical line represents the null value. Diamond represents the summary estimate and associated 95% CI. **CI** = confidence interval; **RR** = relative risk.

increased risks that were significant at approximately 16 and 10 years of follow-up, respectively. An earlier analysis of the Canadian cohort by Terry and colleagues (2002a) showed risk to be approximately 7% higher for 40 or more years of smoking (RR = 1.61; 95% CI, 1.19–2.19; p for trend = 0.009), but the 2002 report was based on 1,893 fewer cases than that of the report by Cui and colleagues (2006). The two analyses adjusted for the same covariates. Although Egan and colleagues (2002) did not observe a significant trend for the association between risk for breast cancer and duration of smoking (p for trend = 0.18) in the NHS-I, the recent updated analysis by Xue and

Figure 6.34 **Forest plot showing association between former smoking and risk for breast cancer, based on the subset of cohort studies published before 2012 and case-control studies published from 2000 to 2011 (n = 25)**

Study	Year	
Hiatt et al.	1988	*
Sillanpaa et al.	2005a	^
Andonova et al.	2010	^
Magnusson et al.	2007	^
Cui et al.	2006	*
Prescott et al.	2007	^
Xue et al.	2011	*
Gammon et al.	2004a	^
Reynolds et al.	2004b	*
Olson et al.	2005	*
Lissowska et al.	2006	^
Luo et al.	2011b	*
Zheng et al.	2002a	^
Slattery et al.	2008	^
Johnson et al.	2000	^
Roddam et al.	2007	^
Kropp & Chang-Claude	2002	^
Gram et al.	2005	*
Ha et al.	2007	*
Al-Delaimy et al.	2004	*
Hiatt & Fireman	1986	*
Li et al.	2005	^
Manjer et al.	2000b	*
Mechanic et al.	2006	^
Brown et al.	2010	^
Overall		

RR axis: .5   .7   1   1.4   2   3.5

RR
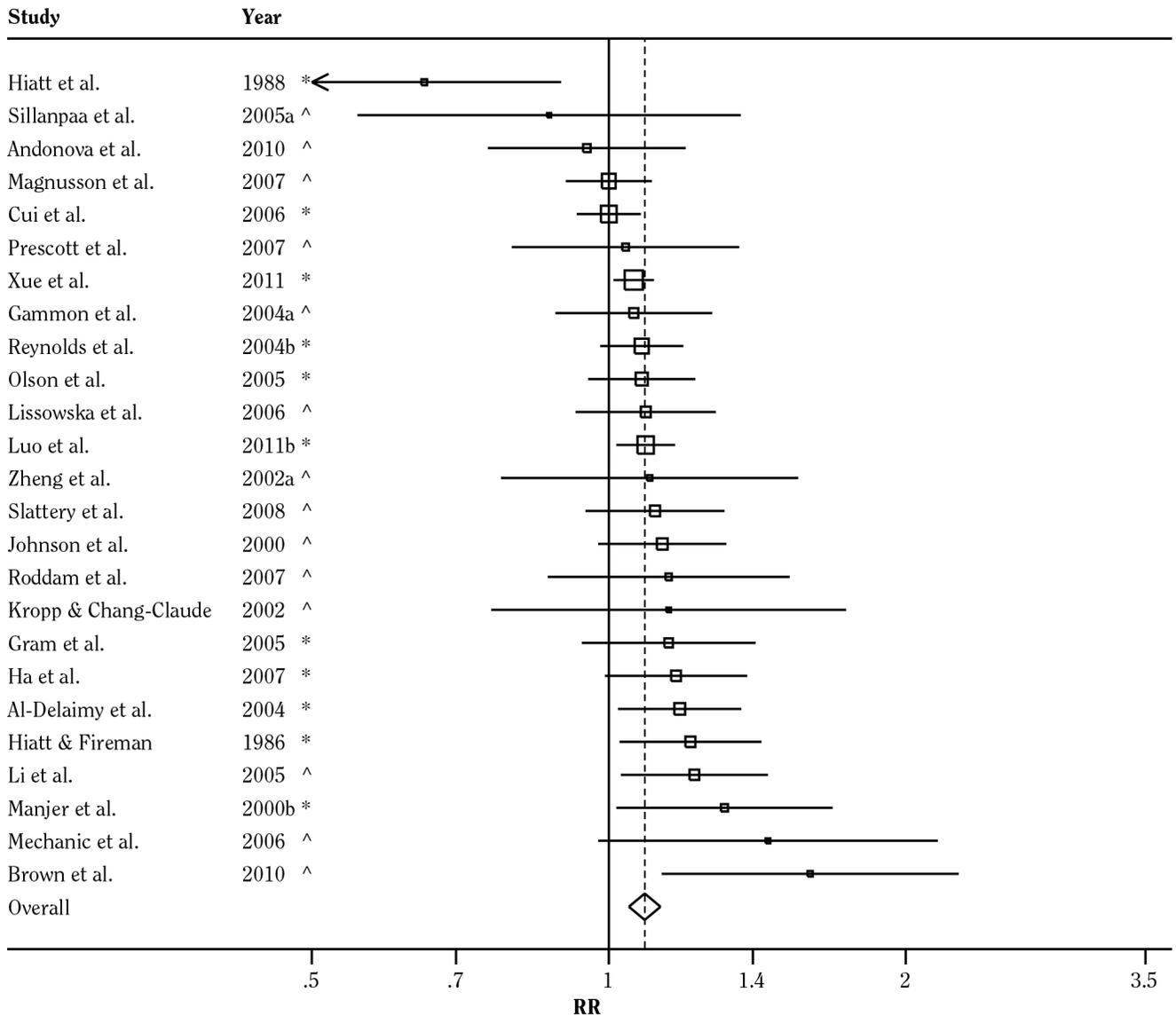
Note: * = cohort study; ^ = case-control study. Meta-analysis RR = 1.09 (95% CI, 1.05–1.13); Begg z = 0.96, p = 0.34; Egger bias = 0.58, p = 0.19. See Table 6.17S (*note f*) for studies excluded. Size of square is proportional to the weights used in the meta-analysis; error bars show the associated 95% CI. Solid vertical line represents the null value. Diamond represents the summary estimate and associated 95% CI. **CI** = confidence interval; **RR** = relative risk.

colleagues (2011) with 30 years of follow-up found a significant trend (p = 0.01). The RRs were 1.04, 1.07, and 1.15 for <20, 20–39, and 40 or more years of smoking, respectively. Luo and colleagues (2011b) reported a highly significant (p trend = 0.0002) increased risk with duration of smoking in the Women's Health Initiative, with an RR of 1.35 (95%

CI, 1.03–1.77) at the highest level (≥50 years). Because all of these studies adjusted for age, it is difficult to attribute these trends to confounding by that variable.

In response to comments posed by Johnson (2004) about analyses of the California Teachers Study data (Reynolds et al. 2004b), Reynolds and colleagues

(2004a) presented essentially the same results for all women (RR = 1.15; 95% CI, 1.00–1.33; p trend = 0.009 at ≥31 years of smoking duration) and for nulliparous women only (RR = 1.13; 95% CI, 0.84–1.52; p trend = 0.081, also at ≥31 years of duration). Two other cohort studies showed increased risks of 26% (Gram et al. 2005) and 18% (Olson et al. 2005), respectively, for the highest categories of smoking duration.

A total of 21 studies reported estimates for duration of smoking, after the 13 exclusions cited above (Table 6.16*S*A and B) (Roddam et al. 2007) not included because only continuous result reported. Nineteen studies with data for smoking duration of 20 or more years have examined the associated risk for breast cancer and were included in the meta-analysis: 7 cohort (Al-Delaimy et al. 2004; Reynolds et al. 2004b; Gram et al. 2005; Olson et al. 2005; Cui et al. 2006; Luo et al. 2011b; Xue et al. 2011) and 12 case-control studies (Johnson et al. 2000; Band et al. 2002; Kropp and Chang-Claude 2002; Zheng et al. 2002a; van der Hel et al. 2003b; Li et al. 2005; Lissowska et al. 2006; Mechanic et al. 2006; Magnusson et al. 2007; Prescott et al. 2007; Rollison et al. 2008; Brown et al. 2010) (Table 6.16*S*, Figure 6.35). The summary estimate (RR) for these studies was 1.16 (95% CI, 1.12–1.21; p_h = 0.318) (Table 6.17*S*). The Egger test was significant, but the Begg test was not, and thus this result may be influenced by publication or small-study bias (see note for Figure 6.35). The summary estimate (RR) was 1.15 (95% CI, 1.10–1.19; p_h = 0.819) for the 7 cohort studies and 1.23 (95% CI, 1.12–1.36; p_h = 0.146) for the 12 case-control studies (Table 6.17*S*). Three case-control studies had cutpoints that were greater than 20 years (Zheng et al. 2002a; van der Hel et al. 2003b; Magnusson et al. 2007), and the reference group in 1 cohort (Gram et al. 2005) and 3 case-control studies was based on no active/no passive exposure (Johnson et al. 2000; Kropp and Chang-Claude 2002; Mechanic et al. 2006). A sensitivity analysis that excluded these 7 studies resulted in similar overall summary estimates for all studies (RR = 1.15; 95% CI, 1.11–1.19; p_h = 0.43), case-control (RR = 1.21; 95% CI, 1.05–1.40), and cohort studies (RR = 1.14; 95% CI, 1.10–1.19).

The same analyses were conducted to estimate the summary RR for less than 20 years of smoking duration to compare it with the result for 20 years or more. The summary estimate for the 19 studies was 1.04 (95% CI, 1.01–1.07) (Table 6.17*S*). There was no evidence of publication or small-study bias according to Begg's or Egger's statistics (p >0.05). There was no difference in the RR between case-control and cohort studies, and the estimate was not attenuated with the exclusion of studies using a no active/no passive reference group or those that had a cutpoint that differed by more than 2 years from the 20 years

of duration used in the meta-analyses. This indicates an increasing trend in risk with longer duration of smoking or a dose-response relationship. These results suggest that active smoking of long duration (i.e., 20 or more years) increases risk for breast cancer by a significant average of 15%. This estimate may be conservative, as some studies indicate that risk continues to increase with smoking over longer periods (Cui et al. 2006; Luo et al. 2011b).

Cigarettes Smoked Per Day

The number of cigarettes smoked per day provides a measure of smoking intensity. In most studies, it represents the intensity of current smoking unless data are available for multiple time points that can be used to interpret the measure as the *usual* intensity of smoking, or intensity over time, the latter often expressed as pack-years of smoking. A recent study (Lubin et al. 2007) suggests that smoking intensity, measured as cigarettes per day, may have complex interactions with duration of smoking on risk of disease: high-intensity effects may diminish over time, while low-intensity effects increase. In contrast, associations of duration or pack-years of smoking with risk may involve residual confounding with age, as older women will have smoked longer but will also have increased risk for breast cancer regardless of smoking. While all studies included in the present meta-analyses of duration and pack-years of smoking adjusted for age, residual confounding may remain that could inflate estimates for longer duration or higher pack-years of smoking. Consequently, meta-analyses were conducted for studies that quantified risk of breast cancer with cigarettes per day, as well as duration of smoking and pack-years of smoking, to provide an alternative measure of dose-response.

A total of 20 studies (9 cohort, 11 case-control) provided a report on cigarettes per day as a measure of the intensity of smoking (Table 6.16*S*A and B) (Roddam et al. 2007 not included because only a continuous result was reported). Higher level of intensity was categorized at 20 cigarettes for 9 studies, at 21 for 6 studies, and at 25 for 3 studies. The cutpoint at 20 is consistent with smoking one pack of cigarettes or more per day. Two of the 20 eligible studies were excluded from the meta-analysis because in 1 (Gram et al. 2005) the highest category was 10 or more cigarettes per day and in the second (Lissowska et al. 2006) it was more than 14. Because the focus of the meta-analysis was on maximum dose, studies that have a maximum-dose category less than 20 have the potential to have subjects with substantially higher levels of smoking included with individuals who smoke considerably less.

Results for low-level compared with high-level smoking intensity differed on the order of 2.7% for all studies, 4.7% for cohort studies, and 3.4% for case-control studies.

Figure 6.35   Forest plot showing association between 20 or more years of smoking duration and risk for breast cancer, based on the subset of cohort studies before 2012 and case-control studies published from 2000 to 2011 (n = 19)

Study	Year	
Lissowska et al.	2006 ^	
Magnusson et al.	2007 ^	
Xue et al.	2011 *	
Prescott et al.	2007 ^	
Olson et al.	2005 *	
Luo et al.	2011b *	
Reynolds et al.	2004b *	
Cui et al.	2006 *	
Brown et al.	2010 ^	
Zheng et al.	2002a ^	
Al-Delaimy et al.	2004 *	
Band et al.	2002 ^	
Gram et al.	2005 *	
Li et al.	2005 ^	
Mechanic et al.	2006 ^	
van der Hel et al.	2003 ^	
Kropp & Chang-Claude	2002 ^	
Rollison et al.	2008 ^	
Johnson et al.	2000 ^	
Overall		

RR scale: .5   .7   1   1.4   2   3.5

RR
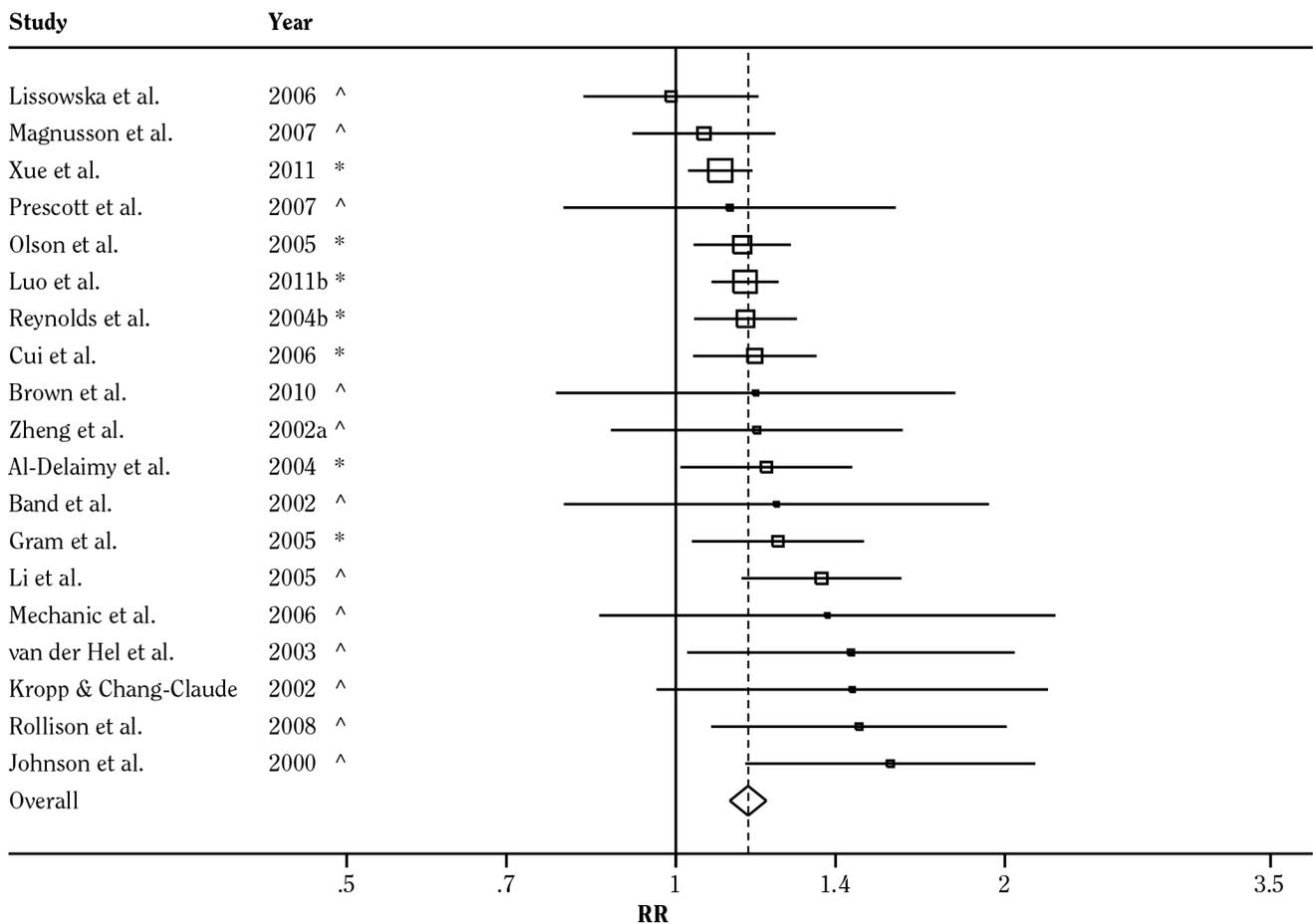
Note: * = cohort study; ^ = case-control study. Meta-analysis RR = 1.16 (95% CI, 1.12–1.21); Begg z = 1.57, p = 0.12; Egger bias = 1.03, p = 0.02. See Table 6.17S (*note g*) for studies excluded. There were three studies with a cutpoint differing from 20 years by more than ± 2 years: 15 or more years (Zheng et al. 2002a and van der Hel et al. 2003) and 11 or more years (Magnusson et al. 2007). Size of square is proportional to the weights used in the meta-analysis; error bars show the associated 95% CI. Solid vertical line represents the null value. Diamond represents the summary estimate and associated 95% CI. **CI** = confidence interval; **RR** = relative risk.

The summary estimate for the 18 studies was 1.10 (95% CI, 1.06–1.16; p_h = 0.031) for fewer than 20 cigarettes smoked per day. Although there was no evidence of publication bias according to the Begg's statistic (p = 0.103), the Egger statistic (p = 0.025) suggested bias was present. The summary estimate was 1.13 (95% CI, 1.09–1.17; p_h = 0.903) for 20 or more cigarettes per day and there was no evidence of publication or small study bias according to Begg's or Egger statistics (Table 6.17S, Figure 6.36). These results appear to be more heavily weighted by the 8 cohort studies. There was significant heterogeneity for the 10 case-control studies for estimates involving 20 or fewer cigarettes per day (p_h = 0.033). When 3 case-control studies that used a no active/no passive reference group were excluded, the overall summary estimate was reduced to 1.08 (95% CI, 1.05–1.12, p_h = 0.179).

Pack-Years of Cigarette Smoking

The number of pack-years of smoking is calculated as the product of intensity (i.e., cigarettes smoked per day) and duration of smoking, and thus this indicator provides an index of lifetime dose of cigarette smoking.

Figure 6.36   Forest plot showing association between 20 or more cigarettes/day and risk for breast cancer, based on the subset of cohort studies published before 2012 and case-control studies published from 2000 to 2011 (n = 18)
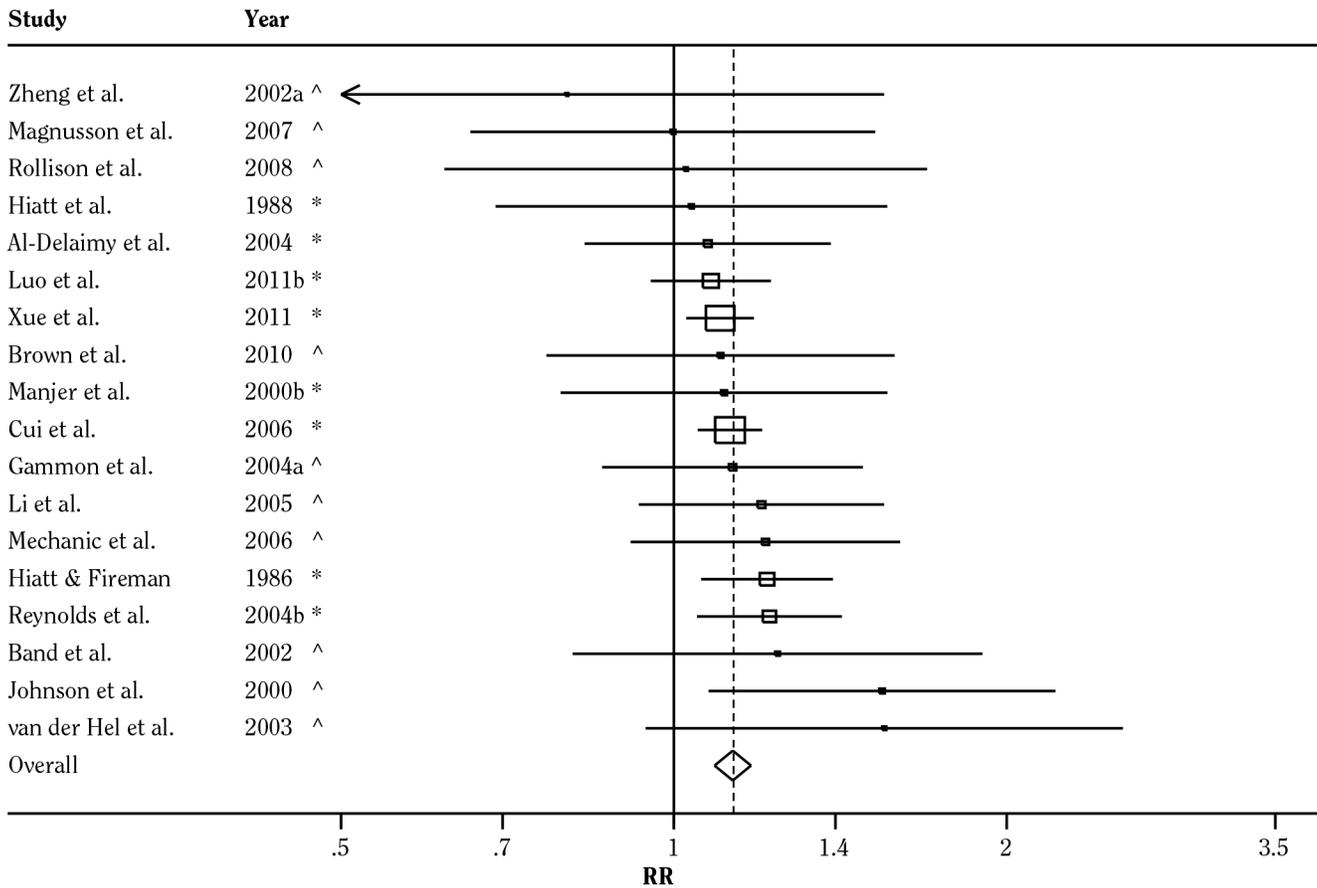
Note: * = cohort study; ^ = case-control study. Meta-analysis RR = 1.13 (95% CI, 1.09–1.17); Begg z = -0.34, p = 0.73; Egger bias = 0.23, p = 0.44. See Table 6.17*S* (*note h*) for studies excluded. Size of square is proportional to the weights used in the meta-analysis; error bars show the associated 95% CI. Solid vertical line represents the null value. Diamond represents the summary estimate and associated 95% CI. **CI** = confidence interval; **RR** = relative risk.

Some investigators prefer this measure, noting that it provides greater analytic power than duration alone (Ha et al. 2007). However, in their modeling of lung cancer and cigarette smoking, Lubin and Caporaso (2006) noted that the measure of pack-years mixes low-intensity smoking over long durations with high-intensity smoking over short periods. Low-dose smoking over a long duration results in increasing trends for risk estimates, termed *exposure enhancement,* and high-dose smoking over short periods produces the reverse trend, termed *reduced potency* (Lubin and Caporaso 2006). In addition, estimates of the usual number of cigarettes smoked per day lose validity over longer durations if smoking is punctuated by intermittent attempts at cessation.

Sixteen studies (6 cohort and 10 case-control) have examined the association between risk for breast cancer and pack-years of smoking and were included in the meta-analysis (Table 6.16*S*A and B). The summary estimate (RR) for the 16 studies was 1.16 (95% CI, 1.11–1.21; p_h = 0.304) for 20 or more pack-years of smoking (Table 6.17*S*, Figure 6.37). The Begg and Egger tests did not reveal any bias (see notes for Figure 6.37). Estimates for 20 or more pack-years did not differ meaningfully between study types: cohort (RR = 1.15; 95% CI, 1.10–1.19; p_h = 0.346) and case-control (RR = 1.21; 95% CI, 1.09–1.34; p_h = 0.314) (Table 6.17*S*). After excluding 1 cohort (Gram et al. 2005) and 3 case-control studies with estimates based on only

Figure 6.37   Forest plot showing association between 20 or more pack-years of smoking and risk for breast cancer, based on the subset of cohort studies published before 2012 and case-control studies published from 2000 to 2011 (n = 16)
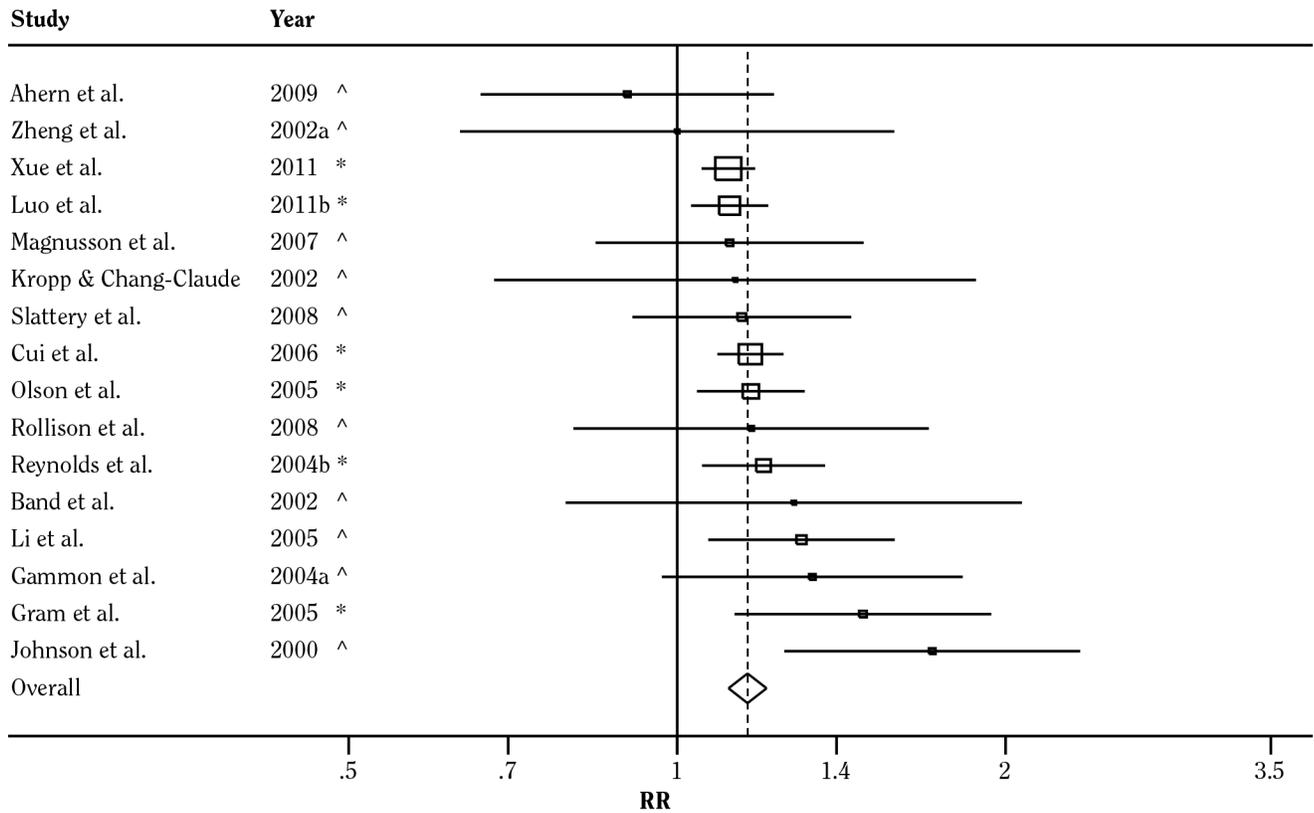
Note: * = cohort study; ^ = case-control study. Meta-analysis RR = 1.16 (95% CI, 1.11–1.21); Begg z = 0.54, p = 0.59; Egger bias = 0.56, p = 0.23. See Table 6.17*S* (*note i*) for studies excluded. There was one study with a cutpoint differing from 20 pack-years by more than ± 5 years: 28 or more years (Li et al. 2005). Size of square is proportional to the weights used in the meta-analysis; error bars show the associated 95% CI. Solid vertical line represents the null value. Diamond represents the summary estimate and associated 95% CI. **CI** = confidence interval; **RR** = relative risk.

a no active/no passive exposure reference group (Johnson et al. 2000; Kropp and Chang-Claude 2002; Gammon et al. 2004a), the overall summary estimate for 20 or more pack-years was slightly attenuated (RR = 1.14; 95% CI, 1.10–1.18; p_h = 0.829), and the RR for case-control studies was reduced by 6%. The overall summary estimate was 1.14 (95% CI, 1.10–1.18; p_h = 0.900) with the exclusion of the case-control study by Li and colleagues (2005), which had a higher cutpoint (more than 52 pack-years) and included only postmenopausal women. The exclusion of this study sharply reduced the RR for the case-control studies to 1.09 (95% CI, 0.96–1.24; p_h = 0.795).

The summary estimate for less than 20 pack-years of smoking was 1.09 (95% CI, 1.03–1.15; p_h = 0.099), which was below the summary estimate of 1.16 (95% CI,

1.11–1.21) for 20 or more pack-years (Table 6.17*S*). This result was primarily due to the cohort studies, for which the summary estimate for fewer than 20 pack-years was 1.04 (95% CI, 1.00–1.09; p_h = 0.872). The result for fewer than 20 pack-years of smoking for case-control studies was substantially higher (RR = 1.20; 95% CI, 1.05–1.37) but the heterogeneity was significant (p_h = 0.023). The summary estimate and the extent of heterogeneity for these case-control studies were substantially decreased when the three studies (Johnson et al. 2000; Kropp and Chang-Claude 2002; Gammon et al. 2004a) using a no active/no passive exposure reference group were excluded (RR = 1.10; 95% CI, 0.97–1.24; p_h = 0.154). Overall, accumulating 20 or more pack-years increased risk for breast cancer by a significant average of 16%, while smoking

for less than 20 pack-years was associated with a smaller increased risk of 9%. The estimate for 20 or more pack-years of smoking may be conservative, because some studies indicate that risk continues to rise with more pack-years (Xue et al. 2011).

Thirteen of the 16 studies with estimates for pack-years of smoking also provided risk by duration (Table 6.16*S*). Estimates across levels of duration and pack-years of smoking were not necessarily consistent for the two measures within a study; the Spearman correlation across studies was 0.62 (p = 0.02). Nonetheless, the summary estimates suggest that long duration of smoking and higher numbers of pack-years of smoking significantly increase risk for breast cancer by a similar amount, approximately 11–21% based on the CIs, depending on study design and sensitivity analysis restrictions (Table 6.17*S*). The summary estimate from case-control studies tended to be higher for both duration and pack-years of smoking than for cohort studies but also less stable. Taken together, the meta-analyses for duration, cigarettes smoked per day, and pack-years provide similar evidence for a dose-response relationship between smoking and breast cancer.

Timing of Exposure to Tobacco Smoke

The timing of smoking relative to critical periods of change in the size and morphology of breast tissue—timeframes such as menarche, during adolescence, or before first pregnancy—may be important. Based on in vitro studies, Russo (2002) hypothesized that smoking is more likely to induce neoplastic changes during these periods, when the susceptibility of the breast to carcinogens is increased. Breast cancer also is more likely to develop in undifferentiated tissues that may be susceptible to tobacco-related and other carcinogens. Results of epidemiologic studies substantiate that nulliparous women have a higher risk than parous women of breast cancer. The lower risk for parous women is attributed to having an early full-term pregnancy and the subsequent increased differentiation in the terminal ducts of the breast (Russo et al. 1992, 2000; Russo and Russo 1995, 2008).

Age at Smoking Initiation

Twenty-two studies with data for age at smoking initiation were evaluated: 8 cohort studies and 14 case-control studies (Table 6.16*S*, see notes for Figure 6.38 for exclusions). The cutpoints for age varied among these studies. Therefore, estimates were allocated into the closest of the following categories: younger than 16 years of age, 16–19 years of age, and 20 years of age and older. The first two categories were combined so that all 22 studies had estimates for those younger than 20 years of age at smoking initiation. Sensitivity analyses stratified the studies by design and excluded studies with large differences in cutpoints or those that used only a no active/no passive exposure reference group.

Figure 6.38 shows results from all 22 studies for those younger than 20 years of age at smoking initiation. The RR summary estimate was 1.11 (95% CI, 1.07–1.16; p_h = 0.088) (Table 6.17*S*). The Begg and Egger tests were not significant (see notes to Figure 6.38; funnel plot not shown). The estimate for the 8 cohort studies (RR = 1.09; 95% CI, 1.06–1.13; p_h = 0.541) was similar to that for the 14 case-control studies (RR = 1.12; 95% CI, 1.02–1.22; p_h = 0.029) (Table 6.17*S*). One cohort study (Gram et al. 2005) and 5 case-control studies (Johnson et al. 2000; Kropp and Chang-Claude 2002; Gammon et al. 2004a; Mechanic et al. 2006; Young et al. 2009) were excluded from the analysis because estimates were based on a no active/no passive exposure reference group. One study was excluded because the age cutpoint was 16 years of age or younger (Egan et al. 2003). These exclusions did not meaningfully alter the summary estimate (RR = 1.09; 95% CI, 1.06–1.13; p_h = 0.597). Nineteen studies (7 cohort, 12 case-control) estimated risk when smoking was initiated at 16 or fewer years of age (RR = 1.08; 95% CI, 1.00–1.15; p_h = 0.065).

Only 13 studies (6 cohort, 7 case-control) reported estimates of risk when smoking initiation occurred from 16–19 years of age (RR = 1.11; 95% CI, 1.07–1.15; p_h = 0.757). Additionally, results for the meta-analysis of the 19 studies that reported estimates for smoking initiation at 20 years of age and older showed a significant summary estimate (RR = 1.08; 95% CI, 1.05–1.12; p_h = 0.672) (Table 6.17*S*). This estimate was only slightly lower than that for those younger than 20 years of age. Thus, these studies did not reveal a clear trend for a change in summary estimates across categories for age at initiation. Few studies tested for trends across age categories and estimates for most studies included in the meta-analyses were similar for those 16 years of age and younger and those 20 years of age or younger (Spearman rank-order correlation = 0.81, p <0.0001). Of note, the estimates in the tails of the distribution of the RRs across studies with either significant protective or increased estimates are from studies that used a no active/no passive exposure reference group. Taken together, the meta-analyses of these studies did not provide clear evidence that initiating smoking during adolescence or young adulthood confers any greater risk than initiation at older ages.

Figure 6.38   **Forest plot showing association between less than 20 years of age at smoking initiation and risk for breast cancer, based on the subset of cohort studies published before 2012 and case-control studies published from 2000 to 2011 (n = 22)**

Study	Year
Gammon et al.	2004a ^
Prescott et al.	2007 ^
Slattery et al.	2008 ^
Xue et al.	2011 *
Young et al.	2009 ^
Zheng et al.	2002a ^
Cui et al.	2006 *
Magnusson et al.	2007 ^
Ha et al.	2007 *
Olson et al.	2005 *
Luo et al.	2011b *
Al-Delaimy et al.	2004 *
Mechanic et al.	2006 ^
Reynolds et al.	2004b *
Kropp & Chang-Claude	2002 ^
Lissowska et al.	2006 ^
Egan et al.	2003 ^
Gram et al.	2005 *
Li et al.	2005 ^
Rollison et al.	2008 ^
Johnson et al.	2000 ^
Brown et al.	2010 ^
Overall	

RR axis: .5   .7   1   1.4   2   3.5

RR
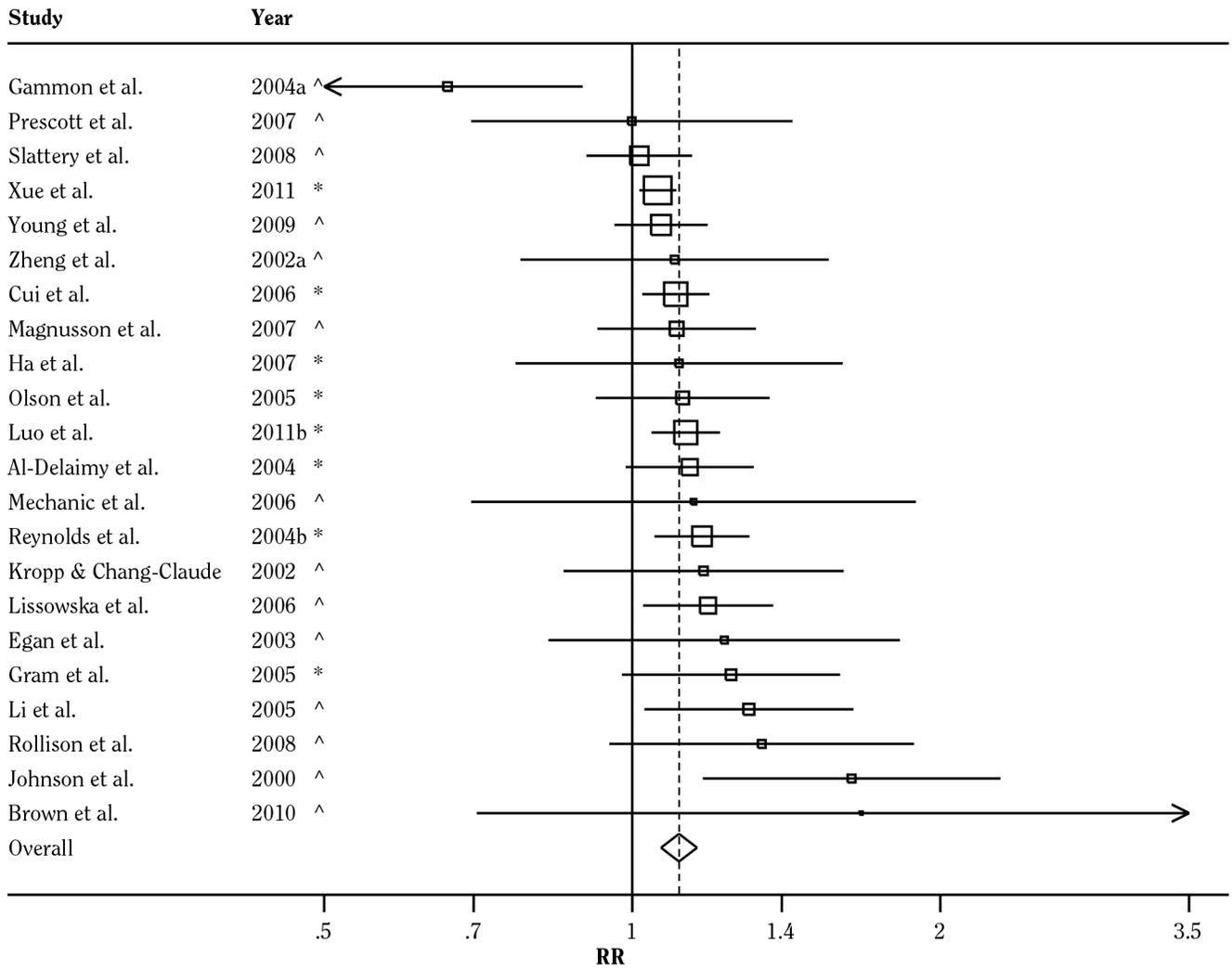
Note: * = cohort study; ^ = case-control study. Meta-analysis RR = 1.11 (95% CI, 1.07–1.16); Begg z = 0.59, p = 0.55; Egger bias = 0.63, p = 0.12. See Table 6.17S (*note j*) for studies excluded. There were six studies with a cutpoint differing from 20 years of age at smoking initiation by more than ± 2 years: 15 years of age and younger (Prescott et al. 2007), 16 years of age and younger (Egan et al. 2003), and 18 years of age and younger (Gammon et al. 2004a; Mechanic et al. 2006; Olson et al. 2005; Rollison et al. 2008). Size of square is proportional to the weights used in the meta-analysis; error bars show the associated 95% CI. Solid vertical line represents the null value. Diamond represents the summary estimate and associated 95% CI. **CI** = confidence interval; **RR** = relative risk.

Smoking Before or During First Full-Term Pregnancy

The effects of smoking before versus after a first full-term pregnancy may be confounded by effects associated with early age at smoking initiation and age at first pregnancy (Cui et al. 2006). Few studies have examined the risk of smoking during pregnancy, for which the results may differ for women who stop smoking when pregnant than for those who continue to smoke during pregnancy. Lawlor and colleagues (2004) conducted a meta-analysis of 11 studies, 2 of which were based on smoking during pregnancy (Innes and Byers 2001; Fink and Lash 2003), to assess the effect of smoking before a first full-term pregnancy. The analysis included estimates from their own cohort, the British Women's Heart and Health Study, 2 earlier cohort studies (Egan et al. 2002; Reynolds et al. 2004b), and 8 case-control studies (Adami et al. 1988; Hunter et al. 1997; Lash and Aschengrau 1999, 2002; Innes and Byers 2001; Band et al. 2002; Kropp and Chang-Claude 2002; Fink and Lash 2003). Based on 6,528 cases, the RR summary estimate was 1.07 (95% CI, 0.94–1.22). The risk was attenuated when 2 influential studies with wide CIs (Lash and Aschengrau 1999; Innes and Byers 2001) were removed (RR = 1.03; 95% CI, 0.93–1.14), which also reduced heterogeneity. These 2 studies and an earlier one based on the NHS-I (Hunter et al. 1997) were 3 of the 11 that reported statistically significant results.

DeRoo and colleagues (2011b) published a meta-analysis on a larger number of studies than the earlier review by Lawlor and colleagues (2004). These authors included an additional 15 reports (Morabia et al. 1996; Egan et al. 2003; Al-Delaimy et al. 2004; Gammon et al. 2004a; Gram et al. 2005; Li et al. 2005; Olson et al. 2005; Cui et al. 2006; Lissowska et al. 2006; Ha et al. 2007; Magnusson et al. 2007; Prescott et al. 2007; Rollison et al. 2008; Slattery et al. 2008; Young et al. 2009). They excluded 2 studies of smoking during first pregnancy based on linked birth and cancer registry data (Innes and Byers 2001; Fink and Lash 2003) and 1 study (Hunter et al. 1997) that overlapped with a subsequent report (Egan et al. 2002); these 3 (i.e., all but Egan et al. 2002) were included in Lawlor and colleagues' (2004) meta-analysis. DeRoo and colleagues' (2011b) summary estimate was 1.11 (95% CI, 1.06–1.16). This higher estimate than that of Lawlor and colleagues (2004) was influenced by several large cohort and case-control studies published between January 2004 and 2009.

Twenty-two studies included in this report provided RR estimates for smoking before or during first full-term pregnancy for the meta-analysis: 9 cohort studies (Al-Delaimy et al. 2004; Lawlor et al. 2004; Reynolds et al. 2004b; Gram et al. 2005; Olson et al. 2005; Cui et al. 2006; Ha et al. 2007; Luo et al. 2011b; Xue et al. 2011) and

13 case-control studies (Innes and Byers 2001; Band et al. 2002; Kropp and Chang-Claude 2002; Fink and Lash 2003; Gammon et al. 2004a; Li et al. 2005; Lissowska et al. 2006; Magnusson et al. 2007; Prescott et al. 2007; Rollison et al. 2008; Slattery et al. 2008; Young et al. 2009; DeRoo et al. 2011a) (Table 6.16S, see notes for Figure 6.39 for exclusions). For these 22 studies, the RR summary estimate was 1.10 (95% CI, 1.04–1.17; p_h = <0.001) (Table 6.17S). This summary result is higher and statistically significant compared with that of Lawlor and colleagues (2004), primarily because it included 5 recent, large cohort studies that reported significant estimates (Al-Delaimy et al. 2004; Gram et al. 2005; Olson et al. 2005; Luo et al. 2011b; Xue et al. 2011). The RR summary estimate was 1.16 (95% CI, 1.12–1.20; p_h = 0.746) for the 9 cohort studies and 1.05 (95% CI, 0.94–1.18; p_h = 0.001) for the 13 case-control studies (Table 6.17S). After excluding 1 cohort study (Gram et al. 2005) and 3 case-control studies (Gammon et al. 2004a; Kropp and Chang-Claude 2002; Young et al. 2009) that were based on estimates using only a no active/no passive exposure reference group, the overall summary estimate increased slightly (RR = 1.11; 95% CI, 1.05–1.18; p_h ≤0.001) due to the increase for case-control studies (RR = 1.09; 95% CI, 0.96–1.23; p_h ≤0.001). The additional exclusion of the 3 case-control studies, which reported estimates for smoking only during pregnancy (Innes and Byers 2001; Fink and Lash 2003; DeRoo et al. 2011a), further increased the RR for case-control studies to 1.13 (95% CI, 1.05–1.23), eliminating the significant heterogeneity (p_h = 0.727). In addition, the overall summary estimate was increased to 1.16 (95% CI, 1.12–1.20; p_h = 0.830). Thus, the 3 case-control studies with risk estimates for smoking only during pregnancy produced heterogeneity and attenuated summary estimates, but those that used a no active/no passive exposure reference group had little or no effect on the summary estimates.

These summary estimates for smoking before or during first pregnancy are only slightly higher than those for ever smoking, and they are quite similar to those for duration of 20 or more years and 20 or more pack-years of smoking. Overall, the studies conducted since 2000 do not provide clear evidence that smoking before first pregnancy confers a greater risk than smoking at any other time in a woman's life. Taken together, the results for earlier age at smoking initiation and smoking before first pregnancy do not support the hypothesis that smoking has greater carcinogenic effects during periods in which breast tissue is less differentiated and theoretically more susceptible.

Menopausal Status

Risk for breast cancer is associated with duration and level of estrogen exposure and evidence suggests that

Figure 6.39   Forest plot showing association between smoking before or during first full-term pregnancy and risk for breast cancer, based on the subset of cohort studies before 2012 and case-control studies published from 2000 to 2011 (n = 22)
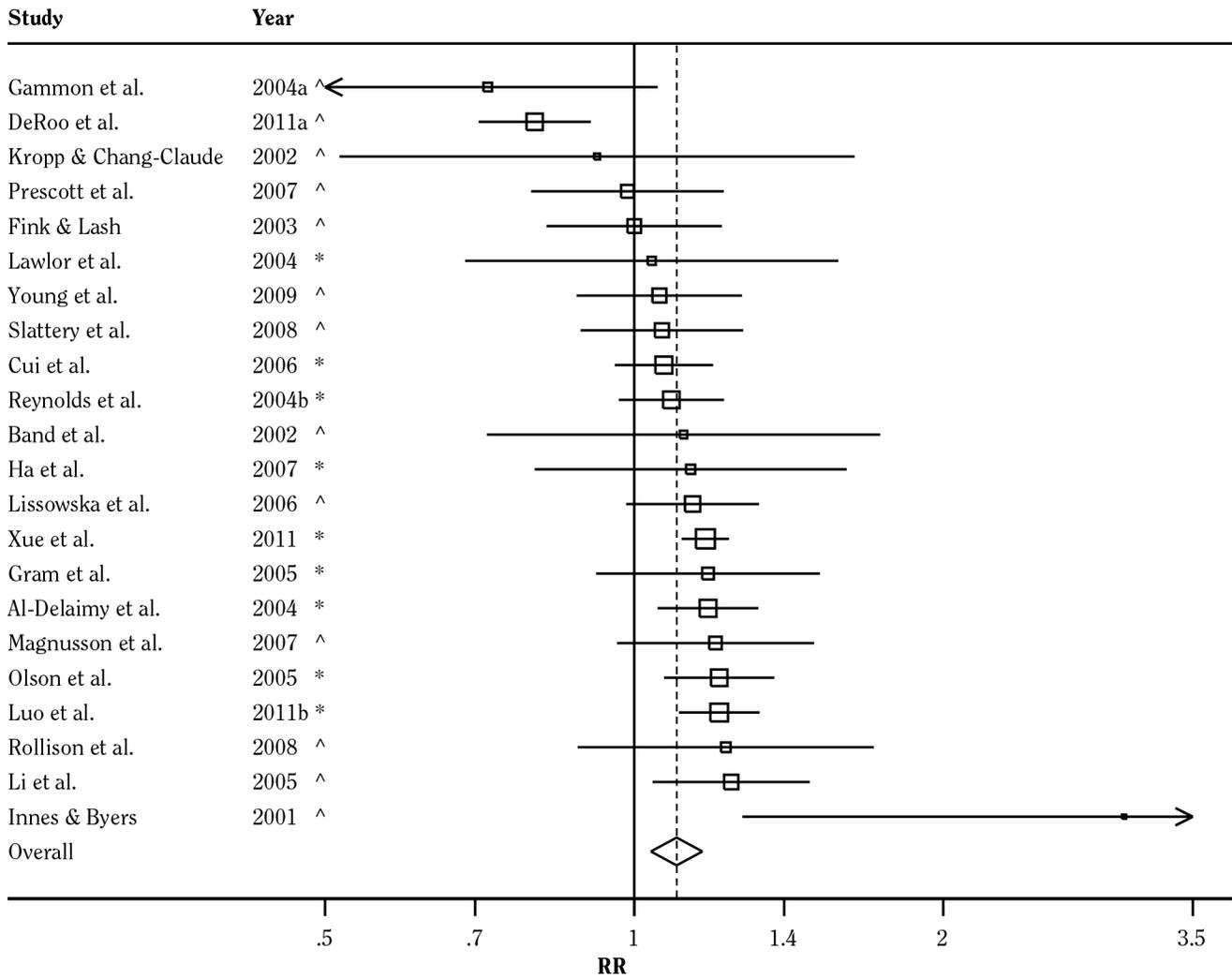
Note: * = cohort study; ^ = case-control study. Meta-analysis RR = 1.10 (95% CI, 1.04–1.17); Begg z = -1.16, p = 0.25; Egger bias = -0.50, p = 0.43. See Table 6.17S (*note m*) for studies excluded. Estimates based on exposure before first pregnancy with the exception of three studies, which reported an estimate based on exposure during first pregnancy (Innes and Byers 2001; Fink and Lash 2003; DeRoo et al. 2011a). Size of square is proportional to the weights used in the meta-analysis; error bars show the associated 95% CI. Solid vertical line represents the null value. Diamond represents the summary estimate and associated 95% CI. **CI** = confidence interval; **RR** = relative risk.

the phenotypic heterogeneity of breast cancer is linked to menopausal status (Lipton 2005). Spicer and Pike (2005) hypothesized that because menopause is associated with a decreased rate of breast cell proliferation compared with that in the premenopausal period, it modifies susceptibility to exposures such as obesity, hormone therapy, and alcohol. It is plausible that if smoking affects hormone

metabolism, the risk of breast cancer due to smoking is similarly modified by menopause.

For some risk factors, such as obesity, risk estimates differ when analyses are stratified by menopausal status (van den Brandt et al. 2000). Menopause could modify the risk of breast cancer associated with smoking by altering hormone metabolism and the sensitivity of breast tissue

to tobacco carcinogens (Kendall et al. 2007). Women who smoke—primarily current, heavy smokers—experience menopause at an earlier age than those who do not smoke (Baron et al. 1990; Midgette and Baron 1990; Kato et al. 1998; Mikkelsen et al. 2007; Sun et al. 2012) and have a higher risk for osteoporosis even when on estrogen therapy (North American Menopause Society 2010), which may be due to altered estrogen metabolism and lower estrogen levels (Kiel et al. 1992). These observations support an anti-estrogenic effect of smoking (Kendall et al. 2007). However, smokers also tend to be leaner, drink more alcohol, and have poorer diets than nonsmokers; all of these factors are also associated with early menopause (Sampson 2002). Moreover, results from several studies have not provided sufficient evidence that estradiol levels in current smokers differ from those in former or never smokers (Longcope and Johnston 1988; Baron et al. 1990; Key et al. 1991; Cassidenti et al. 1992; Kendall et al. 2007; Arslan et al. 2009). Even so, in a recent cross-sectional analysis of the association between endogenous hormones and several risk factors for breast cancer, the levels of all sex hormones were reported to be higher for women who smoked 15 or more cigarettes per day than for never smokers. Hormonal levels, particularly for estrogen, were attenuated with adjustment for BMI, whereas further adjustment for alcohol did not result in any meaningful change (Endogenous Hormones and Breast Cancer Collaborative Group 2011).

Previous reviews did not find evidence to suggest that menopause modifies the risk of breast cancer from smoking (Egan et al. 2002; Terry and Rohan 2002). The Collaborative Group on Hormonal Factors in Breast Cancer and colleagues (2002) reported an RR of 1.07 (standard error = 0.05) for premenopausal women and an RR of 1.12 (standard error = 0.06) for women 50 years of age and older who experienced natural menopause.

Several studies have examined menopausal status specifically, and several have conducted formal tests for interaction with smoking. Table 6.18S shows results for ever smoking from 14 studies stratified by menopausal status and 6 studies in which the entire study sample included only one menopausal group. Of the 20 studies listed, 7 reported data for pack-years of smoking for both menopausal groups and 3 reported results for postmenopausal women only. Overall, results for ever smoking were highly variable for both premenopausal and postmenopausal risks. Menopause can be difficult to define in observational studies, however, which can result in misclassification bias, particularly when age is the only criterion for menopause. Furthermore, not all studies in Table 6.18S accounted for residual confounding by hormonal status or use of HRT. A sensitivity analysis (Table 6.18S)

provides the RR for case-control studies, with the study by Kruk (2007) excluded because of its extreme estimates.

Menopausal Status—Ever Smoking

Among 17 studies, 3 cohort (Hiatt and Fireman 1986; Manjer et al. 2000b; Xue et al. 2011) and 3 case-control (Band et al. 2002; Lissowska et al. 2006; Kruk 2007) studies reported a significantly increased risk for premenopausal women associated with ever smoking. All but 6 studies had an RR greater than 1.10, and no significant inverse associations were reported. The summary estimate (RR) associated with premenopausal smoking for all studies combined was 1.26 (95% CI, 1.11–1.43; $p_h \leq 0.001$) (Table 6.18S). This RR was reduced to 1.18 (95% CI, 1.08–1.29; $p_h = 0.005$) when the single outlying estimate for a case-control study (RR = 2.34) (Kruk 2007) was excluded (Table 6.18S). The summary estimate for the case-control studies was reduced from 1.30 (95% CI, 1.04–1.62; $p_h = 0.001$) to 1.20 (95% CI, 1.02–1.42; $p_h = 0.075$) when the outlier was excluded, a value that is quite similar to the RR for the 4 cohort studies (RR = 1.16; 95% CI, 1.08–1.24; $p_h = 0.628$) (Table 6.18S).

A total of 17 studies reported results for smoking by postmenopausal women. Four out of 6 cohort studies reported positive associations of 1.10 or greater, of which 2 were significant (Olson et al. 2005; Luo et al. 2011b). One cohort study (Xue et al. 2011), however, reported a significant inverse association (RR = 0.91; 95% CI, 0.86–0.96). Three of the 11 case-control studies that included postmenopausal women reported significant positive associations for this group (Johnson et al. 2000; Li et al. 2005; Kruk 2007). Five studies reported an RR greater than 1.10, and none reported a significant inverse association. The summary estimate associated with postmenopausal women for all studies combined was 1.10 (95% CI, 1.02–1.19; $p_h = 0.001$) (Table 6.18S). This RR was reduced to 1.07 (95% CI, 1.00–1.14; $p_h = 0.001$) when the outlying estimate (RR = 1.76) (Kruk 2007) was removed. The summary estimate for the case-control studies was reduced from 1.13 (95% CI, 1.01–1.27; $p_h = 0.001$) to 1.07 (95% CI, 0.98–1.16; $p_h = 0.147$) when the outlier was removed, an estimate virtually identical to the estimate based on the 6 cohort studies (RR = 1.07; 95% CI, 0.97–1.19; $p_h = 0.001$) (Table 6.18S).

Several issues should be considered when evaluating these results for ever smoking in premenopausal versus postmenopausal women. First, the estimates reported by Kruk (2007) are outliers for both menopausal groups and, when these estimates are included, the summary estimates (RRs) are positively biased. The significant inverse association in postmenopausal women reported

by Xue and colleagues (2011) for the NHS-I contrasts with the significant positive associations reported by two other large cohort studies, Women's Health Initiative (Luo et al. 2011b) and the Iowa Women's Health Study (Olson et al. 2005). Previous reports from NHS-I (London et al. 1989; Egan et al. 2002) have indicated a null association and no meaningful difference between menopausal groups, but they were based on fewer cases and less follow-up time than the recent report by Xue and colleagues (2011).

Among the case-control studies, the study by Johnson and colleagues (2000) also provided estimates for smoking by menopausal status that used a small no active/no passive exposure reference group: for premenopausal women, OR = 2.3 (95% CI, 1.2–4.5), and for postmenopausal women, OR = 1.5 (95% CI, 1.0–2.3). These estimates contrast strongly with their results when using a no active-only reference group (Table 6.18*S*): premenopausal women (OR = 1.0; 95% CI, 0.80–1.3); postmenopausal women (OR = 1.2; 95% CI, 1.0–1.4). No other study has contrasted estimates using these two reference groups by menopausal status. It is important to note that Johnson and colleagues (2000) restricted their analysis using a no active/no passive exposure reference group to the approximate 60% of women who reported their residential exposure to passive smoke for at least 90% of their lifetime. This makes a direct comparison of their results difficult.

Menopausal Status—Pack-Years of Smoking

Several studies have reported results for pack-years by menopausal status: 7 for premenopausal and 10 for postmenopausal (Table 6.18*S*). The results across these studies are variable and inconsistent. Two cohort studies that reported results for premenopausal women (Reynolds et al. 2004b; Xue et al. 2011) found significantly increased risks for the highest category of pack-years of smoking (≥30) (RR = 2.05; 95% CI, 1.20–3.49 and RR = 1.27; 95% CI, 1.16–1.38, respectively). Among 5 case-control studies offering estimates for premenopausal women, 2 reported statistically significant positive associations for the highest level of pack-years of smoking (Band et al. 2002: RR = 1.69; 95% CI, 1.10–2.61 for ≥20 pack-years; Slattery et al. 2008: RR = 1.6; 95% CI, 1.1–2.4 for >15 pack-years) in non-Hispanic Whites, while 1 (Johnson et al. 2000) found significant increased risks for fewer pack-years of exposure (RR = 2.30; 95% CI, 1.10–4.70 for 11–20, and RR = 2.40; 95% CI, 1.20–4.70 for 1–10 pack-years). The other 2 studies (Zheng et al. 2002a; Ahern et al. 2009) were essentially null for the association between breast cancer and pack-years of smoking in premenopausal women.

Four cohort and six case-control studies reported estimates for the association of pack-years of smoking

with breast cancer in postmenopausal women. The pooled estimate for 20 or more pack-years was statistically significant in Reynolds and colleagues (2004b) (pooled RR = 1.17; 95% CI, 1.01–1.35), Olson and colleagues (2005) (pooled RR = 1.17; 95% CI, 1.04–1.31), and Luo and colleagues (2011b) (pooled RR = 1.12; 95% CI, 1.03–1.21). Luo and colleagues (2011b) also found a statistically significant increased risk for smoking more than 50 pack-years (RR = 1.18; 95% CI, 1.02–1.22). In contrast, there was a trend toward lower risk with more pack-years of smoking in Xue and colleagues (2011), which reached statistical significance for the highest level of more than 15 pack-years (RR = 0.88; 95% CI, 0.79–0.99). In contrast, only two (Johnson et al. 2000; Li et al. 2005) of the six case-control studies reported statistically significant associations for the highest level of pack-years of smoking in postmenopausal women (RR = 1.60; 95% CI, 1.00–2.60, and RR = 1.30; 95% CI, 1.00–2.60, respectively). It should be noted that the estimates reported by Johnson and colleagues (2000) were based on a no active/no passive exposure reference group.

Only one cohort study (Reynolds et al. 2004b) formally tested for interaction between menopause and smoking across multiple measures. This study found no significant results by the likelihood ratio test for duration of smoking (p = 0.80); cigarettes/per day (p = 0.42); pack-years of smoking (p = 0.07); and years since cessation (p = 0.76).

Menopausal Status—Summary

The results in Table 6.18*S* indicate that considerable heterogeneity exists among studies that report estimates for the association of smoking with breast cancer by menopausal status, although none of the summary estimates was associated with statistically significant publication bias. Although the results of the meta-analysis suggest that risk is greater in premenopausal than in postmenopausal women, it remains uncertain whether the association of smoking with breast cancer differs by menopausal status.

Hormone Receptor Status

ERs and progesterone receptors (PRs) mediate the effects of estrogen and progesterone on the growth, proliferation, and differentiation of breast tumors; response to hormonal treatment; recurrence; and survival. Palmer and Rosenberg (1993) postulated that the expression status of ERs could modulate the anti-estrogenic effects of smoking, and Meek and Finch (1999) reported that smoking alters the expression of ERs. The presence (+) or absence (–) of ER expression in breast tumors is increasingly

recognized as a potential biomarker of etiologically distinct subtypes (Anders et al. 2008; Bertucci et al. 2009; Onitilo et al. 2009). Consequently, some of the more recent studies stratify analyses on ER expression. The information added by cross-classification with the status of PRs remains controversial. In addition to reporting the expression status of ERs and PRs, studies have begun to cross-classify cases by the status of human epidermal growth factor receptor 2 (HER2) because the so-called *triple negative* phenotype (i.e., the combination of negative ER, PR, and HER2 status) is increasingly recognized as distinct and having a poor prognosis (Bauer et al. 2007; ReisFilho and Tutt 2008; Gluz et al. 2009).

Many studies have assessed the risk of breast cancer based on the status of ER expression. In 2 early, small hospital-based studies, Daniell (1980) and Ranocchia and colleagues (1991) observed that the prevalence of smoking was higher among breast cancer cases with ER– tumors than in cases with ER+ tumors, but these studies were underpowered and the data were not rigorously analyzed. Table 6.19S summarizes data from 17 studies that assessed whether the risk for breast cancer differs by ER expression status for ever smoking or by the highest category of cigarettes smoked per day. Althuis and colleagues (2004) reviewed 10 of the studies shown in Table 6.19S (McTiernan et al. 1986; Stanford et al. 1987; Cooper et al. 1989; London et al. 1989; Yoo et al. 1997; Morabia et al. 1998; Huang et al. 2000a; Manjer et al. 2001; Britton et al. 2002; Cotterchio et al. 2003) with hormone receptor-defined breast cancer and found no evidence for a differential association between breast cancer and smoking by hormonal phenotype, but they did not provide a numerical analysis. Four of these studies (Cooper et al. 1989; London et al. 1989; Yoo et al. 1997; Morabia et al. 1998) were reviewed in the 2006 Surgeon General's report.

Hormone Receptor Status—Ever Smoking

Findings from the 17 studies on the association of ever smoking with breast cancer defined by ER status are highly inconsistent (Table 6.19S). Four studies reported significantly increased risks for ER+ breast cancer with ever smoking, with RRs ranging from 1.15–1.42 (Yoo et al. 1997; Al-Delaimy et al. 2004; Li et al. 2005; Luo et al. 2011b). Two studies reported significantly increased risks for ER–breast cancer (Cooper et al. 1989; Manjer et al. 2001), with RRs ranging from 1.63–2.41. One study (Morabia et al. 1998) reported significantly increased risks for both ER+ and ER– breast cancer, with a somewhat stronger association with ER– (RR = 4.01; 95% CI, 1.90–8.46) than ER+ (RR = 2.28; 95% CI, 1.56–3.35) tumors. This study is the only one that used a no active/ no passive exposure reference group (Morabia et al. 1998).

The recent case-control study by Rabstein and colleagues (2010) found a significant inverse association with ER+ breast cancer (RR = 0.79; 95% CI, 0.65–0.95), but no association with ER– breast cancer. The remaining studies reported null results (McTiernan et al. 1986; Stanford et al. 1987; London et al. 1989; Huang et al. 2000a; Britton et al. 2002; Cotterchio et al. 2003; Gammon et al. 2004a; Lissowska et al. 2006; Trivers et al. 2009).

Hormone Receptor Status—Cigarettes Smoked Per Day

Only six studies have reported results on the association between cigarettes smoked per day and breast cancer defined by ER status, and these are also very inconsistent (Table 6.19S). One study (London et al. 1989) reported a significantly increased risk for ER+ breast cancer with 25 or more cigarettes smoked per day (RR = 1.38; 95% CI, 1.04–1.84), and another (Al-Delaimy et al. 2004) reported significantly increased risks for ER+ breast cancer with fewer cigarettes smoked per day: RR = 1.46; 95% CI, 1.14–1.87 for 5–14 cigarettes smoked per day; and RR = 1.45; 95% CI, 1.09–1.93 for 1–4 cigarettes smoked per day. Manjer and colleagues (2001) found significantly increased risks for ER– breast cancer regardless of number of cigarettes smoked per day, and Morabia and colleagues (1998) reported significantly increased risks for both ER+ and ER– breast cancer regardless of level, although the association was somewhat stronger in women with ER– tumors. The remaining two studies reported essentially null results (Li et al. 2005; Lissowska et al. 2006).

Hormone Receptor Status—Methodologic Issues

Some issues affect the interpretation of published results for smoking and breast cancer by hormone receptor status. First, all but two studies (London et al. 1989; Al-Delaimy et al. 2004) in Table 6.19S used case-control designs, which are more subject to bias than other study designs. Second, methods for detecting ER expression have changed over time, and some older studies were based on a mix of methods (Ross and Hortobagyi 2005). Many studies rely on incomplete or inaccurate pathology and medical records and ER status is generally not obtained on in situ tumors. The completeness of data for ER status in the studies in Table 6.19S ranged from 40–100%. Third, few studies have identified consistent risk factors for the ER– phenotype other than race and younger age (Althuis et al. 2004), and thus potential confounders for this type of breast cancer are not yet well characterized. Last, researchers are not sure whether ER status should be cross-classified with PR status. The most recent studies

have characterized breast cancer phenotypes by the combination of ER, PR, and HER2 status or by gene expression phenotypes (luminal A, B, basal-like) (Kwan et al. 2009; Trivers et al. 2009). Kabat and colleagues (2011) recently published an analysis from the Women's Health Initiative on risk of the triple negative phenotype compared with risk for ER+ breast cancer in relation to smoking. RRs (not shown in Table 6.19*S*) were significantly increased in women with ER+ breast cancer for former smoking (1.14; 95% CI, 1.05–1.24), duration of 30 or more years (1.14; 95% CI, 1.01–1.28), 40 or more pack-years of smoking (1.25; 95% CI, 1.06–1.44), and younger than 20 years of age at initiation (1.16; 95% CI, 1.05–1.28). In contrast, there were no significant associations in women with triple negative breast cancer. These results are quite similar to those reported by Luo and colleagues (2011b), who also analyzed tumors by ER/PR status only (not HER2) data from the Women's Health Initiative cohort.

Hormone Receptor Status—Summary

In summary, results from studies conducted to date are inconsistent on the association of smoking with different phenotypes of breast cancer defined on the basis of hormone receptor status.

Exposure to Tobacco Smoke and Risk of Second Primary Contralateral Breast Cancer

Although a recent study indicates that there was a downward trend in the incidence of contralateral breast cancer in the United States from 1975–2006 (Nichols et al. 2011), a summative review published in 1999 documented prevalence estimates ranging from 2–11% (Chen et al. 1999), and a follow-up of 305,533 breast cancer cases in the SEER Program database provided an estimate of 4.3% for the development of a second primary contralateral breast cancer (Bernstein et al. 2003).

A second primary breast cancer has most frequently been defined as a new and independent tumor, although studies have varied on whether carcinoma in situ has been included. The risk of developing a second primary contralateral breast cancer has been evaluated in a number of studies (Kato et al. 1986; Horn and Thompson 1988; Bernstein et al. 1992; Fowble et al. 2001; Trentham-Dietz et al. 2007a; Knight et al. 2009; Li et al. 2009a), primarily over the past decade, as the number of women who have survived breast cancer has steadily increased and there has been a growing interest in modifiable risk factors for this disease. Cigarette smoking has been examined as one

of the primary behavioral risk factors, along with alcohol consumption, obesity, and use of oral contraceptives. In a review by Chen and colleagues (1999) of the 16 studies they examined, 3 included cigarette smoking as a factor of interest (Kato et al. 1986; Horn and Thompson 1988; Bernstein et al. 1992), but there was no strong evidence of a significant increased risk. These 3 studies, along with 4 reports published in 2001 or later (Fowble et al. 2001; Trentham-Dietz et al. 2007a; Knight et al. 2009; Li et al. 2009a), are summarized in Table 6.20*S*. Overall, the findings of these 7 studies are inconclusive with regard to the risk of a second primary contralateral breast cancer in smokers. In the largest cohort of women diagnosed with invasive cancer, the findings for both former and current smoking were not significant (Trentham-Dietz et al. 2007a). In the most recently conducted study, which covered a 15-year follow-up period, Li and colleagues (2009a) reported a significant association between cigarette smoking and both a contralateral breast cancer diagnosis (RR = 2.2; 95% CI, 1.2–4.0) and risk of the first primary breast cancer diagnosis (RR = 1.8; 95% CI, 1.1–3.2). Although Knight and colleagues (2009) evaluated a number of smoking measures, including duration, average packs per day, pack-years, and age at initiation, they found little evidence for an association between cigarette smoking and risk of a primary contralateral breast cancer. That study was focused primarily on premenopausal women, whereas in the study by Li and colleagues (2009a) the majority of women (81%) were postmenopausal and diagnosed with ER+ cancer. Taken together, the results for the association between smoking and having a contralateral breast cancer remain inconclusive.

Genetic Susceptibility to Smoking

The 2004 Surgeon General's report summarized eight studies on the smoking-genotype interaction: one on family history (Couch et al. 2001), one on *BRCA1/2* (Brunet et al. 1998), three on *NAT1* and *NAT2* (Ambrosone et al. 1996; Hunter et al. 1997; Millikan et al. 1998), one on *GSTM1* (Ambrosone et al. 1999a), and two on *CYP1A1* (Ambrosone et al. 1995; Ishibe et al. 1998). The report concluded that susceptible subgroups of women could not be "reliably identified" (USDHHS 2004, p. 312). The Cal/EPA (2005) provided descriptive summaries of studies that focused on susceptible subgroups (i.e., determined by family history, genotype, tumor phenotype); the Canadian Expert Panel tabulated data on the interaction between smoking and a number of genotypes and considered the evidence for *NAT2* to be "persuasive" (Collishaw et al. 2009, p. 47); and the 2009 IARC Monograph Working

Group concluded that results from studies of interactions between smoking and genes were "ambiguous, with the possible exception of *NAT2*" (Secretan et al. 2009, p. 1034).

Family History

Having a family history of first-degree relatives with breast cancer is associated with a doubling to tripling of risk for breast cancer (Goldgar et al. 1994; Pharoah et al. 1997; Poole et al. 1999). This risk is further increased in women with benign breast disease and a family history of breast cancer, especially those with atypical hyperplasia (Collins et al. 2006). This finding provides strong evidence for a genetic predisposition to breast cancer and has led to rapidly expanding efforts to identify specific genetic variants that increase such risk. These may be either rare variants with large effects or the joint action of common variants (SNPs) with small effects that modify susceptibility to behavioral or environmental exposures associated with breast cancer. This section considers evidence for heritable genetic susceptibility to smoking as a risk factor for breast cancer.

Most studies on smoking and breast cancer have controlled for family history, but only a few have assessed the interaction of smoking and family history (Couch et al. 2001; Suzuki et al. 2007). Couch and colleagues (2001) reported that among 132 families with three or more incident cases of breast or ovarian cancer in sisters and daughters, ever smokers had an increased risk (RR = 2.4; 95% CI, 1.2–5.1) for breast cancer compared with never smokers. Risk for ever smokers was even higher (RR = 5.8; 95% CI, 1.4–23.9) in 35 families with five or more breast and/or ovarian cancers. Suzuki and colleagues (2007) also reported a significant interaction between a positive family history of cancer and smoking on risk of breast cancer (p = 0.01). In comparisons with never smokers who did not have a family history, risk was over four times as high (RR = 4.33; 95% CI, 1.65–11.40) in women with a family history of breast cancer who reported more than 30 pack-years of smoking but only about one and one-half times as high in those with a family history who never smoked (RR = 1.44; 95% CI, 1.21–1.71). In addition, Suzuki and colleagues (2007) found a strong dose-response relationship in smokers who had a family history of breast cancer. Risk for breast cancer was nearly twice as high in women who had such a family history and accumulated 30 or fewer pack-years (RR = 1.95; 95% CI, 1.36–2.81) but more than four times as high in women who had a family history of breast cancer and accumulated more than 30 pack-years (RR = 4.33; 95% CI, 1.65–11.40) in comparisons with women without a family history who did not smoke. In contrast, the study did not find an association between smoking and risk for breast cancer among women without

a family history of breast cancer: fewer than 30 pack-years (RR = 0.98; 95% CI, 0.87–1.10) and 30 or more pack-years (RR = 0.97; 95% CI, 0.72–1.31). These studies provide strong evidence that genetic factors represented by family history of breast cancer modify the risk for that cancer associated with smoking. More studies are needed to replicate this interaction of smoking and family history and to identify underlying genetic mechanisms.

BRCA1/BRCA2

An estimated 5–10% of all diagnosed breast cancer is inherited, with 2–3% involving mutations in one of the tumor suppressor genes *BRCA1* or *BRCA2* (Ashworth et al. 2010). These mutations account for nearly 40–50% of familial breast cancer cases (Chen et al. 2006b; Ashworth et al. 2010), and women with these mutations are at high risk for developing breast cancer, especially at an early age (Chen et al. 2006b). The cumulative incidence of breast cancer is also high for those who carry an inherited *BRCA* mutation, with an estimated lifetime risk of at least 43–46% by age 70 (Chen et al. 2006b), although estimates of 60–80% have been proposed (Ashworth et al. 2010). These estimates have varied considerably depending on the patients selected and patterns of inheritance. As a result, there is considerable inconsistency among reports to date.

Eight studies (Brunet et al. 1998; Ghadirian et al. 2004; Colilla et al. 2006; Gronwald et al. 2006; Nkondjock et al. 2006; Breast Cancer Family Registry (BCFR) 2008; Ginsburg et al. 2009; Moorman et al. 2010) have examined whether carriers of *BRCA1* and *BRCA2* mutations are more susceptible or less susceptible to cigarette smoke than are noncarriers. Terry and Goodman (2006) reviewed four of these studies (Brunet et al. 1998; Ghadirian et al. 2004; Colilla et al. 2006; Gronwald et al. 2006); in the earliest one, Brunet and colleagues (1998) reported inverse associations between breast cancer and accumulating 4 or more pack-years in carriers of *BRCA1* (OR = 0.47; 95% CI, 0.26–0.86) and *BRCA2* genes (OR = 0.39; 95% CI, 0.10–1.49). A subsequent study by the same team of investigators, based on an extended dataset of subjects from 52 centers in 11 countries, failed to replicate this finding (Ghadirian et al. 2004). Overall, risk of breast cancer from smoking in this study was not significantly decreased for carriers of *BRCA1* (OR = 1.09; 95% CI, 0.87–1.33) or *BRCA2* (OR = 0.97; 95% CI, 0.68–1.38), and no trend was observed with lifetime smoking (Ghadirian et al. 2004). However, using a retrospective cohort study design that included a subset of participants from the same study population as in Ghadirian and colleagues (2004), Colilla and colleagues (2006) reported a reduced risk of breast cancer among ever smokers with *BRCA1* mutation (RR = 0.63; 95% CI, 0.47–

0.87) and inverse dose-response relationships for both less than 20 pack-years (RR = 0.72; 95% CI, 0.52–1.00) and 20 or more pack-years (RR = 0.41; 95% CI, 0.23–0.71; p trend = 0.0007). The study also reported that women with the *BRCA1* mutation and who also had a specific polymorphism in the *A1B1* (estrogen receptor coactivator) gene who accumulated 20 or more pack-years of smoking had greatly reduced risk (OR = 0.19; 95% CI, 0.07–0.54).

Ginsburg and colleagues (2009) expanded the number of *BRCA1/2* carriers from the study by Ghadirian and colleagues (2004). The reanalysis of the expanded data set revealed no significant association between risk for breast cancer and ever smoking in carriers of *BRCA1* (OR = 1.09; 95% CI, 0.95–1.24) or *BRCA2* (OR = 0.81; 95% CI, 0.63–1.05) (Ginsburg et al. 2009). Carriers of *BRCA1* who were former smokers, however, had a significantly greater risk of breast cancer (OR = 1.27; 95% CI, 1.06–1.50), but no association was found among carriers of *BRCA1* who were current smokers (OR = 0.95; 95% CI, 0.81–1.12). Total lifetime cigarette consumption was significantly and positively associated with breast cancer among carriers of *BRCA1* who were former smokers (p trend = 0.007). The study did not find a significant association with former smoking in *BRCA2* carriers, but current smoking had a nonsignificant inverse association (OR = 0.71; 95% CI, 0.50–1.00). Smoking before the age of 18 was not significant in either carrier group: *BRCA1* (OR = 1.11; 95% CI, 0.89–1.18) or *BRCA2* (OR = 0.78; 95% CI, 0.59–1.04).

Results have been inconsistent in other studies. In a matched case-control study in Poland, Gronwald and colleagues (2006) reported no association of smoking with breast cancer for *BRCA1* carriers (OR = 1.10; 95% CI, 0.8–1.5). Nkondjock and colleagues (2006) conducted a nested case-control study in a cohort of 80 French-Canadian families in which *BRCA1/2* was present in 89 breast cancer cases and 48 controls. The study reported no association with 14 or fewer pack-years (OR = 0.86; 95% CI, 0.34–2.21) or more than 14 pack-years (OR = 0.74; 95% CI, 0.31–1.75) of smoking (p trend = 0.49). However, the BCFR (2008)—a consortium of research groups in the Australia, Canada, and the United States—obtained different results in their case-control study. That study reported increased risks for current smokers with *BRCA1/2* mutations (OR = 2.08; 95% CI, 1.41–3.06) and in *BRCA1* (OR = 2.33; 95% CI, 1.56–3.47) and *BRCA2* carriers (OR = 2.64; 95% CI, 1.78–3.90). Moreover, in carriers of both mutations, risk of breast cancer increased significantly with duration of smoking (approximately 7% per pack-year; p <0.001). Overall, the cumulative incidence of breast cancer by 50 years of age for those with a *BRCA1* mutation was about 60% in smokers versus 35% in nonsmokers, and for a *BRCA2* mutation it was 35% in smokers compared with 15% in nonsmokers (BCFR 2008).

In a case-only analysis, Moorman and colleagues (2010) reported no significant interactions between ever smoking and *BRCA1* or *BRCA2* status.

Lecarpentier and colleagues (2011) evaluated the association of smoking and breast cancer in the French National *BRCA1/2* carrier cohort. Sixty-five percent of the cohort (863 women) had *BRCA1* mutations and the remainder (474) had *BRCA2* mutations. Among the *BRCA1* carriers, risk was increased among current smokers who reported no alcohol consumption (RR = 2.09; 95% CI, 0.94–4.65) but not among those who reported ever use of alcohol (HR = 0.87; 95% CI, 0.52–1.43). This difference between nonusers and ever users of alcohol was even greater among those with 21 or more pack-years of smoking (RR = 3.29; 95% CI, 1.09–9.95 vs. RR = 0.87; 95% CI, 0.45–1.68). Among *BRCA2* carriers, there was no significant increase in risk of breast cancer for either current (RR = 1.39; 95% CI, 0.73–2.63) or former smokers (RR = 1.18; 95% CI, 0.60–2.33), but risk was significantly higher for women who reported 21 or more pack-years (RR = 2.25; 95% CI, 1.05–4.82).

In summary, studies of effect modification of smoking by *BRCA1* or *BRCA2* on breast cancer have been inconsistent. Two studies reported an inverse association (Brunet et al. 1998; Colilla et al. 2006), four reported no association (Ghadirian et al. 2004; Gronwald et al. 2006; Nkondjock et al. 2006; Moorman et al. 2010), and one reported a significant positive association (BCFR 2008). Two studies (Ginsburg et al. 2009; Lecarpentier et al. 2011) reported positive results for some measures of smoking but these were inconsistent and difficult to interpret. For example, Ginsburg and colleagues (2009) reported a positive association in women with *BRCA1* mutations who were former but not current smokers; there were no associations in women with the *BRCA2* mutation. As noted previously, Lecarpentier and colleagues (2011) reported positive associations only in women with *BRCA1* who reported never using alcohol; risk was only significantly increased in *BRCA2* carriers who reported 21 or more pack-years of smoking. Of note, four of these reports were based on overlapping participant populations and contradictory results (Brunet et al. 1998; Ghadirian et al. 2004; Colilla et al. 2006; Ginsburg et al. 2009).

Carcinogen Metabolism

Researchers have also addressed common polymorphisms with low penetrance and small additive or multiplicative impacts on risk of breast cancer (Pharoah et al. 2002). With regard to smoking, researchers have considered common genetic variants in biologic pathways that regulate the metabolism and detoxification of tobacco-related carcinogens (Ambrosone and Shields 1999b; Coyle

2004). Thus, a growing number of studies have been designed to examine genetic polymorphisms in enzyme systems—such as GST, cytochrome P-450, and NATs.

N-*Acetyltransferase* Polymorphisms

The strongest evidence to date for genetic susceptibility to smoking and breast cancer has been for the arylamine NATs, which are enzymes involved in both the detoxification and activation of heterocyclic and aromatic amines (carcinogenic compounds found in cigarette smoke) (Hein 2002). The polymorphisms in the genes for the NAT1 and NAT2 enzymes are very complex; as a result, past studies have been subject to misclassification of the metabolic phenotype, with consequent difficulty in detecting and interpreting associations. Since the first consensus nomenclature was published (Vatsis et al. 1995), the classification has become better standardized with continuing updates (University of Louisville 2013). This improvement has reduced bias in assessing the interaction between NAT phenotypes and smoking and has improved comparisons across studies and the derivation of pooled estimates of effects (Deitz et al. 2004). Evidence clearly indicates that polymorphisms in the *NAT2* gene affect the efficiency of the enzyme system in detoxifying carcinogenic amines and that acetylation status (rapid, intermediate, slow, and very slow) is correlated with carcinogen metabolism, resulting in activation or deactivation of xenobiotics (Hein et al. 2000a,b, 2002). In comparisons with rapid acetylator phenotypes, the slow and very slow acetylator phenotypes have been reported to be associated with an increased frequency of DNA adducts, a phenomenon that appears to be due to reduced detoxification of carcinogenic amines (Pfau et al. 1998; Firozi et al. 2002). Although the prevalence of slow acetylator status varies across populations, it has been reported to be as high as 50–60% in some (Wacholder et al. 2000), with evidence for racial/ethnic variation in the frequencies of *NAT2* genotypes (Garcia-Martin 2008). Previous studies of NAT2 have reported associations with other cancers that may vary due to activation or inactivation of *N*-hydroxylated heterocyclic amines. Slow acetylation increases the risk for bladder cancer and rapid acetylation increases the risk for colon cancer (Abel and DiGiovanni 2008).

Several studies have evaluated the associations of *NAT1* and *NAT2* polymorphisms with breast cancer and many of these have examined interactions with smoking. Only a few studies have examined *NAT1* (Millikan et al. 1998; Krajinovic et al. 2001; Lee et al. 2003; van der Hel et al. 2003b; Zheng et al. 1999), as the majority of studies have focused on *NAT2*. Even with standardization, continuous updates have been made with the identification of new alleles. Currently, acetylation status is based on the categorization of rapid activity *(NAT2*4, NAT2*12, NAT2*13),* slow activity *(NAT2*5, NAT2*6, NAT2*7, NAT2*14),* and intermediate activity (one allele associated with rapid acetylation activity and one with slow activity). Very slow activity is associated with being homozygous for *NAT2*5* (Hein 2009a).

In the mid-1990s, Ambrosone and colleagues (1996) reported that the association between smoking and breast cancer was elevated in women with NAT2 slow acetylator status, while those with a rapid acetylator status had a nonsignificant decreased risk. This finding was replicated 12 years later in a meta-analysis and pooled analysis reported by Ambrosone and colleagues (2008) that in total involved 4,889 premenopausal and 7,033 postmenopausal women. Women with a history of ever smoking who were slow acetylators were at increased risk (vs. never smokers) both overall (RR = 1.27; 95% CI, 1.16–1.40) and by menopausal status (RR = 1.34; 95% CI, 1.17–1.53 for postmenopausal and 1.28; 95% CI, 1.09–1.50 for premenopausal) (Table 6.21*S*). No increased risk was reported in women who were ever smokers and rapid acetylators (RR = 1.05; 95% CI, 0.95–1.17). Risk was further increased in slow acetylators among those with 20 or more pack-years (meta-analysis RR = 1.44; 95% CI, 1.23–1.68), but not in their counterparts who were rapid acetylators (RR = 1.04; 95% CI, 0.87–1.25); this pattern was seen for both premenopausal and postmenopausal women (Table 6.21*S*). The association was also present for duration of smoking 15 or more years in slow acetylators regardless of menopausal status: premenopausal, RR = 1.35 (95% CI, 1.11–1.65); postmenopausal, RR = 1.40 (95% CI, 1.11–1.76) versus never smokers. Results from the pooled analysis were consistent with the meta-analysis, with an overall RR summary estimate of 1.49 (1.08–2.04) for women with a history of 20 or more pack-years of smoking and the NAT2 slow acetylator phenotype compared with never active smokers who had the rapid acetylator phenotype. The interaction of *NAT2* genotype with smoking was significant for ever smoking (p = 0.02), pack-years of smoking (p = 0.03), and duration of smoking (p = 0.007) (Ambrosone et al. 2008).

Before the publication from Ambrosone and colleagues (2008), 1 summary review and 1 meta-analysis reported on the interaction of NAT2 with smoking on risk for breast cancer. Terry and Goodman's (2006) meta-analysis was based on 13 studies and reported an increased risk for breast cancer among postmenopausal women who smoked and were classified as slow acetylators (Table 6.21*S*). Ochs-Balcom and colleagues' (2007) review of 12 studies also found evidence that *NAT2* modified risk for breast cancer among women who smoked. A recent meta-analysis by Zhang and colleagues (2010) provided results for the association of *NAT2* with breast cancer modified by

smoking rather than modification by *NAT2* of the association of smoking with risk of breast cancer. As such, the estimates from this meta-analysis cannot be compared with previous findings. Zhang and colleagues (2010) extracted data from studies to recalculate ORs for the main effects of *NAT2* and *NAT2* modified by pack-years of smoking, but in doing this, they could not take into account covariates from original analyses for the effect of smoking modified by *NAT2*. Nonetheless, a significant interaction was found. Taken together, the results of these meta-analyses suggest that the *NAT2* genotype modifies the risk for breast cancer in women who smoke. In addition, there is an increased risk of about 40–50% in women who have the NAT2 slow acetylation phenotype who smoke.

Two studies have been published since the comprehensive meta-analysis from Ambrosone and colleagues (2008). In a case-control study (717 cases and 735 controls) of Hispanic and non-Hispanic White women in New Mexico, Baumgartner and colleagues (2009) reported an interaction between a history of ever smoking and the *NAT2* phenotype that approached significance in non-Hispanic White women only (p for interaction = 0.06). The risk estimate (OR) for ever smokers with the very slow phenotype was 2.57 (95% CI, 1.49–4.41). In this study, risk was increased similarly in former and current smokers with the very slow phenotype. In Germany, Rabstein and colleagues (2010) reported results for a case-control study involving 1,155 cases and 1,143 controls. The study did not find an interaction between smoking and the NAT2 phenotype, even when results were stratified by ER phenotype.

Finally, a report from the Breast and Prostate Cancer Cohort Consortium (Cox et al. 2011) pooled data for 6,900 cases and 9,903 controls from seven separate studies (CPS-II/1998, NHS-I/1989 and NHS-II/1999, EPIC 1992, Multi-Ethnic Cohort Study/1996, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial/1993, and Women's Health Study/1993). A significant interaction was not found between duration or pack-years of smoking and the NAT2 acetylation phenotype. Risk of breast cancer was increased in those with more than 20 pack-years of smoking and fast acetylation status, which was defined as a combination of rapid and intermediate phenotypes (OR = 1.24; 95% CI, 1.08–1.42), as well as in slow acetylators (OR = 1.25; 95% CI, 1.11–1.39). Adjustment included a number of covariates, but not the use of alcohol. This report weakens the evidence for *NAT2* as an effect modifier of smoking on the risk of breast cancer.

Cytochrome P-450 Polymorphisms

CYP1A1 and *CYP1B1* are gene-encoding enzymes involved in the metabolism of estradiol and PAHs. Muta-

genic intermediates generated in this pathway can damage DNA (Sillanpaa et al. 2007). The *CYP1A1* gene encodes a Phase I enzyme that contributes to aryl hydrocarbon hydroxylase activity and metabolism of PAHs, which have been detected in both normal and cancerous breast tissues (Terry and Rohan 2002; Masson et al. 2005). *CYP1B1* is involved in estrogen homeostasis in normal breast tissue and is expressed in breast tumors (Rylander-Rudqvist et al. 2003).

Studies have not documented an interaction of smoking and polymorphisms in these *CYP* genotypes on risk for breast cancer. Masson and colleagues (2005) reviewed five studies with data on the interaction of smoking and *CYP1A1* polymorphisms on risk for breast cancer (Ambrosone et al. 1995; Bailey et al. 1998; Ishibe et al. 1998; Taioli et al. 1999; Basham et al. 2001), but only one (Ambrosone et al. 1995) provided evidence for a possible interaction, and a formal statistical test was not conducted in that study. Furthermore, results from these studies are difficult to interpret because of their small samples and differences in reference groups, categories of smoking, and definition of interactions. Terry and Goodman (2006) conducted a meta-analysis of four studies (Ambrosone et al. 1995; Ishibe et al. 1998; Basham et al. 2001; Li et al. 2004), three of which (all but Li et al. 2004) were reviewed by Masson and colleagues (2005). The summary estimate among smokers with the wild-type genotype (OR = 1.3; 95% CI, 1.0–1.6) did not differ significantly from those with variant alleles (OR = 1.2; 95% CI, 0.6–2.1), suggesting no interaction.

Studies of the interaction between *CYP1B1* polymorphisms and smoking on risk for breast cancer have produced mixed results. Saintot and colleagues (2003) reported increased risk for breast cancer among former smokers (OR = 1.33; 95% CI, 0.59–2.96) and current smokers (OR = 2.32; 95% CI, 1.00–5.38) with the *CYP1B1 LEU/LEU* genotype compared with nonsmokers with *VAL* alleles. In contrast, Rylander-Rudqvist and colleagues (2003) reported no association between smoking and any *CYP1B1* genotype on risk for breast cancer. The case-control study conducted by Sillanpaa and colleagues (2007) reported unstable findings because of small samples in some strata: for example, risk was increased significantly among smokers who consumed 1–9 cigarettes per day and (a) were carriers of the *CYP1B1 VAL* allele (OR = 2.63; 95% CI, 1.07–6.46) or (b) had the *VAL/VAL* genotype (OR = 5.09; 95% CI, 1.30–19.89; p trend = 0.005), but these increased risks were not observed in women who smoked more than 10 cigarettes per day. Results for duration of smoking and pack-years of smoking were also contradictory.

Sillanpaa and colleagues (2007) also reported a significant increased risk for breast cancer in smokers with the *CYP1B1 VAL* allele who were NAT2 slow acetylators

(OR = 2.46; 95% CI, 1.11–5.45), suggesting a potential three-way interaction between smoking, *CYP1B1,* and *NAT2.* Van Emburgh and colleagues (2008b) reported a significant interaction (p = 0.02) between smoking and the *CYP1B1 119S* allele on risk for breast cancer in African Americans but not in Whites. Taken together, these studies do not provide strong or consistent evidence for modification of risk for breast cancer from smoking by polymorphisms in genes for the CYP enzyme system.

Glutathione S-transferases

GSTs are Phase II enzymes that metabolize and detoxify endogenous and exogenous substances, including tobacco smoke carcinogens—specifically PAHs (Terry and Goodman 2006). DNA adducts are more common in smokers with breast cancer who have certain polymorphisms in genes for the GST enzymes (van der Hel et al. 2003b). The GST enzyme system contains eight families of genes, and polymorphisms have been described in several of these families—mainly mu (M1), theta (T1), and pi (P1) (Vogl et al. 2004; Terry and Goodman 2006). *GSTM1* and *GSTT1* are deletion (*null*) polymorphisms that result in the absence of protein expression.

Terry and Goodman (2006) performed a meta-analysis of seven studies (Ambrosone et al. 1995; Garcia-Closas et al. 1999; Millikan et al. 2000; Zheng et al. 2002a,b; van der Hel et al. 2003b, 2005) that investigated the potential modification by *GSTM1* and *GSTT1* of the association between smoking and risk for breast cancer. Six studies were population-based or nested case-control designs and one was a case-cohort study. Using categories for longest duration of smoking, the RRs from the meta-analysis were 1.4 (95% CI, 1.1–1.9) for *GSTM1null* versus 1.10 (95% CI, 0.80–1.40) for *GSTM1present,* suggesting possible effect modification. In contrast, smoking was associated with breast cancer regardless of *GSTT1* genotype: *GSTT1null* (meta-RR = 1.20; 95% CI, 0.90–1.70) and *GSTT1present* (meta-RR = 1.30; 95% CI, 1.10–1.60).

Several studies have examined the main effects of *GST* polymorphisms on risk for breast cancer stratified by smoking status. Although these studies did not provide estimates by genotype for modification of the association between smoking and breast cancer, many included tests for interaction that can be interpreted as evidence that a polymorphism alters this association. Vogl and colleagues (2004) pooled results from seven case-control studies (Bailey et al. 1998; Maugard et al. 1998; Nedelcheva et al. 1998; Ambrosone et al. 1999a; Zhao et al. 2001; da Fonte de Amorim et al. 2002; Zheng et al. 2002b) and found no evidence of significant interaction between smoking and *GSTM1, GSTT1, or GSTP1* polymorphisms. A study by

Mitrunen and colleagues (2001a), which was not included in the pooled analysis by Vogl and colleagues (2004), did not detect any interaction between a history of smoking and either *GSTM1, GSTM3, GSTP1,* or *GSTT1* genetic polymorphisms. Subsequent studies have not reported significant interactions between *GST* polymorphisms and smoking on risk for breast cancer (Linhares et al. 2005; Ahn et al. 2006; Olsen et al. 2008; Van Emburgh et al. 2008b; McCarty et al. 2009; Andonova et al. 2010). Thus, with the possible exception of *GSTM1,* the evidence to date does not support modification of the breast cancer–smoking association by polymorphisms in the GST enzyme system.

Sulfotransferase 1A1

SULT enzymes activate or inactivate PAHs and heterocyclic amines from cigarette smoke through sulfonate conjugation. A common polymorphism *(ARG213HIS)* in SULT1A1 results in reduced enzyme activity and efficiency of this pathway (Terry and Goodman 2006). Only three studies to date have examined interactions between this polymorphism and smoking on risk for breast cancer (Saintot et al. 2003; Lilla et al. 2005; Sillanpaa et al. 2005b). The case-only study by Saintot and colleagues (2003) suggested interactions between the *HIS* allele and both duration of smoking (>20 years) (OR = 1.71; 95% CI, 0.97–3.03) and intensity of smoking (>5 cigarettes/day) (OR = 1.65; 95% CI, 0.97–2.80). In contrast, two subsequent case-control studies did not find evidence of an interaction between SULT1A1 and smoking (Lilla et al. 2005; Sillanpaa et al. 2005b).

Oxidative Metabolism Genotypes

Smoking is associated with increased oxidative stress (Pryor and Stone 1993), and superoxide dismutase 2 (SOD2) is a mitochondrial enzyme that protects against oxidative stress. A common polymorphism in the gene for SOD2 reduces the activity of this enzyme and is reportedly associated with several cancers, including breast cancer (Millikan et al. 2004; Gaudet et al. 2005). Terry and Goodman (2006) reviewed four case-control studies on the modification of risk for breast cancer by smoking and SOD2 (Mitrunen et al. 2001b; Millikan et al. 2004; Tamimi et al. 2004; Gaudet et al. 2005); in one of the studies, Millikan and colleagues (2004) reported a significant increased risk of breast cancer for smoking duration of more than 20 years in women homozygous for the variant *ALA* allele (OR = 1.5; 95% CI, 1.0–2.2). However, an increased risk for ever smokers who were homozygous for the wild-type *VAL* allele (OR = 2.6; 95% CI, 1.1–6.3) was reported (as calculated by Terry and Goodman [2006] for

the study by Gaudet and colleagues [2005]). Results from the other two studies were null. The overall meta-RR estimate for the four studies was 1.5 (95% CI, 1.1–2.1). Only two other case-control studies have been published since this review (Slanger et al. 2006; Kostrykina et al. 2009); neither found significant interactions between SOD2 and smoking or main effects of SOD2 or smoking on risk for breast cancer.

DNA Repair Genes

Terry and Goodman (2006) reviewed seven studies with data on modification of risk for breast cancer by smoking and DNA repair genotypes, including polymorphisms in *XRCC1*, *XPD*, and *MGMT*. Five studies, which included two or three different polymorphisms in *XRCC1* (*ARG^{399}GLN, ARG^{194}TRP, AND ARG^{280}HIS*) and widely different smoking exposures (ever smoking, duration >20 years, >5 pack-years of smoking), produced inconsistent results (Duell et al. 2001; Metsola et al. 2005; Patel et al. 2005; Shen et al. 2005a; Pachkowski et al. 2006). The meta-analytic summary estimate for smoking exposure was significant only for women homozygous for *194 ARG/ARG*. Two studies of the *XPD LYS751GLN* polymorphism reported nonsignificant increased risks for smokers with the *GLN/GLN* genotype (as calculated by Terry and Goodman [2006] for the studies by Terry and colleagues [2004] and Metsola and colleagues [2005]). A study by Shen and colleagues (2005b) reported increased risk in heavy smokers with *MGMT LEU84PHE* and *ILE143VAL* polymorphisms.

In the NHS-I cohort, Han and colleagues (2003) found no evidence for effect modification of smoking by any of four SNPs (*ARG^{194}TRP, C26602T, ARG^{399}GLN,* and *GLN^{632}GLN*) in *XRCC1*. Subsequently, Han and colleagues (2004) reported no interaction between smoking and SNPs in the *XRCC2, XRCC3,* and *LIG IV* genes, and Han and colleagues (2006) did not report such an interaction in the *MGMT* gene. Shore and colleagues (2008) reported an interaction between smoking and a SNP in the *XPC* gene that approached significance (p = 0.08) in the NYU Women's Health Study. Mechanic and colleagues (2006) found that the combination of smoking and four or more SNPs in several nucleotide excision repair genes *(XPD, XPC, RAD23B, XPG, XPF,* and *ERCC6)* significantly modified the risk for breast cancer in African American, but not White, women. Similarly, Metsola and colleagues (2005) found strong evidence for modification of the association between smoking and the combination of two or more SNPs in *XRCC1* and *XPD* on the risk for breast cancer. Future studies should emphasize interactions between smoking and combinations of SNPs within and across genes (Neumann et al. 2005).

Since 2000, several studies have evaluated SNPs in the nuclear receptor coactivator *AIB1* gene (Colilla et al. 2006), the *IGHMBP2* gene (Shen et al. 2006), the *A-T* gene (Swift and Lukin 2008), the *NOS3* and *MPO* genes (Yang et al. 2007), and the *mEH* gene (de Assis et al. 2002) for interaction with smoking on risk of breast cancer. However, the results have been either null or indicated only weak associations. None of these studies have been replicated to date. Additionally, three studies evaluated the association between smoking and *p53* mutational status as a measure of apoptosis (Conway et al. 2002; Furberg et al. 2002; Gaudet et al. 2008). A recently published analysis of more extensive data from the Long Island Breast Cancer Study Project suggested that cigarette smoking and passive smoking were more strongly associated with p53-negative cancer (Mordukhovich et al. 2010), which contrasts with results reported by Conway and colleagues (2002), Van Emburgh and colleagues (2008a), and an earlier analysis of the Long Island study (Gaudet et al. 2008).

Genetic Susceptibility—Summary

The epidemiologic studies conducted to date have not established clear or consistent evidence for modification of the association between smoking and breast cancer by genes that influence susceptibility to tobacco-related carcinogens. The published reports support only genetic variation in *NAT2* as a potential effect modifier of the association of breast cancer with smoking, although this finding has been weakened by the recent report of Cox and colleagues (2011). Unfortunately, a variety of limitations have affected these studies. First, many have been too small to provide adequate statistical power for detecting interactions between smoking and low-frequency genotypes. Terry and Goodman (2006) reported that statistical power was less than 80% for detecting a risk estimate of at least 2.0 for breast cancer for the majority (68%) of studies in their review. In addition, the definitions of smoking exposure have varied widely across studies, making it difficult to combine estimates in meta-analyses. Most studies have tested only a limited number of selected SNPs in specific groups of candidate genes, targeting mainly those that influence carcinogen metabolism, oxidative stress, or DNA repair. Not all of these studies have established the functionality of SNPs. Only a few studies have analyzed interactions of smoking with haplotype combinations of SNPs within or across genes. Investigators will likely continue to examine this important area of research by combining genomewide association studies with gene expression assays to identify functional gene variants that modify susceptibility to smoking (Chung et al. 2010).

Summary and Review of Active Cigarette Smoking

The 2004 Surgeon General's report on active cigarette smoking concluded that there was (a) no consistent evidence for an association between active smoking and breast cancer, and that (b) subgroups of women could not be reliably identified that were at increased risk of breast cancer due to smoking. Since the previous report, 12 cohort and 30 case-control studies have been published on the association of smoking with breast cancer. Several large cohort studies now provide consistent evidence for a significant, although weak, positive association. While the findings from the case-control studies are more variable, when considered together the results are in keeping with those from the cohort studies. The meta-analyses confirm a weak but statistically significant, positive association of smoking with risk of breast cancer. The estimates for active smoking tend to be higher when based on data from case-control studies than on data from cohort studies; but there is greater heterogeneity among estimates from case-control studies. Sensitivity analyses reveal that this heterogeneity is largely related to issues in the design or analysis of certain studies. When these studies are removed, the summary estimates from the case-control studies converge to agreement with those from the cohort studies. The sensitivity analyses also suggest that the positive association of smoking with breast cancer is statistically robust.

Ever smoking is associated with a significant increase in RR of about 10% (Table 6.17*S*). The magnitude of the association appears to be slightly stronger for current smoking (12%) than for former smoking (9%). It is increased by 16% for duration of 20 or more years, 13% for smoking 20 or more cigarettes per day, and 16% for accumulating 20 or more pack-years. There is no clear evidence that earlier age at initiation of smoking (8%) or smoking before first pregnancy (10%) is associated with a greater risk of breast cancer than is ever smoking. There is evidence, based on the most conservative combined study design estimates, that among ever smokers, premenopausal women have a slightly higher increase in risk than postmenopausal women, 17% versus 7%, respectively (Table 6.18*S*). It remains to be established whether smoking is more strongly associated with a particular tumor phenotype. There is no consistent evidence to date that subpopulations of women with genetic susceptibility to tobacco-related carcinogens (even *NAT2*, given the most recent report by Cox and colleagues [2011]), can be reliably identified as being at increased risk for breast cancer.

The use of a no active/no passive exposure referent appears to have a small impact on most summary estimates, but this can be difficult to interpret because it results in a very small reference group and a loss of statistical power. Future studies need to determine whether statistical adjustment for exposure to passive smoking is adequate. This may require stronger techniques and methods of measuring exposure to secondhand smoke.

Major Summary Points for Active Smoking

1. Based on 22 cohort reports published prior to 2012 and 27 case-control reports published from 2000–2011, evidence suggests that a history of ever smoking is associated with an increase in the RR for breast cancer by an average of 10%; long duration of smoking (20 or more years), greater number of cigarettes smoked per day (20 or more), and more pack-years of smoking (20 or more) significantly increase risk for breast cancer by 13–16%, depending on study design and the exclusion of studies with design or analysis issues.

2. Studies have not clearly determined whether either early age at smoking initiation or smoking before first pregnancy is associated with increased risk for breast cancer over and above the risk due to ever smoking.

3. Studies have not clearly determined whether the use of a restricted no active/no passive exposure reference group or adjustment for exposure to passive smoking meaningfully alters or clarifies the association between smoking and risk for breast cancer.

4. The extent to which the use of alcohol confounds the association between smoking and risk for breast cancer remains uncertain and should be considered in relation to the duration, dose, and timing of smoking.

5. There is emerging evidence to suggest that the risk of breast cancer from smoking may be greater in premenopausal than postmenopausal women, 17% versus 7%, or a relative difference of 9%.

6. There is insufficient evidence to conclude that the risk of breast cancer from smoking differs between women diagnosed with ER+ tumors and those diagnosed with ER– tumors.

7. With the possible exception of the polymorphism in the NAT2 carcinogen metabolism pathway, subgroups of women who are at increased risk of breast cancer because of the interaction between smoking and genotype cannot be identified reliably.

Exposure to Secondhand Smoke and Risk for Breast Cancer

Compared with directly inhaled tobacco smoke or mainstream smoke, the evidence indicates that undiluted sidestream smoke, the major contributor to secondhand smoke (passive smoke, involuntary smoking, environmental tobacco smoke [ETS]), contains higher levels of several substances considered to be carcinogenic, cocarcinogenic, or toxic—including benzene, formaldehyde, catechol, and *N*-nitrosamines (IARC 2004; USDHHS 2010). Measuring exposure to secondhand smoke for assessment of cancer risk poses challenges, however, because an ideal comprehensive assessment should address duration of exposure, dosage (exposure time, number of people who smoke in the immediate environment, number of cigarettes smoked by smokers, ventilation), location of exposure (home, workplace), time period of exposure (childhood, adulthood), and method of assessing exposure (self-report, biologic specimen). Other relevant issues include the pervasiveness of secondhand smoke in the environment, particularly in the past in the United States and some other Western countries, changes in intensity over time, measurement error, and information bias that may dilute estimates of association (Kawachi and Colditz 1996). Methodologic issues in investigating secondhand smoke and disease risk were addressed in the 2006 report of the Surgeon General. Despite strong evidence from cotinine levels of declining exposure to secondhand smoke in the United States, there is no level of exposure considered to be risk free (USDHHS 2006), and high levels of exposure persist for some groups (Chen et al. 2010a).

Exposure to secondhand smoke has been investigated as a risk factor for breast cancer over nearly three decades. Sandler and colleagues (1985a) first evaluated the association between passive smoking exposure and breast cancer in the mid-1980s in a small hospital-based case-control study in North Carolina. In the early 1990s, Wells (1991) analyzed data from Hirayama's large Japanese cohort study (Hirayama 1984, 1990), which was initiated in 1965. Both studies found nonsignificantly increased risks for breast cancer. These and several subsequent studies had limitations, however, such as mixing incident and prevalent cases with breast cancer deaths; using proxy reports; having limited data for duration, dose, location, and timing of exposure; and adjusting inadequately for relevant confounders. Palmer and Rosenberg (1993) cited only the reports from Hirayama (1984), Sandler and colleagues (1986), and Wells (1991); the latter was a reanalysis of the data from the studies by Hirayama (1984) and Sandler and colleagues (1985a). They concluded that "so little research" had been conducted that it was "not possible to reach any conclusions" (Palmer and Rosenberg 1993, p. 152).

Several meta-analyses and monographs about passive smoking and breast cancer have been published or released, some not long before or after the 2006 Surgeon General's report (Khuder and Simon 2000; Khuder et al. 2001; Morabia 2002a; Cal/EPA 2005; Johnson 2005; Lee and Hamling 2006; Nagata et al. 2006; Pirie et al. 2008; Collishaw et al. 2009; Secretan et al. 2009). The authors of these studies have drawn markedly different interpretations and conclusions, despite considerable overlap among some of these reports in the studies reviewed and evaluated through meta-analysis.

Khuder and Simon (2000) published one of the first systematic reviews of passive smoking and risk for breast cancer. That review examined 11 reports (3 cohort and 8 case-control) that were published between 1984 and 2000 (Hirayama 1984; Sandler et al. 1986 [based on Sandler et al. 1985a]; Smith et al. 1994; Morabia et al. 1996; Johnson et al. 1998, 2000; Jee et al. 1999; Lash and Aschengrau 1999; Liu et al. 2000; Marcus et al. 2000; Wartenberg et al. 2000). Two of the three cohort studies examined breast cancer mortality (Hirayama 1984; Wartenberg et al. 2000), and one was reported as an abstract (Johnson et al. 1998). Results were summarized using the random-effects model. The summary estimate of the RR for ever being exposed to secondhand smoke was 1.41 (95% CI, 1.14–1.75). Based on their results, Khuder and Simon (2000) suggested a "possible weak association between passive smoking and breast cancer" (p. 1117) and that more studies were needed. Morabia (2002a) also reviewed the associations between passive smoking, as well as active smoking, and breast cancer. This review considered most of the same studies assessed by Khuder and Simon (2000) but did not calculate a summary estimate. Instead, Morabia (2002a) noted that ORs were greater than 1.5 in 5 of the 11 case-control studies he reviewed and emphasized the importance of separating passive from active exposures in future studies.

The 2004 IARC monograph reviewed results from 5 cohort and 10 case-control studies and concluded that the "collective evidence on breast cancer risk associated with involuntary exposure of never smokers to tobacco smoke is inconsistent" (p. 1410). The monograph emphasized results from the NHS-I (Egan et al. 2002) and the CPS-II (Wartenberg et al. 2000), noting that these large cohort studies "provided no support for a causal relation between involuntary exposure to tobacco smoke and breast cancer in never smokers," that the "lack of a positive dose-response also argue[d] against a causal interpretation of these findings," and that "the lack of an association of breast cancer with active smoking weighs heavily against the possibility that involuntary smoking increases the risk for breast cancer, as no data are available to establish that different mechanisms of carcinogenic action operate at the different dose levels of active and of involuntary smoking" (IARC 2004, p. 1410).

In contrast, a report from 2005 about secondhand smoke as a toxic air contaminant (Cal/EPA 2005), which was also summarized by Miller and colleagues (2007), included an extensive section about breast cancer in which it noted that "the weight of evidence (including toxicology of ETS [environmental tobacco smoke] constituents, epidemiological studies, and breast biology) is consistent with a causal association between ETS exposure and breast cancer in younger, primarily premenopausal women" (Cal/EPA 2005, p. ES8). The pooled RR estimate was 1.68 (95% CI, 1.31–2.15), based on a meta-analysis of 14 studies reporting risk for breast cancer among never-smoking premenopausal women who reported exposure to passive smoking. However, the overall test for heterogeneity was significant (p = 0.001), suggesting substantial inconsistency across studies. When the analysis was restricted to 5 studies (Smith et al. 1994; Morabia et al. 1996; Zhao et al. 1999; Johnson et al. 2000; Kropp and Chang-Claude 2002) with what was considered "better exposure assessment" (Cal/EPA 2005, p. ES-3), the pooled RR estimate was 2.20 (95% CI, 1.69–2.87), and a test for heterogeneity was not significant (p = 0.354).

The Cal/EPA report differed from the 2006 Surgeon General's report with respect to two studies. The Cal/EPA excluded the study by Liu and colleagues (2000) because the panel found that the results were difficult to interpret as the study was clinic based and small (n = 186 cases) and reported results based on a passive smoking index (number of smokers times smoke exposure levels, defined as light, medium, or very heavy). The estimate of breast cancer risk for adult home exposure based on this index was RR = 4.07 (95% CI, 2.21–7.50) (Liu et al. 2000). However, the 2006 Surgeon General's report included estimates from Liu based on number of smokers exposed to smoke in the workplace and on levels of at-home smoke exposure by number of cigarettes smoked per day (≤2, 3–9, 10–19, ≥20) (Liu et al. 2000). In contrast to the estimated quadrupling of risk in the Cal/EPA report, the pooled risk estimate for adult home exposure was 1.47 (95% CI, 0.74–2.95) (Liu et al. 2000); this estimate was used in the meta-analysis in the 2006 Surgeon General's report. Additionally, the 2006 Surgeon General's report included the study by Bonner and colleagues (2005) that was published after the period of inclusion for studies in the Cal/EPA report had passed. This study reported a significant inverse association for exposure at the workplace (calculated pooled OR = 0.79; 95% CI, 0.65–0.96) but no significant effect for exposure at home (calculated pooled OR = 1.16; 95% CI, 0.96–1.41).

In a meta-analysis by Johnson (2005) of the association between passive and active smoking and breast cancer, the analysis for passive smoking was based on 19 studies (7 cohort and 12 case-control) that met specific quality criteria for study design and exposure measurement (Hirayama 1984; Sandler et al. 1985a; Smith et al. 1994; Morabia et al. 1996; Millikan et al. 1998; Jee et al. 1999; Lash and Aschengrau 1999, 2002; Zhao et al. 1999; Delfino et al. 2000; Johnson et al. 2000; Wartenberg et al. 2000; Nishino et al. 2001; Egan et al. 2002; Kropp and Chang-Claude 2002; Shrubsole et al. 2004; Gammon et al. 2004a; Reynolds et al. 2004b; Hanaoka et al. 2005). These studies were mostly the same as those included in the 2005 Cal/EPA report and the 2006 Surgeon General's report. The summary pooled risk estimate for all 19 studies using the broadest definition of passive smoking was 1.27 (95% CI, 1.11–1.45; test for heterogeneity p <0.001). The broadest definition of passive smoke exposure in most studies included the following: exposure from any source, including husband's smoking history; years smoked by spouse; lifetime residential childhood exposure; workplace exposure; and parental exposure. As in the Cal/EPA report, 5 case-control studies strongly influenced the summary of pooled risk estimate (Smith et al. 1994; Morabia et al. 1996; Zhao et al. 1999; Johnson et al. 2000; Kropp and Chang-Claude 2002), because they were considered to have the most complete assessments of exposure. The summary pooled risk estimate (RR) for these 5 studies was 1.90 (95% CI, 1.53–2.37). In contrast, the summary RR was 1.16 (95% CI, 0.95–1.42) for the remaining 7 case-control studies (those considered to have less complete assessments of exposure). The summary estimate for the 7 cohort studies was 1.06 (95% CI, 0.97–1.16). Johnson (2005) also calculated summary estimates for risk of breast cancer among premenopausal women by using data from 14 of the 19 studies. The overall summary estimate was higher for premenopausal women (RR = 1.68; 95% CI, 1.33–2.12; p = 0.002 for heterogeneity) than for all women

and was highest for the 5 studies (as a group) considered to have the most complete assessment of exposure (RR = 2.19; 95% CI, 1.68–2.84). Johnson (2005) did not calculate summary estimates by timing, source, duration, or dose of exposure to passive smoking. The author concluded that "studies with thorough passive smoking exposure assessment implicate passive and active smoking as risk factors for premenopausal breast cancer" but that more cohort studies with thorough exposure assessments were needed (Johnson 2005, p. 619).

Lee and Hamling (2006) conducted a systematic review and meta-analysis of 22 studies (13 case-control, 8 prospective cohort, and 1 nested case-control) involving nonsmoking women that were published through June 2005. RR estimates that adjusted for the greatest number of confounding variables for exposure to second-hand smoke at home, at the workplace, during childhood, during adulthood, or during lifetime were used when available. Results of the meta-analysis included several subgroup variables from the studies—including menopausal status (n = 11), the woman's age or the age of husband (n = 4), and genotype (n = 5). Results were also stratified by location, source, or timing of exposure: home (n = 19), workplace (n = 5), childhood (n = 9), spouse (n = 8), and lifetime (n = 6). A sensitivity analysis removed studies that adjusted for fewer than nine covariates but resulted in little inflation of the RR—from 1.23 (95% CI, 1.03–1.45) to 1.28 (95% CI, 1.07–1.53). Overall, this meta-analysis was similar to the one reported in the 2006 Surgeon General's report, although it excluded the study by Zhao and colleagues (1999) and did not include the study by Bonner and colleagues (2005), which was reported after its publication. The review by Lee and Hamling (2006) also included two abstracts (Rookus et al. 2000; Woo et al. 2000) and a cohort study reported on by Gram and colleagues (2005). The results were similar to those reported in the 2006 Surgeon General's report: a nonsignificant summary estimate based on 9 cohort studies (RR = 1.02; 95% CI, 0.93–1.10), a significant summary estimate based on 13 case-control studies (RR = 1.28; 95% CI, 1.07–1.53), and a significant increased risk for breast cancer among premenopausal women based on 10 studies (RR = 1.54; 95% CI, 1.16–2.05), but with significant heterogeneity (p <0.01). Additionally, risk estimates for small studies (<500 cases) were higher (RR = 1.27; 95% CI, 1.03–1.57) and showed significant heterogeneity compared with large studies (≥500 cases) (RR = 1.01; 95% CI, 0.93–1.09). Lee and Hamling (2006, p. 1,068) noted that "one cannot confidently conclude, based on the evidence available, that ETS exposure increases risk in nonsmokers."

Pirie and colleagues (2008) conducted a meta-analysis of 8 cohort and 17 case-control studies on exposure to secondhand smoke. The analysis included all 21 studies from the 2006 Surgeon General's report and 4 other studies—2 case-control studies (Lissowska et al. 2006; Roddam et al. 2007), 1 cohort study on mortality (Sagiv et al. 2007), and results from the Million Women Study, a cohort study in the United Kingdom (Pirie et al. 2008). Overall, data reported for the cohort studies indicated no association with breast cancer (RR = 0.99; 95% CI, 0.93–1.05), but data reported for the case-control studies noted a significant association (OR = 1.21; 95% CI, 1.11–1.32; p_h <0.0002). When based on data for the cohort studies, results reported by Pirie and colleagues (2008) for exposure to passive smoking as a child and as an adult were identical (RR = 1.00; 95% CI, 0.94–1.07). Analyses were not stratified on menopausal status or source or location of exposure, as they were in the 2006 Surgeon General's report. Conclusions were strongly influenced by results from the cohort studies: "In aggregate little or no adverse effect on the risk of breast cancer" was evident, and the results based on the case-control studies "appear[ed], in aggregate, to be misleading" (Pirie et al. 2008, p. 1,077).

The 2009 Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk—based primarily on its updated review of four studies published in 2005 or later (Bonner et al. 2005; Lissowska et al. 2006; Roddam et al. 2007; Pirie et al. 2008), previous reports by the Cal/EPA, and the 2006 Surgeon General's report—concluded that "the relationship between secondhand smoke and breast cancer in younger, primarily premenopausal women is consistent with causality" but determined that evidence was insufficient for a conclusion on risk of postmenopausal breast cancer (Collishaw et al. 2009, p. 57). In its special report from November 2009 that included an assessment of exposure to secondhand smoke, IARC concluded that "evidence for female breast cancer remains inconclusive" (Secretan et al. 2009, p. 1,033).

Conclusions from Previous Surgeon General's Reports

The 1986 Surgeon General's report was the first to offer a conclusion on passive smoking and cancer, but given available evidence it addressed only lung cancer (USDHHS 1986). This report also concluded that the effects of passive exposure were likely not greater than those effects seen for smokers, echoing a similar conclusion of IARC Monograph 38 of WHO (IARC 1986).

The 2006 Surgeon General's report concluded that the evidence on exposure to secondhand smoke was "suggestive but not sufficient to infer a causal relationship"

with risk for breast cancer (p. 480), based on a review of 7 prospective cohort studies (Hirayama 1984, reanalyzed by Wells [1991]; Jee et al. 1999; Wartenberg et al. 2000; Nishino et al. 2001; Egan et al. 2002; Reynolds et al. 2004b; Hanaoka et al. 2005) and 15 case-control studies (Sandler et al. 1985a; Smith et al. 1994; Morabia et al. 1996; Millikan et al. 1998; Lash and Aschengrau 1999, 2002; Zhao et al. 1999; Delfino et al. 2000; Johnson et al. 2000; Liu et al. 2000; Marcus et al. 2000; Kropp and Chang-Claude 2002; Shrubsole et al. 2004; Gammon et al. 2004a; Bonner et al. 2005). In the 2006 report, pooled risk estimates were derived for all women and stratified by menopausal status and categories related to timing (childhood, adulthood), source (spouse), and location (home, workplace) of exposure. The overall risk estimate (RR = 1.20; 95% CI, 1.08–1.35) was based on the most comprehensive measure of exposure to secondhand smoke. Data from cohort studies indicated no association (RR = 1.02; 95% CI, 0.92–1.13) with breast cancer, but the summary estimate from case-control data showed a significant association (OR = 1.40; 95% CI, 1.17–1.67). The association was particularly strong for premenopausal women (OR = 1.64; 95% CI, 1.25–2.14), based on estimates from 2 cohort studies (Reynolds et al. 2004b; Hanaoka et al. 2005) and 9 case-control studies (Sandler et al. 1985a; Smith et al. 1994; Morabia et al. 1996; Millikan et al. 1998; Delfino et al. 2000; Johnson et al. 2000; Gammon et al. 2004a; Shrubsole et al. 2004; Bonner et al. 2005). The review did not find an association for postmenopausal women (OR = 1.00; 95% CI, 0.88–1.12) based on the same 2 cohort studies (Reynolds et al. 2004b; Hanaoka et al. 2005) and 7 of the 9 case-control studies (Sandler et al. 1985a; Millikan et al. 1998; Delfino et al. 2000; Johnson et al. 2000; Gammon et al. 2004a; Shrubsole et al. 2004; Bonner et al. 2005). The review identified several issues related to these results—including the significant heterogeneity among studies, especially for the case-control studies; the potential for selection and information biases; the lack of consistency between findings for active cigarette smoking and those for exposure to secondhand smoke; and biologic plausibility.

In summary, several reviews and meta-analyses have been conducted to date—including reports by IARC, the Cal/EPA, the Canadian Expert Panel, Surgeon General's reports, and several groups of investigators (Khuder and Simon 2000; Johnson 2005; Lee and Hamling 2006; Pirie et al. 2008). These reports have reached different conclusions about the presence and magnitude of association between passive exposure to smoke and breast cancer despite considerable overlap in the studies reviewed and analyzed. Some of the difference in interpretation is related to the relative weight given by the authors of the reviews and meta-analyses to results from case-control

versus cohort studies. The majority of case-control studies have reported positive associations, with summary estimates (RRs) ranging from 1.2–1.9 depending on the studies included. Results from cohort studies have mostly been null. Compared with cohort studies, case-control studies often include more extensive and rigorous assessments of exposure—including detailed information for timing (childhood, adulthood), location (home, workplace), source (parent, spouse, other), duration, and dose—but these studies are more susceptible to information bias and generally considered less reliable. In addition, most of the case-control studies published before 2006 were small (<100 cases) or moderate (<500 cases) in size and had imprecise estimates. The likelihood of extreme estimates is increased in small studies and leads to significant heterogeneity across studies. In any case, all of the previous reviews have concluded that more and larger studies are needed, particularly those with cohort designs, with more detailed and extensive assessments of exposure.

Cohort Studies

The 2006 Surgeon General's report covered 21 studies, identified through 2005, on the health consequences of involuntary exposure to tobacco smoke. From 2006–2011, 7 cohort studies have evaluated exposure to passive smoking (Table 6.22*S*). As part of the Norwegian-Swedish cohort, Gram and colleagues (2005) followed 102,098 women, 30–50 years of age, for an average of 8–9 years (1991/1992–2000) and ascertained 1,240 incident cases of breast cancer among current or former smokers and never smokers. Exposure to passive smoking at home was assessed from self-reports of living with a smoker, either currently or during childhood. In a multivariate model based on 1,130 cases with complete data, the RR for breast cancer among women who never smoked but reported exposure to passive smoking (n = 24,030) was 1.21 (95% CI, 0.98–1.50) in a comparison with never smokers who reported no exposure to passive smoking (n = 12,743). The study adjusted for multiple covariates—including age, menopausal status, parity, age at birth of first child, use of hormones, BMI, and use of alcohol.

In the Million Women Study, Pirie and colleagues (2008) ascertained 2,344 incident cases in a cohort of 210,647 women, 50–64 years of age, who never smoked, had complete data for passive smoking exposure, and were followed for an average of 3.5 years. Exposure to passive smoking was based on self-reports of living with a parent who smoked at the time the participant was born and when she was 10 years of age, and of currently living with a partner who smoked. Only 17% of women reported not being exposed to passive smoking during childhood or

adulthood, leaving a relatively small reference group with no active/no passive exposure for the analyses. The overall RR was 0.99 (95% CI, 0.93–1.05) for any passive exposure. After adjusting for relevant covariates, including use of alcohol, the study found no increased risk of breast cancer from exposure during childhood (RR = 0.96; 95% CI, 0.88–1.05) or adulthood (RR = 1.02; 95% CI, 0.89–1.16).

Lin and colleagues (2008) reported findings from the Japan Collaborative Cohort Study for Evalustion of Cancer Risk based on 208 incident breast cancer cases in 34,401 women, 40–79 years of age, who were followed an average of 11–13 years. The study assessed exposure to passive smoking based on self-reports—including the estimated frequency of exposure (either sometimes or almost every day)—as adults at home and in public places, and during childhood. There were 196 cases among 32,023 never-smoking women, but the numbers in various analyses ranged from 140–178. After adjusting for relevant covariates, including use of alcohol, RRs for exposure during adulthood at home and in public places almost every day were less than 1.0 (RR = 0.71; 95% CI, 0.48–1.05 and RR = 0.84; 95% CI, 0.51–1.40, respectively). The RR for exposure during childhood was slightly higher (RR = 1.24; 95% CI, 0.84–1.85) but still not significant.

Reynolds and colleagues (2009) reported on passive smoking and risk of breast cancer using data from the WAVE-II survey (1997) of the California Teachers Study. This analysis was based on 1,754 women with incident invasive breast cancer among a cohort of 57,523 women who were lifetime nonsmokers and followed over 10 years. This report updates one published in 2004 that was based on data from the WAVE-I survey (1995) for 1,174 cases among 77,708 lifetime nonsmokers followed over 4 years (Reynolds et al. 2004b). The WAVE-II survey included more extensive questions on frequency, duration, source, and intensity, and there was a large loss to follow-up from WAVE-I to WAVE-II. The RR for breast cancer with ever-lifetime exposure in the WAVE-II survey was 1.10 (95% CI, 0.94–1.30), adjusting for age, race, and other relevant covariates (Reynolds et al. 2009). The RRs were 1.06 (95% CI, 0.94–1.19) and 1.04 (95% CI, 0.91–1.19) for any childhood (<20 years of age) and any adulthood (≥20 years of age) exposures, respectively; and 1.04 (95% CI, 0.92–1.16) and 1.02 (95% CI, 0.93–1.13) for any home and any work exposures, respectively. Exposure before first pregnancy was also associated with a nonsignificant increased risk

(RR = 1.17, 95% CI, 0.96–1.41) in a fully adjusted analysis. There were trends toward increasing risk with duration and intensity of exposure that reached statistical significance only in the highest category of this combined variable (>42 intensity-years)[4] in postmenopausal women (RR = 1.25; 95% CI, 1.01–1.56). In this study, the unexposed reference group constituted only 14% of the women in the cohort. The measure of exposure intensity was highly qualitative (self-report of "a little smoky," "fairly smoky," and "very smoky").

Xue and colleagues (2011) reported updated analyses for the NHS-I on active and passive smoking and risk of breast cancer. Their data included 2,890 incident breast cancer cases among 36,017 nonsmoking women followed from 1982–2006. No significant associations were found for any of the following categories of passive exposure: both parents (RR = 0.90; 95% CI, 0.79–1.03), regular at work (RR = 0.87; 95% CI, 0.78–0.98), regular at home (RR = 1.02; 95% CI, 0.90–1.14), and living with a smoker for 40 or more years (RR = 0.99; 95% CI, 0.74–1.32). Indices that combined information on place (home or work) and duration (<20 vs. ≥20 years) of exposure were not significantly associated with risk. All estimates were adjusted for age and multiple relevant covariates but were not stratified by menopausal status.

Also as shown in Table 6.22S, Luo and colleagues (2011b) reported results for passive smoking and incident breast cancer from the Women's Health Initiative. There were a total of 1,692 incident cases among 41,022 postmenopausal women, who had never smoked, followed over an average of 10.3 years. There were no significant associations between passive exposure during childhood, adulthood at home or at work, or any combination thereof, and risk of breast cancer. The only significant association was for the highest combined category of exposure duration (childhood ≥10 years plus adult at home ≥20 years plus adult at work ≥10 years: RR = 1.32; 95% CI, 1.04–1.67), but the trend across the duration categories for increased risk with greater exposure was not significant (p = 0.10). This is one of the only studies to examine exposure to passive smoking in relation to breast cancer by ER/PR status, but no significant associations were found. All estimates were adjusted for age at enrollment and multiple relevant covariates.

Finally, Chuang and colleagues (2011) reported the RR for childhood exposure from parental smoking (RR = 0.98; 95% CI, 0.91–1.06) based on data from 6 of the 23

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[4]To predict risk of breast cancer for two age groups (<20 years of age and ≥20 years of age), Reynolds and colleagues (2009) combined two metrics (years of exposure and intensity) into a common metric (intensity-years) that included both intensity (smokiness) and duration (years) of exposure.

centers participating in the EPIC; these centers were in France, Italy, The Netherlands, Sweden, Denmark, and Norway. There were 3,187 breast cancer cases among 92,956 premenopausal and postmenopausal women, 25–70 years of age, who reported themselves to be never smokers at recruitment (1992–1998); the mean age at recruitment was 50 years. Follow-up was over an average of 9–10 years. Significant associations were not found for the two frequency categories of exposure in childhood: few times during a week (RR = 0.98; 95% CI, 0.88–1.10) and daily (RR = 1.06; 95% CI, 0.95–1.19). All estimates were adjusted for age at menarche, ever use of oral contraceptives, parity, menopausal status, education, alcohol use, BMI, physical activity, vegetable intake, fruit intake, nonalcoholic energy intake, and adulthood passive smoking.

Several issues should be considered when comparing and combining the results of these seven studies. First, the categories of exposure were generally broad, particularly in the Norwegian-Swedish cohort (Gram et al. 2005). Second, with the exception of the studies by Pirie and colleagues (2008) and Reynolds and colleagues (2009), analyses were not stratified by menopausal status, use of alcohol, or breast cancer phenotype, although most studies adjusted for these potential confounders. The Norwegian-Swedish Cohort (Gram et al. 2005) consisted mostly of premenopausal women at baseline and the Women's Health Initiative cohort (Luo et al. 2011b) was comprised entirely of postmenopausal women; whereas the Million Women Study (Pirie et al. 2008), Japan Collaborative Cohort Study for Evaluation of Cancer Risk (Lin et al. 2008), California Teachers Study (Reynolds et al. 2009), EPIC (Chuang et al. 2011), and NHS-I (Xue et al. 2011) cohorts included both premenopausal and postmenopausal women. This is important because a previous cohort study by Hanaoka and colleagues (2005) (Table 6.14S) reported markedly different risks for premenopausal (RR = 2.6; 95% CI, 1.3–5.2) and postmenopausal women (RR = 0.7; 95% CI, 0.4–1.0). This difference in risk by menopausal status was also found in the meta-analysis of cohort and case-control studies included in the 2006 Surgeon General's report (USDHHS 2006). Pirie and colleagues (2008) stratified estimates by menopausal status but included few premenopausal women (n = 60), and thus the resulting estimate, although significant, was both inverse and imprecise (RR = 0.54; 95% CI, 0.30–0.99). In contrast, the analysis by Reynolds and colleagues (2009) suggests that risk may be increased in postmenopausal rather than premenopausal women. Xue and colleagues (2011), who also stratified by menopausal status, did not provide results that could be used for comparison. Thus, considerable inconsistency remains with regard to the effects of passive smoking exposure by menopausal status.

Third, these cohort studies differ markedly in rates of breast cancer incidence and exposure to passive smoking. In the Japanese cohort study (Lin et al. 2008), which included both in situ and invasive cases, participants had a very low incidence of breast cancer (approximately 58/100,000) compared with the other cohorts (Norwegian-Swedish, approximately 114/100,000; Million Women, approximately 315/100,000; and Women's Health Initiative, approximately 428/100,000). While the difference across these studies for incidence of breast cancer partly reflects the age composition of the respective cohorts, geographic and ethnic/racial differences must be considered also.

Fourth, methods for exposure assessment varied from study to study. For example, the reported prevalence of lifetime (childhood and adulthood) exposure to secondhand smoke varied markedly, from approximately 24% in the Norwegian-Swedish cohort to greater than 90% in the Women's Health Initiative cohort study. As noted in the 2006 Surgeon General's report, these cohort studies lacked updated data about exposure to passive smoking, which can result in some misclassification, especially during long-term followup periods of marked secular change in smoking habits. Xue and colleagues (2011) acknowledged this limitation in the NHS and pointed out that the result would be to attenuate estimates toward the null value because any exposure misclassification may be safely assumed to be nondifferential in a cohort study design. The most recent reports (Reynolds et al. 2009; Luo et al. 2011b; Xue et al. 2011) used novel indices of exposure that combined available information for duration, place, timing, and intensity. The analyses of Reynolds and colleagues (2009) and Luo and colleagues (2011b) suggest increased risk at only the very highest levels of these indices, while the results of Xue and colleagues are essentially null. The analysis of Pirie and colleagues (2008) is unique in restricting the data to women who reported living with a partner. This could be important because women who live alone cannot be passively exposed routinely in the home, a major venue of adult passive exposure. Theoretically, the restriction imposed by Pirie and colleagues (2008) could produce bias because women not living with a partner are likely to differ with respect to multiple risk factors for breast cancer, especially those related to reproductive history.

Case-Control Studies

The 2006 Surgeon General's report evaluated 14 case-control studies on the association between passive smoking and risk for breast cancer. Since then, 10 different case-control studies have been conducted, resulting in 11 published reports (Table 6.23S). Two reports (Metsola

et al. 2005; Sillanpaa et al. 2005a) were based on the same study population; the latter report included adjustment for potential confounders.

North American Studies

Three large case-control studies were conducted in North America (Mechanic et al. 2006; Slattery et al. 2008; Young et al. 2009). In a combined sample of the Ontario Women's Health Study and the Ontario Women's Diet and Health Study (2,751 nonsmoking cases and 3,097 non-smoking controls), Young and colleagues (2009) reported results on the association between exposure to passive smoking and risk for breast cancer. Exposure to passive smoking was self-reported and defined as exposure less than 2 hours per day during childhood and exposure of at least 2 hours per day for workplace and nonworkplace environments (adult exposure) during the 2 years before the study interview. The study reported an overall OR of 0.97 (95% CI, 0.88–1.08) for exposure to passive smoking compared with a no active/no passive exposure reference group. This estimate was adjusted only for age because the change to the risk estimate was less than 10% when the other potential confounders were included. Stratified analyses by timing of exposure (childhood vs. adulthood), menopausal status, or other relevant variables were not provided.

In the Carolina Breast Cancer Study, which included both African American and White women, Mechanic and colleagues (2006) evaluated the association between exposure to passive smoking and risk for breast cancer among 1,211 nonsmoking cases and 1,087 nonsmoking controls. Passive smoking was broadly defined as living with a smoker after 18 years of age. After adjusting for age, age at menarche, age at first full-term pregnancy, parity, family history, and use of alcohol, the study found an increased risk for breast cancer among African American women (OR = 1.40; 95% CI, 1.00–1.90) but not among White women (OR = 1.00; 95% CI, 0.80–1.20) compared with a no active/no passive exposure reference group. Results were not stratified by menopausal status. For African Americans, risk for breast cancer associated with exposure to passive smoking appeared to increase with the number of at-risk genotypes, which consisted of SNPs in DNA repair genes.

In the 4-Corners Breast Cancer Study, Slattery and colleagues (2008) examined the association between exposure to passive smoking and risk for breast cancer among 1,347 nonsmoking cases and 1,442 nonsmoking controls. Data on exposure to passive smoking was self-reported and captured as the number of exposure hours per week, both in and out of the house, during a reference period of 1 year before cancer diagnosis or study interview and 15, 30, and 50 years of age. Analyses were stratified by menopausal status and Hispanic/non-Hispanic White ethnicity. ORs were adjusted for age, study site, BMI, use of aspirin or NSAIDs, parity, use of alcohol, physical activity, and recent use of estrogen. The study found a significant increased risk only in premenopausal Hispanic women reporting more than 10 hours of exposure to passive smoking per week during the reference period compared with a no active/no passive reference group (OR = 2.3; 95% CI, 1.2–4.5). However, there was an inverse association, albeit nonsignificant, between fewer hours of exposure to passive smoking in this subgroup and risk. In this same subgroup, a significant interaction with a SNP in the *IL6* gene also was detected (see "Secondhand Smoke Exposure and Genotype"). The estimates for postmenopausal women were essentially null, and those for non-Hispanic White premenopausal women were increased by about 20%. The overall lifetime summary estimate (OR) calculated for this report was 1.06 (95% CI, 0.88–1.28).

Taken together, these large case-control studies do not provide evidence that exposure to secondhand smoke is a risk factor for breast cancer. However, the assessment of exposure to passive smoking was relatively crude in two studies that did not stratify results for potential effect modifiers—timing of exposure or menopausal status. Three additional case-control studies conducted in North America collected more extensive exposure data, but the results are difficult to interpret because of small samples (Alberg et al. 2004; Rollison et al. 2008; Ahern et al. 2009). In a case-control study in Massachusetts (242 nonsmoking cases, 195 nonsmoking controls), Ahern and colleagues (2009) collected information about exposure to passive smoking according to stage of life (childhood, adulthood), parental source during childhood (father, mother), and location (home, workplace). Overall, the results were null; only two significantly increased risks were reported: one for exposure during childhood from a mother who smoked (OR = 1.9; 95% CI, 1.1–3.3), and the other for postmenopausal women exposed during childhood (OR = 1.8; 95% CI, 1.0–3.3). In a small case-control study in Delaware (124 nonsmoking cases, 116 nonsmoking controls), Rollison and colleagues (2008) collected extensive data on exposure to passive smoking at home during childhood and adulthood and at the workplace in adulthood. Data included estimates of the number of smokers in the household, number of hours of exposure per day, and intensity of exposure (packs of cigarettes smoked per day). Compared with a no active/no passive exposure reference group, the study did not find any significant increased ORs across any exposure category, but statistical power was limited by the small sample. In another small case-control study (115 cases and 115 controls matched for age, race, and

menopausal status), Alberg and colleagues (2004) assessed the association between passive smoking, defined as living with a spouse who smoked, and risk for breast cancer. Data were available for only 62 nonsmoking cases and 66 nonsmoking controls. The OR for breast cancer was 1.2 (95% CI, 0.59–2.4). The study observed a nonsignificant interaction between exposure to passive smoking and the NAT2 phenotype.

European Studies

Five reports based on four case-control studies in Europe have been published since the 2006 Surgeon General's report. Two of these studies were conducted in Poland (Lissowska et al. 2006; Kruk 2007), one in Finland (Metsola et al. 2005; Sillanpaa et al. 2005a), and one in England (Roddam et al. 2007).

The largest European study was conducted by Lissowska and colleagues (2006) and had 1,034 nonsmoking cases and 1,162 nonsmoking controls. Passive smoking was self-reported and defined as adult exposure at home or in the workplace for at least 1 hour per day for at least 1 year. In a comparison with a no active/no passive exposure reference group, this study did not find significant associations between risk for breast cancer and exposure to passive smoking at home, at the workplace, at *both* home and the workplace, or for either the home or workplace. After adjusting for relevant covariates, the OR was 1.10 (95% CI, 0.84–1.45) for either the home or workplace. The initial analyses did not stratify risk by stage of life (childhood, adulthood), age group, or menopausal status. A subsequent reanalysis, however, which was published as a response to a letter to the editor by Johnson (2007), reported results that were stratified by age group and menopausal status (Lissowska et al. 2007). Premenopausal women (Table 6.23S) exhibited increasing ORs for breast cancer by hours of exposure to secondhand smoke per day-years[5]: less than 100, 1.36 (95% CI, 0.67–2.73); 101–200, 1.52 (95% CI, 0.73–3.13); and more than 200, 2.02 (95% CI, 0.94–4.36) (p trend = 0.08). The indicator of hours per day-years was calculated as the product of hours of exposure per day and duration of exposure. Of note, the study did not find similar trends for either of the two age groups (younger than 45 years of age and 45–55 years of age) that included all premenopausal women.

Kruk (2007) reported results from an independent case-control study in Poland (445 nonsmoking cases,

730 nonsmoking controls). For this study, Kruk defined exposure to passive smoking as living with a spouse who smoked and defined dose as number of cigarettes smoked per day. In contrast to Lissowska and colleagues (2007), Kruk (2007) reported significant ORs for premenopausal women (2.86; 95% CI, 1.65–4.97) and postmenopausal women (2.57; 95% CI, 1.73–3.80). These estimates, however, were adjusted only for age among premenopausal women and age and breastfeeding among postmenopausal women, and smokers were mixed with nonsmokers in the reference group. Among case-control studies, this study provides some of the highest ORs for active and passive smoking.

Roddam and colleagues (2007) conducted a study in England of women, 36–45 years of age, who were mostly premenopausal. Exposure to passive smoking at home was defined as living at least 1 year with a partner who smoked, and dose was defined as the number of years of exposure and estimated number of cigarettes smoked per day. After adjusting for relevant covariates, exposure to secondhand smoke was not significantly associated with risk for breast cancer (OR = 0.89; 95% CI, 0.64–1.25) among 297 nonsmoking cases and 310 nonsmoking controls when no passive/no active exposure was the reference group. Estimates were stratified on menopausal status, but the number of perimenopausal/postmenopausal women (n = 23) was too small to provide a meaningful result.

Metsola and colleagues (2005) and Sillanpaa and colleagues (2005a) published results on the same case-control study in Finland. Both focused on the modification of active smoking by selected SNPs in DNA repair and *NAT2* genes, but both reports provided only a cursory description of how exposure to passive smoking was defined in terms of years at home and the workplace. The two reports provided ORs for the association between exposure to passive smoking and risk for breast cancer (153 nonsmoking cases, 169 nonsmoking controls), but only the estimate from Sillanpaa and colleagues (2005a) was adjusted for multiple covariates; this estimate was not significant (OR = 0.85; 95% CI, 0.62–1.16). Stratification on the NAT2 phenotype suggested that risk for breast cancer was increased in women with the slow phenotype who were passively exposed to tobacco smoke (OR = 1.22; 95% CI, 0.75–1.98).

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[5]Day-years: the sum of hours per day exposed to secondhand smoke multiplied by the number of years of all episodes of secondhand smoke exposure, whether at home, at work, or during leisure time.

Asian Studies

Findings from case-control studies carried out in Asia on secondhand smoke have not been published since 2005. However, the 2006 Surgeon General's report did not include the hospital-based, cross-sectional study by Hirose and colleagues (1995) that was conducted in Japan. Using a large administrative database that had data for cigarette smoking and exposure to secondhand smoke, the study identified 1,052 breast cancer cases with survey data and 23,163 controls without a cancer diagnosis. The analysis for passive smoking was limited to women who reported being nonsmokers (560 cases and 11,276 controls). The prevalence of smoking in the control group (14%) was similar to that in the general population of women in Japan (13%). Passive smoking among women who were nonsmokers was defined on the basis of whether the husband smoked and the number of cigarettes he smoked per day (either 0–19 or ≥20). Among premenopausal women, risk for breast cancer increased as the number of cigarettes smoked per day by the husband rose: 0–19 (RR = 0.81; 95% CI, 0.57–1.15) and 20 or more (RR = 1.30; 95% CI, 1.02–1.65). There was no similar dose-response relationship in postmenopausal women: 0–19 (RR = 1.55; 95% CI, 1.10–2.17) and 20 or more (RR = 1.28; 95% CI, 0.92–1.77). The study had several limitations: it was clinic based and may have included prevalent as well as incident cases, data were missing on passive smoking for 38% of nonsmoking women, and risk estimates were adjusted only for age and year of first visit to a clinic.

Meta-Analysis of Breast Cancer Risk Associated with Measures of Secondhand Smoke

A total of 19 new published reports (7 cohort, 12 case-control) were reviewed together with the 20 reports (5 cohort, 15 case-control) that were previously abstracted and analyzed for the 2006 Surgeon General's report. Three of these update previous reports from the same studies and one overlaps with a current report (Table 6.24*S*). RR and OR estimates were based on either single estimates or were pooled across exposure strata and classified similarly to the eight categories reported in the 2006 Surgeon General's report. The same statistical procedures used in the meta-analyses for active cigarette smoking were used for the analyses of exposure to secondhand smoke. Sensitivity analyses considered study design, sample size, and magnitude of exposure effect.

Table 6.24*S* provides a listing of the 39 reports for 34 studies, of which 9 overlap with results on the same study population. Of these, 7 are included in the meta-analyses because they are either the most recent or complete reports from their study. In the case of 1 cohort study (California Teachers Study) and 1 case-control study (Carolina Breast Cancer Study), the best exposure estimates for specific categories were selected for inclusion in the meta-analyses: California Teachers Study (Reynolds et al. 2004b, 2009) and Carolina Breast Cancer Study (Millikan et al. 1998; Marcus et al. 2000; Mechanic et al. 2006). A total of 34 separate reports were included in the broadest category of exposure for the meta-analyses: *Most comprehensive*. RR and OR estimates were pooled across exposure levels to fit into one of the meta-analysis categories when necessary.

Measures of Exposure to Secondhand Smoke

This meta-analysis used eight categories of measures of exposure to secondhand smoke. These categories are not mutually exclusive, and assignments are presented in Table 6.24*S*.

1. **Spouse/partner:** This category was based on exposure during adulthood from a spouse or partner who was a smoker.

2. **Adult—home:** This category was based on exposure during adulthood from any smoker in the home. The category *Spouse/partner* is a subset of *Adult—home* because the location of exposure was assumed to be in the home.

3. **Adult—workplace:** Based on exposure during adulthood from smokers at the workplace, an estimate from this category could be used for any adult. However, most studies with a measure for exposure at the workplace had a measure for exposure at home that took precedence.

4. **Childhood:** This category was based on exposure during childhood to any smoker in the home. Among the 15 studies that provided a childhood estimate, the age definition of childhood varied. Sixteen, 18, or 21 years of age defined the end of childhood exposure in 7 studies (Smith et al. 1994; Marcus et al. 2000; Gammon et al. 2004a; Bonner et al. 2005; Rollison et al. 2008; Chuang et al. 2011; Luo et al. 2011b), and the remaining studies did not define a specific cutoff for age (Johnson et al. 2000;

Liu et al. 2000; Kropp and Chang-Claude 2002; Lin et al. 2008; Pirie et al. 2008; Ahern et al. 2009; Reynolds et al. 2009; Xue et al. 2011).

5. **Adulthood and childhood (or lifelong):** This category was based on lifelong exposure during childhood and adulthood from any individual in any setting. Only seven studies defined exposure in this manner (Smith et al. 1994; Johnson et al. 2000; Kropp and Chang-Claude 2002; Reynolds et al. 2004b; Pirie et al. 2008; Ahern et al. 2009; Luo et al. 2011b).

6. **Adult—any source:** This category was based on the broadest, most inclusive measure available for exposure during adulthood from any source in the following priority: a general estimate for all sources of exposure if available, a comprehensive home exposure, spouse/partner exposure, and workplace exposure. Twenty-six non-overlapping reports included measures that were coded for this category based on a number of descriptive measures, including a general report for overall and nonspecific exposure to passive smoke as an adult (Johnson et al. 2000; Kropp and Chang-Claude 2002; Ahern et al. 2009); exposure specifically noted as from a spouse or partner (Sandler et al. 1985a; Hirose et al. 1995; Morabia et al. 1996; Jee et al. 1999; Nishino et al. 2001; Alberg et al. 2004; Gammon et al. 2004a; Kruk 2007; Roddam et al. 2007; Pirie et al. 2008); cohabitants in general (Smith et al. 1994; Delfino et al. 2000; Liu et al. 2000; Mechanic et al. 2006; Lin et al. 2008; Reynolds et al. 2009; Xue et al. 2011); coworkers (Bonner et al. 2005; Hanaoka et al. 2005); or a combination of cohabitants and coworkers (Shrubsole et al. 2004; Sillanpaa et al. 2005a; Lissowska et al. 2006; Luo et al. 2011b).

7. **Ever in lifetime:** Based on a report of exposure to passive smoke during either childhood or adulthood in studies that assessed exposure across the lifetime, this category can include, for example, an estimate based on exposure during adulthood if exposure during childhood was also assessed and included in the risk estimate. The category *Adulthood and childhood* is a subset of *Ever in lifetime*. Twenty nonoverlapping reports had measures that were coded for this category based on definitions that ranged from very general to specific. One study estimate was based on exposure during childhood and adulthood (Ahern et al. 2009); 5 were based on lifetime exposure in the home (Lash and Aschengrau 1999, 2002; Zhao et al. 1999; Bonner et al. 2005; Slattery et al. 2008); 4 were based on any exposure from a spouse or a parent during the lifetime (Gammon et al. 2004a; Gram et al. 2005; Pirie et al. 2008; Chuang et al. 2011); 1 was based on having lived with a smoker or been exposed to a smoker outside of the home (Hanaoka et al. 2005); 5 were based on having lived with a smoker or been exposed at the workplace (Smith et al. 1994; Morabia et al. 1996; Johnson et al. 2000; Kropp and Chang-Claude 2002; Rollison et al. 2008); and 4 were based on any exposure during childhood or adulthood without information about location or source of exposure (Reynolds et al. 2009; Young et al. 2009; Xue et al. 2011). The broadest measure for *Ever in lifetime* was selected in those studies that reported more than one category of exposure during childhood and adulthood. The home was the most frequently defined location for exposure; outside the home and/or at the workplace were identified less frequently. Studies varied widely in specificity and rigor of the definition of lifetime exposure.

8. **Most comprehensive:** This category was based on the broadest, most inclusive estimate of exposure available from each study. In the meta-analysis, this was always either *Adult—any source* or *Ever in lifetime*, with preference for the latter when both estimates were reported. A careful evaluation was made of the independent contributions of each category to the summary estimate for the *Most comprehensive* (see *Comparison of Adult—Any Source with Ever in Lifetime for Most Comprehensive*).

This meta-analysis applied some changes to the studies reviewed in the 2006 Surgeon General's report, including the exclusion of two mortality studies (Hirayama 1984; Wartenberg et al. 2000), the inclusion of a study conducted in China and published prior to 2005 (Hirose et al. 1995), and changes to several estimates for five studies (Smith et al. 1994; Millikan et al. 1998; Jee et al. 1999; Nishino et al. 2001; Gammon et al. 2004a). These changes are detailed in the notes for Table 6.24*S*. Risk estimates were abstracted for each study, classified into the eight categories described previously, and tabulated together with information on adjusted covariates, including reproductive risk factors, alcohol use, BMI, family history, and menopausal status. The most fully adjusted estimates were selected when available, and a random effects model was used to pool estimates across strata (e.g., race/ethnicity, menopausal status, or dose levels) when necessary.

Adjustment for Selected Covariates

The majority of studies that evaluated exposure to passive smoke adjusted for covariates, most often referencing those that were related to reproduction or estrogen, but also family history, use of alcohol, and BMI. Of the 34 separate studies, only 4 did not adjust for any covariate or adjusted for age only (Sandler et al. 1985a; Jee et al. 1999; Alberg et al. 2004; Metsola et al. 2005).

Most Comprehensive Measures of Passive Smoking

Among the 34 studies included in the meta-analysis of passive smoking and risk for breast cancer, only 7 did not report estimates for measures of active smoking (Jee et al. 1999; Liu et al. 2000; Nishino et al. 2001; Bonner et al. 2005; Pirie et al. 2008; Reynolds et al. 2009; Chuang et al. 2011). Eight of the 34 studies were based on Asian populations (Hirose et al. 1995; Jee et al. 1999; Zhao et al. 1999; Liu et al. 2000; Nishino et al. 2001; Shrubsole et al. 2004; Hanaoka et al. 2005; Lin et al. 2008), and 8 studies included data on the interaction between genotype and smoking for risk for breast cancer (Delfino et al. 2000; Alberg et al. 2004; Gammon et al. 2004a; Metsola et al. 2005; Sillanpaa et al. 2005a; Lissowska et al. 2006; Mechanic et al. 2006; Slattery et al. 2008). Figure 6.40 presents the 34 studies (10 cohort and 24 case-control) that were based on the *Most comprehensive* category, which was derived from either the *Adult—any source* (n = 14) or *Ever in lifetime* (n = 20) measures. Meta-analysis provided an overall summary RR of 1.14 (95% CI, 1.06–1.23), but with significant heterogeneity (p_h <0.001) (Table 6.25*S*). The funnel plot in Figure 6.41 shows evidence of significant skewness, suggesting the presence of publication bias, as indicated by the lack of smaller negative studies. This was further confirmed (Figure 6.40) by Begg's rank correlation test (z = 2.30, p = 0.02) and the Egger test (bias = 1.41, p = 0.007). Stratification by study design (Table 6.25*S*) revealed that the heterogeneity resulted mainly from the variation among the 24 case-control studies (RR = 1.27; 95% CI, 1.11–1.44; p_h <0.000), although significant heterogeneity was also found for the 10 cohort studies (RR = 1.02; 95% CI, 0.95–1.10; p_h = 0.038).

The funnel plot in Figure 6.41 also indicates the presence of some studies with extreme outlier estimates (i.e., those that fall well outside the boundaries of the funnel) (Smith et al. 1994; Morabia et al. 1996; Lash and Ashengrau 1999; Zhao et al. 1999; Kruk 2007). Because extreme estimates can strongly affect a summary estimate, these outlier studies were inspected more closely for potential problems with study design. The case-control studies by Kruk (2007) and Zhao and colleagues (1999) appeared to include smokers along with nonsmokers in the analysis of exposure to passive smoke. Furthermore, the number of cases and controls reported in the tables in both of these studies could not be reconciled with totals provided in the text or in other tables. Excluding these two studies (Table 6.25*S*) attenuated the overall risk estimate (RR = 1.08; 95% CI, 1.01–1.14; p_h = 0.001; n = 32) and the risk estimate for the case-control studies (RR = 1.14; 95% CI, 1.04–1.26; p_h = 0.003; n = 22).

The extreme estimate from Smith and colleagues (1994) was based on a very small subset of cases and controls (n = 193) that represented only 27% of the nonsmokers (n = 703) in the full study. Other studies were also based on a small number of cases. For example, estimates reported by Morabia and colleagues (1996) were based on only 126 cases (620 controls), and the results from the cohort study by Lin and colleagues (2008) were based on only 140 incident cases. However, although small studies are statistically more likely to produce extreme estimates, these studies adjusted for appropriate covariates and did not have other limitations to their respective designs.

Limitations in study design were detected in three other studies that did not provide extreme estimates. Two studies included an unknown percentage of deceased persons for whom information was collected from proxies and did not adjust for menopausal status (Lash and Aschengrau 1999, 2002), and one study included both incident and prevalent cases based on medical records and did not adjust for covariates relevant to breast cancer (including menopausal status) other than age (Jee et al. 1999). Excluding these three studies plus Kruk (2007) and Zhao and colleagues (1999) (Table 6.25*S*) did not meaningfully alter the overall summary estimate (RR = 1.07; 95% CI, 1.01–1.13; p_h = 0.002; Begg z = 2.21; p = 0.03; Egger bias = 0.98; p = 0.02, n = 29).

Because the funnel plot in Figure 6.41 indicated publication bias stemming from small studies, 5 more studies with fewer than 100 cases were excluded (Sandler et al. 1985a; Smith et al. 1994; Delfino et al. 2000; Nishino et al. 2001; Alberg et al. 2004) in addition to the 5 with design limitations (Jee et al. 1999; Lash and Aschengrau 1999, 2002; Zhao et al. 1999; Kruk 2007). The summary estimate (RR) then became 1.06 (95% CI, 1.00–1.12; n = 24). Although significant heterogeneity remained (p_h = 0.010), excluding the 10 studies reduced publication bias, as expected (Begg z = 1.79; p = 0.07; Egger bias = 0.95; p = 0.05). However, the estimate by Morabia and colleagues (1996) remained an extreme outlier. Excluding this study resulted in a summary estimate (RR) of 1.04 (95% CI, 0.99–1.09; p_h = 0.131; n = 23). Figure 6.42

Figure 6.40   Forest plot showing the association between the most comprehensive measure of exposure to second-hand smoke and risk for breast cancer, based on the subset of cohort and case-control studies published before 2012 (n = 34)

Study	Year	
Lin et al.	2008	*
Nishino et al.	2001	*
Sillanpaa et al.	2005a	^
Lash & Aschengrau	2002	^
Roddam et al.	2007	^
Young et al.	2009	^
Chuang et al.	2011	*
Pirie et al.	2008	*
Ahern et al.	2009	^
Shrubsole et al.	2004	^
Xue et al.	2011	*
Gammon et al.	2004a	^
Rollison et al.	2008	^
Slattery et al.	2008	^
Luo et al.	2011b	*
Lissowska et al.	2006	^
Hanaoka et al.	2005	*
Reynolds et al.	2009	*
Mechanic et al.	2006	^
Bonner et al.	2005	^
Alberg et al.	2004	^
Gram et al.	2005	*
Hirose et al.	1995	^
Jee et al.	1999	*
Liu et al.	2000	^
Delfino et al.	2000	^
Johnson et al.	2000	^
Kropp & Chang-Claude	2002	^
Sandler et al.	1985a	^
Lash & Aschengrau	1999	^
Zhao et al.	1999	^
Morabia et al.	1996	^
Smith et al.	1994	^
Kruk	2007	^
Overall		

Note: * = cohort study; ^ = case-control study. Meta-analysis RR = 1.14 (95% CI, 1.06–1.23); Begg z = 2.30, p = 0.02; Egger bias = 1.41, p = 0.007. See Table 6.24*S* for five overlapping reports that were excluded. Size of square is proportional to the weights used in the meta-analysis; error bars show the associated 95% CI. Solid vertical line represents the null value. Diamond represents the summary estimate and associated 95% CI. **CI** = confidence interval; **RR** = relative risk.

Figure 6.41 **Funnel plot showing estimates in the meta-analysis of the most comprehensive measure of exposure to secondhand smoke with risk for breast cancer, based on the subset of cohort and case-control studies published before 2012 (n = 34)**
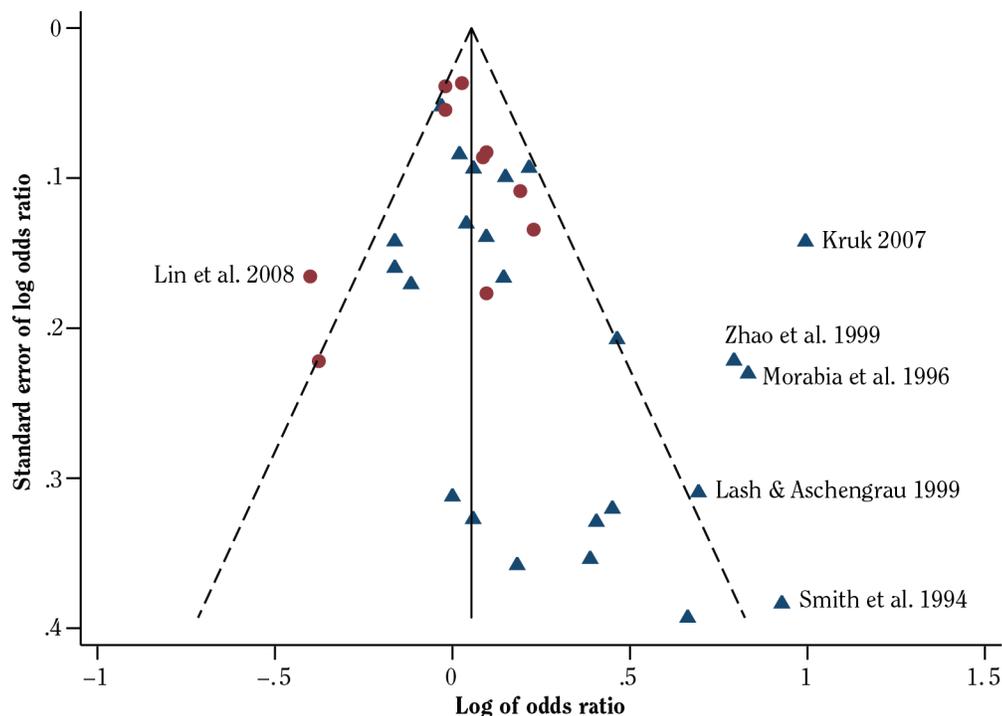
Note: ▲ = cohort study; ● = case-control study. Includes the same studies reported in Figure 6.40.

shows the forest plot for the 23 studies that remained after the exclusions. The accompanying funnel plot in Figure 6.43 shows that publication bias (Begg z = 1.35; p = 0.18; Egger bias = 0.68; p = 0.12; see note for Figure 6.42) and the effects of case-control studies with extreme estimates well outside of the 95% CI of the funnel no longer leveraged the RR. The case-control studies that were removed did not appear to have better assessments of exposure than many other studies that were included. While the estimate for the cohort study by Lin and colleagues (2008) is just outside the outer margin of the funnel, it is balanced by the estimate for the case-control study by Kropp and Chang-Claude (2002).

Comparison of Adult—Any Source with Ever in Lifetime for Most Comprehensive

An evaluation was made of whether an additional source of bias in the meta-analysis of the *Most comprehensive* category was due to a mix of the *Ever in lifetime* (n = 20) and *Adult—any source* (n = 14) measures of exposure (see Table 6.24S for listing of studies). As

described previously, the *Ever in lifetime* category uses a broad definition of passive exposure—that is, it includes studies with estimates based on exposure to passive smoke during childhood and adulthood. In contrast, the *Adult— any source* category provides a measure mainly of current exposure that often includes both source (spouse, partner) and location (home, workplace). The *Most comprehensive* category was based on the *Ever in lifetime* category when both results were available.

The summary RR for all 26 studies with an *Adult— any source* estimate was 1.15 (95% CI, 1.03–1.28; p_h <0.001) (Table 6.25S), and the summary estimate for the subset of 14 studies contributing to the *Most comprehensive* category was nearly identical: RR = 1.15; 95% CI, 0.94–1.39 (data not shown). In contrast, all 20 studies with an estimate for the category *Ever in lifetime* were included in the *Most comprehensive* category. The summary RR for these 20 studies was 1.11 (95% CI, 1.03–1.20; p_h <0.001) (Table 6.25S). There was less indication of publication bias for the 14 studies in the *Adult—any source* exposure category (Begg z = 0.38, p = 0.70; Egger bias = 0.23, p = 0.88)

Figure 6.42 Forest plot showing the association between the most comprehensive measure of secondhand smoke and risk for breast cancer, based on the subset of cohort and case-control studies published before 2012, excluding studies with design or analysis issues (n = 23)

Study	Year	
Lin et al.	2008 *	
Sillanpaa et al.	2005a ^	
Roddam et al.	2007 ^	
Young et al.	2009 ^	
Chuang et al.	2011 *	
Pirie et al.	2008 *	
Ahern et al.	2009 ^	
Shrubsole et al.	2004 ^	
Xue et al.	2011 *	
Gammon et al.	2004a ^	
Rollison et al.	2008 ^	
Slattery et al.	2008 ^	
Luo et al.	2011b *	
Lissowska et al.	2006 ^	
Hanaoka et al.	2005 *	
Reynolds et al.	2009 *	
Mechanic et al.	2006 ^	
Bonner et al.	2005 ^	
Gram et al.	2005 *	
Hirose et al.	1995 ^	
Liu et al.	2000 ^	
Johnson et al.	2000 ^	
Kropp & Chang-Claude	2002 ^	
Overall		

RR: .5 .7 1 1.4 2 3.5
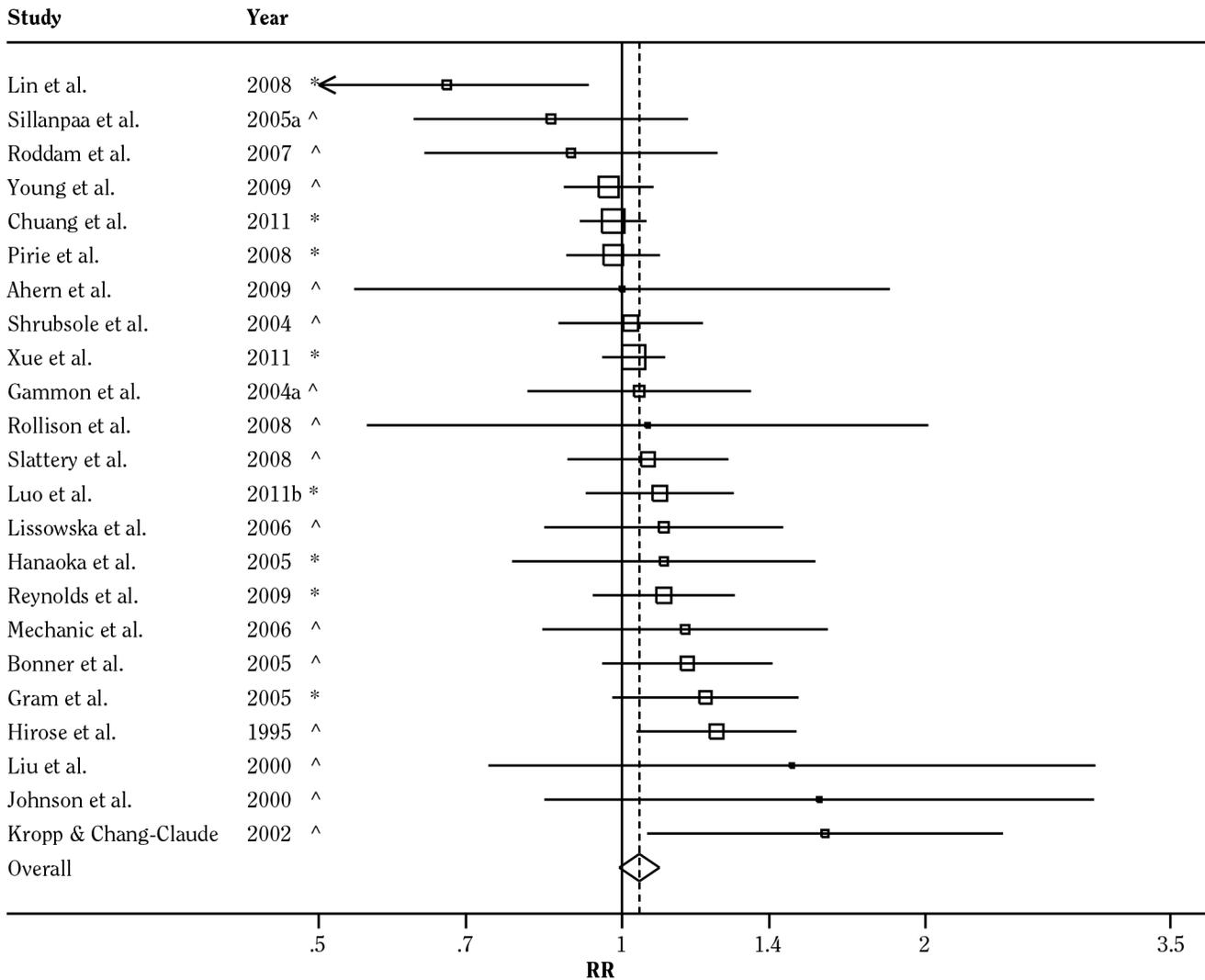
Note: * = cohort study; ^ = case-control study. Meta-analysis RR = 1.04 (95% CI, 0.99–1.09); Begg z = 1.35, p = 0.18; Egger bias = 0.68, p = 0.12. See Table 6.25*S* (*note f*) for studies excluded. Size of square is proportional to the weights used in the meta-analysis; error bars show the associated 95% CI. Solid vertical line represents the null value. Diamond represents the summary estimate and associated 95% CI. **CI** = confidence interval; **RR** = relative risk.

than for the 20 studies in the *Ever in lifetime* category (Begg z = 2.60, p = 0.009; Egger bias = 1.84, p = 0.001), as shown in funnel plots in Figure 6.44.

When small studies, those with design or analysis issues, and the 1 outlier study (Morabia et al. 1996) were excluded from each of the two categories, the RRs were attenuated similarly. The exclusion of 6 of the 14 *Adult— any source* studies resulted in an RR of 1.01 (95% CI,

0.88–1.17; n = 8) (data not shown). The exclusion of 5 of the 20 *Ever in lifetime* studies resulted in an RR of 1.03 (95% CI, 0.99–1.07; n = 15) (Table 6.25*S*). Thus, the exclusion of these 11 studies did not produce differential bias between the *Adult—any source* and *Ever in lifetime* categories that were used for the *Most comprehensive* RR. The RR for all studies in the *Adult—any source* and *Ever in lifetime* categories as well as in the reduced analyses after

Figure 6.43   **Funnel plot for estimates in the meta-analysis of the most comprehensive measure of exposure to secondhand smoke with risk for breast cancer, based on the subset of cohort and case-control studies published before 2012, excluding studies with design or analysis issues (n = 23)**
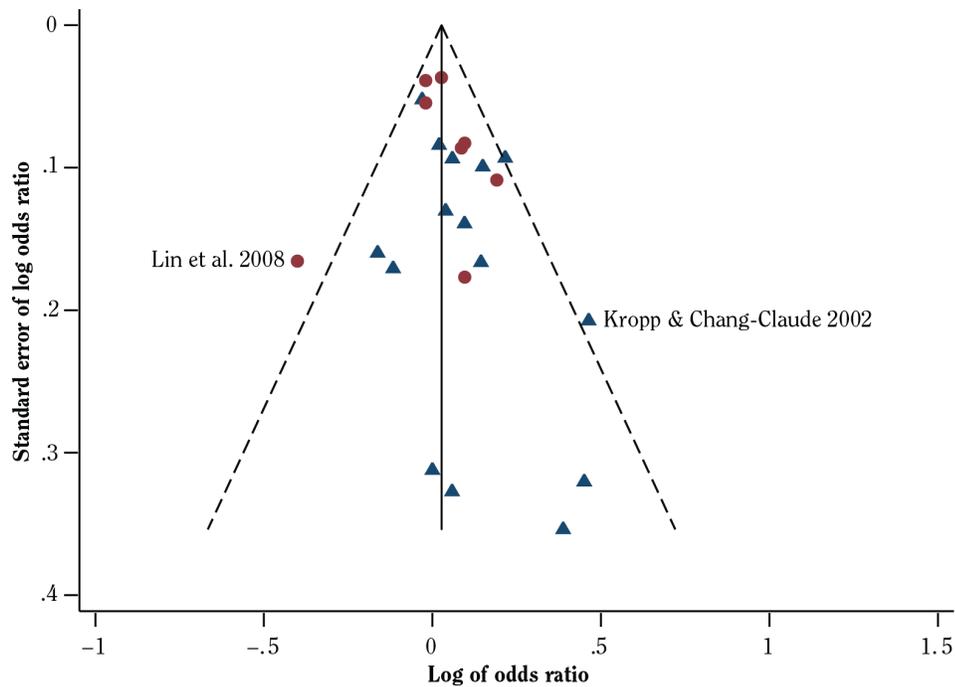
Note: ▲ = cohort study; ● = case-control study. Includes the same studies reported in Figure 6.42.

exclusions were similar. Thus, one of these two categories does not provide a better assessment of exposure than the other, nor is one of the categories a greater source of bias in the meta-analyses than the other.

Comparison of Premenopausal with Postmenopausal for Most Comprehensive

The meta-analysis for the *Most comprehensive* measure of exposure to passive smoke was stratified on menopausal status for all studies with available estimates (Table 6.25S). The summary estimate (RR) for 17 studies with data on exposure among premenopausal women was 1.45 (95% CI, 1.20–1.75; p_h <0.001) (Table 6.25S). The funnel plot in Figure 6.45A displays substantial publication bias associated with an excess of positive estimates from smaller studies with data for premenopausal women (Begg z = 2.97, p = 0.003; Egger bias = 2.61, p = 0.001). Fourteen case-control studies produced a summary estimate of 1.52 (95% CI, 1.23–1.87; p_h <0.001) for premenopausal women, and 3 cohort studies produced a summary estimate for this group of 1.23 (95% CI, 0.69–

2.19; p_h = 0.027) (Table 6.25S). In contrast, the summary estimate (RR) for 17 studies with data for postmenopausal women was 1.11 (95% CI, 0.99–1.25; p_h = 0.001) (Table 6.25S). Although the estimate for 1 study was an extreme outlier (Kruk 2007), the funnel plot for postmenopausal women in Figure 6.45B does not reveal substantial bias (Begg z = 0.91, p = 0.37; Egger bias = 0.78, p = 0.31). For postmenopausal women, the summary estimate for 13 case-control studies was 1.18 (95% CI, 1.00–1.39; p_h = 0.004), and the summary estimate for 4 cohort studies was 1.01 (95% CI, 0.85–1.20; p_h = 0.035) (Table 6.25S). According to Figure 6.45A, estimates for studies that reported exposure among premenopausal women were not randomly distributed within the boundaries of the funnel plot; an excess of small studies had positive estimates; and a few studies were extreme outliers, appearing outside the upper level of the pseudo 95% CI. This is less apparent in the funnel plot for studies that reported exposure among postmenopausal women (Figure 6.45B).

Exclusion of the 11 studies with design or analysis limitations, small samples, or extreme estimates had a major impact on all estimates for the *Most comprehen-*

Figure 6.44 **Funnel plots for estimates in the meta-analysis of *Adult—any source* (n = 14) and *Ever in lifetime* (n = 20) measures of exposure to secondhand smoke that contributed to the *Most comprehensive* exposure category, based on the subset of cohort and case-control studies published before 2012 (n = 34)**

A. *Adult—any source*
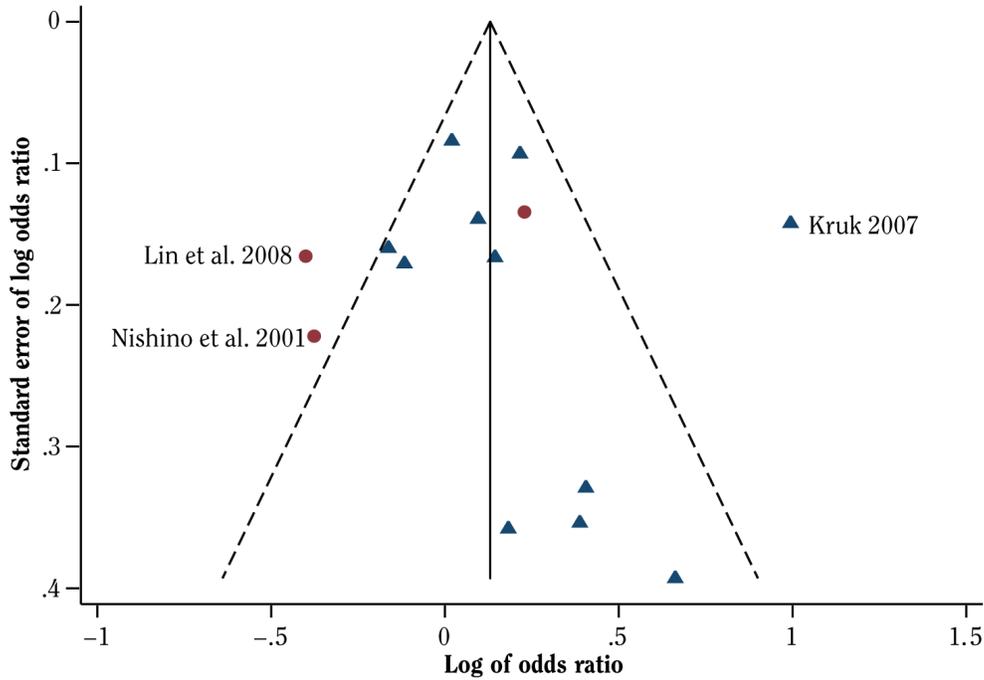
RR = 1.15 (95% CI, 0.94–1.39); Begg z = 0.38, p = 0.070; Egger bias = 0.23, p = 0.88.

B. *Ever in lifetime*
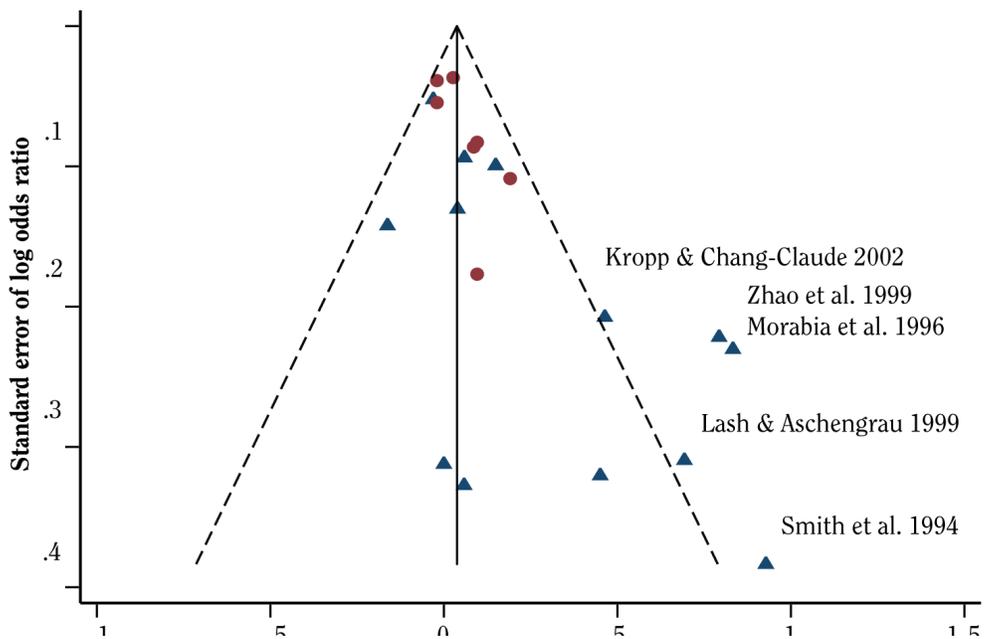
Note: I = cohort study; p = case-control study. Comparison of all 34 studies that contributed to the *Most comprehensive* measure of passive exposure to smoke, stratified by exposure category: *Adult—any source* versus *Ever in lifetime* (See Table 6.24S, *Most comprehensive: Adult—any source* versus *Ever in lifetime*) for studies included in each figure.

Figure 6.45   Funnel plots showing estimates in the meta-analysis of premenopausal (n = 17) and postmenopausal (n = 17) status for the *Most comprehensive* measure of exposure to secondhand smoke with risk for breast cancer, based on the subset of cohort and case-control studies published before 2012

A. Premenopausal
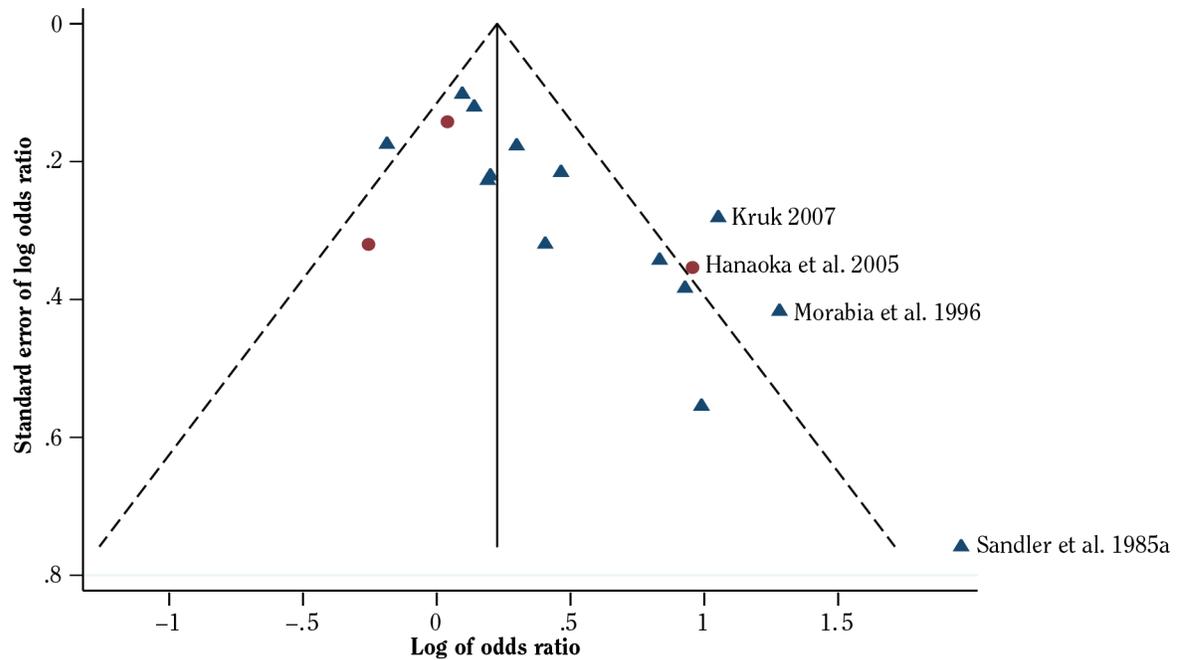
Meta-analysis RR = 1.45 (95% CI, 1.20–1.75); Begg z = 2.97, p = 0.003; Egger bias = 2.61, p = 0.001.

B. Postmenopausal
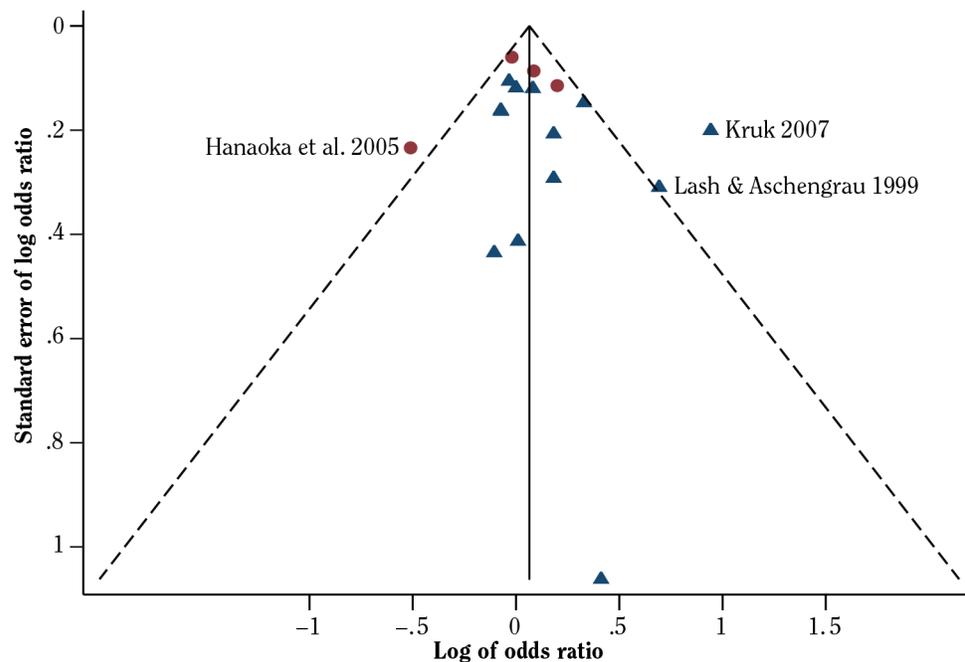
Meta-analysis RR = 1.11 (95% CI, 0.99–1.25); Begg z = 0.91, p = 0.37; Egger bias = 0.78, p = 0.31.

Note: ▮ = cohort study; ● = case-control study. See Table 6.24S (Premenopausal, Postmenopausal) for studies included in each figure. There were two studies with estimates for only premenopausal women (Smith et al. 1994; Morabia et al. 1996), and two studies with estimates for only postmenopausal women (Lash and Aschengrau 1999; Luo et al. 2011b).

sive exposure category, with the summary estimate for all studies decreasing from 1.14 to 1.04 (Table 6.25*S*). The summary estimate for premenopausal women decreased from 1.45 to 1.21 (Table 6.25*S*, Figure 6.46A), and the summary estimate for postmenopausal women decreased from 1.11 to 1.04 (Table 6.25*S*, Figure 6.46B).

Taken together, these sensitivity and stratified analyses suggest that the meta-analysis of the *Most comprehensive* exposure category, which included both the *Adult—any source* and *Ever in lifetime* definitions of exposure, produced highly heterogeneous results, and that the summary estimate was subject to bias from small case-control studies, some of which had extreme (outlier) estimates (Table 6.25*S*). The summary result for premenopausal women may have been influenced by smaller case-control studies that reported statistically significant, positive associations. However, among the three cohort studies, the report by Hanaoka and colleagues (2005), with relatively few breast cancer cases, stands out as reporting a significant increased risk for breast cancer in premenopausal women (RR = 2.6; 95% CI, 1.3–5.2) and a reduced risk in postmenopausal women (RR = 0.70; 95% CI, 0.4–1.0). These findings are inconsistent with those from the other two larger and more recent cohort studies that reported no significantly increased or decreased risk in either premenopausal women, RR = 1.04; 95% CI, 0.79–1.38 (Reynolds et al. 2009); or postmenopausal women, RR = 1.22; 95% CI, 0.97–1.52 (Reynolds et al. 2009) and RR = 1.09; 95% CI, 0.92–1.29 (Luo et al. 2011b).

Other Categories of Passive Exposure

For comparison with the findings of the 2006 Surgeon General's report, Table 6.26*S* summarizes the results of the meta-analysis for other exposure categories: childhood, childhood and adulthood, and adulthood (spouse, home, and workplace). Most of the summary estimates are similar to those in the 2006 report, but several changed because of new studies published since 2006 with data for these categories.

There are now 15 studies (5 cohort and 10 case-control) with estimates for passive smoking exposure from the spouse versus 9 in the 2006 Surgeon General's report. The summary RR for these studies is 1.22 (95% CI, 1.05–1.42; p_h = 0.001), similar to the 2006 estimate of 1.17 (95% CI, 0.96–1.44; p_h = 0.002). However, when 7 studies with design or analysis issues are excluded, the RR drops to 1.05 (95% CI, 0.97–1.13; p_h = 0.185). The previous Surgeon General's report provided a summary RR of 1.01 (95% CI, 0.85–1.19; p_h = 0.006) for 8 studies reporting passive exposure at home. There are now 20 studies for home exposure (7 cohort and 13 case-control), for which the summary RR is 1.16 (95% CI, 1.02–1.31; p_h =

0.001. When 8 studies with design or analysis issues are excluded, the estimate drops considerably, in this case to 1.02 (95% CI, 0.94–1.11; p_h = 0.061). The new summary estimates for exposure in the workplace (RR = 1.03; 95% CI, 0.92–1.15) and during childhood (RR = 1.01; 95% CI, 0.95–1.07) are quite close to the estimates in the 2006 Surgeon General's report. For exposure in childhood and adulthood, however, the previous estimate, based on 4 studies, was 1.39 (95% CI, 0.88–2.18; p_h = 0.021) compared to 1.09 (95% CI, 0.95–1.24; p_h = 0.102) based on a new total of 7 studies.

Results for these exposure categories by menopausal status are considered unstable because they are based on nine or fewer studies. Moreover, only two of the summary RRs are significant: exposure to secondhand smoke at home among premenopausal women (n = 9; RR = 1.35; 95% CI, 1.03–1.78; p_h = 0.003); and, exposure during childhood among postmenopausal women (n = 4; RR = 1.15; 95% CI, 1.03–1.28; p_h = 0.888). In general, point estimates tend to be higher in premenopausal than postmenopausal women, but it is difficult to interpret this difference because the CIs are wide and overlapping.

In Utero Exposure to Secondhand Smoke

Several studies have examined the possible association of in utero exposure to passive smoking with breast cancer in adulthood. Park and colleagues (2008) published a meta-analysis of seven case-control (Sandler et al. 1985b; Sanderson et al. 1996, 1998; Weiss et al. 1997; Innes and Byers 2001; Titus-Ernstoff et al. 2002; Park et al. 2006) and two cohort (Strohsnitter et al. 2005; Sanderson et al. 2006) studies of possible associations between passive exposure to maternal or paternal smoking in utero and subsequent risk of breast cancer. The summary estimate (RR) from Park and colleagues' (2008) meta-analysis was 1.03 (95% CI, 0.93–1.15) for the case-control studies and 0.59 (0.41–0.85) for the cohort studies. However, these results are difficult to interpret because the meta-analysis included a case-control study of active smoking by the participant during pregnancy and her subsequent risk of breast cancer (Innes and Byers 2001), two of the case-control studies appear to have had overlap for the diagnosis time period and geographic location (Sanderson et al. 1996, 1998), and one of the cohort studies had breast cancer mortality as an outcome (Sanderson et al. 2006). Additionally, most studies did not adequately control for potential confounders.

Estimates from three studies that examined in utero exposure to maternal smoking and adjusted for potential confounders in addition to age were 1.3 (95% CI, 0.9–2.1) for women, 50–64 years of age, in western Wash-

Figure 6.46 **Forest plots showing the association between premenopausal (n = 12) and postmenopausal (n = 13) status for the *Most comprehensive* measure of exposure to secondhand smoke with risk for breast cancer, based on the subset of cohort and case-control studies published before 2012, excluding studies with design or analysis issues**

A. Premenopausal
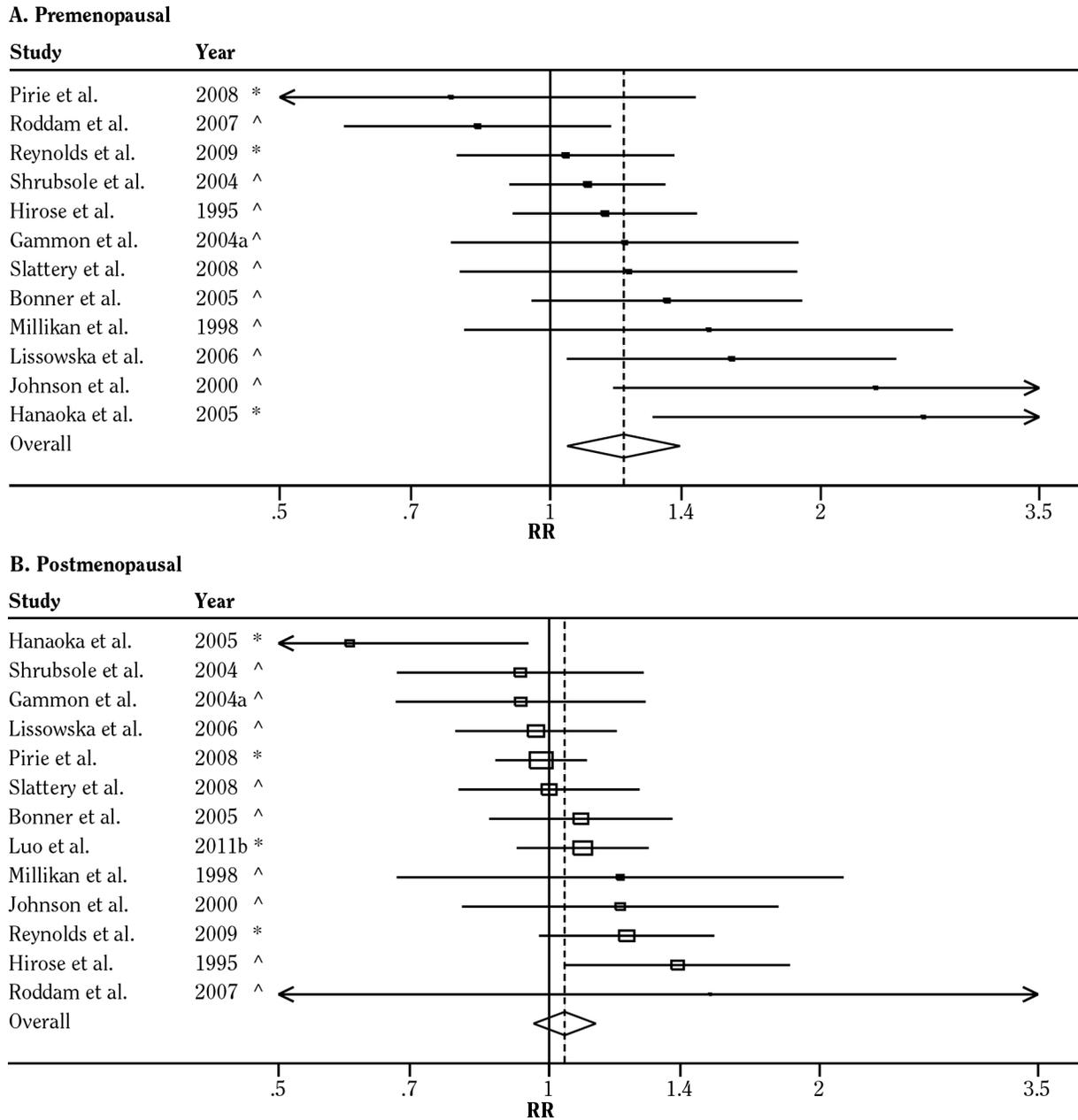
B. Postmenopausal

Note: * = cohort study; ^ = case-control study. See Table 6.24S, *Premenopausal, Postmenopausal,* for studies included in each figure and Table 6.25S (*notes e and f*) for studies excluded. Five studies were excluded from the premenopausal meta-analysis (Sandler et al. 1985a; Smith et al. 1994; Morabia et al. 1996; Delfino et al. 2000; Kruk 2007) and four from the postmenopausal meta-analysis (Sandler et al. 1985a; Lash and Aschengrau 1999; Delfino et al. 2000; Kruk 2007) because of design or analysis issues. There was one study with an estimate for only postmenopausal women (Luo et al. 2011b). Size of square is proportional to the weights used in the meta-analysis; error bars show the associated 95% CI. Solid vertical line represents the null value. Diamond represents the summary estimate and associated 95% CI. **CI** = confidence interval; **RR** = relative risk.

ington state (Sanderson et al. 1996), 1.1 (95% CI, 0.8–1.4) for women younger than 55 years of age in three areas of the United States (Weiss et al. 1997), and 1.21 (95% CI, 0.99–1.47) for women in Warsaw and Lodz, Poland, who were in most instances postmenopausal (Park et al. 2006). In the case-control study by Park et al. (2006), the risk estimate was essentially the same in participants whose mothers had smoked only at times other than during pregnancy (OR = 1.22; 95% CI, 0.81–1.84). Taken together, these studies do not provide consistent evidence that in utero exposure to secondhand smoke is associated with breast cancer.

Secondhand Smoke Exposure and Genotype Interaction

Eight case-control studies have examined potential modification of the effect of exposure to passive smoking by the NAT2 phenotype (Millikan et al. 1998; Delfino et al. 2000; Morabia et al. 2000; Chang-Claude et al. 2002; Alberg et al. 2004; Kocabas et al. 2004; Sillanpaa et al. 2005a; Conlon et al. 2010). None found statistically significant modification of effect, and results were inconsistent across studies for the direction of effect modification. Four studies suggested that risk may be increased in women with the rapid NAT2 phenotype (Millikan et al. 1998; Morabia et al. 2000; Chang-Claude et al. 2002; Kocabas et al. 2004), and three studies suggested that risk is increased with the slow phenotype (Alberg et al. 2004; Sillanpaa et al. 2005a; Conlon et al. 2010). One study (Delfino et al. 2000) reported nonsignificant findings, but numerical results were not provided. A case-only study by Lash and colleagues (2005) also reported a nonsignificant interaction that suggested increased risk in women with the slow NAT2 phenotype. Two studies (Millikan et al. 1998; Morabia et al. 2000) reported that menopausal status further modified the interaction, but they disagreed substantially in their findings. Millikan and colleagues (1998) reported an OR of 2.3 (95% CI, 0.9–6.2) in premenopausal women exposed to passive smoke who had the NAT2 rapid phenotype, as opposed to an OR of 1.2 (95% CI, 0.5–2.8) for women who had the slow phenotype. In contrast, for premenopausal women, Morabia and colleagues (2000) found that risk was not modified by phenotype; RRs were approximately 3.0 for both rapid and slow phenotypes. For postmenopausal women, Millikan and colleagues (1998) found that risk was lower in those with the rapid phenotype (OR = 0.8; 95% CI, 0.4–1.8) than in those with the slow phenotype (OR = 1.9; 95% CI, 0.7–5.2), while Morabia and colleagues (2000) reported that risk was higher in postmenopausal women with the rapid phenotype (OR = 11.6; 95% CI, 2.2–62.2) than in those with the slow phenotype (OR = 1.1; 95% CI, 0.3–4.3). Ambrosone and

colleagues (2008) performed a meta-analysis of several of these studies of exposure to passive smoking and derived a summary estimate (RR) of 1.13 (95% CI, 0.81–1.56) for slow acetylators and 1.19 (95% CI, 0.84–1.68) for rapid acetylators. Significant heterogeneity was present among the estimates, particularly for the rapid phenotype, and thus the authors did not calculate summary estimates by menopausal status.

Only a few studies have examined interactions between exposure to passive smoke and genotypes other than *NAT1/2*. Mordukhovich and colleagues (2010) reported that women with exposure to passive smoking were more likely to have p53-negative tumors, and Lilla and colleagues (2005) examined effect modifications by the *SULT1A1* gene using data from the same German case-control study as Chang-Claude and colleagues (2002). No statistically significant interaction was found. The study suggested a possible three-way interaction between exposure to passive smoke, *SULT1A1,* and *NAT2,* but this was not statistically significant. Millikan and colleagues (2004) found no evidence of an interaction between exposure to passive smoke and *MnSOD* on risk for breast cancer, and Gaudet and colleagues (2005) reported that risk for breast cancer increased with exposure to passive smoke regardless of the *MnSOD* genotype. In a case-only analysis, Bradbury and colleagues (2006) reported departures from multiplicative interaction for the *COM-THL* genotype and history of ever being exposed to passive smoking (OR = 2.0; 95% CI, 0.8–5.2) or of having lived with a smoker after 20 years of age (OR = 2.8; 95% CI, 0.8–10). Evaluating this result requires assumptions that the interaction is multiplicative rather than additive and that genotype and exposure are independent.

Summary and Review of Exposure to Secondhand Smoke

The 2006 Surgeon General's report on secondhand cigarette smoke concluded that there was suggestive but not sufficient evidence to conclude there was a causal association between exposure to secondhand smoke and breast cancer. It also noted that the evidence was mixed and that the positive association was observed primarily among premenopausal women in case-control studies. Since the 2006 report, 5 new cohort and 10 case-control studies have been reported for the association of passive smoking with breast cancer. Additionally, updates have been reported for 2 cohort studies and 1 case-control study.

In general, the new RRs are lower than those previ-

ously reported. For the most part, it continues to be true that case-control studies find statistically significantly increased risk of breast cancer from all or most measures of exposure, while cohort studies do not. However, the case-control studies are more heterogeneous than the cohort studies across all exposure measures. The sensitivity analyses in the present report indicate that the summary estimates are substantially reduced when case-control studies with design and analysis issues or extreme estimates are excluded. The three broadest categories of secondhand smoke exposure, *Adult—any source, Ever in lifetime*, and *Most comprehensive*, are associated with significant increased risks ranging from 1–15% (Table 6.25*S*). However, the corresponding estimates for the most restricted sensitivity analyses are not statistically significant, with risks ranging from 3–4% (Table 6.25*S*). Heterogeneity and publication bias also were reduced. The estimates reported for the most conservative sensitivity analyses provide an estimate that might better approximate the result if there were no publication bias and greater consistency among studies. The sensitivity analyses also reveal how certain studies leverage results. These studies are primarily smaller case-control studies, and it is not obvious that they have better quality exposure assessments. Compared with the results for active smoking, the sensitivity analyses indicate that the positive association of passive smoking with breast cancer is not statistically robust.

The meta-analyses continue to suggest that risk is mainly increased in premenopausal but not in postmenopausal women across all measures, with the exception of childhood exposure. Overall, the RRs for the most conservative summary estimates for premenopausal women are 12–26% higher than for postmenopausal women for the three broadest categories of exposure *(Adult—any source, Ever in lifetime, Most comprehensive)*. However, many studies did not provide results stratified on menopausal status, and the CIs for the summary estimates were wide and overlapping (based on Tables 6.25*S* and 6.26*S*). This difference appears to be magnified by case-control studies with design or analysis issues. Thus, despite the publication of more studies, the results are inconsistent and the evidence for an association of passive smoking with breast cancer remains suggestive only in premenopausal women. To date, there are not enough published studies to evaluate associations with tumor phenotype or effect modification by susceptibility genes.

Major Summary Points on Passive Smoking

1. Based on 34 study reports published before 2012, evidence suggests that exposure to passive smoking—defined most comprehensively to include either *Ever in lifetime* or *Adult—any source* exposure—increases the RR for breast cancer by an average of 11–15%. However, sensitivity analyses suggest that this estimate should be lower because of the strong influence of 11 case-control studies with design or analysis issues. When these studies are excluded, the average increase in risk is substantially reduced to 3–4%.

2. There is emerging evidence to suggest that the risk of breast cancer from passive smoke exposure may be greater in premenopausal than postmenopausal women; 21% versus 4% for the *Most comprehensive* measure, or a relative difference of 16%.

3. There is insufficient evidence to conclude that the risk for breast cancer from exposure to passive smoking is modified by timing, source, location of exposure, estrogen receptor status, or genetic susceptibility.

Exposure to Tobacco Smoke and Breast Cancer Mortality

Smoking could influence breast cancer mortality through effects on incidence, survival, or both. In general, cancer survivors represent a high-risk population that is susceptible to multiple exposures and associated smoking-related noncancer comorbidities, such as heart disease, diabetes, obesity, sarcopenia, osteopenia, and osteoporosis (Fine et al. 1999; Twiss et al. 2001; Demark-Wahnefried et al. 2002; Rao and Demark-Wahnefried 2006; Li 2010). Some of these adverse outcomes are important contributors to mortality in women who are diagnosed with breast cancer and some are associated with cancer treatment (radiation, chemotherapy) (Rao and Demark-Wahnefried 2006; Harris 2008). Thus, a causal association between smoking and breast cancer mortality is difficult to infer because of confounders that are entangled with treatment and other noncancer, smoking-related morbidity that can contribute to mortality.

Active Smoking

In the 2004 Surgeon General's report, only one study was evaluated for the association between active smoking and breast cancer mortality (Calle et al. 1994): the CPS-II reported an increased risk for breast cancer mortality (RR = 1.26; 95% CI, 1.05–1.50) among current smokers compared with lifetime nonsmokers. The increased risk was linked to the number of cigarettes smoked per day and the number of years of smoking. The study did not find an increased risk of mortality among former smokers (RR = 0.85; 95% CI, 0.70–1.03). The 2004 Surgeon General's report suggested that this last finding dampened the other evidence because former smokers may be more likely to be screened and receive earlier diagnoses than current smokers (USDHHS 2004): consequently, these results for current and former smokers may reflect screening behavior rather than a true association (Hirayama 1984; Calle et al. 1994; Wartenberg et al. 2000).

The 2004 Surgeon General's report did not include an early report by Tverdal and colleagues (1993) on a cohort of 24,535 Norwegian women in which an RR of 0.90 (95% CI, 0.4–1.9) was estimated for breast cancer mortality from smoking more than 10 cigarettes per day. Later, the Collaborative Group Report, presenting an analysis of data from 53 studies, included an estimate for risk of breast cancer of 1.03 (SE = 0.02) in smokers who did not report alcohol consumption (Collaborative Group on Hormonal Factors in Breast Cancer et al. 2002). In New York City, Yu and colleagues (1997) conducted a study of the effect of smoking on the survival of 12,989 women diagnosed with incident breast cancer between 1990–1995, using archived data from the Memorial Sloan-Kettering Cancer Center. Among 4,580 cases, 39.4% reported ever smoking. Analyses were mutually adjusted for age, race, and histologic grade. Mortality from breast cancer was significantly increased among ever smokers (RR = 1.32; 95% CI, 1.10–1.70). Risk for mortality from breast cancer was higher among African American women (RR = 1.73; 95% CI, 1.00–2.90) than White women (RR = 1.21; 95% CI, 0.9–1.6). Follow-up was for only 5 years and no differentiation could be made between former and current smokers. In an ancillary analysis of data from the NHS-I, Egan and colleagues (2002) evaluated the association between breast cancer mortality and current and former smoking. The RR for breast cancer death was 1.19 (95% CI, 0.94–1.50) for current smokers and 1.11 (95% CI, 0.89–1.04) for former smokers. In Sweden, Manjer and colleagues (2000a) reported results for the association of smoking with breast cancer mortality in a small cohort study. A total of 792 women diagnosed with breast cancer between 1977–1986 were followed for an average of 12.1 years. The RR of breast cancer mortality in current smokers was 2.14 (95% CI, 1.47–3.10) in a comparison with nonsmokers that adjusted for age, stage at diagnosis, and other confounders.

Since the 2004 Surgeon General's report and through 2011, eight published studies have evaluated the association between smoking and breast cancer mortality (Fentiman et al. 2005; Holmes et al. 2007; Ozasa 2007; Sagiv et al. 2007; Barnett et al. 2008; Dal Maso et al. 2008; Rezaianzadeh et al. 2009; Hellman et al. 2010). Barnett and colleagues (2008) examined incident and prevalent cases; the seven other studies examined only incident cases. Each study used never smokers as the reference group and reported risk estimates for active smoking status. Two of the eight studies reported a significantly increased risk of mortality among ever smokers (Dal Maso et al. 2008; Rezaianzadeh et al. 2009). Elsewhere, Rezaianzadeh and colleagues (2009) observed that among 1,148 women who lived in Southern Iran and were followed for a median of 2.6 years, ever smokers had a 40% increased risk for mortality (95% CI, 1.07–1.86) after adjusting for family income and pathology markers, such as tumor size and grade, lymph node involvement, and metastasis. Data were collected from a hospital-based cancer registry. Detailed information about smoking status was not reported. Only 58% of the women in this group were expected to survive for 5 years, perhaps because of cultural barriers and late access to treatment (Rezaianzadeh et al. 2009). Dal Maso and colleagues (2008) observed similar results in an Italian cohort of 1,453 incident cases followed for 12.6 years: ever smokers had a 30% increased risk for mortality (RR = 1.30; 95% CI, 1.05–1.61) after adjusting for age, residential location, and year of diagnosis. Breast cancer mortality did not appear to differ between former and current smokers. Risk for smoking was somewhat higher in older women (≥55 years of age).

Results from the other six studies were null or inconsistent. Using a small cohort of 166 patients followed for 11 years in the United Kingdom, Fentiman and colleagues (2005) reported nonsignificant protective associations in former smokers, but increased risks in current smokers, for breast cancer-specific and disease-free survival. In contrast, Barnett and colleagues (2008), who studied a much larger cohort of 4,560 incident and prevalent cases followed for a median of 6.8 years in England, found no increased risk of mortality for former or current smokers. This study, however, did not adjust for any covariates. Holmes and colleagues (2007) examined 5,056 incident cases followed for more than 8 years in the NHS-I. After adjusting for age, use of alcohol, diet, and prognostic tumor characteristics, the study did not report

any significant associations for former or current smokers. Similarly, among 1,273 women in the Long Island Breast Cancer Study Project, Sagiv and colleagues (2007) found no significant associations between former or current smoking and breast cancer-specific mortality. In a cohort of Japanese women, Ozasa (2007) reported nearly a fivefold, statistically significant increased risk among former smokers (RR = 4.79; 95% CI, 2.18–10.5), but risk was not significantly increased in current smokers (RR = 1.43; 95% CI, 0.65–3.11). However, the study is difficult to interpret because the number of deaths was small (n = 93) and the CIs varied widely. Most recently, Hellman and colleagues (2010) reported results for smoking and breast cancer mortality from the Copenhagen City Heart Study, which included 528 women with a primary diagnosis of breast cancer. There was no association between breast cancer mortality and former (RR = 0.98; 95% CI, 0.77–1.24) or current smoking (RR = 1.07; 95% CI, 0.94–1.23).

Duration and Intensity of Smoking

Four studies evaluated the association between smoking duration or intensity (pack-years of smoking or cigarettes smoked per day) and breast cancer mortality. In the NHS-I, Holmes and colleagues (2007) did not find an association between an increasing number of cigarettes smoked per day (p trend = 0.77) and breast cancer mortality. Elsewhere, Dal Maso and colleagues (2008) reported a significantly increased risk in breast cancer mortality for smoking more than 25 years (RR = 1.46; 95% CI, 1.12–1.90). However, in this study, risk also increased for smokers who smoked fewer than 15 cigarettes per day (RR = 1.39; 95% CI, 1.02–1.90) but not for those smoking 15 or more cigarettes per day (RR = 1.23; 95% CI, 0.82–1.83). A similar paradoxical finding was reported by Ozasa (2007), who found a significantly increased risk in breast cancer mortality for smoking for 40 or more years (RR = 4.28; 95% CI, 1.01–18.0) but also for women who smoked fewer than 15 cigarettes per day (RR = 2.39; 95% CI, 1.04–5.51). In contrast, Sagiv and colleagues (2007) did not find an elevated risk for smoking 20 or more years (RR = 0.92; 95% CI, 0.57–1.49).

Hormone Receptor Status

Three studies analyzed the association between ER and PR status and breast cancer mortality. ER/PR status is an important predictor of breast cancer survival (Holmes et al. 2007; Sagiv et al. 2007; Dal Maso et al. 2008). In studies by Holmes and colleagues (2007) and Sagiv and colleagues (2007) and compared with ER– tumor status,

ER+ status exhibited nonsignificant protective effects on breast cancer mortality in current and former smokers. In contrast, Dal Maso and colleagues (2008) reported that ever smokers with ER+/PR+ tumor status did not have a significantly increased risk (HR = 1.11; 95% CI, 0.80–1.55) for breast cancer mortality, but the risk was increased significantly (HR = 1.90; 95% CI, 1.28–2.83) in those with other tumor phenotypes when considered as a group. It is reasonable to assume that this "other" category consisted predominantly of ER–/PR– tumors. The results for analyses stratified by menopausal status were null or inconsistent (Holmes et al. 2007; Sagiv et al. 2007).

Exposure to Secondhand Smoke

Only three studies have evaluated the association between breast cancer mortality and exposure to secondhand smoke (Hirayama 1984; Wartenberg et al. 2000; Sagiv et al. 2007). In a Japanese cohort of single-marriage, lifelong never smokers, Hirayama (1984) reported no significant associations between breast cancer mortality and the husband's smoking status. Analyses were stratified for husband's current versus former smoking status, duration and intensity of smoking, and age of the women at baseline and marriage. Later, Wells (1991) reanalyzed these data and reported a nonsignificant increased risk in breast cancer mortality if the husband was an ever smoker (RR = 1.26; 95% CI, 0.8–2.0). Wartenberg and colleagues (2000) analyzed data from the CPS-II cohort and reported no association of breast cancer mortality with exposure (RR = 1.0; 95% CI, 0.8–1.2) while detecting a nonsignificant increased risk among women who were married before 20 years of age to a smoker (RR = 1.2; 95% CI, 0.8–1.8). Johnson (2001) speculated that the study by Wartenberg and colleagues (2000) may have underestimated risk because it did not consider nonspousal sources and long duration of exposure. However, Wartenberg and colleagues (2001) responded that they found no increased risk among women who reported exposure at the workplace (RR = 0.8; 95% CI, 0.6–1.0) or other places (RR = 0.9; 95% CI, 0.7–1.2), and they pointed out that stratification on duration in some other studies resulted in unstable estimates because of small samples. Sagiv and colleagues (2007) examined the association between association and breast cancer using data for 1,273 cases followed for approximately 7 years in the Long Island Breast Cancer Study Project. The study found a small but nonsignificant increased risk (RR = 1.16; 95% CI, 0.63–2.15) among never-smoking women who reported ever living with a smoker.

Summary of Exposure to Tobacco Smoke and Breast Cancer Mortality

To date, the evidence is insufficient to conclude that either active or passive smoking influences breast cancer mortality. Studies have been complicated by problems with misclassifying exposure and a lack of specificity because smoking increases risk for several noncancer, comorbid conditions that contribute to mortality in survivors of breast cancer.

Evidence Synthesis

This section reviews the topic of smoking and risk for breast cancer separately for active and passive smoking, as was done in the 2004 and 2006 Surgeon General's reports. Various panels and committees have taken the same approach, providing separate reviews and conclusions about breast cancer in active and passive smokers. However, the more general question is whether exposure to tobacco smoke causes breast cancer. The review of evidence on mechanisms of breast carcinogenesis included in this chapter does not provide a basis for separating active and passive exposure. Additionally, the mechanisms that may be most prominently involved in the causation of cancer in breast tissue—that is, adduct formation and unrepaired DNA mutations—are equally applicable to active and passive smoking. In the context of the mechanism of carcinogenesis, active and passive smoking would correspond to high-dose and low-dose exposures, respectively. Consequently, this section provides a unified appraisal of the evidence on smoking, whether active or passive, and risk for breast cancer.

Methodologic Issues

The following sections summarize the methodologic issues identified in this review of published studies on the association between risk for breast cancer and either active smoking or exposure to smoking by others (passive exposure). Some of these issues are common to observational studies, but others are more specific to assessing the relationships between exposures to tobacco smoke and disease outcomes. The discussion of analytic limitations addresses the application of meta-analysis to pool and summarize data from studies with disparate designs and methods.

Information and Selection Bias

Most studies conducted to date have relied on self-reported exposure and thus information bias is a concern.

Case-control studies based on self-reported exposure are more susceptible to systematic and random error, referred to as information bias, than are cohort studies in which outcomes occur after exposure is assessed. Random misclassification of exposure attenuates risk estimates toward the null value of 1.0, thus limiting sensitivity for detecting weak but potentially causal associations. Differential misclassification between cases and controls biases risk estimates away from 1.0 in either a positive or negative direction. Some methodologic studies, however, suggest that simple measures of current smoking status are generally reported accurately. West and colleagues (2007) compared smoking misclassification rates across large, population-based surveys in England, Poland, and the United States, finding that the self-reported prevalence of current smoking was underestimated relative to the gold standard of serum cotinine level by 2.8% in England, 4.4% in Poland, and 0.6% in the United States, indicating that the extent of misclassification may vary across populations.

Misclassification of exposure to secondhand smoke may be considerably greater. Using data from Phase I (1988–1991) of the Third National Health and Nutrition Examination Survey (NHANES III), Pirkle and colleagues (1996) found significantly increased serum cotinine levels in many nonsmokers who reported no exposure to secondhand smoke at home or the workplace. Arheart and colleagues (2008) compared self-reports of tobacco use and exposures to secondhand smoke with cotinine levels using combined data from NHANES (1988–1991, 1991–1994, 1999–2000, 2001–2002, 2003–2004). Although the percentage agreement between self-reports and the cotinine data was high (87–92%) for both active smoking and passive exposure, 28% of nonsmokers who reported no exposure to passive smoke had increased levels of serum cotinine.

At present, methods are lacking for measuring long-term, cumulative exposure on either a quantitative or semiquantitative basis with high accuracy. Such measures as duration and pack-years of smoking may be subject to substantial information bias because many smokers cease and then resume smoking repeatedly over time, and their memory of the frequency and length of such episodes may not be clear. Similarly, historic childhood, long-term, and lifetime exposure to passive smoke is subject to greater information bias than are more recent adult exposures. Assessing passive exposure to smoking is further complicated by the need to account for multiple sources and locations of exposure. In addition, such passive exposure has changed at highly variable rates across regions of the United States and across other countries, further complicating assessments of long-term exposure. Compared with

cohort studies, case-control studies of passive exposure to smoking have generally included more comprehensive assessments of the timing, duration, sources, locations, and intensities of exposure. However, the results of case-control studies often display significant heterogeneity, probably reflecting varying information biases in measuring passive exposure to smoking.

Differential information bias between cases and controls can occur when disease status influences the validity of self-reported exposure, particularly if women with breast cancer are aware of the possible association of smoking with risk for breast cancer. Compared with newer studies, older studies may be less subject to differential misclassification bias because participants in those studies could have had less knowledge about the potential link between smoking and the risk for breast cancer. This may not be true for newer studies. As noted previously, some surveys have found that many women now believe that smoking is causally linked to breast cancer (Wold et al. 2005; Wang et al. 2010a).

Selection bias can create either false-positive or false-negative effects in epidemiologic studies. Consequently, studies that produce more extreme estimates should be scrutinized carefully for design issues that could produce selection bias as well as differential information bias. Several such studies were identified in this review for active smoking (Lash and Aschengrau 1999, 2002; Delfino et al. 2000; Kruk 2007) and for passive exposure to smoking (Sandler et al. 1985a; Smith et al. 1994; Jee et al. 1999; Lash and Aschengrau 1999, 2002; Zhao et al. 1999; Morabia et al. 2000; Kruk 2007). Sensitivity analyses indicated that the results for active smoking are relatively robust, with little change in the summary estimates when these studies were excluded. This pattern did not prevail, however, for studies of passive exposure to smoking, where estimates were sharply attenuated when sensitivity analyses were conducted. Therefore, results for passive exposure to smoking may be more subject to positive bias. Finally, the funnel plots for passive smoking provide evidence of publication bias from small positive studies; small studies are statistically more likely to produce extreme estimates, and positive results are more likely to be published.

Confounding and Effect Modification

The association between smoking and breast cancer may be confounded by several established risk factors. Use of alcohol is widely regarded as one of the most important potential confounders because it is a risk factor for breast cancer (Singletary and Gapstur 2001; Boyle and Boffetta 2009) and is positively correlated with smoking (Shiffman and Balabanis 1995). However, assessments of the use of alcohol are subject to similar information biases as those

for smoking, and the strength of the correlation between smoking and alcohol use may vary with age and across populations or subgroups within a population (Caetano et al. 1998; Anthony and Echeagaray-Wagner 2000). Still, the association between use of alcohol and breast cancer is modest (RRs: 1.20–1.40), and the relationship is primarily at high levels of intake (e.g., >2 drinks/day) (Longnecker 1994; Singletary and Gapstur 2001; Boyle and Boffetta 2009), although recent reports from the Million Women Study (Allen et al. 2009) and the NHS-I (Chen et al. 2011c) suggest that risk may also be increased at lower levels of consumption. Nonetheless, the magnitude of any confounding may be trivial in populations of women with a low prevalence and level of alcohol use and/or smoking.

The Collaborative Group on Hormonal Factors in Breast Cancer and colleagues (2002) reported summary estimates of 1.09 for ever smokers, regardless of alcohol use, 1.05 when averaged across strata of alcohol use, and 1.03 when restricted to nondrinkers. The report did not evaluate associations between risk for breast cancer and duration, dose, or timing of smoking. Other than the Collaborative Group Report, no systematic analyses have compared statistical adjustment for alcohol use with restriction to nondrinkers. Most studies reviewed in this report statistically adjusted for the use of alcohol. Although residual confounding may remain after statistical adjustment, restricting analyses to nondrinkers could create selection bias if this subgroup differs systematically from drinkers in terms of smoking duration, dose, or timing. The report from the Million Women Study (Allen et al. 2009) indicates that nondrinkers were, on average, older, heavier, less affluent, less likely to exercise, and less likely to use oral contraceptives or HRT than were drinkers. While alcohol consumption was positively associated in that study with smoking overall, women who drank wine were reported to be less likely to smoke. This suggests that women who drink differ from those who do not on a variety of risk factors, including smoking.

These findings suggest that confounding between alcohol use and smoking is complex, and that restriction of the reference group to nondrinkers or that statistical adjustment for alcohol use will not necessarily result in lower risk estimates for the association between smoking and breast cancer. As noted previously, confounding can obscure associations and create either false-positive or false-negative findings. In the California Teachers Study cohort, Reynolds and colleagues (2004b) reported that the risk of breast cancer for the subgroup of current smokers who were nondrinkers was higher (RR = 1.66; 95% CI, 1.15–2.40) than the estimate for all participants after adjusting for alcohol intake (RR = 1.32; 95% CI, 1.10–1.57). In a case-control study, Li and colleagues (2005) reported

that the risk of breast cancer among current smokers who were never users of alcohol was identical to that of current smokers who consumed at least 8.2 grams of alcohol per day (OR = 1.5; 95% CI, 0.9–2.5) and was higher than that of current smokers who consumed less than 8.2 grams of alcohol per day (OR = 1.3; 95% CI, 0.7–2.3). These observations conflict with the assumption that restriction to nondrinkers or statistical adjustment for alcohol intake will result in a lower estimate of RR for smoking. Thus, the nature and extent of confounding between alcohol use and smoking for risk of breast cancer remains unresolved.

Alcohol is known to enhance the toxic effects of environmental carcinogens on some tissues, and synergy between alcohol and smoking risks has been reported for several health outcomes (IARC 2004; Lowenfels and Maisonneuve 2004). Interaction between smoking and alcohol is known to occur for some cancers, but this has not been examined with respect to breast cancer. The strongest evidence of an interaction is for tissues with direct exposure to both alcohol and tobacco smoke, such as pharyngeal and laryngeal cancers that occur in the upper respiratory tract, and esophageal cancers (Rothman and Keller 1972; Flanders and Rothman 1982; IARC 2004). However, interactions have been reported for tissues without direct exposure, such as the heart and pancreas (Lowenfels and Maisonneuve 2004). Few, if any, studies have tested for interaction between smoking and alcohol use relative to risk of breast cancer.

The use of screening mammography increased rapidly between 1987–2000, then declined or was relatively stable between 2000–2008 (Breen et al. 2011). There is evidence that health behaviors, including smoking and alcohol consumption, influence use of screening. Some studies have reported different rates of screening for smokers than for nonsmokers (Fredman et al. 1999). Trentham-Dietz and colleagues (2007b) reported that among women who reported having annual mammograms, there was an inverse association between smoking and risk for in situ breast cancer (RR = 0.82; 95% CI, 0.70–0.95), but there was no association for women who reported fewer than annual mammograms (RR = 1.04; 95% CI, 0.85–1.28), and a significant positive association for women who reported never having had a mammogram (RR = 1.48; 95% CI, 1.05–2.10). This pattern was consistent across other measures of smoking exposure, including current smoking, duration, cigarettes smoked per day, and pack-years of smoking. This provides evidence that screening behavior may modify the direction of the association of smoking with in situ breast cancer. In addition, it suggests that the association of smoking may be different for in situ than for invasive breast cancer. Of the 67 reports considered for inclusion in the meta-analyses of active smoking in

the present report, 31 (46%) specified that analyses were restricted to invasive cases only, 15 (22%) indicated that they included in situ cases, and 21 (32%) did not specify any stage-specific inclusion criteria. Estimates from studies that include in situ cases, such as those in the report by Trentham-Dietz and colleagues (2007b), may be biased toward the null or even indicate an inverse association with smoking, depending on the number of in situ cases included, due to the negative association between smoking and mammography screening. Taken together, these findings suggest that screening behavior may influence the association between smoking and risk of breast cancer. Studies conducted during the period in which there was a rapid increase in screening may be more susceptible to this influence. In addition, the association between smoking and in situ breast cancer differs from that of invasive breast cancer. Thus, analyses of the association between smoking and risk for breast cancer should account for mammography screening.

Wells (1991) and others (Morabia et al. 1996) proposed that the association between smoking and breast cancer is attenuated when passively exposed women are included in the reference group. As a result, several studies have used never smokers who reported no passive exposure as the reference group (no active/no passive). Results from these studies, however, are inconsistent and the meta-analyses suggest only a small difference between summary estimates based on *no active* exposure groups and those where the reference groups were no active/no passive exposure. Two issues should be considered: (1) the no active/no passive exposure reference group is typically very small and highly selected, which may affect estimates of precision and bias; and (2) passive exposure is difficult to define clearly, especially over time, resulting in misclassification bias. These issues would be more significant if women systematically overreport passive exposure and underreport active smoking, as postulated by Trichopoulos and Lagiou (2004).

The association between risk for breast cancer and smoking could be most apparent among women who initiated smoking before their first pregnancy because of the increased susceptibility of breast tissues to carcinogens before terminal differentiation. However, timing in relation to first pregnancy may be confounded with age at first pregnancy, because older age at first pregnancy is an independent risk factor for breast cancer. Only one-half of the studies that estimated risk for smoking before first pregnancy adjusted for age at first pregnancy (Innes and Byers 2001; Egan et al. 2002; Al-Delaimy et al. 2004; Gram et al. 2005; Lissowska et al. 2006; Ha et al. 2007; Magnusson et al. 2007; Prescott et al. 2007; Young et al. 2009; Luo et al. 2011b; Xue et al. 2011). It is also unclear whether

smoking during pregnancy has a different association with risk for breast cancer than smoking before first full-term pregnancy.

Many studies have examined modification effects of smoking by genes that influence susceptibility to smoking-related carcinogens. Specific groups of candidate genes have been studied that influence carcinogen metabolism, oxidative stress, and DNA repair. Some studies have been more concerned with establishing main effects of genetic variants than with the modification effects of smoking (e.g., Metsola et al. 2005), and few studies have had adequate statistical power to detect interactions. Some studies and meta-analyses provide support for *NAT2* as a genetic variant that modifies smoking risk, but there is little consistent evidence for other genetic variants. Associations between risk for breast cancer and active smoking and passive exposure to smoking could differ according to breast cancer phenotype. Mixing different breast cancer phenotypes may attenuate or distort risk estimates for smoke exposure, especially if underlying mechanisms differ and these phenotypes have different sets of potential confounders. Results stratified by ER status have been inconsistent for active smoking, and only a few studies have evaluated passive exposure to smoking. Sample sizes and statistical power are a problem for these studies because of the relative rarity of the ER–phenotype.

Limitations of Meta-Analysis

For the meta-analyses in this report, estimates from some studies had to be pooled across various strata, including exposure, age, menopausal status, and race/ethnicity; this may have obscured variation across these strata in some studies. Similarly, estimates across categories of exposure to passive smoking had to be pooled to obtain usable estimates for some studies. The net result of this pooling smoothed out variation across strata within some studies that may have been due to real differences, or it could have been likely due to chance. Consequently, the summary estimates from the meta-analyses should be regarded as conservative. Calculating estimates for subgroups in meta-analyses is difficult when studies use different classification criteria or cutoffs for stratification; this was a problem for analyses of timing and the duration of active smoking. In addition, tests for heterogeneity and bias are imprecise and potentially misleading when there are few studies in a subgroup (Sterne and Harbord 2004). Although results for the broadest exposure categories are precise, they may obscure important differences between subgroups. Conversely, effects within subgroups that contain few studies are imprecise and more susceptible to bias, which is difficult to evaluate.

Criteria for Causal Inference

In keeping with Surgeon General's reports since 1964 (USDHEW 1964), this section addresses the evidence for a causal association between tobacco smoke and risk for breast cancer according to the criteria previously used—including consistency across studies, temporal relationship of association, strength of the association, and the biologic plausibility of the association.

Consistency

The replication of associations across studies that differ with regard to study design, study population, and investigators provides evidence of consistency. When all cohort studies prior to 2012 and case-control studies published from 2000 through 2011 were considered together in a meta-analysis of active smoking, significant heterogeneity was found for the effect of ever smoking. When cohort and case-control studies were separated, this heterogeneity was confined to the case-control studies and could be attributed largely to two studies with extreme estimates. The meta-analyses examining the risk of breast cancer with former and current smoking, duration of smoking, cigarettes smoked per day, and 20 or more pack-years of smoking indicated no statistically significant heterogeneity for these variables among either cohort or case-control studies, whether considered separately or when taken together. Results for age at smoking initiation and smoking before first pregnancy were less consistent, with significant heterogeneity among case-control studies. Overall, the summary estimates for case-control and cohort studies were generally in agreement and consistent across exposure categories for active smoking.

Results from the studies of passive exposure to smoking were less consistent, with greater contrasts between cohort and case-control studies for both individual and summary estimates. Cohort studies have generally produced null findings and case-control studies have tended to produce positive results. Case-control studies exhibited significant heterogeneity and evidence for publication bias from small studies. Small studies are more likely than larger ones to produce extreme estimates due to chance. The sensitivity analyses tabulated in Tables 6.25*S* and 6.26*S* indicate that estimates for most categories of passive exposure are attenuated when small studies, those with design or analysis issues, and studies with extreme outlier estimates are all excluded.

There is persistent evidence to suggest that the associations between active smoking and passive smoke exposure and breast cancer are stronger in premenopausal than in postmenopausal women. While the magnitude of

the difference in risk between premenopausal and post-menopausal women may differ by study design, it is consistent across both case-control and cohort studies (Tables 6.18*S* and 6.25*S*). In the 2006 Surgeon General's report, the summary RR for the most comprehensive measure of smoking was 1.64 in premenopausal *versus* 1.00 in post-menopausal women (Table 6.25*S*). Since then, several new and larger studies of passive smoking, including cohort studies, have found substantially lower estimates for pre-menopausal women, compared with studies published through 2005 and reviewed in the 2006 Surgeon General's report. Nonetheless, the difference in risk between pre-menopausal and postmenopausal women remains. However, it is difficult to discern why the association between risk for breast cancer and passive smoke exposure should be stronger than that for active smoking in premeno-pausal women.

Table 6.27*S* summarizes results for active smoking and passive exposure to smoking by study design and exposure category. The table permits a ready comparison of estimates for *Ever smoker* and *Most comprehensive* as the broadest categories for active smoking and exposure to secondhand smoke, respectively. Table 6.27*S* also shows results for the most conservative sensitivity analyses for these categories and for both random and fixed-effect models. The summary estimates from cohort studies and case-control studies are markedly similar across all measures of active smoking and affected little by exclusions in sensitivity analyses. Thus, the overall evidence is relatively consistent for a weak effect of active smoking on risk for breast cancer. The evidence is less consistent for passive exposure to smoking, with marked differences between case-control and cohort studies and greater sensitivity to exclusions for design and analysis issues, sample size, and extreme estimates.

Temporality

Cohort studies are generally regarded as providing stronger evidence than case-control studies for causality because they satisfy the temporality criterion that the measurement of exposure precede the ascertainment of the outcome. Cohort studies published since 2000 generally show a small increased risk for breast cancer associated with active smoking (Manjer et al. 2000b; Egan et al. 2002; Al-Delaimy et al. 2004; Reynolds et al. 2004b; Gram et al. 2005; Olson et al. 2005; Cui et al. 2006; Ha et al. 2007; Luo et al. 2011b; Xue et al. 2011). All of these cohort studies found RRs greater than 1.0, and several reported significantly increased risk for breast cancer across multiple measures of smoking exposure.

The summary RRs from the most restricted meta-analyses of active smoking for cohort studies are 1.10 for ever smokers, 1.09 for former smokers, 1.14 for current smokers, 1.15 for smoking 20 or more years, 1.12 for 20 or more cigarettes smoked per day, and 1.15 for 20 or more pack-years of smoking (Table 6.27*S*). In contrast, the summary RRs for the most restricted analyses for cohort studies that included an assessment of exposure to passive smoking have generally been null, with estimates of 1.01 for *Adult—any source*, 1.02 for *Ever in lifetime*, and 1.02 for *Most comprehensive* (Table 6.27*S*). Taken together, the results from cohort studies support an association between risk of breast cancer and active smoking of long duration but do not provide similar evidence for an association with passive smoking.

With regard to timing, results to date do not support the hypothesis that active smoking or passive exposure to smoking have greater carcinogenic effects during periods when breast tissues are less differentiated and theoretically more susceptible. Summary risk estimates from cohort and case-control studies combined are significantly increased for early age at smoking initiation (20 years of age and younger) and smoking before/during first pregnancy (RRs = 1.11 and 1.10, respectively), but of similar magnitude to current smoking (RR = 1.12), former smoking (RR = 1.09), or ever smoking (RR = 1.09) (Table 6.17*S*). Results for exposure to passive smoking during childhood were generally null, regardless of study design (Table 6.26*S*).

Strength of Association

The results of the meta-analyses for active smoking indicate weak associations, ranging from 9% for the most restricted analysis of ever smoking to 16% for 20 or more years of smoking. The associations for various measures of passive exposure to smoking were similarly weak, 4–14% for the *Most comprehensive* measure, depending upon exclusions and sensitivity analysis. Considering these modest increases, it is not surprising that most studies, particularly in stratified analyses, have not had sufficient statistical power to detect an increased risk. Inconsistent results across studies with different designs and degrees of selection and information bias are not unusual for a risk factor with a weak effect. Given the relatively weak associations, confounding and bias are important concerns.

Mixing genetic subpopulations with different levels of susceptibility can attenuate or obscure the overall associations, but little headway has been made in identifying such subgroups, with the possible exception of *NAT2*. Larger studies are needed to clearly establish the modifi-

cation of effect by genetic susceptibility. If either active smoking or exposure to passive smoking has a causal but weak association with risk for breast cancer, then defining a dose-response gradient of effect will be difficult without more precise measurement of exposures and larger samples.

The evidence to date is not definitive for a dose-response relationship with measures of exposure for active smoking or for exposure to tobacco smoke. Findings are inconsistent with regard to trends across exposure levels (e.g., duration, cigarettes smoked per day, or pack-years of smoking), and only a few reports have formally tested the trends. The meta-analytic results provide weak evidence for a biologic gradient for active smoking in that summary estimates (Table 6.17*S*) are slightly higher for current smokers (RR = 1.12) than former smokers (RR = 1.09) and highest for smoking 20 or more years (RR = 1.16), 20 or more cigarettes smoked per day (RR = 1.13), and accumulating 20 or more pack-years of smoking (RR = 1.16). Quantifying the cumulative dose of secondhand smoke is complex because the assessment should consider multiple sources and locations of exposure in addition to duration. Evidence from recent cohort studies is mixed (Reynolds et al. 2009; Luo et al. 2011b; Xue et al. 2011).

Biologic Plausibility

This chapter and the 2010 Surgeon General's report have addressed tobacco smoke carcinogenesis and mechanisms by which smoking may increase breast cancer risk. Multiple lines of evidence support the biologic plausibility of a causal relationship of tobacco smoke with breast cancer.

Studies have confirmed the presence of short-term biomarkers stemming from exposure to tobacco smoke, such as cotinine, in breast tissues and fluids (Petrakis et al. 1978). Carcinogen-DNA adducts, which are widely regarded as providing one of the best biomarkers of exposure effect (Lodovici and Bigagli 2009), have also been consistently detected in breast tissues and body fluids of smokers (Perera et al. 1995).

The evidence for an anti-estrogenic effect of smoking on breast cancer is weak, leading some to question whether this is a valid explanation for a few studies that have reported inverse associations or for the attenuation of the carcinogenic effects of tobacco smoke (Palmer and Rosenberg 1993). Baron (1996) reviewed evidence for this hypothesis in relation to several hormone-related cancers but found the data for breast cancer to be inconclusive. Studies of the effects of smoking on hormone metabolism and circulating levels have been inconsistent, and mechanisms for an anti-estrogenic effect in breast cancer are

not well established (USDHHS 2004). However, a recent reanalysis of 13 prospective studies including approximately 6,000 postmenopausal women reported that both estrogen and androgen levels were increased in women who smoked 15 or more cigarettes per day (Endogenous Hormones and Breast Cancer Collaborative Group 2011).

Conclusions

1. The evidence is sufficient to identify mechanisms by which cigarette smoking may cause breast cancer.

2. The evidence is suggestive but not sufficient to infer a causal relationship between tobacco smoke and breast cancer.

3. The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and breast cancer.

4. The evidence is suggestive but not sufficient to infer a causal relationship between exposure to secondhand tobacco smoke and breast cancer.

Implications

Sufficient quantitative evidence indicates that smoking—active smoking or passive exposure to smoking—is associated with an increased risk for breast cancer. However, the magnitude of risk is small, and neither active smoking nor passive exposure to smoking constitutes a large risk to the breast health of women. Nonetheless, reducing exposure to tobacco in women is a potential avenue for reducing the burden of breast cancer. Because breast cancer is the most frequent type of cancer in women and accounts for significant morbidity and mortality, research should continue to examine potential causes, including tobacco smoking and exposure to secondhand smoke.

Approximately 20% of women in the United States smoke, with prevalence varying by region (see Chapter 13). Prevalence also varies substantially by race/ethnicity. Over the past two decades, smoking prevalence has declined more rapidly in older age groups than in younger age groups, although the prevalence of smoking among 18- to 25-year-old women is also declining. As a result, prevalence rates do not differ much between women 45–64 years of age and those 18–44 years of age. Selfreported prevalence of exposure to secondhand smoke among

nonsmoking adults also varies widely among the states, from a low of 3.2% in Arizona to a high of 10.6% in West Virginia for exposure at home, and from a low of 6.4% in Connecticut to a high of 11.4% in North Carolina for exposure at the workplace (CDC 2009a). Internationally, the prevalence of smoking among women is not high in some countries (e.g., China, Japan, and Korea) (Table 6.13), but women's exposure to secondhand smoke is pervasive because of high rates of smoking among men (Mackay and Eriksen 2002; WHO 2002).

The extensive review in this chapter indicates that more research should be carried out on the association between tobacco smoke and risk for breast cancer, addressing several specific issues. Further research should explore the risk of exposure in genetically defined subgroups. Genomewide association studies that exam-ine the interaction of multiple genes with smoking and biomarkers of tobacco exposure will undoubtedly be conducted in the future (Taioli 2008). Given the variety and scope of methodologic limitations identified in this review, larger cohort studies are needed that incorporate the best and most complete methods of measuring expo-sure, including exposure biomarkers and genetic suscep-tibility markers, and that oversample younger women and minorities to address the important questions of timing with respect to first pregnancy and smoking in relation to different breast cancer phenotypes. Although these additional population studies are warranted, researchers also need to gain a deeper understanding of the under-lying mechanisms between exposure and disease inci-dence to provide a stronger framework for interpreting epidemiologic evidence.

Adverse Health Outcomes in Cancer Patients and Survivors

As survival from cancer has improved over time, the question of the potential impact of cigarette smoking on cancer patients and survivors is of increasing relevance. This topic is of growing importance, because survival fol-lowing the diagnosis of many types of cancer has improved markedly during the past decades, such that the preva-lence of cancer survivors in the United States is now more than 14 million and increasing (Siegel et al. 2012). This section reviews the evidence concerning cigarette smok-ing as a risk factor for adverse health outcomes in cancer patients during treatment and their survivorship.

Conclusions of Previous Surgeon General's Reports

Previous Surgeon General's reports have not specifi-cally evaluated the evidence concerning cigarette smok-ing and adverse health outcomes in cancer patients. The reports have concluded that there is sufficient evidence to infer that cigarette smoking causes premature death; multiple diseases, including multiple types of malignancy and other adverse health effects; and an overall dimin-ished health status, which predisposes cigarette smok-ers to diverse nonspecific consequences. These findings apply both to cancer patients (i.e., those in the course of diagnosis and treatment) and survivors (i.e., those who have completed treatment). The 2010 Surgeon General's report, *How Tobacco Smoke Causes Disease*, detailed the many mechanisms leading to these adverse health effects (USDHHS 2010). Thus, the evidence from previous Sur-geon General's reports provides a foundation for this review, which is the first in this series of reports to address the consequences of smoking for cancer patients, includ-ing the impact of smoking on cancer-specific outcomes such as recurrence, response to treatment, and toxicities from treatment.

Biologic Basis

For the purposes of this review, "adverse health out-comes" refers to a suite of unfavorable outcomes. The adverse effects of smoking on survival after a diagnosis of cancer could involve treatment-related effects on the tumor (e.g., accelerated growth, progression, metastases, and recurrence), or on the response to treatment (either tumor resistance or treatment-related toxicities). In addi-tion, patients being treated for a cancer are likely to have a greater frequency of other diseases caused by smoking, such as coronary heart disease or chronic obstructive pulmonary disease (COPD), and hence tolerate treatment less well than nonsmokers who are generally healthier. In addition, overall survival following a diagnosis of cancer will reflect the greater risk of smokers for death from any cause (see Chapter 12, "Smoking-Attributable Morbidity, Mortality, and Economic Costs"). A description of the bio-logic basis of the association for each of these potential

outcomes is beyond the scope of this section. However, relevant material on mechanisms of carcinogenesis, disease pathogenesis, and nonspecific effects has received extensive coverage in earlier reports, particularly the 2010 report, and elsewhere in this report (see Chapter 10, "Other Specific Outcomes").

With respect to all-cause mortality, the mortality burden from smoking is largely attributable to its role in causing multiple types of cancer, cardiovascular disease, and COPD. Many aspects of the pathogenesis of these diseases in smokers have been characterized, and these same mechanisms would apply to people with cancer and to cancer survivors. As detailed in the 2004 Surgeon General's report, in addition to causing specific disease endpoints, cigarette smoking causes systemic inflammation and oxidative stress and has widespread and complex effects on immune function (USDHHS 2004). The 2004 report concluded that smoking causes overall poorer health status, leaving smokers with a diminished health status compared to nonsmokers. This diminished health status represents a nonspecific pathway by which cigarette smoking could affect cancer outcomes, such as through increased treatment-related toxicities.

There are also specific biologic lines of evidence to suggest that cigarette smoke could promote tumor development, leading to increased risk for cancer recurrence and lack of response to treatment (USDHHS 2010). The 2010 Surgeon General's report sets out multiple mechanisms by which smoking leads to loss of control of cell replication. In mice engrafted with Lewis lung cancer cells, treatment with cigarette smoke increased tumor size and vascular development (Zhu et al. 2003). In colon cancer cells, cigarette smoke extract (CSE) increased cell proliferation and the level of activation of cyclooxygenase-2 (COX-2) (Liu et al. 2005). In this in vitro model, CSE also increased proliferation and expression of VEGF and MMP expression, which are associated with increased angiogenesis and tumor invasion (Ye et al. 2005b). Momi and colleagues (2013) showed that cigarette smoke increased tumor growth and metastases in pancreatic cancer cells. Inhibition of lipoxygenase or COX-2 partially prevented the increase in tumor growth associated with CSE treatment in colon cancer xenografts (Ye et al. 2005a). Signal transduction through activation of AKT has been implicated as a significant contributor to tobacco-carcinogen induced tumor formation (Memmott and Dennis 2010). Pancreatic ductal cells treated with CSE have decreased autophagy modulated through activation of AKT (Park et al. 2013). An and colleagues (2012) observed that in lung cancer or head and neck cancer cells, CSE induced activation of AKT leading to decreased response to chemotherapy and increased efflux of chemotherapy from cancer

cells. Collectively, these studies demonstrate tumor-promoting activities of cigarette smoke that could contribute to cancer recurrence and lack of response to treatment.

Not all tissues are exposed to the same mixture of tobacco smoke components. However, nicotine does reach all organs through deposition of nicotine-laden particles, absorption, and systemic circulation; consequently, there has been great interest in nicotine as a possible tumor promoter. The potential role of nicotine, and activation of the nicotinic acetylcholine receptor (nAChR), in promoting tumor growth has been extensively studied and was addressed specifically in the 2010 report and in Chapter 5, "Nicotine," of this report. Cigarette smoke can activate systemically expressed nAChRs that are present in both normal and cancerous tissues (Dennis et al. 2005; Hukkanen et al. 2005; Singh et al. 2011; Schuller 2012). Several recent reports support the role of nicotine nitrosamines—such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol—as well as activation of nAChRs and β-adrenergic receptors in contributing to a more aggressive tumor phenotype, as defined by increased proliferation, angiogenesis, migration, invasion, and epithelial-to-mesenchymal transition (Schuller 2008, 2012; Singh et al. 2011; Warren and Singh 2013). The 2010 report (p. 10) concluded that "There is consistent evidence that smoke constituents…nicotine and methyl (4-nitrosamino)-1-(3-pyridyl)-1-butanone can activate signal transduction pathways directly through receptor-mediated events, allowing the survival of damaged epithelial cells that would normally die." Further, nicotine and its activation of the nAChRs may decrease the effectiveness of cancer therapies both in in vitro models and in vivo (Dasgupta et al. 2006; Treviño et al. 2012; Warren et al. 2012; Banerjee et al. 2013). A specific role for nicotine as a determinant of therapeutic response in cancer patients has not yet been identified. In an in vitro model, removing nicotine does not appear to reduce the carcinogenic effect of cigarette smoke (Jorgensen et al. 2010); and nicotine replacement therapy has no appreciable effect on the development of cancer (Murray et al. 2009).

Epidemiologic and Clinical Evidence

Literature Search and Other Methodologic Considerations

The literature search strategy for this wide-ranging review was designed to have high sensitivity, by casting as broad a net as possible in searching the MEDLINE database and then manually identifying articles with evidence

on the association between adverse outcomes in cancer patients and smoking. For example, an initial search comprised key terms that included ("cigarette*" OR "smok*" OR "tobacco") and ("cancer" OR "neoplasm"). Due to the limited data available prior to 1990 and the tremendous changes that have occurred in treatment of cancer patients over time, the search only yielded studies published in 1990 through October 2012. As the relevant evidence accumulated, it was found to be concentrated on the specific topics of the associations between cigarette smoking and (1) overall mortality/survival; (2) cancer-specific mortality/survival; (3) risk of second primary cancers; (4) cancer recurrence/response to treatment; and (5) toxicity associated with cancer treatment. Consequently, for this chapter, the term "adverse health outcomes" represents a suite of outcomes listed above. The evidence was reviewed for each of these topics. Due to the large total numbers of relevant studies, a restriction was made based on sample size for the articles included in the evidence tables. Thus, studies of less than 100 patients were excluded from this evidence review for all disease sites except head/neck and lung where substantially more studies have been performed; thus for head/neck and lung only studies with at least 200 patients were included. In select cases, studies with fewer patients were included if the disease site was rare (such as vulvar or anal cancer) or if a unique finding was present (such as studies evaluating smoking cessation). Only data from original research reports were included in the summary tables, whereas relevant systematic reviews and meta-analyses are discussed within the text but not included in the evidence tables.

Some methodologic issues were applicable across the range of outcomes addressed. First, all evidence was obtained prospectively, such that the measurement of cigarette smoking preceded the occurrence of the health outcomes. Smoking information was collected either via review of medical records or a systematic protocol directly from patients.

Further, the classification of smoking status varied widely across studies, from never/former/current smoking status to current/noncurrent to ever/never and many other classification schemes. In assessing the consequences of smoking, a reference group of never smokers is preferred, although this reference group was not available for all studies. If multiple comparisons were presented, the classification of never/former/current smoker was preferentially included in the summary tables.

A feature common to all of the study populations is that they were composed of cancer patients, but represented a very diverse set of clinical diseases. The observational studies are also complicated by the differing outcomes, which include cancer-free survival, mortality from cancer, and all-cause mortality, ranging from highly specific to very general. For the purposes of this evidence review, unless it was critical to making inferences, such as for the risk of second primary cancers, the approach was to interpret the body of evidence as a whole without looking for variation in the consequences of smoking by type of malignancy, tumor site, or stage of disease.

Cigarette Smoking and All-Cause Mortality in Cancer Patients

Studies in cohorts of cancer patients that assessed the association between cigarette smoking and all-cause mortality are summarized in Table 6.28S, which includes the results from 159 different studies. These studies varied widely in design, sample size and composition, and duration of follow-up. For example, sample sizes ranged from the minimum of 64 (in an anal cancer study) to more than 20,000, follow-up periods ranged from less than 1 year to more than 10 years, and the populations studied included patients with a single type of cancer as well as cohorts comprised of patients with a diverse array of malignancies. Despite the diversity of research approaches, associations indicative of increased risk associated with smoking were observed in most studies (87% or 139/159). Further, statistically significant increased risks were observed in 62% (99/159) of the studies. There was considerable variation in the magnitude of the association between cigarette smoking and all-cause mortality, but in 83 of the studies at least a 50% increase in mortality was observed among cigarette smokers, either overall or in at least one subgroup, compared with never or nonsmokers. These associations are of similar magnitude to the association of smoking with all-cause mortality in general population cohorts (see Chapter 11, "General Morbidity and All-Cause Mortality").

In 35 studies in which RRs were presented for current smokers and former smokers compared with never smokers, the median RRs were 1.22 for former smokers and 1.51 for current smokers. In six of the eight studies that presented the results in a way that allowed for assessment of dose-response, death rates increased with the number of cigarettes smoked (Boffetta et al. 1997; Talamini et al. 2008; Toyooka et al. 2008; Janjigian et al. 2010; Hung et al. 2012; Kawakita et al. 2012), but consistent dose-response trends were not observed in two studies (Dikshit et al. 2005b; Dal Maso et al. 2008). All eight of these studies categorized the data across three categories, and using the lowest category as the referent category (RRs = 1.0), the median RRs for the middle and high categories were 1.48 and 1.75, respectively.

The RRs for all-cause mortality in former smokers was intermediate, between that for never smokers and that for current smokers, suggesting that smoking cessation prolongs survival compared to persistent smoking.

Some studies provide evidence to directly assess whether smoking cessation reduces the mortality rate compared to persistent smoking. Chen and colleagues (2010b) observed that quitting smoking after a cancer diagnosis was associated with significantly reduced risk of death compared to persistent smoking. In a longitudinal study of 264 head and neck cancer patients, Mayne and colleagues (2009) observed that, compared to nonsmokers, the RR among those who remained persistent smokers was in the direction of increased risk (RR = 1.83; 95% CI, 0.85–3.94); whereas among those who had refrained from smoking at any time during follow-up, the RR indicated decreased risk (RR = 0.36; 95% CI, 0.10–1.31). In a meta-analysis comparing lung cancer patients who remained persistent smokers to those who stopped smoking, Parsons and colleagues (2010) observed that persistent smoking was associated with RRs of all-cause mortality in the direction of increased risk in non-small cell lung cancer patients (unadjusted: 4 studies, summary RR = 1.19; 95% CI, 0.91–1.54; adjusted: one study [Nia et al. 2005] RR = 2.94; 95% CI, 1.15–7.54) and in small cell lung cancer patients (unadjusted: two studies, summary RR = 1.18; 95% CI, 1.03–1.36; adjusted: one study [Videctic et al. 2003] RR = 1.86; 95% CI, 1.33–2.59). Not all reported associations were statistically significant, but the direction of the associations was consistent in indicating that the all-cause mortality rate in cancer patients, who were smokers at the time of diagnosis, is greater in those who remain smokers after diagnosis compared to those who quit.

Cigarette Smoking and Overall Survival in Cancer Patients

Overall mortality and overall survival are complementary in assessing the endpoint of vital status; but, because the numerical results differ, the results for overall survival are presented separately in Table 6.29*S* for clarity. The results of 62 studies, in cohorts of cancer patients that reported on the association between cigarette smoking and overall survival, are summarized in Table 6.29*S*. The results of 77% (48/62) of these studies indicated that cigarette smoking was associated with shorter survival after a diagnosis of cancer; for 42% (26/62) of the total studies, the results were statistically significant. For 6 of the studies of overall survival, the results were reported in the text as not statistically significant without providing the estimated effect, so the direction and magnitude of the associations observed in those studies cannot be determined. In the 4 studies in which the RRs were presented for current and former smokers relative to never smokers, the median survival was 19% less in former smokers and 31% less in current smokers. Ang and colleagues (2010) reported a statistically significant trend of 1% worse sur-

vival for each additional pack-year of smoking (p = 0.002). With respect to whether smoking cessation is associated with prolonged survival, Jerjes and colleagues (2012) followed a cohort of oropharyngeal cancer patients and found better survival at 3 and 5 years after diagnosis for those who quit smoking successfully.

Cigarette Smoking and Cancer Mortality in Cancer Patients

The studies conducted in cohorts of cancer patients that assessed cigarette smoking in relation to cancer-specific mortality or cancer-specific survival are summarized in Table 6.30*S*. The results are stratified according to whether the study outcome was cancer mortality or cancer survival (Table 6.30*S*). Of the 58 studies of cancer mortality, 79% (46/58) documented a higher mortality rate in smokers and the association with smoking was statistically significant in 59% (34/59) of the studies. In 15 studies in which the RRs were presented for current and former smokers relative to never smokers, the median RR was 1.03 for former smokers and 1.61 for current smokers. Three studies reported evidence on the presence of a dose-response relationship, with 1 study showing a monotonic gradient (Marks et al. 2009) and 2 others not showing such a gradient (Dal Maso et al. 2008; Toyooka et al. 2008). Nine of the 15 studies yielded results in the direction of poorer cancer-specific survival associated with cigarette smoking (Table 6.30*S*).

Cigarette Smoking and Risk of Second Primary Cancers in Cancer Patients

The studies in cohorts of cancer patients that assessed cigarette smoking in relation to risk of developing a second primary cancer are summarized in Table 6.31*S*. The results of these 26 studies uniformly indicated a positive association of cigarette smoking with increased risk of developing second primary cancers. Not surprisingly, the strongest associations were observed when lung cancer or another smoking-caused cancer was considered as the second primary cancer of specific interest. For example, in studies of lung cancer as a second primary cancer that had a referent category comprised of former smokers or never smokers, the RRs of developing lung cancer as a second primary were elevated from 6-fold to 24-fold (van Leeuwen et al. 1995; Obedian et al. 2000; Ford et al. 2003; Gilbert et al. 2003; Kaufman et al. 2008). Similarly, the results for other malignancies, known to be caused by cigarette smoking, were consistently in the direction of increased risk. Higher risk was observed when the smoking-caused cancers were grouped (Park et al. 2007) or specific malignancies were considered, such as head and neck cancer (Barbone et al. 1996), esophageal cancer (Rossini

et al. 2008), and bladder cancer (Boorjian et al. 2007). The strongest associations tended to be observed when the specific second primary cancer studied was known to be causally associated with active smoking, but the increased risk of any second primary cancer associated with cigarette smoking was still robust. For example, in the 5 studies not specific to smoking-caused cancers that classified smoking as never/former/current, the median RR of second primary cancers was 1.20 for former smokers and 2.20 for current smokers. Four studies assessed dose-response relationships, and all showed evidence that the risk of a second primary cancer increased as the amount of smoking increased (Hiyama et al. 1992; Barbone et al. 1996; Dikshit et al. 2005a; Leon et al. 2009).

Evidence of a synergistic interaction between smoking status and treatment with radiation therapy was observed, with smokers who were treated with radiation therapy having a greater risk of second primary cancers compared to smokers not treated with radiation therapy. In a case-control study of patients with breast cancer plus lung cancer (cases), compared to breast cancer alone (controls), compared to former smokers not exposed to radiation therapy, the RR of lung cancer in current smokers not treated with radiation therapy was 6.0 (95% CI, 3.6–10.1) and in current smokers treated with radiation therapy the RR was 9.0 (95% CI, 5.1–15.9) (Ford et al. 2003). In another case-control study of lung cancer among patients with Hodgkin's disease, risk factors were addressed in a case group (lung cancer and Hodgkin's disease) compared to a control group (Hodgkin's disease alone) (Travis et al. 2002). Risk for lung cancer was assessed for a category of "heavy smokers" (at least one pack or more per day) compared with a category that included lighter smokers and nonsmokers together. There was some indication of greater lung cancer risk associated with both chemotherapy and radiation for those in the heavy smoker category. In a study of bladder cancer following prostate cancer, current smoking was associated with the expected doubling in bladder cancer risk, but the risk was 3.6-fold among current smokers treated with radiation therapy (Boorjian et al. 2007).

Cigarette Smoking and Recurrence and Response to Treatment in Cancer Patients

Tables 6.32*S* and 6.33*S* summarize studies in cancer patients that assessed cigarette smoking and risk of recurrence (Table 6.32*S*) and risk for lack of treatment response (Table 6.33*S*). Recurrence was defined as a second cancer in the same anatomic site as the original primary cancer diagnosis. Of the 51 studies that reported on the association between cigarette smoking and the risk of

recurrence, 82% (42/51) had results showing either a statistically significant association and/or a ≥1.2-fold RR estimate; 53% (27/51) showed elevated risks of recurrence in smokers that were statistically significant. In the 11 studies that classified smoking status as never/former/current, the median RR of recurrence was 1.15 for former smokers and 1.42 for current smokers. Of the three studies that reported evidence of presence of a dose-response relationship (Guo et al. 2009; Marks et al. 2009; Hung et al. 2010), in 2 of the studies there was a consistent increase in risk of recurrence with greater amount smoked (Guo et al. 2009; Hung et al. 2010). The results of the study of Fleshner and colleagues (1999), as recalculated by Aveyard and colleagues (2002), estimated that in bladder cancer patients the RR of recurrence was 0.71 (95% CI, 0.48–1.05) in those who stopped smoking compared to persistent smokers.

The specific outcomes included under response to treatment (Table 6.33*S*) varied and included progression-free survival, complete response, metastasis, local control, and persistent disease. Of the 16 studies addressing cigarette smoking and these outcomes, in 72% (13/18) cigarette smoking had a statistically significant association with a worse response. In 1 study, a dose-response trend was observed, indicating that smoking decreased progression-free survival in head and neck cancer patients by 1% per pack-year of smoking (95% CI, 1.00–1.01; p = 0.002) (Ang et al. 2010).

Cigarette Smoking and Toxicity Associated with Cancer Treatment

Studies in cohorts of cancer patients that addressed the association between smoking and cancer treatment-related toxicity are summarized in Table 6.34*S*. Of the 82 studies that included results for the association between cigarette smoking and treatment-related toxicities, 94% (77/82) showed a positive association between smoking and increased toxicity, with 80% (66/82) statistically significant. Of the 49 studies that used a category of current smoking, 88% (43/49) showed a statistically significant positive association between current smoking and toxicity.

Continued smoking after treatment with radiotherapy increases risk for hospitalization and toxicity compared to those who quit after treatment (RR = 1.3; 95% CI, 1.0–1.7) (Zevallos et al. 2009). Kuri and colleagues (2005) observed that quitting smoking decreases wound healing complications with greater effects noted for longer cessation periods (Table 6.33*S*). In a notable study of the potentially acutely reversible effects of smoking, Bjarnason and colleagues (2009) demonstrated that current smokers during radiotherapy have decreased inci-

dence of Grade 3+ mucositis, if treatments are delivered in the morning instead of the afternoon (42.9% vs. 76%; p = 0.025), suggesting that an acute break in smoking (i.e., a smoking break associated with sleeping at night) may change the toxicity associated with treatment.

Evidence Synthesis

This review is the first in the series of Surgeon General's reports to address the associations between cigarette smoking and adverse health outcomes specifically in cancer patients and survivors. Within this focus on the adverse health effects of smoking among cancer patients and survivors, evidence was summarized on the associations of cigarette smoking with multiple outcomes including all-cause and cancer-specific mortality, risk of second cancer primaries, cancer recurrence, response to cancer treatment, and treatment-related toxicities. The body of evidence was substantial, including 159 studies on all-cause mortality, 62 studies on overall survival, 52 studies on cancer-specific mortality, 15 studies on cancer-specific survival, 33 on risk of second primary cancers, 51 on cancer recurrence, 18 on response to treatment, and 82 on treatment-related toxicities.

In general, the associations were not strong, reflecting their lack of specificity and the many clinical, biological, and behavioral/social factors that determine their occurrence. Additionally, reflecting the age pattern of cancer incidence, many of the studies involved older populations, among whom comorbidities and general health status are powerful determinants of outcomes that need to be considered in characterizing the consequences of smoking. Given the nonspecificity of outcomes and their multiple determinants, smoking would be anticipated to have relatively modest effects. The follow-up time in most studies was relatively brief as well, so longer-term consequences of smoking for survivors may not be fully captured.

As with investigations on other topics related to smoking and health, misclassification of smoking is of concern. Plausibly, persons with cancer and survivors may be reluctant to disclose that they are smoking and those self-reporting as former smokers may include some proportion of current smokers. In other contexts, the potential bias from such misclassification has been examined and set aside as an explanation for observed associations (USDHHS 2004); in studies of cancer outcomes, the benefits of cessation would be reduced if the category of self-reported former smokers includes current smokers as well. Additionally, a substantial number of the studies listed in the evidence tables included former smokers in

the referent category of nonsmokers, rather than having a category of never smokers alone. If the mechanism(s) underlying the effects of smoking on outcomes are long-term, then a referent category of nonsmokers will lead to an underestimation of effect, compared to what would have been observed with a referent category comprised solely of never smokers. Further, all but one study (Marin et al. 2008) included in this review relied on self-reported smoking, and the results of that study, which used serum concentrations of cotinine to assess smoking status, suggested that relying on self-reported smoking underestimated the true association. Marin and colleagues (2008) observed that biochemically measured smoking, but not self-reported smoking, was significantly associated with wound complications.

As this is the first review in the Surgeon Generals' reports on associations of cigarette smoking with adverse health outcomes in cancer patients and survivors, the totality of the evidence is reviewed with reference to the key criteria for causation (USDHEW 1964; USDHHS 2004).

One essential criterion is temporality, that is, smoking needs to be antecedent to the health outcome of interest. All studies were prospective in that the active cigarette smoking occurred, and was assessed before the observation for adverse health outcomes.

Consistency is also critical. For each outcome, there was substantial evidence spanning different populations and types of cancer. Yet, most studies found smoking to have adverse consequences for cancer patients and survivors. The diversity of study populations is striking because not only were these studies carried out in different study locations by many different investigators but the study populations themselves were comprised of cancer patients and survivors who had been diagnosed with a broad spectrum of heterogeneous malignancies. In addition, patients were treated with a wide variety of cancer treatments such as surgery, chemotherapy, radiotherapy, or other anti-cancer agents. This general consistency strengthens the inference that cigarette smoking is causally associated with the overall construct of adverse health outcomes and is not just one or a few of the component endpoints used to define this construct.

In assessing evidence for causation, the strength of association is useful for considering the possibility that bias led to the observed associations. For all-cause mortality, confounding is a potential concern, as smokers may differ from nonsmokers in characteristics that affect risk of dying, such as problem drinking. For this outcome, the observed association in cancer patients and survivors is comparable to that observed in the general population (see Chapter 11). Cancer patients and survivors tend to

be older than the general population, so evidence specific to elderly populations is particularly relevant. A systematic review of smoking and all-cause mortality in people 60 years of age or older estimated a summary RR across studies of 1.83 (95% CI, 1.65–2.03) for current smoking and 1.34 (95% CI, 1.28–1.40) for former smoking (Gellert et al. 2012). Against this backdrop, the evidence for the association between cigarette smoking and all-cause mortality in cancer patients and survivors largely replicates studies in the general population. Compared to never smokers, the median RR was 1.51 for current smokers and 1.22 for former smokers. Studies that assessed dose-response provided evidence that in cancer patients and survivors the risk of dying from any cause increased as the amount smoked increased. The complementary evidence from studies that used overall survival, rather than all-cause mortality, as the endpoint was congruent with these findings. In summary, the evidence is coherent in showing a strong association between cigarette smoking and all-cause mortality/overall survival.

The evidence for cancer-specific mortality as an endpoint also showed a strong, consistent association between current smoking and cancer-specific mortality (median RR = 1.61). But, unlike the other adverse health outcomes considered, the association with former versus never smoking was null (median RR = 1.03); and a dose-response gradient between amount smoked and death from cancer was less consistently observed in this group of studies.

The risk of second primary cancers was consistently increased in smokers, with strong associations present in both current (median RR = 2.20) and former (median RR = 1.20) smokers, compared to never smokers. Strong dose-response trends by number of cigarettes smoked were observed.

The risk of cancer recurrence was consistently elevated in smokers compared to nonsmokers, with stronger associations observed in current smokers than in former smokers. Compared to never smokers, the median RR was 1.15 in former smokers and 1.42 in current smokers. Dose-response trends were observed in the majority of studies and the results of one study indicated that smoking cessation was associated with decreased risk of recurrence. Cigarette smoking was also consistently strongly associated with poorer response to treatment, with evidence of a dose-response trend of worse response with more extensive smoking.

The discussion above has addressed the specific adverse health outcomes. When this entire body of evidence is viewed collectively, there is a consistent and coherent pattern of findings showing that cigarette smoking adversely affects cancer patients throughout their course of treatment and elevates risk for future sec-

ond primary cancers and mortality. Compared to never smokers, the associations are consistently strongest in current smokers, with the associations in former smokers intermediate between current smokers and never smokers. The observed associations were strong, and the magnitude of these associations is even more impressive when one considers the methodologic issues discussed above that would tend to bias these associations toward nonsignificance.

A critical question for assessing whether cigarette smoking is a cause of adverse health outcomes in cancer patients is: Among cancer patients who are current smokers at diagnosis, what is the impact of smoking cessation compared to remaining a smoker? For each of the adverse health outcomes considered, the RRs were weaker for former versus never smokers compared to current versus never smokers. This pattern provides further evidence that removal of the exposure reduces the risk. The studies that provide direct evidence on risks following cessation consistently indicate that, compared to persistent smoking, smoking cessation leads to decreased mortality/improved survival, reduced risk of recurrence, and fewer treatment-associated toxicities. Despite the relatively small size of the evidence-base on cessation, the findings clearly bolster the evidence in favor of a causal association of smoking with adverse outcomes following cancer diagnosis.

With regard to specificity, this criterion has applicability to risk for second primary cancers. In cancer survivors, the increased risk for second primary cancers is greater for those sites for which smoking is a known causal risk factor, compared with the risk for any second primary. This specificity supports the role of smoking in increasing the risk of second cancers among survivors.

The causal criterion of coherence weighed heavily in evaluating the overall body of evidence as to whether cigarette smoking causes adverse health outcomes in cancer patients. There is already an enormous body of evidence on smoking and adverse health effects, which applies to people who have developed cancer and those who have survived following a diagnosis of cancer. Previous Surgeon General's reports have conclusively established that cigarette smoking causes increased all-cause mortality in the general population and, consequently, cigarette smoking would be expected to increase all-cause mortality in cancer patients. Similarly, active cigarette smoking is causally associated with many different types of cancer, so it would be expected a priori that cigarette smoking in cancer patients would be associated with increased risk of developing a second primary cancer known to be caused by cigarette smoking. Thus, the findings reviewed in this section are fully coherent with the general findings on smoking and health.

The preponderance of the evidence on the various outcomes considered indicates that in cancer patients, cigarette smoking is causally associated with increased mortality (i.e., poorer survival) from all-causes, cancer-specific mortality, and second primary cancers. The causality of these associations is fully coherent with the broader body of evidence on smoking and health in the population at large.

In cancer patients, the evidence also indicates that cigarette smoking is a risk factor for recurrence, poorer response to treatment, and increased treatment-related toxicity. The evidence prospectively links smoking to these outcomes. The evidence for each of these outcomes is quite consistent across diverse study populations and measurement approaches.

Conclusions

1. In cancer patients and survivors, the evidence is sufficient to infer a causal relationship between cigarette smoking and adverse health outcomes. Quitting smoking improves the prognosis of cancer patients.

2. In cancer patients and survivors, the evidence is sufficient to infer a causal relationship between cigarette smoking and increased all-cause mortality and cancer-specific mortality.

3. In cancer patients and survivors, the evidence is sufficient to infer a causal relationship between cigarette smoking and increased risk for second primary cancers known to be caused by cigarette smoking, such as lung cancer.

4. In cancer patients and survivors, the evidence is suggestive but not sufficient to infer a causal relationship between cigarette smoking and (1) the risk of recurrence, (2) poorer response to treatment, and (3) increased treatment-related toxicity.

Implications

The evidence summarized in this section documents that cigarette smoking has a profound adverse impact on health outcomes in cancer patients. Considered in the context of current knowledge of the adverse health effects of cigarette smoking in the general population, it is not surprising that cigarette smoking causes adverse health outcomes in cancer patients and survivors. This evidence has clear clinical implications. A cancer patient who is a current cigarette smoker can improve his/her prognosis by quitting smoking at any time. Evidence-based smoking cessation services for cancer patients are likely to have substantial benefits for survival. The evidence reviewed suggests, for example, that risk of dying could be lowered by 30–40% by quitting smoking at the time of diagnosis. For some cancer diagnoses, the benefit of smoking cessation may be equal to, or even exceed, the value of state-of-the-art cancer therapies (Toll et al. 2013). Evidence-based approaches are needed to assure that all cancer patients who smoke are offered effective cessation programs. The American Association of Cancer Research (Toll et al. 2013) and the American Society of Clinical Oncology (Hanna et al. 2013) have recently provided comprehensive recommendations on smoking cessation for cancer patients.

For cancer patients who remain current smokers, current smoking status is a powerful clinical risk indicator that merits the full attention of the health care team and the patient. There are a variety of smoking cessation approaches of proven efficacy, although they have not been specifically tailored to the particular context of the postdiagnosis cancer patient. The potential for increased complications and an altered response to treatment merits emphasis in patient interactions. Although research is needed to enhance the efficacy of approaches to smoking cessation for cancer patients, there is already a compelling rationale for assuring that smoking is addressed using approaches of proven efficacy. There is an evident need for a strategic research agenda to optimize cessation approaches for the particular context of the cancer patient. Effective strategies for patient education should be integral. With regard to treatment of cancer patients who smoke, the evidence reviewed has clinical implications that lead to several questions: (1) Do the optimal approaches to treat cancer differ in patients who are current smokers compared to those who do not smoke? (2) Is it better to make smoking cessation an initial priority before implementing the patient's cancer treatment regimen? Unfortunately, smoking both causes cancer and complicates its course. The evidence considered here, the first time that the topic of smoking and cancer outcomes has been addressed in the Surgeon General's reports, points to yet another avoidable set of adverse outcomes of smoking. Aggressive steps need to be taken to reduce an avoidable burden of morbidity and premature mortality in the at-risk population of cancer patients and survivors.

Evidence Summary

This extensive chapter covers a wide range of evidence on tobacco and cancer. It returns to the topic of smoking and lung cancer, which was the primary focus of the 1964 report. The section on lung cancer describes changes in cigarettes and cigarette smoke, since the first report, and tracks the changes in the types of lung cancer over time. The composition of cigarette smoke has changed to have a greater concentration of tobacco-specific nitrosamines and lower concentration of PAHs. These and other changes in cigarette smoke may have led to the rise of adenocarcinoma of the lung; the changes in composition of tobacco smoke may have implications for other cancers and, possibly, other smoking-caused diseases. The evidence reviewed shows that the risk of lung cancer associated with smoking has increased over time and during the same time period machine-measured yields of tar and nicotine have decreased.

Since the 1964 report, many additional types of cancer have been found to be causally associated with smoking. This report finds the evidence to be sufficient to infer that smoking causes liver cancer and cancer of the colon and rectum. In the 2004 report, the strength of evidence was considered to be "suggestive but not sufficient to infer a causal relationship" for both of these cancers; however, additional studies have sufficiently strengthened the evidence to infer a causal relationship between smoking and liver cancer and cancer of the colon or rectum. For liver cancer, there are several potential confounding factors, including alcohol consumption and infection with hepatitis B virus and hepatitis C virus. The review in this chapter shows that confounding can be set aside as the explanation for the association of smoking with liver cancer. With regard to colorectal cancer, the evidence has emerged in more recent decades linking smoking with this cancer. The epidemiologic studies indicate that the risk is manifest only after an exposure of long duration and, consequently, only recently have epidemiologic studies identified the association of smoking with colorectal cancer.

The association between smoking and breast cancer received detailed consideration in both the 2004 and 2006 reports of the Surgeon General. Substantial new evidence has been reported during the decade following the release of these reports. This report provides a detailed synthesis of the literature on both active smoking and exposure to secondhand smoke. The evidence shows that carcinogens in tobacco smoke do reach the tissues of the breast and active smoking affects sex hormones, which are relevant to breast cancer risk in women, in complicated ways. There are many epidemiologic studies of both active smoking and exposure to secondhand smoke; they are subject to potential bias from the reporting of smoking and exposure to secondhand smoke, and confounding is also a concern. Overall, meta-analysis finds the associations of active smoking and exposure to secondhand smoke with breast cancer risk to be weak, and the evidence was judged to be suggestive that smoking causes breast cancer.

For prostate cancer, the evidence did not show an association of smoking with incidence. The evidence confirmed the association of smoking with higher mortality from prostate cancer and also indicated that smoking may enhance progression. The biological processes underlying the suggestive association between cigarette smoking and prostate cancer mortality, case fatality, and, more seriously, unfavorable pathologic characteristics of the tumor require further investigation, particularly because incidence is not associated with smoking.

This chapter includes a new topic related to smoking and cancer, which bridges across all types of cancer—the impact of smoking on the outcome of cancer. The extensive review, included in this chapter, shows that smoking does adversely affect outcome for those developing cancer. The implications of this finding are clear: patients who develop cancer and who are still smoking need to quit. A cancer patient, who is a current cigarette smoker, can improve his/her prognosis by quitting smoking at any time. Evidence-based smoking cessation services for cancer patients are likely to have substantial benefits for survival.

Chapter Conclusions

Lung Cancer

1. The evidence is sufficient to conclude that the risk of developing adenocarcinoma of the lung from cigarette smoking has increased since the 1960s.

2. The evidence is sufficient to conclude that the increased risk of adenocarcinoma of the lung in smokers results from changes in the design and composition of cigarettes since the 1950s.

3. The evidence is not sufficient to specify which design changes are responsible for the increased risk of adenocarcinoma, but there is suggestive evidence that ventilated filters and increased levels of tobacco-specific nitrosamines have played a role.

4. The evidence shows that the decline of squamous cell carcinoma follows the trend of declining smoking prevalence.

Liver Cancer

1. The evidence is sufficient to infer a causal relationship between smoking and hepatocellular carcinoma.

Colorectal Cancer

1. The evidence is sufficient to infer a causal relationship between smoking and colorectal adenomatous polyps and colorectal cancer.

Prostate Cancer

1. The evidence is suggestive of no causal relationship between smoking and the risk of incident prostate cancer.

2. The evidence is suggestive of a higher risk of death from prostate cancer in smokers than in nonsmokers.

3. In men who have prostate cancer, the evidence is suggestive of a higher risk of advanced-stage disease and less-well-differentiated cancer in smokers than in nonsmokers, and—independent of stage and histologic grade—a higher risk of disease progression.

Breast Cancer

1. The evidence is sufficient to identify mechanisms by which cigarette smoking may cause breast cancer.

2. The evidence is suggestive but not sufficient to infer a causal relationship between tobacco smoke and breast cancer.

3. The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and breast cancer.

4. The evidence is suggestive but not sufficient to infer a causal relationship between exposure to secondhand tobacco smoke and breast cancer.

Adverse Health Outcomes in Cancer Patients and Survivors

1. In cancer patients and survivors, the evidence is sufficient to infer a causal relationship between cigarette smoking and adverse health outcomes. Quitting smoking improves the prognosis of cancer patients.

2. In cancer patients and survivors, the evidence is sufficient to infer a causal relationship between cigarette smoking and increased all-cause mortality and cancer-specific mortality.

3. In cancer patients and survivors, the evidence is sufficient to infer a causal relationship between cigarette smoking and increased risk for second primary cancers known to be caused by cigarette smoking, such as lung cancer.

4. In cancer patients and survivors, the evidence is suggestive but not sufficient to infer a causal relationship between cigarette smoking and (1) the risk of recurrence, (2) poorer response to treatment, and (3) increased treatment-related toxicity.

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Appended Data Table for Figure 6.7

Constituent	Australian cigarettes (mean ratio)	All Canadian brands (mean ratio)	Canadian brands minus those with high nitrosamine levels (mean ratio)
Carbon monoxide	0.710400158	0.777449045	0.817811121
Ammonia	0.51269294	0.59796073	0.566238632
1-Aminonaphthalene	0.579564329	0.665667404	0.614506152
2-Aminonaphthalene	0.590445816	0.962835802	0.962683308
3-Aminobiphenyl	0.525365264	0.633630955	0.590666048
4-Aminobiphenyl	0.522789273	0.798103748	0.776117764
Benzo[a]pyrene	0.980585517	1.164614574	1.234927716
Formaldehyde	1.462076653	1.883862909	2.024465121
Acetaldehyde	0.790774813	0.81519355	0.801937805
Acetone	0.710931913	0.804254018	0.792320326
Acrolein	0.873514538	1.055653336	1.071304063
Propionaldehyde	0.764124697	0.799891575	0.787214724
Crotonaldehyde	0.69829044	1.052097525	1.061305638
Butyraldehyde	0.761127995	0.751470171	0.737407769
Hydrogen cyanide	0.88379734	1.07831255	1.00712086
Mercury	0.741893363	0.855826429	0.836552706
Lead	0.516883748	0.796979939	0.864985319
Cadmium	0.756869227	1.480584253	1.482763826
Nitric oxide	0.431633687	0.453708248	0.349412044
NOx	0.430373867	0.447235391	0.343985547
NNN	0.189049058	0.395874325	0.216319658
NNK	0.39036299	0.80005713	0.720591225
N nitrosoanatabine	0.378315716	0.378661489	0.369640472
N nitrosoanabasine	0.458034812	0.654317302	0.236635881
Pyridine	0.688916673	0.769058306	0.735334105
Quinoline	0.809029158	1.086954987	1.067824242
Hydroquinone	1.08506923	1.16636303	1.19005359
Resorcinol	1.263001552	1.239527142	1.269950615
Catechol	1.02631406	1.543078972	1.575623688
Phenol	1.00065782	1.607645714	1.605486159
m-+p-Cresol	0.929436993	1.367013458	1.348916429
o-Cresol	0.91163895	1.427291472	1.416454834
1,3 Butadiene	0.835073844	0.787929482	0.779409733
Isoprene	0.790517943	0.628854317	0.607039337
Acrylonitrile	0.711987746	0.814724264	0.798543675
Benzene	0.881502879	1.042667139	1.038655292
Toluene	0.748154731	1.006233607	1.022765635
Styrene	0.738534981	0.90339595	0.810247399
Methyl ethyl ketone	0.711908704	—	—

Sources: Counts et al. 2005; World Health Organization 2008. Reprinted with permission from World Health Organization, © 2008.
Note: **NNK** = 4-(methylnitrosamino)-1-(3pyridyl)-1-butanone; **NNN** = N´-nitrosonornicotine; **NOx** = nitrogen oxides.

Appended Data Table for Figure 6.14

A1. Squamous cell carcinoma of the lung, males (rate per 100,000 person-years)

Year	United States (Blacks)	United States (Whites)	Canada	Australia (New South Wales)	Denmark	Norway	Iceland	Sweden	Netherlands (Eindhoven)	Italy (Varese)	Slovenia	Spain	Switzerland	France
1981.5	46.64	25.13	23.63	—	26.08	15.98	9.84	10.80	54.28	48.52	—	17.28	—	—
1984.5	48.02	23.48	24.45	21.04	24.79	14.48	11.87	10.22	49.80	45.94	25.99	20.97	25.75	32.17
1987.5	41.21	22.19	22.83	19.04	22.30	14.59	8.03	9.01	44.93	43.98	30.14	24.21	24.98	30.69
1990.5	39.17	20.54	19.87	17.39	20.12	13.32	10.07	8.94	45.81	34.54	28.80	20.84	21.33	30.95
1993.5	34.03	18.85	18.16	14.96	18.59	14.27	7.45	8.46	36.45	31.62	29.40	24.66	17.43	28.60
1996	—	—	—	—	—	—	—	—	—	—	—	—	17.61	—
1996.5	31.36	15.84	16.49	12.97	17.42	12.75	12.56	6.87	32.94	30.14	29.52	24.87	—	25.16

A2. Squamous cell carcinoma of the lung, females (rate per 100,000 person-years)

Year	United States (Blacks)	United States (Whites)	Canada	Australia (New South Wales)	Denmark	Norway	Iceland	Sweden	Netherlands (Eindhoven)	Italy (Varese)	Slovenia	Spain	Switzerland	France
1981.5	7.79	5.45	4.69	—	4.33	1.88	3.84	1.77	1.63	2.02	—	0.76	—	—
1984.5	9.32	6.13	5.66	2.92	5.02	1.84	3.86	2.07	2.13	2.17	1.24	0.99	2.58	1.06
1987.5	9.40	6.50	6.17	3.37	5.20	2.35	5.39	1.99	2.64	1.92	1.15	0.79	2.43	1.47
1990.5	10.56	6.65	6.26	2.95	5.55	2.94	4.26	2.10	2.64	1.93	1.49	0.37	2.14	1.84
1993.5	9.82	6.66	6.23	3.40	5.98	2.67	5.48	2.44	3.57	1.89	1.69	0.75	2.96	1.34
1996	—	—	—	—	—	—	—	—	—	—	—	—	1.96	—
1996.5	9.35	6.74	6.49	3.45	5.85	3.67	5.70	2.34	3.09	2.56	1.82	0.86	—	1.52

Appended Data Table for Figure 6.14   **Continued**

B1. Small cell carcinoma of the lung, males (rate per 100,000 person-years)

Year	United States (Blacks)	United States (Whites)	Canada	Australia (New South Wales)	Denmark	Norway	Iceland	Sweden	Netherlands (Eindhoven)	Italy (Varese)	Slovenia	Spain	Switzerland	France
1981.5	14.16	12.23	11.79	10.49	13.01	7.73	7.73	—	17.06	12.36	—	7.75	—	—
1984.5	13.70	12.38	10.66	9.44	13.70	7.53	8.01	—	16.20	13.94	12.29	7.32	11.89	8.78
1987.5	14.50	12.30	10.95	7.85	12.64	8.36	9.48	4.78	14.93	15.00	11.81	9.06	10.75	8.30
1990.5	13.05	11.89	9.96	7.29	11.59	8.70	9.16	4.98	16.62	14.19	13.14	10.81	9.15	10.03
1993.5	11.54	10.57	8.69		11.54	8.46	8.33	4.12	14.67	12.68	13.04	9.08	7.62	8.78
1996	—	—	—	—	—	—	—	—	—	—	—	—	8.28	—
1996.5	10.22	10.03	8.39	6.47	10.31	8.40	6.79	3.64	13.55	12.93	12.31	10.33	—	8.16

B2. Small cell carcinoma of the lung, females (rate per 100,000 person-years)

Year	United States (Blacks)	United States (Whites)	Canada	Australia (New South Wales)	Denmark	Norway	Iceland	Sweden	Netherlands (Eindhoven)	Italy (Varese)	Slovenia	Spain	Switzerland	France
1981.5	4.20	5.76	4.57	—	4.15	2.11	5.79	—	1.40	0.83	—	0.50	—	—
1984.5	5.52	6.59	5.35	3.07	5.64	2.32	4.89	—	1.28	1.90	1.73	0.27	1.86	0.70
1987.5	6.12	7.53	5.96	3.23	6.29	2.97	6.07	2.13	2.42	1.42	1.82	0.22	2.53	0.91
1990.5	7.23	7.94	6.33	3.33	6.77	3.95	5.79	2.21	3.56	1.52	2.05	0.36	2.51	1.11
1993.5	6.71	7.73	6.34	3.59	6.84	4.41	5.49	2.50	3.59	1.95	1.93	0.35	2.71	1.17
1996	—	—	—	—	—	—	—	—	—	—	—	—	2.48	—
1996.5	5.51	7.74	6.26	3.37	7.14	4.87	7.08	2.52	4.58	1.45	1.98	0.23	—	1.23

Appended Data Table for Figure 6.14   Continued

C1. Adenocarcinoma of the lung, males (rate per 100,000 person-years)

Year	United States (Blacks)	United States (Whites)	Canada	Australia (New South Wales)	Denmark	Norway	Iceland	Sweden	Netherlands (Eindhoven)	Italy (Varese)	Slovenia	Spain	Switzerland	France
1981.5	27.26	18.47	13.85	—	11.58	7.27	7.85	4.81	9.15	13.81	—	4.15	—	—
1984.5	31.62	19.24	16.05	11.43	13.66	7.83	12.67	5.31	12.35	16.55	9.44	6.54	13.10	7.53
1987.5	32.54	20.59	16.56	11.57	15.39	9.14	11.21	6.09	14.97	20.27	9.18	5.05	12.59	9.37
1990.5	30.86	21.21	15.53	11.73	14.21	10.16	11.80	5.95	12.58	21.67	12.59	6.85	11.90	9.92
1993.5	34.99	21.81	15.77	11.40	14.86	10.62	10.79	6.04	13.13	23.01	11.82	8.17	12.65	11.59
1996	—	—	—	—	—	—	—	—	—	—	—	—	13.32	—
1996.5	32.32	20.77	15.56	11.17	15.29	11.03	12.62	5.95	13.92	21.23	13.38	8.12	—	13.85

C2. Adenocarcinoma of the lung, males (rate per 100,000 person-years)

Year	United States (Blacks)	United States (Whites)	Canada	Australia (New South Wales)	Denmark	Norway	Iceland	Sweden	Netherland $Eindhoven)	Italy (Varese)	Slovenia	Spain	Switzerland	France
1981.5	11.37	10.53	7.75	—	7.02	3.04	8.50	2.92	2.07	2.55	—	1.59	—	—
1984.5	12.81	11.93	10.06	3.70	8.57	3.79	12.95	3.30	2.17	3.14	3.27	1.30	4.26	1.53
1987.5	14.54	13.19	11.12	4.86	10.55	4.32	14.22	3.89	3.08	3.60	3.25	1.87	4.58	1.70
1990.5	15.64	14.60	11.33	5.10	10.61	4.98	12.80	4.27	3.51	3.77	4.20	1.94	4.94	2.03
1993.5	16.68	15.73	12.34	5.23	12.21	6.31	16.23	4.79	4.01	5.44	3.78	2.15	5.71	2.71
1996	—	—	—	—	—	—	—	—	—	—	—	—	5.92	—
1996.5	16.97	15.73	13.52	5.95	13.68	6.69	10.58	5.11	4.08	5.48	5.10	2.86	—	3.26

Source: Devesa et al. 2005. Reprinted with permission from John Wiley & Sons, Inc., © 2005.
Note: Incidence rates were calculated for 3-year time periods: 1980–1982 (plotted at 1981.5), 1983–1985 (plotted at 1984.5), 1986– 1988 (plotted at 1987.5), 1989–1991 (plotted at 1990.5), 1992–1994 (plotted at 1993.5), 1996 (Switzerland only; plotted at 1996), and 1995–1997 (plotted at 1996.5). Incidence rates were age-adjusted by the direct method, using the Segi world standard (Bray et al. 2002), and expressed per 100,000 person-years.

Appended Data Table for Figure 6.17

Study	Design	Country	Population	Effect size (95% CI)	Weight (%)
Austin and Cole 1986	Case-control	United States	All	1.6 (0.7–3.7)	1.56
LaVecchia et al. 1988	Case-control	Italy	All	0.9 (0.6–1.5)	2.84
Tsukuma et al. 1990	Case-control	Japan	All	2.5 (1.4–4.5)	2.45
Choi and Kahyo 1991	Case-control	Korea	Males	1.0 (0.7–1.6)	3.44
Tanaka et al. 1992	Case-control	Japan	All	1.5 (0.8–2.7)	2.34
Takeshita et al. 2000	Case-control	Japan	Males	1.6 (0.7–3.5)	1.64
Hassan et al. 2002	Case-control	United States	All	1.2 (0.6–2.4)	2.00
Farker et al. 2003	Case-control	Germany	All	2.4 (0.9–6.4)	1.20
Marrero et al. 2005	Case-control	United States	All	10.9 (3.5–34.0)	0.96
Franceschi et al. 2006	Case-control	Italy	All	1.1 (0.6–2.2)	2.25
Zhu et al. 2007	Case-control	United States	Males	1.5 (0.8–2.7)	2.44
Hara et al. 2008	Case-control	Japan	All	1.8 (0.6–5.1)	1.07
Case control: Subtotal (I-squared = 53.0%, p = 0.015)				1.6 (1.2–2.1)	24.20
Hirayama 1989	Cohort	Japan	Males	3.1 (1.8–5.4)	2.64
Akiba and Hirayama 1990	Cohort	Japan	Males	1.5 (1.2–1.9)	4.59
Akiba and Hirayama 1990	Cohort	Japan	Females	1.6 (1.2–2.0)	4.43
Hsing et al. 1990	Cohort	United States	Males	2.4 (1.6–3.5)	3.52
Shibata et al. 1990	Cohort	Japan	Males, Cohort I	1.1 (0.2–4.7)	0.55
Shibata et al. 1990	Cohort	Japan	Males, Cohort II	3.6 (0.6–22.3)	0.43
Goodman et al. 1994	Cohort	Japan	All	2.2 (1.5–3.2)	3.54
McLaughlin et al. 1995	Cohort	United States	Males	1.8 (1.4–2.3)	4.47
Nordlund et al. 1997	Cohort	Sweden	Females	0.7 (0.2–2.0)	1.06
Mizoue et al. 2000	Cohort	Japan	Males	3.3 (1.2–9.5)	1.12
Evans et al. 2002	Cohort	China	Males	0.9 (0.8–1.1)	5.01
Evans et al. 2002	Cohort	China	Females	2.0 (0.9–4.2)	1.74
Jee et al. 2004	Cohort	Korea	Males	1.5 (1.3–1.7)	5.13
Jee et al. 2004	Cohort	Korea	Females	1.1 (0.8–1.7)	3.61
Ogimoto et al. 2004	Cohort	Japan	Males, 40–59 years of age	2.0 (0.8–5.1)	1.26
Ogimoto et al. 2004	Cohort	Japan	Males, 60–69 years of age	2.6 (1.2–5.8)	1.65
Ogimoto et al. 2004	Cohort	Japan	Females, 40–59 years of age	2.8 (0.6–13.1)	0.58
Ogimoto et al. 2004	Cohort	Japan	Females, 60–69 years of age	1.5 (0.5–4.9)	0.91
Wen et al. 2004	Cohort	China	Males	1.5 (1.2–1.8)	4.68
Wen et al. 2004	Cohort	China	Females	5.0 (2.4–10.7)	1.79
Yun et al. 2005	Cohort	Korea	Males	1.5 (1.3–1.7)	5.06
Fujita et al. 2006	Cohort	Japan	Anti-HCV positive	9.6 (1.5–61.4)	0.41
Fujita et al. 2006	Cohort	Japan	Anti-HCV negative	1.7 (0.6–5.1)	1.04

Study	Design	Country	Population	Effect size (95% CI)	Weight (%)
Chen et al. 2008	Cohort	China	HBV negative and HCV negative	2.4 (1.2–5.0)	1.88
Chen et al. 2008	Cohort	China	HBV positive and HCV negative	1.1 (0.8–1.5)	4.03
Chen et al. 2008	Cohort	China	HBV negative and HCV positive	1.4 (0.6–3.3)	1.51
Ohishi et al. 2008	Cohort	Japan	All	2.0 (0.8–5.0)	1.39
Koh et al. 2011	Cohort	Singapore	All	1.6 (1.3–2.1)	4.45
Trichopoulos et al. 2011	Cohort	Europe	All	4.6 (1.9–10.9)	1.46
Oh et al. 2012	Cohort	Korea	All	1.3 (0.6–2.6)	1.86
Cohort: Subtotal (I-squared = 69.6%, p = 0.000)				1.7 (1.5–1.9)	75.80
Overall (I-squared = 65.5%, p = 0.000)				1.7 (1.5–1.9)	100.00

Notes: Weights are from random effects analysis. **CI** = confidence interval; **HBV** = hepatitis B virus; **HCV** = hepatitis C virus.

Appended Data Table for Figure 6.18

Study	Design	Country	Population	Effect size (95% CI)	Weight (%)
LaVecchia et al. 1988	Case-control	Italy	All	0.9 (0.6–1.5)	11.29
Choi and Kahyo 1991	Case-control	Korea	Males	1.0 (0.7–1.6)	13.88
Tanaka et al. 1992	Case-control	Japan	All	1.5 (0.8–2.7)	9.18
Hassan et al. 2002	Case-control	United States	All	1.2 (0.6–2.4)	7.78
Hara et al. 2008	Case-control	Japan	All	1.8 (0.6–5.1)	4.05
Ohishi et al. 2008	Case-control	Japan	All	2.0 (0.8–5.0)	5.32
Case-control: Subtotal (I-squared = 0.0%, p = 0.549)				1.2 (0.9–1.5)	51.50
Liaw and Chen 1998	Cohort	China	Males	2.2 (1.4–3.6)	12.09
Jee et al. 2004	Cohort	Korea	Males	1.5 (1.3–1.7)	21.66
Fujita et al. 2006	Cohort	Japan	Anti-HCV positive	9.6 (1.5–61.4)	1.52
Fujita et al. 2006	Cohort	Japan	Anti-HCV negative	1.7 (0.6–5.1)	3.96
Koh et al. 2011	Cohort	Singapore	HBV negative and HCV negative	1.8 (0.6–5.7)	3.69
Trichopoulos et al. 2011	Cohort	Europe	All	4.6 (1.9–10.9)	5.58
Cohort: Subtotal (I-squared = 57.5%, p = 0.038)				2.2 (1.4–3.3)	48.50
Overall (I-squared = 47.1%, p = 0.036)				1.6 (1.2–2.0)	100.00

Note: Weights are from random effects analysis. **CI =** confidence interval; **HBV =** hepatitis B virus; **HCV =** hepatitis C virus.

Appended Data Table for Figure 6.19

Study	Design	Country	Population	Effect size (95% CI)	Weight (%)
Lam et al. 1982	Case-control	China	All	1.3 (0.7–2.4)	2.46
Stemhagan et al. 1983	Case-control	United States	Males	0.7 (0.5–1.1)	3.91
Stemhagan et al. 1983	Case-control	United States	Females	1.0 (0.6–1.7)	2.76
Austin et al. 1986	Case-control	United States	All	1.1 (0.5–2.4)	1.62
Lu et al. 1988	Case-control	China	All	1.1 (0.7–1.8)	3.60
Kew et al. 1990	Case-control	South Africa	Black females	2.2 (0.8–6.1)	1.04
Olubuyide and Bamgboye 1990	Case-control	Nigeria	All	1.7 (0.9–3.1)	2.34
Lin et al. 1991	Case-control	China	Males, HBsAg negative, alcoholic cirrhosis	0.6 (0.4–1.0)	4.18
Ross et al. 1992	Case-control	China	Males	1.8 (0.6–5.6)	0.88
Goritsas et al. 1995	Case-control	Greece	All	1.6 (0.9–2.0)	4.05
Siemiatycki et al. 1995	Case-control	Canada	Males, 35–70 years of age	0.9 (0.4–2.1)	1.47
Koide et al. 2000	Case-control	Japan	All	5.4 (1.1–26.7)	0.45
Lam et al. 2001	Case-control	China	Males, 35–69 years of age	1.6 (1.3–1.9)	6.81
Lam et al. 2001	Case-control	China	Males, 70 years of age and older	1.2 (0.9–1.5)	6.07
Lam et al. 2001	Case-control	China	Females, 35–69 years of age	1.4 (0.8–2.4)	2.99
Lam et al. 2001	Case-control	China	Females, 70 years of age and older	1.4 (0.9–2.0)	4.16
Yu et al. 2002	Case-control	China	All	0.7 (0.3–1.7)	1.31
Munaka et al. 2003	Case-control	Japan	All	1.2 (0.6–2.7)	1.63
Marrero et al. 2005	Case-control	United States	All	12.3 (4.4–34.2)	1.02
Hassan et al. 2009	Case-control	United States	All	1.8 (1.3–2.4)	5.32
Jeng et al. 2009	Case-control	China	All	2.3 (1.5–3.5)	3.97
Soliman et al. 2010	Case-control	Egypt	All	1.4 (0.7–2.8)	1.98
Case-control: Subtotal (I-squared = 66.6%, p = 0.000)				1.4 (1.1–1.7)	64.02
Yu and Chen 1993	Cohort	China	Males	1.2 (0.4–3.1)	1.02
Goodman et al. 1994	Cohort	Japan	All	2.2 (1.5–3.2)	4.43
McLaughlin et al. 1995	Cohort	United States	Males	1.7 (1.3–2.2)	5.97
Chen et al. 1996	Cohort	China	All	3.6 (1.3–10.6)	0.98
Lam et al. 1997	Cohort	China	Males	1.1 (0.4–2.9)	1.08
Liu et al. 1998	Cohort	China	Males, 35–69 years of age	1.4 (1.3–1.5)	8.95
Liu et al. 1998	Cohort	China	Females, 35–69 years of age	1.2 (1.1–1.3)	8.45
Mori et al. 2000	Cohort	Japan	All	2.1 (0.6–7.2)	0.73
Wang et al. 2003	Cohort	China	Males	1.5 (1.1–2.3)	4.37
Cohort: Subtotal (I-squared = 58.9%, p = 0.013)				1.5 (1.3–1.7)	35.98
Overall (I-squared = 63.7%, p = 0.000)				1.4 (1.3–1.6)	100.00

Note: Weights are from random effects analysis. **CI** = confidence interval; **HBsAg** = hepatitis B surface antigen.

Appended Data Table for Figure 6.20

Study	Design	Country	Population	Effect size (95% CI)	Weight (%)
Ross et al. 1992	Case-control	China	Males	1.8 (0.6–5.6)	4.35
Yu and Chen 1993	Case-control	China	Males	1.2 (0.4–3.1)	5.17
Goritsas et al. 1995	Case-control	Greece	All	1.6 (0.9–2.0)	32.78
Hassan et al. 2009	Case-control	United States	All	1.8 (1.3–2.4)	57.70
Subtotal: Case-control (I-squared = 0.0%, p = 0.89)				1.7 (1.4–2.2)	100.00
Overall (I-squared = 0.0%, p = 0.89)				1.7 (1.4–2.2)	100.00

Note: Weights are from random effects analysis. **CI** = confidence interval.

Appended Data Table for Figure 6.21

Study	Design	Country	Population	Effect size (95% CI)	Weight (%)
Lam et al. 1982	Case-control	China	HBsAg negative	2.9 (0.8–10.7)	5.11
Austin and Cole 1986	Case-control	United States	HBsAg negative	1.1 (0.5–2.4)	7.31
Lin et al. 1991	Case-control	China	Males, HBsAg negative, alcoholic cirrhosis negative	0.6 (0.4–1.0)	8.91
Goritsas et al. 1995	Case-control	Greece	HBsAg negative	6.1 (1.5–25.5)	4.73
Yuan et al. 2004	Case-control	United States	Blacks and Whites, HBV negative and HCV negative	1.7 (1.0–3.0)	8.33
Franceschi et al. 2006	Case-control	Italy	HBsAg negative and anti-HCV negative	1.0 (0.5–2.0)	7.88
Hassan et al. 2008	Case-control	United States	Males, HBsAg1 negative and anti-HBc13 negative	2.0 (1.2–3.3)	8.50
Hassan et al. 2008	Case-control	United States	Females, HBsAg1 negative and anti-HBc13 negative	1.1 (0.6–1.9)	8.22
Jeng et al. 2009	Case-control	China	HBsAg negative and anti-HCV negative	44.4 (17.8–116.1)	6.62
Soliman et al. 2010	Case-control	Egypt	HCV negative	0.5 (0.1–1.8)	4.94
Case-control: Subtotal (I-squared = 88.6%, p = 0.000)				1.9 (1.0–3.7)	70.55
Jee et al. 2004	Cohort	Korea	Males, HBsAg negative	1.1 (0.9–1.4)	9.39
Fujita et al. 2006	Cohort	Japan	Anti-HCV negative	1.7 (0.6–5.1)	5.99
Chen et al. 2008	Cohort	China	HBV negative and HCV negative	2.4 (1.2–5.0)	7.57
Koh et al. 2011	Cohort	China	HBsAg negative, anti-HBc negative, anti-HBs negative, and anti-HCV negative	1.6 (0.6–4.2)	6.50
Cohort: Subtotal (I-squared = 40.1%, p = 0.171)				1.5 (1.0–2.2)	29.45
Overall (I-squared = 84.7%, p = 0.000)				1.8 (1.2–2.7)	100.00

Notes: Weights are from random effects analysis. **CI** = confidence interval; **HBc13** = hepatitis B virus core 13; **HBsAg** = hepatitis B surface antigen; **HBV** = hepatitis B virus; **HCV** = hepatitis C virus.

Appended Data Table for Figure 6.22

Study	Design	Country	Population	Effect size (95% CI)	Weight (%)
LaVecchia et al. 1988	Case-control	Italy	All	0.6 (0.4–1.0)	5.41
Tsukuma et al. 1990	Case-control	Japan	All	0.7 (0.3–1.9)	2.75
Choi and Kahyo 1991	Case-control	Korea	Males	0.6 (0.4–1.2)	4.33
Tanaka et al. 1992	Case-control	Japan	All	1.5 (0.8–2.8)	4.24
Takeshita et al. 2000	Case-control	Japan	Males	0.7 (0.3–1.5)	3.26
Farker et al. 2003	Case-control	Germany	All	2.5 (1.2–5.0)	3.79
Marrero et al. 2005	Case-control	United States	All	13.3 (4.5–38.9)	2.23
Franceschi et al. 2006	Case-control	Italy	All	0.8 (0.4–1.5)	4.39
Zhu et al. 2007	Case-control	United States	Males	1.9 (1.0–3.3)	4.64
Hara et al. 2008	Case-control	Japan	All	0.8 (0.3–2.3)	2.41
Hassan et al. 2008	Case-control	United States	All	1.4 (0.9–2.1)	5.56
Case control: Subtotal (I-squared = 76.4%, p = 0.000)				1.2 (0.8–1.9)	43.12
Shibata et al. 1990	Cohort	Japan	Males, Cohort II	2.9 (0.3–29.0)	0.64
Goodman et al. 1994	Cohort	Japan	All	2.3 (1.5–3.6)	5.60
McLaughlin et al. 1995	Cohort	United States	Males	1.5 (1.2–2.0)	6.88
Mizoue et al. 2000	Cohort	Japan	All	2.9 (1.0–8.4)	2.27
Jee et al. 2004	Cohort	Korea	Males	1.1 (1.0–1.3)	7.57
Jee et al. 2004	Cohort	Korea	Females	1.3 (0.8–2.1)	5.22
Ogimoto et al. 2004	Cohort	Japan	Males, 40–59 years of age	2.4 (0.8–6.8)	2.31
Ogimoto et al. 2004	Cohort	Japan	Males, 60–69 years of age	2.7 (1.2–6.1)	3.24
Ogimoto et al. 2004	Cohort	Japan	Females, 60–69 years of age	1.2 (0.2–8.7)	0.81
Fujita et al. 2006	Cohort	Japan	Anti-HCV positive	7.8 (1.1–56.0)	0.83
Fujita et al. 2006	Cohort	Japan	Anti-HCV negative	0.3 (0.0–1.7)	1.01
Chen et al. 2008	Cohort	China	HBV negative and HCV negative	1.0 (0.2–4.6)	1.24
Chen et al. 2008	Cohort	China	HBV postive and HCV negative	1.0 (0.5–2.0)	3.84
Chen et al. 2008	Cohort	China	HBV negative and HCV positive	2.9 (0.9–9.1)	2.01
Ohishi et al. 2008	Cohort	Japan	All	1.1 (0.3–5.1)	1.33
Koh et al. 2011	Cohort	Singapore	All	1.1 (0.8–1.5)	6.47
Trichopoulos et al. 2011	Cohort	Europe	All	2.0 (0.9–4.4)	3.32
Oh et al. 2012	Cohort	Korea	All	1.2 (0.4–3.3)	2.30
Cohort: Subtotal (I-squared = 46.9%, p = 0.015)				1.5 (1.2–1.8)	56.88
Overall (I-squared = 62.7%, p = 0.000)				1.4 (1.1–1.7)	100.00

Notes: Weights are from random effects analysis. **CI** = confidence interval; **HBV** = hepatitis B virus; **HCV** = hepatitis C virus; **HCV** = hepatitis C virus.

Appended Data Table for Figure 6.23

Study	Type of examination	RR (95% CI)
Demers et al. 1988a	Partial endoscopy	2.19 (1.26–3.81)
Kato et al. 1990b	Partial endoscopy	0.83 (0.55–1.27)
Kato et al. 1990c	Partial endoscopy	0.75 (0.43–1.29)
Kato et al. 1990d	Partial endoscopy	1.06 (0.56–2.02)
Shahangian et al. 1991	Partial endoscopy	3.56 (0.91–13.94)
Zahm et al.1991a	Partial endoscopy	2.70 (1.00–7.10)
Honjo et al. 1992a	Partial endoscopy	3.20 (1.74–5.91)
Kune et al. 1992a	Partial endoscopy	2.48 (1.00–6.10)
Giovannucci et al. 1994aa	Partial endoscopy	1.57 (1.16–2.14)
Giovannucci et al. 1994be	Partial endoscopy	2.06 (1.66–2.56)
Martinez et al. 1995	Partial endoscopy	2.29 (1.28–4.07)
Lubin et al. 1997	Partial endoscopy	2.40 (1.10–5.50)
Ji et al. 2006	Partial endoscopy	1.80 (1.50–2.10)
Mitrou et al. 2006	Partial endoscopy	3.37 (2.52–4.50)
Reid et al. 2006	Partial endoscopy	1.82 (1.17–2.84)
Stern et al. 2006	Partial endoscopy	2.20 (1.60–3.00)
Subtotal pooled RR: Partial endoscopy, current smokers		2.05 (1.68–2.51)
Kikendall et al. 1989	Full colonoscopy	2.79 (1.30–5.97)
Cope et al. 1991	Full colonoscopy	2.76 (1.34–5.68)
Monnet et al. 1991a	Full colonoscopy	1.90 (0.90–4.00)
Clark et al. 1993a	Full colonoscopy	1.05 (0.14–7.93)
Olsen and Kronborg 1993	Full colonoscopy	2.00 (1.10–3.50)
Nagata et al. 1999	Full colonoscopy	2.72 (2.02–3.67)
Almendingen et al. 2000	Full colonoscopy	3.80 (0.90–14.40)
Breuer-Katschinski et al. 2000	Full colonoscopy	2.30 (1.10–4.60)
Hoshiyama et al. 2000	Full colonoscopy	2.86 (1.21–6.80)
Inoue et al. 2000a	Full colonoscopy	3.59 (2.19–5.88)
Ulrich et al. 2001	Full colonoscopy	2.10 (1.50–3.10)
Cardoso et al. 2002	Full colonoscopy	1.87 (0.97–3.63)
Erhardt et al. 2002	Full colonoscopy	1.26 (0.72–2.20)
Voskuil et al. 2002	Full colonoscopy	1.71 (0.64–4.52)
Sparks et al. 2004	Full colonoscopy	1.87 (1.34–2.61)
Tiemersma et al. 2004	Full colonoscopy	2.10 (1.38–3.18)
Gong et al. 2005	Full colonoscopy	2.75 (1.76–4.29)
Larsen et al. 2006	Full colonoscopy	1.59 (1.25–2.01)
Ashktorab et al. 2007	Full colonoscopy	14.50 (2.76–76.17)
Subtotal pooled RR: Full colonoscopy, current smokers		2.22 (1.86–2.67)
Overall polled RR: Current smokers		2.14 1.86–2.46)

Source: Adapted from Botteri et al. 2008b, with permission from Elsevier © 2008.

Note: Partial endoscopy group is composed of studies in which some or all controls underwent partial colon examination. Full colonoscopy group is composed of studies in which all controls underwent complete colon examination. **CI** = confidence interval; **RR** = relative risk.

[a]Estimates for males only.

[b]Estimates for distal colon.

[c]Estimates for proximal colon.

[d]Estimates for rectum.

[e]Estimates for women only.

Appended Data Table for Figure 6.24

Study	Type of examination	RR (95% CI)
Kato et al. 1990a	Partial endoscopy	0.93 (0.59–1.49)
Kato et al. 1990b	Partial endoscopy	1.03 (0.57–1.85)
Kato et al. 1990c	Partial endoscopy	0.95 (0.46–1.94)
Shahangian et al. 1991	Partial endoscopy	2.00 (0.56–7.09)
Zahm et al.1991d	Partial endoscopy	1.20 (0.50–2.70)
Honjo et al. 1992d	Partial endoscopy	2.20 (1.10–4.30)
Martinez et al. 1995	Partial endoscopy	1.60 (1.03–2.49)
Lubin et al. 1997	Partial endoscopy	1.50 (1.10–2.10)
Ji et al. 2006	Partial endoscopy	1.10 (1.00–1.20)
Mitrou et al. 2006	Partial endoscopy	1.52 (1.23–1.88)
Reid et al. 2006	Partial endoscopy	1.29 (0.86–1.95)
Stern et al. 2006	Partial endoscopy	1.20 (1.00–1.60)
Subtotal pooled RR: Partial endoscopy, former smokers		1.31 (1.11–1.56)
Kikendall et al. 1989	Full colonoscopy	1.15 (0.57–2.34)
Monnet et al. 1991d	Full colonoscopy	2.70 (1.30–5.70)
Clark et al. 1993d	Full colonoscopy	0.85 (0.12–6.00)
Olsen and Kronborg 1993	Full colonoscopy	2.10 (1.10–3.90)
Nagata et al. 1999	Full colonoscopy	2.71 (1.90–3.85)
Almendingen et al. 2000	Full colonoscopy	1.40 (0.40–4.40)
Breuer-Katschinski et al. 2000	Full colonoscopy	1.00 (0.62–1.70)
Hoshiyama et al. 2000	Full colonoscopy	1.53 (0.61–3.84)
Inoue et al. 2000d	Full colonoscopy	1.10 (0.60–1.90)
Ulrich et al. 2001	Full colonoscopy	1.40 (1.00–1.90)
Cardoso et al. 2002	Full colonoscopy	2.25 (1.36–3.72)
Erhardt et al. 2002	Full colonoscopy	1.97 (1.28–3.03)
Voskuil et al. 2002	Full colonoscopy	2.00 (0.88–4.53)
Sparks et al. 2004	Full colonoscopy	1.75 (1.35–2.28)
Tiemersma et al. 2004	Full colonoscopy	1.62 (1.12–2.33)
Larsen et al. 2006	Full colonoscopy	1.06 (0.79–1.41)
Ashktorab et al. 2007	Full colonoscopy	0.66 (0.07–6.56)
Subtotal pooled RR: Full colonoscopy, former smokers		1.61 (1.37–1.89)
Overall pooled RR: Former smokers		1.47 (1.29–1.67)

Source: Adapted from Botteri et al. 2008b, with permission from Elsevier © 2008.
Note: Partial endoscopy group is composed of studies in which some or all controls underwent partial colon examination. Full colonoscopy group is composed of studies in which all controls underwent complete colon examination. **CI** = confidence interval; **RR** = relative risk.
[a]Estimates for distal colon.
[b]Estimates for proximal colon.
[c]Estimates for rectum.
[d]Estimates for males only.

Appended Data Table for Figure 6.25

Study	Number of cigarettes smoked per day	RR (95% CI)
Akiba and Hirayama 1990	1–4	3.1 (1.4–6.4)
Akiba and Hirayama 1990	5–14	1.0 (0.7–1.6)
Akiba and Hirayama 1990	15–24	0.9 (0.6–1.4)
Akiba and Hirayama 1990	25–34	0.8 (0.2–2.1)
Akiba and Hirayama 1990	35 or more	3.0 (1.0–7.1)
Hsing et al. 1990	1–19	1.6 (0.8–3.3)
Hsing et al. 1990	20–29	1.7 (0.8–3.5)
Hsing et al. 1990	30 or more	1.4 (0.4–4.4)
Hsing et al. 1991	1–9	1.1 (1.0–1.3)
Hsing et al. 1991	10–20	1.2 (1.1–1.3)
Hsing et al. 1991	21–39	1.2 (1.1–1.4)
Hsing et al. 1991	40 or more	1.5 (1.2–1.9)
Adami et al. 1996	—	1.3 (1.1–1.5)
Coughlin et al. 1996	—	1.3 (1.1–1.5)
Rodriguez et al. 1997	—	1.3 (1.2–1.6)
Lotufo et al. 2000	1–19	1.3 (0.5–3.5)
Lotufo et al. 2000	20 or more	1.2 (0.5–2.7)
Rohrmann et al. 2007 (1963 cohort)	—	2.4 (0.9–6.0)
Rohrmann et al. 2007 (1975 cohort)	—	2.2 (0.7–7.1)
Giovannucci et al. 2007	—	1.4 (1.0–1.9)
Batty et al. 2008	—	1.3 (1.0–1.7)
Watters et al. 2009	—	1.7 (1.3–2.3)
Weinmann et al. 2010	—	1.5 (1.1–2.0)

Note: Includes studies reporting a relative risk and 95% confidence interval for current smoking or current number of cigarettes smoked per day. See Table 6.8S for additional studies for which confidence intervals were not reported. **CI** = confidence interval; **RR** = relative risk.

Chapter 7
Respiratory Diseases

Sections of this chapter on the health consequences of smoking are accompanied by evidence tables detailing the studies that were used to evaluate the evidence to assess causality. A supplement to this report is provided that contains these tables. The tables included in the supplement are indicated with an "*S*" where they are called out in the text.

Introduction

Smoking has long been linked to adverse effects on the respiratory system, causing malignant and nonmalignant diseases, exacerbating chronic lung diseases, and increasing the risk for respiratory infections. The observational evidence showing associations with multiple diseases of the respiratory tract is extensive as is the evidence supporting the biological plausibility of smoking as a cause of these associations (U.S. Department of Health and Human Services [USDHHS] 2004, 2010). In addition to finding that smoking caused lung cancer, the 1964 Surgeon General's report also determined that: "Cigarette smoking is the most important of the causes of chronic bronchitis in the United States, and increases the risk of dying from chronic bronchitis and emphysema" (U.S. Department of Health, Education, and Welfare [USDHEW] 1964, p. 31).

This chapter updates previous reviews on smoking and respiratory health, covering chronic obstructive pulmonary disease (COPD), asthma, and idiopathic pulmonary fibrosis (IPF)—a form of interstitial lung disease (see Chapter 4, "Advances in Knowledge of the Health Consequences of Smoking: From 1964–2014," for a detailed description of the conclusions). It also addresses tuberculosis, an infectious disease that has not been previously covered in the reports of the Surgeon General. The understanding of COPD, a leading cause of premature mortality and morbidity, has evolved substantially over the past 5 decades with advances related to its pathogenesis, genetic basis, natural history, and underlying structural changes in the lung. Asthma is the most common chronic disease of childhood and is also very common among adults. This chapter considers the effect of smoking on the incidence and exacerbation of asthma in children and adolescents, and in adults. It also updates the evidence on smoking and IPF, a fibrotic disease of the lung. The emerging evidence on a role for smoking in increasing the risk of developing tuberculosis and for unfavorably affecting its clinical course is examined.

Smokefree policies have now been implemented in many jurisdictions in the United States and other countries (see Chapter 14, "Current Status of Tobacco Control"). This chapter considers the evidence on the benefits of such polices for respiratory illness.

Chronic Obstructive Pulmonary Disease

Perspectives on the epidemiology, genetics, and pathogenesis of COPD have changed profoundly since the 1964 Surgeon General's report (USDHEW 1964). Smoking and chronic respiratory diseases were subsequently covered in numerous reports of the Surgeon General (see Chapter 4 for detailed descriptions of these reports and their conclusions for respiratory illness). This chapter updates previous reviews on COPD, emphasizing how the evidence on smoking and COPD has progressed during the last 50 years and examines how advances in the understanding of the epidemiology, genetics, pathogenesis, and heterogeneity of COPD in relation to smoking will alter disease prevention, management, and prognosis in the future. This chapter does not address the interrelationships among COPD and other common comorbid diseases caused by smoking—cardiovascular diseases and cancer in particular. These comorbidities are strong determinants of outcome for those with COPD (Decramer and Janssens 2013). For each of the primary topics in this chapter, some of the most significant articles were selected to document the progress made over the past 50 years.

Epidemiology of Chronic Obstructive Pulmonary Disease

By the time of publication of the 1964 Surgeon General's report, several key studies had already linked chronic bronchitis to cigarette smoking; and community surveys had characterized the frequency of chronic bronchitis and chronic respiratory symptoms (Short et al. 1939; Stuart-Harris 1954; Higgins 1974; USDHHS 1984). These and other key studies set the stage for the findings of the 1964 report.

COPD, as defined today, was not recognized as a distinct clinical entity in 1964 (Fletcher et al. 1959). Clinicians tended to use the terms "chronic bronchitis" and "emphysema" to refer to the disease constellation now termed COPD; however, the clinical classification lacked specificity and differed across countries. That era preceded the widespread use of spirometry in clinical settings and the availability of computed tomography (CT) to noninvasively determine the presence of emphysema. The time period before, and shortly following, the 1964 report was important in the development of hypotheses related to the pathogenesis of COPD and the role of cigarette smoking in its causation. Two hypotheses were extant: one attributed susceptibility to develop COPD to bronchial hyperresponsiveness, the "Dutch" hypothesis (Orie et al. 1961), and the other to respiratory infections, the "British" hypothesis (Fletcher 1959). The landmark cohort study of London men carried out by Fletcher and Peto (1977) in the 1960s described the progressive decline of lung function with aging and the acceleration of this decline in smokers. In this study, smoking was the dominant determinant of decline beyond that expected from aging alone and infection did not affect the rate of decline.

A key discovery in the early 1960s was the increased risk for COPD associated with α1-antitrypsin deficiency (AAT), a consequence of genetic mutations that increase risk for COPD, particularly in smokers (Eriksson 1965), discussed in more detail below. That discovery identified one genetic factor that increased risk for COPD in smokers and launched substantial research on underlying mechanisms.

Even before the 1964 report, the complexity and overlap of various chronic obstructive lung diseases—chronic bronchitis, asthma, and irreversible obstructive lung disease (primarily emphysema)—were recognized (Fletcher et al. 1959). In its 1995 guidelines, the American Thoracic Society (ATS) proposed a conceptual framework that captured the overlap of the major chronic lung diseases associated with airflow obstruction (Figure 7.1) (ATS 1995). The framework comprises a Venn diagram with overlapping circles indicating chronic bronchitis, emphysema, and asthma, overlaid by a rectangle representing airflow obstruction (Figure 7.1). In this schema, "COPD" comprises persons with chronic bronchitis and/or emphysema, who also have evidence of airflow obstruction (indicated by shading in Figure 7.1). ATS' 1995 definition of COPD referred to chronic airflow obstruction caused by chronic bronchitis or emphysema. The development of guidelines by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) in 2001 changed the approach to the classification of COPD by focusing on the airflow obstruction component (the rectangle in Figure 7.1) rather than symptoms or a clinical diagnosis (Pauwels et al. 2001). GOLD guidelines recommended that lung function be measured after administration of a bronchodilator (to help identify and exclude from the diagnosis of COPD, those people whose primary problem is asthma, although some people with COPD respond to a bronchodilator). The definition of COPD referred to airflow obstruction that is not fully reversible. Thus, since 1964 the concept of permanent airflow obstruction has become central to the identification of COPD, although symptoms and structural changes documented by imaging are considered relevant to clinical management (GOLD 2013).

Given the changes in clinical approaches and definitions during the past 50 years, the prevalence of COPD cannot be readily tracked. The 1964 report did include the findings of several population-based studies that incorporated lung function measures. A study by Ferris and Anderson (1962) in a New Hampshire town determined that "obstruction" (defined as a forced expiratory volume in 1 second [FEV_1]/forced vital capacity [FVC] ratio of less than 60%) was found in 24.9% of male smokers, 7.3% of male nonsmokers, 17.5% of female smokers, and 9.4% of female nonsmokers. Data from the Ferris and Anderson study were reanalyzed to give population-based estimates of what would now be considered "chronic bronchitis," defined as bouts of cough and phlegm for 3 weeks for more than 3 winters (Reid et al. 1964). This symptom pattern was reported by 13% of men and 8% of women. In addition, 72% of men and 30% of women in the study community reported current cigarette, pipe, or cigar smoking (Reid et al. 1964).

By 1979, nationally representative estimates of disease burden became available based on data from the National Health Interview Survey (NHIS). Estimates of the prevalence of COPD (which included physician-diagnosed chronic and unqualified bronchitis [*International Classification of Diseases* (*ICD*)-9 490–491]; emphysema [*ICD*-9 492]; asthma [*ICD*-9 493]; and other chronic obstructive pulmonary diseases and allied conditions [*ICD*-9 494–496]), for 55–84-year-olds in the United States from

Figure 7.1   **Venn diagram with overlapping circles indicating chronic bronchitis, emphysema, and asthma, overlaid by a rectangle indicating airflow obstruction**
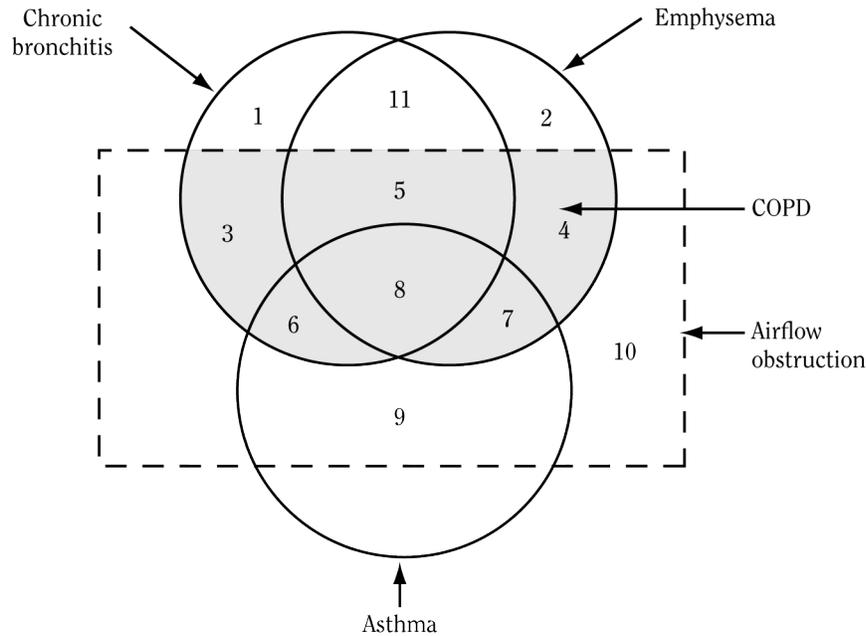
Source: American Thoracic Society 1995. Reprinted with permission from American Thoracic Society, © 2013.
Note: **COPD** = chronic obstructive pulmonary disease.

1979–1985, ranged from 9.4% in 1979 to 11.0% in 1985 among men, and 8.8% in 1979 to 11.9% in 1985 among women (Feinleib et al. 1989). For the U.S. adult population 25 years of age and older, estimates of disease burden based on report of a diagnosis of emphysema or chronic bronchitis were between 5.5% and 6.5% during the period 1980–2000 (Mannino et al. 2002). The most recent national data (2011 Behavioral Risk Factor Surveillance System Data) yields a 6.3% overall estimate of the prevalence of self-reported, physician-diagnosed COPD, chronic bronchitis, or emphysema among adults 18 years of age and older (Figure 7.2) (Centers for Disease Control and Prevention [CDC] 2012a). At the time of this survey, the prevalence of smoking among U.S. adults had decreased to 19% of the population (CDC 2012b).

These figures are likely underestimates, even considering the most recent estimates. COPD is frequently underdiagnosed clinically (Mannino et al. 2000); consequently, the disease burden is likely to be underestimated when based on data from questionnaire-based surveys. The National Health and Nutrition Examination Survey (NHANES) includes lung function data on U.S. adults 25 years of age and older. During 1971–1975, the estimated prevalence of moderate or worse obstruction (FEV_1/FVC

<70% and FEV_1 <80% predicted) was 7.7%, and the estimated prevalence of mild obstruction (FEV_1/FVC <70% and FEV_1 ≥80% predicted) was 7.4%, for a total prevalence of 15.1% (Mannino et al. 2002). By 1988–1994, these estimates had decreased to 6.6% and 6.9%, respectively, with an overall prevalence of 13.5% (Mannino et al. 2002). Spirometry was performed without administration of a bronchodilator so that some of those NHANES participants meeting criteria for obstruction may have had asthma.

Although the prevalence figures do not document a trend of increasing COPD burden since 1964, mortality from COPD has risen progressively in recent decades (Figure 7.3). With regard to the disease now termed COPD, the 1964 Surgeon General's report referred to non-neoplastic respiratory diseases (chronic bronchitis and emphysema, in particular). In 1964, the general category of "other bronchopulmonic diseases" (*ICD*-7 525–524) was the 10th leading cause of death. In 2010, the category of "chronic lower respiratory diseases" (*ICD*-10 J40–47), in which COPD predominates, was the third leading cause of death in the United States (National Center for Health Statistics 2012). This figure highlights the steep rise in women and the recent overtaking of men by women in terms of the

Figure 7.2 **Age-adjusted[a] prevalence of chronic obstructive pulmonary disease (COPD)[b] among adults—Behavioral Risk Surveillance System, United States[c], 2011**
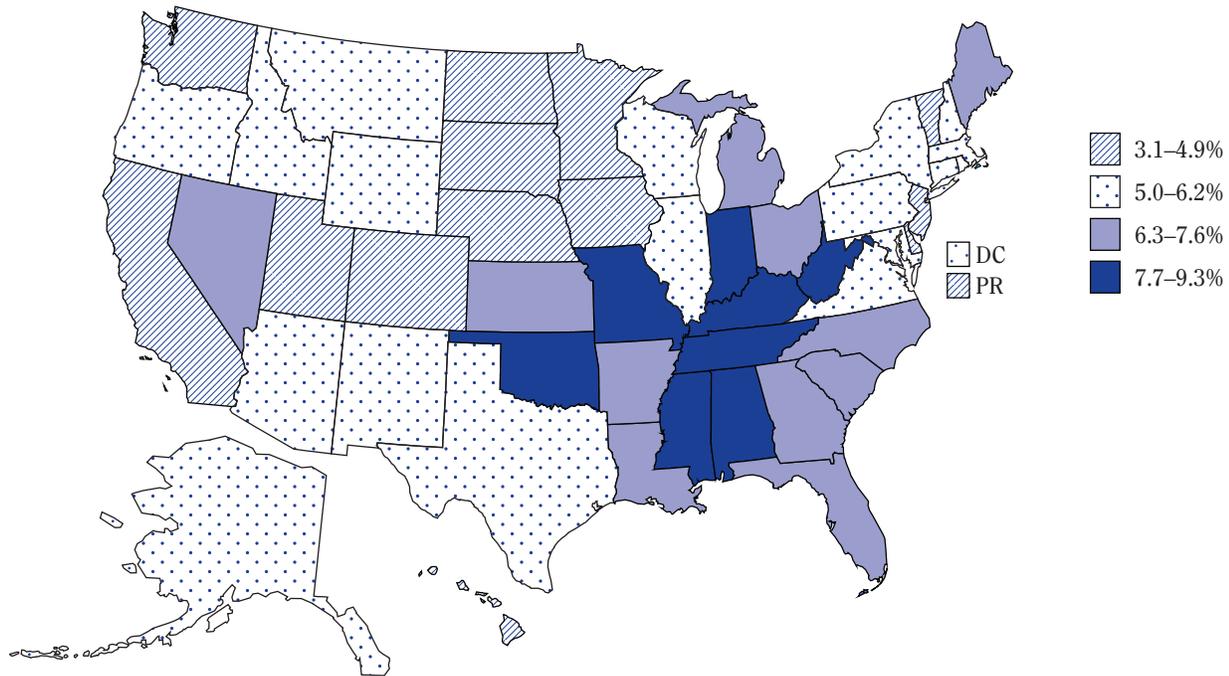
Source: CDC 2012a.
[a]Age-adjusted to the 2000 U.S. standard population, using 5 age groups: 18–44 years, 45–54 years, 55–64 years, 65–74 years, and ≥75 years.
[b]Based on an affirmative response to the question, "Has a doctor, nurse, or other health professional ever told you that you have COPD, emphysema, or chronic bronchitis?"
[c]Includes the 50 states, District of Columbia, and Puerto Rico.

total number of COPD deaths. While the mortality counts are affected by changes in classification, the trends are nonetheless clear.

A separate "COPD" ICD code was introduced in the early 1970s, and by the mid-1980s this became the main code used for COPD deaths (Feinleib et al. 1989). In 1985, 74,662 deaths were attributed to COPD (Feinleib et al. 1989), a number that increased to 119,054 in 2000 (Mannino et al. 2002) and 133,575 in 2010 (Ford et al. 2013). Between the years 2000–2005, the age-adjusted mortality rate for COPD (standardized to the 2000 U.S. standard population) for adults 25 years of age and older remained stable, between 60 and 65 per 100,000 population.

COPD mortality has increased dramatically over the past several decades. Part of this increase is related to changes in how COPD is characterized and classified, but a substantial part is due to male and female birth cohorts with high smoking rates advancing to ages

where death from COPD is more common (older than 70 years of age). Other factors, such as decreasing mortality from other chronic diseases including cardiovascular disease may have contributed. In recent years, the COPD-related mortality rate has stabilized and may show some signs of decreasing in certain age and race-ethnicity groups, reflecting declines in smoking that began several decades ago.

Gender Effects in COPD

The 1964 Surgeon General's report focused on men because of the limited data available on women and smoking at the time. As the disease increased among women, researchers addressed whether risk for COPD from smoking differed by gender. The findings with regard to gender and susceptibility and severity of COPD are mixed. By the

Figure 7.3   Deaths due to chronic obstructive pulmonary disease among adult men and women, 1979–2007, United States
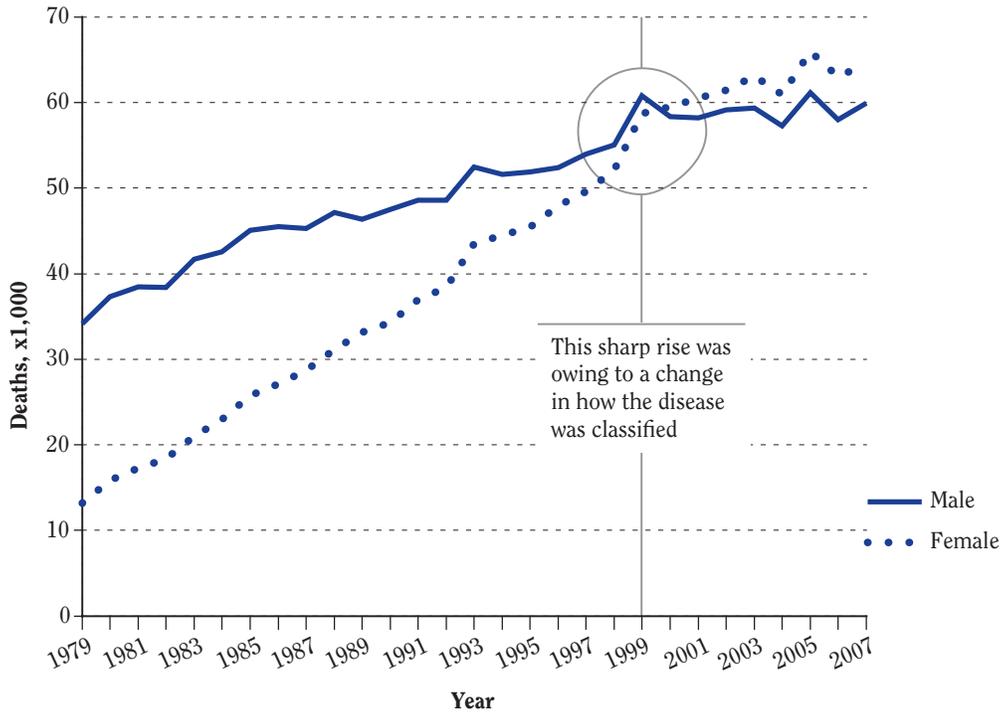
Source: Dance 2012. Reprinted with permission from Macmillan Publishers Ltd., © 2012.

time of the 1984 Surgeon General's report, which focused on COPD, the evidence synthesis resulted in the clearly inclusive statement that "Cigarette smoking is the major cause of chronic obstructive lung disease in the United States for both men and women" (USDHHS 1980, p. 8). The 1980 Surgeon General's report, *The Health Consequences of Smoking for Women,* noted that an epidemic of chronic obstructive lung disease among women had started. In the preface, this report tackled head-on the apparent "Fallacy of Women's Immunity" to the harmful effects of smoking, and highlighted as a key theme that "women are not immune to the damaging effect of smoking already documented for men. The apparently lower susceptibility to smoking-related disease among women smokers is an illusion reflecting the fact that women lagged one-quarter century behind men in their widespread use of cigarettes" (p. v). Whether or not there are gender differences for COPD susceptibility and severity continues to be debated, but the weight of recent evidence does indicate that: (1) smoking is the key risk factor for COPD in men and women, although the dose-response effects may vary, with women potentially more susceptible

at lower exposure; (2) women appear to develop severe COPD at younger ages than men and with lower cumulative cigarette smoke exposure; and (3) men and women now have similar relative risk (RR) of death from COPD.

Prevalence by Gender

During the period between NHANES I (1971–1975) and NHANES III (1988–1994), the prevalence of moderate COPD increased in women (from 50.8 to 58.2 per 1,000 population, not a statistically significant change), while the prevalence decreased in men (from 108.1 to 74.3 per 1,000 population, a statistically significant decrease), but male rates remained higher than those for women (Mannino et al. 2002).

Gender-Specific Manifestations of COPD

The 2001 Surgeon General's report noted the extensive pathologic evaluation of the lungs of male and female

smokers performed by Thurlbeck and colleagues (1974) showing that male smokers had higher emphysema scores, and a greater prevalence of emphysema, when compared to lung sections from female smokers. In a paper by Martinez and colleagues (2007), an analysis of CT data from the National Emphysema Treatment Trial (NETT) revealed that women had significantly less emphysema, despite similar severity of COPD as measured by the level of FEV_1; on histologic section, the airways of women with COPD had smaller lumens and thicker walls. Although some of these differences may represent baseline gender differences between the lungs of men and women, they may also support differences in how COPD develops and progresses in men versus women.

A series of observations during the past decade indicate that women seem to develop more severe COPD at an earlier age, in comparison with men who smoked the same cumulative number of cigarettes. In the NETT study (Martinez et al. 2007), women reported less pack-years[1] of cigarette smoking, but had similarly severe spirometrically defined COPD as men, raising the question of heightened susceptibility in women to the lung-damaging effects of smoking (Gan et al. 2006). Gan and colleagues observed that beyond 45 years of age, female current smokers had a faster annual decline in FEV_1 compared to male smokers.

Silverman and colleagues (1998) noted a high prevalence of women (almost 80%) in a group with severe, early-onset COPD (FEV_1 <40% of predicted at younger than 53 years of age) recruited for a genetic study. In addition, Sorheim and colleagues (2010) observed that in people with COPD before 60 years of age, women had lower FEV_1 and more severe COPD with lower cigarette smoking exposure. In this study, women had greater reductions in FEV_1 than men in the less than 20 pack-year range; after 25–30 pack-years of smoking, the dose-response relationship was similar to that for men.

The COPDGene study enrolled smokers with and without COPD at 21 clinical centers throughout the United States (ClinicalTrials.gov 2013). Participants were self-classified non-Hispanic Whites and African Americans 45–80 years of age with at least 10 pack-years of lifetime smoking. During the study visit, participants underwent spirometry, before and after inhaled bronchodilator, and completed detailed questionnaires on respiratory disease, medical history, and medications. Foreman and colleagues (2011) analyzed data from the first 2,500 individuals in the COPDGene study. Severe, early-onset COPD participants were predominantly women (66%), with proportionally higher rates in African American smokers; in addition to race and gender, maternal smoking and maternal COPD were also associated with severe, early-onset COPD.

Gender-Specific Morbidity and Mortality

Hospitalization rates for COPD have been approximately equal for men and women since 1995 (Akinbami and Liu 2011). However, during the period 1980–2000, annual death rates from COPD increased in men until about 1995 and then stabilized (Figure 7.4). Among women, death rates during this timeframe tripled and continued to increase. In 2000, 59,936 women died from COPD compared to 59,118 men (Mannino et al. 2002). In a more recent assessment of changes in mortality rates due to COPD (Ford et al. 2012), 5,185 individuals from NHANES I were evaluated at follow-up through 1993 (baseline exam 1971–1975, follow-up 1992–1993), and 10,954 participants from the NHANES III Linked Mortality Study (baseline 1988–1994) were followed up through 2006. Age-adjusted mortality rates among participants with moderate to severe COPD, compared to persons with normal spirometry, were higher in both NHANES I and NHANES III, although there was an overall decrease in mortality rates due to COPD in NHANES III compared to NHANES I. Specifically, in NHANES I and NHANES III, respectively, the age-adjusted mortality rates for COPD were 29.9 and 20.2 per 100,000, compared to the age-adjusted mortality rates of 10.4 and 6.2 in participants with normal spirometry. However, further highlighting previous epidemiologic trends, there was a decrease in the mortality rate among men with moderate or severe COPD (decreased by 17.8%) in contrast to the 3% increase in the mortality rate in women (Figure 7.5) (Ford et al. 2012).

The most recent and comprehensive assessment of smoking-related mortality in the United States (Thun et al. 2013) evaluated temporal trends in gender-specific smoking-related mortality across three time periods (1959–1965, 1982–1988, 2000–2010) in seven large cohorts (see Chapter 12, "Smoking-Attributable Morbidity, Mortality, and Economic Costs"). In the "contemporary" cohort that encompassed the years 2000–2010, male and female current smokers had similar RRs for mortality from COPD (26.61 for men, 22.35 for women), with this RR for women representing almost a doubling of risk when compared to the 1982–1988 time period (Figure 7.6).

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[1]Pack-years = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Figure 7.4 Age-adjusted mortality rate from chronic obstructive pulmonary disease among adults 25 years of age or older, by gender, United States, 1968–2010
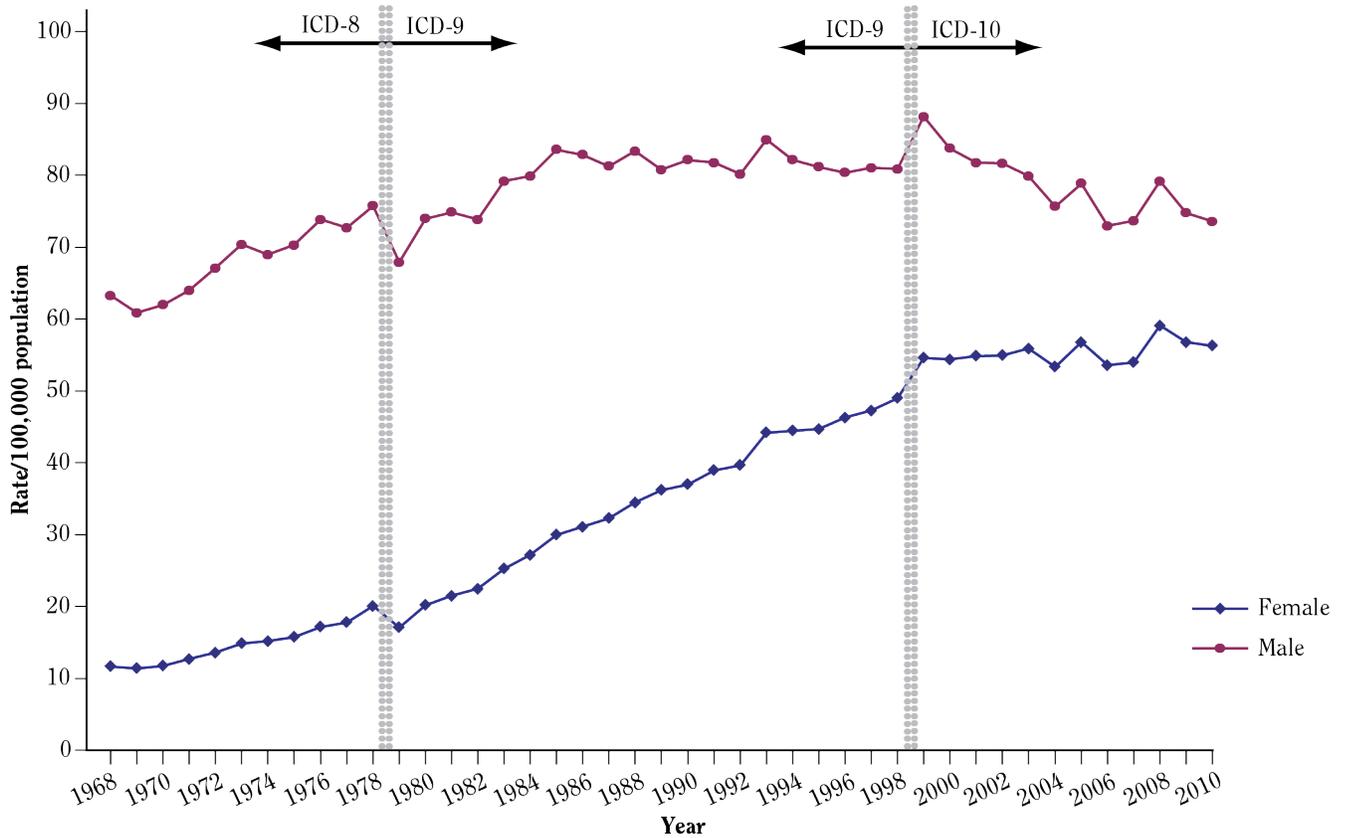
Source: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention (CDC), National Center for Health Statistics, Compressed Mortality File on CDC WONDER Online Database, July 16, 2013.

Genetics and Genomics of COPD

The first significant understanding of the role of genetics in the pathogenesis of COPD began with the 1963 discovery of the increased risk of obstructive lung disease associated with AAT (Laurell and Eriksson 1963). The role of genetic factors in COPD and susceptibility to cigarette smoke was reviewed in the 2010 Surgeon General's report (USDHHS 2010). This section focuses on recent advances in genetics and genomics made possible by the rapid advances in technology since the 2010 report.

Rare Genetic Syndromes with COPD

A small percentage of COPD patients (estimated at 1–2%) have severe AAT deficiency, a Mendelian syndrome often presenting as severe, early-onset COPD (Silverman

and Sandhaus 2009). The genetic basis for severe AAT deficiency is well-understood; a relatively rare alteration in a single DNA nucleotide base in the *SERPINA1* gene sequence causes a single amino acid change in the protein sequence of AAT at amino acid 342. This genetic variant is referred to as the *PI*Z* allele. Other even less common severe AAT deficiency variants lead to very low expression of the normal M protein (e.g., Mheerlen) or the absence of any AAT protein (e.g., Null alleles). Individuals that inherit two severe deficiency variants—most commonly genotype *PI ZZ*—are at substantially increased risk for early-onset COPD. Persons with the *PI ZZ* variant have been described as having lower lobe predominant panlobular emphysema, but a substantial fraction of those affected do not develop an emphysema distribution in this classic pattern (Parr et al. 2004). Severe AAT deficiency is found in approximately 1 in 3,000 Americans, with an increased

Figure 7.5   Age-adjusted all-cause mortality rates per 1,000 person-years (95% confidence interval [CI]) for men and women 25–74 years of age in the United States by survey and Global Initiative for Chronic Obstructive Lung Disease classification
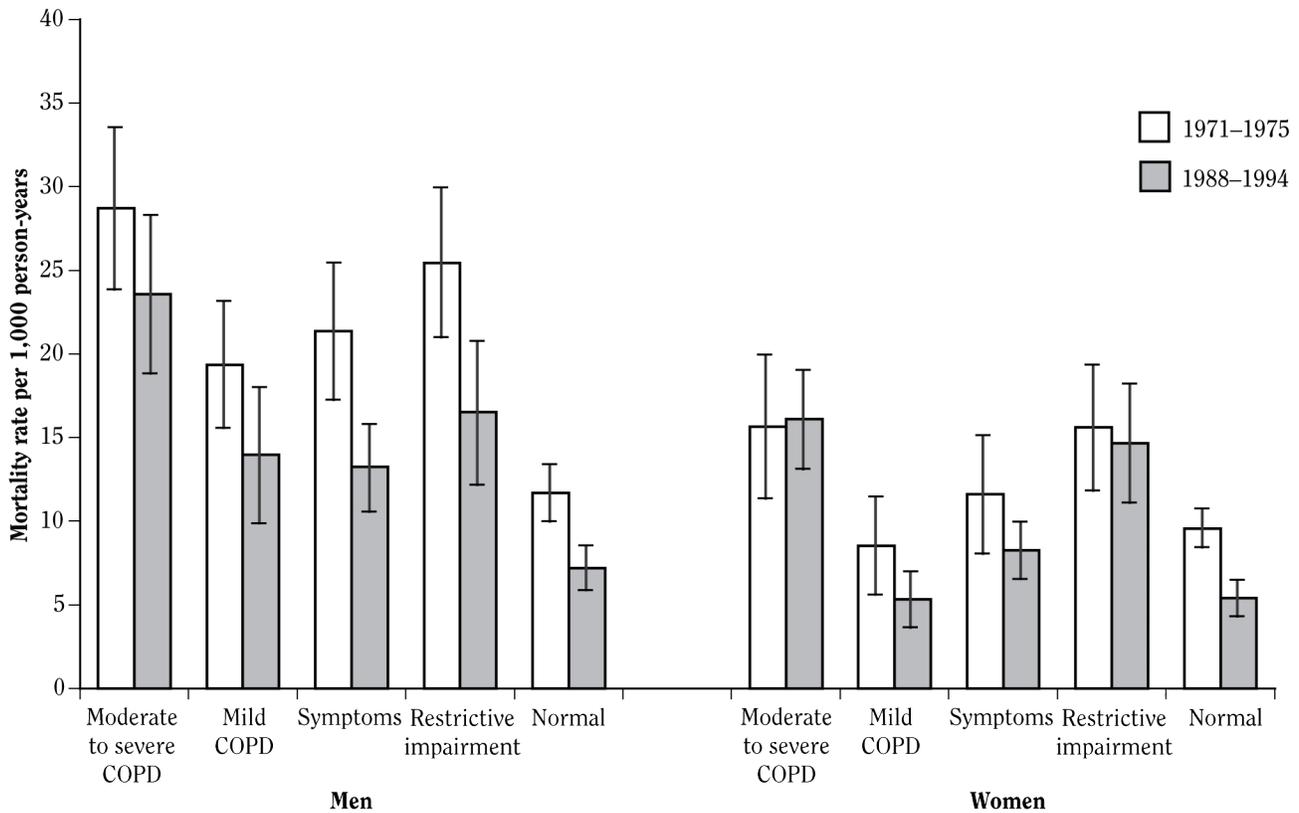
Source: Ford et al. 2012. Generated by James D. Crapo, MD., created specifically for Surgeon General's Report, 2013.
Note: **COPD** = chronic obstructive pulmonary disease.

prevalence in Whites (Silverman et al. 1989). Thus, the genetic variants explain little of the variation in risk for COPD among smokers in the population, but studies in affected individuals have provided important insights into how smoking causes COPD. The discovery of AAT deficiency was a major factor in the formulation of the protease-antiprotease hypothesis for the pathogenesis of COPD (Janoff 1985; USDHHS 2010). This hypothesis relates the development of COPD to an imbalance between the increased proteolytic activity in the lungs of smokers and the diminished activity of the opposing antiproteases, primarily AAT. The primary mechanism for increased COPD risk is likely the reduced plasma levels of circulating AAT in severely deficient persons, which relates to polymerization of the Z protein in the endoplasmic reticulum of hepatocytes (Lomas et al. 1992). However, the Z polymers, which are also detectable within the plasma and in lung tissue samples, appear to have pro-inflammatory activity,

which could also contribute to the pathogenesis of COPD in persons with *PI ZZ* (Mahadeva et al. 2005).

Another *SERPINA1* variant, the *PI*S* allele, leads to a moderate reduction in AAT protein levels; persons that inherit one *PI*S* allele and one *PI*Z* allele (*PI SZ*) are likely at increased risk for COPD (Turino et al. 1996)—although not to the same magnitude of risk as persons with *PI ZZ*. Whether persons with one normal and one severe deficiency *SERPINA1* variant (e.g., *PI MZ*) are at increased risk for COPD has been a controversial issue for decades. In a meta-analysis published in 2004, Hersh and colleagues found that studies, which compared risk in COPD cases to controls, often showed an increased risk for the *PI MZ* genotype, while population-based studies did not demonstrate reduced spirometric values in persons with the *PI MZ* variant. Only a minority of the studies included in this meta-analysis provided results adjusted for cigarette smoking intensity. More recently, Sorheim

Figure 7.6   Changes in rates of death from chronic obstructive pulmonary disease over time among current women and men smokers in three time periods
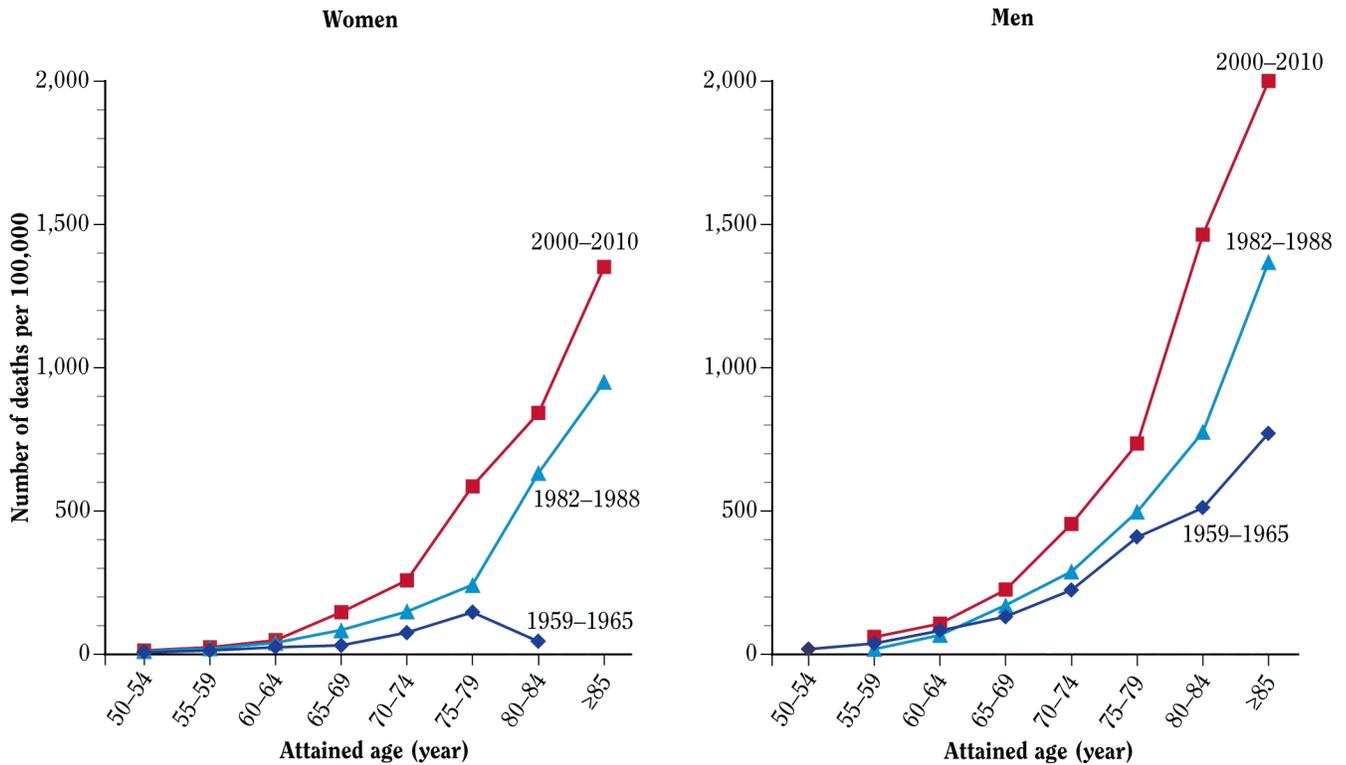
Source: Thun et al. 2013. Reprinted with permission from Massachusetts Medical Society, © 2013.
Note: Data were obtained from the first Cancer Prevention Study (CPS I) for the period 1959–1965, from CPS II for the period 1982–1988, and from 5 contemporary cohort studies for the period 2000–2010.

and colleagues (2010) assessed COPD risk associated with *PI MZ* risk in the Genetics of Chronic Obstructive Lung Disease (GenKOLS) case-control study in Norway and in the International COPD Genetics Network, a family-based study. Although *PI MZ* was not associated with significantly increased risk for COPD, persons with the *PI MZ* variant had a significantly lower FEV_1/FVC ratio in both populations, and an increased risk for CT-defined emphysema was observed in the GenKOLS Study.

Although AAT deficiency is the most widely recognized Mendelian syndrome, which increases risk for COPD, other rare Mendelian syndromes have been studied as well. People with cutis laxa, a very rare syndrome with marked dermatologic manifestations related to skin laxity, can also develop early-onset emphysema due to mutations in several genes, including *ELN* (Corbett et al. 1994) and *FBLN5* (Loeys et al. 2002). Although mutations in these cutis laxa genes do not commonly cause COPD, a rare functional variant in the *ELN* gene has been reported in

several severe early-onset pedigrees (Kelleher et al. 2005; Cho et al. 2009).

Common Genetic Determinants of COPD

Several types of studies have suggested that genetic factors other than AAT deficiency and cutis laxa influence COPD susceptibility. Aggregation of pulmonary function and airflow obstruction was demonstrated beginning in the 1970s in studies in the general population and with twins (Lewitter et al. 1984; Redline et al. 1989). Based on data from familial aggregation analyses, linkage analysis studies were performed using panels of short tandem repeat markers in families from the Boston Early-Onset COPD study for both categorical and quantitative COPD-related phenotypes. These linkage analysis approaches, which have been highly successful in Mendelian syndromes, implicated several genomic regions that may contain susceptibility genes for COPD (Silverman et al.

2002a,b; Palmer et al. 2003). Within these linkage regions, *SERPINE2* (DeMeo et al. 2006) and *XRCC5* (Hersh et al. 2010) on chromosome 2q and *SOX5* (Hersh et al. 2011) on chromosome 12p were suggested as possible COPD susceptibility genes. However, as with many other complex diseases, convincing replication of these linkage-based findings in multiple studies by different investigative groups has thus far been lacking. Therefore, the role of these linkage analysis regions and positional candidate genes remains to be determined.

Similarly, the results of many candidate gene association studies, which compared COPD cases and controls for the distribution of genetic variants within genes, typically selected based on their hypothesized roles in COPD pathogenesis, have been largely inconsistent (Castaldi et al. 2010). By contrast, the application of genome-wide association studies (GWAS) has unequivocally associated common variants in several genetic loci with COPD susceptibility (Table 7.1). Pillai and colleagues (2009) found genome-wide significant associations between COPD and single nucleotide polymorphisms (SNPs that are used as markers across the genome) in the *CHRNA3/CHRNA5/IREB2* region on chromosome 15q25. Of interest, DeMeo and colleagues (2009) performed gene expression studies comparing normal and COPD lung tissues and identified SNPs to be tested for association with COPD in several studies. The association analyses identified *IREB2* as a COPD susceptibility gene. In a GWAS based in the Framingham Heart Study (Wilk et al. 2009), the *HHIP* region was associated with FEV_1/FVC ratio, and this same region nearly reached genome-wide significance with COPD susceptibility in the study by Pillai and colleagues (2009). The *FAM13A* locus has been strongly associated with COPD susceptibility in multiple populations (Cho et al. 2010). In a collaborative GWAS, including four study populations (GenKOLS, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints [ECLIPSE], National Emphysema Treatment Trial/Normative Aging study, and COPDGene), a fourth statistically significant link was found for a region on chromosome 19q (Cho et al. 2012).

Several of these associations for COPD risk have been replicated in other studies. For example, participants with airflow obstruction were identified in the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) and SpiroMeta consortium studies, and compared to controls with normal spirometry; a genome-wide significant association to the chromosome 15q25 region was found (Wilk et al. 2012). The *HHIP* and *FAM13A* associations with COPD have also been replicated in multiple studies (Van Durme et al. 2010; Young et al. 2010a,b; Soler Artigas et al. 2011). Thus, the frustration of inconsistent genetic association results in COPD over the past decade has been replaced by optimism regarding the likely importance of these GWAS-identified loci in COPD susceptibility.

A complicating issue in COPD genetic studies is the overwhelming influence of cigarette smoking on COPD susceptibility. In light of this large effect, most COPD genetics studies have only involved current or former cigarette smokers; however, this approach may have limited detection of gene-by-smoking interactions and hence the identification of those genes determining susceptibility in smokers. In a collaborative study in CHARGE and SpiroMeta of more than 50,000 individuals, genome-wide association analyses of FEV_1 and FEV_1/FVC ratio were performed with joint assessment of main SNP effects and SNP-by-smoking effects. Three novel genome-wide significant regions, on chromosomes 2, 6, and 17, were identified (Hancock et al. 2012).

It is possible that genetic determinants of COPD risk may act through genetic effects which may increase nicotine addiction or smoking intensity. In fact, both the chromosome 15q25 region (which includes genes of several components of the nicotinic acetylcholine receptor, i.e., *CHRNA3* and *CHRNA5*) and the chromosome 19q region (which includes *CYP2A6*) have been associated with smoking pattern (Thorgeirsson et al. 2010; Tobacco and Genetics Consortium 2010). Additional research will be required to determine whether nicotine addiction is the mechanism that links these genetic loci to COPD susceptibility.

Genetic Determinants of COPD-Related Phenotypes

Studies of quantitative disease-related phenotypes may provide increased power to detect significant associations for genetic determinants for a complex disease. Several large-scale collaborative GWAS (CHARGE and SpiroMeta) have been highly successful at identifying multiple genomic regions that influence lung function levels in population-based samples (Hancock et al. 2010; Repapi et al. 2010). A combined analysis of CHARGE and SpiroMeta has identified 26 genome-wide significant regions associated with spirometric measures (Soler Artigas et al. 2011). Of interest, both the *HHIP* and *FAM13A* loci have been associated with lung function values in these general population samples; it is not yet clear how many of the other genomic regions, associated with lung function levels in the general population, also influence COPD susceptibility in smokers (Silverman 2012).

Kong and colleagues (2011) performed GWAS of CT-defined emphysema in three sets of COPD cases (GenKOLS, ECLIPSE, and NETT), using both radiologists' assessments of emphysema severity and quantitative

densitometric measures of emphysema. Although the quantitative densitometric measurements of emphysema did not demonstrate any genome-wide significant associations, borderline genome-wide significant associations near the *BICD1* gene were observed for the endpoint of the radiologists' visual assessment of emphysema severity.

Several GWAS of the rate of FEV_1 decline have been reported. Imboden and colleagues (2012) performed GWAS of FEV_1 decline in a collaborative study of general population participants, including separate analyses in 1,441 persons with asthma and 2,667 in persons who were not asthmatics. However, no significant associations with FEV_1 decline were found across the genome. When Hansel and colleagues (2012) studied FEV_1 decline within 4,048 persons with mild-to-moderate COPD in the Lung Health Study, two genome-wide significant regions were identified, but they were not replicated in other populations. Genetic association analyses in the ECLIPSE and International COPD Genetics Network studies suggested that the *CHRNA3/CHRNA5/IREB2*, *HHIP*, and *FAM13A* COPD GWAS loci influence different aspects of the COPD syndrome (Pillai et al. 2010). For example, the *CHRNA3/5* locus was most strongly associated with emphysema, while the *HHIP* locus was associated with COPD exacerbation frequency.

Gene Expression Studies in COPD

In order to provide insight into the biological pathways involved in COPD pathogenesis, multiple studies have assessed genome-wide gene expression using RNA extracted from lung tissue samples in persons with COPD and controls. Four key lung tissue gene expression studies were compared by Zeskind and colleagues (2008). Ning and colleagues (2004) used both serial analysis of gene expression and microarray analysis in 14 smokers with moderate COPD and 12 smokers with normal spirometry. Golpon and colleagues (2004) studied gene expression using microarrays in 11 COPD cases (6 with AAT deficiency) and 5 controls. Spira and colleagues (2004a) compared lung tissue samples from 18 severe emphysema cases undergoing lung volume reduction surgery to samples from 12 persons with normal spirometry or mild airflow obstruction undergoing resection of a pulmonary nodule. Wang and colleagues (2008) obtained 48 lung tissue samples from persons with a range of spirometric abnormalities, who were undergoing surgical resection of a pulmonary nodule. All four of these studies identified multiple genes that showed significant differential expression between lung tissue samples from persons with COPD and controls, but only minimal overlap in the specific differentially expressed genes was observed across

the four studies. This limited degree of replication could be related to several factors, including the small sample sizes of the studies, differences in the analytical approaches, and variation in inclusion and exclusion criteria for participant selection. Nonetheless, Zeskind and colleagues (2008) used pathway analysis to demonstrate that many of the differentially expressed genes observed in these four studies represented similar biological processes. Further evidence for concordance between different lung tissue gene expression studies was provided by Bhattacharya and colleagues (2009). They assessed lung tissue gene expression using both the presence and absence of COPD (15 COPD cases and 18 smoking controls) and quantitative spirometric measures (56 total persons), and found 254 differentially expressed gene biomarkers. A subset of 84 of these gene biomarkers was also assessed in the Spira and colleagues study (2004a), and this subset of biomarkers generated by Bhattacharya and colleagues was able to differentiate COPD cases versus controls in the Spira data set with 97% predictive accuracy.

Wang and colleagues (2008) showed that some of the variability in lung tissue gene expression resulted from variation in the cellular profiles included within the lung tissue sample. One approach to overcome this source of variability is to focus on a particular cell type, and several studies have focused on airway epithelial cells obtained at bronchoscopy. Spira and colleagues (2004b) pioneered this approach, and they identified genes that were differentially expressed within airway epithelial cells in response to smoking. Ammous and colleagues (2008) found substantial variability in gene expression within the small airways of smokers, suggesting that this distal sampling site could provide especially useful information about COPD pathogenesis.

Protein Biomarkers of COPD

The identification of biomarkers of lung destruction and inflammation in COPD has been a major research focus during the past 50 years (Yoon and Sin 2011; Rosenberg and Kalhan 2012). Yoon and Sin (2011) discussed the optimal characteristics of a COPD biomarker, which include having a close relationship to relevant health outcomes, playing an important biological role in disease, and demonstrating modifiability with effective treatment interventions. Since cigarette smoking induces lung inflammation, ideal COPD biomarkers would differentiate smokers with and without COPD.

This section briefly summarizes some of the key evidence related to the potential of several proteins and protein breakdown products as COPD biomarkers. Because COPD often involves destruction of lung parenchyma,

Table 7.1   **Genome-wide association studies of chronic obstructive pulmonary disease (COPD) and COPD-related phenotypes**

Study	Genome-wide association studies	Primary studies included study	Study population type	Phenotype	Genome-wide significant results
Pillai et al. 2009	COPD affection status	GenKOLS	Case-control	COPD	*CHRNA3/5, IREB2*
Cho et al. 2010	COPD affection status	3 cohorts	Case-control	COPD	*FAM 13A*
Cho et al. 2012	COPD affection status	4 cohorts	Case-control	COPD	Chromosome 19q
Wilk et al. 2012	COPD affection status	CHARGE/SpiroMeta	Case-control	Airflow *obstruction*	*CHRNA3/5*
Wilk et al. 2009	Lung function	Framingham	Population	FEV_1/FVC	*HHIP*
Hancock et al. 2010	Lung function	CHARGE	Population	FEV_1, FEV_1/FVC	9 loci
Repapi et al. 2010	Lung function	SpiroMeta	Population	FEV1, FEV1/FVC	6 loci
Soler Artigas et al. 2011	Lung function	CHARGE/ SpiroMeta	Population	FEV_1, FEV_1/FVC	16 loci
Kong et al. 2011	Lung function decline and emphysema	ECLIPSE	COPD cases	Emphysema	*BICD1*
Imboden et al. 2012	Lung function decline and emphysema	3 cohorts	Population	Lung function decline	None
Hansel et al. 2012	Lung function decline and emphysema	Lung health	COPD cases	FEV_1 decline	Chromosomes 10/14 (not replicated)

Note: **CHARGE** = Cohorts for Heart and Aging Research in Genomic Epidemiology; **ECLIPSE** = evaluation of COPD longitudinally to identify predictive surrogate endpoints; **FEV_1** = forced expiratory volume; **FVC** = forced vital capaity; **GenKOLS** = Genetics of Chronic Obstructive Lung Disease.

development of biomarkers based on breakdown products of lung extracellular matrix components has been pursued. Desmosine and isodesmosine, specific degradation products of elastin, can be measured in the plasma and urine. Small studies have suggested that urinary desmosine levels are increased in response both to current smoking and to COPD (Stone et al. 1995). Clinical trials of AAT augmentation therapy in AAT-deficient persons did not demonstrate consistent effects on urinary desmosine levels (Luisetti et al. 2008). Part of the inconsistency in the results of these interventional trials could be related to technical difficulties in desmosine assays, and more recently developed mass spectrometry approaches may be more reliable (Ma et al. 2003). Mass spectrometry analysis was performed in a total of 390 individuals, including those with stable COPD, individuals with COPD during an exacerbation, and controls with normal spirometry (smokers and nonsmokers) (Huang et al. 2012). Significantly higher desmosine levels were found in blood samples from persons with stable COPD, compared to control smokers or nonsmokers, but urinary desmosine levels were not different when stable COPD cases and controls were compared. During COPD exacerbations, elevated urinary desmosine levels were observed. A more recently characterized degradation product of collagen, proline-glycine-proline, is chemotactic for neutrophils and has been suggested to have higher levels in both serum and induced sputum of persons with COPD than in nonsmoking controls (O'Reilly et al. 2009).

A variety of systemic markers of inflammation have been studied as potential COPD biomarkers. For example, with adjustment for ever smoking status and pack-years of smoking, elevated C-reactive protein (CRP) levels were associated with a significantly increased risk of incident COPD in the Rotterdam Study (van Durme et al. 2009). Of interest, the greatest effect of elevated CRP on COPD risk was observed among former smokers; nonsmokers were not at increased risk if CRP was elevated. Among 34 bloodstream biomarkers assessed in 201 COPD cases and 37 smoking controls from the ECLIPSE study, fibrinogen demonstrated a significantly higher mean level in COPD cases, compared with controls, and was the most reproducible biomarker in blood samples collected 3 months apart (Dickens et al. 2011). However, the relevance of these nonspecific inflammatory markers for COPD pathogenesis, and their response to treatment interventions, remains to be demonstrated.

Proteins synthesized within the lungs may have greater potential to serve as specific COPD biomarkers. Significantly increased serum levels of surfactant protein D (Lomas et al. 2009), decreased serum levels of Clara cell secretory protein 16 (CC16) (Lomas et al. 2008), and increased serum pulmonary and activation-regulated chemokine/chemokine liand-18 (PARC/CCL-18) (Sin et al. 2011) have been found in persons with COPD compared to smokers with normal spirometry. Of interest, treatment of persons with COPD with oral corticosteroids reduced serum surfactant protein D (Lomas et al. 2009) and PARC levels (Sin et al. 2011). In the longitudinal evaluation of lung function in the ECLIPSE study, CC16 levels were associated with both baseline FEV_1 level and change in FEV_1 over 3 years of observation (Vestbo et al. 2011).

Pathogenesis of COPD

Changes in Views of COPD Pathogenesis During the Past 50 Years

Small airway disease and emphysema form the basis for the largely irreversible airway obstruction that characterizes COPD. Emphysema is defined pathologically as the destruction of alveolar tissue with coalescence and enlargement of airspaces. As mentioned above, although these terms were not used then, two observations made around the time of the 1964 Surgeon General's report established the elastase:antielastase hypothesis as the basis for the lung injury that results in emphysema. These seminal findings were: (1) elastases instilled into the lungs of experimental animals resulted in airspace destruction and enlargement (Gross et al. 1965); and (2) persons with deficient AAT are at increased risk for the development of emphysema (Laurell 1963). With many additional concepts added to this basic premise over time, the elastase:antielastase hypothesis, which was extensively discussed in the 2010 Surgeon General's report, remains a central component of our understanding of emphysema 50 years later.

Because AAT is the main inhibitor of neutrophil elastase (NE), this led to the understanding of the inflammatory nature of COPD with neutrophils and NE receiving most attention initially. NE is not only a potent elastase capable of causing experimental emphysema (Janoff et al. 1977; Senior et al. 1977; Snider et al. 1984) but it is also a secretagogue (Nadel 2000; Kohri et al. 2002). In addition, neutrophils produce other serine proteinases with elastolytic activity, as well as matrix metalloproteinase (MMPs), including the elastolytic MMP-9.

Macrophages are the main inflammatory cell patrolling the normal lung parenchyma and their numbers are greatly expanded with long-term smoking (Niewoehner et al. 1974; Merchant et al. 1992). They also produce elastases, including MMP-9 and MMP-12. Results from

gene-targeted knockout mice, combined with cigarette smoking models, demonstrated an interaction between MMP-12 (Hautamaki et al. 1997) and NE (Shapiro et al. 2003) contributing to emphysema in mice. MMPs and serine proteinases work together to degrade the inhibitor of the other and, thus, lead to lung destruction. Proteolytic cleavage products of elastin also serve as a macrophage chemokine (Senior et al. 1984; Houghton et al. 2006) and collagen fragments are chemotactic for neutrophils (Weathington et al. 2006). In addition to matrix destruction, which fuels the positive inflammatory feedback loop, a variety of traditional CC and CXC chemokines have also been implicated in generating the complex inflammatory–immune network in COPD (see the "Immune Function and Autoimmune Disease" section in Chapter 10, "Other Specific Outcomes").

Macrophages also regulate the inflammatory response in COPD. For example, cigarette smoke alters the macrophage phenotype via oxidant-induced inactivation of histone deacetylase-2, shifting the balance toward acetylated or loose chromatin, exposing NF-κB sites, and resulting in transcription of MMPs, pro-inflammatory cytokines such as *IL-8*, and *TNF*-α; this leads to neutrophil recruitment (Ito et al. 2006).

Recently, the role of adaptive immunity in COPD has been appreciated (see Chapter 10). CD8+ T cells are also recruited in response to cigarette smoke and release interferon inducible protein-10 that, in turn, leads to macrophage production of MMPs (Grumelli et al. 2004; Maeno et al. 2007). In further support of T cell involvement, inducible transgenic mice overexpressing interferon gamma (IFN-γ) developed emphysema (Wang et al. 2000). Of note, interferon IFN-γ transgenic mice develop proteinase-mediated emphysema, but not airway disease ("British mice" per the British hypothesis) (Wang et al. 2000), while overexpression of IL-13 produces both emphysema and airway remodeling ("Dutch mice" per the Dutch hypothesis) (Zheng et al. 2000).

The role of B cells and auto-immunity to promote progression of COPD is an emerging concept. B cells accumulate in bronchus-associated lymphoid tissue (BALT) in persons with COPD, particularly those with advanced disease (Hogg et al. 2004). Antibodies have been found against elastin fragments (Lee et al. 2007), as well as immunoglobulin G autoantibodies with avidity for pulmonary epithelium and the potential to mediate cytotoxicity (Feghali-Bostwick et al. 2008).

In summary, cigarette smoke initiates an inflammatory process that later becomes more complex and independent of smoking over time. For example, matrix fragments themselves can continue to drive the inflammation. In the airway, colonization by microorganisms

may sustain inflammation. Hence, smoking cessation, although critical, may not totally reverse progression of advanced COPD.

Over the past decade, the role of structural cell apoptosis, particularly in the vascular endothelial cell, has become recognized as a driver of emphysema (Kasahara et al. 2000). Ceramide released from one apoptotic structural cell can also cause the death of neighboring cells (Petrache et al. 2005). Clearly, the loss of an alveolar unit includes both the cells and matrix. Emphysema could be established either by inflammatory cell-mediated matrix destruction followed by cell detachment and death, or alternatively, cigarette smoke oxidant-mediated structural cell death via a variety of mechanisms, including Rtp801 inhibition of mTOR that leads to inflammation and proteolysis (Yoshida et al. 2010). Likely, both mechanisms are operable.

COPD is characterized by its irreversible nature, raising the important issue of lung repair capacity in COPD. Cigarette smoke has a variety of effects that inhibit repair, ranging from impairing elastin and collagen synthesis and cross-linking (Laurent et al. 1983; Osman et al. 1985) to enhancing epithelial cell death and inhibiting epithelial cell migration and repair (Cantral et al. 1995; Nakamura et al. 1995; Carnevali et al. 1998; Wang et al. 2001; Kotton et al. 2005). There have been hints that repair may be possible. For example, retinoic acid clearly reversed elastase-induced emphysema in rats (Massaro and Massaro 1997), but unfortunately retinoic acid had no effect in human trials (Roth et al. 2006; Stolk et al. 2012). The complex process of elastic fiber production appears to be inefficient, if even possible, following growth and development (Mecham et al. 1995; Shifren and Mecham 2006). Collagen turnover is equally complicated with loss of collagen in the airspace and excess collagen accumulation around the airways (Wright 1995; Wright and Churg 1995). In addition to the complexity of restoring the lung's intricate network of interwoven fibers composed of extracellular matrix components, the role of cell death and regeneration remains uncertain. It is unlikely that lung repair recapitulates lung development, where large airspaces septate to form alveoli. Identification of stem cells residing in the distal small airways or alveoli, and their role in COPD, is an area of active investigation and therapeutic interest.

Current Models of COPD Pathogenesis from Murine and Human Studies

The evolution of the current understanding of COPD presented above is largely derived from observations made in human lung tissue and cells. These observations led to

hypotheses on causal relationships that have been tested in animal models. Animal models have played a major role in our current understanding of the pathogenesis of emphysema, beginning with the classic study by Gross and colleagues demonstrating that pulmonary instillation of an elastase resulted in emphysema (Gross et al. 1965; Snider et al. 1992a,b). Although no animal model replicates all aspects of human disease, COPD has an advantage over many other disease models because the primary causal agent is known—cigarette smoke—and chronic cigarette smoke exposure in experimental animals results in inflammation very similar to that in humans followed by several pathologic changes characteristic of COPD. Such models have been far less useful for drug discovery.

The mouse has been most extensively used in the past two decades because the ability to genetically engineer mice allows for the performance of controlled experiments in mammals. While the airspace of the mouse replicates humans fairly well, airway structure differs greatly. Mice still develop aspects of airway remodeling including inflammation, fibrosis, and mucus hypersecretion, but the findings are much more subtle; because mice lack extensive airway branching, they really do not have small airways, a major site of obstruction in humans. Hence, the understanding of emphysema is much more advanced than that of small airway disease.

The current dominant paradigm of the pathogenesis of emphysema comprises four interrelated events: (1) chronic exposure to cigarette smoke leads to inflammatory and immune cell recruitment within the terminal airspaces of the lung; (2) these inflammatory cells release proteinases that damage the extracellular matrix of the lung; (3) endothelial cells and other structural cells undergo apoptosis due to oxidant stress and loss of matrix-cell attachment; and (4) ineffective repair of elastin and other extracellular matrix components result in airspace enlargement.

Unfortunately, despite strong evidence supporting these basic concepts, a drug therapy has yet to be developed that halts the underlying process that leads to COPD. In part, developing such therapeutic interventions is hindered by insufficient understanding of airway disease and a lack of validated endpoints for short-term trials that are predictive of major clinical endpoints for the long-term. The understanding of the pathogenesis of emphysema is much greater than for airway disease, but emphysema is a less attractive therapeutic target due to its protracted and irreversible nature. Further, human confirmation of disease mechanisms is starting to emerge from genetic studies. For example, although candidate gene association studies are fraught with hazards, a large, well-controlled candidate gene study using multiple replication populations supported a role for MMP-12 in promoting both emphysema and asthma (Hunninghake et al. 2009). The main utility of powerful new genetic approaches has been to define new candidate genes in an unbiased manner, allowing both the confirmation and broadening of understanding of the mechanisms that lead to specific COPD phenotypes.

Lessons from Imaging Studies

The evolution of chest CT imaging, over the past several decades, has created a robust technology for deriving image-based biomarkers that can be used to both visualize and quantify major COPD subtypes. Quantitative volumetric CT is now well-established as a method to assess three critical components of COPD: emphysema (Bankier et al. 2002; Madani et al. 2006, 2008), airway wall thickening (Orlandi et al. 2005; Coxson 2008; Kim et al. 2009b; Washko et al. 2009), and expiratory air trapping (Eda et al. 1997; Matsuoka et al. 2007, 2008). These measures correlate quite well with pathologic measures of emphysema (Bankier et al. 2002; Madani et al. 2006, 2008) and small airway disease (Nakano et al. 2005; McDonough et al. 2011). The particular advantages of CT in phenotypic characterization of COPD include the ability to provide anatomic lobar and sublobar information regarding the distribution and severity of parenchymal abnormalities (Hasegawa et al. 2006; Revel et al. 2008) and the ability to follow abnormalities over time with sequential CT imaging (Shaker et al. 2004; Matsuoka et al. 2006; Dirksen 2008; Stoel et al. 2008). Current cigarette smoking does increase the lung density measurements assessed by CT. This increase is, presumably, related to the accumulation of smoking-related toxins and the associated inflammatory response (Ashraf et al. 2011), which can impact the assessment of emphysema using quantitative densitometric approaches.

Chest CT can be used to subclassify COPD into either emphysema or airway-predominant disease, and to assess the severity and unique patterns of these different expressions of disease (Gevenois et al. 1995, 1996). The degree of emphysema and the degree of gas trapping can be estimated as continuous variables from CT imaging (Kubo et al. 1999; Matsuoka et al. 2008; Gorbunova et al. 2010). In addition, chest CT can be used to define the extent and severity of pulmonary vascular disease, which may be a primary or secondary component of the development of disabling COPD (Barr et al. 2010; Matsuoka et al. 2010). Wells and colleagues (2012) have shown that pulmonary artery enlargement, as detected on chest CT, is associated with enhanced risk for severe exacerbations of COPD.

Researchers have found that the magnitude of emphysema, the severity of image-defined airway inflam-

mation, and gas trapping do not directly correlate with GOLD grade for COPD severity, showing that CT-defined characteristics related to COPD are independent variables from physiologic obstruction (FEV_1). The extent and severity of CT-defined emphysema has been shown to correlate well with clinical parameters such as Modified Medical Research Council dyspnea score, 6-minute walk distance, and number of annual exacerbations; and several groups have documented that emphysema is associated with a greater decrease in FEV_1 over time and increased mortality (McDonough et al. 2011; Nishimura et al. 2012). Increased lung emphysema and airway wall thickness have been positively associated with enhanced risk for COPD exacerbations, independent of the severity of airflow obstruction (Han et al. 2011).

CT imaging can define significant structural and functional lung abnormalities in persons having a substantial smoking history, but who have normal spirometry (FEV_1). These abnormalities include emphysema, evidence of airway wall thickening, and excessive gas trapping on expiratory CT. It is also common for persons with a history of smoking (with or without obstruction) to show substantial gas trapping on expiratory CT scans, although they have no CT evidence of emphysema. Both abnormal gas trapping and physiologic obstruction can be used to define these persons as having COPD; however, their pathophysiology and disease expression are substantially different than that of persons who have an emphysema-predominant form of COPD.

Visual analysis of the pattern and extent of emphysema can identify small amounts of centrilobular emphysema, usually in the upper lobes, in persons who have minimal quantitative emphysema. This appears to be one of the earliest manifestations of lung structural change associated with COPD. Both visual analysis and a quantitative texture-based analysis can be used to identify specific patterns, distributions, and the severity of emphysema including centrilobular, panlobular, and paraseptal patterns.

Evidence Synthesis

This section has reviewed a wide range of evidence related to COPD and smoking. Since the causal conclusion in the 1964 report related to "chronic bronchitis," a term that can be considered equivalent to COPD, there have been great gains in the understanding of the pathogenesis of COPD and the clinical phenotype of COPD, and an understanding of genetic basis of susceptibility to COPD is emerging. Prior reports have advanced the conclusions of the 1964 report and affirmed that cigarette smoking is by far the leading cause of COPD in the United States.

This report addresses additional aspects of the COPD epidemic caused by tobacco smoking: trends in disease prevalence and mortality; gender differences in risk of COPD associated with smoking; advancing understanding of pathogenesis; emerging findings on the genetics of COPD; and phenotypic characterization of COPD using new approaches. Compared with 1964, COPD is a far more prominent cause of death. Age-adjusted mortality rates have risen sharply since 1964 and are only now beginning to drop in men. In contrast, prevalence data do not show a trend of increase, although methods have not been uniform over time and approaches for diagnosis and classification have changed as well.

The epidemiologic and clinical information suggests differences in COPD when comparing men and women. Studies involving the examination of pathology specimens and use of lung imaging suggest that men have more emphysema than women (Thurlbeck et al. 1974; Martinez et al. 2007) and women may be at greater risk than men for early onset COPD (Silverman et al. 1998; Martinez et al. 2007). Additionally, the COPD mortality rate for women has risen more steeply than that for men. A potential biological basis for such gender differences is uncertain at present. New approaches for characterizing COPD using imaging and molecular signatures may provide further insights.

The pathogenesis of COPD has been covered extensively in previous reports, most comprehensively in the 1984 and 2010 reports. Understanding continues to deepen through use of the ever-more powerful tools of molecular biology and animal models. Advances in understanding of the genetic basis of susceptibility to tobacco smoke will provide further insights and perhaps a basis for preventive strategies.

Conclusions

1. The evidence is sufficient to infer that smoking is the dominant cause of chronic obstructive pulmonary disease (COPD) in men and women in the United States. Smoking causes all elements of the COPD phenotype, including emphysema and damage to the airways of the lung.

2. Chronic obstructive pulmonary disease (COPD) mortality has increased dramatically in men and women since the 1964 Surgeon General's report. The number of women dying from COPD now surpasses the number of men.

3. The evidence is suggestive but not sufficient to infer that women are more susceptible to develop severe chronic obstructive pulmonary disease at younger ages.

4. The evidence is sufficient to infer that severe α1-antitrypsin deficiency and cutis laxa are genetic causes of chronic obstructive pulmonary disease.

Implications

Despite substantial progress in the epidemiology, genetics, imaging, and pathogenesis of COPD during the past 50 years, additional research in all of these areas will be required to provide a comprehensive understanding of COPD. A major focus will be to understand the heterogeneity of COPD, which is likely a syndrome of multiple diseases that share the common physiological manifestation of chronic airflow obstruction. Identification of specific subtypes of COPD, which will almost certainly have unique epidemiologic, genetic, and pathobiologic characteristics, has the potential to dramatically alter the approaches to the diagnosis and treatment of COPD. Smoking avoidance will remain the key primary prevention approach for COPD, but for the millions of already affected individuals, translation of the advances in pathogenesis, genetics, and imaging to improved clinical care will provide important challenges for decades to come.

Asthma

Asthma is one of the most common chronic respiratory diseases, affecting approximately 5–10% of the U.S. population (Moorman et al. 2007). The disease usually begins during childhood, but can start at any age. Childhood asthma may go into remission and then recur later in life. Asthma is characterized by variable airflow obstruction, which results in the symptoms of wheezing and dyspnea with exertion (National Asthma Education and Prevention Program 2007). In the modern conceptualization of asthma, chronic airway inflammation is the main underlying pathophysiologic abnormality that causes increased constriction of smooth muscles and decreased airway caliber and there can be an overlap between asthma and COPD (Figure 7.1). Chronic changes in the airway, referred to as *airway remodeling*, can lead to irreversible loss of lung function.

Exposures to allergens and environmental pollutants have long been recognized as factors that can cause or exacerbate asthma, particularly in vulnerable populations (Matsui et al. 2008). Allergic reactions to the antigens of dust mites, cockroaches, and cats have been widely cited as adverse factors in asthma, and both outdoor and indoor exposures to the byproducts of combustion have been linked to poor asthma control (National Heart, Lung, and Blood Institute 2007). This section reviews the accumulating evidence that active cigarette smoking contributes to both the incidence of asthma and its exacerbation.

Conducting epidemiologic studies of the effects of smoking and other environmental factors on asthma is a challenging undertaking. One of these challenges is the nature of asthma itself, which often remits and relapses over time. Indeed, many asthma patients have long periods of symptom-free intervals, only to have the disease return later in life. Consequently, establishing the clear temporal sequence between smoking and the initiation or exacerbation of asthma can be difficult. Moreover, a bias termed the *healthy smoker effect* may complicate epidemiologic studies of asthma and active smoking (Becklake and Lalloo 1990). This bias occurs when persons who have increased susceptibility to the health effects of smoking quit with relatively greater frequency than less susceptible persons, causing an overrepresentation in the remaining cohort of current smokers of those who are less likely to be affected. The topic of active smoking and asthma in children and adults was reviewed in the 2004 report of the Surgeon General (USDHHS 2004) and is updated in this section.

Biologic Mechanisms

The mechanisms by which active smoking could contribute to the causation of asthma include chronic airways inflammation, impaired mucociliary clearance, impaired growth of the lungs during childhood, and increased bronchial hyperresponsiveness (USDHHS 2004, 2006, 2010). Immunologic mechanisms include effects on T cell function (increased development of T helper cell 2 [Th2] pathways relative to Th1 pathways and a higher ratio of Th2/Th1), increased production of IgE, and greater allergic sensitization (see Chapter 10).

Since the publication of the 2004 and 2006 Surgeon General's reports, increasing evidence supports the role of Th2 cells and the related cytokines IL-4, IL-5, and IL-13 in the pathogenesis of asthma, especially severe asthma (Levine and Wenzel 2010). In addition, more studies have been published that support the impact of active smoking on increased Th2 pathway activation and allergic sensitization (Nouri-Shirazi and Guinet 2006; Broide 2008; Nakamura et al. 2008; Van Hove et al. 2008; Baena-Cagnani et al. 2009; Robays et al. 2009). Consequently, greater activation of the Th2 pathway may be one mechanism by which active smoking increases the incidence of asthma and the frequency and severity of exacerbations.

Emerging data suggest that cigarette smoke may increase neurogenic inflammation in the bronchial airway (Bessac et al. 2008; Simon and Liedtke 2008). The human airways are innervated by peripheral sensory neurons with specific receptors that are activated by inhaled noxious agents; neuronal activation may cause neurogenic inflammation of the airway. In particular, cigarette smoke can activate TRPA1s (transient receptor potential cation channel, subfamily A, member 1) in airway sensory neurons and result in inflammation and hyperresponsiveness of the airway (Andre et al. 2008; Bessac et al. 2008; Simon and Liedtke 2008; Lin et al. 2010). The TRPA1 is likely activated by oxidants contained within cigarette smoke.

In experiments with knockout mice, TRPA1-deficient mice, after a challenge with ovalbumin, experienced (1) markedly reduced airway inflammation and eosinophilia, (2) much lower levels of Th2 cytokines (IL-5 and IL-13) and pro-inflammatory cytokines (TNF-α and eotaxin), (3) greatly decreased production of mucous, and (4) a far lower incidence of airway hyperresponsiveness (Caceres et al. 2009). Pharmacologic inhibition of the receptor produced similar results. Although more research is needed, activation of the TRPA1 pathway is a plausible mechanism for the impact of cigarette smoke on inflammation and hyperresponsiveness of the airway.

Description of the Literature Review

For the present review, PubMed was searched for studies that focused on active smoking and asthma and were published from January 1, 2002, to December 31, 2009. The literature review obtained and reviewed studies that evaluated active smoking and the incidence of asthma, asthma status, or exacerbation of asthma in children, adolescents, or adults. The review did not include studies that focused on only respiratory symptoms and did not use a specific definition of asthma. For this review, the evidence cited in the 2004 Surgeon General's report on smoking was synthesized with newly available evidence to formulate revised conclusions.

Epidemiologic Evidence

Smoking and the Incidence of Asthma in Children and Adolescents

Because most asthma begins during childhood and adolescence, exposure to environmental risk factors during this period is of particular interest to researchers who are studying this disease. The 2004 Surgeon General's report on smoking and health reviewed 6 relevant studies; the current literature review identified 12 additional studies. Of these 12, 6 were cross-sectional studies that indicated an association between active smoking and the incidence of asthma during adolescence (Annesi-Maesano et al. 2004; Sturm et al. 2004; Avila et al. 2005; Fernandez-Benitez et al. 2007; Mallol et al. 2007; Gomez et al. 2009); no studies were found that explicitly evaluated smoking in childhood. Cross-sectional studies, however, cannot clearly separate the temporal sequence of initiating smoking and incidence of asthma, a concern because the presence of undiagnosed asthma or airway hyperresponsiveness might make adolescents less likely to smoke.

Three of the 12 new studies used population-based cohorts to evaluate the effect of active smoking on the risk of incident asthma during adolescence (Genuneit et al. 2006; Gilliland et al. 2006; Van de Ven et al. 2007), and a fourth used such a cohort to evaluate incident wheeze (Table 7.2S) (Vogelberg et al. 2007). Each of the first 3 studies associated active smoking with a higher risk of developing new-onset asthma during adolescence. However, none of these 3 studies began at birth; thus, some of the apparent incident asthma in adolescence could represent recurrence. Three of the 4 studies controlled for multiple potential confounders including socioeconomic status (SES) (Gilliland et al. 2006; Van de Ven et al. 2007; Vogelberg et al. 2007). Two studies (Genuneit et al. 2006; Gilliland et al. 2006) found strong evidence of an exposure-response relationship that involved either duration or intensity of smoking. In the analysis of the Children's Health Study in Southern California by Gilliland and colleagues (2006), the selection of different lags between smoking and asthma did not change the association of smoking with the onset of that disease.

Evidence Synthesis

The 2004 Surgeon General's report concluded that the evidence was inadequate to infer the presence or

absence of a causal relationship between active smoking and asthma during childhood or adolescence; the available studies were judged to be inconsistent and to be without adequate control for potential confounders. The new evidence reviewed in the present report links active smoking to an increased risk of developing adolescent asthma; the finding of greater risk is consistent across geographic locations, study designs, and study years. Furthermore, the cohort studies reviewed convincingly demonstrate a temporal association between active smoking and onset of asthma during adolescence, although no study followed a cohort of subjects from birth. The findings are coherent even with a variety of definitions for asthma. The evidence for an exposure-response relationship is convincing, and several studies controlled for key potential confounders. However, the number of studies is limited. As detailed in the previous section, a biologically plausible relationship exists between active smoking and new-onset asthma. The evidence is consistent with the literature on active smoking and the incidence of asthma in adults.

Conclusion

1. The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and incidence of asthma in adolescents.

Smoking and the Exacerbation of Asthma Among Children and Adolescents

Although extensive evidence implicates exposure to secondhand smoke as a cause of exacerbation of asthma among children and adults, there is less information about active smoking. Smoking is normally initiated during adolescence, and as asthma is usually first seen during childhood, active smoking during the teen years could adversely influence the clinical course of asthma soon after its onset. The 2004 Surgeon General's report on smoking and health concluded there was suggestive evidence of a causal relationship between active smoking and exacerbation of asthma among children and adolescents.

The results of three cross-sectional studies provide evidence that active smoking adversely affects control of asthma and leads to more exacerbations, as defined by asthma symptoms or use of health care for asthma (Yarnell et al. 2003; Austin et al. 2005; Navon et al. 2005). Because asthma is frequently characterized by relapse and remission, cross-sectional studies cannot definitively determine the temporal relationship between active smoking and exacerbation of the disease. Prospective cohort stud-

ies demonstrate that active smoking is associated with a higher risk of persistence of asthma in adolescence and early adulthood, but they have not explicitly examined exacerbations as an outcome (Sears et al. 2003; Bacopoulou et al. 2009).

Evidence Synthesis

Since the 2006 Surgeon General's report, only modest additional evidence has emerged for evaluating the impact of active smoking on the risk of exacerbating asthma during childhood and adolescence. Most of the data are cross-sectional and thus, temporality is in question. The evidence from adults is substantially more abundant. The additional evidence related to children and adolescents does not warrant a change in the conclusion reached in the 2004 Surgeon General's report, which is updated below.

Conclusion

1. The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and exacerbation of asthma among children and adolescents.

Smoking and the Incidence of Asthma in Adults

The 2004 Surgeon General's report on smoking and health reviewed 15 cross-sectional and 6 cohort studies that evaluated the relationship between active smoking and adult asthma (USDHHS 2004). Since that report, 10 cross-sectional studies, 2 case-control studies, and 6 cohort studies have been added to the evidence base.

In considering asthma in adults who smoke tobacco, the overlap between asthma and COPD needs to be taken into account (Figure 7.1) (GOLD 2011). Smoking is the dominant cause of COPD (USDHHS 2004), and the clinical features of COPD and asthma can overlap.

Cross-sectional studies can provide information about the association between smoking and asthma, but their findings are subject to potential limitations, including both information bias, presumably from recall bias, and the inability to clearly establish a temporal relationship between smoking and asthma. With regard to recall bias, because the presence of asthma and smoking are assessed at the same time in these cross-sectional studies, persons living with asthma may be more likely than other study participants to remember and report past smoking behavior. In addition, because asthma is often characterized by relapses and remissions, cross-sectional studies

cannot conclusively establish a causal connection between active smoking and the onset of asthma. In fact, the precise point when incident asthma develops may be difficult to identify.

Although cross-sectional studies have these limitations, they can still provide relevant evidence. Of the 10 cross-sectional studies, 9 provided evidence of an association between active smoking and prevalent asthma among adults (Chan-Yeung et al. 2002; Zhang et al. 2002; Gwynn 2004; Tutor and Campbell 2004; Aggarwal et al. 2006; Carter et al. 2006; Frank et al. 2006; Rose et al. 2006; Rahimi-Rad et al. 2008), and 1 revealed no clear association (Raherison et al. 2003). These studies represented a broad range of geographic locations, including China, Europe, India, the Middle East, the United Kingdom, and the United States.

Two case-control studies (one each from Sweden and Finland) of incident asthma found evidence of a relationship between active smoking and asthma (Table 7.3*S*). The Swedish study, a population-based examination of adult-onset asthma, found that current smoking was associated with a higher risk of adult-onset asthma (Toren et al. 2002). The study was limited, however, by its definition of adult-onset asthma, which relied on a self-reported physician diagnosis of asthma and no reported history of wheeze before 16 years of age. Also, past smoking was not evaluated as a risk factor for asthma, and SES, which was not statistically controlled, could have confounded the relationship between active smoking and asthma. Indeed, low SES has many correlates (e.g., poor diet, exposure to allergens, occupational exposure to dust or irritants, and exposure to ambient pollutants) that could act as confounders in the relationship between smoking and asthma in adults. The case-control study from Finland used a more rigorous clinical definition of adult-onset asthma that was based on physician diagnosis (using standardized clinical criteria). The study linked active smoking to a greater incidence of adult-onset asthma (Piipari et al. 2004). The study's conclusions were strengthened by controlling for a broad range of potential confounders, including SES and occupational exposures.

In addition to the two case-control studies, six cohort studies (Table 7.3*S*) have supported an association between active smoking and incident adult asthma. In Norway, a population-based cohort study of a population 15–70 years of age found that smoking was not associated with a greater incidence of asthma during an 11-year follow-up interval (Eagan et al. 2002). In a study of 1,139 New Zealand children born in 1972 and 1973 (Sears et al. 2003), smoking at 21 years of age was associated with self-reported persistent wheezing at age 21, but SES was not controlled and asthma was not specifically assessed. Butland and Strachan (2007) followed a cohort of English

children born during 1 week in 1958 by interview at 17, 33, and 42 years of age. Incident asthma was higher in former smokers and never smokers than in current smokers as would be expected from reverse causation; but odds ratios (ORs) adjusted for gender, atopy, and IgE levels were increased among smokers when wheezing or asthma were examined together as an outcome. This was largely due to the association found in the group with wheezing without asthma. In two other cohort studies, both current and past active smoking were associated with a greater risk of incident adult asthma at 10-year follow-up (Hedlund et al. 2006; Polosa et al. 2008). Hedlund and colleagues (2006), in a Swedish cohort study, controlled extensively for confounders, including SES, and demonstrated a non-significant OR for persistent smoking with significant ORs for former smokers, again demonstrating the effect of reverse causation in the population. A clinical study (Polosa et al. 2008) with careful diagnosis of incident asthma in a population with allergic rhinitis, but no asthma at the start of follow-up, demonstrated a significant increase in new diagnosis of asthma after 10 years of follow-up with an increasing odds ratio with longer duration of smoking. In a 10-year follow-up of a Japanese cohort (Nakamura et al. 2009), a statistically significant increase in self-reported, physician-diagnosed asthma was reported, which was higher than the nonsignificant association demonstrated for former smokers.

Evidence Synthesis

The 2004 Surgeon General's report concluded that evidence linking active smoking to the incidence of asthma in adults was inadequate to infer a causal relationship. Since that time, the evidence base on the impact that active smoking has on the incidence of adult asthma has expanded with two of six cohort studies showing a statistically significant effect with current smoking for incident asthma and several studies having higher rates among former smokers, raising the question of reverse causation.

Conclusion

1. The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and the incidence of asthma in adults.

Smoking and the Exacerbation of Asthma in Adults

The 2004 Surgeon General's report concluded that the evidence was sufficient to infer a causal relationship between active smoking and poor asthma control among

adults, a conclusion that was based on studies demonstrating that active smoking increased the severity of asthma, the frequency of attacks, and the use of emergency health care (i.e., emergency department visits or hospitalizations) for exacerbations. Since the 2004 report, the evidence base has grown substantially, and new reports support this conclusion.

Numerous cross-sectional studies have examined the association between active smoking and exacerbation of asthma among adults, and only one of these studies did not find such an association (Gaga et al. 2005). Multiple cross-sectional studies have found an association of active smoking (compared with not smoking) with undesirable outcomes, including more respiratory symptoms, poorer asthma control, more severe asthma, worse quality of life, greater restriction of activity, more work disability, and higher risk of acute exacerbation requiring emergency health care (Suzuki et al. 2003; Ford et al. 2004; de Vries et al. 2005; Boulet et al. 2006, 2008; Ikaheimo et al. 2006; Laforest et al. 2006; Shavit et al. 2007; Stallberg et al. 2007; Strine et al. 2007; Chaudhuri et al. 2008; Meng et al. 2008; Peters et al. 2008; Seabra et al. 2008; Jang et al. 2009; Kim et al. 2009a). In addition, the baseline comparison in a clinical trial found that persons living with asthma who smoked had more respiratory symptoms, poorer quality of life, and lower daily peak expiratory flow rates (Lazarus et al. 2007) than their counterparts who were nonsmokers.

In 1998, the Copenhagen City Heart Study found that active smokers with asthma had a greater longitudinal decline in lung function, as measured by FEV_1, than nonsmokers with asthma (Lange et al. 1998). Two other prospective cohort studies have confirmed that adult asthmatics who actively smoke have a more rapid decline of FEV_1 than nonsmoking adults with asthma (Table 7.4*S*) (Apostol et al. 2002; James et al. 2005). In addition, a short-term follow-up study observed greater improvement in lung function among adults with asthma who quit smoking than among those who continued to smoke (Chaudhuri et al. 2006). Long-term decline in lung function does not necessarily reflect acute exacerbations, but these studies do establish that active smoking adversely affects the long-term natural history of adult asthma.

Other cohort studies provide evidence that active smoking confers a higher risk of exacerbation (Table 7.4*S*). Two studies found that active smoking was related to a higher risk of acute exacerbation that required emergency health care (Diette et al. 2002; Eisner and Iribarren 2007), and one of these studies (Eisner and Iribarren 2007) found that current smoking was related to greater severity of asthma. In another report from the same cohort used in the study by Eisner and Iribarren (2007), active smoking was associated with a higher risk of complete work disability (Eisner et al. 2006). Elsewhere, a small study

found that active smoking was associated with a lower likelihood of asthma remission (Ronmark et al. 2007). One other cohort study (de Marco et al. 2006), however, found no association between change in smoking habits and severity of asthma at follow-up, as evidenced by the Global Initiative for Asthma (GINA) classification; but that study was underpowered, and the GINA classification is not a validated measure of disease severity for epidemiologic studies.

Cohort studies of adults with asthma have linked active smoking to death from respiratory causes (Omachi et al. 2008) and all-cause mortality (Bellia et al. 2007; Omachi et al. 2008). Although death was not clearly from asthma in these studies, these data indicate that smoking adversely affects life span in adult asthma.

Several randomized controlled trials have evaluated the differential efficacy of asthma therapy in smokers and nonsmokers. Of three trials that evaluated the impact of inhaled corticosteroids in smokers and nonsmokers, two were placebo-controlled (Chalmers et al. 2002; Lazarus et al. 2007), and one compared high- and low-dose therapy (Tomlinson et al. 2005). In the placebo-controlled trials, inhaled corticosteroids had no clinical benefit among smokers, as measured by the primary study endpoint (postbronchodilator FEV_1 and morning peak expiratory flow rate, respectively) (Chalmers et al. 2002; Lazarus et al. 2007). In addition, these trials did not find any benefits for secondary outcomes among nonsmokers, including bronchial hyperresponsiveness (Chalmers et al. 2002; Lazarus et al. 2007) and quality of life (Lazarus et al. 2007). Another trial, which compared high-dose and low-dose beclomethasone (2,000 micrograms [mcg] vs. 400 mcg per day), also found that smoking attenuated the efficacy of inhaled corticosteroids (Tomlinson et al. 2005). Low-dose therapy improved the primary outcome (morning peak expiratory flow rate) among nonsmokers only. Furthermore, the efficacy of high-dose beclomethasone was greatly attenuated in smokers. Elsewhere, a randomized controlled trial of oral corticosteroids (prednisolone 40 milligrams daily) versus placebo found that active smokers had no improvement in FEV_1, daily peak expiratory flow rate, and asthma control, but nonsmokers experienced improvements in all three of these outcomes (Chaudhuri et al. 2003).

Evidence Synthesis

The 2004 Surgeon General's report concluded that the evidence was sufficient to infer a causal relationship between active smoking and both poor asthma control and exacerbation of disease among adults. Subsequently, the evidence base has grown and continues to support this conclusion. Currently, there is substantive evidence of

coherence across a broad range of study outcomes, including such diverse endpoints as lung function, severity of disease, use of emergency health care, and quality of life. Randomized controlled trials provide strong evidence that smoking attenuates the therapeutic response to inhaled and systemic treatment with corticosteroids. Together, evidence from observational and clinical trials shows that active smoking adversely affects the natural history of adult asthma.

Conclusion

1. The evidence is sufficient to infer a causal relationship between active smoking and exacerbation of asthma in adults.

Implications

Asthma is one of the most common chronic diseases of childhood. Asthma is also common among adults. Incidence of asthma is generally highest during childhood, but new cases occur among adults, too. The evidence reviewed in this chapter identifies active smoking as a possible cause of new-onset asthma among adolescents. The chapter also concludes that smoking is a cause of exacerbation of asthma among adults.

The evidence reviewed in this chapter shows that smoking should be considered an avoidable cause of asthma and that people who smoke should be counseled on the potential risk for developing asthma, should they continue to smoke.

Asthma is a chronic disease with a course marked by exacerbations—that is, deterioration—of the disease. Such exacerbations may lead to substantial morbidity and to economic costs from absenteeism, and can result in death. The evidence reviewed in this chapter is sufficient to conclude that active smoking exacerbates asthma in adults. The clinical implications are clear: people with asthma should not smoke.

Tuberculosis

Tuberculosis (TB) was a leading cause of death in the United States at the start of the twentieth century, a time when cigarette smoking was just beginning to become popular among men. Although rates of TB and smoking are both continuing to decline in the United States, the two epidemics continue globally. More than 1.3 billion people worldwide smoke (World Health Organization [WHO] 2010), and estimates indicate that each year sees almost 9 million cases of incident TB and 1.3 million deaths from the disorder (Mathers and Loncar 2006). Moreover, an estimated one-third of the world's population is infected with *Mycobacterium tuberculosis* (*M. tuberculosis*) and, therefore, is at risk of active TB disease. Annually, more than 30% of TB cases worldwide are diagnosed in China and India. These two countries account for more than 40% of the world's smokers (WHO 2008).

Smoking has long been considered a potential risk factor for TB mortality (Doll and Hill 1956), but only recently have large case-control and cohort studies shown that strikingly high rates of TB mortality are attributable to smoking (Jha et al. 2008). Several systematic reviews have assembled evidence of the association between smoking and TB (Davies et al. 2006; Bates et al. 2007; Chiang et al. 2007; Lin et al. 2007; Pai et al. 2007; Slama et al. 2007; WHO and International Union Against Tuberculosis and Lung Disease 2007). Each review found that cigarette smoking is associated with an approximate doubling of risk for TB infection, for having clinical evidence of TB disease, and for TB mortality. An analysis from WHO (2010) of the role of risk factors and social determinants in driving the global TB epidemic concluded that in the 22 countries experiencing 80% of the global TB burden, 23% of the cases can be attributed to smoking. The smoking-attributable burden of TB varies with the epidemiologic characteristics of the population, with the high attributable risks for smoking found in China and India, while HIV is the primary driver for the TB burden in sub-Saharan Africa (Lonnroth et al. 2010). To date, the series of Surgeon General's reports has not systematically assessed the association between smoking and TB.

Biologic Mechanisms

Given its effects on host defenses and the structure and function of the lungs, smoking is a biologically plausible cause of morbidity and mortality from TB (Pai et al. 2007; Stampfli and Anderson 2009; USDHHS 2010). The section on "Immune Function and Autoimmune Disease" in Chapter 10 of this report more fully describes the

effects of smoking on the immune system, indicating multiple underlying mechanisms that may increase the risk for TB in smokers. However, the specific mechanisms by which cigarette smoking may influence risk of infection by *M. tuberculosis* and reactivation of latent TB infection are not completely understood.

Natural History of Tuberculosis

Figure 7.7 shows the natural history of TB from exposure to the organism and the initial infection through death from the disease. Figure 7.8 offers a closer look at the progression to active TB disease among persons exposed to *M. tuberculosis*. In brief, TB follows a two-stage process: infection of the host with *M. tuberculosis* and then the development of active disease (Golub et al. 2013). Infection occurs in an estimated 20–30% of close contacts of people with active disease, and within 2 years, active primary TB develops in 5–10% of those infected (Figure 7.8A) (Comstock et al. 1974; Comstock 1975). However, TB is a unique pathogen in that the first stage of this process can last a lifetime. In what is commonly referred to as latent TB infection, an intact immune system contains the primary infection in a dormant state. Over the course of an infected person's life, the risk that the dormant bacilli will progress to reactivation TB is 5–10% (Comstock et al. 1974; Comstock 1975). People who are immunocompromised have an altered prognosis after infection, with more than 40% experiencing early progression (Figure 7.8B) and the majority reactivating to TB disease later in life if untreated.

Upon developing active TB disease, a small proportion of persons will spontaneously heal without treatment, but without treatment, the majority will ultimately die. Among persons who are treated for TB, treatment failure and/or recurrent disease are serious risks. Recurrence can result from endogenous reactivation of persistent TB bacilli (relapse) or from exogenous reinfection with a new TB strain.

Description of the Literature Review

An initial search of English publications in PubMed was conducted using the key terms "smoking" OR "tobacco" AND "tuberculosis." These broad terms were searched in titles and abstracts. For purposes of reviewing the evidence of smoking as a risk factor for TB infection, TB disease, recurrence, and/or mortality, articles were excluded if they addressed other aspects of the effects of tobacco use on TB severity, treatment, or outcomes without providing evidence of risk. Such articles are discussed in this chapter as appropriate but are not included in the evidence tables (Tables 7.5*S*–7.8*S*). In addition to the PubMed search, references that were included in the systematic reviews and meta-analyses were reviewed, and any publications not previously identified were included. The literature search extended through December 2009.

Epidemiologic Evidence

Risk Factors: Potential Confounders and Modifiers

Three of the major risk factors for TB exposure and infection are predominantly related to SES: immunocompromising diseases, malnutrition, and alcohol consumption. SES itself is another important risk factor, serving as a proxy for many correlates. Attention to these four risk factors is critical in investigating smoking and risk of TB and in ensuring that confounding is considered and interactions with smoking are addressed.

TB and Alcohol Consumption and Tobacco Use

Alcohol consumption and tobacco use have been consistently linked over time, and an association between alcohol use and TB has long been observed. Lonnroth and colleagues (2008) and Rehm and colleagues (2009) reported a strong association between heavy alcohol use and incident TB, citing the pathogenic impact of alcohol on the immune system, which increases risk of reactivation TB. Based on patterns of increased risk ratios for TB, early studies (Brown and Campbell 1961; Lewis and Chamberlain 1963) suggested that alcohol use was the most important risk factor and that tobacco use was only important because most alcoholics in the studies also smoked. The majority of subsequent studies have shown an association between tobacco use and TB disease even when alcohol is considered in the analysis, but the association may be diminished by controlling for alcohol (Lin et al. 2007). Among the prospective cohort studies, one in Korea found alcohol use to be a strong independent risk factor for TB (Jee et al. 2009), and in a study in Taiwan, alcohol use was a stronger risk factor than smoking (Lin et al. 2009a). In both studies, however, smoking was a strong independent risk factor after adjusting for alcohol consumption.

The extent to which alcohol use has been considered as a potential confounding factor for the risk of TB has varied greatly among studies. Despite a lack of uniformity in how alcohol use is addressed, most studies have found

Figure 7.7   Natural history of tuberculosis from exposure to mortality
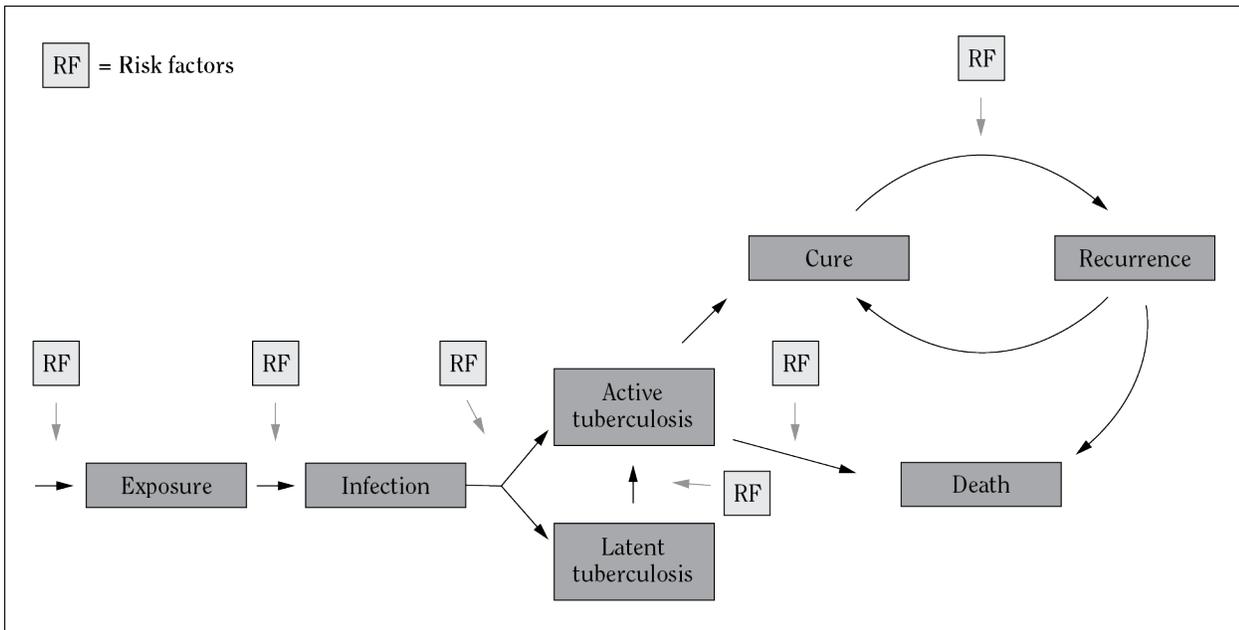
Source: Adapted from Rieder 1995 by the Center for Teaching and Learning with Technology, Johns Hopkins Bloomberg School of Public Health with permission from Springer Science & Business Media B.V., © 1995.

Figure 7.8   Progression to active tuberculosis disease among persons exposed to *M. tuberculosis*
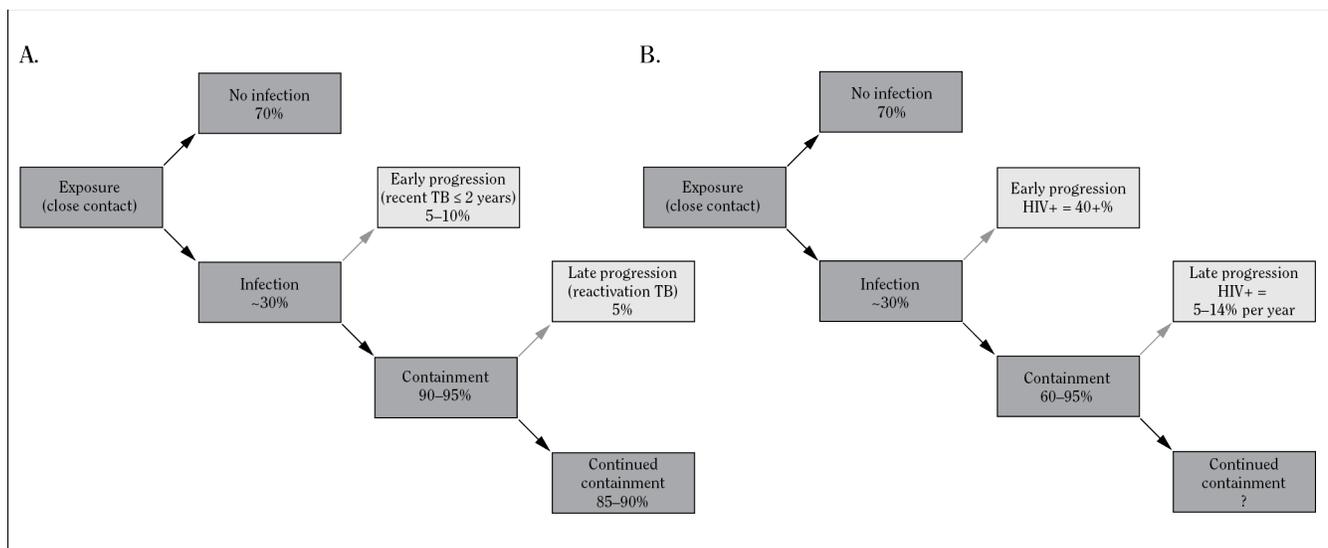
Source: Adapted from Parrish et al. 1998 with permission Elsevier, © 1998.
Note: **HIV** = human immunodeficiency virus. Progression to active tuberculosis disease among (A) healthy persons or (B) immuno-compromised persons exposed to *M. tuberculosis*.

a consistent positive association between smoking and TB after adjusting for alcohol consumption. For example, Gajalakshmi and Peto (2009) conducted a comprehensive investigation of smoking and alcohol use and the risk of TB in India and found that the risk of incident TB was 3.5 times greater for people who were both drinkers and smokers than for those who were not smokers or drinkers. Nondrinking smokers had an RR of 2.6, and nonsmoking drinkers had an RR of 2.1. In a retrospective multilevel analysis of data from the South African Demographic and Health Survey, Harling and colleagues (2008) reported high rates of TB among smokers and alcohol users after adjusting for many factors, including a multilevel adjustment for SES.

TB and Socioeconomic Status

Although poverty is often cited as a risk factor for TB infection and disease, it is best seen as a proxy for multiple other relevant factors, including population density, race/ethnicity, nutritional status, and access to health care. In many countries, those who are poor are more likely to both smoke and to have higher rates of TB infection and disease than those of a higher SES (Chapman and Dyerly 1964; Kuemmerer and Comstock 1967). Harling and colleagues (2008) conducted a multilevel analysis of the impact of demographic, behavioral, and socioeconomic individual risk factors and of group-level measures of SES on risk for TB. This study combined data from the 1998 South African Demographic and Health Survey with data from the 1996 South African national census. Although the study relied on the potentially biased outcome of self-reported TB and linked two cross-sectional studies, it provided a comprehensive analysis of the SES–TB relationship. After adjusting for SES, both alcohol abuse and cigarette smoking were associated with risk for TB. In a meta-analysis, Lin and colleagues (2007) found that the association between smoking and TB mortality was stronger in studies that adjusted for SES than in those that did not, suggesting that not considering SES may lead to an underestimation of measures of association. After adjusting for SES, this same review did not find a difference in risk for pulmonary TB disease associated with smoking. However, the authors did not assess the quality of the SES measurements in each study, thus potentially limiting the interpretation of this summary adjustment.

TB and Gender

Some studies suggest that smoking may account for differences observed between men and women in TB incidence and mortality, primarily because, compared with women, smoking is substantially more common among men, and on average men smoke a greater number of cigarettes. In one of the first studies to investigate the relationship between smoking and TB disease, Lowe (1956) reported a greater proportion of heavy smokers among men than women, but TB cases were more likely to be observed in heavy smokers of either gender compared with controls. Lowe did not observe a significant difference between the smoking habits of cases and controls among persons younger than 30 years of age; this evidence suggests that smoking is a strong contributor to the reactivation of TB in older ages but a weaker contributor to the reactivation at younger ages. Yu and colleagues (1988) also identified differences in risk for TB by age and gender that were attributed to tobacco use, and Nisar and colleagues (1993) suggested that smoking may be a key factor in higher TB disease rates among men because (a) men smoke more than women, and (b) smoking likely increases risk of TB infection, which is a necessary precursor to actual TB disease. More recently, Crampin and colleagues (2004) assessed differences among risk factors for men and women in Malawi. Finally, Lin and colleagues (2009b), in their systematic review and meta-analysis, suggested that smoking may be the cause of gender differences in TB disease because the odds ratio (OR) for men (vs. women) decreased from 1.62 to 1.06 after adjusting for current smoking.

Tobacco and TB

Evidence on tobacco and the natural history of TB suggests that tobacco may affect disease risk at each stage of the disease process, as reviewed below. Consequently, the evidence is considered separately for each stage of TB disease.

Tobacco and TB Infection

To date, evidence on the association between tobacco use and TB infection is limited (Table 7.5*S*). Establishing a temporal relationship between exposure to tobacco smoke and the onset of *M. tuberculosis* is difficult because determining when a person becomes infected is almost impossible—unless this is determined as part of a contact investigation of a person with active TB disease. Only one study, a case-control study of prison inmates in South Carolina carried out by Anderson and colleagues (1997), used smoking data that were collected before assessing the acquisition of *M. tuberculosis*. This study compared two groups. The case group was composed of those who were tuberculin skin test (TST) negative upon incarceration but were found to be TST positive at a follow-up reading. The control group was composed of those with a TST reading that remained negative. Those who developed a

positive TST were assumed to have become infected with TB while incarcerated. After adjusting for age and living conditions, current smokers were more likely to have converted their TST (OR = 1.78; 95% confidence interval [CI], 0.98–3.21) than the reference group (never and past smokers). In addition, inmates who had smoked for more than 15 years had twice the odds of converting their skin tests (OR = 2.12; 95% CI, 1.03–4.36) as the reference group (nonsmokers), suggesting that the cumulative effects of long-term smoking have a greater impact on risk than the number of cigarettes smoked per day. One major limitation of this study was that cases were more likely than controls to have been previously exposed to people with TB, a risk factor for infection that was not controlled for in the analysis.

Only three studies had the primary objective of investigating the association between smoking and latent TB infection (Anderson et al. 1997; Plant et al. 2002; den Boon et al. 2005). The study in South Africa by den Boon and colleagues (2005) reported an almost twofold increased risk for latent TB infection among adults who were ever smokers. However, because of the cross-sectional design of the study, researchers could not determine whether the association was temporally correct (i.e., that smoking came before infection). Additionally, smoking may affect the size of the TST and thus the chance for a positive finding, and cross-sectional data are subject to differential survival from higher losses of heavier smokers or of persons with more severe primary infection. Hussain and colleagues (2003) performed a cross-sectional study of prisoners in Pakistan, a region with a moderately high burden of TB that is not influenced substantially by HIV infection. They found an increased risk for latent TB infection among current smokers, with the OR rising from 2.6 for those who smoked 1–5 cigarettes per day to 3.2 for those who smoked more than 10 cigarettes per day.

In a study of Vietnamese immigrants, Plant and colleagues (2002) detected an increased risk of latent TB infection among those who were ever smokers. The strongest ORs were reported among people with a TST induration cutoff of 5 millimeters (mm) (OR = 2.31; 95% CI, 1.58–3.38). The ORs were lower for those with cutoffs of 10 mm (OR = 1.53; 95% CI, 1.13–2.09) or 15 mm (OR = 1.37; 95% CI, 0.95–1.97), which are categories less likely to be contaminated with infections from non-TB mycobacteria. The researchers concluded that smoking increases the risk of mycobacterial infections, of which TB is likely to be the primary contributor. Although smaller tuberculin reactions may be associated with non-TB mycobacteria, smokers may have smaller reactions because of the effects of smoking on cell-mediated immunity. The study reported a 3–5% increase in risk of TB infection per year of smoking exposure.

The majority of studies that have addressed smoking and latent TB infection have not had smoking as the primary exposure of interest but do provide relevant evidence. For example, Kuemmerer and Comstock (1967) noted that children who were living in households where both parents smoked were twice as likely to be infected latently with TB as those who were living in a household with one or no parent smoking. Although the study found that crowding and prior household exposure to TB increased the risk of infection, it did not adjust for these potential confounding factors. In India, Singh and colleagues (2005) investigated the prevalence of TB infection among children of adults with pulmonary TB. For such children, it is well-accepted that a positive TST is the result of recent exposure to TB, and thus exposure to cigarette smoke was likely at the time of acquisition of TB infection. Children exposed to a household TB patient who smoked were almost three times as likely as their counterparts to be infected with TB. Children of adults who smoked and were sputum positive for TB were more likely to be infected than children of adults who did not smoke but were sputum positive for TB, suggesting that smoking raises the risk of TB infection beyond the strong risk of exposure to a highly infectious TB case. A study in South Africa by den Boon and colleagues (2007) suggests that smoking adds to the infectiousness of persons with TB. This study found more than a fourfold increased risk (OR = 4.60; 95% CI, 1.29–16.45) of latent TB infection among children living with an active TB case who were exposed to secondhand smoke (vs. no such exposure). In households without a current TB case, passive smokers were at a moderately increased risk of latent TB infection, but the risk decreased and was not statistically significant after adjusting for other factors.

Nisar and colleagues (1993), who investigated the potential increased risk of latent TB infection among nursing home residents in the United Kingdom, found evidence that smoking increases the prevalence of TB infection in elderly persons and may explain higher rates of positive TB cases in men compared with women. Current smokers had greater TB infection rates than former smokers, who had greater rates than never smokers. The study also found an association between increasing pack-years and increased prevalence of latent TB infection. Length of stay, however, was not associated with increased prevalence of latent TB infection.

Several studies have investigated risk factors for latent TB infection among people in prisons and homeless shelters. In their study of prisoners in Pakistan, Hussain and colleagues (2003) reported weak evidence of a dose-response relationship—with ORs of 2.6, 2.8, and 3.2 for latent infection among current smokers of 1–5, 6–10,

and more than 10 cigarettes smoked per day, respectively. Among prisoners in Lebanon, a study by Adib and colleagues (1999) found a modestly increased risk of latent TB infection (OR = 1.2; 95% CI, 1.1–1.3) among current smokers but no indication of a dose-response relationship with amount smoked. In their study of South Carolina inmates, Anderson and colleagues (1997) reported an almost twofold increased risk of latent TB infection (OR = 1.78; 95% CI, 0.98–3.21) among current smokers (vs. never and former smokers). Similarly, in a homeless population with a 75% rate of latent TB infection in Barcelona, Spain, Solsona and colleagues (2001) found an increased risk (OR = 1.72; 95% CI, 1.02–2.86) of infection among current smokers. In a study of migrant workers in California, McCurdy and colleagues (1997) found a threefold increased risk of latent TB infection among former smokers (OR = 3.11; 95% CI, 1.20–8.09) but less than a twofold increase (OR = 1.87; 95% CI, 0.73–4.80) among current smokers.

Tobacco and TB Disease

This section reviews studies of evidence on the association between smoking and clinical TB, with a focus on prospective cohort studies (Table 7.6*S*).

In studies in Hong Kong, Leung and colleagues (2003, 2004, 2007) investigated the association between smoking and TB disease in younger (≤64 years of age) and older (>64 years of age) TB patients and among people with silicosis (a population at high risk for TB). In most of the populations, smokers had an approximately twofold increased risk for TB, and although alcohol use was a strong contributor to TB risk in each study, smoking had a strong, independent effect after controlling for alcohol consumption. Although former smokers had a lower risk for TB than current smokers, time elapsed since quitting did not affect risk for TB (Leung et al. 2007).

A few studies have specifically addressed the change in risk for TB upon quitting smoking. Based on a follow-up of the British Doctors' Study, Doll and colleagues (1994) reported a 2.8 mortality ratio among current smokers compared with nonsmokers, and a 2.0 mortality ratio among former smokers compared with nonsmokers (Table 7.8*S*). Prospective cohort studies with large populations and many years of follow-up offer the strongest evidence of a link between smoking and TB. In a cohort based in Taiwan's NHIS, Lin and colleagues (2009a) found a twofold increased risk for TB among current smokers compared with never smokers after controlling for several risk factors. Risk was only slightly diminished for ever smokers. Alcohol use was controlled for in the analysis and reported to be a much stronger risk factor for TB than smoking, although smoking remained associated with TB

after controlling for alcohol consumption. In Taiwan, the OR for TB among elderly smokers was 0.78, versus 2.87 for the comparable group in Hong Kong (Leung et al. 2004). This risk difference cannot be attributed to smoking intensity, because the elderly in Taiwan smoked 15 cigarettes per day compared with 11 by those in Hong Kong.

Jee and colleagues (2009)—who conducted a cohort study in Korea using the Korean Cancer Prevention Study of more than 1.3 million middle-class, primarily middle-aged men and women—found increased risk for incident TB disease among male current smokers but not among their female counterparts. The analysis considered alcohol use as a potential confounder and found a dose-response relationship between use of alcohol and amount smoked. Although SES was not included in the Korean analysis, little variability was expected within this relatively homogenous and middle-class population.

Several studies, mostly case-control in design, conducted in India found a strong risk for TB among smokers. When evaluating studies in India and some other countries, the types of products smoked need specific consideration because individuals may smoke cigarettes or bidis, the latter the most common type of smoked tobacco in India, or both. With TB mortality as the outcome of interest, Gupta and colleagues (2005) found that smoking bidis was not less hazardous than smoking cigarettes and that the duration of bidi smoking conveyed greater risk for TB mortality than did the number of bidis smoked per day (Table 7.8*S*). After adjusting for several sociodemographic factors in a population of primarily low and middle socioeconomic classes, Prasad and colleagues (2009) reported a fourfold increased risk for TB among current smokers in a case-control study. The study also found a strong dose-response relationship between increasing pack-years and duration of smoking on risk for TB. However, the analysis found that the number of cigarettes or bidis smoked per day did not affect risk for TB. The authors concluded that the effects of smoking for a prolonged period of time are more important to the development of TB disease than a large number of cigarettes smoked per day.

The effect of passive smoking on risk for TB disease has been reported in several settings. Studies among children are informative because both TB infection and TB disease in children are considered to have been recently acquired. Altet and colleagues (1996), who conducted a case-control study that investigated the effect of passive smoking on the development of TB disease among recently infected children of active smokers, found that exposure to passive smoke increased risk for TB disease fivefold, with the greatest risk among children younger than 10 years of age. Similarly, Kuemmerer and Comstock (1967) reported an increased risk for TB disease among

children exposed to two parents who smoked, compared with one or no parent who did so (Table 7.5S). A strong dose-response relationship was found between risk for TB and an increasing number of cigarettes smoked to which children were exposed per day. This study was one of a few to use a biological marker for measuring tobacco exposure, finding that mean levels of cotinine in the urine were significantly greater among contacts that developed TB disease. Use of a biomarker removes potential bias associated with self-reported exposure to tobacco.

In a study by Alcaide and colleagues (1996) that addressed the combined risk of TB among young adults who were exposed to both active and passive smoking (Table 7.6S), active smokers who were contacts of pulmonary TB cases had a 3.6-fold increased risk of developing TB, but those exposed to both active and passive smoking had an OR of 5.1. In a study in Thailand among children younger than 15 years of age, Tipayamongkholgul and colleagues (2005) found a ninefold increased risk for TB disease with close passive exposure to smoke and no known direct contact with a person with TB. In another study from Thailand, in a comparison with nonsmokers and after adjusting for body mass index, Ariyothai and colleagues (2004) found that passively exposed adult smokers were at increased risk for TB (OR = 2.37; 95% CI, 0.94–6.01). The adjusted risks among current (OR = 2.70; 95% CI, 1.04–6.97) and former smokers (OR = 2.88; 95% CI, 0.85–9.78) did not differ materially. Exposure to secondhand smoke in the outdoors or in an office was a more significant factor than such exposure in the home, but very few study participants reported this kind of exposure in the home. By contrast, in a study in Estonia, Tekkel and colleagues (2002) found that exposure to secondhand smoke in the office was not associated with risk of pulmonary TB, but exposure to smoke in the home was associated with a twofold increased risk.

Several studies have included smoking as a potential risk factor for TB in investigations in which smoking was not the primary exposure of interest. For example, in three West African countries, Lienhardt and colleagues (2005) conducted a case-control study on host-related and environment-related factors for TB. After adjusting for various host and environmental factors, current and former smokers had increased risks for TB, about a doubling and a 50% increase, respectively. The study observed a significant dose-response relationship between incidence of TB and three factors: duration of smoking, alcohol use, and drug use. In a study of a population in King County, Washington, Buskin and colleagues (1994) did not find excess risk for TB among smokers after adjusting for age and alcohol consumption. However, among current smokers, the authors observed a dose-response relationship

with number of cigarettes smoked per day and number of years of smoking. In China, as part of a mass routine chest radiograph campaign in Shanghai, Yu and colleagues (1988) found heavy smokers to have a twofold increased risk for pulmonary TB (RR = 2.17; 95% CI, 1.29–3.63), but light and moderate smokers did not have an excess risk. Much earlier, Adelstein and Rimington (1967) conducted a mass chest radiograph survey in East Cheshire, United Kingdom, and found that male smokers had a fivefold increased risk for TB compared with nonsmokers, but a very small number of TB cases limited the analyses.

Tobacco and Recurrent TB Disease

The literature investigating smoking as a risk factor for recurrent TB disease is limited and not all studies differentiate between relapse and disease resulting from reactivation of an exogenous reinfection (Table 7.7S). Thomas and colleagues (2005), who investigated predictors of relapse among pulmonary TB patients who had completed therapy in a Directly Observed Treatment, Short course program in South India, found that smoking was associated with increased risk for relapse (OR = 3.1; 95% CI, 1.6–6.0). The authors found three risk factors to be associated with increased risk of TB recurrence: smoking, drug sensitivity profile, and adherence level to TB therapy. Age, gender, education, alcohol use, and initial weight were not associated with increased risk. In a similar study in Brazil, d'Arc Lyra and colleagues (2008) reported an increased risk for relapse among ever smokers (current smokers and former smokers who had given up smoking less than a year from time of interview) compared with never or former smokers (those who had given up smoking 1 year or more) (OR = 2.34; 95% CI, 1.17–4.68). These studies (Thomas et al. 2005; d'Arc Lyra et al. 2008) adjusted for several socioeconomic factors, but none were associated with increased risk for TB relapse.

In their Hong Kong study of tobacco and TB in the elderly, Leung and colleagues (2004) reported an increased risk (OR = 2.48; 95% CI, 1.04–5.89) of being retreated for TB—in this study assumed to be a relapse—among current smokers compared with never smokers after adjusting for many factors, but not SES. Elsewhere, two studies (Chang et al. 2004; Millet et al. 2009) that did not clearly define smoking and appeared to rely on an "ever" versus "never" classification did not find smoking to increase risk of relapse. In Korea, the cohort study by Jee and colleagues (2009), the largest to date to investigate the risk for recurrence in smokers and nonsmokers, used long-term follow-up of cohort members with past TB to investigate recurrent TB, including both relapse and potentially exogenous reinfection. In the study, men who

were current smokers had moderately increased risk for recurrence (hazard ratio [HR] = 1.3; 95% CI, 1.2–1.4), but risk was not significantly increased among women who were current smokers, although the HR was of a similar magnitude as that for men (HR = 1.2; 95% CI, 0.8–1.6). Heavy alcohol consumption was associated with recurrent TB in men in this study (HR = 1.2; 95% CI, 1.0–1.3).

Tobacco and TB Mortality

The literature assessing risk of mortality among smokers with TB is somewhat limited, and most studies have not accounted for potential confounding factors, such as delays in diagnosis, HIV infection, or site of disease (Table 7.8S). When Doll (1999), Doll and Hill (1954, 1956, 1964), and Doll and colleagues (1994) began their study of a cohort of British physicians in 1951, treatment for TB was just beginning, and physicians were at high risk from occupational exposure (from their patients). Pulmonary TB was one of more than 25 diseases found in this long-term study to be linked to cigarette smoking. Mortality rates for TB observed after 5 years of follow-up showed trends similar to those observed more than 40 years later (Doll and Hill 1956; Doll et al. 1994). In both the 1956 and 1994 reports, TB mortality rates were elevated in older men who were smokers, and a dose-response relationship was observed with daily amount smoked, with TB mortality as high as 29/100,000 in 1956 and 20/100,000 in 1994 in the group reporting the highest levels of smoking in 1951.

In China, in a retrospective cohort study that assessed the impact of tobacco on the deaths of 1 million people, male smokers had a moderately increased risk for TB mortality compared with their nonsmoking counterparts (RR = 1.20; SE = 0.04) (Liu et al. 1998). The study found a similar, albeit not significant, risk among female smokers (RR = 1.29; SE = 0.08). Urban dwellers of both genders had a higher risk for TB mortality (RR = 1.42; SE = 0.05 for males and RR = 1.56; SE = 0.09 for females) than did those in rural areas. In Hong Kong, a case-control study found, after adjusting for age and education, a 2.5-fold increased risk for TB mortality among middle-aged men and a nonsignificantly increased risk among similarly aged women (Lam et al. 2001). In this study, a strong dose-response relationship with numbers of cigarettes smoked per day was observed among both middle-aged and elderly men. The study identified very few deaths from TB among women, limiting analyses of smoking and TB. In Korea, the cohort study by Jee and colleagues (2009) found that mortality increased 58% in men (HR = 1.58; 95% CI, 1.27–1.97) and 55% in women (HR = 1.55; 95% CI, 1.00–2.41) who were current smokers. Among former smokers, risk of mortality doubled among women

(HR = 2.16; 95% CI, 1.35–3.46).

In India, Gajalakshmi and colleagues (2003) and Gupta and colleagues (2005) used different sources of data to attribute between 140,000 and 149,000 TB deaths per annum to smoking, a number that represents half of annual deaths from TB in India. Later, in a nationally representative study in India, Jha and colleagues (2008) attributed 38% of TB deaths among men to smoking. Compared with never smokers, TB mortality increased between twofold and fourfold among male smokers (Gajalakshmi et al. 2003; Jha et al. 2008) and threefold among female smokers (Jha et al. 2008).

Finally, a study in Africa by Sitas and colleagues (2004) compared deaths from diseases known to be associated with tobacco use with deaths from medical conditions unrelated to tobacco use and found that, among deaths from TB, 28% of those for men and 7% of those for women were attributable to smoking. The authors found that smoking was associated with an increased risk of mortality (OR = 1.61; 95% CI, 1.23–2.11).

Tobacco and Type/Severity of TB Disease

Although the association between tobacco use and TB disease has been widely investigated, available studies have not clarified whether smoking affects risk only for pulmonary or also for extrapulmonary TB. In Hong Kong, Leung and colleagues (2004) reported that male current smokers were three times as likely as male never smokers to develop pulmonary TB but were significantly less likely to develop extrapulmonary TB. Later, Lin and associates (2009b) confirmed these results in a study in Taiwan, finding that nonsmokers had increased risk for extrapulmonary TB. In a study in Nepal, Sreeramareddy and colleagues (2008) found that current smokers were 66% less likely to develop extrapulmonary TB than they were pulmonary TB, and this pattern extended to those who had quit smoking 6 months before TB diagnosis (OR = 0.45; 95% CI, 0.21–1.09 for extrapulmonary vs. pulmonary TB). Researchers in a study from Turkey reported similar findings (OR = 0.54; p = 0.025 for an extrapulmonary site vs. a pulmonary site) (Musellim et al. 2005). The meta-analysis by Lin and colleagues (2007) found a higher risk of TB, both pulmonary and extrapulmonary, in smokers than in nonsmokers. When studies were restricted to those that included only pulmonary TB cases, the association was stronger than was found when studies that included both pulmonary and extrapulmonary TB cases were considered (2.01 vs. 1.49). This difference did not reach statistical significance.

One study addressed smoking and the severity of TB. Among a cohort of more than 13,000 TB patients in Spain, Altet-Gomez and colleagues (2005) reported that

smokers were 50% more likely than nonsmokers to develop pulmonary disease and almost twice as likely to have cavitary disease.

Evidence Synthesis

Evidence on the relationship between smoking and TB needs to be assessed within the framework offered by the natural history of the infection. Smoking may have an effect at multiple stages of this natural history (Figure 7.7), and thus the evidence should be considered separately for the risks of TB infection, TB disease, recurrent TB disease, and TB mortality (see Table 7.9 for a summary of evidence from three systematic reviews on the association between smoking and three TB outcomes: infection, active disease, and mortality due to TB [van Zyl Smit et al. 2010]). This framework focuses on two questions: (1) Is the risk of incident TB infection higher in smokers than in nonsmokers, and (2) in persons with TB infection, does the course of TB infection differ between smokers and nonsmokers with regard to risk for TB disease, recurrence, and mortality?

TB Infection

The available studies consistently show that smokers are at a greater risk for TB than nonsmokers (RR = 1.2–2.7), but all but one of the studies are cross-sectional in design, leaving the temporality of causation ambiguous. Only the nested case-control study among TST converters found that smoking occurred prior to incident infection (Anderson et al. 1997). The literature has not consistently demonstrated dose-response relationships between TB infection and the number of cigarettes smoked per day or pack-years. Adjusting for alcohol consumption as a potential confounder reduced the strength of the association between tobacco and latent TB infection in a meta-

analysis, but the association remained significant (Lin et al. 2007).

Biologic evidence supports the plausibility of increased risk for TB infection among smokers because tobacco smoke has been shown to cause mechanical disruption of ciliary function, alter mucociliary clearance in the airways (Arcavi and Benowitz 2004), and inhibit macrophage responses, thus increasing the likelihood that *M. tuberculosis* organisms reach the alveoli where TB infection begins (Altet et al. 1996). Although such factors as age, gender, and SES have also been associated with risk of TB infection, smoking has been shown to be an independent risk factor. Exposure to an infectious TB case is necessary for TB infection to occur, but collective evidence suggests that persons exposed to tobacco smoke, either actively or passively, are at greater risk of becoming infected with TB than those who are not exposed to tobacco smoke.

TB Disease

The evidence reviewed in this section implicates smoking as a cause of TB disease. The infectious organism that causes tuberculosis, *M. tuberculosis*, is, of course, the necessary cause of TB. However, other agents can increase risk for TB by acting to increase the risk for infection or by increasing the risk for disease in those who are infected. Within the framework for causal inference used in the Surgeon General's reports, such additional risk factors that are neither necessary nor sufficient have been interpreted as causal. For example, the 2004 report identified smoking as a causal risk factor for cervical cancer, while acknowledging the necessary role of human papilloma virus (USDHHS 2004). Cohort studies showed that human papilloma virus-infected women who smoked developed cervical intraepithelial neoplasia at a higher rate than nonsmokers. The evidence on smoking and TB is thus interpreted

Table 7.9   Meta-analysis of the association between smoking and latent tuberculosis (TB) infection, progression to active disease, and mortality from active TB

Outcome	Pooled RR (95% CI)		
	Slama et al. 2007	Lin et al. 2007	Bates et al. 2007
TB infection	~ 1.8 (1.5–2.1)	1.7–2.2 (1.5–2.8)	~ 1.7 (1.5–2.0)
TB disease	~ 2.3 (1.8–3.0)	~ 2.0 (1.6–2.6)	~ 2.3 (2.0–2.8)
TB mortality	~ 2.2 (1.3–3.7)	~ 2.0 (1.1–3.5)	~ 2.1 (1.4–3.4)

Source: Adapted from van Zyl Smit et al. 2010 with permission from European Respiratory Society, © 2010.

Note: **CI** = confidence interval; **RR** = relative risk.

with recognition of the necessary role of *M. tuberculosis*.

The association between smoking and TB disease is consistent across studies, and findings from several prospective cohort studies confirm previous findings that were largely based on case-control studies. The association is found consistently across different populations and geographic regions, although the most informative studies have been conducted in Asian countries where smoking is common among men and TB disease remains frequent. Most studies have observed dose-response relationships with indicators of the extent of smoking, strongly suggesting that an increased number of cigarettes smoked per day, increased years of smoking, and earlier age at the start of smoking are all associated with increased risk for TB disease.

In interpreting the results of these studies, the main limitation is the incomplete consideration of some potential confounding factors, leaving the possibility of residual confounding. However, prospective cohort studies carried out by Jee and colleagues (2009) and Lin and associates (2009b) have controlled for age, gender, and alcohol use. Aside from smoking, SES has many correlates that are relevant to risk for TB disease, including nutrition, housing, and other exposures. Although various studies have measured SES in different ways, the association between smoking and risk for TB disease persists after adjusting for SES. The body of evidence is greater for pulmonary TB disease than for extrapulmonary TB (Lin et al. 2007). Finally, although research demonstrates a strong association between smoking and TB disease, it is still not clear whether the association reflects an increased risk of infection or of reactivation to active TB disease.

TB Recurrence

Only a few studies present evidence of an association between smoking and risk for recurrent TB disease (Table 7.7*S*). Unfortunately, when studying recurrent TB, differentiating between relapse due to treatment failure and reactivation of a subsequent infection with *M. tuberculosis* can be difficult. Studies with short follow-up of patients who have completed treatment—for example, the one by Thomas and colleagues (2005) in South India— suggest that relapse is more likely to occur among smokers than nonsmokers. Studies with longer follow-up are more likely than those with a short follow-up to include both TB cases from relapse and TB cases developing from exogenous reinfection; the former studies report a consistent twofold to threefold increased risk for recurrent TB associated with smoking. Temporality is inherent when investigating recurrent disease, but a dose-response relationship has not been reported. In the Korean cohort study by Jee and colleagues (2009), smoking increased the risk of recurrence by 30% in men but not significantly so in women, and a dose-response relationship with amount smoked was not observed. Overall, the evidence suggests a heightened risk for recurrent TB among smokers.

TB Mortality

The body of evidence for increased risk of mortality among TB patients who smoke has increased considerably over time. Smokers have a greater risk for TB mortality than nonsmokers because of a worsening of the natural history of TB in smokers. Additionally, the impairment of lung function caused by smoking, including the development of COPD, could increase the risk of death from respiratory failure. The several large case-control studies in India and China that have investigated deaths associated with smoking have consistently identified a strong association between smoking and TB mortality, with high attributable risks for smoking. Although most of the mortality evidence comes from studies in India and China, studies from Korea and South Africa provide similar results, suggesting that smoking increases risk for TB mortality across a range of settings in both low- and high-income countries. Two studies found a strong, positive dose-response relationship between number of cigarettes smoked per day and TB mortality (Liu et al. 1998; Lam et al. 2001), but the Korean study did not (Jee et al. 2009). The potential confounders included most commonly in these mortality analyses were age, gender, and education; three of the analyses controlled for alcohol use. Overall, the studies considered in this review consistently show an association between smoking and TB mortality, but the potential limitation among these studies of possible misclassification (in either direction) of TB deaths must be considered.

Conclusions

1. The evidence is sufficient to infer a causal relationship between smoking and an increased risk of *Mycobacterium tuberculosis* disease.

2. The evidence is sufficient to infer a causal relationship between smoking and mortality due to tuberculosis.

3. The evidence is suggestive of a causal relationship between smoking and the risk of recurrent tuberculosis disease.

4. The evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and the risk of tuberculosis infection.

5. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and the risk of tuberculosis infection.

6. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and the risk of tuberculosis disease.

Implications

Tobacco smoking contributes to the burden of TB worldwide, potentially increasing risk for TB infection, disease, recurrence, and mortality. In 2008, TB killed 1.3 million people worldwide, and tobacco use may have accounted for more than one-half of those deaths in some regions (WHO 2010). Reduction of the consumption of tobacco at the population level will reduce TB infection, disease, and mortality. In short, tobacco control can contribute to TB control. There is currently a strong interest in determining the impact of smoking cessation for newly diagnosed TB patients, with the hypothesis that TB patients who smoke are at increased risk of failing treatment, sustaining a relapse, and/or dying. Cessation efforts among TB patients offer an opportunity to target a vulnerable population that, as a result of having the disease, may be motivated to quit. The effect of smoking on TB disease represents an important motivation for cessation that can be added to the numerous other risks of smoking. The most effective and efficient cessation strategies need to be determined, but they are likely to differ by the epidemiology and smoking behaviors of the targeted population.

Idiopathic Pulmonary Fibrosis

The diffuse parenchymal lung diseases are a heterogeneous group of disorders of known and unknown causes with distinct clinicopathologic characteristics. Among these diseases, the evidence on risk associated with cigarette smoking has been variable. For example, cigarette smoking is associated with an increased risk for IPF, desquamative interstitial pneumonia, and interstitial lung disease but with a decreased risk for sarcoidosis and hypersensitivity pneumonitis (Travis et al. 2002; USDHHS 2004). The focus of the present review is on IPF, the most common and also the most severe of the idiopathic interstitial pneumonias (Raghu et al. 2011). This topic was reviewed in the 2004 Surgeon General's report, *The Health Consequences of Smoking*; at that time, the evidence was determined to be "inadequate to infer the presence or absence of a causal relationship between active smoking and IPF" (USDHHS 2004).

The prevalence of IPF is much lower than that of COPD (USDHHS 2004). The prevalence of IPF is estimated at only 2 to 43 cases per 100,000 persons (Coultas et al. 1994; Raghu et al. 2006, 2011), but IPF is likely underdiagnosed as well. These prevalence estimates reflect not only the low incidence of the disease but also the high case-fatality rate.

Description of the Literature Review

A MEDLINE search was conducted to identify new studies on the biological mechanisms of IPF and observational studies published during 2005–2012 in order to update a review on this topic published in 2006 (Taskar and Coultas 2006). The search strategy included using the terms "smoking," "IPF," and "pulmonary fibrosis"; in addition, after the MEDLINE search was completed, the bibliographies of relevant articles were reviewed to identify literature not found by the search.

Biological Evidence

Although the biological mechanisms leading to pulmonary fibrosis continue to be an active area of investigation, available evidence suggests that both environmental and genetic factors contribute to the disorder (Garantziotis and Schwartz 2006; King et al. 2011; Chilosi et al. 2012; Faner et al. 2012; Macneal and Schwartz 2012). Additionally, smoking has numerous effects on the immune system that may be relevant (see Chapter 10). The process

leading to pulmonary fibrosis is posited to start with alveolar epithelial injury from a number of possible inhaled toxicants, such as cigarette smoke or asbestos fibers. This epithelial micro-injury is followed by a complex process that involves multiple pathways of injury and repair (King et al. 2011). The process appears to be lengthy and leads to gradual fibrosis of the lung with stiffening and impaired gas exchange. Some of these same general mechanisms figure in the pathogenesis of COPD (Chilosi et al. 2012; Faner et al. 2012). Emerging evidence points to genetic factors that may be involved in the pathogenesis of IPF; these genes are relevant to host defenses, cell-cell adhesion, and DNA repair (King et al. 2011).

Epidemiologic Evidence

Epidemiologic evidence on the association between cigarette smoking and IPF has been reviewed previously (USDHHS 2004; Taskar and Coultas 2006) and is updated in this section. The sources of epidemiologic evidence have included the results from both descriptive and analytical studies. The descriptive studies have been comprised of a small case series of patients with IPF, disease registries (Coultas et al. 1994; Gribbin et al. 2006), and large health care administrative databases (Raghu et al. 2006). Of the analytical studies, 10 have been case-controls, 1 of familial idiopathic interstitial pneumonia, and 1 autopsy series (Table 7.10*S*).

Descriptive Studies

The prevalence, incidence, and mortality rates associated with IPF are consistently higher among men than women and increase markedly with advancing age (Coultas et al. 1994; Gribbin et al. 2006; Raghu et al. 2006). These two patterns are consistent with the higher frequency of smoking among men and with the mechanism of repeated micro-injury to the alveolar epithelium occurring with aging.

Subclinical interstitial lung abnormalities are also found among smokers (Lederer et al. 2009; Katzenstein et al. 2010; Washko et al. 2011; Doyle et al. 2012). Using high-resolution CT scanning, Washko and colleagues (2011) examined the lungs of 2,416 smokers 45 years of age or older who had accumulated at least 10 pack-years of smoking. Of these smokers, 8% had interstitial lung abnormalities associated with subpleural abnormalities. These abnormalities were associated with restrictive physiological impairment and impaired 6-minute walking distance (Doyle et al. 2012). Moreover, interstitial lung abnormalities were associated with older age, current smoking (OR = 1.67; 95% CI, 1.14–1.43), and greater exposure to tobacco smoke (OR = 1.08; 95% CI, 1.01–1.15) for each 10 pack-years of smoking (Washko et al. 2011). In addition, two studies of lung specimens obtained from lobectomies performed for lung cancer showed that interstitial fibrosis is common in smokers (Kawabata et al. 2008; Katzenstein et al. 2010). Airspace enlargement with fibrosis was present in 18% of moderate smokers in one of these studies (Kawabata et al. 2008), and in the other, Katzenstein and colleagues (2010) found interstitial fibrosis in more than 25% of the slides taken from the lobectomy specimens in 60% of smokers.

Analytical Studies

Of the 12 studies reported in Table 7.10*S*, 5 of them, all published 1990–2005, have been reviewed previously (Taskar and Coultas 2006). Of the 10 case-control studies presented in the table, 6 reported significant associations between ever or former smoking and IPF, with the OR (95% CI) ranging from 1.57 (1.01–2.33) to 5.4 (2.30–12.66). These 6 studies were conducted in five different countries: Japan, Mexico, Sweden, the United Kingdom, and the United States. The risk of current smoking was examined in only 1 study and was found to be nonsignificant (Miyake et al. 2005). The largest studies of environmental and occupational risk factors for IPF conducted in the United States (Baumgartner et al. 1997, 2000) and the United Kingdom (Hubbard et al. 1996) had nearly identical results, with an OR (95% CI) for smoking of 1.59 (1.1–2.4) and 1.57 (1.01–2.43), respectively. In 3 studies, there was evidence for a dose-response effect using pack-years of smoking, but the analyses were limited by small numbers in some categories of dose (Hubbard et al. 1996; Baumgartner et al. 1997; Miyake et al. 2005).

These epidemiologic studies had a number of limitations, including inconsistent adjustment for potential confounders, small samples, and missing data. Adjustment for potential confounders was reported in only 4 of these 10 studies. Moreover, when adjustment for confounders was performed, there was variation in the variables used, which included age, gender, region, family history of IPF, occupational and environmental exposures, and comorbid conditions. Small samples with limited statistical power may explain the lack of significant associations in 2 studies (Scott et al. 1990; Miyake et al. 2005). In the study conducted by Hubbard and colleagues (2008) of the association between IPF and cardiovascular disease, misclassification of missing data on the smoking status from 14% of cases and 16% of controls may have resulted in an underestimation of the risk of smoking.

In addition to the case-control design, the association between cigarette smoking and lung fibrosis has been examined using other study designs, including one on familial interstitial pneumonia (Steele et al. 2005) and in an autopsy sample (Schenker et al. 2009). Steele and colleagues (2005) identified 111 families with familial interstitial pneumonia, defined as two or more cases of probable or definite idiopathic interstitial pneumonia in individuals related within three degrees. Among these families, 309 individuals had definite or probable disease, with 80% classified as IPF, and 360 were unaffected. Overall, ever smoking was associated with an increased risk of familial interstitial pneumonia (OR = 3.6; 95% CI, 1.3–9.8 after adjustment for age and gender). Moreover, the average number of pack-years of smoking was significantly higher among affected family members than among those unaffected (16.6 vs. 6.9).

In their autopsy study, Schenker and colleagues (2009) examined 112 consecutive specimens from Hispanic males and described a range of pathologic abnormalities, including smoking-related small airways disease (54.5%) and interstitial fibrosis (19.1%). After adjustment for age and exposure to mineral dust, pathologic evidence of smoking-related small airways disease was strongly associated with interstitial fibrosis (OR = 5.03; 95% CI, 1.12–22.68).

Evidence Synthesis

Since the publication of the 2004 Surgeon General's report on the health consequences of smoking, there have been advances in our understanding of the biological mechanisms involved in the development of IPF and an increase in the number of epidemiologic investigations on this topic. Major issues considered in the interpretation of epidemiologic evidence include the potential for bias and confounding and a lack of statistical power. Although the case-control design, used for most of the studies reported in Table 7.10*S*, is subject to potential biases, the consistency of the findings, combined with the use of different control groups, including healthy controls, community controls, and clinic/hospital controls, suggests that bias alone is not a likely explanation for the findings. Con-

trol for potential confounding factors was not consistent among the epidemiologic investigations reviewed here, but in most studies when there was adjustment for possible confounders, significant associations between smoking and IPF remained. Additionally, given the paucity of confirmed risk factors for IPF, confounding seems an unlikely explanation for this association.

Plausibility is strong, and a causal association is coherent with the current understanding of the toxic biological effects of cigarette smoke, which causes cellular injury. This injury starts a cascade of genetically determined repair responses that may result in fibrosis among persons with genetically abnormal host defenses or repair mechanisms. Moreover, this sequence of biological events, starting with cellular injury and ending with fibrosis, provides support for the criterion of temporality. Looking across the epidemiologic studies, an association of IPF with smoking was found in different populations of patients and controls from different countries and over different periods of time. Although the overall strength of association between smoking and IPF is relatively small (OR = 1.6) (Taskar and Coultas 2006), misclassification of both diagnosis and exposure may have reduced the magnitude of the association. The limited evidence on an increasing strength of association with a greater number of pack-years of smoking supports the biologic-gradient criterion (i.e., dose-response).

Conclusion

1. The evidence is suggestive but not sufficient to infer a causal relationship between cigarette smoking and idiopathic pulmonary fibrosis.

Implications

Further research is needed to address gaps in the current evidence, and to establish sufficient evidence for a causal relationship between cigarette smoking and IPF to be adequately assessed.

Impact of Smokefree Policies on Respiratory Outcomes

The evidence of the impact of smokefree policies within indoor environments on multiple health outcomes is reviewed in this and previous reports. In Chapter 8, "Cardiovascular Diseases" it was concluded that "The evidence is sufficient to infer a causal relationship between the implementation of a smokefree law or policy and a reduction in coronary events among populations under 65 years of age." Previous Surgeon General's reports have concluded that exposure to secondhand smoke causes cough, phlegm, wheeze, and breathlessness among children; lower respiratory illnesses in infants and children; and the onset of wheeze illnesses and exacerbation of asthma among children and adults.

Despite the limited evidence for causal relationships between exposure to secondhand smoke and the risk for other acute and chronic respiratory diseases in adults, researchers have examined the consequences of the implementation of a smokefree law or policy for the number of hospital admissions for respiratory diseases. Eisner and colleagues (2005, 2009a,b) reported findings suggesting that chronic exposure to secondhand smoke increases the risk of COPD and is associated with exacerbation of respiratory symptoms. Evidence reviewed in the 2010 Surgeon General's report documented the mechanisms by which exposure to the complex chemical mixture of combustion compounds in tobacco smoke causes inflammation and oxidative stress. Flouris and Koutedakis (2011) reported results suggesting that exposure to secondhand smoke can produce adverse inflammatory and respiratory effects within 60 minutes of exposure and that these effects persist for at least 3 hours after the exposure. Earlier work by Flouris and colleagues (2009, 2010) provide additional evidence of the acute and short-term effects of exposure to secondhand smoke on lung functions and immune responses. Additionally, as previous Surgeon General's reports have reviewed (USDHHS 2006), the implementation of smokefree laws improves the respiratory health of bar and restaurant workers (Eisner et al. 1998; Menzies et al. 2006; Ayres et al. 2009; Wilson et al. 2012). Hence, there are biological and observational data suggesting that the implementation of smokefree legislation or policies could result in reduced respiratory symptoms and adverse respiratory events.

A recent review (Tan and Glantz 2012) and other recent papers (Vander Weg et al. 2012; Millett et al. 2013; Sims et al. 2013) found significant declines in hospitalizations for respiratory diseases, following the implementation of a smokefree law or policy. In a meta-analysis of 11 studies of smokefree laws covering workplaces, restaurants, and bars, Tan and Glantz (2012) reported a pooled RR of 0.76 (95% CI, 0.68–0.85) for hospital admissions for respiratory disease following the implementation of a smokefree law or policy, with the strongest effects found for asthma and lung infections (Figure 7.9). The 11 studies evaluate comprehensive smokefree laws covering workplaces, restaurants, and bars in countries (Ireland and Scotland), states (Arizona and Delaware), and the city of Toronto, Canada.

Millett and colleagues (2013) found a significant decline in admissions for childhood asthma after the implementation of English smokefree legislation in July 2007 (adjusted risk ratio = 0.91; 95% CI, 0.89–0.93). The effect persisted over the first 3 years after implementation and was observed among children from different age, gender, and SES groups and among those residing in urban and rural locations in England. Sims and colleagues (2013) similarly evaluated the July 2007 English smokefree legislation and found that it was associated with a 4.9% (95% CI, 0.6%–9.0%) decline in emergency admissions for asthma in the adult population. Vander Weg and colleagues (2012) analyzed the patterns of hospital admissions for COPD, among Medicare beneficiaries 65 years of age and older, following the implementation of 938 smokefree laws passed by municipalities, counties, and states between 1991–2008. Adjusting for the trend of an increase in COPD admission rates, this analysis found a significant decline in COPD admission following smoking bans. However, in a smaller study in Rhode Island, Roberts and colleagues (2012) did not observe a decline in asthma admissions following the implementation of their statewide smokefree ordinance.

These results suggest that the relationship between acute and chronic exposure to secondhand smoke and respiratory disease outcomes merits further review and investigation. The lack of assessments of pre- and postexposure in almost all studies has been a limitation.

Figure 7.9   Forest plot for hospital admissions for respiratory disease following the implementation of a smokefree law or policy

Location	Author and year	ES (95% CI)
Workplaces Only		
Toronto, Canada (phase 1)	Naiman et al. 2010	1.09 (0.96–1.24)
Toronto, Canada (phase 1)	Naiman et al. 2010	0.84 (0.62–1.15)
United States	Dove et al. 2011	0.55 (0.27–1.13)
Toronto, Canada (phase 1)	Naiman et al. 2010	1.02 (0.90–1.15)
Subtotal (I-squared = 44%, p = 0.148)		1.00 (0.87–1.14)
Workplaces and Restaurants		
Toronto, Canada (phase 2)	Naiman et al. 2010	0.94 (0.83–1.05)
Lexington-Fayette Co., KY	Rayens et al. 2008	0.78 (0.71–0.86)
Toronto, Canada (phase 2)	Naiman et al. 2010	0.65 (0.49–0.85)
Toronto, Canada (phase 2)	Naiman et al. 2010	0.81 (0.73–0.91)
Subtotal (I-squared = 66.5%, p = 0.030)		0.81 (0.73–0.91)
Workplaces, Restaurants, and Bars		
Ireland	Kent et al. 2012	1.18 (0.86–1.60)
Toronto, Canada (phase 3)	Naiman et al. 2010	0.73 (0.65–0.82)
Arizona	Herman and Walsh 2010	0.77 (0.68–0.86)
Delaware	Moraros et al. 2010	0.95 (0.90–0.99)
Ireland	Kent et al. 2012	0.60 (0.39–0.91)
Scotland	Mackay et al. 2008	0.81 (0.78–0.83)
Toronto, Canada (phase 3)	Naiman et al. 2010	0.48 (0.36–0.63)
Ireland (LRTI)	Kent et al. 2012	0.83 (0.61–1.13)
Ireland (pneumonia)	Kent et al. 2012	0.71 (0.52–0.98)
Toronto, Canada (phase 3)	Naiman et al. 2010	0.64 (0.58–0.72)
Ireland	Kent et al. 2012	0.62 (0.22–1.75)
Subtotal (I-squared = 88.0%, p = 0.000)		0.76 (0.68–0.85)

0.1   0.2   0.5   1   2   5

Relative risk of hospitalization

Source: Adapted from Tan and Glantz 2012 with permission from Wolters Kluwer Health, © 2012.
Note: **CI** = confidence interval; **ES** = effect size (relative risk); **LRTI** = lower respiratory tract infection. 95% CI for each study. The size of the shaded area around each point is proportional to the weight in the random effects meta-analysis. Error bars indicate 95% CI for each study. See Tan and Glantz 2012, Tables S1–S4 for further details about each risk estimate or study.

Evidence Summary

This chapter has reviewed updated evidence on COPD, a disease causally linked to smoking in the 1964 report. Mortality from COPD continues to rise, and smoking remains responsible for the majority of cases. For asthma, another obstructive lung disease, the evidence was found to be sufficient to infer that smoking is a cause of incident asthma in adolescents. The benefits of smoke-free policies have been shown previously for workers with asthma; evidence considered in this report points to a reduction in the admissions for respiratory diseases following implementation of a smokefree policy.

TB was once a leading cause of death in the United States. Now far less frequent in the United States, it remains prominent elsewhere and caused 1.4 million deaths worldwide in 2011 (WHO 2013). Evidence reported over the last decade is sufficient to lead to a conclusion that smoking increases the risk for TB and for dying from TB. For IPF, the evidence was suggestive of a causal association.

Implications

The evidence reviewed in this chapter reaffirms the potential for avoiding a substantial burden of respiratory disease through tobacco control. It reaffirms the possibility of avoiding much of the burden of COPD in the United States and reducing the occurrence of asthma in youth and young adults. Most significantly, the evidence considered here points to an opportunity to reduce the burden of disease and mortality from TB. Smoking has received little attention in relation to TB until recently. Smoking cessation should be integral to the management of the millions of people receiving treatment for this disease worldwide. Few etiological risk factors have been found for IPF; continued research on smoking and IPF is needed, given the potential to prevent another respiratory disease with a high fatality rate.

Chapter Conclusions

Chronic Obstructive Pulmonary Disease

1. The evidence is sufficient to infer that smoking is the dominant cause of chronic obstructive pulmonary disease (COPD) in men and women in the United States. Smoking causes all elements of the COPD phenotype, including emphysema and damage to the airways of the lung.

2. Chronic obstructive pulmonary disease (COPD) mortality has increased dramatically in men and women since the 1964 Surgeon General's report. The number of women dying from COPD now surpasses the number of men.

3. The evidence is suggestive but not sufficient to infer that women are more susceptible to develop severe chronic obstructive pulmonary disease at younger ages.

4. The evidence is sufficient to infer that severe α1-antitrypsin deficiency and cutis laxa are genetic causes of chronic obstructive pulmonary disease.

Asthma

1. The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and incidence of asthma in adolescents.

2. The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and exacerbation of asthma among children and adolescents.

3. The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and the incidence of asthma in adults.

4. The evidence is sufficient to infer a causal relationship between active smoking and exacerbation of asthma in adults.

Tuberculosis

1. The evidence is sufficient to infer a causal relationship between smoking and an increased risk of *Mycobacterium tuberculosis* disease.

2. The evidence is sufficient to infer a causal relationship between smoking and mortality due to tuberculosis.

3. The evidence is suggestive of a causal relationship between smoking and the risk of recurrent tuberculosis disease.

4. The evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and the risk of tuberculosis infection.

5. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and the risk of tuberculosis infection.

6. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to secondhand smoke and the risk of tuberculosis disease.

Idiopathic Pulmonary Fibrosis

1. The evidence is suggestive but not sufficient to infer a causal relationship between cigarette smoking and idiopathic pulmonary fibrosis.

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Appended Data Table for Figure 7.2[a,b]

State[c]	Percent COPD
Alabama	9.06
Alaska	5.88
Arizona	5.08
Arkansas	7.22
California	4.45
Colorado	4.58
Connecticut	5.67
Delaware	4.80
District of Columbia	4.65
Florida	7.13
Georgia	6.91
Hawaii	4.15
Idaho	5.02
Illinois	5.89
Indiana	7.86
Iowa	4.65
Kansas	6.23
Kentucky	9.29
Louisiana	6.55
Maine	6.86
Maryland	5.81
Massachusetts	5.38
Michigan	7.40
Minnesota	3.92
Mississippi	7.92
Missouri	7.55
Montana	5.39
Nebraska	4.61
Nevada	6.93
New Hampshire	5.92
New Jersey	4.84
New Mexico	5.77
New York	5.56
North Carolina	6.50
North Dakota	4.39
Ohio	7.07
Oklahoma	8.02
Oregon	5.43
Pennsylvania	6.09

State[c]	Percent COPD
Rhode Island	5.88
South Carolina	7.07
South Dakota	4.90
Tennessee	8.71
Texas	5.54
Utah	4.21
Vermont	4.42
Virginia	5.78
Washington	3.90
West Virginia	8.03
Wisconsin	5.04
Wyoming	5.64
Puerto Rico	3.10

Source: CDC 2012a.
Note: COPD = chronic obstructive pulmonary disease.
aAge-adjusted to the 2000 U.S. standard population, using five age groups: 18–44 years, 45–54 years, 55–64 years, 65–74 years, and 75 years of age and older.
bBased on an affirmative response to the question, "Has a doctor, nurse, or other health professional ever told you that you have COPD, emphysema, or chronic bronchitis?"
cIncludes the 50 states, District of Columbia, and Puerto Rico.

Appended Data Table for Figure 7.9

Study	Place	Location	Effect size, relative risk (95% CI)
Naiman 2010	Workplaces only	Toronto, Canada (phase 1)	1.09 (0.96–1.24)
Naiman 2010	Workplaces only	Toronto, Canada (phase 1)	0.84 (0.62–1.15)
Dove 2011	Workplaces only	United States	0.55 (0.27–1.13)
Naiman 2010	Workplaces only	Toronto, Canada (phase 1)	1.02 (0.90–1.15)
Subtotal: Workplaces only (I-squared = 44%, p = 0.148)			1.00 (0.87–1.14)
Naiman 2010	Workplaces and restaurants	Toronto, Canada (phase 2)	0.94 (0.83–1.05)
Rayens 2008	Workplaces and restaurants	Lexington-Lafayette County, Kentucky	0.78 (0.71–0.86)
Naiman 2010	Workplaces and restaurants	Toronto, Canada (phase 2)	0.65 (0.49–0.85)
Naiman 2010	Workplaces and restaurants	Toronto, Canada (phase 2)	0.81 (0.73–0.91)
Subtotal: Workplaces and restaurants (I-squared = 66.5%, p = 0.030)			0.81 (0.73–0.91)
Kent 2012	Workplaces, restaurants, and bars	Ireland	1.18 (0.86–1.60)
Naiman 2010	Workplaces, restaurants, and bars	Toronto, Canada (phase 3)	0.73 (0.65–0.82)
Herman 2010	Workplaces, restaurants, and bars	Arizona	0.77 (0.68–0.86)
Moraros 2010	Workplaces, restaurants, and bars	Delaware	0.95 (0.90–0.99)
Kent 2012	Workplaces, restaurants, and bars	Ireland	0.60 (0.39–0.91)
Mackay 2008	Workplaces, restaurants, and bars	Scotland	0.81 (0.78–0.83)
Naiman 2010	Workplaces, restaurants, and bars	Toronto, Canada (phase 3)	0.48 (0.36–0.63)
Kent 2012	Workplaces, restaurants, and bars	Ireland (LRTI)	0.83 (0.61–1.13)
Kent 2012	Workplaces, restaurants, and bars	Ireland (pneumonia)	0.71 (0.52–0.98)
Naiman 2010	Workplaces, restaurants, and bars	Toronto, Canada (phase 3)	0.64 (0.58–0.72)
Kent 2012	Workplaces, restaurants, and bars	Ireland	0.62 (0.22–1.75)
Subtotal: Workplaces, restaurants, and bars (I-squared = 88.0%, p = 0.000)			0.76 (0.68–0.85)

Source: Adapted from Tan and Glantz 2012 with permission from Wolters Kluwer Health, © 2012.
Note: CI = confidence interval. The size of the shaded area around each point is proportional to the weight in the random effects meta-analysis. Error bars indicate 95% CI for each study. See Tan and Glantz 2012, Tables S1–S4 for further details about each risk estimate or study.

Chapter 8
Cardiovascular Diseases

> Sections of this chapter on the health consequences of smoking are accompanied by evidence tables detailing the studies that were used to evaluate the evidence to assess causality. A supplement to this report is provided that contains these tables. The tables included in the supplement are indicated with an "*S*" where they are called out in the text.

Introduction

Previous Surgeon General's reports have provided comprehensive reviews of the evidence on both smoking and exposure of nonsmokers to tobacco smoke as causes of cardiovascular diseases (CVDs) (see Table 4.2) (U.S. Department of Health and Human Services [USDHHS] 1983, 2004, 2006). This chapter provides a brief overview of that extensive body of evidence and an update on several aspects of the relationships between CVD and smoking or involuntary exposure to tobacco smoke, emphasizing studies that were published since the last reviews of active smoking in 2004 and of secondhand smoke in 2006. Additionally, two new evidence reviews are included which indicate that exposure to secondhand smoke causes stroke and that implementation of a smokefree law or policy reduces coronary events among people younger than 65 years of age.

The 50-year span from the landmark 1964 Surgeon General's report to today covers a period of remarkable change in the pattern of CVD occurrence in this country. In the first half of the twentieth century, CVD, including coronary heart disease[1] ([CHD] also known as ischemic heart disease), stroke, congestive heart failure, coronary artery disease, and peripheral arterual disease (PAD), became the leading cause of death in the United States and in most other developed nations (Table 8.1) (National Heart, Lung, and Blood Institute [NHLBI] 2012). As shown in Figure 4.1, the death rate from CVD in the United States peaked just before the 1964 report and then, starting in the late 1960s, began to decline sharply. From 1968–2010, the age-adjusted death rate for CVD declined by 69.0%, while the rate of death from all causes declined 42.7% (Table 8.2). From 1999–2008, average annual percent declines in the age-adjusted death rates of interest were 4.2% for total CVD, 5.3% for CHD, and 5.0% for stroke (Table 8.3). This decline in age-adjusted CVD mortality rates has recently slowed, averaging from 2% up to over 4% a year (Table 8.3) (Ford and Capewell 2011; Luepker 2011).

Why did death rates for CVD decline progressively from 1968–2008? In a 1978 conference, NHLBI explored the basis of the decline in CHD mortality (Feinleib et al. 1979) and proposed numerous possible explanations, including classification artifacts, the advent of hospital coronary care units and consequent improved survival, advances in coronary artery surgery, and broad social changes in knowledge and attitudes about CHD accompanied by a trend toward more favorable coronary risk factor profiles, such as decreased cigarette smoking. At about the same time, using risk estimates from the Framingham Heart Study to assess drivers of the falling CHD mortality rate, Stern (1979) concluded that both improved diet and reductions in smoking had contributed to the decline. Later, Goldman and Cook (1984), who used a modeling approach based upon national data on risk factors and lifestyle trends from the National Health and Nutrition Examination Survey (NHANES), estimated that 54% of the decline in the CHD mortality rate in the United States from 1968–1976 was from decreases in total cholesterol values and smoking. Further estimates of the contribution of declines in smoking were provided by Hunink and colleagues (1997) and Ford and coworkers (2007). Hunink and colleagues (1997) estimated that 50% of the decline in CHD mortality from 1980–1990 in the United States was accounted for by improvements in risk factors, but estimated that only about 6% of the decline was due to reductions in smoking. In a later analysis, Ford and colleagues (2007) estimated similarly that about 44% of the decline in CHD mortality from 1980–2000 was due to changes in risk factor levels, with only about 12% of the decline due to reductions in smoking.

Similar declines in CVD morbidity and mortality have been observed in other developed nations (Ford and Capewell 2011). There, evaluations of the potential role of risk factor shifts in these changes have suggested that the declines were due more to reductions in the levels of

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[1]Coronary heart disease, otherwise known as ischemic heart disease (IHD), is a condition that affects the supply of blood to the heart. Throughout this chapter, the term CHD is used instead of IHD for consistency.

Table 8.1   Cardiovascular diseases^a

Aortic aneurysm/ Abdominal aortic aneurysm	Occurs when the large blood vessel (the aorta) that supplies blood to the abdomen, pelvis and legs becomes abnormally large or balloons outward. This type of aneurysm is most often found in men over age 60 who have at least one or more risk factor, including emphysema, family history, high blood pressure, high cholesterol, obesity and smoking.
Acute coronary syndrome	Acute coronary syndrome is an umbrella term for when blood supplied to the heart muscle is decreased or blocked, leading to a heart attack. The common signs of acute coronary syndrome are chest pain or discomfort, which may involve pressure, tightness or fullness; pain or discomfort in one or both arms, the jaw, neck, back or stomach; shortness of breath; feeling dizzy or lightheaded; nausea; or sweating.
Angina pectoris	Also called angina, is the medical term for chest pain or discomfort due to coronary heart disease. Angina pectoris occurs when the heart muscle doesn't get as much blood as it needs. This usually happens because one or more of the heart's arteries is narrowed or blocked, also called ischemia. Stable angina refers to "predictable" chest discomfort associated with physical exertion or mental or emotional stress. Unstable angina refers to unexpected chest pain and usually occurs at rest. It is typically more severe and prolonged. Unstable angina should be treated as an emergency.
Atherosclerosis	A form of arteriosclerosis in which the inner layers of artery walls become thick and irregular because of deposits of fat, cholesterol and other substances. This buildup is called plaque and can cause arteries to narrow, reducing the blood flow through them. Eventually plaque can erode the wall of the artery and diminish its elasticity. Plaque deposits can rupture, causing blood clots to form at the rupture that can block blood flow or break off and travel to another part of the body. This is a common cause of heart attack or ischemic stroke.
Coronary heart disease (CHD)/ Coronary artery disease (CAD)	The most common type of heart disease. It is when plaque builds up in the heart's arteries, a condition called atherosclerosis. As plaque builds up, the arteries narrow, making it more difficult for blood to flow to the heart. If blood flow becomes reduced or blocked, angina (chest pain) or a heart attack may occur. Over time, coronary artery disease can also lead to heart failure and arrhythmias.
Heart attack/ Acute myocardial infarction (AMI)	Occurs when a blocked coronary artery prevents oxygen-rich blood from reaching a section of the heart muscle. If the blocked artery is not reopened quickly, the part of the heart normally nourished by that artery begins to die. Symptoms can come on suddenly but may start slowly and persist over time. Warning signs include discomfort in the chest (pressure, squeezing, fullness), discomfort in other upper-body areas (arms, back, neck, jaw or stomach), shortness of breath, a cold sweat, nausea or lightheadedness.
Heart failure/ Congestive heart failure	Occurs when the heart can't pump enough blood to the organs. The heart works, but not as well as it should. Heart failure is almost always a chronic, long-term condition. The older you are, the more common congestive heart failure becomes. Your risk also rises if you are overweight, diabetic, smoke, abuse alcohol or use cocaine. When a heart begins to fail, fluid can pool in the body; this manifests as swelling (edema), usually in the lower legs and ankles. Fluid also may collect in the lungs, causing shortness of breath.
Ischemic heart disease (IHD)	A heart problem caused by heart arteries that are narrowed. When there are blockages in arteries, they become narrowed, which means less blood and oxygen reaches the heart muscle. When more oxygen is needed, such as while exercising, the heart cannot meet the demands. The lack of oxygen caused by ischemic heart disease can produce chest pain, discomfort known as angina pectoris or even a heart attack.
Ischemic stroke	Occurs when a blood clot or other particle blocks an artery in the brain or an artery leading to the brain. This causes brain cells to die or be injured. Cerebral thrombosis and cerebral embolism are ischemic strokes.

Table 8.1   Continued

Peripheral arterial disease (PAD)	Occurs when narrow arteries reduce blood flow to the limbs, mainly in the legs and feet. Symptoms can include pain in the legs or buttocks when exercising that goes away when the activity is stopped.
Platelet	An element in blood that aids in blood clotting.
Stroke	An interruption of blood flow to the brain causing paralysis, slurred speech and/or altered brain function. About nine of every 10 strokes are caused by a blockage in a blood vessel that carries blood to the brain; this is known as an ischemic stroke. The other type of stroke is known as hemorrhagic, caused by a blood vessel bursting. Warning signs include sudden numbness or weakness of the face, arm or leg (especially on one side); sudden confusion, trouble speaking or understanding; sudden trouble seeing in one or both eyes; sudden trouble walking, dizziness, loss of balance or coordination; sudden, severe headache with no known cause.
Sudden cardiac death	Can occur when someone in sudden cardiac arrest is not treated promptly. Sudden cardiac arrest occurs when the heart's electrical system malfunctions and the heart suddenly stops beating often without warning. While the terms "sudden cardiac arrest" and "heart attack" are often used as if they are synonyms, they aren't. Sudden cardiac arrest can occur after a heart attack, or during recovery. Heart attacks increase the risk for sudden cardiac arrest, but most heart attacks do not lead to sudden cardiac arrest. Immediate CPR can double or triple the chances of survival from sudden cardiac arrest.
Thrombosis	The formation or presence of a blood clot inside a blood vessel or chamber of the heart.

Source: American Heart Association 2013.
[a]Cardiovascular disease (CVD) is a term that refers to the entire group of heart and blood vessel diseases.

Table 8.2   Age-adjusted death rates and percentage change for all causes and for cardiovascular diseases (CVDs), United States, 1968 and 2010

Causes of death	Deaths/100,000 population		1968–2008 difference	Percentage change
	1968	**2010**		
All causes	1,304.5	747.0	-557.5	-42.7
CVD[a]	759.5	235.5	-524.0	-69.0
CHD	482.6	113.6	-369.0	-76.5
Stroke	162.5	39.1	-123.4	-75.9
Other CVD	114.4	82.8	-31.6	-27.6
Non-CVD	545.0	511.5	-33.5	-6.1

Source: National Heart, Lung, and Blood Institute 2013, personal communication.
Note: **CHD** = coronary heart disease.
[a]Excludes congenital malformations of the circulatory system.

Table 8.3 **Average annual percentage change in age-adjusted death rates for all causes and for cardiovascular diseases (CVDs), United States, 1968–2008**

Years	All causes	Total CVD[a]	CHD	Stroke	Other CVD	All other causes
1968–1978	-2.2	-3.6	-2.9	-4.2	-6.7	-0.7
1979–1988	-0.6	-2.2	-2.9	-3.7	0.9	1.0
1989–1998	-0.9	-1.8	-2.8	-0.9	-0.1	-0.1
1999–2008	-1.8	-4.2	-5.3	-5.0	-1.7	-0.4

Source: National Heart, Lung, and Blood Institute 2012 (Chart 3-7).
Note: **CHD** = coronary heart disease.
[a]Excludes congenital malformations of the circulatory system.

risk factors than to advances in treatment (Capewell et al. 1999; Laatikainen et al. 2005; Hardoon et al. 2008). A study in Scotland showed that a reduction in smoking was the main contributing factor to declining CHD mortality (Capewell et al. 1999), and in Finland, reductions in risk factors were estimated to explain 53–72% of the decline in CHD mortality between 1982–1997, again with reductions in smoking as a major contributing factor (Laatikainen et al. 2005).

Ford and Capewell (2011), in an updated discussion of factors that have contributed to the decline in CVD mortality, compared declines in per capita consumption of cigarettes and the prevalence of current smoking among adults in the United States (see trends in Chapter 13, "Patterns of Tobacco Use Among U.S. Youth, Young Adults, and Adults") with declines in several other major CVD risk factors, including the prevalence of hypertension, mean total cholesterol levels in adults 20–74 years of age, prevalence of obesity, prevalence of diabetes, and trends in physical activity. The authors reviewed major trends in each of these risk factors in relation to policies designed to improve them and noted that "the successful application of policy to lower tobacco use has been held up as a useful public health paradigm to change other lifestyle factors in the population" (p. 13). The authors further noted the contribution of the 1964 Surgeon General's report toward making the reduction of the prevalence of smoking a national priority.

Although the estimates of the proportion by which reductions in smoking contributed to the decline in CVD

mortality have varied, all of the analyses reviewed above lead to a conclusion that a reduction in smoking in past decades was one of the major contributing factors to the declines in CVD morbidity and mortality in the United States and other developed countries (Stern 1979; Goldman and Cook 1984; Hunink et al. 1997; Capewell et al. 1999; Laatikainen et al. 2005; Ford et al. 2007; Hardoon et al. 2008; Ford and Capewell 2011).

Table 8.4 **Prevalence of cardiovascular diseases (CVDs), United States, 2008[a]**

Disease	Prevalence
CVD	82,600,000
Hypertension	76,400,000
CHD	16,300,000
AMI	7,900,000
Angina pectoris	9,000,000
Stroke	7,000,000
Heart failure	5,700,000
Congenital heart defects	1,000,000
Arterial fibrillation	2,200,000
Peripheral arterial disease	8,500,000

Source: National Heart, Lung, and Blood Institute 2012 (Table 2-1).
Note: **AMI** = acute myocardial infarction; **CHD** = coronary heart disease.
[a]Not all diseases listed in this table are caused by smoking.

Figure 8.1   Death rates for heart disease in males by age and race/ethnicity, United States, 2008
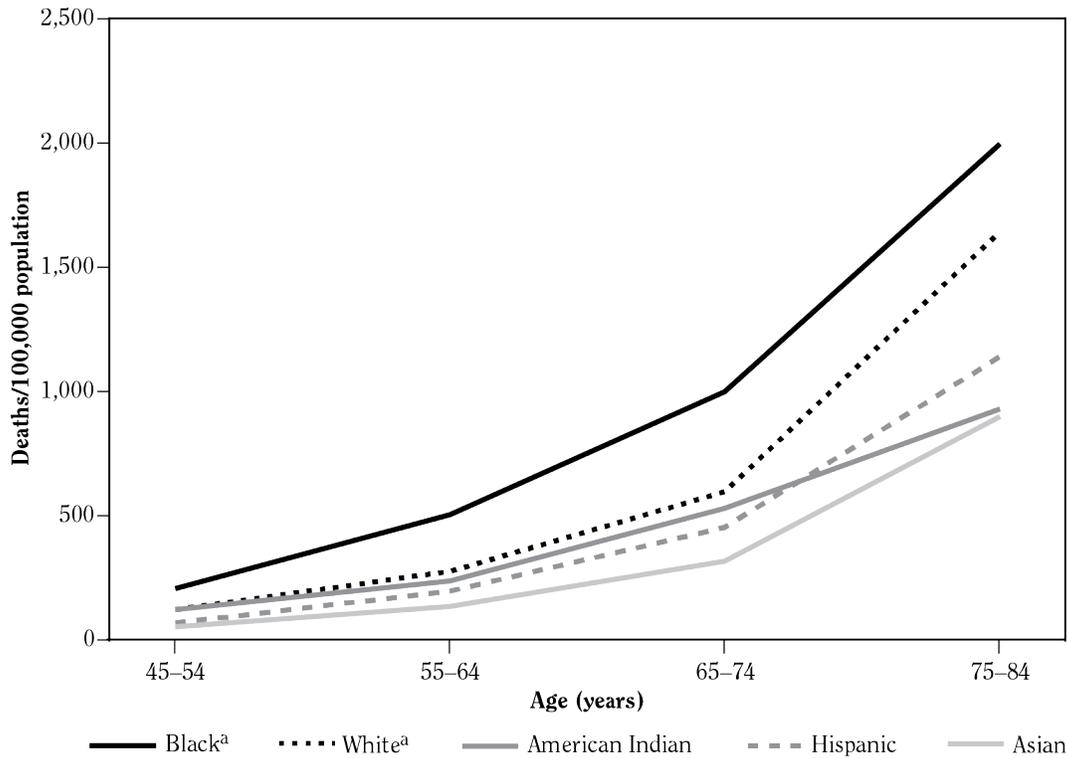
Source: National Heart, Lung, and Blood Institute 2012.
[a]Non-Hispanic.

Despite the progress in reducing rates of CVD in the United States and across the industrialized world, CVD continues to cause a very large number of deaths worldwide (Luepker 2011). During 1979–2008, the age-adjusted rate of death from CVD in the United States per 100,000 people dropped by slightly more than half, from 535.8 to 244.6, but due to population growth, this decline has only translated into a decline in the total number of deaths from CVD since 2000 (NHLBI 2012).

In the United States, CVD is one of the most common noncommunicable diseases (Table 8.4), with estimated annual incidence of 715,000 heart attacks and 795,000 strokes (Go et al. 2013). Rates of CVD remain high in both genders and among all racial/ethnic groups, and increase with age (Figures 8.1 and 8.2). However, even as rates have declined in past decades, the age-adjusted annual death rates for CVD have remained higher for males than for females, and they are highest among non-Hispanic Blacks across all age groups.

Figure 8.2   Death rates for heart disease in females by age and race/ethnicity, United States, 2008
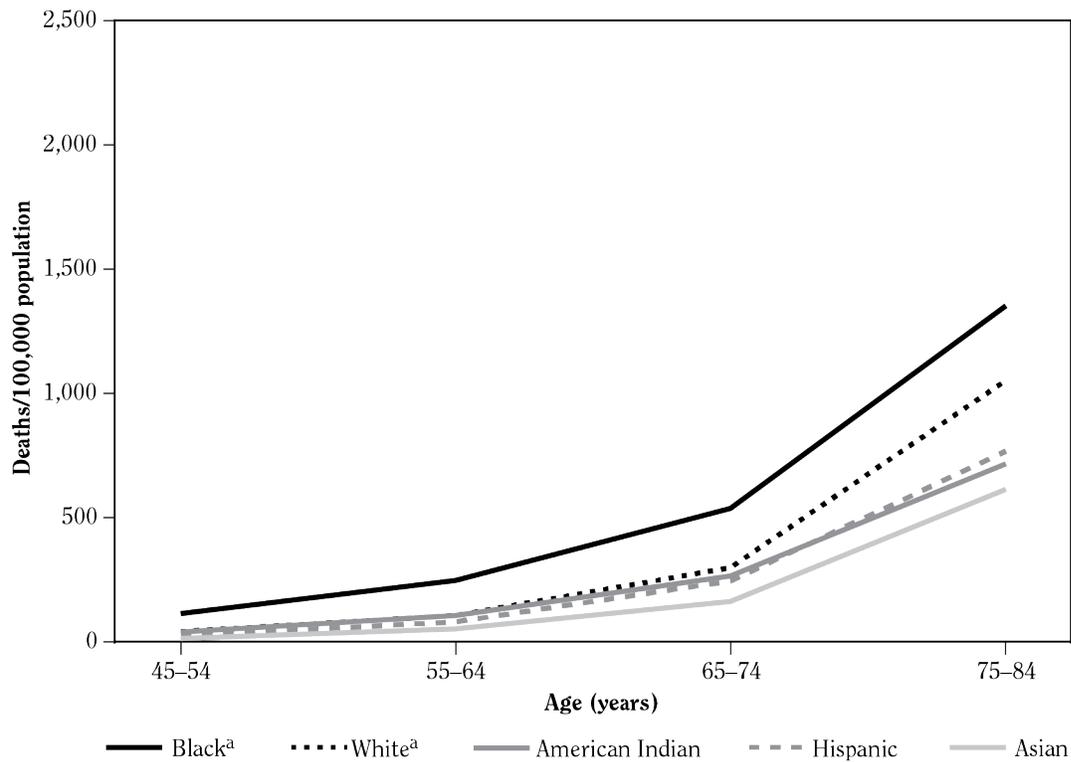
Source: National Heart, Lung, and Blood Institute 2012.
[a]Non-Hispanic.

Tobacco Use and Cardiovascular Diseases: Evolution of the Evidence

For more than half a century, evidence has accrued indicating that exposure to tobacco smoke is causally related to CHD, stroke, atherosclerosis, aortic aneurysm, peripheral vascular disease, and subclinical CVD (e.g., increased carotid intima-media thickness, intermittent claudication, lacunar infarcts, and similar markers of sub-clinical atherosclerosis). Research has driven ever-stronger conclusions on the causation of various CVD by active smoking and exposure to secondhand smoke (USDHHS 2004, 2006).

In fact, the relationship between tobacco use and the risk of CVD was considered in the very first Surgeon General's report in 1964, and this relationship has been examined in numerous subsequent reports of the Surgeon General through 2012. During this period, understanding of this relationship has evolved to encompass multiple specific cardiovascular conditions and various modes of tobacco exposure as well as the physiological mechanisms linking these exposures and outcomes.

Mechanisms by Which Smoking Causes Cardiovascular Diseases

Mechanistic studies at the time of the 1964 Surgeon General's report focused on the pharmacologic effects of nicotine. At that time the acute cardiovascular effects of smoking and nicotine were considered to resemble those of excitation of the sympathetic nervous system, but researchers found these short-term effects could not account for the long-term association between cigarette smoking and CHD (see Chapter 5, "Nicotine").

The 1983 Surgeon General's report summarized accumulating evidence that cigarette smoking accelerates atherosclerosis, and the report linked smoking with other mechanisms that precipitate thrombosis, hemorrhage, or vasoconstriction, which lead to vascular occlusion and ischemia. Specifically, the report noted the effects of cigarette smoking on blood lipids and hemostasis (USDHHS 1983). The report emphasized the roles of nicotine and carbon monoxide in pathogenesis, but it also noted that exposure of laboratory animals to whole tobacco smoke produced endothelial damage and activated platelets. Evidence was also presented that cigarette smoke induces inflammation that could aggravate atherogenesis. Smokers were noted to have lower concentrations of high-density lipoprotein cholesterol, a recognized risk factor for CHD, although the mechanism was unclear. By the time of the 2004 Surgeon General's report, understanding of the mechanisms of smoking-caused CVD had advanced considerably. That report indicated that the key aspects of pathogenesis of smoking-induced heart disease included (1) endothelial dysfunction, (2) a prothrombotic effect, (3) inflammation, (4) altered lipid metabolism, (5) increased demand for myocardial oxygen and blood, and (6) decreased supply of myocardial blood and oxygen.

The 2006 Surgeon General's report provided evidence that exposure to secondhand smoke increases the risk of CHD in exposed nonsmokers. In addition, that report provided the first evidence that very low levels of exposure have disproportionate effects on CHD risk and the risk flattens out at higher levels of cigarette consumption, indicating that the dose-response relationship for smoke exposure and CHD is nonlinear.

The 2010 Surgeon General's report reviewed in great detail the mechanisms by which cigarette smoking leads to CHD; Figure 8.3 provides an overview of the mechanisms considered (Benowitz 2003). In addition to supporting the findings of previous reports, the 2010 report concluded that smoking produces insulin resistance that, together with chronic inflammation, can accelerate the development of both macrovascular and microvascular complications, including nephropathy, and the use of nicotine replacement and medications to aid smoking cessation in smokers with CHD produces far less risk than continued smoking.

Since the 2010 Surgeon General's report, considerable research on the mechanisms by which smoking affects cardiovascular function has been conducted, but those mechanisms have proven to be extremely complex. A brief review of some of the newer findings is presented below. Additionally, readers of this report can consult an extensive review by Csordas and Bernhard (2013), which provides a detailed discussion of the biology of the atherogenic effects of cigarette smoking.

Smoking, Atherogenesis, and Acute Coronary Events

The process of atherogenesis is initiated by the adherence of activated monocytes to damaged endothelial cells, which is followed by the migration of the monocytes into the subendothelium, their differentiation into macrophages, and then the formation of foam cells (USDHHS 2010). A chronic inflammatory state develops in which macrophages promote the development of plaque by secreting various inflammatory mediators. Inflammatory cells contribute to the destabilization and ultimate rupture of the plaque, which in turn results in local vasoconstriction and thrombosis. The occlusion of arteries results in acute vascular events, including myocardial infarction (MI) and stroke. Cigarette smoking is associated with all of the mechanisms by which atherothrombosis occurs: endothelial dysfunction, thrombosis, inflammation, and altered lipid metabolism (USDHHS 2010). Recent studies on these mechanisms are described in the following section, which also comments on newer studies of the constituents of tobacco smoke that are relevant to atherothrombosis.

Cigarette smoke delivers polycyclic aromatic hydrocarbons, including benzo[*a*]pyrene, which are ligands for the aryl hydrocarbon receptor (AhR). Cigarette smoke extract upregulates the expression of a number of inflammatory genes, and this upregulation is inhibited by a chemical inhibitor of AhR (Wu et al. 2011). Furthermore, cigarette smoke extract stimulates the accumulation of cholesterol within macrophages in vitro, an effect that is mediated at least in part by the CXCR2 chemotactic receptor. This receptor is believed to play an important role in inflammatory diseases, including atherosclerosis (Bosivert

Figure 8.3   Overview of mechanisms by which cigarette smoking causes an acute cardiovascular event
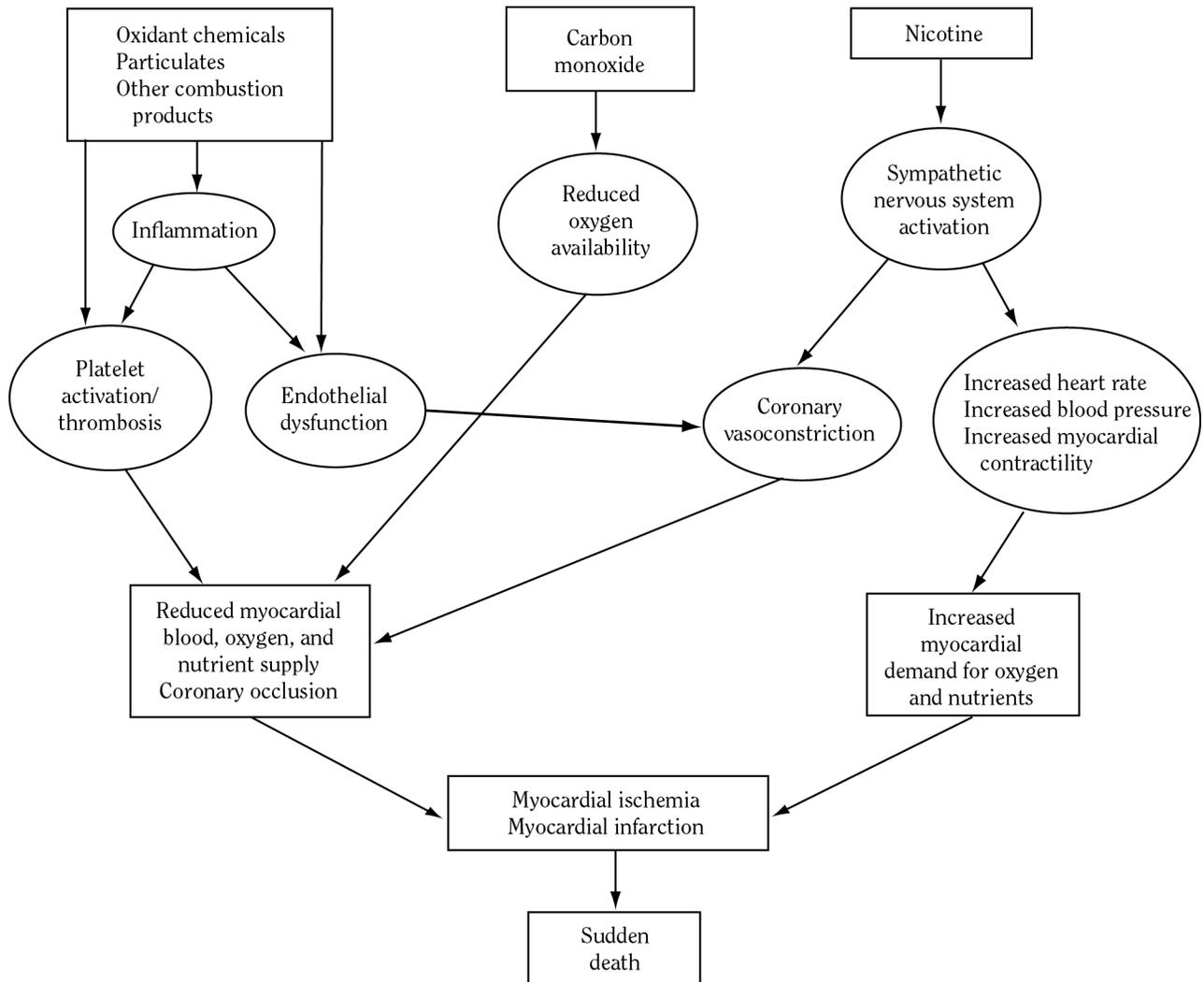
Source: Adapted from Benowitz 2003 with permission from Elsevier, © 2003.

et al. 1998). 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), another agonist at the AhR, accelerates the progression of atherosclerosis in apolipoprotein E-deficient mice (Wu et al. 2011). The progression of atherosclerosis from TCDD is inhibited by antagonists of both AhR and CXCR2, indicating that AhR activation mediated by CXCR2 could mediate the atherogenic effects of polycyclic aromatic hydrocarbons in smokers (Wu et al. 2011).

Nicotine is a sympathomimetic agent that increases heart rate and cardiac contractility, transiently increas-

ing blood pressure and constricting coronary arteries (see Chapter 5). Nicotine may also contribute to endothelial dysfunction, insulin resistance, and lipid abnormalities. However, international epidemiologic evidence, and data from clinical trials of nicotine patches, suggests that chemical components in smoke other than nicotine are more important in elevating the risk of death from MI and stroke. For a detailed discussion of these issues, see Chapter 5.

Smoking and Endothelial Function

The vascular endothelium, which consists of cells that line the blood vessels, is an organ that is central for normal cardiovascular functioning. The endothelium promotes the dilation of blood vessels to maintain organ blood flow, antagonizes thrombosis, and exerts anti-inflammatory effects. Endothelial function relies on the production and release of nitric oxide, but cigarette smoking reduces the availability of this molecule (USDHHS 2010; Csordas and Bernhard 2013). This effect of reduced availability of nitric oxide is mediated by oxidants and free radicals in cigarette smoke and by free radicals that are generated by the endothelial cells themselves. Cigarette smoking activates the enzyme nicotinamide adenine dinucleotide phosphate oxidase, which generates endothelial cell reactive-oxygen species (ROS), high levels of which contribute to endothelial dysfunction (Takac et al. 2012). Cigarette smoke-derived ROS also release nuclear factor-kappa B (NF-κB), which promotes the expression of pro-inflammatory cytokines and adhesion molecules. This results in the reduction of the anti-adhesive properties of the endothelium and the enhanced adhesion of platelets and leukocytes to the arterial wall. In addition, the endothelium regulates the release of factors involved in blood clotting, such as tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1). Exposure to cigarette smoking results in greater release of tPA and less release of PAI-1, promoting a prothrombotic state.

Plasma levels of adiponectin are lower in smokers, but they increase after the smoker quits (Tsai et al. 2011). Adiponectin is a hormone that is released from adipocytes (fat cells) and has insulin-sensitizing and anti-atherogenic properties (Lihn et al. 2005). In addition, adiponectin messenger RNA (mRNA) is expressed in peripheral blood mononuclear cells. Importantly, this hormone inhibits the expression of endothelial cell adhesion molecules. Adiponectin mRNA levels in blood mononuclear cells are lower in smokers, and they decline in relation to the number of cigarettes smoked per day (Tsai et al. 2011). Thus, the effects of smoking on both circulating and local adiponectin could contribute to atherogenesis.

Flow-mediated dilation (FMD), which is the dilation of blood vessels in response to increased blood flow, is mediated by the endothelium and is widely used as a test of endothelial function. Previously both active smoking and exposure to secondhand smoke were shown to impair FMD (USDHHS 2006, 2010). Recent studies have shown that brief exposure to secondhand smoke (1 hour or less) results in endothelial damage, as evidenced by reduced FMD, the release of von Willebrand factor antigen (which is stored in endothelial cells and released in response to endothelial cell injury), and the release of endothelial progenitor cells (which serve as a repair mechanism for endothelial injury) and of endothelial microparticles (Heiss et al. 2008; Di Stefano et al. 2010; Bonetti et al. 2011a).

Quitting smoking is associated with improved endothelial function, as assessed by FMD (Johnson et al. 2010). However, parental smoking has been found to be associated with reduced FMD in children 3–18 years of age, and this impairment persists into adulthood (28–45 years of age), even after controlling for smoking status (Juonala et al. 2012). This observation suggests that some of the effects of exposure to cigarette smoke on the endothelium can last a long time or even be permanent.

Prothrombotic Effects of Cigarette Smoking

Cigarette smoking promotes thrombosis by activating platelets and promoting the effects of the clotting factors; the activation of platelets plays a critical role in the formation of the thrombi that cause acute coronary events (USDHHS 2004, 2010). Smokers have higher circulating levels of markers of platelet activation, including platelet factor 4 and β-thromboglobulin, but the levels of these factors decline after smoking cessation (Caponnetto et al. 2011). Notably, exposure to secondhand smoke for just 1 hour results in marked activation of platelets (Yarlioglues et al. 2012).

A number of mechanisms for the platelet-activating effects of smoking have been explored. Cigarette smoking increases levels of platelet activating factor (PAF) and of PAF-like lipids, with the latter effect perhaps related to the oxidation of phospholipids (Lehr et al. 1994, 1997; USDHHS 2010). In addition, oxidative stress impairs the release of nitric oxide, as mentioned earlier in this chapter. Nitric oxide inhibits the activation of platelets (Kubes et al. 1991; Tsao et al. 1994). The impaired release of nitric oxide can be partially reversed by the administration of antioxidants, such as vitamin C (Lehr et al. 1994, 1997). Moreover, cigarette smoking increases the formation of thromboxane A2, a platelet-derived factor that promotes platelet aggregation, and it inhibits the endothelial release of prostacyclin, which reduces platelet aggregation (Nowak et al. 1987). In a study in mice, acrolein, an unsaturated aldehyde present in high concentrations in

cigarette smoke, when delivered by inhalation resulted in increased adenosine diphosphate-induced platelet aggregation, a greater number of circulating platelet-leukocyte aggregates, higher levels of platelet factor 4, and increased platelet-fibrinogen binding, all having prothrombotic effects (Sithu et al. 2010).

Cigarette smoking also has a number of effects on the coagulation system that promote thrombosis. Smoking increases the generation of von Willebrand factor, thrombin, and fibrinogen, and it impairs fibrinolysis, a process that is critical to the dissolution of blood clots (Matetzky et al. 2000; Sambola et al. 2003; MacCallum 2005). Moreover, endothelial dysfunction caused by smoking reduces the release of tPA and increases the expression of PAI-1 (Newby et al. 2001).

The binding of activated platelets to leukocytes results in both pro-inflammatory and prothrombotic effects. This binding is modulated by the cluster of differentiation (CD)40 receptor and its ligand. Smokers demonstrate both an increased number of platelet-monocyte aggregates and greater upregulation of the CD40/CD40 ligand system (Harding et al. 2004).

Cigarette smokers have higher levels of thrombopoietin than do nonsmokers (Lupia et al. 2010). This is important because thrombopoietin is a growth factor that simulates the proliferation and differentiation of megakaryocytes, resulting in increased numbers of mature platelets and enhanced platelet activation in response to different stimuli.

Smoking also changes the structure of platelets, with smokers demonstrating altered platelet membrane fluidity, which is associated with the effects of oxidants on lipids. Smoking changes the ultrastructure of the fibrin network and is associated with a more prominent globular nature and increased pseudopodia formation (Pretorius 2012).

In contrast, the efficacy of the drug clopidogrel has been shown to be greater in smokers than in nonsmokers (Berger et al. 2009). Clopidogrel is widely used to treat acute coronary syndrome and to prevent stenosis after the placement of a coronary stent. This beneficial effect is hypothesized to be due to greater baseline platelet aggregation in smokers and/or to greater generation of the active metabolite of clopidogrel because of the induction of CYP1A2 enzymatic activity. The enhanced antiplatelet effect of clopidogrel in smokers, however, when measured using in vitro tests, disappears after quitting smoking, supporting the idea that the greater effect in smokers is due to the hypercoagulable state.

Cigarette Smoking and Inflammation

Inflammation plays an important role in the pathogenesis of both atherosclerosis and acute coronary syndromes (Libby 2013); numerous relevant reviews on various aspects of smoking and inflammation have been published and the topic was covered extensively in the 2010 Surgeon General's report (Arnson et al. 2010; Goncalves et al. 2011; Lee et al. 2012). Cigarette smoking results in a chronic systemic inflammatory response, as evidenced by higher levels of leukocytes (particularly neutrophils), C-reactive protein (CRP), interleukin-6 (IL-6), fibrinogen, soluble intercellular adhesion molecule-1, and monocyte chemoattractant protein-1 in smokers than in nonsmokers (Levitzky et al. 2008). Recent studies have shown that smokers have higher levels of the pro-inflammatory mediators tumor necrosis factor-α and IL-1B (Petrescu et al. 2010; Barbieri et al. 2011).

Research has also shown that exposure to secondhand smoke is associated with chronic inflammation. A study by Jefferis and colleagues (2010b) found that serum cotinine in nonsmokers was positively associated with white blood cell count and with levels of CRP, IL-6, fibrinogen, and matrix metalloproteinase 9. In that study, the CRP levels of nonsmokers (those at the two lowest exposure levels) were about one-third lower than the levels of active smokers, but CRP levels increased more sharply among nonsmokers at higher exposure levels suggesting a possible nonlinear dose-response relationship.

An important mechanism by which smoking produces an inflammatory response is the activation of the NF-κB pathway (Goncalves et al. 2011). Activation of this pathway results in NF-κB transduction to the cell nucleus, where it induces transcription of many genes involved in immune regulation. Cigarette smoke, smoke extracts, and smoke vapor have all been shown to activate the NF-κB pathway (Rom et al. 2013). Oxidative stress results in the generation of ROS, of nitric oxide resulting in the generation of peroxynitrite, and of aldehydes, such as acrolein and crotonaldehyde, all of which activate NF-κB (Rom et al. 2013). Other potential mediators of inflammation include lipopolysaccharides (endotoxins), which are found in tobacco smoke.

Cigarette smoking also increases the number of macrophages, a key cellular defense mechanism against inhaled agents (Goncalves et al. 2011). Activation of NF-κB by smoke induces the expression of adhesion molecules while also promoting the migration of macrophages.

Cigarette smoke stimulates macrophages to release pro-inflammatory markers, ROS, and proteolytic enzymes. Activation of macrophages by smoking also increases the activity of metalloproteinase enzymes, which degrade collagen and contribute to unstable coronary plaques and acute coronary syndrome (O'Toole et al. 2009). Thus, smoking leads to inflammation through multiple pathways.

In addition to causing coronary artery disease, smoking causes stroke, including subdural hematoma. The chronic inflammatory state induced by smoking is thought to be a critical element in the development, progression, and rupture of cerebral aneurysms, a process that results in intracranial hemorrhage (Chalouhi et al. 2012).

Updated Summaries of the Evidence: Active Smoking

Previous Surgeon General's reports have reviewed the evidence that both cigarette smoking and exposure to secondhand smoke cause CVD (USDHHS 1983, 2004, 2006). Evidence related to the actual mechanisms by which cigarette smoking and exposure to tobacco smoke cause CVD and related atherosclerosis was also previously reviewed in detail (USDHHS 2010). The present section provides an update of that evidence. This update is not comprehensive, nor does it cover all topics; rather, it gives examples of new findings that expand upon findings in previous reports or that increase our understanding of conclusions drawn from earlier evidence.

Coronary Heart Disease

In characterizing the risk of CHD caused by cigarette smoking, the effect of smoking is generally expressed in terms of either the relative risk (RR) or the excess risk (Thun et al. 1997). At the most basic level, the RR is determined by dividing the CHD rate for the population of smokers by the rate for lifetime nonsmokers. In contrast, the excess risk is the difference between the rates of disease for smokers and nonsmokers. Figure 8.4 shows how these two estimates differ when applied to smoking. The graph shows the RRs and excess death rates for CHD from the Cancer Prevention Study II (CPS-II), which was sponsored by the American Cancer Society (Thun et al. 1997). Among men, the RRs were highest at relatively young ages (40–54 years of age) and declined steeply with advancing age. This pattern of a declining RR with age should not be interpreted as indicative of the population disease burden of CHD from smoking, however. In fact, even as the RR declined with increasing age, the excess risk rose substantially because of the increasing background rate of CHD mortality in nonsmokers at older ages. At older ages, many other risk factors, and age itself, are also powerful

determinants of CHD risk, and drive up the rate in non-smokers.

The most recent findings using the pooled results from five contemporary cohorts on the risk of CHD from smoking show that the RRs associated with smoking among populations 55 years of age and older have increased from those in CPS-II about two decades earlier (Thun et al. 2013). Among men, the multivariate-adjusted RR for CHD mortality increased from 1.78 (95% confidence interval [CI], 1.69–1.77) in the CPS-II cohort to 2.50 (95% CI, 2.34–2.66) in the more contemporary cohorts. Among women, the multivariate-adjusted RR for CHD increased from 2.0 (95% CI, 1.88–2.13) in the CPS-II cohort to 2.86 (95% CI, 2.65–3.08) in the contemporary cohorts. Thun and colleagues (2013) also reported on 50-year trends in smoking-related mortality in the United States based on data from the CPS-I compared with the CPS-II and pooled data from the five contemporary cohorts. Table 8.5 shows the CHD mortality rates per 100,000 for men and women 55 years of age and older by category of smoking history (never, current, former) across time in these three cohorts. For both male and female never smokers, the decline in mortality rates for CHD from CPS-I to the more recent contemporary cohorts was greater than the comparable decline among current smokers (men, 75.5% vs. 62.9%; women, 82.3% vs. 68.0%). Among former smokers, the declines (71.7% in men, 80.8% in women) were somewhat larger than they were in current smokers (62.9% in men, 68.0% in women) but smaller than they were in never smokers. As a result, the multivariate-adjusted RR for CHD mortality associated with current smoking also increased for both men and women, as reported above. The supplemental tables provided by Thun and colleagues (2013), which are not included in this chapter, show that the RR for death from CHD in the five contemporary cohorts exceeded 3.0 among male and female current smokers who were 55–74 years of age at baseline (the RR

Figure 8.4   Relative risk and excess death rate for coronary heart disease among men, by age group
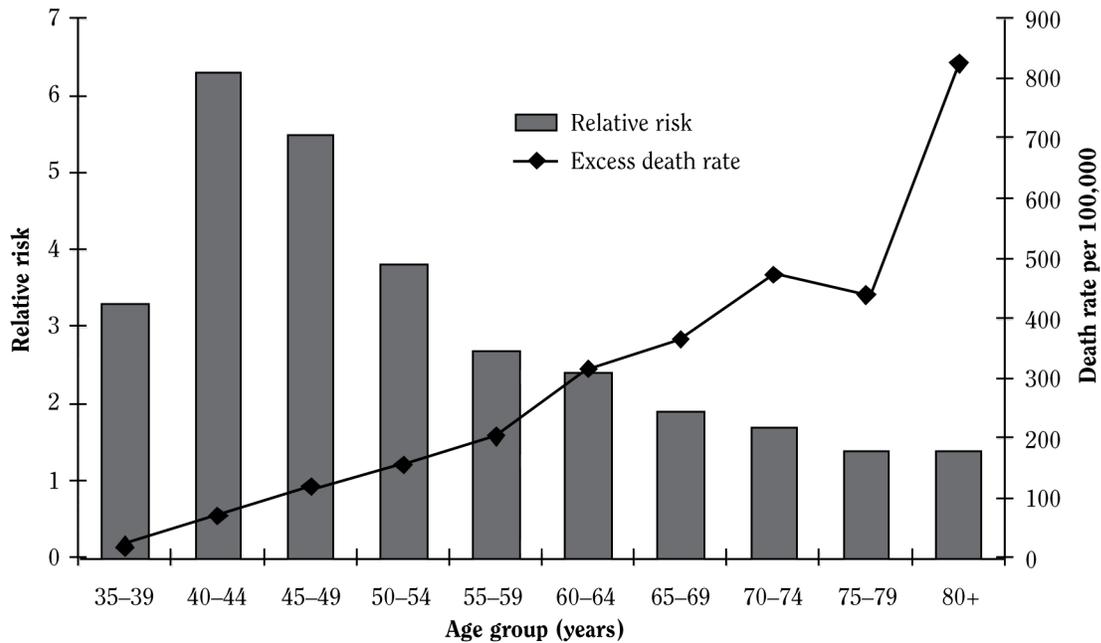
Source: Burns 2003. Adapted from Thun et al. 1997 with permission from Elsevier, © 2003.
Note: Data are from the American Cancer Society's Cancer Prevention Study II.

reached 3.9 among men 60–64 years of age at baseline and 3.8 among women 60–64 and 65–69 years of age at baseline). Thus, among those men and women 55–74 years of age in these contemporary cohorts who smoked, an estimated two-thirds of CHD deaths were attributable to their smoking.

In another analysis of pooled data from eight prospective studies, the majority of CHD cases were attributable to smoking among both men and women 40–89 years of age at baseline (Tolstrup et al. 2013). Relative to never smokers, CHD risk among current smokers was highest in the youngest and the lowest in oldest participants. Among women 40–49 years of age, the hazard ratio (HR) over the period 1974–1996 was 8.5 (95% CI, 5.0–14.0) and 3.1 (95% CI, 2.0–4.9) among women 70 years of age and older. Although the largest absolute difference in excess deaths was in the oldest participants, the proportion of CHD attributable to smoking increased among younger smokers. Among women smokers 40–49 years of age, 88% of CHD was attributable to smoking. The attributable proportions of CHD for other ages were 81% for women smokers 50–59 years of age, 71% for 60–69 years of age, and 68% for women smokers 70 years of age and older.

Previous Surgeon General's reports (USDHHS 2001, 2004) found that the proportion of deaths from CHD attributable to smoking among women appeared to be increasing. Some studies have identified smoking as a strong risk factor for MI in women younger than 50 years of age, overall (Rosenberg et al. 1985; Croft and Hannaford 1989; Prescott et al. 1998; Dunn et al. 1999; Stampfer et al. 2000), and among women who were racial/ethnic minorities, such as African Americans (Liao et al. 1999; Rosenberg et al. 1999). Evidence in the earlier reports documented high attributable risk for smoking in the case of MI in younger women who smoked. The findings of the pooled contemporary cohorts reported by Thun and colleagues (2013) document how the risks have increased among women during the last three decades. The Nurses' Health Study, one of the five cohorts in the pooled analyses, provides more detailed analyses of the risks of smoking for women (Kenfield et al. 2008, 2010). Among women who initiated smoking at an earlier age and smoked more cigarettes per day, the multivariate-adjusted RR for CHD death exceeded 4.0 in a comparison with never smokers. In addition, in the multivariate-adjusted analysis based with smoking status updated from the biennial study questionnaire, the RR for the overall sample approached 4.0 (3.91; 95% CI, 3.41–4.48) (Kenfield et al. 2008). Later, Huxley and Woodward (2011) performed a meta-analysis of 75 cohort studies with 2.4 million participants that adjusted

Table 8.5

Mortality rates from coronary heart disease adjusted to the U.S. 2000 standard populations, in men and women 55 years of age and older in Cancer Prevention Study I (CPS-I), CPS-II, and contemporary cohorts

	Never smokers			Current smokers			Former smokers		
	CPS-I	CPS-II	Contemporary cohorts	CPS-I	CPS-II	Contemporary cohorts	CPS -I	CPS-II	Contemporary cohorts
Men (rate/100,000)	1,678.67	852.71a	411.17a	2,403.70	1,289.73a	891.64a	1,977.97	1,026.76a	558.93a
Women (rate/100,000)	952.02	464.05a	168.69a	1148.82	676.13a	368.00a	1,107.60	553.82[a]	212.64[a]

Source: Thun et al. 2013.
[a]Age-standardized rate is significantly different from the rate in the earlier time period.

for various CVD risk factors. Although the absolute rates of CVD are lower among women than among men, the increment in risk from smoking is proportionally larger, often yielding higher RRs for women compared with men in epidemiologic studies. In the meta-analysis, the RR was significantly higher among women than among men for CHD (fatal and nonfatal), with the female/male ratio for the RR being 1.25 (95% CI, 1.12–1.39; p<0.0001). As discussed above, the recent Pooling Project on Diet and Coronary Heart Disease (Tolstrup et al. 2013) showed that the majority of CHD cases among smokers were attribut-able to smoking. These findings confirm a clear finding of previous Surgeon General's reports (USDHHS 2001, 2004): for women, and particularly women younger than 50 years of age, a high proportion of CHD is attributable to smoking in this group.

Cigarettes Smoked Per Day

The data on risks of exposure to secondhand smoke and CHD indicate that the dose-response relationship between such exposure and cardiovascular effects is non-linear (USDHHS 2010). The RR is higher than projected from downward extrapolation of RRs observed in active smokers. Interestingly, the substantial cardiovascular risk attributable to involuntary exposure to secondhand smoke (USDHHS 2006), combined with the approach in most CVD studies of not excluding from the control group per-sons who had exposure to secondhand smoke, has resulted in the underestimation in many research reports of the effects of active smoking. The underestimation of the risk for active smoking results from making comparisons to never smokers including both those having no exposure

Previous Surgeon General's reports (USDHHS 2004, 2010) showed an increased risk of having CHD at all lev-els of cigarette smoking, and greater risks were evident even for persons who smoked fewer than 5 cigarettes per day (Rosengren et al. 1992; Luoto et al. 2000; Prescott et al. 2002; Bjartveit and Tverdal 2005; Pope et al. 2009; Schane et al. 2010). The evidence reviewed in the 2010 Surgeon General's report showed an increase in CHD risk with more cigarettes smoked per day only up to about 25 cigarettes; from that point, the risk imposed by further increases in cigarette consumption grew by smaller incre-ments (Neaton and Wentworth 1992; Rosengren et al. 1992; Thun et al. 1997). In contrast, data from the five contemporary cohorts (Thun et al. 2013) show a signifi-cantly increasing trend for increased risk of CHD mortal-ity for both men (p <0.0001) and women (p <0.003) up to 40 cigarettes per day. In the Nurses' Health Study, the trend for increased risk of CHD mortality from smoking was significant through 35 or more cigarettes per day (RR = 4.92; 95% CI, 3.67–6.58) (Kenfield et al. 2008).

to secondhand smoke as well as those never smokers who have current or past exposure to secondhand smoke.

Information on exposure to secondhand smoke based on biomarkers has been relatively limited in epidemiologic studies. Among the British men studied by Whincup and colleagues (2004) in a study on passive smoking and risk of CHD and stroke, however, about three-fourths had their level of exposure to secondhand smoke confirmed by a cotinine level above 0.7 nanograms/milliliter (ng/mL) when baseline blood samples were collected in 1978–1980. Exposure data for the United States are not available before NHANES III, Phase 1 (Pirkle et al. 2006), which was conducted from 1988–1991, but measurements of cotinine in never and former smokers taken at the time documented that exposure to secondhand smoke was highly prevalent (88% exposed), and a substantial proportion had levels above 0.7 ng/mL (among men 40–59 years of age, 17% of never smokers and 24% of former smokers) (Centers for Disease Control and Prevention [CDC] 2013, unpublished data). Previous Surgeon General's reports (USDHHS 2006, 2010) have reviewed the risk from such levels of exposure to secondhand smoke. However, the potential impact of declines in exposure to secondhand smoke in the United States over the last several decades (Pickett et al. 2006; Pirkle et al. 2006; CDC 2009a, 2010) on the continuing decline in CVD age-adjusted death rates since the late 1960s has not been explored or evaluated.

Smoking Cessation

The risks of MI and death from CHD have been found to be lower among former smokers than among current smokers in many studies, including those with data adjusted for levels of other risk factors (Gordon et al. 1974; Åberg et al. 1983; USDHHS 1990; Kuller et al. 1991; Frost et al. 1996). Studies have also demonstrated a rapid reduction in risk after cessation among populations at high risk for CHD (Ockene et al. 1990) and among both men and women (Kawachi et al. 1993, 1994; Critchley and Capewell 2003; Anthonisen et al. 2005; Kenfield et al. 2008).

More than 25 years ago, the term "smoker's paradox" was given to the observation that following an acute MI (AMI), smokers appeared to experience lower mortality rates than nonsmokers (Sparrow and Dawber 1978; Kelly et al. 1985). The conclusion offered in a leading textbook (Libby et al. 2007) on heart disease suggests that the observation that being a smoker at the time of an AMI could predict a better clinical outcome is likely not due to any benefit from smoking but rather could be due to the younger age (estimated to be about a decade) at which smokers typically present with a first AMI. In a recent systematic review of 17 studies to investigate this

issue, some data from 6 studies that were conducted in the earlier prethrombolytic and thrombolytic treatment era supported the "smoker's paradox" hypothesis, but in the 11 other studies the review found none of a contemporary population with acute coronary syndrome that supported the hypothesis (Aune et al. 2011). In addition to possible explanations suggested by previous reviews of confounding due to age and comorbidity of smokers (Burns 2003; Libby et al. 2007), Aune and colleagues (2011) noted that smokers with an AMI could have a greater out-of-hospital case fatality rate (Sonke et al. 1997; McElduff and Dobson 2001; Elosua et al. 2007), thereby erroneously lowering their apparent mortality rate because of failure to document these deaths. Additionally, the fibrin-rich thrombus in smokers with stent thronbosis-segment elevation MI could make them more amenable to fibrinolytic therapy (Grines et al. 1995; Sambola et al. 2003; Kirtane et al. 2005).

Thun and colleagues (2013), in detailed supplemental tables for men and women 55 years of age and older, reported declines in CHD mortality in former smokers by years since quitting in comparison with current smokers as well as continuing elevations of risk in comparison with never smokers. For women, the pattern of declining risks with duration since quitting was somewhat stronger, with the RR for CHD mortality, in a comparison with continuing smoking, decreasing to 0.63 (95% CI, 0.52–0.78) 2–4 years after quitting and declining to about 0.40 for 30 or more years since quitting. For men, declines in risk of CHD mortality after quitting were also observed, but they were less pronounced than those for women. In comparison with current smokers, the RR for men who quit did not drop significantly below a risk equal with current smokers until more than 10 years after quitting. In comparison with never smokers, former smokers had a relative risk of CHD mortality of 1.9 10–19 years after quitting among both men and women.

Although these data from the five contemporary cohorts show less decline with duration of quitting, participants in the cohorts were 55 years of age and older when follow-up began in 2000 (Thun et al. 2013). In contrast, analyses of the Multiple Risk Factor Intervention Trial (MRFIT) (1990, 1996) and the Lung Health Study (Anthonisen et al. 2005) cohorts, in which sustained quitters were compared with current smokers, found an estimated decline of two-thirds in risk of death from CVD. Similarly, in a large population-based cohort of men and women (the Norwegian Counties Study), Vollset and colleagues (2006) showed the powerful effect on CVD mortality in middle age (40–70 years of age) of continuing to smoke versus quitting. In 25 years of follow-up, over twice as many women who continued to smoke died of CVD compared with former smokers (6.28% vs. 2.86%);

for men, the rates were 17.05% for current smokers and 9.03% for former smokers. Hence, the benefits of quitting smoking on reduced risk for CHD mortality have been well documented (USDHHS 1990, 2004, 2010).

Sudden Death

Sudden death is the sudden, abrupt loss of cardiac function in a person who may or may not have a diagnosed heart disease, for whom the time and mode of death are unexpected and where death occurs instantly or shortly after the onset of symptoms (American Heart Association 2013). An estimated 70–85% of sudden deaths are due to cardiac arrest from untreated cardiac arrhythmias; often cardiac arrest is the first manifestation of CHD (USDHHS 2004; CDC 2010; Fishman et al. 2010). Annually, over 380,000 people in the United States experience sudden cardiac arrest, and an estimated 92–95% die before reaching a hospital or another source of emergency assistance (Pell et al. 2003; CDC 2010; Roger et al. 2012).

Epidemiologic evidence indicates that cigarette smoking is associated with sudden cardiac death of all types. Burns (2003) indicated that among persons who had smoked, the RR was higher for sudden cardiac death than for CHD or MI. Other reports have found that the RR for sudden death among current smokers, in comparison with lifetime nonsmokers, often exceeded 3.0 (U.S. Department of Health, Education, and Welfare [USDHEW] 1971, 1979; Dawber 1980; Kannel and Thomas 1982; USDHHS 1983; Wannamethee et al. 1995; Sexton et al. 1997). In multivariate analyses of combined data from the Framingham Heart Study and the Albany Cardiovascular Health Center Study that examined sudden cardiac death in men 45–64 years of age, cigarette smoking was the risk factor that was judged to be the most potent contributor to risk based upon multivariate statistical testing (Kannel et al. 1975). In a study of data from the National Center for Health Statistics' 1986 National Mortality Followback Survey among persons with no history of CHD, cigarette smoking was the only modifiable risk factor associated with sudden coronary death. Among persons with known CHD it was one of several modifiable factors associated with an increased risk of sudden coronary death (Escobedo and Zack 1996; Escobedo and Caspersen 1997). Cigarette smoking was also associated with risk of sudden cardiac death in the 18-year follow-up of the Honolulu Heart Program (Kagan et al. 1989) and in the 28-year follow-up of the Framingham Heart Study (Cupples et al. 1992). In addition, in a recent report on the cohort of 161,808 postmenopausal women who participated in the Women's Health Initiative, the multivariate-adjusted HR for sudden cardiac death among women without prior CHD was 3.12 (95% CI, 2.12–4.60) for current smokers compared with former/never smokers (Bertoia et al. 2012).

In a meta-analysis of 20 prospective cohort studies among patients after MI, Critchley and Capewell (2003) reported on the pooled effects for smoking cessation with a 36% decrease in all-cause mortality and a 32% decrease in recurrent MI. Earlier, Hallstrom and colleagues (1986) found that the risk of recurrent cardiac arrest among smokers surviving out-of-hospital cardiac arrest was lower among persons who then stopped smoking than among those who continued to smoke. Peters and colleagues (1995), reporting from the Cardiac Arrhythmia Suppression Trial, found an association between smoking cessation and a reduction in death from cardiac arrhythmia for patients who had left ventricular dysfunction after MI. Similarly, Shah (2010) in a literature review, reported that among patients with left ventricular dysfunction after MI the risk of all-cause mortality was reduced significantly at the 6-month follow-up among smokers who quit (HR = 0.57; 95% CI, 0.31–0.91), as was risk of death or recurrent MI (HR = 0.68; 95% CI, 0.47–0.99).

Cerebrovascular Disease/Stroke

Previous Surgeon General's reports (2004, 2010) have reviewed the evidence on the relationship between smoking and cerebrovascular disease. Judging from the findings of these reports and a variety of other studies, it is apparent that after adjustment for other risk factors, cigarette smokers have a higher risk of stroke and higher mortality from cerebrovascular disease than do lifetime never smokers, and there is a dose-response relationship with smoking (USDHHS 1983, 2001, 2004; Neaton et al. 1984; Colditz et al. 1988; Wolf et al. 1988; Kannel and Higgins 1990; Kuller et al. 1991; Freund et al. 1993; Hames et al. 1993; Håheim et al. 1996; Tanne et al. 1998; Hart et al. 1999; Jacobs et al. 1999; Sharrett et al. 1999; Djoussé et al. 2002).

The Atherosclerosis Risk in Communities (ARIC) study found a range of adjusted RRs for specific forms of stroke among current smokers in comparisons with a combination of former and never smokers: cardioembolic stroke (1.95; 95% CI, 1.28–2.98), lacunar stroke (2.23; 95% CI, 1.49–3.34), and nonlacunar stroke (1.66; 95% CI, 1.30–2.11) (Ohira et al. 2006). This variability in RR is consistent with the differing etiologies of stroke subtypes (O'Donnell et al. 2010a; Bezerra et al. 2012). Similarly, smoking cessation is associated with a reduced risk of stroke generally (Samet 1990; USDHHS 1990, 2004; Shah and Cole 2010); some of this benefit may be

obtained within months of quitting and could be a function of decreases in blood coagulability and other acute mechanisms of stroke following cessation.

Thun and colleagues (2013), in their analysis of five contemporary cohorts, found a multivariate-adjusted RR of 2.10 (95% CI, 1.87–2.36) for any stroke death associated with current smoking among women 55 years of age and older. For men in that age group, the RR was 1.92 (95% CI, 1.66–2.21). By age, the risk for stroke among current smokers was highest among men 60–64 years of age (RR = 3.9; 95% CI, 3.2–4.8) and among women 65–69 years of age (RR = 3.8; 95% CI, 2.3–6.3). Among both men and women, risk decreased with greater duration of cessation (Thun et al. 2013).

Aortic Aneurysm

Aortic aneurysms have severe consequences, including death. Autopsy studies show that smoking in adolescence and young adulthood causes early abdominal aortic atherosclerosis in young adults (USDHHS 2012). Other mechanisms by which smoking might injure the abdominal aorta include chronic inflammation and damage to elastin (USDHHS 2010). In the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study, McGill and colleagues (2008) analyzed autopsy specimens of coronary arteries and the abdominal aorta from almost 3,000 15- to 34-year-olds (Whites and Blacks), who had died of external causes (accidents, homicides, suicides). Tobacco use was associated with the prevalence of early lesions in the abdominal aorta, which were more severe and advanced than lesions in the coronary arteries.

Peripheral Arterial Disease

Cigarette smoking and diabetes are well established as major risk factors for PAD, as reported in previous Surgeon General's reports. A strong dose-response relationship between smoking and PAD has been observed even after adjustment for other CVD risk factors (Weiss 1972; Kannel and Shurtleff 1973; USDHHS 1983; Wilt et al. 1996; Price et al. 1999; Meijer et al. 2000; Ness et al. 2000). The 1964 report commented on Buerger's disease, a fairly rare subset of PAD cases, and concluded that "Buerger's disease, or thromboangiitis obliterans, has been traditionally associated with smoking, and the literature contains numerous clinical reports describing the arrest of Buerger's disease when smoking is stopped and its reactivation on resumption of smoking" (USDHEW 1964, p. 326). Later, data from the Framingham Heart Study

demonstrated an increased risk of PAD among both young and older male and female cigarette smokers after adjustment for other cardiovascular risk factors (Freund et al. 1993). In addition, the authors found that risk rose significantly with an increase in the number of cigarettes smoked per day. The Framingham Offspring Study ported a similar finding (Murabito et al. 2002). Earlier, several researchers observed a significantly higher rate of late arterial occlusion in patients who continued to smoke after peripheral vascular surgery than in those who stopped smoking (Wray et al. 1971; Ameli et al. 1989; Wiseman et al. 1989). In a Swedish study among smokers with claudication, progression to critical limb ischemia was reduced in those who stopped smoking (Jonason and Bergström 1987).

While many studies of PAD have not had a detailed focus on smoking, a recent prospective analysis using the Women's Health Study evaluated the relationships of smoking and smoking cessation with symptomatic PAD (Conen et al. 2011). In a cohort of 39,825 women who were followed for a median of 12.7 years, the age-adjusted incidence rate for PAD showed a strong risk gradient beginning with never smokers, then former smokers, current smokers reporting less than 15 cigarettes per day, and finally current smokers reporting 15 or more cigarettes per day. In the multivariate analysis with smoking status updated during follow-up with additional covariates, the RR for PAD among former smokers was 3.16 (95% CI, 2.04–4.89). For the two strata of current smokers, the RR was 11.94 (95% CI, 6.90–20.65) and 21.08 (95% CI, 13.10–33.91), respectively. The analysis also found a strong association with reduction in RR by duration of cessation, with the fully adjusted HR declining to 0.39 (95% CI, 0.24–0.66) for abstinence of less than 10 years, to 0.28 (95% CI, 0.17–0.46) for 10–20 years, and to 0.16 (95% CI, 0.10–0.26) for more than 20 years.

Pipes and Cigars

Compared with persons who smoke cigarettes, smokers who smoke pipes or cigars exclusively have a lower risk for many smoking-related diseases (National Cancer Institute [NCI] 1998). Smoke from pipes and cigars contains the same toxic substances as cigarette smoke, but those who use a pipe or cigar usually smoke at a lower frequency; observation indicates that they tend not to inhale the smoke, thus reducing their exposure to its toxic substances (USDHEW 1979; NCI 1998; Shanks et al. 1998). Evidence indicates that former cigarette smokers are more likely to inhale pipe or cigar smoke than are primary pipe and cigar smokers who have never smoked cigarettes (Pechacek et al. 1985; Turner et al. 1986; Ockene

et al. 1987). Ockene and colleagues (1987), who reported data from over 8,000 tobacco users in the MRFIT, found that former cigarette smokers who switched to a pipe or cigar were more likely to report inhaling the smoke into their lungs than were pipe or cigar smokers who had not smoked cigarettes previously; and these former cigarette smokers had higher biochemical measures of exposure. Based on these and other data, NCI (1998) concluded that former cigarette smokers who switch to a pipe or cigar are more likely to have higher doses to the lungs of toxic chemicals in tobacco smoke than are pipe and cigar smokers who never smoked cigarettes. As a result, NCI (1998) concluded that former cigarette smokers who currently smoke cigars are more likely to inhale more deeply than cigar smokers who have never smoked cigarettes, and their risks are intermediate between cigarette smokers and cigar smokers who have never smoked cigarettes.

In recent years, both the sale and consumption of small, cigarette-like cigars have increased, and data indicate that the dual use of cigars and cigarettes is becoming common (CDC 2011; Richardson et al. 2012), in turn suggesting the potential for increased health effects from cigars. Although previous research suggested that exclusive use of cigars may pose lower risks for smoking-related diseases (NCI 1998) than those imposed by cigarettes, the manner in which these cigarette-like cigars are consumed and the risk they pose merit careful attention.

Methods to Reduce Risk

Smoking cessation remains one of the most effective strategies for both the primary and secondary prevention of CVD (CDC 2013). Regardless, for those smokers who continue to use tobacco, particularly combustible forms of tobacco, a limited number of studies (clinical trials, prospective cohort studies, and other research) have attempted to evaluate methods for reducing CVD risks by lowering the levels of exposure to combusted tobacco.

The 2010 Surgeon General's report reviewed the evidence that reducing smoking in the absence of cessation could improve the clinical outcomes of heart disease. In some, but not all studies, reductions in cigarette use by as much as 50% or down to less than 10 cigarettes per day were followed by reductions in exposure to nicotine as well as improvements in values for hemoglobin, leukocyte counts, and fibrinogen and cholesterol levels (Hurt et al. 2000; Eliasson et al. 2001; Hughes et al. 2004; Hatsukami et al. 2005; Joseph et al. 2005). However, these improvements were minor compared with those observed in individuals who stopped smoking. Further, none of the studies

showed improvements in clinical outcomes of heart disease, which is consistent with evidence that even low levels of exposure to tobacco smoke substantially increase the risk of cardiac events. The 2010 Surgeon General's report also reviewed the epidemiologic evidence that reducing cigarette consumption could lower the risk of all-cause and CVD mortality and concluded that the results are inconclusive as to whether reducing cigarette consumption reduces overall or CVD mortality. The recently published findings of two new long-term prospective cohort studies support that conclusion (Hart et al. 2013).

Appendix 14.5 reviews the various pharmacologic aids to smoking cessation. Because of growing interest in noncigarette sources of nicotine as a policy option (see Chapters 15, "The Changing Landscape of Tobacco Control: Current Status and Future Directions" and 16, "A Vision for Ending the Tobacco Epidemic: A Society Free of Tobacco-Related Death and Disease"), the CVD risks of nicotine replacement therapy (NRT) are reviewed here. In the studies of reduced smoking, there were some improvements in values for hemoglobin, leukocyte counts, and fibrinogen and cholesterol levels among study participants who were using NRTs (Hurt et al. 2000; Eliasson et al. 2001; Hughes et al. 2004; Hatsukami et al. 2005; Joseph et al. 2005). In addition, clinical trials of smoking cessation have shown improvements in lipid profiles even in persons using NRTs (Allen et al. 1994; Lúdvíksdóttir et al. 1999). Other studies have shown improvements in markers of thrombogenesis among participants in smoking cessation trials who abstained from smoking but were using medicinal nicotine (Benowitz et al. 2002; Haustein et al. 2002). Earlier, Mahmarian and colleagues (1997) measured the effects of smoking and the use of nicotine patches on myocardial perfusion in patients with known CHD and concluded that these patches were safe for smokers with heart disease.

The Lung Health Study provided an important opportunity to examine the natural history and safety of prolonged use of nicotine polacrilex gum (NP) among thousands of trial participants who quit smoking (Murray et al. 1996). In a 5-year follow-up of 3,094 users of NP, rates of hospitalization for CVD conditions and CVD deaths were not related either positively or negatively to the use of NP, to the dose of NP, or to concomitant use of NP and cigarettes. Although the hemodynamic effects of nicotine intake could potentially have implications for risk of CVD (USDHHS 2010), the results from the study by Murray and colleagues (1996) and from other studies (Joseph et al. 1996; Tzivoni et al. 1998) suggest that combustion compounds in tobacco smoke, such as carbon monoxide and nitrogen oxides, are the primary contributors to increased cardiovascular risk.

The available evidence suggests that the long-term use of medicinal nicotine (see Appendix 14.5 for discussion of new products) would not substantially increase risk of CVD. Nevertheless, because smoking cessation is strongly established as markedly reducing the risk of MI, sudden death, and stroke, cessation and abstinence, not medicinal nicotine, should be stressed as the goal for interventions dealing with dependence on tobacco.

Updated Evidence Reviews

Exposure to Secondhand Smoke and Stroke

This section comprehensively updates the evidence on exposure to secondhand smoke and risk of stroke that was presented in the 2006 Surgeon General's report, *The Health Consequences of Involuntary Exposure to Tobacco Smoke* (USDHHS 2006). That report, which addressed the biologic basis for the possible effects of exposure to secondhand smoke on risk for CVD (including cerebrovascular disease), summarized evidence from six studies (Lee et al. 1986; Donnan et al. 1989; Sandler et al. 1989; Howard et al. 1998b; Bonita et al. 1999; You et al. 1999) that examined the association between exposure to secondhand smoke and risk of stroke. One of the six studies used a prospective cohort design (Sandler et al. 1989); that study and one by Bonita and colleagues (1999) were the only two of the six to find a significant increase in the risk of stroke among persons exposed to secondhand smoke. According to the 2006 report, "The evidence is suggestive but not sufficient to infer a causal relationship between exposure to secondhand smoke and an increased risk of stroke" (USDHHS 2006, p. 15).

Active smoking is a major cause of cardiovascular morbidity and mortality, including cerebrovascular disease (USDHHS 2006, 2010). The 2010 Surgeon General's report offered an indepth review of the mechanisms by which active smoking contributes to the risk of cerebrovascular disease. As for CHD, the major mechanisms include promoting the development of atherosclerotic disease, narrowing the lumen of the vessels, increasing endothelial dysfunction, and damaging the vessel wall (Wells 1994; Ahijevych and Wewers 2003; Ambrose and Barua 2004; Barnoya and Glantz 2005; USDHHS 2010). The relative strength of the association between active smoking and cerebrovascular events differs by stroke subtype, with stronger associations for ischemic stroke than for hemorrhagic stroke (Shah and Cole 2010). The risk of subarachnoid hemorrhage stroke is most strongly associated with smoking (Woo et al. 2009; Kim et al. 2012; Juvela et al. 2013; Vlak et al. 2013; Zhang in press). Exposure to secondhand smoke also contributes to risk of stroke via several acute mechanisms, such as inflammation, vasoconstriction, and enhanced formation of clots (Ahijevych and Wewers 2003; Ambrose and Barua 2004; USDHHS 2010).

Additionally, studies provide evidence that exposure to secondhand smoke may increase the risk of hypertension, a potent risk factor for stroke. For example, in a study of 579 Japanese women, Seki and colleagues (2010) found that women exposed to secondhand smoke had significantly higher average blood pressures than women who were unexposed. In Germany, a study by Simonetti and colleagues (2011) of 4,236 preschool children found that even after adjustment for multiple possible confounding factors, children exposed to secondhand smoke through parental smoking at home had significantly higher average blood pressures than children who were unexposed.

Epidemiologic Evidence

Epidemiologic evidence of the association between exposure to secondhand smoke and risk of stroke was summarized in a systematic review and meta-analysis by Oono and colleagues (2011). This section is based heavily on their work because the meta-analysis was comprehensive and recent. The section also focuses on an updated and enhanced literature search.

Meta-Analyses

In their meta-analysis, Oono and colleagues (2011) summarized evidence from 20 studies that provided 35 estimates of the association between exposure to secondhand smoke and risk of stroke of any type, including subarachnoid hemorrhage (Figure 8.5). The majority of these studies provided separate effect estimates for men and women. For the association between exposure to secondhand smoke and incident stroke, the authors reported an overall pooled RR estimate of 1.25 (95% CI, 1.12–1.38);

Figure 8.5   Forest plot of studies examining the association between exposure to secondhand smoke and risk of stroke, stratified by study design

Study	Population		Effect size (95% CI)	% Weight
Prospective				
Gillis et al. 1984	Male		0.33 (0.04–2.84)	0.23
Gillis et al. 1984	Female		1.88 (0.22–16.02)	0.23
Sandler et al. 1989	Male		0.97 (0.65–1.46)	3.31
Sandler et al. 1989	Female		1.24 (1.03–1.49)	5.44
Yamada et al. 2003	Male		1.13 (0.19–6.58)	0.33
Yamada et al. 2003	Female		0.94 (0.57–1.55)	2.62
Iribarren et al. 2004	Male		1.02 (0.71–1.48)	3.62
Iribarren et al. 2004	Female		1.17 (0.92–1.50)	4.83
Whincup et al. 2004	Male		1.54 (0.68–3.47)	1.32
Qureshi et al. 2005	Female		0.90 (0.60–1.30)	3.46
Wen et al. 2006	Female		1.52 (1.08–2.15)	3.83
Hill et al. 2007 (Study 1)	Male		1.59 (1.14–2.21)	3.96
Hill et al. 2007 (Study 1)	Female		0.90 (0.67–1.21)	4.30
Hill et al. 2007 (Study 2)	Male		1.82 (1.20–2.77)	3.20
Hill et al. 2007 (Study 2)	Female		1.17 (0.76–1.82)	3.06
Glymour et al. 2008 (Study 1)	Male		1.63 (0.83–2.70)	2.12
Glymour et al. 2008 (Study 1)	Female		1.46 (1.00–2.18)	3.43
Glymour et al. 2008 (Study 2)	Male		1.76 (1.31–2.41)	4.21
Glymour et al. 2008 (Study 2)	Female		1.56 (0.91–3.12)	2.00
Jefferis et al. 2010a[a]	Male and female		0.94 (0.80–1.11)	5.65
Subtotal (I-squared = 47.3%, p = 0.010)			1.22 (1.08–1.38)	61.15
Case-control				
Lee et al. 1986	Male		0.84 (0.31–2.27)	0.94
Lee et al. 1986	Female		0.92 (0.51–1.65)	2.14
Donnan et al. 1989	Male and female		1.60 (0.60–3.90)	1.05
Bonita et al. 1999	Male		2.10 (1.33–3.32)	2.91
Bonita et al. 1999	Female		1.66 (1.07–2.57)	3.05
You et al. 1999	Male and female		1.70 (0.98–2.92)	2.35
Anderson et al. 2004	Male		0.50 (0.20–1.30)	1.05
Anderson et al. 2004	Female		1.30 (0.70–2.30)	2.10
McGhee et al. 2005	Male		1.31 (0.87–1.99)	3.24
McGhee et al. 2005	Female		1.57 (1.11–2.24)	3.77
Subtotal (I-squared = 26.5%, p = 0.200)			1.41 (1.15–1.72)	22.59
Cross-sectional				
Howard et al. 1998b	Male and female		1.06 (0.64–1.75)	2.60
Iribarren et al. 2001	Male		0.27 (0.11–0.57)	1.30
Iribarren et al. 2001	Female		0.89 (0.57–1.38)	3.02
Zhang et al. 2005	Female		1.44 (1.20–1.72)	5.49
He et al. 2008	Female		1.65 (1.17–2.32)	3.85
Subtotal (I-squared = 80.6%, p = 0.000)			1.03 (0.69–1.53)	16.26
Overall (I-squared = 54.2%, p = 0.000)			1.25 (1.12–1.38)	100.00

0.35   1   2   6   16

Source: Adapted from Oono et al. 2011 with permission from Oxford University Press, © 2011.

Note: Weights are from random effects analysis. **CI** = confidence interval.

[a]Excludes former smokers.

this estimate included information from 10 cohort studies (Gillis et al. 1984; Sandler et al. 1989; Yamada et al. 2003; Iribarren et al. 2004; Whincup et al. 2004; Qureshi et al. 2005; Wen et al. 2006; Hill et al. 2007; Glymour et al. 2008; Jefferis et al. 2010a), 6 case-control studies (Lee et al. 1986; Donnan et al. 1989; Bonita et al. 1999; You et al. 1999; Anderson et al. 2004; McGhee et al. 2005), and 4 cross-sectional studies (Howard et al. 1998b; Iribarren et al. 2001; Zhang et al. 2005; He et al. 2008)—totaling 5,894 cases of stroke among 885,307 participants. Although the risk of stroke associated with active smoking varies by the type of stroke (USDHHS 2004; Shah and Cole 2010), the analysis did not explore variation in risk of incident stroke by type. The authors also examined the dose-response relationship between exposure to secondhand smoke and risk of stroke by pooling the 3 studies (You et al. 1999; Zhang et al. 2005; He et al. 2008) that provided information about the number of cigarettes smoked per day to which participants were exposed. According to the meta-analysis and using as a reference group those exposed to zero cigarettes smoked per day, the pooled RR for stroke increased as the number of cigarettes rose: 5–9 (1.16; 95% CI, 1.06–1.27), 10–14 (1.31; 95% CI, 1.12–1.54), 15–39 (1.45; 95% CI, 1.19–1.78), and 40 or more (1.56; 95% CI, 1.25–1.96). Elsewhere, studies by Whincup and colleagues (2004) and Jefferis and colleagues (2010a) used serum cotinine levels to assess the effects of exposure to secondhand smoke; neither study found significant associations between such exposure defined by cotinine level and incident stroke; however, Jefferis and colleagues (2010a) did observe a dose-response relationship between serum cotinine levels and risk of incident stroke.

The limitations of the meta-analysis by Oono and colleagues (2011) largely reflect those of the broader literature on the topic of exposure to secondhand smoke and risk of stroke. The studies in this meta-analysis used various definitions of exposure to secondhand smoke and stroke and adjusted for a variety of possible confounders. The quality of exposure assessment and the potential for recall bias varied across the studies, however. The meta-analysis did not reveal any evidence of publication bias among the population of studies, but formal tests for publication bias have limitations themselves (Deeks et al. 2005), are based on only the published literature, and do not rule out the possibility that there are additional negative findings or studies that have never been published. Although Oono and colleagues (2011) observed a dose-response association between exposure and risk of stroke, this finding was based on only 3 studies that used a common definition of quantitative exposure to secondhand smoke (number of cigarettes smoked per day by smokers in the family and/or in the workplace); this common definition allowed pooling of data. Overall, the meta-analysis

by Oono and coworkers (2011) encompassed studies from multiple geographic areas (Asia, Australia, United Kingdom, and United States) and included large numbers of men and women, but the authors did not formally assess the quality of the studies. However, when the pooled analysis was limited to the 10 prospective cohort studies (generally considered the highest-quality design for observational studies), the pooled RR estimate was significant (1.22; 95% CI, 1.08–1.38) and highly consistent with the overall pooled estimate.

Description of the Literature Review

To identify new studies and other reports that were not included in the 2011 meta-analysis by Oono and colleagues, a systematic review was conducted using a broad search strategy. The search examined PubMed, EMBASE, Cochrane Library, and Web of Science for publications through February 2012. The following search string was used:

> "Tobacco Smoke Pollution" [MeSH] OR (tobacco AND smoke AND pollution) OR secondhand smok* OR second hand smok* OR SHSE OR involuntary smok* OR passive smok* OR passive cigarette smok* OR passive tobacco smok* OR Tobacco-exposed OR ("passive exposure" AND smok*) OR (Environmental Tobacco Smok*) OR (Environmental Pollution [MeSH] AND Tobacco Smoke)

> AND

> Stroke [MeSH] OR stroke* OR (Brain AND Vascular AND Accident*) OR CVA* OR "brain infarction" [MeSH] OR (brain AND infarction*) OR "Brain Stem Infarctions" [MeSH] OR "Cerebral Infarction" [MeSH] OR haemorrhage OR hemorrhage OR haemorrhages OR hemorrhages OR cerebral OR cerebrovascular OR (ischaemic AND attack*) OR (ischemic AND attack*) OR transient ischemic attack (TIA) OR Ischemic Attack, Transient [MeSH] OR Brain Ischemia [MeSH] OR Cerebral Hemorrhage [MeSH] OR Intracranial Hemorrhages [MeSH] OR Cerebrovascular Disorders [MeSH] OR Cerebral Arterial Diseases [MeSH] OR (brain AND ischemia) OR mortality [majr] OR "cardiovascular disease" [tiab]. LIMIT: animals [MeSH] NOT (humans [MeSH] AND animals [MeSH])

The search identified 880 unique records, but only 2 relevant reports—those of Molgaard and colleagues (1986) and O'Donnell and colleagues (2010b)—were not included in the review by Oono and colleagues (2011). This finding suggests that their meta-analysis was comprehensive in the evidence considered.

The study by Molgaard and colleagues (1986) was an early retrospective case-control study that used telephone interviews (for cases) and in-person interviews (for controls) to assess both exposure to secondhand smoke and active smoking. In this small study (40 cases and 120 controls), active smoking was significantly associated with stroke, but the odds ratios (ORs) for stroke from exposure to secondhand smoke in the home, workplace, or from past exposure due to parents' or siblings' smoking were not in a consistent direction or significant statistically. In the other relevant study by O'Donnell and colleagues (2010b) that was not included by Oono and colleagues (2011) in their meta-analysis, the report was only available in abstract form. This report was part of INTERSTROKE, a multinational case-control study designed to examine risk factors for stroke and stroke subtypes in 23 countries, but these results have not yet been published in a peer-reviewed journal. O'Donnell and colleagues (2010b) reported ORs for stroke based on the number of days per week that persons were exposed to secondhand smoke. Using people having no exposure to secondhand smoke as the reference group, the OR for stroke was 1.4 (95% CI, 1.1–1.8) for less than 1 day of exposure; 1.4 (95% CI, 1.1–1.7) for 1–6 days of exposure, and 1.7 (95% CI, 1.3–2.1) for daily exposure. Significant associations were observed for both ischemic stroke and intracerebral hemorrhage.

The large prospective cohort study by Iribarren and colleagues (2004) that was included in the pooled estimate by Oono and colleagues (2011) reported results from a cohort of 27,698 lifelong nonsmokers with no history of stroke. The participants, who were enrolled in a private health plan in northern California, underwent health checkups between 1979–1985. During this time, investigators collected information about exposure to secondhand smoke as well as demographic and other health information. The researchers used a questionnaire to obtain information about exposure to secondhand smoke in the home, workplace, and in other social settings. To capture information about incident stroke cases, investigators sought hospital discharge data (both inside and outside the health plan) and linkage to mortality data. In all, 706 cases of incident ischemic stroke (93 fatal) and 151 TIAs (all nonfatal) were ascertained during a median 16 years of follow-up. Using as the referent those persons having no hours per week of exposure to secondhand smoke in the home, the multivariable-adjusted RR estimate for ischemic stroke from 20 hours or more per week of exposure to secondhand smoke in the home was 1.42 (95% CI, 1.08–1.88). The association was stronger for women than for men. Results were adjusted for hypertension, diabetes, total cholesterol, level of education, and race/ethnicity.

In this study, out-of-home exposure to secondhand smoke was not associated with risk of ischemic stroke: RR = 0.90 (95% CI, 0.67–1.21). Neither home nor out-of-home exposure to secondhand smoke was associated with risk of TIA. This study by Iribarren and colleagues (2004) represents one of the first rigorously conducted prospective cohort studies to examine the association between exposure to secondhand smoke and incident stroke, and it is also one of the few studies to have distinguished between ischemic stroke and TIAs. Stroke and TIAs have similar underlying etiologies, but TIAs last only a few minutes and are far less serious; major symptoms typically disappear in less than 24 hours.

The study by Glymour and colleagues (2008) examined the association between spousal smoking status and risk of stroke. The study focused on data from 16,225 participants in the Health and Retirement Study, a prospective cohort study of U.S. adults 50 years of age and older and their spouses. The analytic study population was restricted to participants who did not self-report stroke at baseline. Investigators conducted interviews to obtain information about smoking status (cigarettes only) for each spouse pair. Incident stroke cases were based on self-report of a doctor's diagnosis of fatal or nonfatal stroke (from participant or proxy interviews); TIAs were not considered to be strokes. During a median 9 years of follow-up, participants reported 1,130 incident cases of stroke. In a comparison with never smokers who were married to a nonsmoking spouse, the multivariable-adjusted RR estimate of incident stroke for never smokers married to a current smoker was 1.42 (95% CI, 1.05–1.93). Results were similar for men and women. In the study, results were adjusted for socioeconomic indicators, obesity, overweight, and diagnosed hypertension, diabetes, and heart disease.

Studies of the effects of smokefree laws on the rates of acute cardiovascular events potentially offer additional population-level data on the association between exposure to secondhand smoke and risk of stroke. Most of these studies have focused on hospital admissions for acute coronary events; however, several included stroke as a separate outcome. In one study, Juster and colleagues (2007) analyzed trends in monthly hospital admissions for AMI or stroke in the state of New York to identify any associations between admission rates and the implementation in 2003 of a comprehensive smokefree law that prohibited smoking in all worksites. The authors found

that hospital admission rates for AMI were lower after the ban was implemented but that admission rates for stroke were not significantly affected. Elsewhere, the New Zealand Ministry of Health (2006) commissioned and funded a study to evaluate the effects of a national smokefree law, also implemented in 2003. Investigators observed fewer admissions for stroke after the ban was implemented, but this result did not reach significance in a regression analysis. Herman and Walsh (2011) compared hospital admissions before and after the implementation of a comprehensive smokefree law in Arizona. These investigators observed significant reductions in hospital admissions for AMI, angina, stroke, and asthma in counties with no previous bans in comparisons with counties that already had smokefree laws in place. In a similar analysis of the comprehensive nationwide smokefree law the Republic of Ireland implemented in 2004, Stallings-Smith and colleagues (2013) reported significant reductions in national all-cause mortality and reductions in CHD, stroke, and chronic obstructive pulmonary disease (COPD) mortality. Reductions in CHD and stroke were seen at 65 years of age and older, but not in those 35–64 years of age. The impact on national stroke mortality rates in Scotland also was evaluated after the introduction of comprehensive smokefree legislation in 2006 (Mackay et al. 2013). Analyses of both national hospital admissions and prehospital deaths due to stroke suggest that there was a selective but significant reduction in cerebral infarction following the implementation of the smokefree legislation but no significant impact on intracerebral hemorrhage or unspecified stroke.

Summary

To date, more than 20 individual-level studies, including 10 prospective cohort studies, have examined the association between exposure to secondhand smoke and risk of stroke. Overall, the published evidence shows a moderate independent association between exposure to secondhand smoke and the risk of stroke. Pooled RR estimates from meta-analyses indicate an approximate 20–30% increase in the risk of stroke from exposure to secondhand smoke; a risk estimate which is very comparable to that for CHD and exposure to secondhand smoke. More limited data suggest a dose-response relationship, with the highest risk at the highest levels of exposure to secondhand smoke (Oono et al. 2011). In addition, evidence from recent ecological studies suggests a possible reduction in hospitalizations for stroke after regional or national implementation of smokefree laws (Carter et al. 2006; New Zealand Ministry of Health 2006; Herman and Walsh 2011; Mackay et al. 2013; Stallings-Smith et al. 2013).

The mechanistic evidence to support a causal association between exposure to secondhand smoke and risk of stroke comes largely from literature that has firmly established the causal role of exposure to secondhand smoke in the development of CHD (USDHHS 2010). Experimental human and animal studies demonstrate that exposure to secondhand smoke has both acute and chronic effects on the human vasculature, including the initiation and promotion of atherosclerotic disease, inflammation, the formation of thromboses, and coagulation (Ambrose and Barua 2004; USDHHS 2010).

Conclusions

1. The evidence is sufficient to infer a causal relationship between exposure to secondhand smoke and increased risk of stroke.

2. The estimated increase in risk for stroke from exposure to secondhand smoke is about 20–30%.

Implications

Worldwide, stroke is the second-leading cause of death (World Health Organization 2011). Although the increase in risk of stroke associated with exposure to secondhand smoke is modest, the continued use of cigarettes in much of the world, combined with the billions of people worldwide potentially at risk for suffering a stroke in their lifetimes, indicates that a substantial reduction in the stroke burden could be achieved if exposure to secondhand smoke was either reduced or eliminated altogether.

Impact of Smokefree Laws on Acute Cardiovascular Events

This section reviews the evidence that the implementation of national, state, and local smokefree laws (eliminating smoking in enclosed public places and workplaces, including restaurants and bars) results in a reduction of cardiovascular morbidity and mortality, as manifested by lower rates of hospital admissions or deaths, from coronary events (AMI, acute coronary syndrome, acute coronary events [ACE], and CHD), other heart disease (angina and out-of-hospital sudden coronary death [SCD]), and cerebrovascular events (stroke and TIA). Because randomized controlled trials cannot be carried out to assess large-scale public policy interventions, such as the adoption and implementation of a smokefree law, the evidence to evaluate this issue is based on assessments of observations following implementation of such smokefree laws in one or multiple settings (i.e., workplaces only; workplaces and restaurants only; or workplaces, restaurants, and bars). The study designs involve interrupted time series analyses or other forms of nonrandomized comparisons.

Summary of Evidence from Previous Surgeon General's Reports

Exposure to tobacco smoke from either active or secondhand smoke has been determined to be a major cause of cardiovascular morbidity and mortality. The 2006 Surgeon General's report concluded that "The evidence is sufficient to infer a causal relationship between exposure to secondhand smoke and increased risks of coronary heart disease morbidity and mortality among both men and women" (p. 15). Earlier in this chapter, the evidence was reviewed on exposure to secondhand smoke and the risk of stroke. That review concluded that "The evidence is sufficient to infer a causal relationship between exposure to secondhand smoke and increased risk of stroke." In 2010. the Institute of Medicine (IOM) Committee on Secondhand Smoke Exposure and Acute Coronary Events concluded that "there is scientific consensus that there is a causal relationship between secondhand smoke exposure and cardiovascular disease" (IOM p. 219). The 2006 Surgeon General's report and the 2010 IOM review demonstrate agreement between their conclusions based on the substantial scientific literature, the evidence related to the

pathophysiology of exposure to secondhand smoke, and the plausibility of a causal relationship between briefer, recent exposures to smoke and acute coronary events (USDHHS 2006; IOM 2010).

Biologic Basis

Both the IOM (2010) and the Surgeon General's (USDHHS 2010) reports reviewed the evidence on the mechanisms underlying the cardiovascular effects of mainstream smoke and exposure to secondhand smoke. The IOM review found that "several components of secondhand smoke, including carbonyls and particulate matter, have been shown to exert significant cardiovascular toxicity" (p. 83). Within this body of evidence, the experimental research by Heiss and colleagues (2008) on the acute and sustained impact on the vascular biology of typical levels of exposure to secondhand smoke for just 30 minutes provides an understanding of how brief exposures in settings where smoking is permitted (e.g., bars and restaurants) could increase the risk of an acute cardiovascular event for up to 24 hours following the exposure. In an accompanying editorial, Celermajer and Ng (2008) noted that the results of this study show that such brief exposures to secondhand smoke can result in "a sustained and complex adverse response that threatens cardiovascular homoeostasis with potentially important health consequences" (p. 1773). More recently, in a study of 33 healthy nonsmokers, Frey and colleagues (2012) presented evidence that 30 minutes of exposure to "aged" secondhand smoke in relatively low concentrations (typical of those found in community settings, such as a bar or restaurant where smoking is permitted) results in significant decreases in endothelial function. The results from their study suggest that the impact of 30 minutes of exposure to secondhand smoke on endothelium-dependent dilation of the brachial artery may be produced at even lower levels of exposure than those examined in the earlier study by Heiss and colleagues (2008).

There is now a substantial body of evidence that has been reviewed in previous Surgeon General's reports (USDHHS 2006, 2010) and in other evidence reviews (California Environmental Protection Agency 2005; Callinan et al. 2010; IOM 2010) documenting that smokefree legislation and policies are effective in reducing exposure among both nonsmoking restaurant and bar

workers and the general population of nonsmokers. Thus, it typically has been assumed that the smokefree laws evaluated in the available epidemiologic literature have produced reductions in exposure to secondhand smoke. However, few of the epidemiologic studies have included measurements of changes in population exposures to secondhand smoke. The IOM Committee (2010) noted that this gap in the evidence was a significant weakness of the available population-based studies of changes in the risk of ACEs after the implementation of smokefree laws.

However, previous reports and reviews, particularly the 2006 Surgeon General's report and the 2010 IOM report, have found that smokefree legislation significantly reduces the concentrations of indicators of secondhand smoke (e.g., the levels of fine particulate matter [$PM_{2.5}$] in the air of enclosed environments, such as bars). Similarly, the levels of two important biomarkers of smoking or exposure to secondhand smoke (i.e., nicotine and its metabolite, cotinine) are reduced in nonsmokers who spend time in environments covered by new smokefree laws following implementation of these laws. Based on this evidence, the IOM report (2010) concluded that exposure to secondhand smoke is substantially reduced after implementation of smokefree policies.

In one of the strongest evaluations of the implementation of a country-wide smokefree law, Haw and Gruer (2007) and Pell and colleagues (2008) presented data from assessments of serum cotinine concentrations in representative samples of the Scottish population and among patients admitted with acute coronary syndrome. For Scottish adult nonsmokers in the general population 18–74 years of age, the geometric mean level of cotinine declined by 39% (95% CI, 29%–47%) from 0.43 ng/mL at baseline to 0.26 ng/mL after the legislation was implemented (Haw and Gruer 2007). Pell and colleagues (2008) measured cotinine concentrations among male and female nonsmokers, nonsmokers who were admitted with acute coronary syndrome, and among nonsmokers 45 years of age or older in the general population. Before the legislation was implemented, nonsmoking men and women had equal geometric mean levels of cotinine (0.66 ng/mL). Among nonsmoking men, the cotinine level decreased by 38% to 0.41 ng/mL, and among nonsmoking women, it decreased by 47% to 0.35 ng/mL (Pell et al. 2008). Smaller decreases were observed among nonsmokers with acute coronary syndrome, where the decline was 18% (from 0.68 ng/mL to 0.56 ng/mL). The geometric mean level of cotinine in saliva among nonsmokers 45 years of age or older decreased 42% (from 0.43–0.25 ng/mL) (Pell et al. 2008).

Epidemiologic Evidence

The body of evidence from the studies of the effects of the implementation of smokefree laws has expanded rapidly in recent years. At the time of the IOM (2010) review, there were 11 publications based upon eight assessments of the effects of smokefree laws on numbers or rates of hospitalization for ACEs. One meta-analysis (discussed below) was published in 2012 (Tan and Glantz 2012). Since the publication of this meta-analysis, 12 additional studies have been published or are currently in press.

Meta-Analyses

In addition to the meta-analysis covered in the IOM Committee (2010) review, three meta-analyses have summarized the evidence on the effects of smokefree laws on hospitalization rates for ACEs, including AMI; all three concluded that the implementation of these laws is followed by immediate reductions in these rates (Lightwood and Glantz 2009; Meyers et al. 2009; Mackay et al. 2010). The meta-analysis by Tan and Glantz (2012) reviewed a much larger body of literature, evaluating new study populations and locations, as well as extending evaluations of earlier studies. This review also included an evaluation of how the effect size varied by the degree of comprehensiveness of the smoking restriction (i.e., whether it covered workplaces only, workplaces and restaurants, or workplaces, restaurants, and bars). CDC considers a state or local jurisdiction to have a comprehensive smokefree law or policy when it prohibits smoking in these three venues (i.e., private-sector worksites, restaurants, and bars) because evidence indicates that they are the major sources of exposure to secondhand smoke for nonsmoking employees and the public (USDHHS 2006; CDC 2011). Finally, the meta-analysis included an assessment of whether the effect of smokefree laws increased with the time since they took effect.

A total of 47 studies were identified in the meta-analysis by Tan and Glantz (2012) that examined the association between a smokefree law and selected outcomes, including hospitalization rates or mortality due to cardiovascular or respiratory disease (36 were in peer-reviewed publications, and there were 7 abstracts, 1 presentation, and 3 reports by state health departments). Of these studies, 2 were excluded (Xuereb et al. 2011; Rodu et al. 2012) as lacking sufficient data to calculate the RR with a 95% CI for the observed effects before and after the implementation of the smoking law or between localities with and without such a law. Because the RR of coronary heart disease due to smoking has been observed to decrease with

age (USDHHS 2004, 2010), in the 7 studies that included results stratified by age, the study effects for the samples 65 years of age or younger (or the closest alternative cut-off point) were used in the primary meta-analysis. The primary analysis used the effect estimated from the longest available follow-up period. After all available studies were screened for inclusion criteria and for missing or incomplete data, 43 publications were included (Tables 8.6*S*–8.8*S*).

Coronary Events

Figure 8.6 presents a forest plot showing the effect size and 95% CI for each study that estimated the impact of a smokefree law on the rate of coronary events (including AMI, acute coronary syndrome, ACE, and CHD). (*Note:* The grouping of clinical outcome categories in the studies as "coronary events" was performed by Tan and Glantz [2012] because statistical testing showed similarities in how clinical outcomes performed under such testing.) Details on the designs of the studies included in this analysis are provided in Table 8.6*S*. For the 35 studies of comprehensive smokefree laws (i.e., laws covering workplaces, restaurants, and bars), the estimated pooled effect size was RR = 0.85 (95% CI, 0.82–0.88). For studies reporting the effects for laws covering workplaces only, the RR was 0.92 (95% CI, 0.88–0.96); and for laws covering both workplaces and restaurants, the RR was 0.95 (95% CI, 0.88–1.02) and thus was not significant.

Consistent with the fact that the RR for CHD declines with age, an analysis of the six studies that reported results stratified by age found no significant decline in AMI or in total coronary events among older patients (median cut-off of 70 years of age, range 60–75 years of age) following the implementation of a comprehensive smokefree law (RR = 0.973; 95% CI, 0.918–1.032 and RR = 0.980; 95% CI, 0.953–1.008, respectively). The observed reductions in AMI hospitalization rates following implementation of the smokefree law were very similar for females (RR = 0.897; 95% CI, 0.847–0.950) and males (RR = 0.912; 95% CI, 0.872–0.955) in analyses that covered all three levels of the implemented smokefree laws. It has been suggested that the impact of a new smokefree law could increase over time due to increased compliance with the law, increased adoption of voluntary household smokefree home rules, or increased quitting among smokers (CDC 2006), but contrary to the findings of previous meta-analyses (Lightwood and Glantz 2009; Meyers et al. 2009; Mackay et al. 2010), this analysis did not observe a progressive reduction in AMI risk associated with increasing time since the smokefree law had been implemented (Figure 8.7).

Cerebrovascular Events

Figure 8.8 presents a forest plot showing the effect size and 95% CI for each study that included data estimating the impact of a smokefree law on the rate of cerebrovascular events, including stroke and/or TIA. Details on the designs of the studies included in this analysis are provided in Table 8.7*S*. For the five studies of comprehensive smokefree laws, the estimated pooled effect size stated as an RR was 0.81 (95% CI, 0.70–0.94).

Of the five studies evaluating the impact of comprehensive smokefree laws on the rate of cerebrovascular events, two (in France and Toronto) reported results from smokefree laws which covered only workplaces or workplaces and restaurants. Although the pooled effect size for comprehensive smokefree laws was significant, one possible shortcoming in considering the five studies together is that there was considerable variability in design across the group. As discussed earlier in this chapter, two recent analyses of the impact of national comprehensive smokefree legislation in the Republic of Ireland (Stallings-Smith et al. 2013) and in Scotland (Mackay et al. 2013) evaluated the impact on hospital admissions and deaths from stroke. In Ireland following the 2004 smokefree legislation, a significant reduction in national stroke mortality was seen in people 65 years of age and older, but not in those 35–64 years of age. In Scotland, a significant reduction in the incidence of cerebral infarction was observed following the implementation of the 2006 smokefree legislation, but no significant impact on intracerebral hemorrhage or unspecified stroke.

Other Heart Disease

In Figure 8.9, a forest plot shows the effect size and 95% CI in 10 studies that estimated the impact of a smokefree law on the rate of other heart disease endpoints, including angina and out-of-hospital SCD. Details on the designs of the studies included in this analysis are provided in Table 8.8*S*. For the five studies of comprehensive smokefree laws (i.e., whether it covered workplaces only, workplaces and restaurants, or workplaces, restaurants, and bars), the estimated pooled effect size was RR = 0.61 (95% CI, 0.44–0.85). Notably, although this pooled effect size was significant, there was considerable variability in the design and outcomes measured (i.e., angina and out-of-hospital SCD) across the five studies. Four studies evaluated the impact of less comprehensive smokefree laws (covering workplaces and restaurants only) on the rates of other heart disease outcomes.

Figure 8.6   Forest plot for studies on the relationship between smokefree laws and coronary events

Location	Author and year	ES (95% CI)
Workplaces Only		
Barcelona, Spain (female)	Villalbi 2009	0.88 (0.84–0.92)
Barcelona, Spain (male)	Villalbi 2009	0.87 (0.84–0.90)
France (partial ban)	Dautzenberg 2008	0.99 (0.94–1.04)
Spain	Villalbi 2011	0.86 (0.84–0.88)
Toronto, Canada (phase 1)	Naiman 2010	1.03 (0.94–1.12)
United States	Shetty 2010	0.96 (0.90–1.02)
Buenos Aires, Argentina	Ferrante 2012	0.92 (0.87–0.97)
Subtotal (I-squared = 86.8%, p = 0.000)		0.92 (0.88–0.96)
Workplaces and Restaurants		
Germany	Sargent 2012	0.91 (0.88–0.95)
Lexington-Fayette Co., KY (female)	Hahn 2011	0.77 (0.62–0.96)
Lexington-Fayette Co., KY (male)	Hahn 2011	1.11 (0.91–1.36)
Monroe County, IN	Seo 2007	0.48 (0.24–0.96)
Olmsted Co., MN (ordinance #1)	Hurt 2011	0.90 (0.73–1.10)
Toronto, Canada (phase 2)	Naiman 2010	0.99 (0.92–1.07)
Kanawha Co., WV	Gupta 2011	1.02 (0.92–1.12)
Subtotal (I-squared = 62.1%, p = 0.015)		0.95 (0.88–1.02)
Workplaces, Restaurants, and Bars		
Arizona	Herman 2011	0.84 (0.60–0.93)
Boise, ID	Heinz 2007	0.82 (0.66–1.01)
Christchurch, New Zealand (age 30–55)	Barnett 2009	1.15 (0.94–1.40)
Christchurch, New Zealand (age 55–74)	Barnett 2009	0.86 (0.77–0.97)
Cork and Kerry Cos., Ireland	Cronin 2012	0.84 (0.76–0.92)
Delaware	Moraros 2010	0.91 (0.87–0.95)
England	Sims 2010	0.98 (0.96–0.99)
France (complete ban)	Dautzenberg 2008	0.84 (0.77–0.92)
Graubunden, Switzerland	Bonetti 2011b	0.79 (0.69–0.90)
Greeley, CO	Bruintjes 2011	0.73 (0.59–0.90)
Hattiesburg, MS	McMillen 2010	0.87 (0.74–1.01)
Helena, MT	Sargent 2004	0.60 (0.36–0.99)
Ireland	Kent 2012	0.89 (0.70–1.13)
Italy (20 regions)	Barone-Adesi 2011	0.97 (0.95–0.99)
Italy (4 regions)	Vasselli 2008	0.86 (0.83–0.92)
Massachusetts	Dove 2010	0.90 (0.86–0.95)
New York State	Juster 2007	0.80 (0.80–0.80)
North Carolina	NCTPCB 2011	0.79 (0.75–0.83)
Ohio	Bruckman 2011	0.96 (0.95–0.98)
Olmsted Co., MN (ordinance #2)	Hurt 2011	0.55 (0.44–0.68)
Piedmont, Italy	Barone-Adesi 2006	0.89 (0.81–0.98)
Pueblo, CO	CDC 2009b	0.59 (0.49–0.70)
Saskatoon, Canada	Lemstra 2008	0.87 (0.84–0.90)
Starkville, MS	McMillen 2010	0.72 (0.48–1.10)
Ticino, Switzerland	Di Valentino 2011	0.79 (0.70–0.88)
Toronto, Canada (phase 3)	Naiman 2010	0.81 (0.75–0.88)
Tuscany, Italy	Gasparrini 2009	0.95 (0.89–1.00)
Uruguay	Sebrié 2013	0.81 (0.72–0.89)
Iceland	Gudnason 2009	0.83 (0.68–1.02)
Santa Fe, Argentina	Ferrante 2012	0.65 (0.59–0.70)
Scotland	Pell 2008	0.83 (0.82–0.84)
Ticino, Switzerland	Di Valentino 2010	0.82 (0.76–0.89)
Piedmont, Italy	Barone-Adesi 2009	0.94 (0.90–0.97)
Rome, Italy	Cesaroni 2008	0.89 (0.85–0.93)
Italy (20 regions)	Barone-Adesi 2011	0.95 (0.93–0.98)
Subtotal (I-squared = 98.0%, p = 0.000)		0.85 (0.82–0.88)

0.1   0.2   0.5   1   2   5

Relative risk of hospitalization

Source: Adapted from Tan and Glantz 2012 with permission from Wolters Kluwer Health, © 2012.
Note: The size of the shaded area around each point is proportional to the weight in the random effects meta-analysis. Error bars indicate 95% CIs for each study. **CDC** = Centers for Disease Control and Prevention; **CI** = confidence interval; **ES** = effect size (relative risk); **NCTPCB** = North Carolina Tobacco Prevention and Control Branch.

Figure 8.7   Metaregression for reduction in risk of hospitalization (or death) associated with implementation of comprehensive smokefree laws and acute myocardial infarction by time since implementation
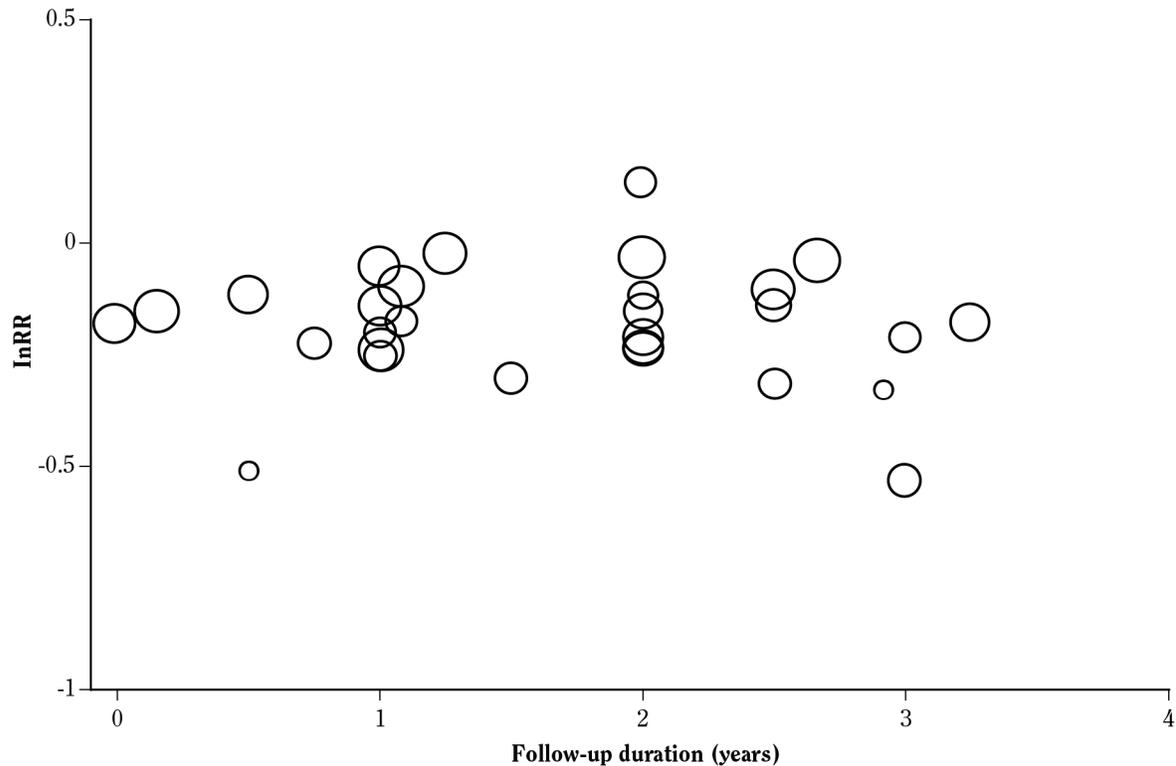
Source: Adapted from Tan and Glantz 2012 with permission from Wolters Kluwer Health, © 2012.
Note: The size of the points is proportional to the weight in a random effects metaregression. Each locality studied for a smokefree law was associated with one follow-up time per outcome.

Recent Studies

Of the 12 additional studies identified following the publication of the Tan and Glantz (2012) meta-analysis, 11 included an assessment of the impact of a smokefree law on at least one cardiovascular outcome. One of the new studies presents updated data on studies already included in the meta-analysis (Hurt et al. 2012), a second is a brief report from The Netherlands (de Korte-de Boer et al. 2012), and two are reports on effects in smaller states or regions (Roberts et al. 2012; Johnson and Beal 2013). One study analyzed data on Medicare beneficiaries from 1991–2008 (Vander Weg et al. 2013), and another analyzed partial smokefree legislation in the city of Girona, Spain (Agüero et al. 2013). Overall, these six studies which included 11 different CVD outcomes show a similar pattern of results in terms of the direction and size of measured effect, and thus including them in the meta-analysis would likely not substantially change the main findings.

In one of the studies (Barr et al. 2012), the effect of comprehensive smokefree laws on AMI was evaluated in 387 U.S. counties among Medicare enrollees from 1999–2008. This analysis addressed several methodological weaknesses identified in the IOM Committee review (2010), including heterogeneity in the previous studies in design, target populations, statistical analyses, choices of control groups, and types of smoking restrictions investigated. One of the particularly challenging methodological issues, which was addressed by Barr and colleagues (2012), was how to adjust for the secular trend of declining CVD morbidity and mortality. The IOM Committee (2010) discussed the potential impact of the manner in which adjustments for this secular trend are addressed in evaluating the impact of smokefree laws on coronary events, and found that under the assumption of linearity in the secular trend of declining AMI rates, implementation of a comprehensive smokefree law was associated with a significant decrease in AMI admissions in the 12 months

Figure 8.8   Forest plot for studies on smokefree laws and cerebrovascular accidents
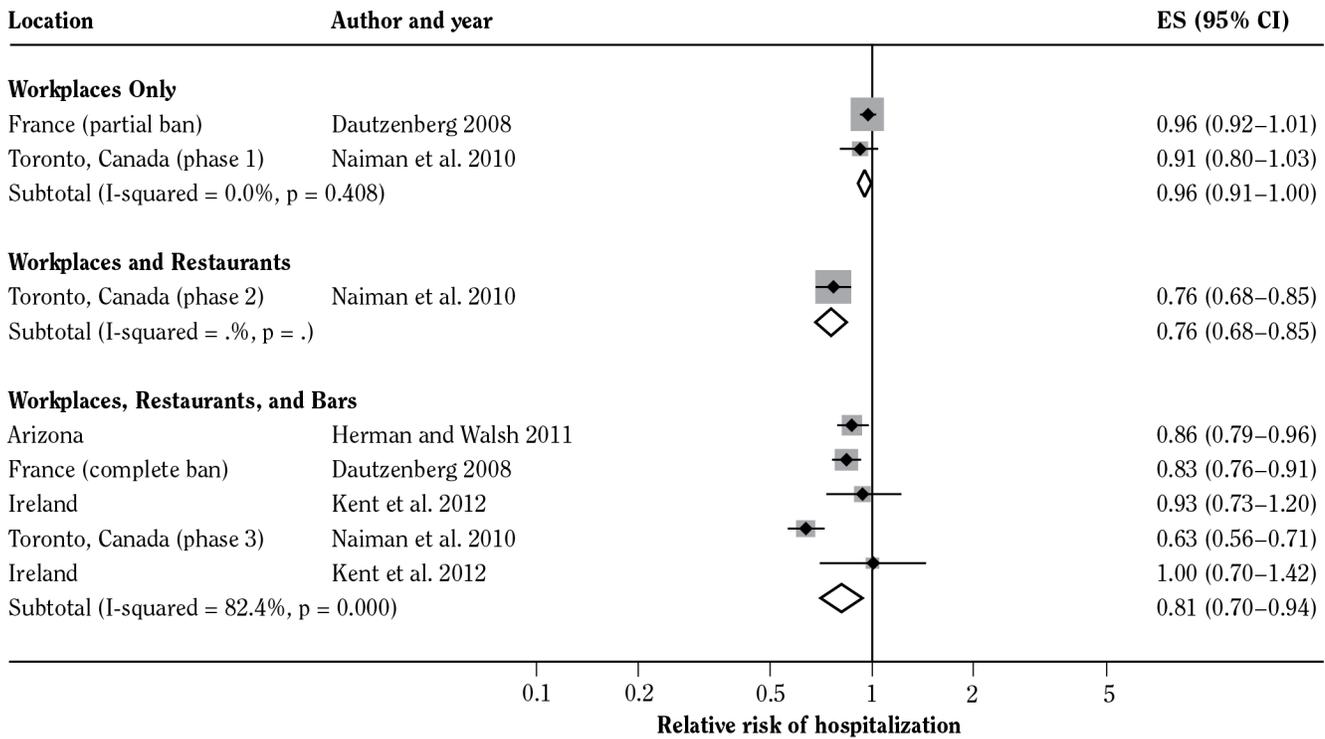
Location	Author and year		ES (95% CI)
Workplaces Only			
France (partial ban)	Dautzenberg 2008		0.96 (0.92–1.01)
Toronto, Canada (phase 1)	Naiman et al. 2010		0.91 (0.80–1.03)
Subtotal (I-squared = 0.0%, p = 0.408)			0.96 (0.91–1.00)
Workplaces and Restaurants			
Toronto, Canada (phase 2)	Naiman et al. 2010		0.76 (0.68–0.85)
Subtotal (I-squared = .%, p = .)			0.76 (0.68–0.85)
Workplaces, Restaurants, and Bars			
Arizona	Herman and Walsh 2011		0.86 (0.79–0.96)
France (complete ban)	Dautzenberg 2008		0.83 (0.76–0.91)
Ireland	Kent et al. 2012		0.93 (0.73–1.20)
Toronto, Canada (phase 3)	Naiman et al. 2010		0.63 (0.56–0.71)
Ireland	Kent et al. 2012		1.00 (0.70–1.42)
Subtotal (I-squared = 82.4%, p = 0.000)			0.81 (0.70–0.94)

0.1   0.2   0.5   1   2   5

Relative risk of hospitalization

Source: Adapted from Tan and Glantz 2012 with permission from Wolters Kluwer Health, © 2012.
Note: Weights are from random effects analysis. The size of the shaded area around each point is proportional to the weight in the random effects meta-analysis. Error bars indicate 95% CI for each study. See Table 8.5 and Tables 8.6*S* and 8.7*S* for further details about each risk estimate or study. **CI** = confidence interval; **ES** = effect size (relative risk).

following implementation. However, additional analyses, which evaluated the sensitivity of the results to the degree of adjustment for the underlying nonlinear trend in CVD morbidity and mortality, found that the estimated effect was attenuated to nearly zero under a nonlinear model of secular trend.

A study by Vander Weg and colleagues (2012) also evaluated the impact of smokefree laws on rates of hospitalization for heart attack and lung disease among Medicare beneficiaries. This study reported that the rates of hospitalization for AMI dropped over 20% in the 36 months following the implementation of new laws that made workplaces, restaurants, and bars smokefree. The study had several strengths that were not present in the paper by Barr and colleagues (2012): (1) It was a national study, (2) it covered a much longer time period, and (3) it included "control" outcomes of diseases not caused by exposure to smoke. Thus, these two studies of older Medicare populations (Barr et al. 2012; Vander Weg et al. 2012) had methodological strengths but inconsistent findings of effects.

In their study, Barr and colleagues (2012) also discussed some cautions about the overall positive pattern of results reviewed in the meta-analyses described above. These authors offered two potential factors that may contribute to the apparently discrepant findings in their analysis of data from a cohort of Medicare enrollees when considered against the results reported in the meta-analyses. First, the analysis was limited to older persons. Barr and colleagues (2012) noted that in comparison with younger people, older populations may spend much less time in the types of environments covered by smokefree laws (i.e., workplaces, restaurants, bars). Previous research, conducted in Italy, found an 11% decline in AMI rates among persons younger than 60 years of age, but among those 60 years of age or older there was no significant effect (Barone-Adesi et al. 2006). Tan and Glantz (2012), in their meta-analysis, found that no significant reductions in coronary events were observed in older populations following the implementation of a comprehensive smokefree law. Hence, the impact of implementing smokefree laws

Figure 8.9   Forest plot for studies on smokefree laws and other heart disease
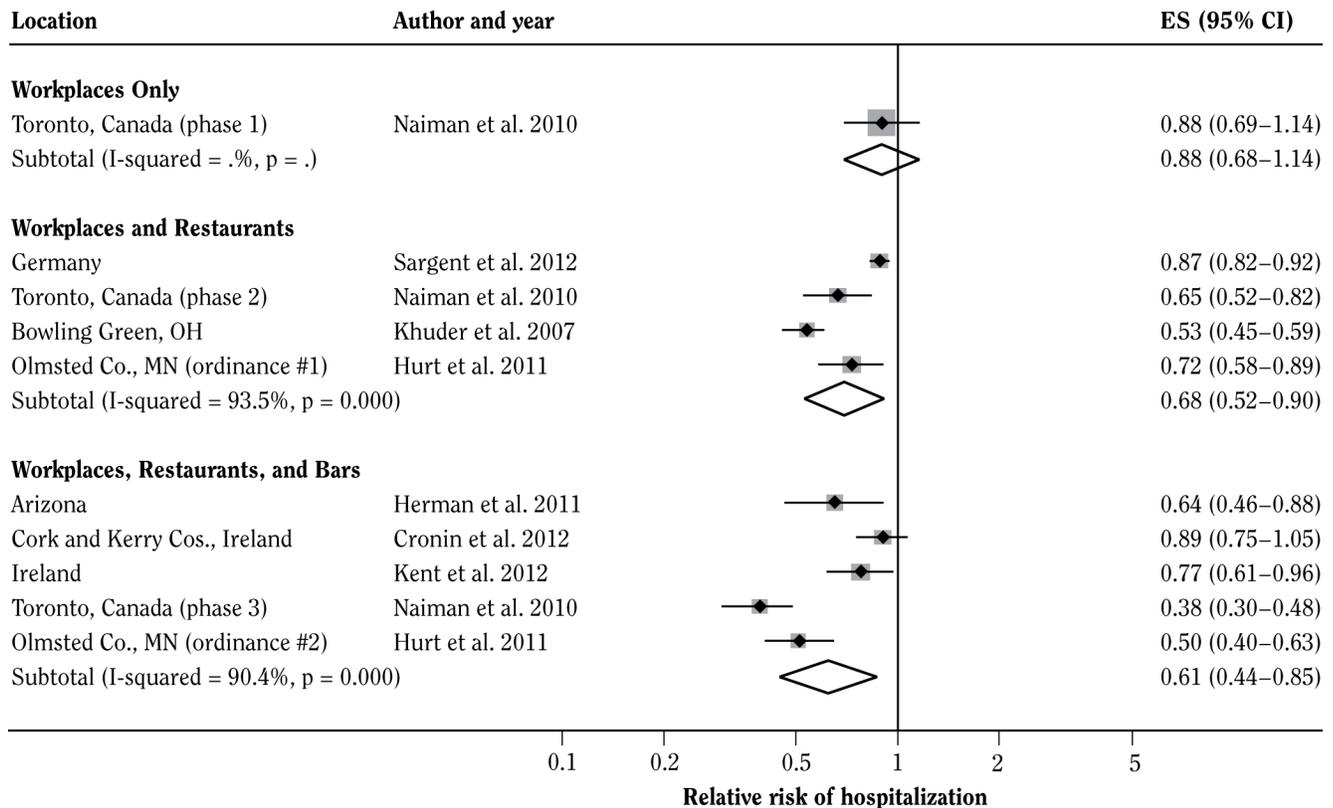
Location	Author and year		ES (95% CI)
Workplaces Only			
Toronto, Canada (phase 1)	Naiman et al. 2010		0.88 (0.69–1.14)
Subtotal (I-squared = .%, p = .)			0.88 (0.68–1.14)
Workplaces and Restaurants			
Germany	Sargent et al. 2012		0.87 (0.82–0.92)
Toronto, Canada (phase 2)	Naiman et al. 2010		0.65 (0.52–0.82)
Bowling Green, OH	Khuder et al. 2007		0.53 (0.45–0.59)
Olmsted Co., MN (ordinance #1)	Hurt et al. 2011		0.72 (0.58–0.89)
Subtotal (I-squared = 93.5%, p = 0.000)			0.68 (0.52–0.90)
Workplaces, Restaurants, and Bars			
Arizona	Herman et al. 2011		0.64 (0.46–0.88)
Cork and Kerry Cos., Ireland	Cronin et al. 2012		0.89 (0.75–1.05)
Ireland	Kent et al. 2012		0.77 (0.61–0.96)
Toronto, Canada (phase 3)	Naiman et al. 2010		0.38 (0.30–0.48)
Olmsted Co., MN (ordinance #2)	Hurt et al. 2011		0.50 (0.40–0.63)
Subtotal (I-squared = 90.4%, p = 0.000)			0.61 (0.44–0.85)

0.1   0.2   0.5   1   2   5

Relative risk of hospitalization

Source: Adapted from Tan and Glantz 2012 with permission from Wolters Kluwer Health, © 2012.
Note: Weights are from random effects analysis. The size of the shaded area around each point is proportional to the weight in the random effects meta-analysis. Error bars indicate 95% CI for each study. See Table 8.5 and Tables 8.6*S* and 8.7*S* for further details about each risk estimate or study. **CI** = confidence interval; **ES** = effect size (relative risk).

on older populations appears to be small and/or nonsignificant. This outcome could be due to either a smaller reduction in exposure to secondhand smoke in some older populations following implementation of smokefree laws and/or the potential that secondhand smoke poses a smaller RR for triggering cardiovascular events in older populations.

The potential for publication bias has been addressed in published meta-analyses (Meyers et al. 2009), including a possible trend toward smaller estimated effects among more recent and larger studies, many of which were conducted in Europe (Mackay et al. 2010). In the Tan and Glantz (2012) meta-analysis, the Egger test for publication bias was significant (p = 0.007) and the funnel plot suggested possible publication bias (Figure 8.10). However, Tan and Glantz (2012) reported that a meta-analysis using the nonparametric trim-and-fill estimates of the effects produced very similar results, weighing against a strong influence of publication bias.

Evidence Summary

There is a scientific consensus that exposure to secondhand smoke causes increased risk for acute cardiovascular events or hospitalizations. Further, there is strong evidence that a comprehensive smokefree law eliminating smoking in all indoor areas of public places and workplaces, including restaurants and bars, reduces exposure to secondhand smoke. The epidemiologic evidence reviewed in this section indicates that the evidence is sufficient to conclude that if the implementation of a smokefree law results in a decrease in exposure to secondhand smoke, a reduction in ACEs will follow. Most studies on this topic have assessed the impact of smokefree laws on hospitalization rates for acute coronary events, using various indicators. For these outcomes, the evidence among younger populations is consistent, robust, and reflects a

Figure 8.10   Funnel plot for risk estimates used in the meta-analysis on the association between smokefree legislation and hospitalizations for cardiac diseases
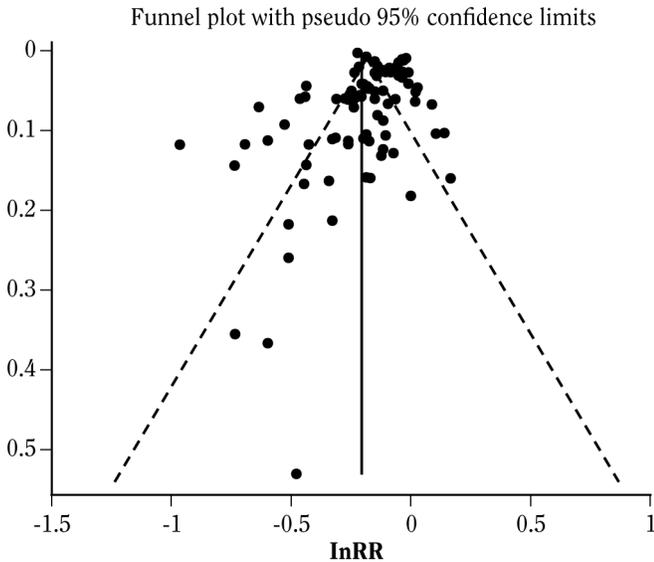
Funnel plot with pseudo 95% confidence limits

Source: Adapted from Tan and Glantz 2012 with permission from Wolters Kluwer Health, © 2012.
Note: Solid vertical line represents the summary estimate of the effect of all ordinances on hospital admissions (assuming a fixed effects meta-analysis), and the dashed lines represent the 95% confidence interval.

dose-response effect related to the comprehensiveness of the laws.

For some specific heart disease outcomes, including angina, out-of-hospital SCD, and cerebrovascular events, the evidence is more limited and less robust in its consistency but still suggestive of an association. For these latter categories of CVD, there is biologic plausibility for inferring that there could be a causal reduction of occurrence after the implementation of a smokefree law. For stroke, the new conclusion that exposure to secondhand smoke can cause stroke increases the plausibility that smokefree policies, which reduce exposure to secondhand smoke, could reduce stroke incidence and mortality. The two recent reports on the impact on stroke incidence and mortality following national comprehensive smokefree legislation in the Republic of Ireland (Stallings-Smith et al. 2013) and in Scotland (Mackay et al. 2013) provide additional evidence of the potential effect. However, because of the limited body of evidence, and the potential for publication bias in this smaller body of evidence, some caution is

needed in drawing causal conclusions with regard to the impact of a smokefree law or policy on stroke.

Conclusions

1. The evidence is sufficient to infer a causal relationship between the implementation of a smokefree law or policy and a reduction in coronary events among people younger than 65 years of age.

2. The evidence is suggestive but not sufficient to infer a causal relationship between the implementation of a smokefree law or policy and a reduction in cerebrovascular events.

3. The evidence is suggestive but not sufficient to infer a causal relationship between the implementation of a smokefree law or policy and a reduction in other heart disease outcomes, including angina and out-of-hospital sudden coronary death.

Implications

As reviewed in Chapter 14, "Current Status of Tobacco Control," of this report, substantial progress toward eliminating exposure among nonsmokers to secondhand smoke has been made over the last 50 years. Nevertheless, the population in over half of the United States is not adequately protected from involuntary exposure to secondhand smoke by comprehensive smokefree policies covering public and private workplaces, restaurants, bars, and other public enclosed environments (CDC 2011). Max and colleagues (2012) have estimated that in 2006 over 42,000 deaths in this country were caused by exposure to secondhand smoke. This estimate included almost 34,000 deaths from CHD. Based on the findings of this evidence review, many of these deaths could be averted if comprehensive smokefree policies were implemented nationwide.

Racial/Ethnic Disparities

Past studies of racial and ethnic differences in CVD risk from smoking have found conflicting results. This topic is briefly reviewed here, and several recent articles are summarized, but a complete review of this topic is beyond the scope of this current report. Huxley and colleagues (2012) analyzed data from the ARIC study, which

included a cohort of 14,200 participants, of whom 27% were African American. After controlling for various CVD risk factors, including number of cigarettes smoked per day, there was no significant difference in the HR by race/ethnicity, and the benefits of quitting were the same for both groups.

Mortality rates for CHD and stroke have continued to decline in the United States, but disparities in acute CHD mortality between Blacks and Whites persist and even appear to be increasing (Keenan and Shaw 2011; Safford et al. 2012). In a study of 24,443 men and women enrolled in the Reasons for Geographic and Racial Differences in Stroke study, Black men and women were found to die from CHD at twice the rate found for their White counterparts (Safford et al. 2012). These differences were due primarily to higher incidence of CVD risk factors, including current smoking. Among Hispanics/Latinos, the importance of smoking as a major CVD risk factor was reported recently (Daviglus et al. 2012). Higher smoking rates, in particular, were observed among Puerto Rican men (34.7%) and women (31.7%) and Cuban men (25.7%) and women (21.2%). Because of the increasing rates of other CVD risk factors, particularly diabetes mellitus, in Hispanic/Latino populations, greater attention should be paid to these smoking rates as a part of CVD prevention.

Evidence Summary

Research carried out since the mid-twentieth century has produced an extensive body of evidence showing that smoking tobacco is causally related to almost all major forms of CVD. Exposure to tobacco smoke is associated with accelerated atherosclerosis, which begins in adolescence and young adulthood, and an increased risk of AMI, stroke, PAD, aortic aneurysm, and sudden death. Smoking appears to have both causal relationships and possible synergistic interactions with other major risk factors for CHD, including hyperlipidemia, hypertension, and diabetes mellitus. Additionally, the new findings from the present report indicate that smoking should be considered an important and modifiable risk factor for the development of diabetes (see Chapter 10, "Other Specific Outcomes").

The cardiovascular risk attributable to cigarette smoking increases sharply at low levels of cigarette consumption and with exposure to secondhand smoke. Thus, it was concluded in the 2010 Surgeon General's report that "Low levels of exposure, including exposures to secondhand tobacco smoke, lead to a rapid and sharp increase in endothelial dysfunction and inflammation, which are implicated in acute cardiovascular events and thrombosis" (p. 9). The new finding in the present report, that exposure to secondhand smoke causes an increased risk of stroke, extends the list of adverse CVD outcomes caused by exposure to tobacco smoke. Cardiovascular risk is not reduced by smoking cigarettes with lower machine-delivered yields of nicotine or tar. The new findings in this report that comprehensive smokefree laws produce a reduction in ACEs, particularly among younger populations, provides further evidence that even brief exposures to tobacco smoke have the potential to lead to significant acute CVD risks.

The constituents of tobacco smoke considered responsible for the increased risk of CVD include oxidizing chemicals, nicotine, carbon monoxide, and particulate matter. Oxidizing chemicals, including oxides of nitrogen and many free radicals, increase lipid peroxidation and contribute to several potential mechanisms of CVD, including inflammation, endothelial dysfunction, oxidation of low-density lipoprotein, and activation of platelets.

Nicotine is a sympathomimetic drug that increases heart rate and cardiac contractility, transiently increasing blood pressure and constricting coronary arteries. Nicotine may also contribute to endothelial dysfunction, insulin resistance, and lipid abnormalities. However, international epidemiologic evidence, and data from clinical trials of nicotine patches, suggests that chemicals other than nicotine are more important for the elevated risk of death from MI and stroke. Carbon monoxide reduces the delivery of oxygen to the heart and other tissues, can aggravate angina pectoris or PAD, and can lower the threshold for arrhythmias in the presence of CHD. Exposure to particles is associated with oxidant stress and cardiovascular autonomic disturbances that potentially contribute to ACEs.

Cigarette smoking causes ACEs, such as MI and sudden death, by adversely affecting the balance of myocardial demand for oxygen and nutrients and coronary blood flow. Smoking results in increased myocardial work, reduced coronary blood flow, and enhanced thrombogenesis. Enhancement of thrombogenesis appears to be particularly important, in that smokers with AMI have less severe underlying coronary artery disease than do nonsmokers with MI, but smokers have a greater burden of thrombus.

Several potential mechanisms appear to contribute to the effects of smoking in accelerating the onset of atherosclerosis. These mechanisms include inflammation, endothelial dysfunction, impaired insulin sensitivity, and lipid abnormalities. Cigarette smoking causes diabetes and aggravates insulin resistance in persons with diabetes. The mechanism appears to involve both the effects of oxidizing chemicals in the smoke and the sympathomimetic effects of nicotine.

The evidence continues to expand that smoking cessation reduces the risk of CVD. Data from more recent cohorts indicate that the risk among younger adults for CVD caused by smoking may be increasing (Thun et al. 2013; Tolstrup et al. 2013). For example, the Pooling Project on Diet and Coronary Heart Disease (Tolstrup et al. 2013) reported that among women 40–49 years of age, the HR for CHD death from smoking was 8.5 and that 70–90% of ACEs and deaths among smokers, and particularly younger women smokers, is attributable to smoking. Results from these pooled cohorts suggest that the population attributable fraction of CHD caused by smoking could be more than half among younger populations (Thun et al. 2013; Tolstrup et al. 2013). Although these findings indicate that the benefits of smoking cessation are strongest among younger adults, these studies also show that the largest impact on the absolute number of CHD deaths that could be averted would result from smoking cessation in older adults.

The evidence reviewed in this chapter indicates that exposure to secondhand smoke causes increased risk for ACEs including hospitalizations. More than 20 individual-level studies, including 10 prospective cohort studies, show a moderate independent association between exposure to secondhand smoke and risk of stroke. Pooled estimates of RR from meta-analyses indicate an estimated 20–30% increase in risk of stroke from exposure to secondhand smoke. More limited data suggest a dose-response relationship, with the highest risk at the highest levels of exposure (Oono et al. 2011). In addition, evidence from recent ecological studies suggests a possible reduction in hospitalizations for stroke after regional implementation of smokefree laws (Carter et al. 2006; New Zealand Ministry of Health 2006; Herman and Walsh 2011; Mackay et al. 2013; Stallings-Smith et al. 2013). Further, there is strong evidence that a comprehensive smokefree law eliminating smoking in all indoor areas of public places and workplaces, including restaurants and bars, reduces exposure to secondhand smoke. The epidemiologic evidence reviewed in this section indicates that the evidence is sufficient to conclude that if the implementation of a smokefree law results in a decrease in exposure to secondhand smoke, a reduction in ACEs will follow. Most studies on this topic have assessed the impact of smokefree laws on hospitalization rates for ACEs, including AMI, acute coronary syndrome, and CHD. For these outcomes, the evidence among younger populations is consistent, robust, and reflects a dose-response effect related to the comprehensiveness of the laws.

Chapter Conclusions

1. The evidence is sufficient to infer a causal relationship between exposure to secondhand smoke and increased risk of stroke.

2. The estimated increase in risk for stroke from exposure to secondhand smoke is about 20–30%.

3. The evidence is sufficient to infer a causal relationship between the implementation of a smokefree law or policy and a reduction in coronary events among people younger than 65 years of age.

4. The evidence is suggestive but not sufficient to infer a causal relationship between the implementation of a smokefree law or policy and a reduction in cerebrovascular events.

5. The evidence is suggestive but not sufficient to infer a causal relationship between the implementation of a smokefree law or policy and a reduction in other heart disease outcomes, including angina and out-of-hospital sudden coronary death.

Implications

Despite the consistent and significant declines in age-adjusted cardiovascular mortality rates in the United States since the mid-1960s, this group of diseases remains the leading cause of mortality in this country, annually causing over 800,000 deaths overall (NHLBI 2012). CHD remains the single largest cause of death, causing over 400,000 deaths per year. Cerebrovascular disease also continues as a leading cause of death, causing over 130,000 deaths per year. The evidence indicates that further reducing both active smoking and exposure to secondhand smoke can continue to contribute significantly to reducing the rates of CVD morbidity and mortality (Mozaffarian et al. 2008; Ford and Capewell 2011; Luepker 2011). In Chapter 12, "Smoking-Attributable Morbidity, Mortality, and Economic Costs," of this report, updated estimates of smoking-attributable mortality are provided, indicating that 194,000 deaths from CVD in this country are caused annually by smoking or exposure to secondhand smoke.

As reviewed in Chapter 13, steady progress has been made in reducing the prevalence of smoking in both youth and adults in this country. Preventing the use of tobacco products by youth and young adults remains a primary CVD prevention approach (USDHHS 2012). For adults, smoking cessation, particularly as early in life as possible, is the most effective approach for reducing the risks associated with tobacco use. The updated evidence in this chapter on the high RRs for CHD and other heart diseases in younger populations for active smoking underscores the potential for rapidly reducing the CVD burden in younger adults. This is particularly true for younger women, among whom smoking is a primary and highly preventable cause for a very high proportion of early CHD events (Kenfield et al. 2008, 2010).

Smokefree policies also have the potential to be one of the most effective and cost-effective approaches for reducing ACEs in this country and around the world. Preliminary evidence suggests that implementation of smokefree policies also has the potential to reduce other CVD events, particularly SCDs. It has been estimated that exposure to secondhand smoke causes over 33,000 CHD deaths each year in the United States.

The growing disparities by socioeconomic factors, in both the levels of risk factors and CVD morbidity and mortality rates, point to the need to extend initiatives to reduce risk factors, including smoking cessation and reductions in exposure to secondhand smoke, more effectively into these high-risk populations (Cooper et al. 2000; Keenan and Shaw 2011; Daviglus et al. 2012; NHLBI 2012).

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Appended Data Table for Figure 8.5

Study	Design	Population	Effect size (95% CI)	Weight (%)
Gillis et al. 1984	Prospective	Male	0.33 (0.04–2.84)	0.23
Gillis et al. 1984	Prospective	Female	1.88 (0.22–16.02)	0.23
Sandler et al. 1989	Prospective	Male	0.97 (0.65–1.46)	3.31
Sandler et al. 1989	Prospective	Female	1.24 (1.03–1.49)	5.44
Yamada et al. 2003	Prospective	Male	1.13 (0.19–6.58)	0.33
Yamada et al. 2003	Prospective	Female	0.94 (0.57–1.55)	2.62
Iribarren et al. 2004	Prospective	Male	1.02 (0.71–1.48)	3.62
Iribarren et al. 2004	Prospective	Female	1.17 (0.92–1.50)	4.83
Whincup et al. 2004	Prospective	Male	1.54 (0.68–3.47)	1.32
Qureshi et al. 2005	Prospective	Female	0.90 (0.60–1.30)	3.46
Wen et al. 2006	Prospective	Female	1.52 (1.08–2.15)	3.83
Hill et al. 2007 (Study 1)	Prospective	Male	1.59 (1.14–2.21)	3.96
Hill et al. 2007 (Study 1)	Prospective	Female	0.90 (0.67–1.21)	4.30
Hill et al. 2007 (Study 2)	Prospective	Male	1.82 (1.20–2.77)	3.20
Hill et al. 2007 (Study 2)	Prospective	Female	1.17 (0.76–1.82)	3.06
Glymour et al. 2008 (Study 1)	Prospective	Male	1.63 (0.83–2.70)	2.12
Glymour et al. 2008 (Study 1)	Prospective	Female	1.46 (1.00–2.18)	3.43
Glymour et al. 2008 (Study 2)	Prospective	Male	1.76 (1.31–2.41)	4.21
Glymour et al. 2008 (Study 2)	Prospective	Female	1.56 (0.91–3.12)	2.00
Jefferis et al. 2010[a]	Prospective	Male and female	0.94 (0.80–1.11)	5.65
Subtotal: Prospective (I-squared = 47.3%; p = 0.010)			1.22 (1.08–1.38)	61.15
Lee et al. 1986	Case-control	Male	0.84 (0.31–2.27)	0.94
Lee et al. 1986	Case-control	Female	0.92 (0.51–1.65)	2.14
Donnan et al. 1989	Case-control	Male and female	1.60 (0.60–3.90)	1.05
Bonita et al. 1999	Case-control	Male	2.10 (1.33–3.32)	2.91
Bonita et al. 1999	Case-control	Female	1.66 (1.07–2.57)	3.05
You et al. 1999	Case-control	Male and female	1.70 (0.98–2.92)	2.35
Anderson et al. 2004	Case-control	Male	0.50 (0.20–1.30)	1.05
Anderson et al. 2004	Case-control	Female	1.30 (0.70–2.30)	2.10
McGhee et al. 2005	Case-control	Male	1.31 (0.87–1.99)	3.24
McGhee et al. 2005	Case-control	Female	1.57 (1.11–2.24)	3.77
Subtotal: Case-control (I-squared = 26.5%, p = 0.200)			1.41 (1.15–1.72)	22.59
Howard et al. 1998b	Cross-sectional	Male and female	1.06 (0.64–1.75)	2.60
Iribarren et al. 2001	Cross-sectional	Male	0.27 (0.11–0.57)	1.30
Iribarren et al. 2001	Cross-sectional	Female	0.89 (0.57–1.38)	3.02

Appended Data Table for Figure 8.5   Continued

Study	Design	Population	Effect size (95% CI)	Weight (%)
Zhang et al. 2005	Cross-sectional	Female	1.44 (1.20–1.72)	5.49
He et al. 2008	Cross-sectional	Female	1.65 (1.17–2.32)	3.85
Subtotal: Cross-sectional (I-squared = 80.6%; p = 0.000)			1.03 (0.69–1.53)	16.26
Overall (I-squared = 54.2%; p = 0.000)			1.25 (1.12–1.38)	100.00

Source: Adapted from Oono et al. 2011 with permission from Oxford University Press, © 2011.
Note: Weights are from random effects analysis. **CI** = confidence interval.
[a]Excludes former smokers.

Appended Data Table for Figure 8.6

Study	Place	Location	Effect size, relative risk (95% CI)
Villalbi 2009	Workplaces only	Barcelona, Spain (female)	0.88 (0.84–0.92)
Villalbi 2009	Workplaces only	Barcelona, Spain (male)	0.87 (0.84–0.90)
Dautzenberg 2008	Workplaces only	France (partial ban)	0.99 (0.94–1.04)
Villalbi 2011	Workplaces only	Spain	0.86 (0.84–0.88)
Naiman 2010	Workplaces only	Toronto, Canada (phase 1)	1.03 (0.94–1.12)
Shetty 2010	Workplaces only	United States	0.96 (0.90–1.02)
Ferrante 2012	Workplaces only	Buenos Aires, Argentina	0.92 (0.87–0.97)
Subtotal: Workplaces only (I-squared = 86.8%, p = 0.0000)			0.92 (0.88–0.96)
Sargent 2012	Workplaces and restaurants	Germany	0.91 (0.88–0.95)
Hahn 2011	Workplaces and restaurants	Lexington-Fayette County, Kentucky (female)	0.77 (0.62–0.96)
Hahn 2011	Workplaces and restaurants	Lexington-Fayette County, Kentucky (male)	1.11 (0.91–1.36)
Seo 2007	Workplaces and restaurants	Monroe County, Indiana	0.48 (0.24–0.96)
Hurt 2011	Workplaces and restaurants	Olmstead County, Minnesota (ordinance 1)	0.90 (0.73–1.10)
Naiman 2010	Workplaces and restaurants	Toronto, Canada (phase 2)	0.99 (0.92–1.07)
Gupta 2011	Workplaces and restaurants	Kanawha County, West Virginia	1.02 (0.92–1.12)
Subtotal: Workplaces and restaurants (I-squared = 62.1%, p = 0.015)			0.95 (0.88–1.02)
Herman 2011	Workplaces, restaurants, and bars	Arizona	0.84 (0.60–0.93)
Heinz 2007	Workplaces, restaurants, and bars	Boise, Idaho	0.82 (0.66–1.01)
Barnett 2009	Workplaces, restaurants, and bars	Christchurch, New Zealand (30–55 years of age)	1.15 (0.94–1.40)
Barnett 2009	Workplaces, restaurants, and bars	Christchurch, New Zealand (55–74 years of age)	0.86 (0.77–0.97)
Cronin 2012	Workplaces, restaurants, and bars	Cork and Kerry Counties, Ireland	0.84 (0.76–0.92)
Moraros 2010	Workplaces, restaurants, and bars	Delaware	0.91 (0.87–0.95)
Sims 2010	Workplaces, restaurants, and bars	England	0.98 (0.96–0.99)
Dautzenberg 2008	Workplaces, restaurants, and bars	France (complete ban)	0.84 (0.77–0.92)
Bonetti 2011b	Workplaces, restaurants, and bars	Graubunden, Switzerland	0.79 (0.69–0.90)
Bruintjes 2011	Workplaces, restaurants, and bars	Greeley, Colorado	0.73 (0.59–0.90)
McMillen 2010	Workplaces, restaurants, and bars	Hattiesburg, Mississippi	0.87 (0.74–1.01)
Sargent 2004	Workplaces, restaurants, and bars	Helena, Montana	0.60 (0.36–0.99)
Kent 2012	Workplaces, restaurants, and bars	Ireland	0.89 (0.70–1.13)
Barone-Adesi 2011	Workplaces, restaurants, and bars	Italy (20 regions)	0.97 (0.95–0.99)
Vasselli 2008	Workplaces, restaurants, and bars	Italy (4 regions)	0.86 (0.83–0.92)
Dove 2010	Workplaces, restaurants, and bars	Massachusetts	0.90 (0.86–0.95)
Juster 2007	Workplaces, restaurants, and bars	New York State	0.80 (0.80–0.80)

Appended Data Table for Figure 8.6   Continued

Study	Place	Location	Effect size, relative risk (95% CI)
NCTPCB 2011	Workplaces, restaurants, and bars	North Carolina	0.79 (0.75–0.83)
Bruckman 2011	Workplaces, restaurants, and bars	Ohio	0.96 (0.95–0.98)
Hurt 2011	Workplaces, restaurants, and bars	Olmstead County, Minnesota (ordinance 2)	0.55 (0.44–0.68)
Barone-Adesi 2006	Workplaces, restaurants, and bars	Piedmont, Italy	0.89 (0.81–0.98)
CDC 2009b	Workplaces, restaurants, and bars	Pueblo, Colorado	0.59 (0.49–0.70)
Lemstra 2008	Workplaces, restaurants, and bars	Saskatoon, Canada	0.87 (0.84–0.90)
McMillen 2010	Workplaces, restaurants, and bars	Starkville, Mississippi	0.72 (0.48–1.10)
Di Valentino 2011	Workplaces, restaurants, and bars	Ticino, Switzerland	0.79 (0.70–0.88)
Naiman 2010	Workplaces, restaurants, and bars	Toronto, Canada (phase 3)	0.81 (0.75–0.88)
Gasparrini 2009	Workplaces, restaurants, and bars	Tuscany, Italy	0.95 (0.89–1.00)
Sebrié 2013	Workplaces, restaurants, and bars	Uruguay	0.81 (0.72–0.89)
Gudnason 2009	Workplaces, restaurants, and bars	Iceland	0.83 (0.68–1.02)
Ferrante 2012	Workplaces, restaurants, and bars	Santa Fe, Argentina	0.65 (0.59–0.70)
Pell 2008	Workplaces, restaurants, and bars	Scotland	0.83 (0.82–0.84)
Di Valentino 2010	Workplaces, restaurants, and bars	Ticino, Switzerland	0.82 (0.76–0.89)
Barone-Adesi 2009	Workplaces, restaurants, and bars	Piedmont, Italy	0.94 (0.90–0.97)
Cesaroni 2008	Workplaces, restaurants, and bars	Rome, Italy	0.89 (0.85–0.93)
Barone-Adesi 2011	Workplaces, restaurants, and bars	Italy (20 regions)	0.95 (0.93–0.98)
Subtotal: Workplaces, restaurants, and bars (I-squared = 98.0%, p = 0.000)			0.85 (0.82–0.88)

Source: Adapted from Tan and Glantz 2012 with permission from Wolters Kluwer Health, © 2012.
Note: **CDC** = Centers for Disease Control and Prevention; **CI** = confidence interval; **NCTPCB** = North Carolina Tobacco Prevention and Control Branch.

Appended Data Table for Figure 8.7

lnrr	Follow-up duration (years)
-.1743534	1.083333
-.1984510	1
-.1397619	2
-.1508229	2
-.1791266	3.25
-.0943106	1.083333
-.0202027	1.25
-.1743534	0
-.2523149	1
-.2382572	2
-.3147107	2.5
-.1392621	2.5
-.5108256	0.5
-.1165338	2
-.0304592	2
-.1508229	0.1666667
-.1053605	2.5
-.2226437	1.75
-.2357223	1
-.0366640	2.666667
-.1165338	0.5
-.5276328	3
-.3011051	1.5
-.2107210	3
-.1392621	1
-.3285040	2.916667
-.2357223	2
-.0512933	1
-.2107210	1

Source: Adapted from Tan and Glantz 2012 with permission
from Wolters Kluwer Health, © 2012.
Note: Each locality studied for a smoke-free law was associated
with one follow-up time per outcome.

Figure 8.8   Appended Data Table

Study	Place	Location	Effect size (95% CI)
Dautzenberg 2008	Workplaces only	France (partial ban)	0.96 (0.92–1.01)
Naiman et al. 2010	Workplaces only	Toronto, Canada (phase 1)	0.91 (0.80–1.03)
Subtotal: Workplaces only (I-squared = 0.0%, p = 0.408)			0.96 (0.91–1.00)
Naiman et al. 2010	Workplaces and restaurants	Toronto, Canada (phase 2)	0.76 (0.68–0.85)
Subtotal: Workplaces and restaurants (I-squared = %, p =)			0.76 (0.68–0.85)
Herman 2011	Workplaces, restaurants, and bars	Arizona	0.86 (0.79–0.96)
Dautzenberg 2008	Workplaces, restaurants, and bars	France (complete ban)	0.83 (0.76–0.91)
Kent et al. 2012	Workplaces, restaurants, and bars	Ireland	0.93 (0.73–1.20)
Naiman et al. 2010	Workplaces, restaurants, and bars	Toronto, Canada (phase 3)	0.63 (0.56–0.71)
Kent et al. 2012	Workplaces, restaurants, and bars	Ireland	1.00 (0.70–0.94)
Subtotal: Workplaces, restaurants, and bars (I-squared = 82.4%, p = 0.000)			0.81 (0.70–0.94)

Source: Adapted from Tan and Glantz 2012 with permission from Wolters Kluwer Health, © 2012.
Note: See Tables 8.5 and Tables 8.6*S* and 8.7*S* for further details about each risk estimate or study. **CI** = confidence interval.

Appended Data Table for Figure 8.9

Study	Place	Location	Effect size, relative risk (95% CI)
Naiman et al. 2010	Workplaces only	Toronto, Canada (phase 1)	0.88 (0.69–1.14)
Subtotal: Workplaces only (I-squared = %, p =)			0.88 (0.69–1.14)
Sargent et al. 2012	Workplaces and restaurants	Germany	0.87 (0.82–0.92)
Naiman et al. 2010	Workplaces and restaurants	Toronto, Canada (phase 2)	0.65 (0.52–0.82)
Khuder et al. 2007	Workplaces and restaurants	Bowling Green, Ohio	0.53 (0.45–0.59)
Hurt et al. 2011	Workplaces and restaurants	Olmsted County, Minnesota (ordinance 1)	0.72 (0.58–0.89)
Subtotal: Workplaces and restaurants (I-squared = 93.5%, p = 0.000)			0.68 (0.52–0.90)
Herman 2011	Workplaces, restaurants, and bars	Arizona	0.64 (0.46–0.88)
Cronin et al. 2012	Workplaces, restaurants, and bars	Cork and Kerry Counties, Ireland	0.89 (0.75–1.05)
Kent et al. 2012	Workplaces, restaurants, and bars	Ireland	0.77 (0.61–0.96)
Naiman et al. 2010	Workplaces, restaurants, and bars	Toronto, Canada (phase 3)	0.38 (0.30–0.48)
Hurt et al. 2011	Workplaces, restaurants, and bars	Olmsted County, Minnesota (ordinance 2)	0.50 (0.40–0.63)
Subtotal: Workplaces, restaurants, and bars (I-squared = 90.4%, p = 0.000)			0.61 (0.44–0.85)

Source: Adapted from Tan and Glantz 2012 with permission from Wolters Kluwer Health, © 2012.
Note: See Tables 8.5 and tables 8.6*S* and 8.7*S* for further details about each risk estimate or study. **CI** = confidence interval.

Chapter 9
Reproductive Outcomes

Chapter Conclusions *499*

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Sections of this chapter on the health consequences of smoking are accompanied by evidence tables detailing the studies that were used to evaluate the evidence to assess causality. A supplement to this report is provided that contains these tables. The tables included in the supplement are indicated with an "*S*" where they are called out in the text.

Introduction

Tobacco use before and during pregnancy remains a major cause of reduced fertility as well as maternal, fetal, and infant morbidity and mortality. Smoking prevalence among women grew in the decades before the 1964 Surgeon General's report, *Smoking and Health: Report of the Advisory Committee of the Surgeon General of the Public Health Service*, and continued to increase across the 1970s as products were aggressively marketed to women (U.S. Department of Health and Human Services [USDHHS] 2001). Despite declines in recent decades, more than 400,000 live-born infants are exposed in utero to tobacco from maternal smoking annually (Hamilton et al. 2012; Tong et al. 2013). The women most likely to smoke are among the most vulnerable—those disadvantaged by low income, low education, and mental health disorders, further exacerbating the adverse health effects from smoking on mothers and their offspring (Adams et al. 2008; Holtrop et al. 2010; Maxson et al. 2012; Page et al. 2012a). Women in these groups are also less likely to quit smoking when they become pregnant and are more likely to relapse after delivery (Adams et al. 2008). Reducing the prevalence of smoking among pregnant women and women of reproductive age remains a critical component of public health efforts to improve maternal and child health.

This chapter includes the following updates to previous Surgeon General's reports:

An overview of surveillance systems of pregnant women that include data related to prenatal smoking status.

- A review of what is currently known about smoking cessation during pregnancy, including clinical- and policy-based interventions.

- A summary of the advances in our understanding of the mechanisms underlying previously established effects of tobacco on reproductive health since the 1964 report. Topics include fetal growth, preeclampsia, stillbirth and perinatal mortality, sudden infant death syndrome (SIDS), and neurocognitive development.

- Evidence reviews for outcomes not addressed or not causally related to smoking in previous Surgeon General's reports, including congenital malformations, male sexual function, neurobehavioral disorders of childhood, ectopic pregnancy, and spontaneous abortion. These topics were last reviewed in the 2004, 2006, and 2010 Surgeon General's reports.

Surveillance

Before 1989, surveillance of the prevalence of smoking during pregnancy in the United States was limited to self-reported data collected through periodic surveys, which sampled new mothers or reproductive age women, regarding their most recent pregnancy within the last 5 years (Table 9.1). The earliest data available are from the 1967 National Natality Survey, which sampled married women with live-born infants (Kleinman and Kopstein

1987). In 1989, smoking status during pregnancy was added to the U.S. Standard Certificate of Live Birth, and New York City, the District of Columbia, and all states, except California, collected this information (Tolson et al. 1991). In 2003, the U.S. Standard Certificate of Live Birth was revised to include the average number of cigarettes smoked per day during the 3 months before pregnancy and during the first, second, or third trimesters of

Table 9.1   Data sources for smoking prevalence during pregnancy

Data source	Sample	Year(s)	Smoking question
National Natality Survey	• Married women whose infants were born alive	1967–1980	Women asked whether smoked during the 12 months before delivery. If yes, women asked about average number of cigarettes smoked/day after finding out they were pregnant (Kleinman and Kopstein 1987)
National Survey of Family Growth	• Girls and women 15–44 years of age during their most recent pregnancy	1982, 1988, 1995, 2002, 2006–2010	Women were first asked how much they smoked cigarettes before they learned they were pregnant. Then they were asked whether they smoked at all after they learned they were pregnant. If response was yes, women were asked the amount they smoked during pregnancy after learning they were pregnant (CDC 2013b)
National Health Interview Survey	• Women 18–44 years of age who had given birth within the past 5 years	1985, 1990, 1998, 2005, 2010	2010 survey, women asked whether they smoked when they became pregnant. If yes, they were asked about whether they smoked at any time during pregnancy and whether they quit for 7 days or longer during pregnancy. Among those who quit, they were also asked about whether they relapsed to smoking during pregnancy (CDC 2013a)
National Maternal and Infant Health Survey	• Nationally representative sample • 11,000 women who had live births, 4,000 who had late fetal deaths, and 6,000 who had infant deaths	1988	Women asked whether they smoked cigarettes in the 12 months before delivery, number of cigarettes smoked during pregnancy, quit smoking for at least 1 week during pregnancy (Sanderson et al. 1991)
National Pregnancy and Health Survey	• Women delivering live-born infants in hospitals in the contiguous 48 states with 200 or more births/year	1992–1993	Women asked whether smoked in last 3 months of pregnancy, number of days a week smoked, average number of cigarettes smoked/day, and the most number of cigarettes smoked in a day (USDHHS 1996)
U.S. Standard Certificate of Live Birth	• All births	1989–ongoing	1989 version of birth certificate collects average number of cigarettes smoked at any time during pregnancy. 2003 version of birth certificate collects average number of cigarettes smoked during the 3 months before pregnancy and during the first, second, or third trimester of pregnancy. Smoking data are available for New York City, the District of Columbia, and all states except California (Osterman et al. 2011)
Pregnancy Risk Assessment Monitoring System	• Representative sample of women who delivered live infants	1987–ongoing	Survey administered 2–6 months after birth and includes data on smoking in 3 months before pregnancy, last 3 months of pregnancy, and after delivery at the time of survey administration (Tong et al. 2013)

Notes: **CDC** = Centers for Disease Control and Prevention; **USDHHS** = U.S. Department of Health and Human Services.

pregnancy (Osterman et al. 2011). Because the 1989 and 2003 birth certificate smoking variables are not comparable and state uptake of the 2003 revised birth certificate has been gradual (in 2011, 38 states had implemented the 2003 revised birth certificate, and it is anticipated that all states will have made the transition by 2014), national prenatal smoking trend data after 2002 are not available. In 2002, an estimated 11.5% of singleton, live-born infants were exposed to maternal smoking in utero (Dietz et al. 2010). Of these, an estimated 5.3–7.7% of preterm deliveries, 13.1–19.0% of term low birth weight deliveries, 23.2–33.6% of SIDS, and 5.0–7.3% of preterm-related deaths were attributable to prenatal smoking.

The Pregnancy Risk Assessment Monitoring System (PRAMS) is another source of state- and population-based data on smoking during pregnancy. In this survey, a questionnaire is administered 2–6 months after delivery to women with a live birth. Using 2010 data from 27 PRAMS states/sites, 23% of women who delivered live infants reported smoking in the 3 months before pregnancy; 11% in the last 3 months of pregnancy; and 16% 2–6 months after delivery (Tong et al. 2013). There was large variation by state in the prevalence of smoking during the last 3 months of pregnancy, ranging from 2.3% in New York City to 30.5% in West Virginia. Demographic groups with the highest prevalence of prenatal smoking were 20–24 year olds (17.6%), American Indian/Alaska Natives (26.0%), women with less than 12 years of education (17.4%), unmarried (18.6%), and those with an annual income of less than $15,000 per year (19.0%) (Tong et al. 2013).

Underreporting of smoking among pregnant women has been documented through biochemical confirmation of self-report in clinical trials and population-based studies. In an analysis of 1999–2006 National Health and Nutrition Examination Survey data, which compared self-reported smoking status to serum cotinine, 22.9% of pregnant smokers and 9.2% of nonpregnant smokers of reproductive age did not accurately disclose their smoking status (Dietz et al. 2010). Such nondisclosure likely contributes to underreporting of prenatal smoking status on birth certificates and in self-administered surveys. It is unknown whether and to what extent nondisclosure of smoking status has changed over time. Existing surveillance systems of pregnant women do not currently gather data on noncigarette tobacco products such as little cigars/cigarillos, hookah, snus, or electronic cigarettes.

Cessation

Smoking cessation in pregnancy has been associated with improvements in outcomes including fetal growth restriction and preterm delivery (McCowan et al. 2009; Baba et al. 2012). The first study of a smoking cessation intervention for pregnant women was published in 1976 and included brief advice from a physician to quit (Baric et al. 1976). Numerous intervention trials have been conducted since then, and results have been generally positive with regard to pregnancy outcomes (Lumley et al. 2009), although the increasing importance of including biochemical validation of cessation in research protocols has also been recognized (Kendrick et al. 1995). Behavioral counseling has been shown to have a modest effect, resulting in about an additional 1 in 20 pregnant women quitting (Lumley et al. 2009), and the current best-practice guidance for prenatal smoking cessation entails psychosocial counseling delivered in the prenatal care setting (Fiore et al. 2008; American Congress of Obstetricians and Gynecologists [ACOG] 2010). However, even with universal implementation of this best-practice approach, the prevalence of smoking among pregnant women was projected to decline by no more than approximately 1% in a model of smoking among pregnant women based on 2004 U.S. data (Kim et al. 2009). Therefore, other interventions are also needed in order to have a substantial public health impact.

In addition to behavioral interventions, a number of studies have assessed the safety and efficacy of nicotine replacement therapy (NRT) for cessation during pregnancy. A 2012 meta-analysis of six randomized controlled trials (RCTs) of NRT found no significant difference for smoking cessation in later pregnancy after using NRT as an adjunct to behavioral support as compared to control (relative risk [RR] = 1.33; 95% confidence interval [CI], 0.93–1.91, 1,745 women) (Coleman 2012). Both placebo and nonplacebo controlled studies were assessed (placebo RCTs: RR = 1.20; 95% CI, 0.93–1.56, four studies, 1,524 women; nonplacebo RCTs: RR = 7.81; 95% CI, 1.51–40.35, two studies, 221 women), suggesting clinical heterogeneity and uncontrolled biases in the nonplacebo controlled trials. There was insufficient evidence to conclude that NRT had a positive or negative effect on rates of miscarriage, stillbirth, premature birth, birthweight, low birthweight, admissions to neonatal intensive care, or neonatal

death compared to the control groups. Nonadherence to NRT treatment was reported among the majority of participants in five of the six NRT trials (range of 7.2–29% of patients adhering to NRT treatment). A recent observational study of pregnant smokers utilizing national smoking cessation services in the United Kingdom found that use of a NRT patch along with a faster-acting form was associated with higher odds of quitting compared with no medication (odds ratio [OR] = 1.93; 95% CI, 1.13–3.29, p = 0.016), whereas use of a single form of NRT showed no benefit (OR = 1.06; 95% CI, 0.60–1.86, p = 0.84) (Brose et al. 2013). Research is needed to further assess the efficacy and safety of NRT as well as understanding the reasons for nonadherence to NRT treatments. Currently, ACOG (2010) recommends NRT only if behavioral therapy fails to achieve smoking cessation and it must be administered under the supervision of a physician.

In addition to the current clinical guidelines, section 4107 of the *Patient Protection and Affordable Care Act*, which took effect on October 1, 2010, requires state Medicaid programs to cover tobacco-cessation counseling and drug therapy for pregnant women without cost sharing. The update of *Treating Tobacco Use and Dependence* guidelines (Fiore et al. 2008) note that although the use of NRT exposes pregnant women to nicotine, smoking exposes them to nicotine plus numerous other chemicals that are injurious to the woman and fetus, and these concerns must be considered in the context of inconclusive evidence that cessation medications boost abstinence rates in pregnant smokers.

Studies of contingency management interventions, in which quitting is rewarded with financial incentives, show promise, including higher quit rates (34% of women in the intervention arm quit compared to 7.1% of women receiving standard care) and improvements in infant birth weight (Higgins et al. 2010, 2012). The effectiveness of

contingency management across diverse populations and settings and the cost-benefit of implementing these interventions have not been evaluated.

Studies of the effects of interventions to prevent relapse after delivery have been mixed and limited by methodologic weaknesses; a 2009 Cochrane review found the evidence "insufficient to support the use of any specific behavioral intervention for helping smokers who have successfully quit for a short time to avoid relapse" (Hajek et al. 2009).

There is growing evidence that tobacco control policies may be effective in reducing the prevalence of prenatal smoking and improving birth outcomes. Studies conducted in Scotland and Belgium found that implementation of national smokefree air laws had a significant effect on reducing the prevalence of prenatal smoking and decreased the risk of preterm delivery (Mackay et al. 2012; Cox et al. 2013). In an analysis of 2000–2005 PRAMS data from 29 states linked to state tobacco control data, state tobacco control policies, taxes, and smokefree air laws were found to be effective in reducing maternal smoking (Adams et al. 2012). For example, a $1.00 increase in cigarette taxes and prices increased the quit rate among pregnant women from 44.1–48.9% and decreased the percentage who relapsed in the early postpartum period. Additionally, the same study found that implementing a full worksite smoking ban increased quits during pregnancy by an estimated 5%. Several studies of local ordinances in the United States have also documented reduced prevalence of smoking (Nguyen et al. 2013), and reductions in preterm births (Page et al. 2012b). Tobacco control policies are continually being implemented at local and state levels, and there is a need for evaluation of these policies and their effects on the prevalence of smoking and birth outcomes in pregnant women.

Advances in the Understanding of Tobacco and Reproductive Health

The 1964 Surgeon General's report stated that infants of smokers are more likely than those of nonsmokers to be born at less than 2,500 grams (g) (U.S. Department of Health, Education, and Welfare [USDHEW] 1964); since that time, the list of adverse reproductive health outcomes associated with maternal smoking has grown dramatically (see Table 4.4S). For many of these outcomes, however, the mechanisms through which tobacco acts to

cause adverse effects are still not completely understood. As the landscape of commercial tobacco products changes and new nicotine-delivery devices are introduced into the market, gaining a better understanding of the underlying pathophysiologic mechanisms and the components responsible is of increasing urgency, as is identifying the most effective approaches to decrease the prevalence of prenatal and postnatal smoking.

Fetal Growth

The effects of maternal smoking during pregnancy on birth weight have been recognized since the first Surgeon General's report on smoking and health, in which it was observed that infants of smokers are more likely than those of nonsmokers to be born weighing less than 2,500 g, even after stratification by social class (USDHEW 1964).

Since the 1964 Surgeon General's report, new insights have been gained into the potential underlying mechanisms and clinical implications of reduced birth weight. In the 1960s, the terms low birth weight and preterm delivery were used interchangeably; however, recognition that they are not synonymous eventually led to the transition to the use of alternative outcomes (Wilcox 2001). Low- and normal-birth weight outcomes have largely been replaced with outcomes related specifically to gestational age and/or fetal growth. Intrauterine growth retardation (IUGR) (the lower tenth percentile for the gestational age), birth weight in units of standard deviations (z-scores), term birth weight, gestational-age adjusted birth weight, mean gestational age, and percentage of deliveries that are preterm (less than 37 completed weeks gestation) are all commonly used.

The 2004 Surgeon General's report found the evidence sufficient to infer causal relationships between smoking and fetal growth restriction and between smoking and decreased gestation/increased preterm delivery. Since then, newer studies have included consideration of the effects of active maternal smoking on both fetal growth and gestational age, and of active smoking and exposure to secondhand smoke on fetal growth. For example, in a large study of midtrimester cotinine levels and birth outcomes, women with cotinine levels indicative of exposure to secondhand smoke below the threshold for active smoking (10 nanograms/milliliter [ng/mL]), but above the limit of detection (0.05 ng/mL) were compared with women who had levels below the limit of detection. Women with cotinine levels between 0.05–10 ng/mL delivered infants with a mean overall decrease in birth weight of 109 g after adjustment for a number of variables and for gestational age. Women with cotinine levels in the active smoking range (above 10 ng/mL) delivered infants with a mean reduction in birth weight of 327g compared with women who had levels below the level of detection (Kharrazi et al. 2004). Other estimates for active smoking range from about 200–300 g (USDHHS 2001).

Studies of birth outcomes in mothers who use smokeless tobacco during pregnancy offer new insights into the mechanisms underlying reductions in birth weight among infants of smokers. It has been hypothesized that exposure to cigarette smoke results in fetal growth restriction through products of combustion (e.g., carbon monoxide [CO]) and associated hypoxia, nicotine-mediated vasoconstriction of uteroplacental vessels, or both (Lambers and Clark 1996). However, it has been questioned whether vasocontrictive effects of nicotine are sufficient to overcome placental circulatory reserve (Benowitz and Dempsey 2004). If nicotine-related mechanisms are important, negative associations between birth weight and exposure to smokeless tobacco use and to cigarette smoking would be expected. However, the associations between smokeless tobacco use and birth weight deficits found in studies that include an adjustment for gestational age are modest; estimated deficits range from 17–93 g (England et al. 2003, 2012; Gupta and Sreevidya 2004; Steyn et al. 2006; Juárez and Merlo 2013). Two of these estimates were not significant (Steyn et al. 2006; England et al. 2012). Smokeless tobacco use has also been associated with a modest increase in the risk for being small for gestational age. In a population-based study using birth registry data in Sweden, smokeless tobacco use and smoking were both associated with term small for gestational age (defined as birth weight more than two standard deviations below the mean for gestational age among term infants), but the magnitude of the association was smaller for smokeless tobacco use (adjusted odds ratio [AOR] = 1.21; 95% CI, 1.02–1.43 and AOR = 2.76; 95% CI, 2.62–2.91, respectively) (Baba et al. 2012). None of the studies of smokeless tobacco and pregnancy outcomes conducted thus far have included adjustment for exposure to secondhand smoke.

Taken together, these data provide support that nicotine makes a relatively modest contribution to the effects of tobacco use on fetal growth when compared with the larger contribution of the combination of both nicotine and products of combustion in cigarette smoke. However, it will be difficult to accurately quantify the specific contribution of nicotine until studies are done that include biomarkers of nicotine exposure (e.g., cotinine) and measures of exposure to secondhand smoke.

Studies of tobacco use and birth weight must necessarily include consideration of the concurrent effects on gestational age. Maternal smoking is associated with a 27% increase in the risk of preterm delivery compared with nonsmokers (Shah and Bracken 2000). Several studies have also found an increased risk of preterm delivery among smokeless tobacco users compared with tobacco nonusers (Gupta and Sreevidya 2004; Baba et al. 2012; England et al. 2013). In Sweden, continued snuff use and smoking during pregnancy were each associated with

increased risks of preterm birth, and the magnitudes of the associations were similar to one another (adjusted estimated pooled OR = 1.29; 95 % CI, 1.17–1.43, AOR = 1.30; 95% CI, 1.25–1.36, respectively) (Baba et al. 2012). In a study of pregnant women in India, smokeless tobacco users delivered 6.2 days earlier on average than nonusers (p <0.001). In addition, smokeless tobacco use was associated with preterm delivery overall (AOR = 1.5, p = 0.05) and with preterm delivery at less than 32 and less than 28 weeks' gestation (AOR = 4.9; 95% CI, 2.1–11.8; AOR = 8.0; 95% CI, 2.6–27.2, respectively) (Gupta and Sreevidya 2004). In South Africa, snuff users delivered at a slightly reduced gestational age compared with tobacco nonusers (37.9 and 38.3 weeks, respectively, p = 0.003), but there was no significant increase in preterm delivery at less than 36 weeks gestation (Steyn et al. 2006). Together, these studies support an association between smokeless tobacco use and preterm delivery and raise important concerns about the potential effects of nicotine exposure during pregnancy.

Evidence from studies of gene-environment interactions support the hypothesis that components of tobacco other than nicotine may contribute to tobacco-related adverse pregnancy outcomes. Genes that encode enzymes associated with the metabolism of other compounds found in tobacco smoke, such as polycyclic aromatic hydrocarbons (PAHs) and nitrosamines, have been associated with adverse birth outcomes in smokers, including preterm delivery and restricted fetal growth (Wang et al. 2002; Nukui et al. 2004; Grazuleviciene et al. 2009; Aagaard-Tillery et al. 2010). For example, the effects of maternal smoking on the risk of IUGR appear to be modified by maternal *CYP1A1* and *GSTT1* genotypes; in one study, cigarette smoking in women with *GSTT1* deletions appeared to be associated with more extreme birth weight reduction and increased risk of IUGR compared with women who used tobacco but did not have the deletion (Wang et al. 2002). In the same study, cigarette smoking in women with *CYP1A1* heterozygous and homozygous variant types was also associated with more extreme reductions in birth weight and with IUGR compared with women who smoked but who had wild-type variants. Women with both the *CYP1A1* variant genotype and the *GSTT1* deletion had the greatest reduction in birth weight (Wang et al. 2002). In contrast, a subsequent study showed no association between gene polymorphisms of *CYP1A1* and birth weight, but did show associations with *GSTT1* deletions (Nukui et al. 2004). Studies of allelic variants affecting nicotine metabolism and birth weight have been inconclusive (Aagaard-Tillary et al. 2010). Additional studies of tobacco-related adverse pregnancy outcomes among women with different genotypes may help to further define pathways between different components in tobacco and adverse pregnancy outcomes.

The clinical significance of the effects of smoking on fetal growth has been a topic of debate for decades, and the relationship between smoking-related birth weight reductions and infant mortality has been studied in detail. It has long been recognized that low birth weight babies of smokers have lower mortality than low birth weight babies of nonsmokers. This phenomenon was cited early on as support that smoking improved survival, rather than causing harm (Yerushalmy 1971). An alternative explanation is that the smaller size of infants of smokers does not in itself affect survival, so smaller infants of smokers have better survival rates than other infants of the same weight. Indeed, when birth weight distributions for infants of smokers and nonsmokers and their corresponding mortality rates are examined, the infants of smokers have higher mortality at every birth weight, when each population is adjusted to its own z-scale of birth weight (Wilcox 2001). This provides strong evidence that smoking affects infant mortality and that this effect is independent of birth weight, in contrast to early explanations that smoking somehow confers an advantage to smaller babies (Yerushalmy 1971). In other words, infants of nonsmokers may be less likely to be born at a low birth weight than infants of smokers, but when they are, the underlying etiologies of low birth weight are associated with higher mortality (Wilcox 2001).

Preeclampsia

Among the most dramatic advances in our understanding of the pathophysiology of reproductive health outcomes are developments in the field of preeclampsia. Preeclampsia is a syndrome of reduced organ perfusion attributable to vasospasm and endothelial activation with an onset after 20 weeks of gestation. It is marked by proteinuria, hypertension, and dysfunction of the endothelial cells lining the uterus (Sibai et al. 2005). Smoking is inversely associated with preeclampsia; the pooled risk reduction is 32% (Conde-Agudelo et al. 1999). The 2004 Surgeon General's report found the evidence sufficient to infer a causal relationship between smoking and a reduced risk of preeclampsia (USDHHS 2004).

The discovery of an animal model in which almost all the complications of preeclampsia (hypertension, proteinuria, cerebral edema, hematologic abnormalities, and fetal growth restriction) can be initiated by administration of the anti-angiogenic protein soluble fms-like tyrosine kinase-1 (sFlt-1) to rats has led to the construction of a working model for preeclampsia (Levine and Karumanchi

2005). Pro-angiogenic factors, including VEGF, promote angiogenesis in the placenta while anti-angiogenic factors inhibit angiogenesis. Anti-angiogenic factors include sFlt-1, a splice variant of VEGF receptor 1 and a major placental inhibitor of angiogenesis. Circulating sFlt-1 binds VEGF and placental growth factor, preventing them from binding with cell-surface receptors. Production of excess sFlt-1 and other anti-angiogenic factors leads to an imbalance between pro- and anti-angiogenic factors and results in the clinical manifestation of preeclampsia including vasoconstriction and a state of generalized endothelial dysfunction. The molecular basis of placental dysregulation of angiogenic factors is currently the subject of ongoing research (Steinberg et al. 2009; Maynard and Karumanchi 2011).

A new preeclampsia model provides a plausible explanation for reduced preeclampsia risk from cigarette smoking. Smoking in pregnancy has been associated with reduced sFlt-1 levels compared with nonsmokers, in women with and without preeclampsia (Jeyabalan et al. 2008), and cigarette smoke extract decreases sFlt-1 production in placental villous explants (Maynard and Karumanchi 2011). Because a reduced risk of preeclampsia has not been observed in smokeless tobacco users (Wikström 2010; England et al. 2013), it seems likely that one or more products of combustion is responsible for the reduced risk of preeclampsia seen in smokers, and not nicotine. CO is one promising candidate for a mediator, as it has vasoprotective properties, and CO and CO-releasing molecules lower sFlt-1 and soluble endoglobin in in vitro cultures.

Stillbirth and Perinatal Mortality

In the 1969 Surgeon General's report supplement, it was stated that prenatal smoking may be associated with stillbirth (fetal death after 28 weeks gestation) and neonatal death (death within 28 days of birth) (USDHEW 1969). In the 2001 Surgeon General's report, it was noted that cigarette smoking was consistently associated with stillbirth (USDHHS 2001), with an increased risk of 40% (Cnattingius et al. 1988) to 60% (Raymond et al. 1994). Underlying factors were attributed to IUGR, placental complications, or both. Neonatal mortality was also noted to be increased in infants of smokers by 20% (Cnattingius et al. 1988; Malloy et al. 1988). Perinatal mortality was noted to be increased by 20–30% with 3.4–8.4% of perinatal deaths attributable to smoking (DiFranza and Lew 1995).

Since the 1964 Surgeon General's report, there has been significant progress in understanding the increased perinatal and infant mortality in offspring of smokers.

Smoking likely increases perinatal mortality through numerous mechanisms, including abruption, placenta previa, preterm delivery, and premature and prolonged rupture of the membranes, and through physiologic responses of the fetus and newborn to stress (Meyer and Tonascia 1977). For example, an abnormal adrenal response of the fetus or neonate to hypoxia could affect cardiac function and survival (Slotkin 1998), and hypoxia from sleep apnea or airway obstruction could precipitate respiratory failure in a susceptible infant (Horne et al. 2005).

Some studies support a role for nicotine in the effects of smoking on stillbirth and perinatal mortality (see Chapter 5, "Nicotine"). Nicotinic acetylchonine receptors (nAChRs) are receptors that are ordinarily activated by endogenous acetylcholine, but that also can be stimulated by nicotine, resulting in disruption of normal cholinergic signaling (Albuquerque et al. 2009). nAChRs are expressed early in fetal development in the central, peripheral, and enteric nervous systems (reviewed by Abbott and Winzer-Serhan 2012), and transient, regional patterns of increased nAChR expression occur throughout perinatal and postnatal development. nAChRs are involved in neurogenesis, migration, differentiation, and synaptogenesis, in regulating the growth of developing neurites, guiding pathfinding of these projections, and mediating pruning of hippocampal and cortical neurons through effects on apoptosis (Dywer et al. 2008). Depending on the subunit composition, and the dose and duration of exposure, exogenous nicotine can activate or inactivate a given receptor, potentially altering fetal development. For example, animal models show that nicotine exposure in the fetus causes cell damage, and reduces cell number, and impairs synaptic activity. Receptor stimulation by nicotine leads to errors in cell development, including premature change from cell replication to differentiation and initiation of apoptosis (Slotkin et al. 1987; Slotkin 1998; Dwyer et al. 2008). Because nicotinic receptors continue to emerge after organogenesis, periods of fetal vulnerability likely extend into the second and third trimesters of pregnancy (Slotkin 1998).

Human and animal studies suggest that nAChRs in the brainstem nuclei control cardiopulmonary integration and arousal during early life (reviewed by Dwyer 2008). Gestational nicotine exposure in rat pups blunted the ventilator response to hypercapnia and hypoxia/hypercapnia in the first days of life, perhaps through effects in carotid body oxygen sensing or central processing (Huang et al. 2010). Prenatal nicotine exposure in rat pups also resulted in increased mortality in response to hypoxia (Slotkin et al. 1995), while human preterm infants of maternal smokers exhibit increased obstructive apnea and

decreased arousal in response to apnea events (Sawnani et al. 2004). Additional data suggest that gestational smokeless tobacco exposure also increases the risk of apnea, of a similar magnitude to that seen with smoking (Gunnerbeck et al. 2011), further supporting a role for nicotine in underlying pathophysiologic processes.

Extensive animal research has generated plausible models to explain how nicotine could increase the risk of perinatal mortality (see Chapter 5) (Slotkin 1998). During parturition, a massive release of catecholamines from the fetal adrenal medulla protects the fetus from hypoxia and maintains blood flow to the brain and heart (Lagercrantz and Slotkin 1986). However, prenatal nicotine exposure in rat models causes immature chromaffin cells in the adrenal gland to differentiate prematurely, resulting in loss of the normal direct stimulation of the adrenal gland by hypoxia and a complete absence of catecholamine release, which in turn causes an impaired cardiac response (Slotkin 1998). This results in the loss of a critical protective response to hypoxia, which would lead to an increased risk of infant mortality (Figure 9.1) (Slotkin 1998).

Studies of stillbirth have also been conducted among smokeless tobacco users. In a study in India, researchers reported an adjusted risk for stillbirth three times higher for mothers who used smokeless tobacco than for those who do not use any tobacco. Some evidence for a dose-response relationship was found using frequency of use (Gupta and Subramoney 2006). A previous study from India also found an increased risk of stillbirth or perinatal death with use of smokeless tobacco (primarily chewing tobacco) (Krishna 1978). In a large study of Swedish women, snuff users had an increased risk of stillbirth compared with tobacco nonusers (AOR = 1.6; 95% CI, 1.1–2.3); the risk was higher for preterm stillbirth (AOR = 2.1; 95% CI, 1.3–3.4). For women smoking 1–9 cigarettes per day and smoking more than 10 cigarettes per day, the AORs for stillbirth were 1.4 (1.2–1.7) and 2.4 (2.0–3.0), respectively. When women with preeclampsia, antenatal bleeding, or small for gestational age deliveries were excluded, the smoking-related risks of stillbirth was markedly attenuated while the elevated risk for snuff users remained at the same level. These findings suggest

Figure 9.1   Catecholamine response to hypoxia by nicotine-exposed and unexposed rats
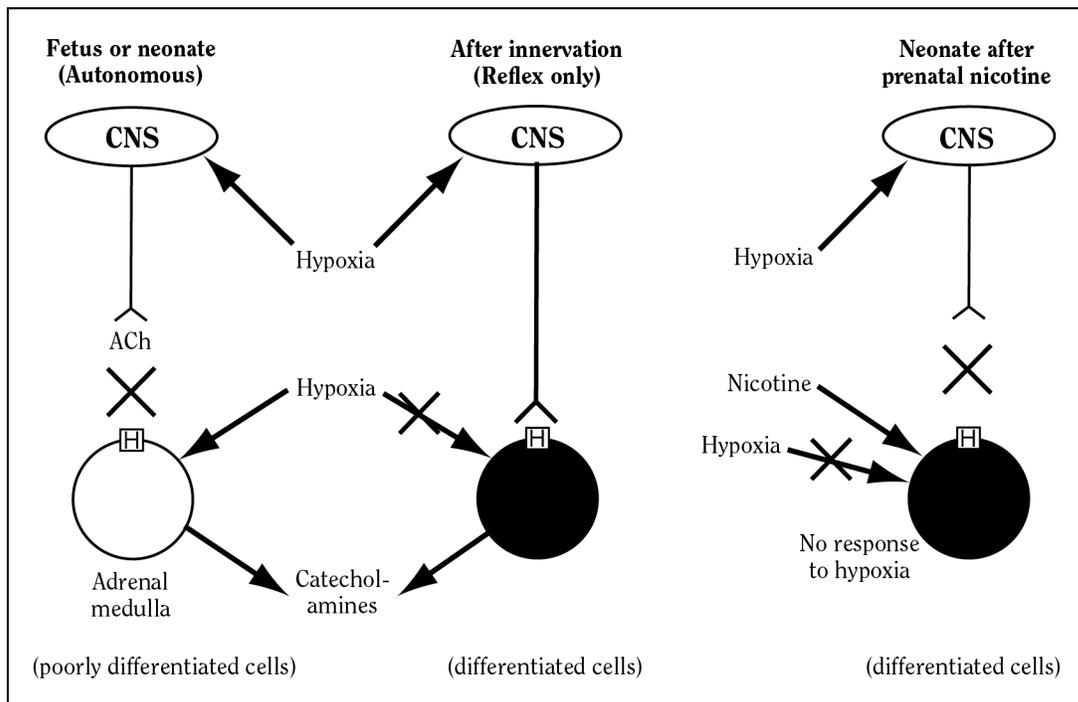
Source: Slotkin 1998. Reprinted with permission from American Society for Pharmacology & Experimental Therapeutics, © 1998.
Note: **CNS** = central nervous system.

that the mechanisms underlying the associations between smoking and stillbirth and between smokeless tobacco use and stillbirth both involve nicotine, but other factors may also contribute to increased risk in smokers (Wikström et al. 2010).

Sudden Infant Death Syndrome

SIDS is currently defined as "…sudden death of an infant under one year of age which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history" (Willinger et al. 1991, p. 681). A causal association between SIDS and smoking during and after pregnancy was established in 2004 (USDHHS 2004), more than 30 years after the landmark Collaborative Perinatal Project (CPP) first described an elevated risk of SIDS in infants of smokers. Approximated 42,000 pregnant women were enrolled, making the CPP the largest U.S.-based cohort study of pregnancy and childhood to date (reviewed by Klebanoff 2009).

Major risk factors for SIDS include prone/side sleep position, soft sleep surface, maternal smoking during pregnancy, secondhand tobacco smoke, bed sharing, and overheating (American Academy of Pediatrics [AAP] 2011). Following the release in 1992 of the recommendation that infants be placed in a nonprone position for sleep, there was a dramatic drop in the number of SIDS deaths, although this decline has plateaued. As the deaths related to prone sleeping declined, the fraction of deaths attributable to smoking increased (AAP 2011). In more recent years, the fraction of SIDS deaths attributable to smoking may be stabilizing; it is estimated that 23.2–33.6% of SIDS deaths were attributable to prenatal smoking in 2002; after extrapolating, based on trends in prenatal smoking, it was estimated that 20.2–29.3% of SIDS deaths were attributable to prenatal smoking in 2009 (Dietz et al. 2010). Guidelines for death scene investigations and autopsies are available to improve standardization of data collected and, ultimately, to improve the consistency of cause-of-death determination. However, these guidelines are not universally practiced (Camperlengo et al. 2012).

A number of hypotheses regarding the underlying causes of SIDS have been proposed. These include dysfunctional and/or immature cardiorespiratory systems; dysfunctional and/or immature arousal systems, with resulting failure to respond to stressors with normal protective responses (AAP 2011); potentiation of the laryngeal chemoreflex (Thach 2008); respiratory obstruction; bacterial toxins; thermal stress; and failure of the diaphragm with inactivation of intercostal muscles (reviewed by Harper and Kinney 2010; Goldwater 2011).

Many of these hypothesized mechanisms are unified in the triple risk model of SIDS. In this model, death from SIDS occurs in the presence of three overlapping factors: (1) a vulnerable infant, (2) a critical developmental period in homeostatic control, and (3) an exogenous stressor(s). A number of different factors (including prenatal tobacco exposure) may make the infant vulnerable to sudden death during the critical period. SIDS then occurs only in the presence of exogenous stressors, such as bed sharing and overbundling (Figure 9.2) (Filiano and Kinney 1994).

Epidemiologic data support that a high-risk scenario as described in the triple risk model could increase the risk of SIDS. In a recent meta-analysis, the authors found that the risk of SIDS associated with bed sharing was higher for infants whose mothers smoked (combined OR = 6.27; 95% CI, 3.94–9.99), than for infants whose mothers did not smoke (combined OR = 1.66; 95% CI, 0.91–3.01) (Vennemann et al. 2012). This finding suggests that the combination of the effects of tobacco exposure on infant vulnerability and stress related to the sleep environment may combine synergistically to increase the risk of death (Alsweiler et al. 2012).

Nicotine may play an important role in increasing the risk of SIDS in infants of smokers (see Chapter 5). In animal models, exogenous nicotine administered to pregnant rats alters the expression of nAChRs in the brainstem in areas involved in autonomic function, and affects fetal autonomic activity and medullary neurotransmitter receptors (Duncan et al. 2009). In studies of human infants, prenatal tobacco exposure affects recovery from hypoxia in preterm infants (Thiriez et al. 2009); infants also display impaired arousal patterns that correspond to cotinine levels (Richardson et al. 2009). These changes in autonomic function and/or arousal could increase the risk of SIDS (reviewed by AAP 2011), although a causal pathway has not been established.

Neurocognitive Development

Maternal smoking and exposure to secondhand tobacco smoke during pregnancy are hypothesized to affect physical and mental development in infancy and early childhood. Earlier Surgeon General's reports examined this topic and reported possible effects. However, at the time of the 2004 report, the evidence was considered "inadequate to infer the presence or absence of a causal relationship between maternal smoking and physical growth and neurocognitive development of children" (USDHHS 2004, p. 28), and in the 2006 Surgeon General's report's examination of the evidence related to exposure to secondhand smoke also found the evidence "inadequate" (USDHHS 2006).

Figure 9.2   Triple-risk model for sudden infant death syndrome (SIDS)

0–12 Postnatal months

Critical developmental period

Intrinsic risk factors
- Male gender
- Prematurity
- Genetic polymorphisms
- Prenatal exposures to cigarettes and/or alcohol

SIDS

Vulnerable infant

Exogenous stressor

Extrinsic risk factors
- Prone or side sleep position
- Bed sharing
- Overbundling
- Soft bedding
- Face covered
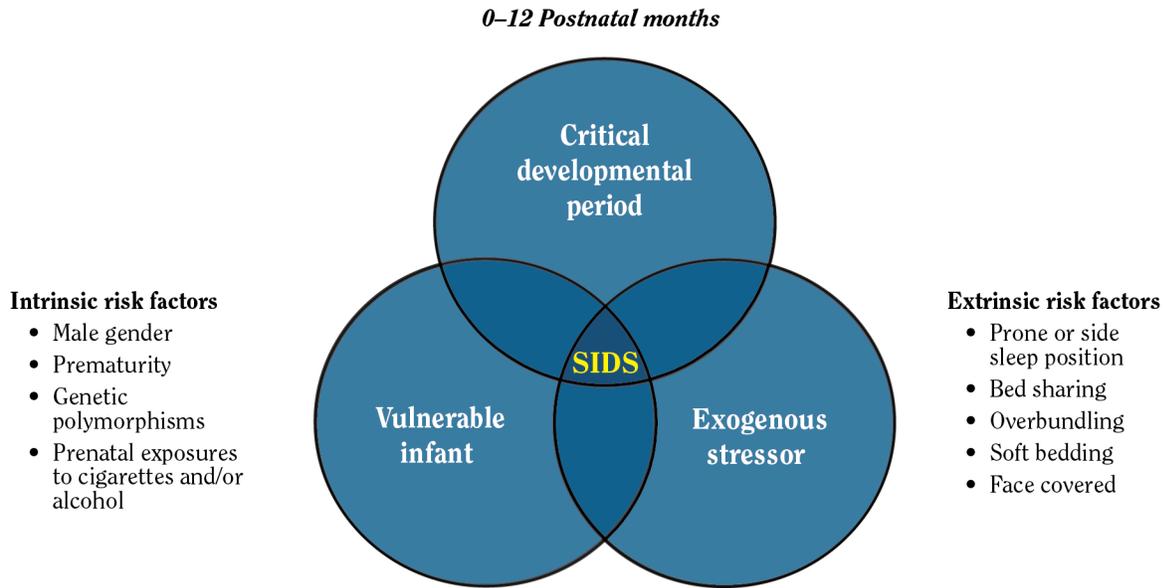
Source: Trachtenberg et al. 2012. Reprinted with permission from American Academy of Pediatrics, © 2012.

Researchers have suggested that prenatal exposure to smoking impairs neurologic development and intellectual abilities through its effects on the central nervous system (reviewed by Bublitz and Stroud 2012). Although the results of studies of the effects of maternal smoking on cognitive development in infants and young children have been inconsistent, studies of the associations between maternal smoking and children's lower performance on assessments of verbal skills in general, as well as on specific language and auditory tests, have been more consistent (reviewed in USDHHS 2010). Postnatal exposure to secondhand smoke may also be important, but is difficult to separate from prenatal exposure, because the two are correlated.

Studies of the effects of prenatal smoking on infant brain structure and function in humans are limited (reviewed by Bublitz and Stroud 2012), but data from a large study of more than 5,000 pregnant women suggest that prenatal tobacco use had negative effects on fetal head growth and caused structural alterations in the cerebellum, consistent with cell loss (Roza et al. 2007). Studies of auditory brainstem responses (evoked by the brainstem and used as a measure of auditory function) in infants are consistent with the dysregulation of auditory processing associated with prenatal tobacco exposure (Peck et al. 2012), which could contribute to learning disabilities and language impairment. Studies of brain structure and function in older children with prenatal tobacco exposure are limited by the difficulty of accounting for tobacco exposure after birth and other potential confounders, such as an absence of repeated measurements of tobacco exposure from pregnancy through adolescence and the lack of prospective monitoring of developmental and behavioral outcomes (Bublitz and Stroud 2012).

Updated Evidence Reviews

Congenital Malformations

Major structural birth defects as well as other birth defects may occur because of a malformation, disruption, or deformation of one or more parts of the body, or they can result from a chromosomal abnormality. Major birth defects can have serious adverse effects on the health, development, or functional abilities of the affected child (Centers for Disease Control and Prevention [CDC] 2008). Each year, approximately 3% of newborns in the United States are born with major birth defects, and the prevalence of all major birth defects combined has remained relatively stable in the United States from the 1970s through recent years (CDC 2008).

To date, the evidence on smoking and birth defects has been most abundant and consistent for orofacial clefts. The 2004 Surgeon General's report found the evidence to be suggestive of a causal relationship between maternal smoking and orofacial clefts. The 2010 Surgeon General's report did not include conclusions related to causality. It did provide an update of studies related to smoking and orofacial clefts, which included results of a 2004 meta-analysis that found a small but positive association with maternal smoking for cleft lip with or without cleft palate (CL/P) and for cleft palate (CP) alone (Little et al. 2004a,b; USDHHS 2010). Subsequent to that meta-analysis, eight studies have shown positive associations between periconceptional maternal smoking and orofacial clefts (Little et al. 2004a; Bille et al. 2007; Romitti et al. 2007; Johansen et al. 2009; Leite and Koifman 2009; Shaw et al. 2009; Lebby et al. 2010; Zhang et al. 2011), one of which used midpregnancy cotinine levels to more accurately ascertain prenatal smoking exposure (Shaw et al. 2009); three of these (Little et al. 2004a; Honein et al. 2007 [contains data that overlap with Romitti et al. 2007]; Shaw et al. 2009) were reviewed in the 2010 Surgeon General's report. Although the magnitude of the association between periconceptional maternal smoking and orofacial clefts is relatively modest, this remains one of the most consistent findings in etiologic research on the causes of birth defects. In addition, despite some presumed misclassification of maternal smoking given that most studies rely on self-reported exposure, methodologic research suggests the finding is quite robust and corrections for likely levels of misclassification would result in somewhat higher effect estimates (MacLehose et al. 2009).

This section summarizes the evidence for associations between maternal prenatal smoking and specific birth defects. Topics include orofacial clefts, clubfoot, gastroschisis (abdominal wall defect), congenital heart defects, craniosynostosis (premature closure of cranial sutures), and anorectal atresia. This section also summarizes the 2010 Surgeon General's report review of specific genetic risk factors for congenital malformations, and their potential interactions with tobacco exposure in the etiology of birth defects.

Biologic Basis

The embryonic period is a time of rapid differentiation, and the developing organs are particularly susceptible to the effects of exogenous agents. The stage of embryonic development determines the embryo's susceptibility to environmental factors, and the embryo is most easily disturbed during the organogenesis period, from day 15 to day 60 after conception. In addition, each system or organ of an embryo has a critical period when its development may be altered. Tobacco smoke includes about 7,000 different compounds, many of which could have deleterious effects on a fetus during development and potentially cause major birth defects (Talbot 2008; Rogers 2009; USDHHS 2010). Specific constituents of concern include nicotine, CO, aromatic amines, and cadmium (Nelson 2001; Rogers 2009). The 2010 Surgeon General's report covered the biologic basis for injury to the fetus by maternal smoking at length.

Maternal smoking could interfere with normal organ development in offspring in several ways, including through fetal hypoxia, alterations in essential nutrients, teratogenic effects, and DNA damage. These effects could be related to exposure to tobacco smoke components such as CO, nicotine, cadmium, and PAHs (Chernoff 1973; Mochizuki et al. 1984; Lammer et al. 2004; Munger et al. 2004; Ziaei et al. 2005). In addition, certain populations with genetic polymorphisms may be more susceptible to damage attributable to exposure to tobacco smoke because of alterations in metabolic pathways (see the section "Smoking and Maternal and Fetal Genetic Polymorphisms" later in this chapter).

Nicotine has diverse pharmacologic and toxicologic properties, which are discussed in Chapter 5. The Office of Environmental Health Hazard Assessment of the California Environmental Protection Agency lists nicotine as a developmental toxicant. In addition, nicotine is a vasoconstrictor and is known to cross the placenta and concentrate in the fetus at levels slightly higher than those in the mother.

CO is a by-product of combustion and thus is present in tobacco smoke and is found in higher levels in smokers than nonsmokers (USDHHS 2010). CO is a potent toxin whose primary target organ is the brain, and the fetus is more susceptible to the toxic effects of CO than is the mother. Exposure to CO from which the mother will fully recover could end in permanent neurologic damage to the fetus or even death (e.g., stillbirth) (Norman and Halton 1990; Koren et al. 1991; Rogers 2009). The fetal effects of CO are well studied in animals (Koren et al. 1991; Penney 1996) and include central nervous system abnormalities in fetuses and pups of pregnant rats with long-term exposure to CO (Storm and Fechter 1985a,b; Storm et al. 1986; Fechter 1987; Carratù et al. 1993a,b; Packianathan et al. 1993). CO-induced hypoxia appears to be related to congenital anomalies including cleft lip and CP in susceptible strains of mice (Millicovsky and Johnston 1981a,b; Bronsky et al. 1986; Bailey et al. 1995). An association with cleft lip was demonstrated in a rat model in which the medication phenytoin was administered to pregnant rats to induce embryonic hypoxia (Webster et al. 2006). Subsequent human epidemiologic studies of birth defects in relation to CO levels from air pollution early in pregnancy found associations between higher CO levels and various cardiac defects, but the findings were not consistent (Ritz et al. 2002; Gilboa et al. 2005).

Thus, the evidence suggests likely impacts of nicotine and CO on fetal development. The combination of exposure to nicotine and hypoxia could decrease the supply of nutrients and oxygen to the embryonic tissues through a vasoconstrictive impact, resulting in congenital defects (Lambers and Clark 1996).

Tobacco smoke contains heavy metals, including cadmium, which is of particular concern because of its potential teratogenic effects (Chang et al. 1980; Carmichael et al. 1982). Cadmium crosses the placenta, and in animal studies has been associated with adverse effects on fetal growth (Carmichael et al. 1982; Goyer 1991) and orofacial clefts (Mulvihill et al. 1970; Ferm 1971; Chernoff 1973), limb reduction anomalies, central nervous system defects, and some other birth defects (Ferm 1971; Barr 1973; Carmichael et al. 1982; Goyer 1991).

Reductions in serum folate levels mediated by maternal smoking have also been associated with orofacial clefts (McDonald et al. 2002; Mannino et al. 2003; Ortega et al. 2004). This is further supported by two studies that found that intake of vitamins containing folic acid was associated with a decreased risk of orofacial clefts (Itikala et al. 2001; Bailey and Berry 2005). However, one large study—the National Birth Defects Prevention Study (NBDPS), a multisite population-based case-control study in 10 sites that began in 1997, did not observe an interaction between intake of folic acid and maternal smoking in

the etiology of orofacial clefts (Honein et al. 2007). This is perhaps due in part because NBDPS largely enrolled cases conceived after folic acid fortification of enriched cereal grains in the United States when folic acid intake among all women was considerably higher than before fortification. However, the lack of interaction might also be due to the lack of an association between tobacco and folic acid preventable birth defects. Smoking has not been associated consistently with neural tube defects, an outcome causally associated with decreased folate and one that has been significantly reduced by folic acid fortification (Hackshaw et al. 2011).

PAHs are products of the partial combustion of carbon-containing materials and are found in tobacco smoke (International Agency for Research on Cancer 1986, 2004; U.S. Environmental Protection Agency 1992). Studies have reported direct fetotoxic and teratogenic effects associated with PAHs, as well as adverse effects on reproduction. Other effects include immunotoxicity, endocrine effects, and toxic effects on the lungs. The toxic effects and dose-response relationships described for PAHs are primarily based on experiments in animals. Lupo and colleagues (2012) reported an association between occupational PAH exposure and gastroschisis among mothers 20 years of age or older (OR = 2.53; 95% CI, 1.27–5.04), but no association among mothers younger than 20 years of age. The most commonly observed effects of PAHs in animal studies are growth retardation and fetal mortality, but a few experiments have demonstrated anatomic teratogenic effects. The number of surviving offspring is reduced in these experiments, so it appears that the dose-range over which surviving, but malformed, offspring are produced is narrow (USDHHS 2010).

Description of the Literature Review

To update the epidemiologic literature on smoking and birth defects, a comprehensive literature search was undertaken using PubMed to capture English-language publications from 1999 through July 2012. The studies included in the review presented the outcome of either all birth defects or specific types of birth defects, and their potential association with maternal smoking, paternal smoking, or maternal exposure to secondhand smoke. Search terms included the following: (1) smoking and defect, (2) smoking and cleft, (3) smoking and heart defect, (4) smoking and gastroschisis, (5) smoking and cryptorchidism, (6) smoking and atresia, (7) smoking and congenital, (8) smoking and clubfoot, (9) smoking and renal, (10) smoking and craniosynostosis, (11) smoking and hypospadias, (12) tobacco and defect, (13) tobacco and cleft, (14) tobacco and heart defect, (15) tobacco and gastroschisis, (16) tobacco and cryptorchidism, (17)

tobacco and atresia, (18) tobacco and congenital, (19) tobacco and clubfoot, (20) tobacco and renal, (21) tobacco and craniosynostosis, (22) tobacco and hypospadias, (23) smoking and malformation, and (24) tobacco and malformation. Additional articles were identified by examining the reference lists of articles identified by these searches, by searching PubMed for specific investigators, and by reviewing previous Surgeon General's reports.

Methodologic Considerations

Several methodologic challenges need to be addressed in studies of maternal smoking and congenital malformations. Case definitions can be heterogeneous across studies, but most authors attempt to remove cases associated with syndromes from the analysis. Isolated defects are sometimes studied alone, and other times they are combined with multiple defects: defined as those affected by two or more major defects in different organ systems (Rasmussen and Moore 2001). In case-control studies, periconceptional smoking status is generally obtained following delivery and after women have knowledge of their child's congenital malformation, introducing possible bias due to differential disclosure of smoking status among mothers with affected versus unaffected children. When suspected, confounding needs to be addressed through adjusted, matched, or stratified analysis. In meta-analyses, it is often difficult to fully account for confounding with the variation in treatment of confounders across studies. Finally, the selection of control groups could affect the results of case-control studies. For example, the selection of control groups with conditions also potentially associated with maternal tobacco use, such as other types of malformations, could result in bias.

Epidemiologic Evidence

Tables 9.2 and 9.3*S*–9.8*S* summarize studies that examined prenatal maternal smoking as a risk factor for specific defects. Defects include orofacial clefts, clubfoot, gastroschisis, congenital heart defects, craniosynostosis, and anorectal atresia. The following sections summarize the key findings from those studies. Because Little and colleagues (2004b) completed a meta-analysis of publications through 2001, specific studies are reviewed for orofacial clefts for 2002 through July 2012 (Table 9.3*S*). For all other defects, the literature is reviewed from 1999 through July 2012 (Tables 9.4*S*–9.8*S*).

Orofacial Clefts

CL/P and CP are birth defects that occur when the upper lip or the palate do not close correctly during fetal development. With a cleft lip, the tissue that makes up

the lip does not join completely between the fourth and seventh week of pregnancy. With CP, the tissue that makes up the palate (roof of the mouth) does not join correctly between the sixth and ninth week of pregnancy. CL/P and CP are embryologically distinct entities, and these phenotypes have somewhat different epidemiologic characteristics. For example, CL/P is more frequent among males and CP more frequent among females; CP is less common among Hispanics than other racial/ethnic groups, but this difference is not present for CL/P (Genisca et al. 2009). Studies that assessed CL/P and CP separately for their potential association with maternal smoking found that the risk estimates for the two defect types were generally similar (Little et al. 2004a; Krapels et al. 2006; Bille et al. 2007; Honein et al. 2007).

A 2011 systematic review and meta-analysis by Hackshaw and colleagues included publications from 1959–2010. Of the 38 case-control and cohort studies, 13 showed a significant association between maternal smoking and an increased risk for CL/P, and the pooled OR was 1.28 (95% CI, 1.20–1.36). Restriction of the analysis to prospective studies did not change the findings (OR = 1.24; 95% CI not included), nor did restricting to studies with AORs (1.26; 95% CI, 1.18–1.34). The earlier meta-analysis of orofacial clefts by Little and colleagues (2004b) still contributes to this knowledge base since it included several studies that were excluded from the Hackshaw meta-analysis (Kelsey 1978; Hwang et al. 1995; Lieff 1999).

Table 9.2 **Summary of a systematic review of maternal smoking during pregnancy and its relationship with specific congenital malformations**

Outcome	Number of studies published, 1959–2010	Findings (95% CI)
Orofacial clefts	38	OR = 1.28 (1.20–1.36)
Clubfoot	12	OR = 1.28 (1.10–1.47)
Gastroschisis	12	OR = 1.50 (1.28–1.76)
Congenital heart defects	25	OR = 1.09 (1.02–1.17)
Craniosynostosis	5	OR = 1.33 (1.03–1.73)
Anorectal atresia	7	OR = 1.20 (1.06—1.36)

Source: Hackshaw et al. 2011.
Notes: **CI** = confidence interval; **OR** = odds ratio.

In their meta-analysis, Little and colleagues (2004b) included 24 case-control and cohort studies published between 1974–2001. The authors found a consistent association between maternal smoking and CL/P (RR = 1.34; 95% CI, 1.25–1.44) and between smoking and CP (RR = 1.22; 95% CI, 1.10–1.35). Most of the studies in this meta-analysis included consideration of confounders, such as maternal age and education; and some adjusted for parity, marital status, and race/ethnicity; and 5 addressed maternal alcohol use. Adjusted relative risks in individual studies were generally similar to crude RRs, but crude RRs were included in the meta-analysis unless only adjusted RRs were available. When the analysis was restricted to studies with isolated CL/P, or to studies that did not use controls with malformations, the findings did not change. Five of 9 studies with information about the number of cigarettes smoked per day showed evidence of a weak dose-response relationship for CL/P. Eight studies were examined for a dose-response relationship with CP; no clear evidence was observed.

Two recent studies of orofacial clefts and smoking that showed significant positive associations, and were not included in the Hackshaw meta-analysis, further strengthen the evidence for this relationship (Shaw et al. 2009; Lebby et al. 2010). One of the largest studies (Romitti et al. 2007) used NBDPS, which included data from interviews with 1,128 cases of persons with orofacial clefts. For all orofacial clefts combined, the crude OR (1.37; 95% CI, 1.20–1.57) was very similar to the ORs in both the 2004 and 2011 meta-analyses (Little et al. 2004b; Hackshaw et al. 2011), and included adjustment for folic acid, study site, prepregnancy obesity, alcohol use, gravidity, maternal age, maternal education, and maternal race/ethnicity.

As previously discussed, most studies of maternal smoking and CL/P are case-control studies, and necessarily rely on maternal self-reported smoking history obtained after delivery. This method for obtaining exposure data can result in bias if women who smoked and had adverse pregnancy outcomes are more or less likely to deny smoking than women who smoked and did not have adverse outcomes. However, in a study of the potential contributions of misclassification of maternal smoking status on studies of CL/P using Bayesian models with and without correction for reporting bias, the authors found that associations between maternal smoking and CL/P was strengthened slightly and remained significant after correction for expected levels of bias (MacLehose et al. 2009). In addition, despite other potential threats to validity, the findings on orofacial clefts and smoking have been quite consistent across study design and location.

A study in California used midpregnancy serum cotinine concentration (a metabolite of nicotine) to classify maternal smoking status (Shaw et al. 2009). Active smoking was defined as serum cotinine concentration of at least 2 ng/mL, and 11 exposed cases were identified. Maternal smoking was found to be associated with CL/P before (OR = 2.1; 95% CI, 1.0–4.4) and after adjusting for maternal age, race, and serum folate level (AOR = 2.4; 95% CI, 1.1–5.3). It is unknown to what extent the use of midpregnancy cotinine levels results in the misclassification of early pregnancy smoking; women still smoking in the middle of pregnancy were presumably also smoking in early pregnancy, but some of those smoking in early pregnancy might have stopped by the middle of pregnancy and therefore would be inappropriately included in the unexposed group, potentially attenuating the effect estimate. Although the sample size was relatively small, this key study with a biomarker for smoking exposure helps support the many consistent reports of weak associations between smoking and orofacial clefts based on self-reported smoking exposure in early pregnancy. The findings regarding a possible dose-response relationship between smoking and the risk for orofacial clefts have been mixed, with some studies finding evidence of a positive relationship (Little et al. 2004a,b; Bille et al. 2007; Honein et al. 2007) but not all (Krapels et al. 2006; Grewal et al. 2008).

The findings on exposure to secondhand smoke and orofacial clefts have been inconsistent, but there is some evidence of risk in settings where maternal smoking is relatively uncommon but exposure to secondhand smoke is high. For example, in China, the prevalence of smoking among reproductive age women is low (1.5%), while exposure to secondhand smoke is high (over 50%) (CDC 2012). Three studies conducted in China reported positive associations between maternal exposure to secondhand tobacco smoke and orofacial clefts; one included adjustment for potential confounders (occupation, flu or fever, and infant gender) (Table 9.3*S*) (Li et al. 2010; Jia et al. 2011; Zhang et al. 2011).

Idiopathic Talipes Equinovarus (Clubfoot)

Idiopathic talipes equinovarus or clubfoot is a serious birth defect that requires medical treatment and often surgery (Table 9.4*S*). There are some complexities in accurately capturing clubfoot with surveillance or research studies, and appropriately excluding those with positional foot deformities. However, despite these challenges, the findings for maternal smoking and clubfoot have been quite consistent. Six of eight studies published in 2000

or later found significant, positive associations between maternal smoking and the occurrence of congenital clubfoot (Honein et al. 2000, 2001; Skelly et al. 2002; Dickinson et al. 2008; Parker et al. 2009; Kancherla et al. 2010); three of these six studies also reported evidence of a dose-response relationship with smoking level, one did not find a dose-response relationship, and two did not assess dose.

In the study by Honein and colleagues (2000), the effect of smoking varied by self-reported family history. The OR of clubfoot associated with maternal smoking among those without a family history was 1.34 (95% CI, 1.04–1.72), but the effect estimate was much stronger, albeit imprecise (OR = 20.3; 95% CI, 7.9–52.2), for those with a positive first-degree family history. Skelly and colleagues (2002) also used self-reported smoking and found a dose-response relationship: among women who smoked 20 or more cigarettes daily, the OR for clubfoot was 3.9 (95% CI, 1.6–9.2), but among those who smoked fewer than 10 cigarettes daily it was 1.5 (95% CI, 0.9–2.5).

Dickinson and colleagues (2008) analyzed linked data from the North Carolina Birth Defects Monitoring Program and North Carolina birth certificates and health services and found a significant association between maternal smoking and clubfoot (OR = 1.40; 95% CI, 1.07–1.83), when controlling for maternal age, race/ethnicity, infant's gender, and timing of prenatal care initiation; the authors did not find a dose-response relationship. Parker and colleagues (2009) used 2001–2005 data from 10 population-based surveillance systems in the United States. Information on smoking was obtained from birth certificates and was linked to data on birth defects from surveillance systems. The ORs for clubfoot were 1.45 (95% CI, 1.32–1.60) for women who smoked 1–10 cigarettes per day and 1.88 (95% CI, 1.64–2.14) for women who smoked more than 10 cigarettes per day (Parker et al. 2009). Kancherla and colleagues (2010) analyzed population-based surveillance data from the Iowa Registry for Congenital and Inherited Disorders. The study found that maternal smoking was associated with clubfoot with an OR of 1.5 (95% CI, 1.2–1.9). It is important to note that there is a small overlap between the Parker and colleagues 2009 study (10-state analysis) and the Kancherla and colleagues 2010 study (Iowa analysis) since Iowa is 1 of 10 states included in the paper by Parker and colleagues and some of the years overlap.

Hackshaw and colleagues (2011) pooled data from 12 studies on clubfoot and smoking and found an OR of 1.28 (95% CI, 1.10–1.47) (Table 9.2). When restricted to studies that addressed potential confounders, the results were not substantially different from the pooled analysis of all studies (OR = 1.44; 95% CI, 1.20–1.71).

Gastroschisis

Gastroschisis is a congenital defect in which the abdominal contents protrude through an opening in the anterior abdominal wall. It is strongly associated with young maternal age (Rasmussen and Frias 2008). From 2000–2011, 12 studies have investigated the potential association between maternal smoking and gastroschisis and 8 reported a significant association (Table 9.5S).

A retrospective case-control study conducted from 1995–1999 in the United States and Canada examined the association of gastrochisis with maternal smoking using control infants with malformations or who were hospitalized for other reasons. The study found maternal smoking during the first 2½ months of pregnancy to be associated with gastroschisis (Werler et al. 2003), and the authors also observed evidence of a dose-response relationship. Feldkamp and colleagues (2008) used birth certificates data to assess smoking and they used birth defects surveillance data to identify cases of gastroschisis. When adjusted for maternal age and prepregnancy body mass index (BMI), the authors found a significant association between smoking during the first trimester and gastroschisis (Feldkamp et al. 2008).

Werler and colleagues (2009) compared cases and age-matched controls from NBDPS to study maternal smoking and gastroschisis. The overall AOR was 1.5 (95% CI, 1.2–1.9), and a dose-response relationship was observed. After stratification by maternal age, however, the association was present only in women who were 25 years of age or older (Werler et al. 2009). This interaction between smoking and maternal age was similar to the one described by Feldkamp and colleagues (2008). More recently, an analysis based on birth certificate data from Washington state found an association between smoking during pregnancy and gastroschisis after adjusting for birth year, maternal age, race, urban-rural residence, county of residence, paternal age, and baby's gender (Chabra et al. 2011).

Finally, Hackshaw and colleagues (2011) included 12 published studies on gastroschisis in their meta-analysis and found a significant association with maternal smoking (OR = 1.50; 95% CI, 1.28–1.76) (Table 9.2). When restricted to studies that addressed confounding, the authors found similar results (OR = 1.44; 95% CI, 1.20–1.71).

Congenital Heart Defects

Congenital heart defects are the most common type of birth defect, affecting nearly 1% of births in the United States, and including many specific types of congenital

heart defects with relatively high morbidity and mortality (Reller et al. 2008). From 1999–2012, 15 published studies evaluated the association between smoking and congenital heart defects, and 9 reported significant assocations for one or more types of specific heart defects (Table 9.6*S*). The most consistent finding has been an associations between maternal smoking and atrial septal defects reported by 4 studies (Källén 1999a; Malik et al. 2008; Kučienė and Dulskienė 2010; Alverson et al. 2011).

Data from the Swedish Child Cardiology and Medical Birth Registries were used to assess the associations of maternal smoking with 30 categories of congenital heart defects (Källén 1999a). In this study, maternal smoking was ascertained during the first prenatal visit rather than after the pregnancy outcome was known, reducing the potential for recall bias. Significant associations were seen for transposition of the great arteries, atrial septal defects, and for patent ductus arteriosus in full-term infants. The author did not observe a dose-response relationship for the association with patent ductus arteriosus (Källén 1999a).

In the Baltimore-Washington Infant Study, the authors assessed risk factors for single ventricle defects and found ORs above unity for both maternal and paternal smoking. These findings were not significant, however, and they were not adjusted for potential confounders (Steinberger et al. 2002). A more recent analysis from the Baltimore-Washington Infant Study assessed all congenital heart defects without other birth defects and found associations between maternal smoking and secundum-type atrial septal defects, right outflow tract defects, l-transposition of the great arteries, and truncus arteriosus (Alverson et al. 2011).

Data from NBDPS was used by Malik and colleagues (2008) to study the relationship between smoking and various heart defects; the authors found that atrial septal defects were associated with smoking at all levels of exposure (1–14, 15–24, ≥25 cigarettes/day) but no dose-response relationship was observed. Other congenital heart defect phenotypes were also assessed, but did not show evidence of associations with maternal smoking. Baardman and colleagues (2012) found evidence of interactions between smoking and BMI ≥25 for all congenital heart defects (p = 0.027), septal defects (p = 0.036), conotruncal defects (p = 0.020), and for outflow tract anomalies (p = 0.024).

Hackshaw and colleagues (2011) combined all cardiovascular and congenital heart defects, but did not present results for specific phenotypes. Overall, the pooled OR from 25 published studies showed a small but significant elevation in risk for congenital heart defects (OR = 1.09; 95% CI, 1.02–1.17) (Table 9.2). When the analysis was restricted to studies that addressed confounding, the results were similar to the original analysis in both instances (OR = 1.10; 95% CI, 1.02–1.20).

Craniosynostosis

Premature fusion of one or more of the cranial suture of the skull results in craniosynostosis, a serious birth defect that usually requires surgical correction. Without timely treatment, craniosynostosis can result in serious consequences including restriction of brain growth. The critical timing of fetal exposure is unclear, but might extend beyond early pregnancy. Several publications have addressed the possible association between maternal smoking and craniosynostosis (Table 9.7*S*). A birth defects registry linkage study found an association between smoking and craniosynostosis among isolated cases (OR = 1.67; 95% CI, 1.27–2.19) (Källén 1999b). In addition, the author saw evidence of a dose-response relationship with smoking and differences in effects for different cranial sutures; the highest OR was observed if the sagittal suture was affected (Källén 1999b).

In the United States, maternal smoking was associated with isolated craniosynostosis in a metropolitan Atlanta, Georgia, population (OR = 1.92; 95% CI, 1.01–3.66) (Honein and Rasmussen 2000). In contrast, a case-control study using NBDPS data did not find a significant association (Carmichael et al. 2008). In the same study, for heavy smoking in the third month of pregnancy and in the second trimester, moderately increased ORs were observed (OR = 1.6; 95% CI, 0.9–2.6; and OR = 1.6; 95% CI, 0.9–2.8, respectively).

In The Netherlands, a study of infants with sagittal synostosis did not find an association with maternal smoking (Butzelaar et al. 2009). Hackshaw and colleagues (2011) analyzed five studies and found a positive association between smoking and craniosynostosis (OR = 1.33; 95% CI, 1.03–1.73) (Table 9.2). When the analysis was restricted to studies that addressed confounding, the findings did not change (OR = 1.33; 95% CI, 1.04–1.63).

Anorectal Atresia

Anorectal atresia is a defect that occurs when there is faulty separation of the rectum and urogenital system or failure of the anal membrane to rupture (Stevenson 1993). Four studies have been published since 1999 (Table 9.8*S*); one reported a significant association, two reported borderline/nonsignificant associations, and one found an association with paternal but not maternal smoking. Hackshaw and colleagues (2011) reviewed seven papers and reported a positive association (OR = 1.20; 95% CI, 1.06–1.36) (Table 9.2). In addition, a recent meta-analysis of risk factors for anorectal malformations reported pater-

nal smoking as a risk factor (pooled OR = 1.53; 95% CI, 1.04–2.26) (Zwink et al. 2011).

Other Defects

There have been some studies of central nervous system defects, including neural tube defects, but case definitions have varied and most have not shown an association with maternal smoking (To and Tang 1999; Suarez et al. 2008, 2011; Van Landingham et al. 2009; Miller et al. 2010; Yin et al. 2011). Hackshaw and colleagues (2011) analyzed 17 studies and found no association between maternal smoking and anencephaly/spina bifida, but the authors found a small association with all central nervous system defects combined (pooled OR = 1.10; 95% CI, 1.01–1.19). When the analysis was restricted to studies that addressed confounding, the association was no longer signficant (OR = 1.13; 95% CI, 0.99–1.28).

Cryptorchidism or undescended testes commonly occurs with prematurity, but is typically only monitored by birth defects surveillance systems among term infants. However, it is unclear if all studies examining the potential association between cryptorchidism and smoking limited their analyses to term infants. Although a weak association between maternal smoking and cryptorchidism has been described in some studies (Akre et al. 1999; Biggs et al. 2002), other more recent studies have not reported an association (Pierik et al. 2004; Kurahashi et al. 2005a; Damgaard et al. 2008) or noted an association only among mothers who smoked heavily (Thorup et al. 2006; Jensen et al. 2007). Hackshaw and colleagues (2011) analyzed 18 studies and found a small but significant elevation in risk of cryptorchidism from maternal smoking (OR = 1.13; 95% CI, 1.02–1.25). When the analysis was restricted to studies that addressed potential confounding, the findings did not change (OR = 1.16; 95% CI, 1.08–1.25). However, the observed effect might be due at least in part to prematurity and the association between tobacco exposure and preterm birth.

Hypospadias is a birth defect in boys in which the opening of the urethra is not located at the tip of the penis, and there are different degrees of hypospadias ranging from first degree (relatively minor) to second and third degree (more severe). Most of the studies to date have not found significant associations between maternal smoking and hypospadias, and a few studies have found an inverse association (Källén 2002; Pierik et al. 2004; Carmichael et al. 2005; Brouwers et al. 2007). Hackshaw and colleagues (2011) analyzed 15 studies and found a small negative association between smoking and hypospadias (OR = 0.90; 95% CI, 0.85–0.95). When the analysis was restricted to studies that addressed confounding, the findings did not change (OR = 0.89; 95% CI, 0.83–0.96).

Smoking and Maternal and Fetal Genetic Polymorphisms

Studies of the differences in the human metabolism of toxic constituents in tobacco smoke are summarized in the 2010 Surgeon General's report (Benowitz et al. 1999; Lee et al. 2000; Yang et al. 2001; USDHHS 2010). Initial investigations of the mechanisms of maternal or fetal metabolism of tobacco smoke toxins and adverse birth outcomes were conducted in studies of birth defects, and several studies examined the potential interaction of maternal exposure to tobacco smoke and maternal and/or neonatal genotypes in association with orofacial cleft in newborns. The genetic polymorphisms that code for the expression inflammatory response and immune mediator enzymes and that were examined included *TGF*-α and *TGF*-β*3*, *MSX1*, and *EPHX1*, as well as gene variants of both phase I activation and phase II detoxification enzymes *CYP1A1, GSTM1, GSTT1, NAT1,* and *NAT2*. Prenatal exposure to tobacco smoke was typically measured by maternal self-reports of active smoking, exposure to secondhand smoke, and of paternal active smoking. Most of these studies examined the *TGF*-α genotype in neonates. In one study, genotyping was performed in both neonates and parents.

A case-control study of infants with a *TGF*-α *TAQ1* genotype that contained a rare allele and whose mothers had smoked during pregnancy found a significantly elevated risk for CP in offspring (Hwang et al. 1995). In a large population-based case-control study conducted by the California Birth Defects Monitoring Program registry, the risks of CP and CL with or without CP were significantly elevated among White infants with *TGF*-α *rare genotypes (*A2*) whose mothers were heavy smokers (Shaw et al. 1996). However, three subsequent case-control studies (Christensen et al. 1999; Romitti et al. 1999; Beaty et al. 2001) that failed to replicate these findings had fewer cases and one study used a lower cutpoint for smoking than that used by Shaw and colleagues (1996). None of the five studies cited above presented regression models with terms for estimating maternal smoking levels and the *TGF*-α genotype interactions. Zeiger and colleagues (2005) conducted a meta-analysis of data from these 5 studies and found a marginally significant interaction between maternal smoking and infant *TGF*-α *allele genotypes (*A2*) in relation to CP (OR = 1.95; 95% CI, 1.22–3.10). A Human Genome Epidemiology review that assessed 47 published studies on the potential association between *TGF*-α and orofacial clefts produced somewhat inconsistent findings (Vieira 2006), but concluded that *TGF*-α likely had a role in modifying the risk of orofacial clefts.

Romitti and colleagues (1999) also examined the *TGF*-β*3* genotype and maternal smoking in relation to the risk of CP or CL/P. These researchers found a significantly elevated risk for the conditions among infants who were homozygous for the common *1* allele at the *X5.1* or *5´UTR.1* site and whose mothers had smoked 10 or more cigarettes per day. There was no evidence of an interaction for infant genotypes that included the rare *2* allele.

Hartsfield and colleagues (2001) did not observe any significant interaction between maternal smoking and *null GSTM1* genotypes in a case-control study of isolated cleft lip and CP. van Rooij and colleagues (2001) examined the association of maternal prenatal smoking and the maternal *GSTT1* genotype and found that mothers who smoked and carried the *GSTT1 null* genotype had a marginally higher risk for delivering an infant with oral clefting than that of nonsmokers who carried the wild-type genotype. Although the RR was not statistically significant, it was almost five times greater when both mothers and their infants carried the *GSTT1 null* genotype. There was no evidence of an interaction between maternal smoking and the *CYP1A1* genotype with a recessive allele in relation to oral clefting.

In a case-control study, the *CYP1A1*, *GSTT1*, and *GSTM1* polymorphisms were also examined as risk factors for hypospadias (Kurahashi et al. 2005b). The study did not observe any increased risk of hypospadias among children born to mothers who smoked and had various genotypes, including *CYP1A1 *MSPI* variant allele genotype or the *GSTT1 null* genotype or *GSTM1 null* genotype. In a case-only, haplotypic analysis of an intronic *CA* repeat of the *MSX1* gene in 206 infants with oral clefting, there was evidence for an interaction with maternal prenatal smoking (Fallin et al. 2003). In the Iowa study (Romitti et al. 1999), infants whose *MSX1 X1.3* or *MSX1 X2.4* genotype contained the *2* allele and whose mothers smoked 10 or more cigarettes per day also had a significantly elevated risk of CP. In a study of limb deficiency defects, Carmichael and colleagues (2004) did not observe any significantly elevated risk for infants with *MSX1* intronic *CA* repeat genotype whose mothers smoked during pregnancy. In another case-control study from the California Birth Defects Monitoring Program, the *NAT1 1088* genotype *A/*A* and the *NAT1 1095* genotype *A/*A*, but not *NAT2* polymorphisms, were strongly associated with isolated oral clefting in infants whose mothers had smoked during pregnancy (Lammer et al. 2004).

Evidence Synthesis

A modest but consistent association has been documented between maternal smoking during early pregnancy and orofacial clefts, and the evidence has continued to accumulate and strengthen since the 2004 Surgeon General's report. The literature is diverse and includes observations from cohort and case-control studies, and meta-analyses have produced significant pooled risk estimates even after restricting to cohort studies or studies which addressed confounding. One study with the advantage of incorporating biomarkers to objectively assess maternal smoking exposure showed a more than twofold increased risk of orofacial clefts with maternal smoking exposure. However, the results of studies examining a dose-response relationship between smoking and orofacial clefts have been mixed. Two cohort studies that both collected tobacco exposure data before delivery support the notion that a temporal relationship exists, showing an effect of maternal smoking during the time period critical for closure of the palate. Case-control studies often have significantly more power to detect risk factors for birth defects and have supported the association between maternal smoking and orofacial clefts. The plausibility of an association between maternal smoking and orofacial clefts is further supported by animal studies showing an association between cadmium and clefting and between hypoxia-inducing compounds and clefting.

The relatively weak associations described in observational studies and the lack of evidence for a dose-response relationship could reflect exposure misclassification in which some women who smoke do not disclose their smoking status, attenuating the magnitude of the effect estimate. Alternatively, a weak association could result if only certain subgroups of the population, such as those with specific genetic risk factors, are at increased risk of orofacial clefts from exposure to maternal smoke. Given the strong association with a positive family history of orofacial clefts, there are likely some genetic factors that have a major impact on risk of clefting and potentially on the association between smoking and orofacial clefts.

Although the evidence base regarding other major birth defects is growing, associations with maternal smoking are less clear. The evidence has been relatively consistent for clubfoot and gastroschisis (Tables 9.4*S* and 9.5*S*), and has been somewhat less consistent for congenital heart defects, craniosynostosis, and anorectal atresia (Tables 9.6*S*–9.8*S*). The studies have been most consistent for clubfoot, but the diagnosis of this defect and ascertainment for studies can be problematic as some positional foot deformities might be erroneously included as "clubfoot"; and there could be some selection bias in who is identified as having clubfoot rather than a less serious positional foot deformity, such as if those with better access to high-quality care are more likely to have an accurate diagnosis.

Many studies reported significant associations between maternal smoking and congenital heart defects, but the findings are not consistent across the specific phenotypes. The most consistent finding to date is for an association between atrial septal defects and maternal smoking. However, the relationships between maternal smoking and these adverse outcomes deserve further study to better understand which of these outcomes might potentially be prevented.

The published data on the role of specific genetic risk factors and their interactions with maternal smoking in the etiology of birth defects has expanded over the past decade, but there has been little consistency across studies. The literature is most extensive for orofacial clefts, but it remains unclear which genes might be most important in the causal pathways associated with smoking. At this point, there are no specific genes for which the evidence is strong enough to conclude that they clearly modify the relationship between smoking and orofacial clefts. The data on gene-environment interactions for other major birth defects is much more limited than that for orofacial clefts.

Conclusions

1. The evidence is sufficient to infer a causal relationship between maternal smoking in early pregnancy and orofacial clefts.

2. The evidence is suggestive but not sufficient to infer a causal relationship between maternal smoking in early pregnancy and clubfoot, gastroschisis, and atrial septal heart defects.

Implications

Mothers who smoke early in pregnancy increase their risk for having an infant with an orofacial cleft. Although the attributable fraction for this exposure might be quite low, this is a completely preventable cause of a major birth defect. This risk might be greater in women with specific genetic risk factors, but research to date has not identified consistent genetic factors modifying this relationship. Efforts to reduce smoking before conception and during early pregnancy should include the provision of information on the risk of orofacial clefts.

Neurobehavorial Disorders of Childhood

This section reviews the evidence for associations between prenatal smoking and a set of neurobehavioral disorders of childhood. Previous Surgeon General's reports have considered exposure to secondhand smoke during childhood and maternal smoking during pregnancy and their effects on neurodevelopmental outcomes of children (USDHEW 1979; USDHHS 1980, 2004, 2006, 2010). However, this review goes a step further by examining prenatal exposure to tobacco smoke and these specific disorders—attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder, anxiety disorders, depression, Tourette syndrome, schizophrenia, and intellectual disability.

Biologic Basis

There are multiple biologic mechanisms through which prenatal smoke exposure could affect risk for neurobehavorial disorders in the offspring. Most research on biologic mechanisms focuses on the impact of smoking-related compounds on placental development and on nicotine's effects on the fetal brain. The effects of prenatal smoking by the mother on the placenta are described in the 2010 Surgeon General's report and include cellular and molecular abnormalities of the villous system that could lead to impaired exchange between the mother and fetus of metabolic products, oxygen, and nutrients (USDHHS 2010). A substantial body of animal research demonstrates the effects of maternal nicotine exposure on offspring neurodevelopment, including promotion of neural cell replication, initiation of a switch from cell replication to differentiation, enhancement or retardation of axonogenesis or synaptogenesis, and disruption of regulation of apoptosis (reviewed by Pauly and Slotkin 2008) (see Chapter 5). In addition, animal studies have shown associations between prenatal nicotine exposure and behavioral abnormalities also seen in children of smokers, including hyperactivity, cognitive impairment, increased anxiety, somatosensory deficits, changes in sensitivity to nicotine and other psychostimulants, and alterations in nicotine self-administration (Herrmann et al. 2008; reviewed by Pauly and Slotkin 2008). Animal studies have generally shown positive associations between prenatal exposure to nicotine and anxiogenic behavior, as well as some evidence of neurodevelopmental changes, supporting a biologic basis for this association. A 2008 review concluded that the association between prenatal nicotine exposure and anxiogenic behavior is strong in rats, but that additional research is needed to establish a link in humans (Winzer-Serhan 2008). Causal relationships between smoking and long-term cognitive and behavioral outcomes in humans are difficult to establish due to numerous potential confounding factors (Goriounova and Mansvelder 2012).

Description of the Literature Review

A systematic literature review was conducted to identify potentially relevant published research evaluating the relationship between prenatal smoking exposure and the selected neurobehavioral disorders of interest. References and abstracts were extracted from PubMed using key words for the disorders and associated MeSH terms (Table 9.9) as well as the smoking-related key words "maternal smoking." The time period of study, 2000–2012, was chosen to cover the period following that of the previous Surgeon General's reviews on neurocognitive development, which included reference to neurobehavioral disorders (USDHHS 2004).

Epidemiologic Evidence

Disruptive Behavioral Disorders

A large number of studies have evaluated the association between prenatal tobacco smoke exposure and disruptive behavioral disorders in children, specifically ADHD, ODD, and conduct disorder (Table 9.10S). In total, 82 studies addressing the relationship between childhood disruptive behavioral disorders, or disruptive symptoms,

Table 9.9   Key words used in the systematic literature review of prenatal smoking and neurobehavioral disorders among offspring

Disorder	Key words
Attention deficit hyperactivity disorder	attention deficit disorder attention deficit hyperactivity disorder ADHD ADD
Oppositional defiant disorder	oppositional defiant disorder
Conduct disorder	conduct disorder
Depression	Depression
Anxiety	Anxiety
Tourette syndrome	Tourette
Schizophrenia	Schizophrenia
Intellectual disability	Intellectual disability mental retardation

Note: **ADD** = attention deficit disorder; **ADHD** = attention deficit hyperactivity disorder.

and prenatal tobacco smoke exposure were identified and included in the review.

In addition to the 82 studies, several systematic reviews and meta-analyses have been conducted that synthesize the large number of studies that assess the association between prenatal smoking exposure and ADHD. Langley and colleagues conducted a meta-analysis of studies published before June 2005 and ultimately included 5 case-control studies that covered a total sample of 1,265 participants; the researchers reported a pooled OR of 2.40 (95% CI, 1.61–3.52) for an ADHD diagnosis among the children of mothers who smoked during pregnancy (Langley et al. 2005). Langley and colleagues further concluded that there is a dose-response relationship between the number of cigarettes smoked and ADHD symptoms. In a later study, the authors studied offspring conceived with assisted reproductive technologies and compared those who were genetically related and unrelated to the woman who underwent the pregnancy (Thapar et al. 2009). They anticipated that the association between maternal smoking and ADHD would persist regardless of whether mother and offspring were related. They found that the magnitude of the association between prenatal smoking and parent-reported ADHD symptoms was significantly higher in the related pairs than in the unrelated pairs, suggesting that the previously observed association between maternal smoking in pregnancy and ADHD could be due to unrecognized confounding related to heritability.

Two systematic reviews concluded that there may be an association between prenatal smoking exposure and childhood ADHD (Linnet et al. 2003; Latimer et al. 2012). In 2003, Linnet and colleagues reviewed the findings of 6 case-control studies and 18 cohort studies. They concluded that there may be an association between exposure to tobacco smoke in utero and ADHD and ADHD symptoms, but that a more definite conclusion could not be made with the evidence available at the time due to methodologic issues of the reviewed studies. These issues pertained to the retrospective report of exposure information, dichotomization of exposure, selective attrition, low statistical power, poor definition of the outcome of interest (ADHD), and a failure to control for potentially relevant confounders. More recently, Latimer and colleagues (2012) reviewed literature published between 1966–2009 that evaluated the relationship between disruptive behavioral disorders and environmental risk factors, including maternal smoking. The authors noted there was a large volume of literature on ADHD, and that despite methodologic limitations (including exposure measures that are highly susceptible to recall bias and the lack of adjustment for relevant sociodemographic confounders), the literature provides some evidence of a link between prenatal smoking and the presence of disruptive

behavioral disorders in children. Hence, the authors of two systematic reviews concurred that there is some evidence for an association between prenatal smoking and disruptive behaviors in offspring, such as those associated with ADHD.

Seventy studies document an association between prenatal smoking exposure and disruptive behavioral symptoms or disorders, including hyperactivity (Table 9.10*S*). Most controlled for potential confounding variables, but many studies suffered from the methodologic limitations listed by Linnet and colleagues (2003) and Latimer and colleagues (2012), above. Retrospective reporting of prenatal smoking exposure and failure to rigorously assess child outcomes were among the methodologic limitations of these studies. A notable exception is a nested case-control study of 3,965 Danish children that were matched on age, gender, and date of birth, which used diagnoses from medical records and assessed prenatal smoking during pregnancy (Linnet et al. 2005). Linnet and colleagues concluded that, controlling for other risk factors, prenatal smoking increased the risk for hyperkinetic disorder (the ICD equivalent of ADHD: RR = 1.9; 95% CI, 1.3–2.8).

A dose-response relationship was also reported by Koshy and colleagues (2011) in a study of 1,074 school-aged children. This study found an association between parents' retrospective reports of the number of cigarettes smoked during pregnancy and current parent-reported ADHD diagnosis among their children, although the CIs were wide (smokers: OR = 3.19; 95% CI, 1.08–9.49; heavy smoker: OR = 10.03; 95% CI, 1.62–61.99).

A number of studies have directly considered genetic factors and suggest an independent contribution of genetic factors to the association between maternal smoking and ADHD (Maugham et al. 2004; Knopik et al. 2006; D'Onofrio et al. 2008; Thapar et al. 2009; Lindblad and Hjern 2010; Obel et al. 2011; Langley et al. 2012). As reviewed earlier, Thapar and colleagues (2009) used a sample of children conceived through assisted reproductive technologies and demonstrated that the association between smoking during pregnancy and ADHD symptoms was stronger and statistically significant only among biologically related mother-child dyads. Langley and colleagues (2012) documented independent associations between ADHD in offspring and both maternal and paternal smoking, suggesting that ADHD was due to genetic or household-level confounding and not only intrauterine effects. However, researchers suggest that there is a strong likelihood of genetic and socioeconomic confounding, because parents with ADHD are more likely to fall in lower socioeconomic strata with this association strongly confounded by socioeconomic factors (Lindblad and Hjern 2010).

The evidence for maternal smoking exposure and ADHD overlaps substantially with that of the other disruptive behavioral disorders (ODD and conduct disorder) and much of the research is relevant for all three behavioral disorders, due in part to phenotypic overlap. Because the majority of studies assess the association between prenatal smoking exposure and disruptive behavioral disorders or symptoms collectively, the current epidemiologic evidence may not fully characterize the independent risks for ADHD, ODD, conduct disorder, and associated symptoms. There are several notable additions to the ADHD literature that focus on ODD and conduct disorder independent of ADHD (Wakschlag et al. 2002, 2006a,b, 2010; Nigg and Breslau 2007; Becker et al. 2008; Boden et al. 2010). For example, Boden and colleagues (2010) documented a strong association between prenatal smoking exposure and ODD and conduct disorder in a birth cohort of 926 children, evaluated for ODD and conduct disorder at 14–16 years of age and smoking exposure assessed at birth (*p* <0.01 for both outcomes). In a longitudinal study of 823 school-aged children, Nigg and Breslau (2007) noted that after controlling for other risks, retrospective report of prenatal smoking doubled the risk of ODD and conduct disorder; the adjusted association with ADHD was not statistically significant. In summary, the evidence shows associations with increased rates of behavior problems, including ADHD, ODD, and conduct disorders. However, concerns about unresolved confounding persist, limiting the ability to draw firm conclusions.

Anxiety and Depression

Internalizing disorders are characterized by depressed mood, anxiety, somatic, and cognitive symptoms (as opposed to externalizing disorders which are characterized by antisocial behaviors, conduct problems, and impulse-control disorders). Anxiety and depression are both considered to be internalizing conditions (American Psychiatric Association 2013). Thirteen articles were included in the review of epidemiologic evidence for an association between prenatal smoking and anxiety, depression, or internalizing symptoms in general (Table 9.11*S*). Of the 12 articles, 10 focused on depression or anxiety, alone or in combination with each other, or internalizing behaviors in general. One reported on anxiety and ADHD but not depression, and 1 reported on depression without anxiety. The study on anxiety and ADHD found no association between maternal smoking and anxiety among a clinic-recruited group of 275 children 5–17 years of age with ADHD (Freitag et al. 2012). The study that assessed depression without anxiety was a prospective birth cohort study and no association between prenatal smoking and depressive symptoms was observed after controlling for exposure to secondhand smoke (Maughan et al. 2001).

In 7 of the 10 studies examining depression and anxiety, the authors did not find an association between prenatal smoking and depression and/or anxiety (disorders or symptoms) among the offspring at various ages (Hill et al. 2000; Kardia et al. 2003; Whitaker et al. 2006; Gatzke-Kopp and Beauchaine 2007; Biederman et al. 2009; Lavigne et al. 2011; Liu et al. 2011). In a study of 678 preschool children (4-year-olds), a retrospective report of smoking during pregnancy was not associated with meeting diagnostic criteria for depression or anxiety on the Diagnostic Interview Schedule for Children (Lavigne et al. 2011). No association was found between prenatal exposure and symptoms of anxiety or depression in 611 offspring when they were adults in a cohort study with prospective reporting of maternal smoking; however, this study did find an association of prenatal exposure and anger temperament (Liu et al. 2011).

Finally, two studies (Whitaker et al. 2006; Gatzke-Kopp and Beauchaine 2007) that used the child behavior checklist (CBCL) to measure internalizing symptoms, including depression and anxiety, found no associations between maternal smoking and offspring outcomes. In a study of 171 children 7–15 years of age with clinical levels of psychopathology, the types of symptoms were contrasted across three levels of smoking exposure: exposure to prenatal smoking, secondhand exposure to smoking among mothers during pregnancy, and no exposure (Gatzke-Kopp and Beauchaine 2007). The researchers found no association between prenatal smoking exposure (vs. no exposure or secondhand exposure of mother during pregnancy) and symptoms of depression, dysthymia, or anxiety on the CBCL; however, there was an association with externalizing symptoms. There was also no association observed in a cohort study between maternal report of smoking at birth and internalizing symptoms at 3 years of age (Whitaker et al. 2006).

In three studies the authors did report positive associations between prenatal smoking and internalizing symptoms in children as measured by the CBCL. Two of these studies were prospective (Indredavik et al. 2007; Robinson et al. 2008). Indredavik and colleagues (2007) enrolled women by 20 weeks gestation, collected information on smoking during pregnancy at enrollment, and completed a CBCL on 84 children when they were 14 years of age. Several potential confounders were examined in the adjusted analysis, including income, parental antisocial tendencies, and birth weight. The authors estimated that 19% of the variance in externalizing behaviors was accounted for by maternal prenatal smoking, and 8.9% of internalizing behaviors. Robinson and colleagues (2008) enrolled women during pregnancy (18 weeks gestation), and assessed 1,707 offspring using the CBCL at 2 and at 5 years of age. This study reported a significant association

between internalizing behaviors and maternal smoking at 2 years of age (OR = 1.26; 95% CI, 1.02–1.55); but no difference was observed at 5 years of age (Robinson et al. 2008). In a retrospective study of maternal smoking and behavior disorders in children, the authors found a significant association with internalizing behaviors (OR = 1.28; 95% CI, 1.1–1.6), but not externalizing behaviors (Teramoto et al. 2005).

In summary, three studies reported associations between exposure to prenatal smoking and internalizing symptoms, both in preschool-age children and adolescents; however, four studies examining symptoms did not find an association. Of the three studies that measured smoking prospectively, two found a positive association with internalizing symptoms (Indredavik et al. 2007; Robinson et al. 2008), and one found an association with anger temperament in adulthood, but not with symptoms of depression or anxiety (Liu et al. 2011). These findings may point to a possible nonspecific association between exposure to prenatal smoking and neurobehavioral disorders or symptoms of these disorders.

Tourette Syndrome

Two articles were identified that address maternal prenatal smoking and Tourette syndrome in offspring; neither study found a significant association (Table 9.12*S*). The limited evidence available for review was insufficient to permit meaningful synthesis.

Schizophrenia

There have been very few articles published after 1999 that address maternal smoking and schizophrenia in offspring. These studies are limited by small sample size, the use of surrogate markers for schizophrenia rather than the disease itself, the use of inappropriate control groups, and reliance on recall of maternal smoking status obtained many years after the pregnancy (Zammit et al. 2009; Baguelin-Pinaud et al. 2010; Hunter et al. 2011). In a meta-analysis of obstetric complications and schizophrenia published in 2002, there was no significant association observed between maternal smoking and offspring schizophrenia; however, even when the samples from only two studies were included in the analysis, the pooled sample size of cases was small (Cannon et al. 2002). Therefore, the limited evidence available for review was insufficient to permit meaningful synthesis.

Intellectual Disability

For the purposes of this review, intellectual disability was defined as having intelligence quotient (IQ) scores in health or educational records that fell at or below 70 or

test scores within the intellectual disability range, as indicated on psychometric tests, such as the Wechsler Intelligence Scale for Children-Revised.

Twelve articles were identified that assessed the relationship between prenatal exposure to maternal tobacco smoke and the risk of intellectual disability in their children (Table 9.13*S*). Of the 12 articles, 10 demonstrated a significant association between prenatal exposure to maternal tobacco smoke and intellectual disability and/or low intellectual performance in unadjusted analyses. However, the observed associations in all 10 studies were attenuated or disappeared after adjusting for maternal education and/or maternal IQ (Fried and Watkinson 2000; Cornelius et al. 2001; Fried et al. 2003; Breslau et al. 2005; Mortensen et al. 2005; Batty et al. 2006; Huijbregts et al. 2006; Alati et al. 2008; Braun et al. 2009; Lundberg et al. 2010).

Braun and colleagues (2009) examined the association between prenatal exposure to tobacco smoke and intellectual disability in early childhood using data from a cohort of children born during 1994–1996. This study defined intellectual disability as having an IQ score below 70 points and found the risk of intellectual disability was mildly elevated among 8-year-old children whose mothers smoked during pregnancy (RR = 1.52; 95% CI, 1.27–1.83), but was no longer significant (RR = 1.12; 95% CI, 0.92–1.36) after adjustment for maternal education, maternal race, maternal age, marital status, and gender of child (Braun et al. 2009).

The association between maternal smoking during pregnancy and intellectual disability was also examined in adolescents and young adults. Kafouri and colleagues (2009) assessed the relationship between cognitive functioning in adolescent offspring 12–18 years of age and maternal cigarette smoking during pregnancy. This study used an extensive 6-hour battery of tests in which cognitive abilities were evaluated based on 33 tasks measuring verbal and visual memory, visuospatial skills, verbal abilities, processing speed, motor dexterity, and resistance to interference and found no difference between the cognitive abilities in adolescent offspring that were exposed to maternal cigarette smoking during pregnancy compared to those unexposed after adjustment for maternal education.

Lundberg and colleagues (2010) examined the association between maternal smoking during pregnancy and the risk of intellectual impairment among young adult male offspring at 18 years of age. This study found an increased risk of intellectual impairment (OR = 1.91; 95% CI, 1.81–2.00), but the effect was attenuated (OR = 1.22; 95% CI, 1.14–1.31) after adjustment for other parental factors.

In a cohort study by MacArthur and colleagues (2001), there were differences in IQ as a function of the mother's pregnancy smoking behavior, but smoking did not remain an independent predictor after accounting for confounding factors. Further, the early hazards of smoking during pregnancy seemed to resolve by later childhood, with no evidence of direct long-term effects on cognitive functioning. The authors concluded that effects observed in early childhood, which arise from smoking during pregnancy, are significantly attenuated or disappear by later childhood, with no evidence of long-term effects on cognitive functioning.

Evidence Synthesis

Although specific mechanisms linking prenatal exposure to smoking with specific behavioral conditions have not been determined, there is some evidence from human and animal studies that supports a biological basis for the association between exposure to prenatal smoking and some neurobehavioral conditions. The 2004 Surgeon General's report concluded that the evidence was inadequate to infer the presence or absence of a causal relationship between maternal smoking and either physical growth or the collective neurocognitive development of children.

Although there is consistent evidence supporting an association between prenatal smoking exposure and disruptive behavioral symptoms among children, and ADHD in particular, the magnitude of the estimated associations diminishes when family, social, and psychosocial factors are included in multivariate models. Reliance on retrospective reporting of smoking history, which is subject to recall bias, limits the ability to draw conclusions about the temporal nature of the relationship; however, select studies that did collect exposure during pregnancy corroborate the direction of findings from the retrospective studies. Much of the published literature failed to control for many potential confounders and failed to use standard criteria for the assessment of outcomes.

The literature is limited and conflicting on the relationship between prenatal smoking exposure and anxiety and depression symptoms and disorders in children. The studies reviewed here showed no consistent association between exposure to prenatal smoking and a later diagnosis of depression or anxiety.

The available evidence is quite limited and mixed on the association between prenatal smoking and both Tourette syndrome and schizophrenia among exposed children. The research on these conditions is subject to significant methodologic limitations, including small sample size, lack of an appropriate control group, low response rate, and retrospective report of smoking by

mothers. Given the limited information available for these conditions, conclusions cannot be made regarding the consistency, strength, specificity, or temporal nature of the potential relationship.

Although there is evidence of an association between prenatal exposure to maternal smoke and intellectual disability, several studies suggest that this finding is substantially attenuated or eliminated when controlling for maternal education, IQ, and other sociodemographic covariates. This is similar to the pattern documented among studies of maternal smoking and disruptive behavioral disorders.

Conclusions

1. The evidence is suggestive, but not sufficient, to infer a causal relationship between maternal prenatal smoking and disruptive behavioral disorders, and attention deficit hyperactivity disorder in particular, among children.

2. The evidence is insufficient to infer the presence or absence of a causal relationship between maternal prenatal smoking and anxiety and depression in children.

3. The evidence is insufficient to infer the presence or absence of a causal relationship between maternal prenatal smoking and Tourette syndrome.

4. The evidence is insufficient to infer the presence or absence of a causal relationship between maternal prenatal smoking and schizophrenia in her offspring.

5. The evidence is insufficient to infer the presence or absence of a causal relationship between maternal prenatal smoking and intellectual disability.

Implications

There are high rates of neurobehavioral disorders among children, particularly disruptive behavioral disorders, depression, and anxiety (CDC 2010; Merikangas et al. 2010; Ghandour et al. 2012; Substance Abuse and Mental Health Services Administration 2012); these disorders have an impact on social and academic functioning, employment, and health throughout the lifespan. Additional research is needed to better understand the potential impact of exposure to prenatal smoking on neurodevelopment in general as well as on specific neurobehavioral conditions.

Ectopic Pregnancy and Spontaneous Abortion

The 2010 Surgeon General's report included a chapter that comprehensively covered the topic of the adverse reproductive effects of active smoking and exposure to secondhand smoke. Since the reviews carried out for the 2010 report, which included papers published up to 2009, additional significant findings have been reported for several outcomes, including spontaneous abortion and ectopic pregnancy. Building upon the reviews in the 2004 and 2010 reports, this section reassesses the state-of-the-evidence for these two outcomes, giving consideration to the more recent publications.

Ectopic Pregnancy

Ectopic pregnancy (EP) is a condition affecting 1–2% of pregnancies (CDC 1995; Van Den Eeden et al. 2005) in which implantation of a fertilized ovum takes place outside of the uterus, most often in the fallopian tubes. The etiology of EP is not fully understood, but appears to involve the motility and patency of the fallopian tubes. Risk factors associated with EP include advanced maternal age, history of prior spontaneous abortion, number of sexual partners, history of surgical procedures affecting the fallopian tubes, use of an intrauterine device (IUD) for birth control, history of sexually transmitted infections (STIs), and vaginal douching (Kendrick et al. 1997, Pisarska et al. 1998; Bouyer et al. 2003). Affected women are at increased risk of infertility and recurrent ectopic pregnancy in subsequent pregnancies, as would be expected in women with tubal damage.

The 2004 Surgeon General's report found the evidence suggestive, but not sufficient, to infer a causal relationship between smoking and ectopic pregnancy. The 2010 Surgeon General's report provided an update on studies published after the 2004 report, but did not formally evaluate the evidence for causality. This section reviews the epidemiologic and biological evidence for an association between prenatal smoking and increased risk of EP.

Biologic Basis

The human fallopian tube promotes embryonic development and transports the embryo to the uterus for implantation and has three anatomical regions: (1) the infundibulum, which picks up the oocyte cumulus complex after it is ovulated from the ovary; (2) the ampulla, where fertilization occurs; and (3) the isthmus, which conducts

sperm to the ampulla and provides a site for preimplantation development (Shaw et al. 2010a). All regions have ciliated and secretory epithelial cells and smooth muscle cells, and proper functioning of each region is necessary for normal reproduction. Ciliated cells move the gametes and embryo along the tube, and can accomplish this function with no decrease in transit time, even when smooth muscle activity is blocked by a β-adrenergic agonist (Halbert et al. 1976a,b). Secretory cells secrete substances that facilitate maturation and transport of gametes; local vasculature also contributes to the secretory process and the formation of fallopian tube fluid (Shao et al. 2012).

EP is thought to be the result of the retention of the embryo within the fallopian tube due to structural damage or functional impairment of the tube, allowing implantation to occur (Shaw et al. 2010a; Shao et al. 2012). A number of studies have examined potential mechanisms through which EP may occur. For example, a reduction in the number of ciliated cells was observed in fallopian tubes containing an EP and in the biopsies of women, who were undergoing tubal surgery and later developed a tubal pregnancy (Vasquez et al. 1983). However, in a study of human fallopian tube sections from women undergoing sterilization procedures, there were no differences between smokers and nonsmokers in the density of ciliation or in the expression of ciliogenic transcription factors (Pier and Kazanjian 2013). Ciliary beat frequency was not examined in this study.

The oviduct appears to be an in vivo target of cigarette smoke and its components; and fallopian tube damage or dysfunction is believed to be involved. Contraction of both the human oviduct (Neri and Eckerling 1969) and the rabbit oviduct (Ruckebusch 1975) is altered by exposure to tobacco smoke. Inhalation of mainstream or sidestream smoke caused blebbing of the oviductal epithelium and decreased the ratio of ciliated to secretory cells in hamsters (Magers et al. 1995). In a study of hamsters, in which the oviduct was directly observed before, during, and after inhalation of tobacco smoke at doses equivalent to those received by humans, both mainstream and sidestream smoke decreased ampullary smooth muscle contractions and slowed embryo transport through the oviduct (DiCarlantonio and Talbot 1999). Nicotine altered the motility of the oviducts of rhesus monkeys (Neri and Marcus 1972), decreased oviductal blood flow (Mitchell and Hammer 1985), decreased sodium and potassium levels in oviductal epithelial cells of mice (Jin et al. 1998), and increased lactate dehydrogenase levels in the oviduct epithelium of rats (Rice and Yoshinaga 1980). These effects could alter the oocyte transport rate in the fallopian tube (Talbot and Riveles 2005). Other individual components

found in tobacco smoke have also been examined. For example, cadmium decreases oocyte transport and delays intrauterine implantation in mice and rabbits (Saksena 1982; Shao et al. 2012).

Since the publication of the 2010 Surgeon General's report, several studies on mechanisms through which smoking increases the risk of EP have been published. As previously discussed, a reduction in the number of ciliated cells was observed in fallopian tubes containing an EP and in the biopsies of women undergoing tubal surgery who later developed a tubal pregnancy (Vasquez et al. 1983). However, in a study of human fallopian tube sections from women undergoing sterilization procedures, there were no differences between smokers and nonsmokers in the density of ciliation or in the expression of ciliogenic transcription factors (Pier et al. 2013).

PROKR1 is an angiogenic molecule that regulates smooth muscle contraction and is involved in intrauterine implantation. Investigators studied whether tubal receptor expression of *PROKR1* was altered in women who smoked by collecting sera and fallopian tube samples from women undergoing hysterectomy (Shaw et al. 2010b). *PROKR1* transcription was higher in the fallopian tubes from smokers. Cotinine treatment of fallopian tube explants and oviductal epithelial cells increased *PROKR1* expression, and this effect was negated by treatment with nicotinic acetylcholine receptor α-7- antagonist. This suggests that smoking could predispose the fallopian tube to the implantation of the embryo by increases in tubal *PROKR1*.

Description of the Literature Review

This section explores available epidemiologic studies of the association between cigarette smoking (and other forms of tobacco use) and EP. A literature search was conducted for studies published from 2000 through November 2012 to cover the period following that of the 2004 and 2010 Surgeon General's reports using the PubMed system of the National Library of Medicine. The search terms included "smok*" and "tobacco" and "ectopic" and "preg."

Epidemiologic Evidence

A large number of epidemiologic studies have addressed smoking and EP (Table 9.14*S*). Methodologic challenges to studies of EP include adequate consideration of potential confounders, such as history of previous STIs and pelvic inflammatory disease (PID) and the selection of appropriate control groups (Weiss et al. 1985).

Since the 2004 Surgeon General's report, two studies (both discussed in the 2010 Surgeon General's report)

addressing previous methodologic limitations related to the selection of control groups and adjustment for confounders have been published; both found significant associations between smoking and EP (Bouyer et al. 2003; Karaer et al. 2006). These studies also found evidence of a dose-response relationship between the number of cigarettes smoked per day and EP, as have many previous studies (Handler et al. 1989; Coste et al. 1991; Saraiya et al. 1998; Bouyer et al. 2003; Karaer et al. 2006), but not all (Chow et al. 1988; Stergachis et al. 1991). Since the 2010 Surgeon General's report, an additional study has been published in which hospital discharge records from over 4 million pregnancies were examined using the National Inpatient Sample. Roeland and colleagues (2009) found an elevated risk for EP among smokers; however, smoking status was obtained from *ICD-9* codes (a method with low sensitivity), and there was no adjustment for potentially important confounders.

An earlier meta-analysis of data from nine studies (Levin et al. 1982; World Health Organization [WHO] 1985; Chow et al. 1988; Handler et al. 1989; Coste et al. 1991; Kalandini et al. 1991; Stergachis et al. 1991; Parazzini et al. 1992; Phillips et al. 1992), all of which included adjustment for potential confounders, yielded an OR from the pooled data on EP from smoking of 1.77 (95% CI, 1.31–2.22) (Castles et al. 1999). In a subanalysis of three studies that adjusted for history of PID, IUD use, sterilization, and EP (Levin et al. 1982; Chow et al. 1988; Parazzini et al. 1992), the pooled OR was 1.91 (95% CI, 1.29–2.56). No subsequent meta-analyses have been conducted.

Studies that included examination of former smokers (either those who quit before conception compared with those who never smoked), or more detailed analysis of age at initiation, years since quitting, duration and/or intensity of smoking, have generally not found significant associations with past smoking (Kalandidi et al. 1991; Stergachis et al. 1991; Parazzini et al. 1992; Phillips et al. 1992; Saraiya et al. 1998; Karaer et al. 2006). However, two studies did show evidence of an increased risk in past smokers (Chow et al. 1988; Bouyer et al. 2003).

All studies reviewed included confounder-adjusted analyses except one (Roelands et al. 2009). Of these analyses, all but one (Parrazzini et al. 1992) yielded OR or RR point estimates greater than one, and in most, the association was statistically significant (WHO 1985; Chow et al. 1988; Handler et al. 1989; Kalandidi et al. 1991; Phillips et al. 1992; Saraiya et al. 1998; Bouyer et al. 2003; Karaer et al. 2006). The specific confounders addressed through adjustment or exclusions varied across studies, but most analyses included maternal demographics and a combination of factors related to past obstetrical outcomes (prior EP, spontaneous abortion), gynecological and surgical history (past PID, STIs, contraceptive use including IUDs, abdominal surgery), and lifestyle factors (number of sexual partners, douching, and age at first intercourse).

Methodologic challenges related to case-control studies of EP include overcoming bias introduced by selection of control groups, which exclude women with induced abortions. For example, a control group of women with term deliveries that excludes pregnancies ending in induced abortion would likely result in bias favoring characteristics associated with induced abortion (Weiss et al. 1985), such as smoking. Several approaches to address this issue have been suggested, such as excluding from case and control groups women most likely to seek an abortion, such as those using contraceptives and those who were unmarried at the time of conception. In four studies in this review (Chow et al. 1988; Saraiya et al. 1998; Bouyer et al. 2003; Karaer et al. 2006), cases and controls were selected to address this methodologic issue. In all four studies, adjusted models yielded significant associations, and two of these showed evidence of a dose-response relationship (Saraiya et al. 1998; Bouyer et al. 2003).

Evidence Synthesis

Although the precise mechanisms through which smoking could increase risk of EP remain unclear, in vitro and in vivo studies demonstrate that exposure to tobacco smoke adversely affects oviductal functioning and that nicotine can impair oviductal physiology. Animal studies suggest fallopian tubes exposed to cigarette smoke have decreased ciliary beat frequency, cilia-dependent oocyte retrieval rate, adhesion of the oocyte cumulus complex to the fallopian tube, and smooth muscle activity, providing evidence of biologic plausibility for a causal relationship. A number of epidemiologic studies provide consistent evidence of an independent association between maternal smoking and EP. This consistency is greater when restricted to studies which includes adjustment for important potential confounders and careful selection of control groups (Chow et al. 1988; Stergachis et al. 1991; Saraiya et al. 1998; Bouyer et al. 2003; Karaer et al. 2006). Of these studies, all but one identified smoking status as smoking at the time of conception, although this was done retrospectively. Evidence of a dose-response relationship within this group of studies was less consistent. Full adjustment for potential confounders is a methodologic limitation in studies of smoking and EP. Some studies showed minimal or no attenuation after adjustment for confounders (Coste et al. 1991; Bouyer et al. 2003), while others showed some attenuation (Parazzini et al. 1992; Phillips et al. 1992; Saraiya et al. 1998). Among studies in which crude and

adjusted risks were reported, only one demonstrated a change from a significant to a nonsignificant association after adjustment (Parazinni et al. 1992).

Epidemiologic studies combined with in vitro and in vivo studies, document the consistency of findings and biologic plausibility that maternal smoking adversely affects the oviduct in ways that increase the risk of EP.

Conclusion

The evidence is sufficient to infer a causal relationship between maternal active smoking and ectopic pregnancy.

Implications

Data from animal and epidemiologic studies support smoking as a causal risk factor for EP. The evidence of an association between smoking and EP is sufficient to warrant intensified efforts to promote smoking cessation among women of reproductive age and during preconception care. More research is needed to better characterize potential mechanisms, through which smoking affects the success of implantation and placentation.

Spontaneous Abortion

Spontaneous abortion (SAB) is typically defined as the involuntary termination of an intrauterine pregnancy before 20 weeks of gestation, although some studies define SAB as occurring before 28 weeks. Studies have reported recognized SABs in approximately 12% of pregnancies, and, most occur before 12 weeks gestation (Regan et al. 1989). However, very early pregnancy loss may go unrecognized and/or unreported. An estimated 31% of all conceptions end in pregnancy loss, and 22% of conceptions end before the pregnancy is recognized (Wilcox et al. 1988). Studies of embryonic tissue from SABs suggest that 22–61% of losses have an abnormal karyotype (Kline et al. 1989). In addition to fetal abnormalities, other factors that likely contribute to SAB include anatomical abnormalities of the mother's uterus, immunologic disturbances, thrombotic disorders, and endocrine abnormalities (Christianson 1979; Cramer and Wise 2000; Regan and Rai 2000). Infections may also play a role, but data are limited and inconsistent (Cramer and Wise 2000; McDonald and Chambers 2000; Matovina et al. 2004; Rai and Regan 2006).

The 2004 Surgeon General's report found the evidence suggestive, but not sufficient, to infer a causal relationship between smoking and SAB. The 2010 Surgeon General's report provided an update on studies published after the 2004 report, but did not formally evaluate the evidence for causality. This section reviews the epidemiologic and biological evidence for associations between prenatal smoking and increased risk of SAB.

Biologic Basis

The mechanisms through which smoking may increase the risk of SAB are unclear. Mechanistic pathways that have been evaluated through in vitro studies include the effects of tobacco exposure on uterine microvasculature, cytotrophoblast invasion, mitotic activity, differentiation, and attachment during placental development, and on embryonic development (Talbot 2008). In vivo studies also suggest an effect of tobacco and/or nicotine on oocyte quality and embryo development (reviewed by Soares and Melo 2008). Other proposed pathways include fetal hypoxia from exposure to CO, and vasoconstrictive and antimetabolic effects resulting in placental insufficiency and the subsequent death of the embryo or fetus (Salafia and Schiverick 1999; Practice Committee of the American Society for Reproductive Medicine 2012). Finally, cadmium is absorbed from cigarette smoke and has been associated with numerous adverse effects on reproductive function, including retardation of trophoblast development, placental necrosis, abnormal embryonic development, and interference with cell adhesion in the postimplantation embryo (Thompson and Bannigan 2008).

Description of the Literature Review

This section explores available epidemiologic studies of the association between cigarette smoking (and other forms of tobacco use) and SAB. A literature search was conducted for studies published from 2000 through November 2012 to cover the period following that of the 2004 and 2010 Surgeon General's reports using the PubMed system of the National Library of Medicine. The search terms included "smok*," "tobacco," "abortion," "miscarriage," and "preg."

Epidemiologic Evidence

A large number of epidemiologic studies have addressed smoking and SAB (Table 9.15*S*). However, methodologic challenges have made the study of potential associations between maternal smoking and SAB difficult. Many early pregnancy losses are not recognized or reported, making it difficult to study losses across the full gestational age span, unless women are enrolled in a study before conception. The etiology of SAB is multifactorial and the mechanisms are not well understood; thus, the ability to clinically categorize cases of SAB is limited,

especially in large epidemiologic studies. Because it is unlikely that tobacco exposure would have similar effects on SAB risk in women across etiologic subgroups, combining cases of SAB could bias potential associations with tobacco toward the null. For example, many early pregnancy losses are associated with karyotypically abnormal embryos. Although it would be optimal to study SAB cases with normal and abnormal embryo karyotype separately, the embryo karyotype is unknown in many studies. Full adjustment for potential confounding from other exposures, such as alcohol use, substance abuse, and STIs, is difficult, especially in large studies. In case-control studies, the selection of an appropriate control group is important in order to avoid bias. For example, women with term births (a commonly selected control group) may differ in their prevalence of smoking from women who have elective terminations and preterm births (often omitted from control groups). Finally, exposure misclassification due to maternal nondisclosure of smoking status, or other factors, could result in bias toward the null.

Most studies reviewed at the time of the 2004 Surgeon General's report indicated an increased risk of SAB in active smokers. In a meta-analysis of data from 13 studies, the pooled crude ORs for SAB in smokers were slightly elevated at 1.24 (95% CI, 1.19–1.30) for cohort studies and 1.32 (1.18–1.48) for case-control studies (DiFranza and Lew 1995). Finally, in the largest study to date of karyotyped miscarriages (n = 2,376), Kline and colleagues (1995) observed an association between active smoking and SAB that was confined to losses of chromosomally normal conceptions (AOR = 1.3; 95% CI, 1.1–1.7). This finding supports the association that smoking increases risk of SAB through toxic effects that occur during gestation. However, George and colleagues (2006) also found that smoking was significantly associated with SAB with unknown and abnormal fetal karyotype, but not with SAB with normal karyotype. The number of SAB cases with a normal karyotype was small (n = 75) and a large percentage of SAB cases were of unknown karyotype (George et al. 2006). Further, the collection of samples for cotinine measurement in both studies by George and colleagues (2006) and by Ness and colleagues (1999) occurred at the time of the miscarriage, and so cotinine levels did not necessarily reflect tobacco exposure at or before conception. There have been no new studies since the 2010 Surgeon General's report that have examined the risk of SAB from maternal smoking by karyotype.

Eight new studies from a number of different countries were evaluated in the 2010 report and included case-control (Chatenoud et al. 1998; Ness et al. 1999; Rasch 2003; Wisborg et al. 2003; George et al. 2006; Nielsen et al. 2006), cohort (Windham et al. 1999), and cross-sectional

(Mishra et al. 2000) study designs. Analyses included adjustment for various potential confounders, such as use of oral contraceptives, IUDs (Nielsen et al. 2006), alcohol and caffeine (Chatenoud et al. 1998; Ness et al. 1999; Windham et al. 1999; Rasch 2003; Wisborg et al. 2003; George et al. 2006), illicit substances (Ness et al. 1999), history of STIs (Ness et al. 1999), and folate levels (George et al. 2006). Five of eight studies found significant positive associations between smoking and SAB in adjusted models (Chatenoud et al. 1998; Ness et al. 1999; Mishra et al. 2000; George et al. 2006; Nielsen et al. 2006); in one study the association was not significant for smoking overall, but was significant when the number of cigarettes smoked per day among smokers was examined (AOR = 1.20; 95% CI, 1.04–1.39 per 5 cigarettes/day) (Nielsen et al. 2006).

Two studies used cotinine to verify exposure to tobacco smoke and found relatively higher risks of SAB compared with other studies (AORs = 1.8; 95% CI, 1.3–2.6; and 2.1; 95% CI, 1.4–3.3) (Ness et al. 1999; George et al. 2006). In contrast, two studies of Danish women (one large cohort study of 24,608 pregnant women and one case-control study of women with SAB or a live fetus at 6–16 weeks gestation) found no association between smoking and SAB after adjustment for multiple potential confounders (Rasch 2003; Wisborg et al. 2003). In a cohort study of pregnant women at 12 weeks gestation or less and enrolled in a prepaid health plan, Windham and colleagues (1999) did not find a significant association between smoking and SAB (AOR = 1.3; 95% CI, 0.9–1.9). In the latter study, however, the association was marginally significant when the analysis was restricted to loss after 10 weeks gestation (AOR = 1.6; 95% CI, 1.0–2.4) (SAB at a later gestational age is more likely to have a normal karyotype than an SAB at an earlier gestational age).

Since the publication of the 2010 Surgeon General's report, several studies have examined the effects of maternal active smoking on SAB risk, with mixed results (Table 9.15*S*). In a case-control study of Japanese women with early SAB and using women with term births as a control group, AORs for smoking 1–19 and 20 or more cigarettes per day were 1.30 (95% CI, 0.84–2.02) and 2.39 (95% CI, 1.26–4.53), respectively (p for trend = 0.02) (Baba et al. 2011). ORs were adjusted for numerous factors, including BMI and alcohol intake.

In a cross-sectional survey of cosmetologists, realtors, teachers, nurses, and retail clerks, Gallicchio and colleagues (2009) found a significant association between smoking and SAB after adjusting for age, race, education, and alcohol use (AOR = 1.53; 95% CI, 1.09–2.16).

Maconochie and colleagues (2007) conducted a nested case-control study and found a significant association between smoking and SAB for women smoking 11–20

cigarettes per day (AOR = 1.68; 95% CI, 1.16–2.42), but not for smoking 1–10 or more than 20 cigarettes per day and Bhattacharya and colleagues (2010) also found a modest but significant association (AOR = 1.13; 95% CI, 1.05–1.22), but results were adjusted only for age and year of event, and smoking status was obtained from medical coding and was missing for a large proportion of women. Only one of the studies reviewed included evidence of a dose-response relationship (Baba et al. 2011). The remaining studies found no evidence (Maconochie et al. 2007) or did not report associations by cigarettes smoked per day (Gallicchio et al. 2009; Bhattacharya et al. 2010). Other studies found no association between smoking and SAB (Blohm et al. 2008; Zhang et al. 2010; Campbell et al. 2011).

Several studies have examined the role of maternal smoking and SAB among women undergoing assisted reproductive technology (methods to achieve pregnancy by artificial or partially artificial means) procedures. Because women receiving these services undergo intense follow-up, the timing of conception and tobacco exposure status at conception are often known, allowing researchers to overcome methodologic limitations often present in other populations. In a meta-analysis of studies addressing the effects of tobacco use on outcomes among assisted reproductive technology patients, the pooled OR for SAB was 2.65 (95% CI, 1.33–5.30) (Waylen et al. 2009). However, studies included in this meta-analysis had several methodologic limitations, including the inability to control for confounders (Harrison et al. 1990; Pattinson et al. 1991; Hughes et al. 1992; Maximovich et al. 1995; Gustafson et al. 1996; Soares et al. 2007), use of repeated measures without documentation that the appropriate statistical analysis was used (Hughes et al. 1992; Winter et al. 2002), and poorly defined smoking status (Maximovich et al. 1995; Winter et al. 2002). In a subanalysis of three studies which were unlikely to be affected by confounding due to maternal age, the association between smoking and SAB was no longer significant (OR = 1.88; 95% CI, 0.55–6.27) (Waylen et al. 2009).

Evidence Synthesis

In summary, there are multiple potential mechanisms through which smoking during pregnancy could increase risk for SAB. Several studies published since the 2004 Surgeon General's report address previous methodologic limitations. These studies have included consideration of a number of potentially important confounders, such as alcohol and illicit substance use, and history of STIs. Studies using biochemical validation of tobacco exposure had positive and significant associations (Ness et al. 1999; George et al. 2006). Evidence of a dose-response

relationship was found in some recent studies (Nielsen et al. 2006; Baba et al. 2011), but not in all (Mishra et al. 2000; Maconochie et al. 2007). Overall, results of epidemiologic studies remain mixed, and many studies have important methodologic limitations, including reliance on women with term births as controls, lack of data on many relevant confounders, unknown embryonic/fetal karyotype, and uncertainty regarding level of exposure to tobacco during periods critical to the outcome.

Conclusion

The evidence is suggestive, but not sufficient, to infer a causal relationship between maternal active smoking and spontaneous abortion.

Implications

SAB is multifactorial and the mechanisms are not yet well understood; however, the evidence of an association between smoking and SAB is sufficient to warrant intensified efforts to promote smoking cessation before conception and during early prenatal care. More research is needed to better characterize potential mechanisms through which smoking might affect the success of implantation and placentation.

Male Sexual Function

Erectile dysfunction (ED) is defined as the persistent inability of a man to attain and maintain an erection that is adequate for satisfactory sexual performance (NIH Consensus Development Panel on Impotence 1993). According to the National Health and Social Life Survey, 18% of U.S. men, 50–59 years of age, had ED in 1992 (Laumann et al. 1999). This prevalence rate relied on a probability sample that included 1,410 men, 18–59 years of age. Later, the National Health and Nutrition Examination Survey of 2001–2002 estimated that 18.4% of U.S. men, 20 years of age and older, had ED and that the condition affected 18 million men nationwide (Saigal et al. 2006; Selvin et al. 2007). Using data from the Massachusetts Male Aging Study (Feldman et al. 1994), estimates of the prevalence of complete ED among men 40–70 years of age exceeded 10% during 1987–1989; estimates of at least mild ED exceeded 50%. According to an estimate derived from longitudinal results of the Massachusetts Male Aging Study in the late 1990s, 25.9 cases of new-onset (incidence) ED occurred per 1,000 men annually (Johannes et al. 2000).

Hormonal derangement, psychogenic factors, neurologic disorders, and vascular insufficiency have been

implicated in the etiology of ED, as have several other factors. Objectively demonstrable ED has been found in patients who have had a myocardial infarction, undergone coronary artery bypass surgery, suffered a cerebrovascular accident, or have peripheral vascular disease or hypertension (Melman and Gingell 1999). In addition, reports of patients with vasculogenic ED have suggested predisposing vasculopathic risk factors, such as cigarette smoking, high-fat diets, higher risk serum lipid levels, hypertension, physical inactivity, and obesity (Goldstein and Hatzichristou 1994; Kendirci et al. 2007; Miner and Billups 2008). Several large epidemiologic studies have explored the extent to which these factors impair erectile function (Feldman et al. 1994, 2000; Derby et al. 2000a,b; Johannes et al. 2000). The results of these studies imply that modifying risk factors may reduce the occurrence of ED. For example, Esposito and colleagues (2004, 2009) assessed the effects of increased physical activity and weight loss on erectile function in overweight men and found that both could improve penile function.

A growing body of literature shows that tobacco smoke adversely affects sexual health and erectile function in particular (Bornman and du Plessis 1986; Juenemann et al. 1987; Mannino et al. 1994; Polsky et al. 2005; Shiri et al. 2006; He et al. 2007; Kupelian et al. 2007, 2010; Harte and Meston 2008; Tostes et al. 2008). Cigarette smoking may affect erectile function through its atherogenic effects on penile vasculature in a manner that is analogous to the effects of heart disease on coronary circulation. This chapter summarizes and evaluates current observational, clinical, and experimental data that link cigarette smoking with ED, including the relevant pathophysiologic concepts.

Conclusions from Previous Surgeon General's Reports

The 2004 report indicated that on the basis of case series and population-based studies as well as experimental evidence from human and animal studies, cigarette smoking is a risk factor for erectile dysfunction (USDHHS 2004). However, the evidence was considered not sufficient to infer a causal relationship.

Biologic Basis

One possible mechanism for ED is smoking-induced endothelial dysfunction of the penile vasculature. Both the endothelium of the blood vessels supplying the penis and the lining of the lacunar spaces within that organ release vasoactive substances that contribute to the control of the relaxation of smooth muscle that is required for erection (Lue and Tanagho 1987; Lue 2000).

Saenz de Tejada and colleagues (1989), as part of an investigation of the consequences of diabetes mellitus on endothelial function in the penis of men with ED, examined the effect of smoking on penile vasculature. Using isolated strips of human corpora cavernosa of the penis taken at surgery, researchers compared isometric tension results from impotent men with and without diabetes who were smokers (i.e., with at least a 5 pack-year[1] history of smoking) or nonsmokers. They found that a history of smoking was not associated with greater impairment of endothelium-mediated relaxation responses.

In a study of rats, Xie and colleagues (1997) examined the long-term effects of smoking on the endothelial synthesis of nitric oxide (NO) in the penis; NO is the principal vasoactive mediator of penile erection (Burnett 1997). In the study, rats were passively exposed to cigarette smoke for 60 minutes at a time once per day, 5 days per week, for 8 weeks. Immunoblot analyses of the protein expression of eNOS in penile tissue from exposed rats did not reveal any diminution of eNOS expression in a comparison with control rats. Overall, however, the study confirmed that NOS enzymatic activity (which combines neuronal and endothelial sources) and specifically the protein expression of the neuronal form of NOS in the penis were markedly reduced in rats that were passively exposed to cigarette smoke compared with unexposed rats. These findings suggest that smoking selectively impairs neuronal mechanisms, particularly the neuronally based NO signal transduction pathway associated with penile erection. The rat model, however, may not be relevant for humans.

Several studies in humans have demonstrated reduced endothelium-derived NO production as a result of acute and chronic smoking (Celermajer et al. 1993; Shen et al. 1996; Adams et al. 1997; Puranik and Celermajer 2003; Brunner et al. 2005; Tostes et al. 2008). In addition, the adverse effect of chronic smoking on vascular medial elastic fibers has been cited as a possible contributor to smoking-induced ED (Ambrose and Barua 2004; Guo et al. 2006). The critical effects of smoking-induced oxidative stress on ED, mediated through the formation of superoxide radicals, have been evaluated. Support for a role of oxidative injury includes the generation of superoxides by cavernosal smooth muscle cells following noxious stimuli, inhibition of cavernosal smooth muscle relaxation by

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[1]Pack-years = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

inhibition of copper/zinc superoxide dismutase, improvement of diabetes-related erectile function in animal models following therapy using antioxidants or free oxygen radical scavengers, and the elevated production of cavernosal reduced nicotinamide adenine dinucleotide phosphate oxidase-derived superoxides that has been observed in vasculogenic ED (Mok et al. 1998; DeYoung et al. 2004; Koupparis et al. 2005; Shukla et al. 2005; Kovanecz et al. 2006; Ozkara et al. 2006; Hotston et al. 2007; Tostes et al. 2008).

Saenz de Tejada and colleagues (1989), looked at whether smoking affects the neurogenic mechanisms that are responsible for erection. The researchers found that the impairment of neurogenically mediated relaxation of penile smooth muscle obtained from smokers (in an analysis that combined results from men with and without diabetes) did not differ from the impairment observed in nonsmokers (men with and without diabetes). Adaikan and Ratnam (1988) found that the actions of nicotine are both contractile and relaxant. If ED results from exogenously administered nicotine during smoking, it may be because of the acute vasoactive modulatory effects of this agent on the penile vasculature.

In a randomized, double-blind, placebo-controlled trial, Harte and Meston (2008) investigated the acute effects of an intermediate dose of nicotine on physiological and subjective sexual arousal in nonsmoking men. The study measured objective (through assessments of penile circumference via plethysmography) and subjective (through self-reports) differences in response to sexual stimuli with and without acute nicotine exposure in 28 men and found a 23% reduction in physiological sexual arousal with exposure to nicotine. The study's authors attributed these findings to the sympathomimetic effects of nicotine-causing vasoconstriction (i.e., anti-erectogenic) through the release of epinephrine and norepinephrine (Lue and Tanagho 1987; Harte and Meston 2008). Based on self-reports from men in this study, sexual arousal did not decrease after the administration of nicotine. Thus, the authors postulated that the effects of nicotine were more likely physiological than cognitive.

Clinical Evidence

Studies on Penile Tumescence

The monitoring of nocturnal penile tumescence (NPT) is a noninvasive diagnostic technique that can quantify the physiology of erection during the naturally occurring cycle of sleep-related erections. These spontaneous episodes of tumescence normally accompany rapid eye movement sleep and are diminished in men with ED that is presumed to be organic (vasculogenic, neurogenic, anatomic, or endocrinologic) (Karacan et al. 1978; Allen and Brendler 1992). Several early investigations of the objective basis for vasculogenic ED applied NPT monitoring. Elist and colleagues (1984) confirmed NPT-monitored abnormalities in 20 smokers with ED, of whom 7 (35%) displayed normal NPT-monitored results after 6 weeks of not smoking. Virag and colleagues (1985) found that smokers constituted 72% of patients with abnormal NPT results but only 32% of patients with normal NPT results. Karacan and colleagues (1978), in a study of 168 heavy smokers (one or more packs of cigarettes smoked per day) and 632 light smokers (less than one pack smoked per day), found that during a sleep-related erection the penis was significantly less rigid at each decade of life after 30 years of age in heavy smokers than in light smokers. The study also found that the duration of maximal tumescence was significantly lower among heavy smokers 30 years of age and younger and those 51–60 years of age than in age-equivalent light smokers.

In an investigation of 314 smokers with ED, Hirshkowitz and colleagues (1992) found a significant inverse correlation between penile rigidity during a sleep-related erection and number of cigarettes smoked per day (r = -0.12; p = 0.04). These investigators also showed that the duration of maximal tumescence was significantly shorter at the penile base (p ≤0.05), and the duration of detumescence (i.e., the decline from full erection to flaccidity) was also shorter (p = 0.06), among men who smoked 40 or more cigarettes per day than among men who smoked 1–19 or 20–39 cigarettes per day (p = 0.14).

Vascular Hemodynamics of the Penis

Impaired blood flow to the penis has been assessed using various measurement techniques. A widely used early method was the Doppler ultrasound of arterial pulsations in the flaccid, unstimulated penis. Although this method is no longer used, findings from studies that used this method remain relevant with respect to the pathogenesis of smoking-related vascular disease of the penis. The penile-brachial index (PBI)—the ratio of penile to brachial systolic blood pressures—can be calculated from values obtained through Doppler ultrasound. Reduced PBI values have been associated with impairment of the erectile process (Kempczinski 1979). Using Doppler ultrasound, Wabrek and colleagues (1983) did not find a significant association between cigarette smoking and abnormal PBI values, and Virag and colleagues (1985) also did not find an independent effect of smoking on PBI. The latter study,

however, revealed a synergistic effect of smoking on PBI in combination with such other arterial risk factors as diabetes, hyperlipidemia, and hypertension.

Smokers in a study by Condra and colleagues (1986), however, had significantly lower PBI values than did nonsmokers. In another study, DePalma and colleagues (1987) found that cigarette smoking carried a significantly higher probability of abnormal (49%) than normal (28%) vascular laboratory findings, including those for PBI—an effect that was not observed for age, hypertension, diabetes, or prior myocardial infarction. A study by Hirshkowitz and colleagues (1992) found consistent reductions in PBI among 314 cigarette smokers with ED. The investigators found significant correlations between the number of cigarettes smoked per day and the magnitude of these reductions in PBI for the left dorsal artery (r = -0.14; p = 0.01) and right cavernosal artery (r = -0.13; p <0.03).

More recent investigations have used a pharmacologic stimulus in combination with duplex ultrasonography to characterize the vascular competence of penile arteries. This technique has been used since the discovery that a pharmacologic stimulus to induce an artificial erection provides a better assessment of the physiologic responsiveness of these arteries than that provided during the resting state (Abber et al. 1986). Using this technique and applying a combined set of ultrasonographic parameters to establish normal vascular findings, Shabsigh and colleagues (1991) found a consistent, marginally significant difference in vascular impairment between smokers and nonsmokers. Kadioğlu and colleagues (1995) also observed that penile vascular parameters were abnormal to a greater extent among smokers than among nonsmokers, although the differences were not significant. Overall, PBI testing suggests deleterious effects of smoking on the resting-state circulation of the penis, and sonographic evaluation of the penis following pharmacostimulation additionally suggests deleterious effects of smoking on changes in dynamic blood flow in that organ.

To better understand the hemodynamic mechanisms involved in the development of ED among smokers, Elhanbly and colleagues (2004) studied 109 patients with ED (71 current smokers and 38 nonsmokers). Evaluation included the monitoring of nocturnal penile tumescence and rigidity (NPTR) with a device called a RigiScan, followed by pharmacopenile duplex ultrasonography and redosing pharmacocavernosometry. NPTR results were abnormal for 86% of smokers and 55% of nonsmokers (p = 0.02), but the difference in peak systolic velocity of the cavernosal artery between smokers and nonsmokers (26.8 and 31.2 centimeters/second, respectively) was not significant. The latter finding suggests that vascular pathology in ED is more likely related to veno-occlusive dysfunction than to pure arterial insufficiency. Further vascular test-

ing in the study by Elhanbly and colleagues (2004) with redosing pharmacocavernosometry revealed abnormal maintenance flow (>5 mL/minute) in 89% of smokers but only 47% of nonsmokers (p <0.01). Based on these findings, including the higher incidence of abnormal maintenance flow in the smoker group, the authors concluded that veno-occlusive dysfunction plays a substantial role in the development of ED in smokers.

Vascular Morphology

Clinicians and researchers have frequently used arteriographic studies to characterize the vascular anatomy of the penis in patients with ED. For example, investigators have used arteriography to confirm the presence and location of arteriographic lesions in smokers with ED. In one study, Virag and colleagues (1985) found a 67.8% prevalence of arteriographic abnormalities in the four main blood vessels of the penis among patients in whom organic ED had been established by NPT monitoring, of whom 86% were smokers. Similarly, Bahren and colleagues (1988) found that 82% of their patient groups with arteriographically proven peripheral arteriosclerotic lesions were heavy smokers. In a study by Forsberg and colleagues (1989), men with ED underwent screening studies of penile blood flow to identify abnormalities. Using pharmacostimulation and angiography in 17 men, the study found significant distal lesions of penile vessels in all but 1 of the 17 men; 14 (82%) of the men were identified as smokers. Later, Rosen and colleagues (1991) conducted a comprehensive evaluation of penile circulation in cigarette smokers with ED. According to the study, smoking represents a significant independent risk factor in the development of atherosclerotic lesions in the internal pudendal and common penile arteries. This study also determined that the number of pack-years smoked was independently associated with hemodynamically significant atherosclerotic disease in the hypogastric-cavernous arterial bed supplying the penis: for each 10 pack-years of smoking, the RR of this disease was 1.31 (95% CI, 1.05–1.64) compared with 1.03 (95% CI, 1.01–1.05) for 1 pack-year of smoking.

Histopathology

Mersdorf and colleagues (1991), who investigated the effects of cigarette smoking on erectile tissue, found degenerative tissue changes (including decreases in smooth muscle content, sinusoidal endothelium, nerve fibers, and capillaries and an increase in collagen density) in the erectile tissue of smokers. These alterations are consistent with the alterations of tissue observed in other vascular diseases.

Experimental Evidence

This section reviews experiments carried out in humans and animals to test the effects of cigarette smoking on erectile function (Table 9.16S). Experimental approaches can control for exposure to cigarette smoking and provide the possibility of a rigorous evaluation of the consequences of smoking for ability to achieve an erection.

Human Studies

Gilbert and colleagues (1986) may have been the first to report on an experimental evaluation of the hypothesized association between cigarette smoking and ED. The study made polygraphic recordings of the erections in smokers as they viewed erotic videos. The study population consisted of 42 males who self-reported to be heterosexual cigarette smokers, 18–44 years of age, in good health. Unknown to the experimenter, participants were assigned to and randomly selected from three groups: one group smoked high-nicotine cigarettes during the experiment (0.9 milligrams [mg] nicotine/cigarette), a second group smoked low-nicotine cigarettes (0.002 mg nicotine/cigarette), and a third, the control group, sucked on a hard mint candy. Before the experiment, smokers were required to abstain from smoking for 2 hours. At baseline, measures of cardiovascular responses were obtained as participants watched erotic videos. The study found that smoking two, but not one, high-nicotine cigarettes significantly decreased the rate at which the diameter of the penis increased in a comparison with the other two conditions (low-nicotine cigarettes, control) during the erectile stimulus (p <0.001). The study also determined that high-nicotine cigarettes caused significantly more vasoconstriction and a higher heart rate than did low-nicotine cigarettes. Glina and colleagues (1988) monitored intracavernous pressures to try to determine whether cigarette smoking interfered with vasoactive, drug-induced erectile responses. Twelve chronic smokers, 22–65 years of age, were not permitted to smoke on test days, except if directed. Each participant underwent pharmacostimulation at baseline and 1 week later immediately after exposure to nicotine (smoking two cigarettes, each with 1.3 mg of nicotine). Investigators obtained measurements of intracavernous pressure 20 minutes after pharmacostimulation. The study found that all 12 men obtained an erection (by clinical judgment) at baseline, compared with only 4 (33%) men after smoking two cigarettes, corresponding to a significant decrease in mean intracavernous pressures from 85.83 millimeters of mercury (Hg) at baseline to 53.50 mm Hg after smoking. In a visual depiction

of the effects of cigarette smoking on arterial flow to the penis, Levine and Gerber (1990) described a pelvic arteriographic study of a man, 38 years of age, who had a 25 pack-year smoking history when he presented for evaluation of ED. A complete baseline evaluation, including pelvic arteriographic studies, showed no abnormalities. However, repeat pelvic arteriography immediately after the patient smoked two cigarettes revealed a decrease in the caliber of the entire pudendal artery and nonvisualization of the deep penile artery. The investigators suggested that acute vasospasm was responsible for the observed effects.

A study of smoking cessation by Guay and colleagues (1998) enrolled 10 men, 32–62 years of age, who had at least a 30 pack-year smoking history and were currently smoking one pack of cigarettes or more per day. Participants used the RigiScan technique at home to monitor NPTR. The study required the monitoring of sleep-related penile erections on two successive nights—the first night following a usual day of smoking and the second night following discontinuation of smoking for a 24-hour interval. An additional component of the study involved repeat monitoring for 1 month in four men who did not smoke, although these men were administered transdermal nicotine patches (21 mg) during that time. The study found that erectile parameters improved to a statistically significant degree in the men who had stopped smoking for 24 hours. Erectile parameters improved even more in the men who did not smoke but wore a nicotine patch for 1 month. The study investigators concluded that eliminating cigarette smoking improves erectile function and that chemicals contained in cigarette smoke other than nicotine are primarily responsible for the damaging effects.

Sighinolfi and colleagues (2007) also evaluated the acute effects of smoking cessation on penile hemodynamics. These investigators assessed 20 active smokers, 31–48 years of age, who had ED, per the five-item International Index of Erectile Function (IIEF) questionnaire. These smokers had consumed 20–40 cigarettes per day for a mean of 7 years (range: 5–8 years). Participants underwent penile color Doppler ultrasonography following pharmacostimulation at baseline and underwent Doppler ultrasonography again at 24–36 hours after they withdrew from smoking. At baseline, 10 (50%) of the 20 participants had abnormal peak systolic velocity values and 15 (75%) had abnormal end diastolic velocity values. But after they withdrew from smoking, none of the 20 had an abnormal peak systolic velocity and only 3 (15%) had abnormal end diastolic velocity values. The study suggests that chronic cigarette smoking adversely affects erection, with a predominant effect on the veno-occlusive function of the penis.

Animal Studies

Animal models provide another useful approach to investigating the association between cigarette smoking and ED. Juenemann and colleagues (1987) used an in vivo canine model to monitor arterial inflow, intracavernous pressure, and venous outflow of the penis during stimulation of the cavernous nerve to produce an erection without perfusion of the penis, as well as with regulated penile perfusion before and after acute inhalation of cigarette smoke (1.4 mg nicotine per cigarette). After exposure to smoking (one to six cigarettes), and compared with nonsmoking conditions at baseline, peak arterial inflow was significantly diminished, peak intracavernous pressure was significantly diminished and could not be maintained, and venous outflow was not significantly restricted. Measurable serum nicotine and cotinine levels obtained in the dogs following exposure to smoking were consistent with concentrations found in human smokers, but no changes in arterial blood gases or systemic blood pressure were observed throughout the investigation. The study concluded that smoking exerts a localized deleterious effect on the neurovascular mechanisms required for penile erection, with a particular impairment of the veno-occlusive mechanism that is associated with maintaining an erection.

Xie and colleagues (1997) used a rat model to evaluate the long-term effects of cigarette smoking on erection. Investigators monitored neurostimulated erections in vivo after exposing rats to a constant influx of cigarette smoke in an enclosed cage for a 60-minute session once per day, 5 days per week, for 8 weeks. Compared with controls, smoke-exposed rats exhibited increased intracavernous pressure, but they also developed systemic hypertension. After standardizing intracavernous pressures to systemic blood pressures in the rats exposed to cigarette smoke, intracavernous pressures were not different between exposed rats and controls.

Description of the Literature Review

This section explores available observational data on the association between cigarette smoking (and other forms of tobacco use) and ED. A literature search conducted through May 2010, using the PubMed system of the National Library of Medicine, was supplemented with professional knowledge of other resources. The search terms included "erectile dysfunction and smoking" and "erectile dysfunction and tobacco."

Epidemiologic Evidence

Unlike quantitative data on tobacco smoking and erectile performance, observational data rely on self-reporting and other subjective instruments (e.g., logs, questionnaires, and inventories of sexual function). A single-item assessment (e.g., "Do you experience difficulty getting and/or maintaining an erection that is rigid enough for satisfactory sexual intercourse?") has been widely used, particularly for population-based epidemiologic studies (Derby et al. 2000a).

A multi-item questionnaire to distinguish between erectile and ejaculatory dysfunction was developed by the Krimpen Study in The Netherlands (Blanker et al. 2001). This type of questionnaire has been useful as a single, direct, practical tool to ascertain the presence of ED. However, this methodology, as with any self-report, introduces the possibility of information bias, probably in this case with a tendency toward underreporting ED. Differential underreporting of this condition by smoking status would bias estimates of the effects of smoking.

Case Series

Cigarette smoking has been linked to ED in several clinical reports, most of which would qualify as observational case series. As such, they are limited by not having true comparison groups, but they are reviewed here because they are cited often in the literature, and data from more formal studies are limited.

Wabrek and colleagues (1983) studied men who were referred to a hospital-based medical sexology program for evaluation and management of ED. Of 120 men, 50% were smokers, including users of cigarettes, cigars, or pipes. Elsewhere, in a study of 440 men who were referred for clinical evaluation of ED, 64% were smokers, defined as smoking more than 15 cigarettes per day for at least 15 years (Virag et al. 1985). Bornman and du Plessis (1986) observed similar results among 300 men who were screened for impotence at an andrology clinic. Of those who were diagnosed with either psychogenic or vasculogenic impotence, 62% were smokers and had smoked approximately 25 cigarettes per day for more than 20 years.

Condra and colleagues (1986) attempted to provide comparative information using a study of 178 men who were referred for clinical evaluation for ED. In all, 51.4% of the men were current cigarette smokers and 81% were either current or former cigarette smokers. These estimates exceeded the 38.6% and 58.3% estimates, respectively, that were ascertained from the general population (Canada) using concurrent survey data.

Finally, Tengs and Osgood (2001) identified 19 clinical studies of ED involving 3,819 men that had been published in the previous 20 years. Pooling the prevalence of current smoking across the series, they found that 40% of those with ED were current smokers.

Cross-Sectional Studies

Cross-sectional, random surveys of sample populations offer more population-based appraisals of the association of cigarette smoking and ED (Table 9.17S).

The Vietnam Experience Study of 1985–1986 surveyed 4,462 U.S. Army Vietnam-era veterans, 31–49 years of age (Mannino et al. 1994). The study found prevalence rates of ED of 2.2% among never smokers, 2.0% among former smokers, and 3.7% among current smokers (p = 0.005). The association was significant for current smokers (OR = 1.5; 95% CI, 1.0–2.2) even after adjusting for such factors as vascular disease, psychiatric problems, hormonal factors, substance abuse, marital status, race, and age.

In Italy, a cross-sectional study by Parazzini and colleagues (2000) assessed the prevalence of ED in 2,010 men, 18 years of age and older, in 1996–1997. After controlling for multiple variables—including age, marital status, socioeconomic status, and chronic diseases—the authors found an increased risk of ED for current smokers (OR = 1.7; 95% CI, 1.2–2.4; p <0.05) and former smokers (OR = 1.6; 95% CI, 1.1–2.3; p <0.05) compared with lifetime nonsmokers.

The Krimpen Study described previously was a community-based investigation conducted in Rotterdam, The Netherlands, between 1995–1998 that surveyed 1,688 men, 50–78 years of age (Blanker et al. 2001). In this study, smokers were more likely than nonsmokers to report ED (AOR = 1.6; 95% CI, 1.1–2.3; p <0.05). In Spain, Martin-Morales and colleagues (2001) conducted a cross-sectional study of the prevalence of ED in 1998–1999. Among 2,476 men, 25–70 years of age, the authors found that cigarette smoking was significantly associated with ED (AOR = 2.5; 95% CI, 1.64–3.80; p <0.05).

To investigate relationships between smoking and both risk of ED and the prognosis for the condition, Shiri and colleagues (2005) performed a population-based study of 1,442 men, 50–75 years of age, in Finland who had responded to a series of baseline and follow-up questionnaires. The risk for ED from smoking was relatively small (OR = 1.4; 95% CI, 0.9–2.3), and the authors also found that smokers had reduced odds of recovering from ED compared with never smokers (OR = 0.6; 95% CI, 0.2–1.4). In Australia, the association between cigarette smoking and ED was examined as part of the 2001 Australian Study of Health and Relationships. This major national survey of sexual and reproductive health had a large, representative sample of 8,367 Australian men, 16–59 years of age, who were interviewed between mid-2001 and mid-2002 (Millett et al. 2006). The study found that smokers were more likely than nonsmokers to have ED. This association was stronger for heavier smokers: 20 cigarettes or fewer smoked per day (AOR = 1.24; 95% CI, 1.0–1.52; p <0.05), more than 20 cigarettes smoked per day (AOR = 1.39; 95% CI, 1.05–1.83; p <0.05).

In the Global Study of Sexual Attitudes and Behaviors, Moreira and colleagues (2006) investigated the prevalence of sexual problems in Korea. Here, the evaluation of sexual dysfunction relied entirely on self-reporting through a nonvalidated questionnaire. Among the 600 men, 40–80 years of age, who completed the survey, both current and former smoking was associated with erectile and ejaculatory dysfunction.

In Hong Kong, Lam and colleagues (2006b) conducted a cross-sectional survey of 819 Chinese men, 31–60 years of age, to evaluate the association between smoking and ED, which was defined as self-reported dissatisfaction with and/or erection difficulty during sexual intercourse. The authors also used a questionnaire that had not been validated. The authors found that smoking 20 or more cigarettes per day was associated with a 47% increased risk of ED (OR = 1.47; 95% CI, 1.00–2.16; p <0.05) when never smoking was the referent. This study also found that the risk of dissatisfaction with sexual intercourse was significantly lower for former smokers than smokers who were consuming 20 or more cigarettes per day.

In another Asian study, He and colleagues (2007) reported on the association between cigarette smoking and ED among 7,864 Chinese men, 35–74 years of age, who did not have clinical vascular disease. The evaluation examined serum concentrations of cholesterol and triglycerides, the assessment of clinical vascular disease was based on self-reports (Gades et al. 2008). The authors reported a significant dose-response relationship between the risk of ED and cigarette smoking: OR = 1.41 (95% CI, 1.09–1.81). In a comparison with never smokers, the study also found a significant dose-response relationship between the number of cigarettes smoked per day and risk of ED: smoking 1–10 cigarettes per day (age-adjusted OR = 1.22; 95% CI, 0.88–1.68); 11–20 cigarettes per day (age-adjusted OR = 1.39; 95% CI, 1.05–1.85); more than 20 cigarettes per day (age-adjusted OR = 1.70; 95% CI, 1.13–2.56). The authors suggested that cigarette smoking may contribute to approximately 11.8 million cases of ED in China.

Cohort Studies

The Health Professionals Follow-up Study began in 1986 as a prospective cohort study of heart disease and cancer among 51,529 male health professionals in the United States. In a cross-sectional analysis of 34,282 of these men, 53–90 years of age, that controlled for age, marital status, and other variables, Bacon and colleagues (2003) found an increased probability of ED among

current smokers versus nonsmokers (OR = 1.3; 95% CI, 1.1–1.4; p <0.05). In another study, Bacon and colleagues (2006) examined prospectively the impact of obesity, physical activity, alcohol use, and smoking on the development of ED among 22,086 men, 40–75 years of age, in the same cohort. The RR of developing ED during the 14-year follow-up among smokers was 1.5 (95% CI, 1.3–1.7). According to the authors, obesity and smoking were positively associated and physical activity was inversely associated with ED.

Findings from the baseline phase of the Massachusetts Male Aging Study—a community-based survey conducted from 1987–1989 of 1,290 men, 40–70 years of age, living in the Boston, Massachusetts, area—did not support an independent association between cigarette smoking and ED (Feldman et al. 1994). Here, the probabilities of complete ED were 11.0% for smokers and 9.3% for nonsmokers, which included former smokers and never smokers (p >0.20). However, the prospective phase of the Massachusetts Male Aging Study, which extended over a median of 9 years, found the comorbidity-adjusted rate of incident ED to be significantly higher among cigarette smokers (24%) than nonsmokers (14%) (OR = 1.97; 95% CI, 1.07–3.63; p = 0.03) (Feldman et al. 2000). The classification of ED on this study was based on an algorithm derived by a discriminant analysis of 13 questions.

When performing cross-sectional analyses of predictors of ED using the baseline data from the Massachusetts Male Aging Study, Kleinman and colleagues (2000) used two new methods for classifying ED. Their field study method, which corresponded to the approach used by Feldman and colleagues (2000), relied on responses to an original questionnaire from men who were attending a urology clinic and answers to a single question to self-rate ED. Their second method was based on responses to an expanded follow-up questionnaire given to a sample of men in the clinic. The field study method found an association between smoking and ED (OR = 1.39; 95% CI, 1.07–1.80), but the expanded questionnaire did not (OR = 0.95; 95% CI, 0.72–1.22).

Using data from the Boston Area Community Health (BACH) survey, Kupelian and colleagues (2007) assessed associations between active and passive smoking and ED. The study used the IIEF questionnaire to assess ED among a random sample of 2,301 racially and ethnically diverse men (approximately one-third each Black, White, and Hispanic), 30–79 years of age (mean age: 47.6 years). After controlling for age and various comorbidities, the study found an association between increased pack-years and greater severity of ED. The dose-response relationship was most prominent among those with 20 or more pack-years of exposure. The BACH survey did not collect information on time since quitting smoking, and so the impact of cessation on erectile function over time could not be assessed.

Finally, Kupelian and colleagues (2010) investigated the relative contributions of modifiable risk factors to ED in a follow-up study of the BACH survey and obtained results consistent with previously published data. The authors found that increased duration and intensity of smoking were associated with greater risk of ED.

Dose-Response Relationships

Several epidemiologic analyses have explored relationships between the amount of exposure to tobacco and the extent of ED. Among currently smoking veterans, the Vietnam Experience Study of 1985–1986 did not show any relationship between ED and the number of cigarettes smoked daily or the number of years of smoking (Mannino et al. 1994). In contrast, in an Italian cross-sectional study, Parazzini and colleagues (2000) found that duration of smoking was associated with an increased risk of ED: for men who smoked less than 20 years, the OR was 1.2 (95% CI, 1.0–7.4); and for men who smoked 20 or more years, the OR was 1.6 (95% CI, 1.1–2.3).

In a case-control study of Canadian men, 50–80 years of age, Polsky and colleagues (2005) investigated the associations between an array of lifestyle and medical factors, including smoking and taking drugs for cardiovascular disease, and ED. The study compared 101 men who had clinically diagnosed ED with 234 controls who had various benign urological conditions. Based on questionnaires completed by participants, the estimated OR was 2.2 (95% CI, 1.17–3.94; p value not reported) for ED in former smokers compared with nonsmokers. The OR for current smokers was not elevated, however, raising the possibility of reverse causation. The study found that those with at least 10 pack-years of smoking had twice the risk of ED as never smokers. The fact that current smoking was not a risk factor for ED was attributed by the authors to the possible bias introduced by the potentially higher likelihood of smokers with symptoms of ED to be encouraged and motivated to quit smoking and thus not be included as smokers in this study.

Interactions with Other Risk Factors, Medications

Several studies have analyzed the combined effects of cigarette smoking and other risk factors in the development of ED. Goldstein and colleagues (1984) examined the clinical characteristics of 19 potent patients who underwent pelvic irradiation for prostate cancer. Fourteen of the 15 patients who displayed diminished erectile capacity

after radiation were cigarette smokers, but only 1 of the 4 who preserved their previous erectile capacity was a cigarette smoker. The strong association of cigarette smoking with erectile impairment after radiation in this study led investigators to propose a synergistic role of smoking, and conceivably other vasculopathic risk factors, in radiation-associated ED.

In the baseline phase of the Massachusetts Male Aging Study, Feldman and colleagues (1994) found that cigarette smoking was not an independent risk factor for ED. In that same study, however, the associations of several risk factors with ED were greatly increased in current cigarette smokers. This synergy was demonstrated for persons who had ED and were being treated for heart disease (from 21% for current nonsmokers to 56% for current smokers), treated for treated hypertension (from 8.5% to 20%), and not treated for arthritis (from 9.4% to 20%) and for persons who were receiving various medications, including cardiac drugs (from 14% to 41%), antihypertensives (from 7.5% to 21%), and vasodilators (from 21% to 52%). Similarly, in an Italian cross-sectional study, smoking increased the AORs for ED associated with diabetes by 13% and with hypertension by 39% (Parazzini et al. 2000).

Shiri and colleagues (2006) investigated the role of vascular disease in causing smoking-related ED in men—50, 60, or 70 years of age—in Finland. This questionnaire-based study assessed responses to a series of three surveys that were mailed to the study cohort (3,143 men in 1994; 2,837 men in 1999; and 2,510 men in 2004). Compared with never smokers who did not develop vascular disease (defined as hypertension, heart disease, or cerebrovascular disease), the study found that the risk of developing ED was approximately three times as high (adjusted incidence density ratio = 3.1; 95% CI, 1.3–7.5) among men who smoked in 2004 and developed vascular disease during the study period. An increased risk of ED was not demonstrated for smokers who did not develop vascular disease (adjusted incidence density ratio = 1.0; 95% CI, 0.5–1.8). The study also found that former smokers who had ED at the start of the study in 1994 had a significantly increased risk of developing vascular disease during the remainder of the study period. The authors concluded that smoking may cause ED because it can cause vascular disease, and they further noted the possible utility of this diagnosis (ED) as a marker of silent vascular disease in former smokers.

Gades and colleagues (2005) conducted a questionnaire-based study to evaluate the association between smoking and ED in a randomly selected cohort of 1,329 men, 40–79 years of age, from Minnesota. The authors found that among smokers, the OR for ED decreased with increasing age. In comparisons with never

smokers and former smokers in the same age groups, current smokers in their forties had the highest odds of ED (OR = 2.74; 95% CI, 0.44–16.89), followed by smokers in their sixties (OR = 1.70; 95% CI, 0.82–3.51), fifties (OR = 1.38; 95% CI, 0.51–3.74), and seventies (OR = 0.77; 95% CI, 0.27–2.21). The declining effect with increasing age may reflect the increasing prevalence of risk factors for ED other than smoking at older ages.

Effects of Smoking Cessation

Forsberg and colleagues (1989) presented case reports of two cigarette smokers, 20 and 27 years of age, whose ED returned in concordance with improved results for penile vascular tests following cessation. In a study by Elist and colleagues (1984), 8 of 20 men with ED who had smoked one to two packs of cigarettes per day for at least 5 years recovered the ability to achieve functional erections after abstaining from cigarette smoking for 6 weeks. In this study, objective testing criteria confirmed that 7 responders recovered normal erectile activity from levels that were abnormal at baseline.

Population-based reports offer additional perspectives on the premise that modifying smoking behavior affects the occurrence of ED. For example, the Vietnam Experience Study of 1985–1986 determined that the prevalence of ED was comparable between former smokers and nonsmokers and that the prevalence estimates for those groups were significantly lower than those for current smokers (Mannino et al. 1994). Similarly, the longitudinal phase of the Massachusetts Male Aging Study determined that incident ED was no more likely among former smokers than among nonsmokers, but it was more common in current smokers than in former smokers and nonsmokers (Feldman et al. 2000).

These results from population-based studies could suggest that smoking cessation leads to a recovery of functional erection status. However, this conclusion is challenged by results from the prospective evaluation of men who discontinued smoking during the almost 9-year follow-up period of the Massachusetts Male Aging Study (Feldman et al. 2000). According to that analysis, the covariate-adjusted incidence of ED was not significantly reduced after smoking cessation (p = 0.28). The nature of the population in the Massachusetts study merits emphasis, however, because the men who quit smoking had started at an early age (mean age: 16.6 years) and had accumulated substantial lifetime exposure to tobacco smoke before quitting (mean pack-years: 39.4). Data from other studies help to refine our understanding of the effects of cessation on ED. For example, Derby and colleagues (2000b) found that cessation during middle age—after a

significant lifetime exposure to cigarette smoke—may fail to modify the occurrence of ED because long-term vascular effects of smoking may persist after cessation.

Travison and colleagues (2007) analyzed the data from the Massachusetts Male Aging Study and found that smoking and self-assessed health status were associated with progression only. Specifically, the odds of a progression of ED doubled with smoking status. The study did not reveal a corresponding decrease in likelihood of remission (i.e., by stopping smoking). The authors concluded that abstaining from smoking may help to protect against the progression of ED, but smoking has little effect on the likelihood of remission once ED begins.

Evidence Synthesis

Mounting evidence indicates that cigarette smoking constitutes a risk factor for ED. The consistency of such a relationship is supported by case series, cross-sectional, and prospective population-based studies that have evaluated rates of ED among smokers. The population-based studies afford a more accurate observational basis for this assessment than do uncontrolled case series, but the number of such studies is limited. Prospective cohort studies are particularly critical in providing evidence not subject to the various limitations of cross-sectional studies. Their results confirm the temporality of the association (i.e., smoking appropriately antedates ED). Several studies demonstrate an increased risk with greater exposure to cigarette smoke. Observational findings demonstrate that cessation of cigarette smoking may lead to a recovery of erectile function only if the discontinuation occurs after a limited extent of lifetime smoking.

The coherence of the relationship between smoking and ED is supported by studies that indicate plausible mechanisms for such a connection. The acute deleterious effects of smoking on erectile function result at least in part from nicotine in cigarette smoke. Nicotine pharmacologically induces vasospasm of penile arteries, thus altering the dynamics of the local blood flow required for erection. The chronic deleterious effects of smoking on erectile function result from impaired vascular physiology of the erectile tissue, as evidenced by degenerative morphologic changes in the tissue of smokers. Studies in animals point to damaging effects of smoking on tissue-dependent erection regulatory factors. In sum, several lines of evidence support the inference of a causal relationship between cigarette smoking and ED.

Conclusion

The evidence is sufficient to infer a causal relationship between smoking and erectile dysfunction.

Implications

The clinical studies and basic scientific research summarized in this section support a causal relationship between cigarette smoking and ED. The current knowledge about the condition affirms recommendations for quitting smoking to limit the risk of ED. Promoting abstinence from smoking to prevent ED is clinically appropriate.

Evidence Summary

This chapter summarizes the consequences of smoking across a wide array of adverse reproductive health effects both immediate and longer-term. The evidence reviewed shows that smoking affects the likelihood of pregnancy, the outcome of pregnancy, and the future health of the child.

This report returns to the topic of smoking during pregnancy and congenital malformations. The 2004 Surgeon General's report found the evidence to be suggestive to infer a causal relationship between maternal smoking during pregnancy and orofacial clefts. Substantial additional evidence supports the strengthening of this conclusion to sufficient. For other congenital abnormalities, the evidence was not sufficient to infer causality and was quite limited in extent for some.

Evidence reviews were also conducted on a number of neurobehavioral disorders, including disorders not included in previous reports: ADHD, ODD, conduct disorder, anxiety, depression, Tourette syndrome, schizophrenia, and intellectual disability. Data show consistent support for an association between maternal prenatal smoking and childhood disruptive behavioral disorders, and ADHD in particular; but the results are attenuated when adjusted for sociodemographic and psychosocial factors. The evidence was determined to be suggestive but not sufficient to infer causality. Additional studies are needed that prospectively collect data on smoking exposure during pregnancy and control for relevant confounders.

Studies of maternal prenatal smoking and anxiety and/or depression did not show significant associations in either children or adult offspring, although a small number of studies found associations with internalizing symptoms in children at ages ranging from 2–14 years of age; positive findings in children at 2 years of age were no longer present by 5 years of age. Additional prospective, longitudinal studies are needed to understand the association of maternal prenatal smoking and both symptoms and diagnoses of anxiety and depression throughout childhood and into adolescence. The evidence was determined to be inadequate to infer a causal relationship.

Data on prenatal smoking and Tourette syndrome and schizophrenia were very limited and did not consistently show significant associations. The evidence for these two outcomes was determined to be inadequate to infer a causal relationship.

Studies of smoking and intellectual disability in child and young adult offspring have not shown significant associations after adjustment for maternal education, IQ, and/or other sociodemographic variables. Evidence was determined to be inadequate to infer a causal relationship; however, additional prospective studies that collect and control for potential confounding variables could benefit the field.

New evidence on two other reproductive health outcomes, EP and SAB, has strengthened support for a causal association for EP and is suggestive of an effect on SAB.

Finally, this report finds the evidence sufficient to infer that smoking adversely affects male reproductive functioning. The 2004 Surgeon General's report found the evidence to be suggestive, but additional experimental and observational studies have been carried out and there are several documented pathways by which smoking impairs male sexual functioning. The 2004 report found that smoking reduced fertility. Thus, for couples who smoke and want to have children, their smoking decreases the likelihood of a successful pregnancy.

Chapter Conclusions

Congenital Malformations

The evidence is sufficient to infer a causal relationship between maternal smoking in early pregnancy and orofacial clefts.

1. The evidence is suggestive but not sufficient to infer a causal relationship between maternal smoking in early pregnancy and clubfoot, gastroschisis, and atrial septal heart defects.

Neurobehavioral Disorders of Childhood

1. The evidence is suggestive but not sufficient to infer a causal relationship between maternal prenatal smoking and disruptive behavioral disorders, and attention deficit hyperactivity disorder in particular, among children.

2. The evidence is insufficient to infer the presence or absence of a causal relationship between maternal prenatal smoking and anxiety and depression in children.

3. The evidence is insufficient to infer the presence or absence of a causal relationship between maternal prenatal smoking and Tourette syndrome.

4. The evidence is insufficient to infer the presence or absence of a causal relationship between maternal prenatal smoking and schizophrenia in her offspring.

5. The evidence is insufficient to infer the presence or absence of a causal relationship between maternal prenatal smoking and intellectual disability.

Ectopic Pregnancy

1. The evidence is sufficient to infer a causal relationship between maternal active smoking and ectopic pregnancy.

Spontaneous Abortion

1. The evidence is suggestive but not sufficient to infer a causal relationship between maternal active smoking and spontaneous abortion.

Male Sexual Function

1. The evidence is sufficient to infer a causal relationship between smoking and erectile dysfunction.

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Chapter 10
Other Specific Outcomes

Sections of this chapter on the health consequences of smoking are accompanied by evidence tables detailing the studies that were used to evaluate the evidence to assess causality. A supplement to this report is provided that contains these tables. The tables included in the supplement are indicated with an "*S*" where they are called out in the text.

Introduction

This chapter addresses evidence on smoking and health effects over a range of specific diseases and nonspecific but adverse consequences. Previous Surgeon General's reports have reviewed age-related macular degeneration, dental diseases, and diabetes. Since the last reviews were carried out on those topics, additional significant findings have been reported. Building on the reviews in the 2004, 2006, and 2010 reports, this chapter reassesses the state-of-the-evidence for these conditions giving consideration to more recent publications. Smoking and immunity, rheumatoid arthritis and systemic lupus erythematosus, and inflammatory bowel disease are being covered for the first time in this Surgeon General's report.

Eye Disease: Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is the leading cause of blindness for persons 65 years of age and older in the United States (Congdon et al. 2004). Researchers have sought to identify modifiable risk factors and to test strategies to modify the natural history of AMD, but preventive therapy is not available for early AMD. Located at the center of the optical axis, the macula is a component of the retina and contains the fovea, a highly specialized area that is responsible for high-resolution vision. The retina consists of neural tissues, including photoreceptors, which convert energy from visible light to electrical signals and sends these signals to the brain for processing. Photoreceptors (rods and cones) in the retina have high metabolic requirements; they replace their outer segments daily. The metabolic functions of the retina are supported by retinal pigment epithelium (RPE), which phagocytizes an estimated 25,000–30,000 outer segment membranes per day. This high rate of activity is made possible by an exchange of nutrients and the removal of waste within the retinal blood supply through the choriocapillaris. RPE and its anchor, Bruch's membrane, form a blood-retinal barrier to this exchange. Thus, the complex of choriocapillaris, RPE, and Bruch's membrane serves as the nutritional source for the sensory retina. Researchers hypothesize that AMD stems from changes in each of the tissues in this complex.

AMD is an umbrella term for a variety of degenerative changes in the macula. The disease's early stages are characterized by pigmentary disturbances, development of drusen (deposits of extracellular material), and atrophic changes. The late stages are characterized by RPE atrophy; loss of photoreceptors (which occurs in atrophic AMD or geographic atrophy [GA]); and, less commonly, neovascular (NV) AMD. With NV AMD, new but unstable blood vessels develop in the choroid and grow under or through the RPE via breaks in Bruch's membrane. Leakage from these NV membranes may lead to detachment of RPE, hemorrhage, and the later formation of a disciform scar. The late stages of AMD are associated with loss of vision—classically the loss of central vision, which is critical for such activities as reading and performing near work (such as typing, cooking, and sewing).

With the discovery of highly significant associations between AMD and several complement pathway-associated genes, a coherent story for inflammation as the model for AMD pathogenesis is emerging (Anderson et al. 2010). Morphologic changes associated with AMD include thickening of Bruch's membrane, the formation of basal deposits within Bruch's membrane, and accumulation of drusen. Drusen accumulate within Bruch's membrane in the same area in which basal deposits form. A wide variety of complement-related molecules have been reported in

drusen; some authorities regard these molecules as the byproduct of chronic local inflammatory processes. The dysregulation of the complement cascade is likely an early predisposing step in the development of drusen, but the role of the complement in advanced AMD, either NV or GA, is not yet clear. At least two types of drusen are recognized clinically based on their appearance. Small, hard drusen are a common feature of aging; while large, soft drusen are commonly found with aging, but are also a risk factor for the development of advanced AMD. Drusen can appear and disappear over time, however, making them unstable biomarkers for risk of AMD (Bressler et al. 1995; Klein et al. 1997). Moreover, most persons with large, soft drusen do not develop advanced AMD (Klein et al. 1997), and the epidemiologic patterns associated with advanced AMD may not be the same as those for drusen-defined early AMD. Thus, the specific phenotypes of early AMD that are most likely to progress to NV or GA AMD need further characterization. This lack of specificity should be considered when interpreting evidence of the association between smoking and early versus advanced AMD.

Conclusions from Previous Surgeon General's Reports

The 2004 Surgeon General's report on smoking and health, based on research available at the time, offered the following conclusions (U.S. Department of Health and Human Services [USDHHS] 2004):

1. The evidence is suggestive but not sufficient to infer a causal relationship between current and past smoking, especially heavy smoking, with risk of exudative (neovascular) age-related macular degeneration.

2. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and atrophic age-related macular degeneration.

Biologic Basis

The inflammation model of AMD posits that smoking, against a background of genetic susceptibility, leads to changes in RPE, Bruch's membrane, and choroidal endothelium and generates a local inflammatory response (Wang et al. 2009a). This response is dysregulated and ongoing in genetic-susceptible persons who lack appropriate modulating factors, leading to lysis of bystander cells and the development of advanced AMD (Anderson

et al. 2010). Oxidative stress is one of the primary proposed mechanisms for smoking-related damage to retinal structures (Rahman and MacNee 1996); cigarette smoke is a strong oxidant, and smoking results in systemic oxidative stress. Immunohistochemical evidence shows oxidative byproducts of photoreceptor fatty acids in the outer segments of photoreceptors in RPE and in autoantibodies to these byproducts in AMD (Gu et al. 2003). Oxidative stress—the result of damage done by free radicals to protein and lipids and, possibly, to DNA—may contribute to cell injury within RPE and apoptosis, a key histopathologic finding in GA AMD (Del Priore et al. 2002). The decreased ability of RPE to phagocytize cellular products leads to the accumulation of debris in Bruch's membrane; this debris interferes with the exchange of nutrients between RPE and the choriocapillaris. Upregulation of the complement alternative pathway is a proposed mechanism for the development of AMD; smoking alters the ability of the *CFH* gene to bind with the *C3* gene, which may activate the alternative pathway of the complement (Kew et al. 1985).

The macula is a particularly attractive target for oxidative stress because of its high exposure to light, high metabolic rate, and high concentrations of fatty acids. But the macula is also rich in antioxidative protective mechanisms, including an array of antioxidant nutrients, and enzymes and melanin. Smoking, however, may increase oxidative stress on the macula by robbing it of its defenses (Hammond et al. 1996) and reducing macular pigment and plasma levels of antioxidants.

Vascular insufficiency may also figure in, or at least be a contributing mechanism to, the pathogenesis of AMD. Changes in the choroidal circulation may impair the ability of RPE to dispose of waste substances, leading to the accumulation of waste material. The rate and volume of blood flow through the choriocapillaris is high in response to the demands of the pigmented epithelium and photoreceptors, but smoking can alter choroidal blood flow (Bettman et al. 1958). Smoking also affects the vasculature through increased platelet adhesions and hypoxia from elevated levels of carboxyhemoglobin, which may add to the stimulation of new vessel growth.

Highly suggestive evidence for a link between smoking and AMD comes from studies of mice exposed to chronic smoke versus those raised in filtered air. In such comparisons, mice exposed to smoke had thicker Bruch's membranes, more basal laminar deposits, and relatively higher percentages of apoptotic RPE cells and immunolabeling for markers of oxidative damage (Wang et al. 2009b; Cano et al. 2010)—all signs of early AMD.

In conclusion, multiple pathways are likely responsible for the degenerative changes in the macula with

age, and a reasonable basis exists for presuming that the effects of smoking may operate through one or more of these pathways.

Description of the Literature Review

For this update, the National Library of Medicine's PubMed service was used to search for articles about smoking and AMD. The first search yielded 362 results using the terms "macular degeneration" AND "smok*" (limited to English and humans). The second search yielded an additional 280 results using the terms "age-related macular degeneration" OR "senile macular degeneration" OR "age related maculopathy" OR "choroidal neovascularization" (CNV) OR "drusen" OR "geographic atrophy" OR "atrophic macular degeneration" AND ("cigarette" OR "smoking" OR "tobacco" OR "smok*"). Both searches were completed as of March 1, 2010. The reference list of each article was reviewed to determine whether any article had been missed by the two searches. In all, this discussion includes 84 articles that were not used during the previous review by the Surgeon General in 2004.

Epidemiologic Evidence

In assessing the relationship between AMD and smoking, there are several methodologic issues to be considered. First, advanced AMD occurs primarily in older persons; indeed, an estimated 12% of the U.S. population 80 years of age or older has advanced AMD (Friedman et al. 2004). Second, the life expectancy of smokers is less than that of nonsmokers, and so the selective survival of smokers into the at-risk age range is an issue. Third, because relatively few older smokers could be recruited into studies or otherwise included in these investigations, the power to detect associations with smoking in all but the largest studies is limited. The limited numbers also reduce the power to detect incident cases among smokers in prospective studies and may be a source of bias, because smokers and those with vision loss are often less likely to return for follow-up.

One way to circumvent the problem of studying clinically symptomatic AMD would be to assess the association between smoking and precursor lesions or early AMD, but these earlier stages of AMD are imperfect surrogates for risk of advanced AMD, the outcome of interest.

For example, in a large clinical trial, the best predictors of 5-year incidence of advanced AMD were very large areas affected by drusen with increased retinal pigment or a large area of depigmentation with drusen; even eyes affected to this degree, however, had only a 20% chance of progression to advanced AMD within 5 years (Davis et al. 2005). Thus, some risk factors may be misclassified when researchers use early or intermediate AMD lesions as surrogates for advanced AMD, and the associations observed between smoking and early lesions and those between smoking and advanced AMD are unlikely to be consistent.

These potential difficulties notwithstanding, most of the relevant studies have found an increased risk between some measures of smoking and clinical signs of AMD. However, more evidence is available on the association between smoking and intermediate or advanced AMD than on the association between smoking and signs of early AMD, and the specific clinical manifestations of early or intermediate AMD associated with smoking differ among the studies.

Tables 10.1*S*–10.4*S* summarize evidence by type of study: (1) case-control (Table 10.1*S*), (2) cross-sectional (Table 10.2*S*), (3) prospective cohort (Table 10.3*S*), and (4) other types (Table 10.4*S*). Of these various study designs, data from cohort studies are most informative because by repeatedly observing the development of AMD and its precursors, data from prospective cohorts are informative on the association between smoking and AMD across its natural history. The recent wave of case-control studies has focused on identifying genetic determinants of risk for AMD. Of the numerous case-control studies that have been reported, the earliest was conducted in 1979. Some of these studies have small samples and limited statistical power, and the basis for establishing the presence of AMD has differed across the studies. Regardless, most of the studies found significant associations between current or ever smoking and AMD. In addition, dose-response relationships were found with several measures of smoking, including duration and pack-years.[1] Several other studies have not found any such association.

Prospective cohort studies, which have addressed both early and late AMD, offer the most substantial evidence. In one major population-based study (the Beaver Dam Eye Study in Wisconsin), smoking status and pack-years at baseline were not associated with any of the signs of early AMD. However, in the 5-, 10-, and 15-year follow-ups, current smoking at baseline was related to the incidence of large, soft drusen—with significant dose-response relationships observed at the 5- and 10-year follow-ups with pack-years at baseline (Klein et al. 1993, 1998, 2002,

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[1]The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

2008a). A population-based cohort study in Australia that used the same system for grading AMD found no relationship between smoking and early signs of AMD at baseline, but at 5-year follow-up reported increased risk for incident retinal pigment abnormalities with current smoking at baseline (but with no dose-response relationship and increased risk was only found among men) (Mitchell et al. 2002). The 10-year follow-up of the same cohort did not confirm this finding (Smith et al. 1996; Mitchell et al. 2002; Tan et al. 2007). A longitudinal study in an older population in Salisbury, Maryland, found that current smoking was a risk factor for progression to large drusen or pigmentary abnormalities (Chang et al. 2008).

For early-stage AMD, several cross-sectional studies have produced relevant but mixed results. One cross-sectional study of Latinos found a relationship between smoking, particularly smoking for 5 or more pack-years, and increased odds of soft drusen (Fraser-Bell et al. 2006). Another cross-sectional study, which included Mexican Americans, did not find a relationship between current smoking and soft drusen (Klein et al. 1999). Other cross-sectional, population-based studies or longitudinal cohort studies have not found any relationship between smoking and early signs of AMD (Delcourt et al. 1998; Arnarsson et al. 2006; Wong et al. 2006; Chakravarthy et al. 2007; Klein et al. 2007; Cackett et al. 2008; Chang et al. 2008; Baker et al. 2009; Coleman et al. 2010). Using smoking status as the only baseline metric makes it difficult to interpret analyses of prospective studies, because smoking status will likely change over time and may need more complex modeling.

Strong evidence from several studies in widely differing populations suggests that smoking is associated with advanced AMD, both NV and GA. In the Australian prospective study, both the baseline results, and the 10-year follow-up, identified an association between current smoking and increased risk of NV AMD and GA AMD (Smith et al. 1996; Tan et al. 2007). A relationship was not found, however, with pack-years. Other cross-sectional, population-based studies have found a dose-response relationship between pack-years of smoking and advanced AMD. Studies in Holland, France, and Singapore, for example, reported increased odds of NV AMD with greater pack-years (Vingerling et al. 1996), and studies in France, Japan, and Singapore related pack-years with advanced AMD (Delcourt et al. 1998; Cackett et al. 2008; Yasuda et al. 2009). Notably, a large case-control study across multiple sites in Europe found increased odds of NV AMD and GA AMD with current smoking and a dose-response relationship between pack-years and NV AMD (Chakravarthy et al. 2007). In the Southeastern United States, a large clinic-based sample of intermediate and severe AMD cases,

with ethnically matched controls, found a dose-response relationship between pack-years and intermediate AMD and NV AMD (Schmidt et al. 2005).

Two large prospective cohorts of health professionals in the United States, the Nurses' Health Study (NHS) (women) and the Physicians' Health Study (men), found significantly greater risks of AMD (defined as clinical manifestations of AMD causing loss of vision) associated with increased pack-years (Christen et al. 1996; Seddon et al. 1996). In the NHS, the cases were either NV AMD or GA AMD, while in the Physicians' Health Study, about one-third of AMD cases were advanced. A large case-control study using the United Kingdom General Practice Database identified 18,007 persons with physician-diagnosed AMD (not further specified); these persons were compared to 86,169 controls who were matched for age, gender, and the general practice in which they were enrolled (Douglas et al. 2007). This study found an increased risk of AMD with current smoking (odds ratio [OR] = 1.17; 95% confidence interval [CI], 1.11–1.23) and former smoking (OR = 1.14; 95% CI, 1.09–1.20). These lower risks may reflect the uncertainty of the AMD phenotype in the database. In the United States, a study of male twins found an increased risk of AMD (not further categorized but including advanced AMD and some intermediate grades of AMD) with current smoking that bordered on statistical significance (OR = 1.91; 95% CI, 0.99–3.66) (Seddon et al. 2006a).

In a study of 104 families (also in the United States) in which siblings were discordant for CNV and the normal siblings were past the age of diagnosis of the affected sibling, Kim and colleagues (2008a) found an increased risk of CNV with 10 or more pack-years (OR = 1.97; 95% CI, 1.12–3.46). Another case-control study, this one of persons 75 years of age or older from the Medical Research Council Trial of Assessment and Management of Older People in the Community in the United Kingdom, found a relationship between current smoking and advanced AMD (Evans et al. 2005; Khan et al. 2006). In a study by Khan and colleagues (2006), a total of 40 pack-years or more was associated with increased odds of NV AMD and GA AMD. The Age-Related Eye Disease Study in the United States, a clinical trial of the use of antioxidants and vitamins and the risk of AMD, had a large population of cases with a variety of signs of AMD and an average 6.3 years of follow-up to examine progression to advanced AMD. Incident NV AMD in the Age-Related Eye Disease Study was related to having more than 10 pack-years (OR = 1.55; 95% CI, 1.15–2.09), as was incident central GA AMD (OR = 1.82; 95% CI, 1.25–2.65) (Clemons et al. 2005). The Complications of Age-related Macular Degeneration Prevention Trial looked at the prevention of vision loss in CNV and GA AMD. After

a 5- to 6-year follow-up, the risk of CNV was greater in current smokers (OR = 1.98; 95% CI, 1.16–3.39) than in never smokers; the increased risk was not seen in smokers who had quit at an indeterminate time. The study found a modestly increased risk of GA AMD with current smoking that failed to reach statistical significance (Complications of Age-related Macular Degeneration Prevention Trial Research Group 2008).

Inconsistent findings were observed only in the Beaver Dam Eye Study, the prospective, population-based cohort study in Wisconsin, in which cross-sectional risks for NV AMD were found for both current smoking and total pack-years among women at baseline. The subsequent longitudinal observations failed to confirm the findings (Klein et al. 1993, 1998, 2002, 2008a). Many of the more recent reports have addressed the genetic basis of AMD, including possible genetic determinants of the risk for AMD associated with smoking. As summarized in Tables 10.1*S*–10.4*S*, researchers have accumulated compelling evidence for the relationship of genetic variants to advanced AMD and have identified gene-smoking interactions for advanced AMD. In most of these studies, however, smoking has been categorized as "current," "past," or "never" at best, or as "ever" versus "never." Although smoking is a significant, independent risk factor for advanced AMD, many studies have not found evidence for an interactive effect of smoking with the genetic variants under investigation (Schmidt et al. 2005; Seddon et al. 2006b; Sepp et al. 2006; DeAngelis et al. 2007; Schaumberg et al. 2007; Scott et al. 2007; Tam et al. 2008; Wang et al. 2008a, 2009b,c; Despriet et al. 2009; Park et al. 2009). Smoking is also a risk factor for the progression of AMD (Baird et al. 2008), but many of the studies noted above were underpowered to detect gene-smoking interactions.

Four studies found evidence for an interaction of smoking with a genetic factor in regard to risk for AMD:

- Schmidt and colleagues (2006) investigated the joint effect of smoking and two susceptibility genes for AMD and found that (a) smoking did not increase the risk for AMD in the absence of high-risk genotypes for both genes, and (b) one allele appeared to exert the strongest effect in smokers. However, another study did not find evidence for an interaction with this gene while finding an independent effect of smoking on AMD (Francis et al. 2007).

- Chu and colleagues (2008) found in a Han Chinese population an interaction between being a heterozygote for a variant in the *CFH* gene and smoking and increased risk of NV AMD but not for homozygotes. The null result in homozygotes suggests that the

interaction they found might have been statistically significant by chance.

- Tuo and colleagues (2008)—using multiple sources of cases from a clinical trial, case series, and population-based study—found a significant interaction between ever smoking and a variant in the *HTRA1* gene. Together, the risk variant and smoking increased the odds of AMD to 17.71 (95% CI, 7.49–41.88) using never smoking and absence of the risk variant as the referent. The study also found significant independent effects of ever smoking.

- Spencer and colleagues (2007) found a protective effect for intermediate and advanced AMD considered together in smokers with a haplotype spanning the *CFH* gene, but did not observe a main protective effect for the gene per se. The association between smoking and increased risk of AMD was significant in the interaction model.

Taken together, these studies provide strong evidence for a causal relationship between smoking and AMD. Further work is needed on the possible interactions of smoking with high-risk genetic polymorphisms.

The evidence suggests that current smokers have a greater risk of advanced AMD than former smokers, and some studies have found that former smokers have a significantly greater risk of advanced AMD than never smokers (Eye Disease Case-Control Study Group 1992; Christen et al. 1996; Seddon et al. 1996, 2006a; Vingerling et al. 1996; Delcourt et al. 1998; McCarty et al. 2001; Mitchell et al. 2002; Evans et al. 2005; Schmidt et al. 2005; Fraser-Bell et al. 2006; Khan et al. 2006; Chakravarthy et al. 2007; Francis et al. 2007; Tan et al. 2007; Cackett et al. 2008; Complications of Age-related Macular Degeneration Prevention Trial Research Group 2008). The relationship appears to have depended, at least in part, on time since quitting smoking. In cases in which a person had quit smoking for 20 years or more, his or her risk for AMD was no different than that of a never smoker (Christen et al. 1996; Vingerling et al. 1996; Delcourt et al. 1998; Evans et al. 2005; Khan et al. 2006; Chakravarthy et al. 2007), but such risk was elevated in most studies in which quitting time was less than 20 years. In the NHS, risk for AMD did not differ between current smokers and those who had quit smoking for 15 years or more (OR = 0.9; 95% CI, 0.6–1.3) (Seddon et al. 1996). The prospective cohort study in Australia found that, compared with never smokers, the relative risk (RR) of incident GA AMD was 2.9 (95% CI, 0.9–9.4) for those who had quit smoking for 17 years or more and 4.4 (95% CI, 1.2–15.8) for those who had quit smoking for less than 17 years (Tan et al. 2007).

Evidence Synthesis

The additional findings since the 2004 Surgeon General's report strengthen the evidence that current smoking is associated with advanced AMD, both NV and GA. The association is found across a range of populations and through various study designs. Dose-response relationships have been described, and prospective cohort studies have shown increased risk for both the incidence and progression of AMD. The risk persists across a variety of genetic variants that are strongly associated with AMD. Quitting smoking appears to decrease the risk of AMD, but several decades after quitting smoking, the risk remains higher for former smokers than for never smokers. Quitting for at least 20 years is associated with decreased risk of AMD in a few studies. Results from mouse models further bolster these findings, supporting the biological plausibility of a causal association. In studies in which mice were reared in environments contaminated with smoke, the mice showed histologic retinal changes similar to those observed in persons with AMD. The lack of association between smoking and early AMD in epidemiologic studies may result from misclassification that arose from the imprecise designation of early AMD with resulting bias toward the null. Further work on improving early classification systems is warranted. Smoking may also be related to the progression of AMD to the NV form although not related to the onset of early lesions.

Conclusions

1. The evidence is sufficient to infer a causal relationship between cigarette smoking and neovascular and atrophic forms of age-related macular degeneration.

2. The evidence is suggestive but not sufficient to infer that smoking cessation reduces the risk of advanced age-related macular degeneration.

Implications

The role of smoking in causing advanced AMD, which results in loss of vision, is a significant public health concern and a major clinical issue in the United States. The public health burden of AMD will increase because the at-risk population of elderly is growing. Current smoking is a risk factor for advanced AMD and progression of AMD, but further work is needed to determine the extent to which quitting smoking and greater time since quitting smoking attenuate the risk. Because smoking causes both nuclear cataracts (USDHHS 2004) and AMD, it is important for ophthalmologists, optometrists, and other health care providers to assess and address the smoking status of their patients.

Dental Disease

Diseases of the teeth and their supporting structures have a significant impact on social, economic, and personal well-being. In 2009, more than $102 billion was spent on dental care in the United States (National Center for Health Statistics 2012), and acute dental conditions resulted in an estimated 1.6 million days of missed school and 2.4 million days of lost work annually (USDHHS 2000).

Conclusions from Previous Surgeon General's Reports

The 2004 Surgeon General's report on the health consequences of smoking reviewed the evidence on the association between active smoking and two major dental diseases: periodontitis and caries. The report concluded that the evidence was sufficient to infer a causal relationship between smoking and periodontitis. Data on the association between smoking and caries were much more limited and inconsistent. Thus, the 2004 report concluded that the evidence was insufficient to infer the presence or absence of a causal relationship between smoking and coronal caries (caries affecting the crown and not the root portion of the tooth). The report also concluded that the evidence was suggestive but not sufficient to infer a causal relationship between smoking and caries of exposed root surfaces.

This section updates the earlier review, covering the full scope of evidence on the relationships between active and passive smoking and dental caries through 2011. It also considers associations between smoking and dental implants through 2010.

Smoking and Dental Caries

Dental caries is a multifactorial disease marked by the localized destruction of susceptible hard tissues by acidic byproducts from bacterial fermentation of dietary carbohydrates (Selwitz et al. 2007). The disease process starts with microbiological shifts in the complex bacterial biofilm (dental plaque) that covers the surface of a tooth. The incidence of dental caries is affected by the flow and composition of saliva, exposure to fluoride, consumption of dietary sugars, and patterns of preventive behaviors (e.g., daily brushing with fluoride toothpaste). If left untreated, caries can lead to incapacitating pain, bacterial infection that leads to pulpal necrosis, tooth extraction, loss of dental function, and even acute systemic infection.

To measure the prevalence of dental caries affecting the enamel covered crowns of the teeth, most epidemiologic studies conducted during the past 70 years have used some variation of the DMF index (Klein et al. 1938), a count of the number of permanent teeth that are decayed (D), missing due to caries (M), or filled (F). The DMF index is a measure of disease severity, not just the prevalence of caries. The DMF index has its variants: DMFT, for which "T" stands for "permanent teeth"; and DMFS, for which "S" stands for tooth surfaces. The "M" component of the index may be omitted in adult studies because of the uncertainty as to why a tooth is missing; therefore, some studies report DFT or DFS scores. Other studies report the components of DMFT individually, such as DT, FT, and MT. Root-surface caries (R) is almost always scored and reported separately from coronal caries and is usually designated as RDFS or RDS (the "M" component is not reported for root-surface caries). For primary teeth (i.e., deciduous teeth or baby teeth), the index uses lowercase letters to designate teeth or tooth surfaces that are decayed, missing due to dental caries, or filled (i.e., dmft or dmfs).

Biologic Basis

Several mechanisms support a possible causal association between active smoking and dental caries. Perhaps the most consistent explanation, other than causation among studies that have found a relationship between smoking and caries, is that smokers tend to practice less frequent or less effective oral hygiene and plaque removal (Preber and Kant 1973; Macgregor and Rugg-Gunn 1986; Andrews et al. 1998).

Findings on biological mechanisms also offer explanations for associations between smoking and caries. Several studies found that active smoking might lower the pH or reduce the buffering capacity of saliva (Heintze 1984; Parvinen et al. 1984), which could impair its function as a protective factor against demineralization of tooth enamel (Edgar and Higham 1996). In contrast, however, one review concluded that smoking increases the flow rate of saliva (Macgregor 1989), which raises pH and increases the calcium concentration of saliva (ten Cate 1996). These factors tend to favor remineralization of the enamel. Thus, smoking may actually exert a protective effect against caries. Overall, the evidence is inconclusive as to whether smoking plays a major role in the impairment of salivary function that would be relevant to the development of dental caries.

Investigators also offer several hypotheses for the biological mechanisms through which maternal smoking and exposure to secondhand smoke may increase the risk for dental caries in children. Based on an in vitro study that found tobacco extract promotes the growth of cariogenic *Streptococcus mutans* (Lindemeyer et al. 1981) and studies that suggested cariogenic bacteria are transmittable in saliva from mother to infant (Ettinger 1999). Aligne and colleagues (2003) speculated that mothers who smoke may be more likely than nonsmoking mothers to transmit cariogenic bacteria to their children. Aligne and colleagues (2003) speculated that the immunosuppressive properties of secondhand tobacco smoke (Edwards et al. 1999) may increase the risk for dental caries. In addition, some evidence indicates that maternal smoking during pregnancy may disturb tooth formation in infants (Heikkinen et al. 1997) and could increase later susceptibility to dental caries (Ayo-Yusuf et al. 2007).

Behavioral factors may also affect the association between active or secondhand smoke and caries; such an association may be partly due to lower rates of dental care utilization among smokers than nonsmokers in many developed nations (Mucci and Brooks 2001; Netuveli et al. 2006; Yusof et al. 2006; Millar and Locker 2007; Ohi et al. 2009). In particular, differences in patterns of seeking dental care by smoking status may partially explain why smokers may be more likely than nonsmokers in some studies to have untreated caries but less likely to have evidence of treated disease.

Description of the Literature Review

The 2004 Surgeon General's report on the health consequences of smoking included a review of epidemiologic studies from the National Library of Medicine's PubMed database published in the English language from 1965–2000 (USDHHS 2004). This review updates that 2004 report by using the same Medical Subject Headings (MeSH) ("smoking," "tobacco," "dental caries," and "tooth demineralization") to search for English-language articles

published from 2000–2011. Reference lists from published studies and review articles were searched to identify additional studies not in PubMed.

Epidemiologic Evidence

Active Smoking and Dental Caries

Table 10.5*S* summarizes the findings from 14 cross-sectional studies, 1 cohort study, and 1 case-control study published between 2005–2011 that met the selection criteria for this report. These 16 studies were conducted in 11 countries. Of the 14 cross-sectional studies, 4 studies (Dye et al. 2007; Ojima et al. 2007; Iida et al. 2009; Skudutyte-Rysstad et al. 2009) presented data on the estimated proportion of the population that had untreated decay at the time of the survey. Two cross-sectional studies (Dye et al. 2007; Du et al. 2009) reported the proportion of the population that had experienced either treated or untreated dental caries at some time. The five studies that presented prevalence data by smoking status (Dye et al. 2007; Ojima et al. 2007; Du et al. 2009; Iida et al. 2009; Skudutyte-Rysstad et al. 2009) found a significantly greater prevalence of untreated caries among current smokers than never smokers. In a nationally representative survey of the U.S. population, Dye and colleagues (2007) found no significant difference by smoking status in the prevalence of experience with caries among adults, but prevalence was very high for all groups (91.2–92.8%). Ten of the 14 cross-sectional studies presented data for some variation or component of the DMF index: 8 of the studies separately considered the mean number of DT or DS (in addition to reporting on DMFT or DMFS), and 2 of the studies reported on only mean DMFT or DMFS. Seven of the 8 studies that reported data on mean DT or DS found a significantly higher mean number of DT or DS among current smokers than among nonsmokers (Birnboim-Blau et al. 2006; Dye et al. 2007; Hamasha and Safadi 2008; Roberts-Thomson and Stewart 2008; Vellappally et al. 2008; Kumar et al. 2010; Campus et al. 2011); 1 study found no difference in mean DT by smoking status (Aguilar-Zinser et al. 2008). However, in 3 of the 7 studies (Birnboim-Blau et al. 2006; Dye et al. 2007; Hamasha and Safadi 2008) that found a significant higher mean number of DT or DS among current smokers than nonsmokers, current smokers also had significantly fewer filled teeth or tooth surfaces and significantly more missing teeth or tooth surfaces than nonsmokers. Such a pattern suggests that some of the differences in the severity of caries between smokers and nonsmokers may be due to differences in their utilization of dental services rather than differences in rates of disease.

In the one cohort study, a 3-year prospective Swedish study of girls 12 years of age at baseline (Bruno-Ambrosius et al. 2005), girls who smoked in eighth grade (the end of the second year of the study) experienced significantly higher 3-year increments in DMFS than girls who did not smoke (7.7 versus 1.9; p <0.001).

In the one case-control study, Ditmyer and colleagues (2010) identified case and control groups from the same cross-sectional survey. This study compared the odds of current smoking among adolescents with four or more DMFT (case group) with the odds of current smoking among those with no history of caries in their permanent dentition (control group). Adolescents in the case group were significantly more likely than those in the control group to be current smokers (OR = 1.85; 95% CI, 1.68–2.06).

Secondhand Smoke and Dental Caries

Previous reports from the Surgeon General have not reviewed the possible association between dental caries and secondhand smoke. To establish the literature base for this review, investigators searched the PubMed database for English-language papers that were published on the topic from 1965–2011. The search used the following MeSH keywords: "tobacco smoke pollution" and "dental caries." Reference lists from published studies and review articles were also searched to identify studies not in PubMed.

The search identified 15 published articles; 3 were excluded because they were either short summaries of an original article published in another journal or were a letter to the editor about a published study. One additional study on the exposure to secondhand smoke and dental caries was identified in the literature search for active smoking and caries. Thus, 13 studies were included in this review (Table 10.6*S*).

Of the 13 studies, 11 used a cross-sectional study design, 1 was a case-control study based on a cross-sectional survey, and 1 was a prospective cohort study. The studies were conducted in seven countries. Most of the studies classified children's exposure (or presumed exposure) to secondhand tobacco smoke by using self-reports from parents or guardians. Most studies defined exposure to secondhand smoke as the presence of one or more smokers in the child's home, but 1 study (Ditmyer et al. 2010) defined it simply as exposure to secondhand smoke. In the study by Aligne and colleagues (2003), children's exposure to secondhand tobacco smoke was based on their level of serum cotinine. Although the studies used a range of case definitions for dental caries, they consistently found that caries were more common among children exposed to secondhand tobacco smoke than among those not exposed, at least for primary dentition.

Evidence Synthesis

The 2004 Surgeon General's report identified 15 studies, published from 1952–1999, that explored the association between smoking and dental caries (USDHHS 2004). Since that review (i.e., from 2000–2011), 16 additional epidemiologic studies were published on this association, thus greatly expanding the extent of the evidence. The literature consistently suggests that smokers experience a greater prevalence of dental caries and have a higher DMF index than persons who have never smoked. Compared with earlier studies, the more recent studies have consistently adjusted for potential confounders. The findings of some cross-sectional studies indicate a dose-response relationship between smoking and dental caries, with the prevalence of caries generally rising with increasing daily consumption of cigarettes (Aguilar-Zinser et al. 2008; Campus et al. 2011).

However, the patterns of untreated and treated disease suggest that at least some portion of the observed difference may be attributable to such factors as differential use of dental services and other health behaviors. In industrialized nations, dental caries and cigarette smoking are more prevalent among persons in lower socioeconomic status (SES) groups than those in higher SES groups (Dye et al. 2007; Centers for Disease Control and Prevention [CDC] 2010). SES is a strong correlate of factors—such as diet, use of dental services, and oral hygiene practices—that affect dental caries status (USDHHS 2000). Several studies found that decayed or missing teeth are more prevalent among smokers but that restored teeth are more common among nonsmokers (Birnboim-Blau et al. 2006; Dye et al. 2007; Hamasha and Safadi 2008). This pattern for dental caries is consistent with differences between smokers and nonsmokers in their use of dental care or the type of care received, which could account for at least some of the observed differences in caries status between the two groups. According to a nationally representative survey of adults in the United States, current smokers are much less likely than never smokers to have seen a dentist during the preceding 12 months (Dye et al. 2007). According to the 2009 National Health Interview Survey, the proportion of persons who received dental care during the preceding year was strongly associated with SES, with estimates ranging from 39% of those living below the federal poverty level to 77.5% of those living at or above 400% of the federal poverty level (National Center for Health Statistics 2011). Beyond SES differences in the use of dental care, many oral health-related behaviors differ between smokers and nonsmokers. For example, compared with nonsmokers, smokers tend to practice less frequent or less effective oral hygiene and plaque removal (Andrews et al. 1998; Hellqvist et al. 2009).

Similarly, significant behavioral differences between smokers and nonsmokers may increase their children's risk for dental caries, complicating any causal interpretations of the evidence on secondhand smoke and caries. For example, in a study of 3- and 5-year-old children in Belgium, Leroy and colleagues (2008) reported that such practices as applying sugary substances to pacifiers, "cleaning" a pacifier in the parent's mouth, and giving the child sugar-containing beverages between meals are more common among parents who currently smoke than among those who do not. That study adjusted for multiple potential confounders in its analysis and still found a significant association between current smoking and dental caries in the 5-year-old children and a doubling in risk in the 3-year-old children, but the latter finding failed to reach significance (OR = 1.98; 95% CI, 0.68–5.76). Even so, the large number of socioeconomic and behavioral differences in the study between parents who smoked and those who did not raises the possibility of residual confounding of the association between exposure to secondhand tobacco smoke and dental caries despite the authors' use of multivariable regression analysis.

Conclusions

1. The evidence is suggestive but not sufficient to infer a causal relationship between active cigarette smoking and dental caries.

2. The evidence is suggestive but not sufficient to infer a causal relationship between exposure to tobacco smoke and dental caries in children.

Implications

In developed nations, smoking is strongly associated with sociodemographic characteristics and a wide range of health behaviors that also are strongly associated with elevated risk for caries. Given the public health importance of dental caries, further research on smoking is needed with careful attention to confounding.

Smoking and the Failure of Dental Implants

A dental implant is an artificial tooth root that supports restorations to replace one or more missing teeth. A variety of dental implant systems that rely on surgical implantation in alveolar bone are available commercially. Endosseous implants are used most frequently. Although the size, shape, and coating of endosseous dental implants vary, the majority anchor the implant to the bone through

osseointegration. Osseointegration is a direct structural connection at the light microscopic level between bone and the surface of the implant (Brånemark 1985). Most osseointegrated dental implants are manufactured from pure titanium or titanium alloy, and the surface of the implant may be roughened by manufacturing processes or coated by various substances to achieve better integration with the bone.

Because no soft tissue or periodontal ligament is detectable at the interface between the implant and bone, the biologic mechanism of anchoring differs between natural tooth roots, where anchoring relies on both the soft tissue and the ligament(s), and dental implants, where anchoring is achieved by osseointegration. Strong evidence indicates that smoking is a risk factor for the destruction of hard and soft tissue around natural teeth (Bouclin et al. 1997; USDHHS 2004; Palmer et al. 2005; Bergstrom 2006; Warnakulasuriya et al. 2010). Thus, smoking may increase the risk for failure of dental implants (Hinode et al. 2006; Baig and Rajan 2007; Strietzel et al. 2007). This topic has not been reviewed in previous Surgeon General's reports.

Biologic Basis

Several mechanisms likely increase the risk for the failure of dental implants as a result of smoking. First, smoking is an established cause of periodontitis (USDHHS 2004), and a growing body of literature suggests that smoking may be a risk factor for peri-implantitis (inflammation that affects the bone supporting the implant) and bone loss (Strietzel et al. 2007; Heitz-Mayfield 2008; Renvert and Persson 2009).

The mineralization of the bone adjacent to the implant surface is crucial to the stability and success of osseointegrated implants. Early failures of dental implants may result from an inability to establish an intimate bone-implant contact (Esposito et al. 1998). Localized infection and impaired wound healing are two factors that can lead to such failures; both are associated with smoking (Shibli et al. 2010). Furthermore, peri-implantitis may disrupt the bond between the implant and surrounding mineralized tissue after the establishment of osseointegration; this could lead to late implant failure (Esposito et al. 1998). In addition, smokers tend to experience more peri-implant bone loss than nonsmokers (Strietzel et al. 2007).

Description of the Literature Review

To establish the literature base on this topic for the present review, investigators searched the PubMed database for studies that were published through December 2010. This search used the following MeSH keywords:

"dental implants" or "dental implants, single-tooth" and "smoking" or "tobacco smoke pollution." In addition, reference lists from published studies and review articles were searched to identify studies not in PubMed. To be included, studies had to be original investigations that had implant survival or failure as outcomes and reported those outcomes by smoking status.

Epidemiologic Evidence

Of the 69 studies included in this review, 40 were classified as retrospective cohort studies, nearly all of which were based on reviews of clinical records (Table 10.7*S*). The remaining studies were either prospective cohort studies or clinical trials that included information about smoking status at baseline.

In most of the studies, patients received multiple dental implants, and the number of implants placed per patient varied widely. Most studies, however, reported outcome data with the implant as the unit of analysis, with analyses generally ignoring the clustering of implants within individuals. Few studies reported failure rates (the number of failures per implant month at risk), but they generally reported the number or proportion of implants that failed. Some studies reported the proportion of individuals who experienced one or more failed implants. Few studies reported estimates of epidemiologic parameters (e.g., RR) that would readily allow cross-study comparisons of the relative proportions of implants that failed among smokers and nonsmokers. Consequently, for most studies, the authors of the present report calculated a crude estimate of RR based on data included in the published paper.

Of the 69 studies, 58 (84%) found that smokers experience a higher proportion of implant failures than nonsmokers. However, the differences in proportions were statistically significant in just 28 (40.6%) of the 69 studies, per the test statistics reported by the authors of the original studies or through the crude confidence limits of parameter estimates calculated for this report (i.e., the 95% confidence limits of crude OR or RR estimates excluded 1.0).

Several studies estimated hazard ratios (HRs) using multivariable models that adjusted for potential confounders (Wilson and Nunn 1999; Berge and Gronningsaeter 2000; Eckert et al. 2001; Chuang et al. 2002; Baelum and Ellegaard 2004; Woo et al. 2004; Ellegaard et al. 2006; Al-Nawas et al. 2007; Balshe et al. 2008; Holahan et al. 2008). In the majority of these studies, smokers had significantly higher HRs than nonsmokers.

Evidence Synthesis

This review included 69 epidemiologic studies on the association between smoking and failure of osseointegrated dental implants; 49 (62%) of these studies were published from 2001–2009. Most of the studies were methodologically weak and potentially affected by selection bias, uncontrolled confounding, low statistical power, or analytic approaches that ignored clustering effects. Nevertheless, the large majority of studies found that smokers experience a greater proportion of implant failures than nonsmokers. All 10 of the cohort studies that adjusted for potential confounders found higher HRs for smokers (Wilson and Nunn 1999; Berge and Gronningsaeter 2000; Eckert et al. 2001; Chuang et al. 2002; Baelum and Ellegaard 2004; Woo et al. 2004; Ellegaard et al. 2006; Al-Nawas et al. 2007; Balshe et al. 2008; Holahan et al. 2008).

Several published meta-analyses (not shown in Table 10.7*S*) have included subsets of the studies included in this review. For example, Hinode and colleagues (2006) pooled 19 prospective or retrospective cohort studies and calculated an overall OR of 2.17 (95% CI, 1.67–2.83) for the association between smoking and implant failure. Similarly, Strietzel and colleagues (2007) calculated a summary OR of 2.25 (95% CI, 1.96–2.59) in their meta-analysis of 29 cohort studies. Finally, Klokkevold and Han (2007) conducted a systematic review and meta-analysis of 14 studies, finding a pooled difference in the cumulative survival of implants that was 2.68% (95% CI, 1.10–4.26%) lower in smokers than in nonsmokers.

Conclusion

1. The evidence is suggestive but not sufficient to infer a causal relationship between cigarette smoking and failure of dental implants.

Implications

The existing evidence suggests that smoking may compromise the prognosis for osseointegrated dental implants. Thus, an intervention to discontinue tobacco use should be part of the treatment plan for persons who are considering a dental implant.

Diabetes

This section addresses type 2 diabetes mellitus. The prevalence of type 2 diabetes in the United States has increased dramatically during the past few decades, in parallel with the rapid rise in the country's prevalence of overweight and obesity. According to CDC (2011), 25.8 million Americans, or 8.3% of the population, had diabetes in 2010. About 1.9 million new cases of diabetes, mostly type 2, are diagnosed in U.S. adults (CDC 2011). The raw and age-adjusted prevalence of diabetes is substantially higher in minority populations. Among persons 20 years of age and older in 2007–2009, the non-age-adjusted prevalence of diabetes was 12.6% for non-Hispanic Blacks, 11.8% for Hispanics, 8.4% for Asian Americans, and 7.1% for non-Hispanic Whites (CDC 2011). Diabetes is a leading cause of cardiovascular mortality. Nearly two-thirds of people with diabetes die of cardiovascular disease (Nathan et al. 1997). Diabetes is also the leading cause of new cases of blindness, kidney failure, and nontraumatic lower-limb amputation (CDC 2011). Beyond its unfortunate consequences for quality of life, the economic cost of diabetes is high. In 2007, the estimated total cost of diagnosed diabetes in the United States was $174 billion, including $116 billion from direct medical costs and $58 billion from three indirect costs: disability, work loss, and premature mortality (CDC 2011).

A growing body of evidence from epidemiologic studies suggests that smoking is associated with increased risk of type 2 diabetes (Willi et al. 2007), and studies of pathogenesis also support a potential causal relationship between smoking and diabetes (Xie et al. 2009). However, type 2 diabetes is multifactorial in etiology. The rising prevalence worldwide is generally attributed to increasing overweight and obesity, which is now an important concern in both high- and low-income countries. In many high-income countries, the prevalence of diabetes has risen even as smoking rates have dropped (Chen et al. 2012).

The 2010 Surgeon General's report (USDHHS 2010) reviewed the evidence on the role of smoking in diabetes. This chapter reviews evidence on the association between active smoking and the incidence of diabetes and evaluates the extent to which the evidence supports a causal relationship between smoking and that disorder. Because of limited evidence, this chapter will not review the evidence on the effects of passive smoking on diabetes, the adverse effects of smoking on the development of

diabetic complications, or the benefits of smoking cessation among people with diabetes. These topics were discussed in a comprehensive review by Tonstad (2009).

Biologic Evidence

Several biologic mechanisms may explain an association between cigarette smoking and the incidence of type 2 diabetes. First, although smokers tend to be leaner than nonsmokers, many epidemiologic studies have shown that smoking is independently associated with an increased risk of central obesity (Barrett-Connor and Khaw 1989; Shimokata et al. 1989; Visser et al. 1999; Canoy et al. 2005). Central obesity is a well-established risk factor for insulin resistance and diabetes. The accumulation of visceral adipose tissue is influenced by the concentration of cortisol (Pasquali and Vicennati 2000), and smokers tend to have higher concentrations of fasting plasma cortisol than nonsmokers (Cryer et al. 1976; Friedman et al. 1987), which might be a consequence of the stimulation of sympathetic nervous system activity induced by smoking (Grassi et al. 1992, 1994). In addition, the differential effects of tobacco smoking on sex hormones may help to explain the positive association between smoking and the central accumulation of fat. Smoking has independent effects on estrogens and androgens in women (Michnovicz et al. 1986; Barrett-Connor and Khaw 1987; Friedman et al. 1987; Khaw et al. 1988) (also see the "Breast Cancer" section of Chapter 6, "Cancer") and decreases plasma testosterone in men (Meikle et al. 1988). These effects may promote the accumulation of abdominal fat, especially in men.

Second, smoking increases inflammatory markers (Arnson et al. 2010) and oxidative stress (Morrow et al. 1995) and impairs endothelial function (USDHHS 2004, 2006, 2010). These mechanisms have been strongly implicated in the development of insulin resistance and irregularities in glucose metabolism (Maritim et al. 2003; Dandona et al. 2004; Potenza et al. 2009).

Third, human experiments using the glucose-clamp technique have found that acute infusion of nicotine aggravates the insulin resistance status in people with type 2 diabetes (Axelsson et al. 2001). Furthermore, cigarette smoking clearly worsens metabolic control, and people with diabetes who smoke require a larger dose of insulin to achieve a level of metabolic control similar to that of nonsmokers (Madsbad et al. 1980). These findings indicate that people with diabetes may be particularly susceptible to the detrimental effects of smoking on insulin resistance (Berlin 2008; Chiolero et al. 2008).

Finally, human and animal studies have found that functional nicotinic receptors are present on pancreatic islet and beta cells, and nicotine can, at least in part, reduce the release of insulin through neuronal nicotinic acetylcholine receptors on islet cells (Yoshikawa et al. 2005). Moreover, several studies in animal models have revealed that exposure to nicotine, particularly in the prenatal or neonatal phases of life, can cause dysfunction of beta cells and increase beta-cell apoptosis, which is mediated via the mitochondrial and/or death receptor pathway (Holloway et al. 2005; Bruin et al. 2007, 2008; Somm et al. 2008).

Thus, taken together, multiple lines of evidence from animals and humans strongly support the hypothesis that cigarette smoking and exposure to nicotine can adversely affect insulin action and the function of pancreatic cells, both of which play fundamental roles in the pathogenesis of diabetes (Xie et al. 2009).

Epidemiologic Evidence

Description of the Literature Review

This systematic review and meta-analysis updates the literature from the 2007 review and meta-analysis by Willi and colleagues (2007) covering the association between active smoking and type 2 diabetes. The present review examined articles published between May 2007 (the cutoff date for the paper by Willi and colleagues [2007]) and January 2010. Using the same strategy as that employed by Willi and colleagues (2007), articles were identified through a search of PubMed and Embase. The search incorporated MeSH terms across three themes: smoking or cigarette; diabetes mellitus or glucose metabolism irregularity; and studies with a prospective design. For inclusion in the meta-analysis, studies had to meet several criteria:

- Report data from an original study (i.e., not just review articles)

- Focus on an adult population (i.e., 16 years of age or older)

- Incorporate level of smoking intensity or exposure to nicotine as a primary predictor or one of the cofactors for risk of diabetes, not just as a covariate or confounder

Studies were excluded if they met any of the following conditions:

- Included participants with previously diagnosed diabetes at the beginning of the study

- Used inappropriate comparison groups (i.e., a comparison group other than nonsmokers or former smokers)

- Could not provide original data after inquiries from investigators

If data from a study were reported in several publications, the most relevant or most recent publications were used to avoid double counting.

Methods

The present review abstracted and reviewed 25 studies (Cassano et al. 1992; Perry et al. 1995; Rimm et al. 1995; Kawakami et al. 1997; Njølstad et al. 1998; Sugimori et al. 1998; Uchimoto et al. 1999; Manson et al. 2000; Nakanishi et al. 2000; Strandberg and Salomaa 2000; Hu et al. 2001; Wannamethee et al. 2001; Will et al. 2001; Montgomery and Ekbom 2002; Sawada et al. 2003; Carlsson et al. 2004; Eliasson et al. 2004; Sairenchi et al. 2004; Foy et al. 2005; Lyssenko et al. 2005; Patja et al. 2005; Tenenbaum et al. 2005; Waki et al. 2005; Houston et al. 2006; Meisinger et al. 2006) from the meta-analysis by Willi and colleagues (2007). Two of the 25 studies (Cassano et al. 1992; Sawada et al. 2003) were excluded from the present review because smoking was used as only a confounder for risk of diabetes. The study by Perry and colleagues (1995) was also excluded, because similar results were reported in a later report (Wannamethee et al. 2001).

This review also abstracted and included 21 new studies (Burke et al. 2007; Cugati et al. 2007; Dehghan et al. 2007; Holme et al. 2007; Hur et al. 2007; Mozaffarian et al. 2007, 2009; Onat et al. 2007; Schulze et al. 2007; Hayashino et al. 2008; Lyssenko et al. 2008; Magliano et al. 2008; Nagaya et al. 2008; Nichols et al. 2008; Park et al. 2008; Chien et al. 2009; Cho et al. 2009; Cullen et al. 2009; Hippisley-Cox et al. 2009; Laaksonen et al. 2010; Yeh et al. 2010) that were not part of the meta-analysis by Willi and colleagues (2007). In addition, based on a careful review of reference lists from all relevant publications, 3 studies published before 2007 (Keen et al. 1982; Bonora et al. 2004; Harding et al. 2006) were included. Therefore, this updated meta-analysis included 46 studies about active smoking and risk of type 2 diabetes.

Study Characteristics

Table 10.8*S* depicts the characteristics of the 51 studies that were selected for the present meta-analysis. All were prospective cohort studies: 44 reported the incidence of diabetes as the sole outcome of interest, and 2 reported the incidence of diabetes plus impaired glucose

tolerance (Carlsson et al. 2004; Houston et al. 2006). The association between smoking and risk of diabetes was the primary focus of 27 studies, and smoking was included as one of the cofactors in the other 19 studies.

The diagnosis of diabetes was ascertained by biologic measures in 28 studies, reported by patients or physicians in 11 studies, and determined by other methods (e.g., examination of hospital medical registries and insurance registries) in 7 studies. Because the definition of diabetes and the cutoff points used to establish its presence changed from 1980–2009, the fasting glucose thresholds varied across studies (15 studies did not explicitly describe criteria for this threshold):

- 140 milligrams (mg)/deciliter (dL) (7.8 millimoles per liter [mmol/L]) or higher for 6 studies

- 126 mg/dL (7.0 mmol/L) or higher for 20 studies

- 120 mg/dL (6.6 mmol/L) or higher for 1 study

- 110 mg/dL (6.1 mmol/L) or higher for 3 studies

- 100 mg/dL (5.6 mmol/L) or higher for 1 study

The meta-analysis included more than 3.9 million participants and 140,813 cases of diabetes, with the number of participants in the studies ranging from 241 to 2,540,753. Follow-up ranged from 3.5–30 years, with a median of 10 years. Two studies included only women, 13 included only men, and the remaining 31 included both men and women. Among these 31 studies, 6 reported results for both genders and for the total population, and 5 studies reported results separately by gender.

The studies in the meta-analysis adjusted for many risk measures, such as:

- Age (42 studies)

- Body mass index (33 studies)

- Intensity of physical activity (28 studies)

- Level of alcohol consumption (24 studies)

- Heredity or family history of diabetes (19 studies)

- Gender (19 studies)

- Level of education (13 studies)

- Diet (11 studies)

- Waist circumference or waist-to-hip ratio (11 studies)

- Race or ethnicity (6 studies)

Finally, statistical models in 24 of the studies controlled for biomarkers, such as fasting glucose, insulin, and lipid profile.

Risk of Diabetes: Smokers Compared With Nonsmokers

Based on 51 comparisons from the 46 studies, active smokers had an increased risk of developing type 2 diabetes compared with nonsmokers, with a pooled RR of 1.37 (95% CI, 1.31–1.44) (Figure 10.1). There was evidence of heterogeneity of the RRs across studies (Q statistic = 273.1; P <0.001; I^2 = 82%) that was statistically significant, given the extremely large number of participants in the analysis. Among the 51 comparisons, 40 showed a significantly increased risk of diabetes among smokers, 10 showed a nonsignificant association between smoking and risk of diabetes (in 8 of these studies the RR exceeded 1.00; in 2 it did not), and 1 showed a significant inverse association between smoking and risk of diabetes.

The pooled risk changed little (RR = 1.42; 95% CI, 1.34–1.51) when the two largest studies, which may have dominated the results (Will et al. 2001; Hippisley-Cox et al. 2009), were excluded in a sensitivity analysis (results not shown in a table or figure).

The Begg funnel plot was used to evaluate publication bias (Begg and Mazumdar 1994; Egger et al. 1997). Visual inspection revealed asymmetry and the possibility of publication bias, although the finding was not significant (p = 0.552) (Figure 10.2A). Therefore, a sensitivity analysis was conducted using the trim-and-fill procedure, which conservatively imputes studies to mirror the positive studies that cause asymmetry in funnel plots (Figure 10.2B). The pooled RR incorporating the imputed studies remained significant (RR = 1.26; 95% CI, 1.21–1.33).

Subgroup Analysis

To explore potential heterogeneity, analyses were stratified by several key study characteristics and clinical factors (Table 10.9). In each stratified analysis, smokers demonstrated a significantly increased RR for diabetes. The quality of the study characteristics did not influence the results substantially. A stronger association between smoking and incident diabetes was found in studies in which blood glucose was measured to assess the presence of diabetes at baseline and endpoint, compared with studies that relied on reports by patients or physicians or on registry data. Studies that used higher fasting glucose thresholds as the definition of diabetes also showed a stronger association between smoking and diabetes.

Dose-Response Analysis

To generate pooled estimates for the dose-response analysis, the meta-analysis examined studies in which measures of association were stratified by level of smoking intensity. These levels were categorized as never, former, light (0–19 cigarettes smoked/day in most studies; 0–15 cigarettes/day in some studies), and heavy (20 or more cigarettes/day in most studies; 15 or more in some studies). As shown in Table 10.9 and Figure 10.3, the RR increased with higher levels of smoking intensity. When compared with never smokers, former smokers had an RR of 1.14 (95% CI, 1.09–1.19). Compared with nonsmokers, light smokers had an RR of 1.25 (95% CI, 1.14–1.37), and heavy smokers had an RR of 1.54 (95% CI, 1.40–1.68).

Smoking Cessation

A review by Filozof and colleagues (2004) found that smoking cessation improves insulin sensitivity in spite of short-term weight gain. In the Atherosclerosis Risk in Communities Study, the risk of incident type 2 diabetes for short-term quitters was above that for current smokers, but it then decreased to the level of never smokers at 12 years (Yeh et al. 2010). Another large cohort study found that smoking cessation reduced RRs for diabetes to those for never smokers after 5 years for women and 10 years for men (Will et al. 2001). Finally, a cohort study from Korea (Hur et al. 2007) showed that smoking cessation is followed by a decreasing risk of diabetes that reaches that of never smokers in the long term.

Summary

Consistent with the meta-analysis of 25 studies published before 2007 (Willi et al. 2007), the results from this updated meta-analysis provide compelling evidence that active smoking increases risk of developing type 2 diabetes. The association persisted and remained significant in all stratified analyses by various study and participant characteristics. Furthermore, the meta-analysis revealed a clear dose-response relationship—that is, risk of diabetes increases with increasing levels of smoking intensity. The variety of potential confounding factors considered and the finding of a dose-response relationship weigh against the possibility of residual confounding as the explanation for the association between smoking and diabetes.

Figure 10.1   Adjusted relative risk (RR) of diabetes, current smokers compared with nonsmokers

Study		RR (95% CI)	% Weight
Keen et al. 1982		1.18 (0.44–3.15)	0.22
Rimm et al. 1995		1.96 (1.50–2.56)	1.78
Kawakami et al. 1997		2.51 (1.30–4.84)	0.46
Njølstad et al. 1998		0.82 (0.59–1.13)	1.42
Sugimori et al. 1998		1.42 (1.10–1.83)	1.88
Uchimoto et al. 1999		1.47 (1.13–1.92)	1.80
Manson et al. 2000		1.63 (1.50–1.77)	3.63
Nakanishi et al. 2000		2.90 (1.67–5.03)	0.63
Strandberg and Salomaa 2000		1.62 (1.01–2.59)	0.81
Hu et al. 2001		1.30 (1.15–1.47)	3.21
Wannamethee et al. 2001		1.74 (1.24–2.44)	1.34
Will et al. 2001 (females)		1.07 (1.03–1.11)	3.98
Will et al. 2001 (males)		1.19 (1.15–1.24)	3.98
Montgomery and Ekbom 2002		2.40 (1.34–4.30)	0.57
Bonora et al. 2004		0.91 (0.52–1.60)	0.61
Carlsson et al. 2004		1.06 (0.87–1.30)	2.36
Eliasson et al. 2004		3.76 (1.52–9.32)	0.26
Sairenchi et al. 2004 (females)		1.39 (1.20–1.61)	2.93
Sairenchi et al. 2004 (males)		1.27 (1.16–1.39)	3.59
Foy et al. 2005		2.15 (1.20–3.86)	0.57
Lyssenko et al. 2005		1.50 (1.07–2.10)	1.33
Patja et al. 2005		1.41 (1.26–1.57)	3.35
Tenenbaum et al. 2005		1.94 (1.16–3.25)	0.70
Waki et al. 2005 (females)		1.42 (0.95–2.12)	1.05
Waki et al. 2005 (males)		1.25 (1.07–1.47)	2.80
Harding et al. 2006		1.15 (0.90–1.46)	1.98
Houston et al. 2006		1.65 (1.28–2.13)	1.88
Meisinger et al. 2006 (females)		1.38 (1.03–1.84)	1.62
Meisinger et al. 2006 (males)		1.69 (1.34–2.13)	2.07
Burke et al. 2007		2.05 (1.23–3.40)	0.72
Cugati et al. 2007		1.57 (1.03–2.40)	0.96
Dehghan et al. 2007		1.16 (0.96–1.40)	2.48
Holme et al. 2007		1.15 (0.93–1.42)	2.25
Hur et al. 2007		1.60 (1.29–1.98)	2.25
Mozaffarian et al. 2007		1.60 (1.34–1.91)	2.63
Onat et al. 2007		0.60 (0.41–0.87)	1.17
Schulze et al. 2007		1.90 (1.47–2.46)	1.85
Hayashino et al. 2008		1.99 (1.30–3.05)	0.94
Lyssenko et al. 2008		1.39 (1.23–1.57)	3.21
Magliano et al. 2008		1.66 (1.11–2.49)	1.02
Nagaya et al. 2008		1.10 (0.96–1.26)	3.06
Nichols et al. 2008		1.37 (1.22–1.54)	3.28
Park et al. 2008		1.73 (1.22–2.46)	1.25
Chien et al. 2009		1.01 (0.83–1.22)	2.46
Cho et al. 2009		2.20 (1.50–3.22)	1.12
Cullen et al. 2009		1.35 (1.20–1.51)	3.29
Hippisley-Cox et al. 2009 (females)		1.27 (1.23–1.31)	4.00
Hippisley-Cox et al. 2009 (males)		1.25 (1.21–1.29)	4.02
Mozaffarian et al. 2009		1.30 (1.04–1.63)	2.10
Laaksonen et al. 2010		1.78 (1.20–2.65)	1.06
Yeh et al. 2010		1.31 (1.04–1.65)	2.08
Overall (I-squared = 81.7%, p = 0.000)		1.37 (1.31–1.44)	100.0

0   1.0   2.0   3.0   4.0   5.0

Note: **CI** = confidence interval.

Figure 10.2   Log relative risk of diabetes for current smokers, funnel plots without (A) and with 225 (B) trim-and-fill procedure

A. Begg's funnel plot with pseudo 95% confidence limits

B. Begg's funnel plot with pseudo 95% confidence limits (using trim-and-fill method)

Note: **lnrr** = natural log of relative risk.

Table 10.9   Stratified analyses of pooled relative risk (RR) for incident diabetes from smoking

Stratified analysis	Number of comparisons	Pooled RR (95% CI)	Heterogeneity
Adjustment for confounding factors			
Minimal (≤3)	6	1.44 (1.08–1.92)	0.012
Moderate (4–7)	15	1.33 (1.18–1.50)	<0.001
Substantial (≥8)	30	1.39 (1.32–1.47)	<0.001
Type of outcome measure			
Biologic	29	1.39 (1.29–1.49)	<0.001
Reported by patient or physician	14	1.37 (1.23–1.53)	<0.001
Registry or database	8	1.31 (1.23–1.39)	0.063
Type of screening at baseline			
Biologic measures	29	1.39 (1.29–1.51)	<0.001
Reported by patient or physician or database	22	1.35 (1.27–1.44)	<0.001
Fasting glucose threshold (mg/dL)			
≥140	6	1.74 (1.39–2.18)	0.014
≥126 or 120	22	1.42 (1.29–1.57)	<0.001
≥110 or 100	4	1.26 (1.04–1.53)	0.013
Not specified	19	1.32 (1.24–1.41)	<0.001
Mean follow-up (years)			
≤10	24	1.46 (1.33–1.60)	<0.001
>10	25	1.32 (1.25–1.40)	<0.001
Year of publication			
Before 2000	6	1.45 (1.08–1.94)	0.001
2000–2005	19	1.39 (1.27–1.52)	<0.001
2006–2009	26	1.36 (1.28–1.43)	<0.001
Smoking intensity/exposure to nicotine			
Primary predictor	31	1.42 (1.32–1.53)	<0.001
Cofactor for risk	19	1.32 (1.25–1.39)	0.001
Mean age (years)			
<50	26	1.37 (1.29–1.45)	<0.001
≥50	25	1.38 (1.28–1.49)	<0.001
Mean BMI			
<25	20	1.40 (1.26–1.55)	<0.001
≥25	27	1.36 (1.29–1.43)	<0.001
Missing information	4	1.53 (1.16–2.02)	0.060
Study location			
America	10	1.38 (1.24–1.55)	<0.001
Europe or Australia	25	1.36 (1.29–1.44)	<0.001
Asia	16	1.41 (1.25–1.59)	<0.001
Gender			
Male	24	1.41 (1.31–1.52)	<0.001
Female	12	1.26 (1.15–1.38)	<0.001
Both genders	19	1.44 (1.31–1.58)	0.008

Table 10.9   Continued

Stratified analysis	Number of comparisons	Pooled RR (95% CI)	Heterogeneity
Smoking intensity[a]			
Former smokers vs. never smokers	33	1.14 (1.09–1.19)	0.033
Light smokers vs. nonsmokers	22	1.25 (1.14–1.37)	<0.001
Heavy smokers vs. nonsmokers	23	1.54 (1.40–1.68)	<0.001

Note: **BMI** = body mass index (weight in kilograms divided by height in meters squared); **CI** = confidence interval;
mg/dL = milligrams per deciliter.
[a]Light smoking defined in most studies as current smoking of 0–19 cigarettes/day (0–15 in some studies), and heavy smoking defined in most studies as current smoking of 20 or more cigarettes/day (15 or more in some studies).

Figure 10.3   Pooled relative risk of diabetes associated with various levels of smoking intensity
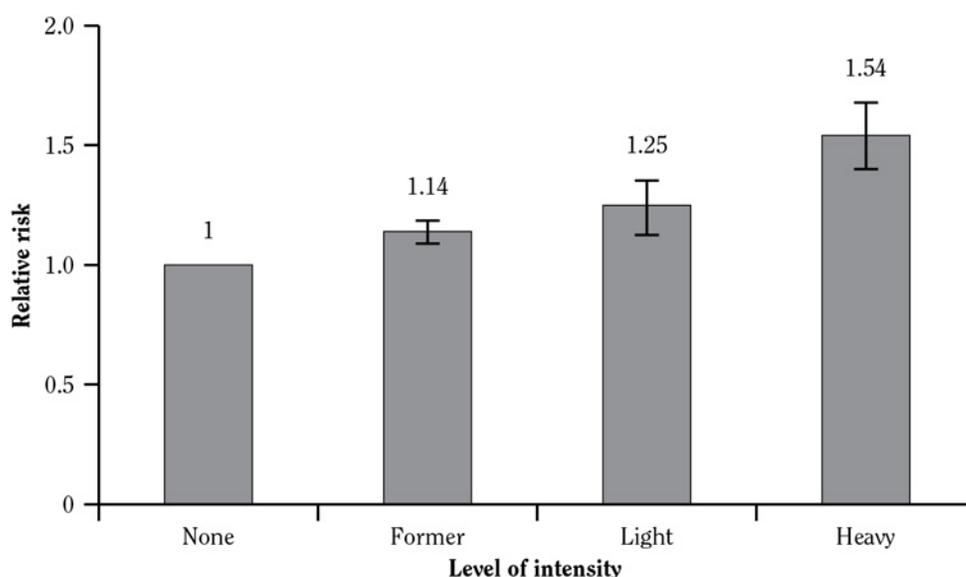
Note: Light smoking defined in most studies as current smoking of 0–19 cigarettes/day (0–15 in some studies), and heavy smoking defined in most studies as current smoking of 20 or more cigarettes/day (15 or more in some studies).

Evidence Synthesis

All studies included in the meta-analysis were of the cohort design and prevalent diabetes cases were excluded at baseline, establishing an unambiguous temporal relationship between smoking and diabetes. Various lines of evidence support biological plausibility. A series of biologic experiments in animals and humans provides convincing evidence that cigarettes and one pharmacologically active component in cigarette smoke, nicotine, are strongly implicated in the development of insulin resistance and irregularities in glucose metabolism.

The association is strong and consistent. The meta-analysis revealed that smoking is associated with a 30–40% increased risk of developing type 2 diabetes, and the results were robust in various stratified analyses. Additionally, the positive association between smoking and diabetes has been replicated in numerous studies in multiple countries. The quantitative summary shows that as the amount of smoking increases (defined by number of cigarettes smoked/day), the RR of diabetes increases in a dose-response manner. Furthermore, the meta-analysis described in this chapter found that former smokers have a lower risk of developing diabetes than current smokers.

Alternative explanations for causation can be set aside. Smoking is associated with other behaviors—such as physical inactivity, poor diet, and high alcohol intake—that favor weight gain and/or diabetes, but most of the

studies in this meta-analysis controlled for such factors. Thus, residual confounding seems unlikely as an explanation for the association of smoking with diabetes. Furthermore, RRs were not attenuated in the studies that carefully adjusted for these confounding factors, indicating that the effects of smoking are independent of other lifestyle factors.

Concerns about specificity of causation do not apply in interpreting this association as smoking is associated with multiple diseases through many different mechanisms and pathways, and multiple factors contribute to the risk of diabetes. Lack of specificity is not a requisite for inference of causality (USDHHS 2004).

Conclusions

1. The evidence is sufficient to infer that cigarette smoking is a cause of diabetes.

2. The risk of developing diabetes is 30–40% higher for active smokers than nonsmokers.

3. There is a positive dose-response relationship between the number of cigarettes smoked and the risk of developing diabetes.

Implications

Smoking should be considered an important and modifiable risk factor for the development of diabetes. Given the increasing epidemic of diabetes worldwide and the high prevalence of smoking in most developing countries, reducing tobacco use should be promoted as a key public health strategy to prevent and control the global epidemic of diabetes. Because smoking is also associated with increased risk of cardiovascular disease and death among persons with diabetes (Al-Delaimy et al. 2001, 2002; Spencer et al. 2008), it has enormous implications for diabetes, increasing its incidence and its complications.

Immune Function and Autoimmune Disease

This section considers the evidence related to the adverse effects of smoking on the immune system and whether smoking is a cause or contributory cofactor in immunologically mediated diseases. This section also covers the current understanding of the cellular and molecular mechanisms by which smoking affects immunity (Holt and Keast 1977; Sopori 2002; Stampfli and Anderson 2009). Previous reports from the Surgeon General have not covered this topic in depth. Several reports have covered effects of smoking on respiratory immunity, most recently in 2010, and diseases for which the immune system plays a key role (Tables 10.10–10.12) (USDHHS 2010).

Description of the Literature Review

The theme of smoking, immunity, and immunologically mediated diseases covers a wide range of topics and potential search terms. To develop this section, literature databases were searched through March 2012, using a search string strategy that combined the following key search terms:

Smoking OR smoke OR cigarette OR cigarette smoke OR cigarette smoke extract OR tobacco OR tobacco smoke individually with each of the following key descriptors of immunity: immunity, host defense, adaptive, innate, infection, immune disease, autoimmunity, rheumatoid, lupus, multiple sclerosis, HIV/AIDS, virus, influenza, RSV, adenovirus, bacteria, pseudomonas, *Haemophilus,* streptococcus, cancer, adenocarcinoma, NSCLC, small cell lung cancer, immune surveillance, lymphocyte, T cell, B cell, humoral response, antibody, NK cell, NKT cell, dendritic cell, granulocyte, neutrophil, macrophage, monocyte, TAM, tumor associated macrophage, tolerance, central tolerance, peripheral tolerance, innate immunity, PRR, PAMP, DAMP, HMGB1, Toll-like receptor, TLR (collectively and individually for the known TLRs), myeloid differentiation factor 88 (MyD88), RIG, helicase, alarmin, type 1 interferon response, inflammasome, Th1, Th2, Th17, Treg, Breg, CTL, cytotoxic T cell, mononuclear cell, macrophage, M1, M2, eosinophil, neutrophil, dendritic cell, epithelium,

Table 10.10   Conclusions about the adverse effects of tobacco use and exposure to tobacco smoke on infectious diseases, from previous Surgeon General's reports

Selected conclusions	Year and page number of Surgeon General's report
1. The evidence is sufficient to infer a causal relationship between smoking and acute respiratory illnesses, including pneumonia, in persons without underlying smoking-related chronic obstructive lung disease.	2004, p. 27
2. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and acute respiratory infections among persons with preexisting chronic obstructive pulmonary disease.	2004, p. 27
3. The evidence is sufficient to infer a causal relationship between secondhand smoke exposure from parental smoking and lower respiratory illnesses in infants and children.	2006, p. 14
4. The increased risk for lower respiratory illnesses is greatest from smoking by the mother.	2006, p. 14

Source: U.S. Department of Health and Human Services 2004, 2006.

post-translational modification, carbonylation, acetylation, nitrosylation, unfolded protein stress response, heme oxygenase (HMOX), carbon monoxide, nicotine, acrolein, aryl hydrocarbon receptor, AHR, epigenetic, microRNA, regulatory RNA, HDAC, histone modification.

This search strategy returned more than 5,000 primary references. The subsequent analysis focused on (a) evidence from larger, well-powered studies and major meta-analyses of the clinical and epidemiologic literature and (b) basic science papers published since 1985, which covers a timeframe known for major technical advances in cellular and molecular immunology. However, some relevant smaller scale clinical investigations and some earlier basic science papers have also been considered because of their quality and relevance.

Overview of Innate and Adaptive Immune Defense

The immune system exerts its beneficial and detrimental effects via a complex, highly cross-regulated network of cellular and molecular defense mechanisms. Therefore, any discussion of the effects of smoking on immunity should consider the multiple and richly interconnected tiers of immunological defenses that include innate defense mechanisms, such as barrier functions, soluble defense molecules, and cellular defenses and adaptive immune responses (Figure 10.4).

Immunity comprises an array of defense mechanisms that protect the host from infection by pathogens (Holt et al. 2008; Kohlmeier and Woodland 2009). Many of these defense mechanisms are mediated by protective inflammation. The immune system also plays a central role in internal homeostasis, guarding against malignant transformation to prevent cancer and responding to tissue damage after injury (Oppenheim and Yang 2005; Rock et al. 2010; Vesely et al. 2011). In health, the immune system does not normally damage host tissue or attack the diverse self-antigens in the human body because of a state of self-tolerance (Wing and Sakaguchi 2010). However, when turned against the host, immune mechanisms can contribute to an array of disorders, many of which have an inflammatory basis and, in extreme cases, provoke autoimmune diseases, such as systemic lupus erythematosus (SLE or lupus).

Conventionally, the immune system is divided into two broad tiers: innate immunity and adaptive immunity. Innate immunity represents a large family of effector mechanisms, including barrier functions, soluble defense molecules that provide nonspecific protection against harmful agents, and cellular defenses triggered by pattern recognition receptors (PRRs) that recognize conserved pathogen-associated molecular patterns (PAMPs) (Table 10.13) (Janeway 1989; Kawai and Akira 2011). Innate immune mechanisms play an important role in responding to tissue damage. These responses arise when so-called damage associated molecular patterns (DAMPs) that are normally cryptic, become exposed after injury and activate immune cells via PRRs (Matzinger 2002; Rock et al.

Table 10.11   Conclusions about the adverse effects of tobacco use and exposure to tobacco smoke on asthma, from previous Surgeon General's reports

Selected conclusions	Year and page number of Surgeon General's report
1. In persons with asthma, the evidence is inadequate to infer the presence or absence of a causal relationship between smoking and acute asthma exacerbation.	2004, p. 27
2. The evidence is sufficient to infer a causal relationship between active smoking and respiratory symptoms in children and adolescents, including coughing, phlegm, wheezing, and dyspnea.	2004, p. 27
3. The evidence is sufficient to infer a causal relationship between active smoking and asthma-related symptoms (i.e., wheezing) in childhood and adolescence.	2004, p. 27
4. The evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and physician-diagnosed asthma in childhood and adolescence.	2004, p. 27
5. The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and a poorer prognosis for children and adolescents with asthma.	2004, p. 27
6. The evidence is sufficient to infer a causal relationship between active smoking and all major respiratory symptoms among adults, including coughing, phlegm, wheezing, and dyspnea.	2004, p. 28
7. The evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and asthma in adults.	2004, p. 28
8. The evidence is sufficient to infer a causal relationship between active smoking and poor asthma control.	2004, p. 28
9. The evidence is sufficient to infer a causal relationship between parental smoking and ever having asthma among children of school age.	2006, p. 14
10. The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure from parental smoking and the onset of childhood asthma.	2006, p. 14
11. The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and adult-onset asthma.	2006, p. 16
12. The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and a worsening of asthma control.	2006, p. 16
13. The evidence is sufficient to conclude that there is a causal relationship between active smoking and wheezing severe enough to be diagnosed as asthma in susceptible child and adolescent populations.	2012, p. 9

Source: U.S. Department of Health and Human Services 2004, 2006, 2012.

2010). The term "alarmin" describes collectively an array of structurally diverse host proteins that are released after tissue injury or during infection to mobilize host defense and tissue repair mechanisms. These innate immune mediators include interleukin-1alpha (IL-1α) and related members of the IL-1 family (e.g., IL-18, IL-33), S100 proteins, defensins, heat-shock proteins (HSPs), uric acid, antibacterial peptides, hepatoma-derived growth factor, eosinophil-derived neurotoxin, cathelicidins, nucleotides, interferons (IFNs), and high mobility group box 1 (HMGB1) (Oppenheim and Yang 2005).

The main cell types involved in mediating innate immunity are epithelial cells and leukocytes, especially granulocytes (neutrophils and eosinophils) and mononuclear lineage cells (monocyte and macrophage subpopulations) (Figure 10.5). Macrophages play a critical role in the destruction of pathogens and the removal of cell debris and dying cells (Metschnikoff 1887; Murray and Wynn 2011), but neutrophils and other cell types have important phagocytic activities (Walsh et al. 1999; Soehnlein and Lindbom 2010). Macrophage phagocytosis is usually accompanied by macrophage activation, which

Table 10.12 **Conclusions about the adverse effects of tobacco use and exposure to tobacco smoke on chronic obstructive pulmonary disease, from previous Surgeon General's reports**

Selected conclusions	Year and page number of Surgeon General's report
1. Active smoking causes injurious biologic processes (i.e., oxidant stress, inflammation, and a protease-antiprotease imbalance) that result in airway and alveolar injury. This injury, if sustained, ultimately leads to the development of chronic obstructive pulmonary disease.	2004, p. 27
2. The evidence is sufficient to infer a causal relationship between active smoking and chronic obstructive pulmonary disease morbidity and mortality.	2004, p. 28
3. The evidence is inadequate to infer the presence or absence of a causal relationship between a lower cigarette tar content and reductions in chronic obstructive pulmonary disease-related mortality.	2004, p. 28
4. The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and risk for chronic obstructive pulmonary disease.	2006, p. 16
5. The evidence is inadequate to infer the presence or absence of a causal relationship between secondhand smoke exposure and morbidity in persons with chronic obstructive pulmonary disease.	2006, p. 16
6. Oxidative stress from exposure to tobacco smoke has a role in the pathogenetic process leading to chronic obstructive pulmonary disease.	2010, p. 11
7. Protease-antiprotease imbalance has a role in the pathogenesis of emphysema.	2010, p. 11
8. Inherited genetic variation in genes such as *SERPINA3* is involved in the pathogenesis of tobacco caused chronic obstructive pulmonary disease.	2010, p. 11
9. Smoking cessation remains the only proven strategy for reducing the pathogenetic processes leading to chronic obstructive pulmonary disease.	2010, p. 11

Source: U.S. Department of Health and Human Services 2004, 2006, 2010.

leads to a proinflammatory and procoagulant state. Other cells—notably natural killer (NK) cells and natural killer T (NKT) cells (Berzins et al. 2011; Sun and Lanier 2011), mast cells (Galli et al. 2005), and nuocytes (Neill et al. 2010), which lack conventional surface markers—constitute important components of innate immunity. Innate reactions characteristically can be activated very rapidly but do not hold a molecular memory of past immunologic exposures.

The main cell types involved in mediating adaptive immunity are T and B lymphocytes (T cells and B cells) (Figure 10.5). In contrast to innate immunity, adaptive immunity retains memory of past insults, such that if an individual encounters the same insults later in life, a much more rapid and amplified response can be mounted. T cells respond mostly to short peptide fragments of foreign proteins (antigens) presented in the context of major histocompatibility complex (MHC) Class I or II (MHC I or II) proteins (Zinkernagel and Doherty 1974).

Antigens must usually be presented to T cells by specialized antigen-presenting cells, of which the dendritic cell subtypes are among the most important (Steinman and Cohn 1973; Banchereau and Steinman 1998). Presentation of soluble, mainly extracellular proteins is mediated by MHC II, whereas intracellular proteins (for example from an intracellular pathogen such as a virus) are presented on MHC I molecules. T cells, with the surface marker CD4, classically recognize MHC II, whereas CD8 positive (CD8+) lymphocytes recognize antigen on MHC I molecules. Human self-antigens are also presented on MHC I molecules constitutively but do not trigger immune reactions because of tolerance (i.e., protective processes). T cells exert their effects by differentiating into effector cells able to secrete cytokines and chemokines that regulate defensive inflammation. Some T lymphocytes differentiate into cytotoxic cells that kill cellular targets. B cells recognize unprocessed antigen in its natural configuration and exert their effects largely by producing one of the five major

Figure 10.4   Overview of immune defects caused by smoking in the lungs
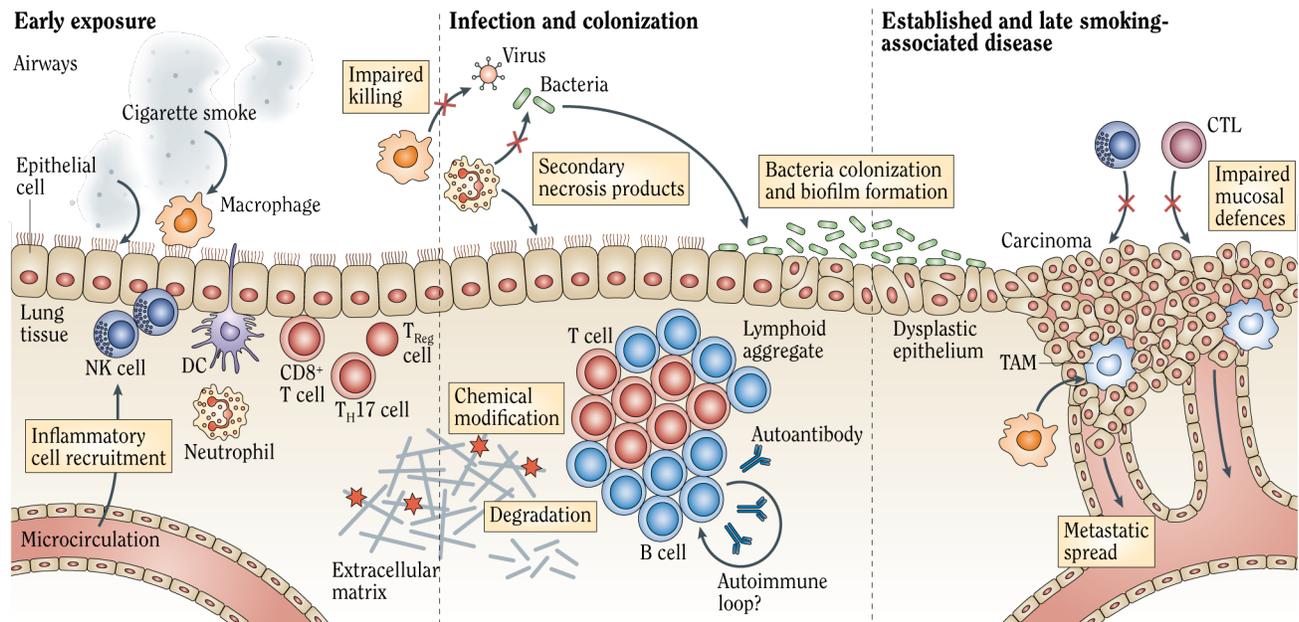
Source: Stampfli and Anderson 2009. Reprinted with permission from Macmillan Publishers Ltd., © 2009.
Note: Cigarette smoke has both proinflammatory and immune-suppressive effects on the immune system. Acute effects of smoke on macrophages and epithelial cells promote inflammation by inducing the recruitment of cells from the microcirculation to the lungs. At the same time, cigarette smoke impairs innate defense mechanisms by macrophages, epithelial cells, dendritic cells, and natural killer cells, thereby increasing the risk, severity, and duration of infection. The transition to a more severe expression of smoking-associated disease is marked by the impaired ability of macrophages to kill bacteria or viruses, the loss of ability to remove dead cells, the degradation and chemical modification of the extracellular matrix, the increasing retention of oligoclonally expanded CD8+ T cells and the induction of interleukin-17-secreting effector T cells. After long-term exposure to cigarette smoke, germinal centers with T cells and B-cell zones may form at the site, supporting the production of pathogenic autoantibodies and driving autologous disease. Loss of mucosal defenses can lead to bacterial colonization (as occurs in around 30% of long-term smokers with chronic obstructive pulmonary disease). Concurrently, somatic mutations in the epithelium and alteration of macrophage phenotype promote inflammation and the development of cancer (carcinoma in situ) that has a high chance of metastatic spread. **CD** = cluster of differentiation; **CTL** = cytotoxic lymphocytes; **DC** = dendritic cell; **NK** = natural killer; **TAM** = tumor-associated macrophage.

classes of immunoglobulin (Ig) antibodies. This process requires antigen presentation and help from CD4+ T cells, which are designated as CD4+ T helper (Th) cells.

The division between innate immunity and adaptive immunity is convenient but does not reflect the intimate interaction between the two. For example, stimulation of dendritic cells by PRR not only activates these cells to move to secondary lymphoid organs and present antigen but also shapes the nature of the subsequent immune reaction, as PRR stimulation induces specific costimulatory molecules and immune mediators that control T cell polarization and acquisition of effector function (Macagno et al. 2007).

Both overactivated or inappropriate innate and adaptive immune responses can directly damage the host,

which leads to inflammation, tissue damage, and disease (Murray and Wynn 2011; Park et al. 2012). Mechanisms underlying these immune-driven pathologies are complex and may include innate and adaptive processes targeted at environmental agents, as well as autoreactive responses that drive autoimmune diseases. The latter are associated with a breakdown in tolerance. Tolerance is conventionally described as constituting central tolerance, where self-reactive lymphocytes are killed by apoptosis in the thymus, or peripheral tolerance, where potentially self-reactive cells survive but are rendered immunologically nonresponsive (Wing and Sakaguchi 2010; Zanoni and Granucci 2011).

Immune surveillance does more than just detect and eliminate or contain pathogens. The immune system

Table 10.13   Pathogen-associated molecular patterns and their respective pattern recognition receptors

Species	PAMPs	TLR usage	PRRs involved in recognition
Bacteria, mycobacteria	LPS	TLR4	
	lipoproteins, LTA, PGN, lipoarabinomannan	TLR2/1, TLR2/6	NOD1, NOD2, NALP3, NALP1
	flagellin	TLR5	IPAF, NAIP5
	DNA	TLR9	AIM2
	RNA	TLR7	NALP3
Viruses	DNA	TLR9	AIM2, DAI, IFI16
	RNA	TLR3, TLR7, TLR8	RIG-I, MDA5, NALP3
	structural protein	TLR2, TLR4	
Fungus	zymosan, beta-glucan	TLR2, TLR6	Dectin-1, NALP3
	Mannan	TLR2, TLR4	
	DNA	TLR9	
	RNA	TLR7	
Parasites	tGPI-mutin *(Trypanosoma)*	TLR2	
	glycoinositolphospholipids *(Trypanosoma)*	TLR4	
	DNA	TLR9	
	hemozoin *(Plasmodium)*	TLR9	NALP3
	profilin-like molecule *(Toxoplasma gondii)*	TLR11	

Source: Kawai and Akira 2011. Reprinted with permission from Elsevier, © 2011.

Note: **LPS** = lipopolysaccharide; **PAMP** = pathogen-associated molecular pattern; **PRR** = pattern recognition receptor; **TLR** = Toll-like receptor.

is also very actively involved in maintaining homeostasis and continually surveys tissues to eliminate damaged cells and cells that are undergoing malignant transformation (Vesely et al. 2011).

With regard to the effects of cigarette smoking on immunity, a critical issue is the degree to which the marked effects of smoking on inflammation are considered immune effects. Because inflammation is an effector arm of immunity and subserves a defensive role in health, this chapter considers adverse effects of smoking on inflammation, particularly where inflammation is directly part of host defense.

Nature of Cigarette Smoking in Relation to Immunity

Cigarette smoke is a damaging and proinflammatory complex mixture that can also directly suppress innate and adaptive immune processes (Sopori 2002; Barnes 2004; van der Vaart et al. 2004; Stampfli and Anderson 2009; Vesely et al. 2011), making it a highly unusual insult in the context of immunity.

As reviewed in detail in previous Surgeon General's reports, the gas and particulate phases of cigarette smoke contain more than 7,000 chemical compounds (USDHHS 2004, 2010). These compounds include direct carcinogens (e.g., methylcholanthrene, benzo[*a*]pyrenes [B[*a*]P], and acrolein); toxins (e.g., carbon monoxide [CO], ammonia, acetone, nicotine, and hydroquinone); reactive solids with chemically catalytic surfaces; and oxidants (e.g., superoxide and nitrogen oxides). These components, either individually or in combination, can affect aspects of the immune system. Freshly generated smoke is a reactive mixture abounding in oxidative moieties that are highly chemically reactive (Kodama et al. 1997). Furthermore, smoke condensate can generate secondary oxidative moieties and form multiple types of chemical adducts. These can be formed either directly or secondarily as a consequence of the induction of enzymes, such as nitric oxide synthase, in the host (Rahman et al. 2002). The targets for chemical modification include cell membrane lipids, proteins, intracellular matrix/scaffolds and extracellular matrix, DNA, and organelles. The induced damage can inactivate or perturb the normal function of these critical targets. The modifications can be particularly compromising when they impinge on immune signaling pathways

Figure 10.5   Diagram of innate and adaptive immunity
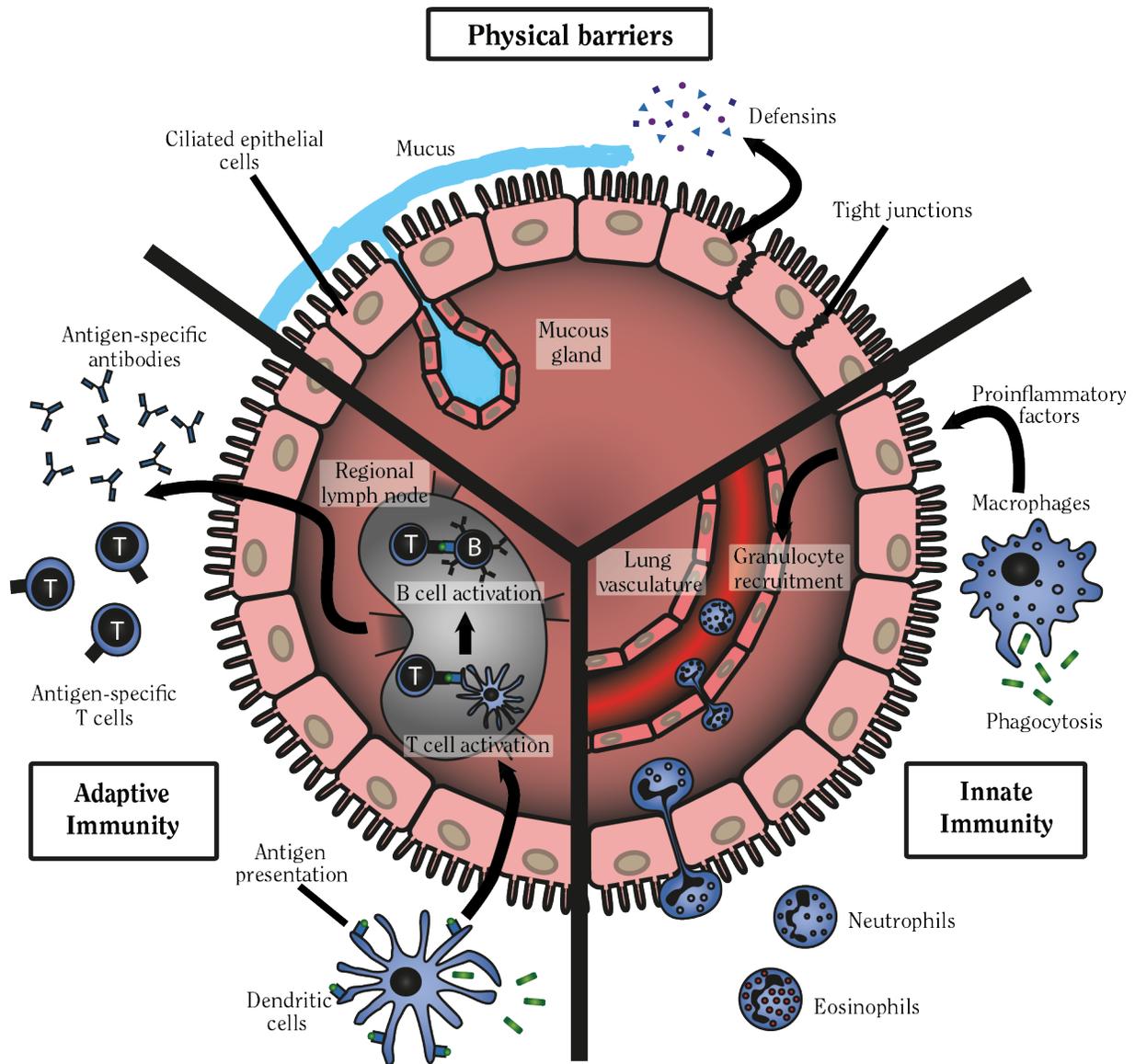
Source: Illustration created by Jake Nikota for this Surgeon General's report.
Note: To illustrate the various aspects of the immune system, the figure is divided into physical barriers, innate, and adaptive immunity. While this separation is convenient, there is an intimate interaction between innate and adaptive immunity, and individual components never respond in isolation. The ciliated respiratory epithelium forms a physical barrier through tight junctions between individual cells and protects by sweeping particles away in the overlying mucus gel layer. A number of innate defense molecules, including defensins, are found in the epithelial lining fluid. In addition to their barrier function, epithelial cells also have potent innate defense capabilities. The main cell types associated with innate immunity are mononuclear lineage cells (monocyte and macrophage subpopulations) and granulocytes (neutrophils and eosinophils). Macrophages are considered the most important phagocytes, playing a critical role in the destruction of pathogens and the removal of dying cells. Other innate immune cells are natural killer cells, natural killer T cells, mast cells, dendritic cells, and nuocytes. Innate immune responses are activated rapidly but do not hold a molecular memory. T and B lymphocytes (T and B cells) are part of the adaptive immune system. Adaptive immunity retains memory, providing protection against subsequent insult by the same pathogen. T cells respond to short peptide fragments of foreign proteins (antigens) presented by specialized antigen-presenting cells, of which dendritic cells are the most important. Dendritic cells reside within the tissue where they capture antigen. Following activation, dendritic cells migrate to secondary lymphoid organs and present antigen to T cells. Cluster of differentiation (CD)4 T cells exert their effects by differentiating into effector cells that are capable of secreting cytokines and chemokines that regulate inflammation. CD8 T lymphocytes differentiate into cytotoxic cells that kill cellular targets. B cells exert their effect largely by producing antibodies. This process requires antigen presentation and help from CD4+ T cells.

and the extracellular matrix via acetylation, nitrosylation, carbonylation, and oxidation, which can affect cell survival, activation, and differentiation of the effector cells drawn to the sites of smoking-induced damage and inflammation. Furthermore, changes in the conformation of cellular proteins induced by smoking can trigger secondary responses, notably the unfolded protein response (Kelsen et al. 2008).

The diverse and sometimes seemingly contradictory effects of smoking on immunity are best understood by considering that smoking is both an activating and suppressing stimulus (Sopori 2002; Barnes 2004; Stampfli and Anderson 2009); that the components of smoke have different pharmacokinetic distributions to different organs; and that the nature of the effects of smoking vary over time. Smoking exerts its effects systemically, as well as in the lungs. The net effect in any given target organ reflects the intersection of the pharmacodynamics of the disposition of various smoke components and secondarily generated reactive intermediates in the context of individual genetic susceptibility, all of which vary markedly among people and probably over time.

A highly informative pattern has emerged from studies of animals. The pattern is often divided into acute, subchronic, and chronic exposure to smoke, where initially strong effects on acute exposure are compensated subchronically by adaptive processes (e.g., induction of detoxifying and antioxidant enzymes), but in genetically susceptible backgrounds, chronic long-term damage results from attrition and defenses becoming overwhelmed (USDHHS 2010). After smoking cessation following shorter term exposure to smoke, the changes are often reversible, but at critical points, the damage to the immune system can be irreversible.

Although tobacco smoke is almost always thought of as a proinflammatory substance, smoking also has suppressive and paradoxical anti-inflammatory effects via its oxidants, CO, nicotine, and some aromatic compounds that modify transcriptional programs (e.g., by activating aryl hydrocarbon receptors [AHRs]). Thus, smoking is able to transiently suppress the key defense process in innate immunity—increasing the likelihood of infection—but later can also promote and amplify inflammation. This property is exemplified by the observation that airway inflammation in people with chronic obstructive pulmonary disease (COPD) who quit smoking increases rather than decreases in the first year after smoking (Willemse et al. 2004). This temporal pattern reflects that active smoking continues to suppress certain defensive inflamma-

tory effector processes in the background of cumulative worsening damage and underlying inflammation. This paradigm of acute-on-chronic cumulative damage is very useful when comparing and understanding the very large experimental dataset on smoking and immunity.

Adverse Effects of Cigarette Smoke on Specific Cellular and Molecular Mechanisms

There is convincing evidence that cigarette smoke impacts a wide range of host defense functions (Sopori 2002; Barnes 2004; van der Vaart et al. 2004; Stampfli and Anderson 2009; Vesely et al. 2011). Some findings across studies have been inconsistent and controversial. These inconsistencies are likely caused in part by differences in key characteristics of study participants, such as smoking history, genetic susceptibility, and SES. Similar methodological issues can apply to animal models and in vitro systems, in which smoke exposure parameters, such as frequency, duration, and mode of smoke exposure (nose-only versus whole body exposure; sidestream smoke included or excluded) vary greatly among studies. Additionally, experimental systems do not fully represent the circumstance of human smoking, but the results are informative on particular elements of immune response and mechanisms.

The following discussion addresses the effects of cigarette smoke on individual components of the immune system, starting with how inhaled cigarette smoke impacts the respiratory epithelium, as these are the first cells to be exposed to cigarette smoke, followed by more classical innate immune cells, including mononuclear cells and macrophages, and finally adaptive immune cells. The cellular and molecular mechanisms discussed in this section are often studied in isolation in experimental investigations. However, the effects of smoking mediated through these mechanisms occur in the context of the full immune system, and every effect observed in an experimental system, even if statistically significant, may not affect overall immunity. As discussed above, the immune system exerts its effects via a complex, highly cross-regulated and often redundant network of cellular and molecular defense mechanisms. Therefore, moving from observations related to the effect of smoking on a particular element of the immune system to a broader interpretation can be problematic.

Figure 10.6   The respiratory epithelium
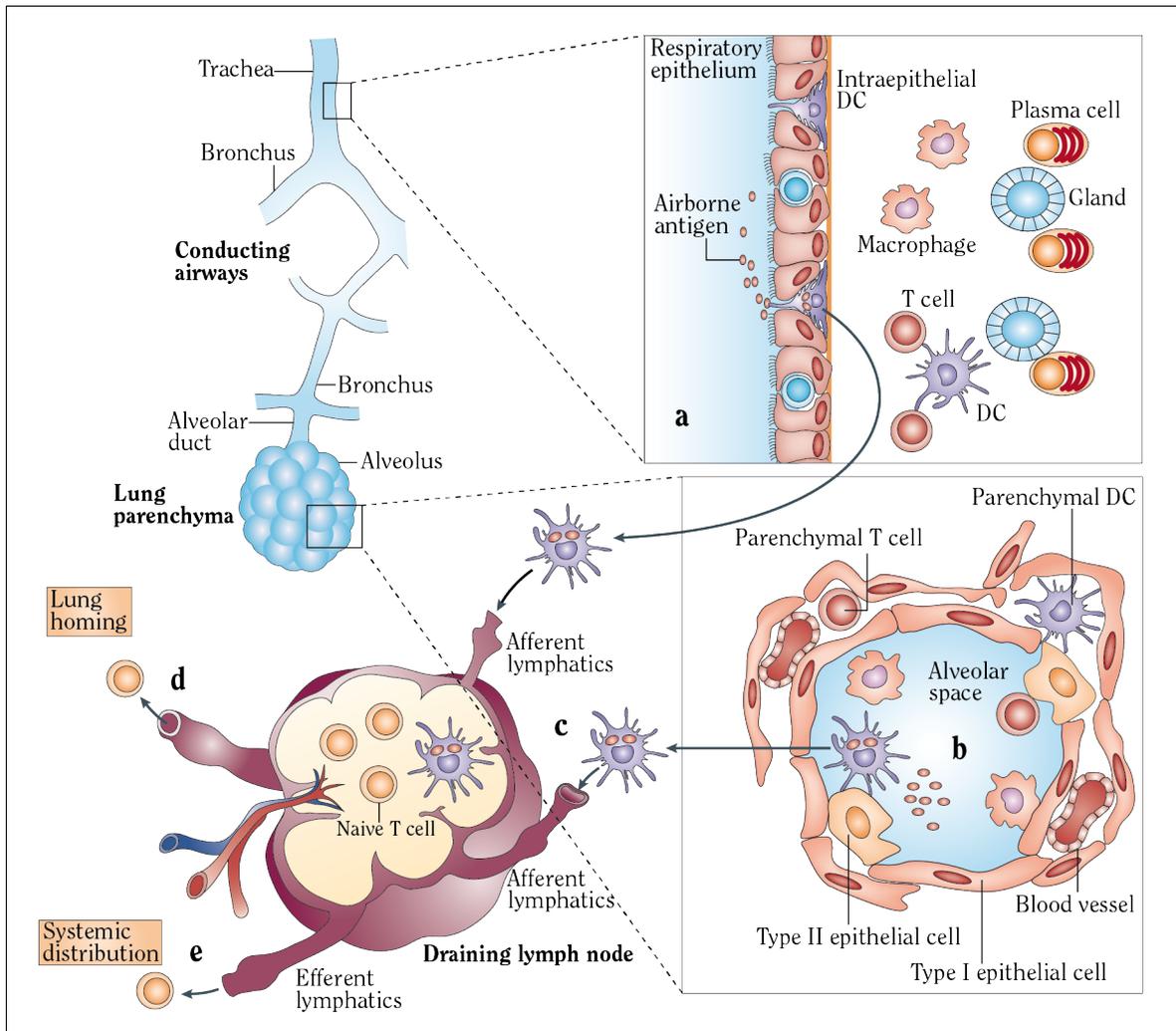
Source: Holt et al. 2008. Reprinted with permission from Macmillan Publishers Ltd., on behalf of Cancer Research UK, © 2008.
Note: Local immune cells in the two lung compartments showing capture of airborne antigens and subsequent recognition by T cells in the draining lymph nodes. Luminal antigens are sampled by dendritic cells that are located within the surface epithelium of the bronchial mucosa **(a)** or in the alveoli **(b)**. Antigen-bearing dendritic cells upregulate CC-chemokine receptor 7 and migrate through the afferent lymphatics to the draining lymph nodes and present antigenic peptides to naïve antigen-specific T cells **(c)**. Activated T cells proliferate and migrate through the efferent lymphatics and into the blood via the thoracic duct. Depending on their tissue-homing receptor profile, effector T cells will exit into the bronchial mucosa through postcapillary venules in the lamina propria or through the pulmonary capillaries in the lung parenchyma **(d)**, or disseminate from the bloodstream throughout the peripheral immune system (e.g., to other mucosal sites) **(e)**. **DC** = dendritic cell.

Respiratory Epithelium

Tobacco smoke reaches the respiratory epithelium at very high concentrations, so that many of the defined effects of smoking on immune effector pathways are exerted on this tissue (Figure 10.6). Far more than a simple barrier, epithelial cells are able to sense microbial agents through PRRs and exert direct antimicrobial effector function (Gribar et al. 2008). This innate immune recognition enables epithelial cells to respond to antigens and allergens, thereby initiating the first step in the host-pathogen interaction, triggering early host defense, and priming the adaptive immune response concurrently. Depending on the level of the airway, the airway epithelium is comprised of a variety of ciliate cells (not found below the bronchi) and secretory cells. This pattern is held in fixed ratio in health, but may change toward more secretory cells, particularly mucus secreting goblet cells as a result of infection. Similarly, the secreted mucins vary in rheology and composition in response to insults. Intercalated between and below the epithelial cells, per se, are antigen-presenting cells (e.g., dendritic cells) and several intraepithelial leukocytes (Lambrecht et al. 1998). The fluid that bathes the epithelium contains an abundance of antioxidants, antiproteases, and innate defense molecules (Widdicombe 1995). Cigarette smoke diminishes key antibacterial defense proteins within the airway lining fluid, including surfactant proteins, beta-defensins, secretory leucocyte protease inhibitors, and lysozymes (Shibata et al. 2008). The epithelium is also metabolically active and able to transform a range of xenobiotics in tobacco smoke. These enzyme systems are induced by cigarette smoke (Spira et al. 2004) and detoxify pollutants but can also convert some carcinogens to more active forms as reviewed in the 2010 Surgeon General's report.

The ciliated respiratory epithelium is a critical defensive barrier able to protect the host against harmful environmental agents. The epithelium forms a barrier via tight junctions between cells and protects by sweeping particles away in the overlying mucus gel layer. Cigarette smoke disrupts the tight bonds at the adherent junctions between epithelial cells, compromising the integrity of the physical epithelial barrier and leading to increased alveolar epithelial permeability (Boucher et al. 1980; Jones et al. 1980). This increased permeability of the respiratory epithelium exposes the lung tissue to inhaled substances, such as microbial agents and other environmental factors. Cigarette smoke further exerts a rapid and adverse effect on mucociliary clearance (Jones et al. 1980; Burns et al. 1989; Dye and Adler 1994).

In vitro studies have demonstrated that cigarette smoke extract activates epithelial cells to produce pro-inflammatory mediators such as IL-8 (Mio et al. 1997).

Contrasting with these observations, cigarette smoke extract attenuates in vitro production of proinflammatory mediators by epithelial cells following stimulation with PAMPs, such as the Toll-like receptor 4 (TLR4) ligand lipopolysaccharide (LPS) (Laan et al. 2004). Cigarette smoke extract also suppresses type I IFN-mediated antiviral immunity following stimulation with double-stranded RNA, a mimic of viral replication, and rhinovirus in lung fibroblast and epithelial cells (Bauer et al. 2008a; Eddleston et al. 2011). In agreement with this observation, influenza-infected nasal epithelial cells from smokers produced less type I IFN than similarly infected nasal epithelial cells from nonsmokers (Jaspers et al. 2010). Moreover, in vitro exposure to cigarette smoke extract modulated rhinovirus-induced chemokine production by airway epithelial cells. Although the neutrophil chemoattractant IL-8 increased in response to rhinovirus infection, expression of chemokine (C-X-C motif) ligand 10 (CXCL-10)—also known as IP-10— and chemokine (C-C motif) ligand 5 (CCL5) was attenuated by cigarette smoke extracts (Eddleston et al. 2011).

Recent evidence from animal models suggests that smoke-exposed epithelium upregulates retinoic acid early transcript 1, the ligand for NK group 2D (NKG2D), rendering it susceptible to NKG2D-mediated cytotoxicity (Borchers et al. 2009). These results imply that aberrant NKG2D ligand expression in the pulmonary epithelium may contribute to the development of structural changes found in COPD and emphysema.

In summary, there is evidence that cigarette smoke activates the airway epithelium to produce proinflammatory mediators, but suppresses the response of the epithelium to viral and bacterial PAMPs. The majority of reports published to-date utilized in vitro exposure of epithelial cell lines or primary cells to cigarette smoke extract. Studies are required to validate these observations in smokers. There is further evidence that smoking compromises airway epithelial host defense by altering the lining fluid, usually by chemical or oxidative inactivation; paralyzing ciliary beating; and damaging the tight junctions between airway epithelial cells.

Alveolar Macrophages and Mononuclear Cells

Alveolar macrophages play a key role in sensing and eliminating hazardous agents due to their strategic positioning in the luminal space of the lung (Twigg 2004; Murray and Wynn 2011). In health, macrophages protect the host because of their ability to recognize, phagocytose, and destroy pathogens; clear cellular debris before triggering secondary inflammation; and release proresolution and healing growth factors. However, in disease, the destructive capacity of macrophages may damage host tissue,

their failure to clear debris may perpetuate inflammation, and their adoption of certain phenotypes may promote tissue scarring and also exert strong immune suppression on lymphocytes. Partly for these reasons, alveolar macrophages have been discussed as central orchestrators of COPD (Barnes 2004).

Cigarette smoking increases the number of macrophages in the alveolar space of smokers and patients with COPD and activates macrophages to produce proinflammatory mediators, reactive oxygen species, and proteolytic enzymes (Hoidal and Niewoehner 1982; de Boer et al. 2000; Russell et al. 2002), providing a cellular mechanism that links smoking with inflammation and tissue damage. Moreover, cigarette smoking compromises the ability of alveolar macrophages to phagocytose bacteria and apoptotic cells (King et al. 1988; Berenson et al. 2006; Hodge et al. 2007, 2008). The process of removing moribund cells in a sterile manner before they proceed to full necrosis and rupture is called efferocytosis (Vandiver et al. 2006). With regard to COPD, a disease with a high number of apoptotic cells in the lungs, it is tempting to speculate that failure to clear dead cells may lead to secondary inflammation through the release of a number of DAMPs or alarmins, including HMGB1, adenosine triphosphate, HSPs, and IL-1α. Moreover, failure to engage anti-inflammatory and quiescence mechanisms that are usually activated during normal efferocytosis may further perpetuate cigarette smoke-induced inflammation (Liu et al. 2008a). Although of interest, further investigation is required to establish the relevance of these processes to cigarette smoke-induced inflammation and, importantly, human health.

As for the epithelium, smoke impairs PAMP sensing and signaling in humans and mice (Soliman and Twigg 1992; Drannik et al. 2004; Chen et al. 2007b; Gaschler et al. 2008). In a study by Gaschler and colleagues (2009), macrophages isolated from cigarette smoke-exposed mice expressed a skewed inflammatory mediators profile after stimulation with nontypeable *Haemophilus influenza* (NTHi), which caused attenuated levels of TNF-α. In parallel, levels of CCL2, CXCL10, and CCL9 increased significantly.

Nuclear factor-kappa B (NF-κB) is a key inflammatory and regulatory transcription factor. Smoking impairs NF-κB pathway activation in macrophages in response to innate immune stimuli—such as LPS from Gram-negative bacteria, the prototypical agonist of TLR4 (Laan et al. 2004; Birrell et al. 2008). This effect is dependent on oxidative stress, which promotes chemical modification of transduction intermediates in the TLR4/MyD88 pathway by carbonylation (Bozinovski et al. 2011).

Functional phenotyping and gene profiling studies support the division of macrophages into two polarized subsets (Biswas and Mantovani 2010). Mirroring the CD4 Th1/Th2 cell paradigm (Mosmann et al. 1986), macrophages have been divided into the classically activated M1 phenotype at one extreme and the alternatively activated M2 phenotype at the other. M1 and M2 polarization relates to broad transcriptional profiles induced by different activation signals, giving rise to macrophage populations with markedly different properties. M1 cells are classically induced by IFN-γ and are primed for TNF-α production and protease release. M2 polarization is associated with induction of acidic mammalian chitinase and is classically induced in response to helminthic parasites (Mantovani et al. 2005). The balance and intensity of this skewing has direct implications for immunity and disease because effective host defense requires a pathogen-appropriate macrophage activation program. At the level of macrophages, smoking alters the transcriptional profile of effector cells generating an intermediate phenotype. Smoking seems to favor neither of these subsets. Instead, smoking skews the inflammatory mediator profile while suppressing key effector functions, creating a distinctive activation state that distinguishes smokers from nonsmokers (Woodruff 2005; Shaykhiev et al. 2009). This state has been described as "partial M1 deactivation/partial M2 activation" of macrophages. As this skewing is at least partially reversible by reduced glutathione, it is dependent on oxidative damage of effector pathways, but the precise molecular pathways have not been elucidated. This skewing of polarity diminishes the effectiveness of macrophages as agents of host defense, promotes secondary inflammation with attendant proteolytic tissue destruction linked to emphysema, and promotes a profibrotic program related to fixed small airway airflow limitation. Moreover, mononuclear lineage cells are essential for tumor induction, growth, and metastasis under a wide variety of conditions (Condeelis and Pollard 2006). Therefore, smoking induces a partial M2-like state, as this phenotype is most closely associated with cancer. Established tumors have a large volume fraction of macrophages that adopt a strongly immunosuppressive state (tumor-associated macrophages) that prevents immune destruction of tumors. However, while smoking can induce M2-like gene programming, smoke-skewed macrophages are more likely to be polarized further in the direct tumor microenvironment.

In summary, there is clear evidence that exposure to cigarette smoke is associated with an increase in macrophages in the alveolar space in humans, as well as in experimental animals. Although cigarette smoke activates these macrophages to produce proinflammatory and tissue-damaging mediators, smoke paradoxically compromises the ability of alveolar macrophages to sense and phagocytose microbial agents and apoptotic cells.

NK and NKT Cells

NK cells are generally considered innate immune cells that play a critical role in host defense against microbial agents and tumors (Sun and Lanier 2011). Unlike T and B cells, NK cells do not express antigen-specific receptors that are generated through VDJ (variable, diversity, and joining gene segments) recombination (Murphy 2012). NK cells exert their effector function through direct cell cytotoxicity via the release of perforin and granzymes, Fas cell surface death receptor ligand-induced apoptosis, and proinflammatory cytokine and chemokine release (Hamerman et al. 2005; Swann et al. 2007). Defects in NK function in smokers were first observed in the 1970s (Ferson et al. 1979) and have been replicated since that time (Tollerud et al. 1989; Lu et al. 2006; Mian et al. 2008). The suppressive effect of smoke exposure on NK cell function and number persists after smoking cessation (Hersey et al. 1983).

NKT cells are a small population of thymus-derived T cells expressing an alpha-beta T cell receptor (TCR) (Berzins et al. 2011). Unlike conventional T cells, NKT cells recognize lipid antigens presented on cluster of differentiation (CD1), a small family of nonclassical MHC I-like proteins. NKT cells are viewed as regulatory lymphocytes that play an important role in promoting immunity to tumors, and microbial agents, and suppressing cell-mediated autoimmunity. Kim and colleagues (2008a) described a novel role of CD1-restricted NKT cell-dependent macrophage activation in the development of prolonged inflammatory changes after viral lung infection. However, the study did not address the impact of cigarette smoke on NKT cells after viral infection. Additionally, Vijayanand and colleagues (2007) observed only low numbers of NKT cells in airway biopsies, bronchoalveolar lavage, and induced sputum of subjects with COPD and healthy control subjects; no significant differences were observed between the two groups, an observation consequently confirmed by others.

In summary, evidence suggests that cigarette smoke suppresses NK cell function in humans, as well as in experimental models. In contrast, the effect of smoking on the NKT cell is understudied and clear conclusions cannot be drawn from the current literature.

Dendritic Cells

Lung dendritic cells are highly efficient antigen-presenting cells. Dendritic cells are indispensable to the initiation of T cell immunity (Mellman and Steinman 2001) and, via a range of PRRs, are an effective component of innate immune defense. Anatomically, dendritic cells are highly susceptible to the effects of smoking because they are usually located subjacent to the respiratory epithelium, although their cellular processes and some cells are also found in the airspace (Figure 10.6) (Jahnsen et al. 2006). Although they are highly efficient in mediating T cell activation, dendritic cells in lung tissue are normally quiescent and only trigger immune reactions after migrating to the T cell area of lymph nodes and upregulating co-stimulatory molecules. However, in diseased tissue, dendritic cells may become competent to activate T cells locally. As with other immune cells, subpopulations with distinct functions are known, and dendritic cells in the lung are often divided into myeloid and plasmacytoid dendritic cells (Tsoumakidou et al. 2008).

Dendritic cell-directed chemokine CCL20 is upregulated in the airways of people with COPD (Demedts et al. 2007), and functional studies in mice have shown that this chemokine contributes to the infiltration of dendritic cells after exposure to cigarette smoke (Bracke et al. 2006). Functionally, increased numbers of dendritic cells likely contribute to the adjuvant properties of cigarette smoke, in part through granulocyte macrophage colony-stimulating factor (GM-CSF)-dependent mechanisms (Trimble et al. 2008). Further evidence suggests that myeloid dendritic cells in the lung promote Th1 and Th17 responses in human emphysema (Shan et al. 2009), linking dendritic cells with disease progression in COPD. However, other evidence indicates that exposure to cigarette smoke decreases the number of dendritic cells in mice (Robbins et al. 2004, 2008). Functional studies suggest that exposure to cigarette smoke decreases the expression of costimulatory molecules and the Th1 cell-inducing cytokine IL-12 and IL-23 by dendritic cells, at least in smoke exposure models involving mice (Robbins et al. 2004, 2008; Kroening et al. 2008). These effects have been linked to immune skewing, predisposing to asthma (Vassallo et al. 2005).

A limited number of studies have investigated the effect of cigarette smoking on dendritic cells in the lungs of healthy smokers and people with COPD. As discussed by Tsoumakidou and colleagues (2008), different and seemingly conflicting results have been reported on the number and function of dendritic cells in COPD. For example, clinical studies show that smokers have a reduced number of dendritic cells in large airways (Rogers et al. 2008) and an increased number, with an immature phenotype, in small airways (Demedts et al. 2007). Complicating the interpretation of the clinical data further is the observation that the number of dendritic cells may expand and contract very rapidly, particularly in response to steroid treatments (Brokaw et al. 1998). In nonhuman primates, the Th1 cell-suppressing and Th2 cell-inducing activity of smoke was most pronounced when exposure

commenced in utero (Wang et al. 2008b). In vitro, ciga-rette smoke extract augmented the production of IL-8 and suppressed the release of TNF-α, *IL-6*, and IFN-α by plas-macytoid dendritic cells. This effect appeared to be medi-ated via suppression of PI3K/Akt signaling in plasmacytoid dendritic cells (Mortaz et al. 2009). Mechanistically, both oxidative stress and nicotine have been associated with induction of a proinflammatory dendritic cell state (Vas-sallo et al. 2008).

In summary, dendritic cells play an important role in the initiation and perpetuation of innate and adap-tive immune responses. The effect of cigarette smoke on dendritic cells is mixed. Some evidence indicates that the number of dendritic cells increases in response to expo-sure to cigarette smoke in humans and mice, although other reports are contradictory. Clinically, these differ-ences may relate to the site that was studied, as smoke may affect dendritic cells differentially in the large and small airways. Data may also be influenced by cur-rent treatment with anti-inflammatory agents that are known to affect dendritic cells. Differences observed in animal studies may result from differences between exposure protocols.

Mast Cells

Mast cells are innate immune sentinel cells that reside in proximity to epithelia, blood vessels, nerves, smooth muscle cells, and mucus-producing glands (Galli et al. 2005). Upon activation, mast cells release a range of different bioactive molecules, including histamine. Research has long shown that mast cells are involved in defense against parasites and closely associated with aller-gic disorders, playing a critical role in type 1 hypersensi-tivity reactions (Bischoff 2007). Although evidence reveals that smokers have higher numbers of mast cells in their sputum compared with former smokers (Wen et al. 2010), the impact of cigarette smoke on the function of mast cells and their role in the pathogenesis of smoking-related disorders is poorly understood (Mortaz et al. 2011). In people with COPD, mast cell populations are associated with phenotype and severity (Andersson et al. 2010; Bal-larin et al. 2012).

Nuocytes

Nuocytes are a novel lineage of immune effector cell and are distinguished by their lack of conventional surface markers (Neill et al. 2010). Nuocytes represent an innate effector cell that appears to play a critical role in type 2 immune responses. The effect of smoking on these cells is not known.

T Cells

T cells are centrally important immune initiators, regulators, and effectors (Castellino and Germain 2006; Zhu et al. 2010). CD4+ Th cells recognize processed extracellular antigen presented in the context of MHC II molecules and differentiate into armed effectors that are able to mediate effects via distinct cytokine secretion pat-terns. Mosman and colleagues (1986) were the first to describe Th1 cells and Th2 cells as two functional subsets of CD4+ T cells. This division is based on cytokine produc-tion: Th1 cells produce IL-2, IFN-γ, and GM-CSF; and Th2 cells produce IL-3, IL-4, IL-5, and IL-13 (Mosmann 1992). Th1 cell-polarized responses are associated with delayed type hypersensitivities, macrophage activation, and immunoglobulin G (IgG) responses. Th2 cell-polarized responses are linked to atopy, allergy, and immunoglobulin (IgE) production. While mechanisms that control Th1 cell- and Th2 cell-polarization are well-understood, research is expanding into other CD4+ T cell subsets, including Th9 and Th17, as well as regulatory T cells and T follicular helper cells (Zhu et al. 2010). CD8+ T cells respond to intracellular antigens presented on MHC I molecules and develop into cytokine-secreting and cytotoxic effectors. Because TCR binding to antigen is highly specific and few primary cells are matched to a given antigen, expansion of responsive clones is a central process in immunity. After expansion and execution of their effector function, the majority of T cells die by apoptosis, leaving only a small residual number of antigen-experienced memory cells.

Cigarette smoke has strong and direct effects on the gene expression profile of the T cell (Charlesworth et al. 2010). Evidence suggests that smoke affects T cell polarity—that is, the net pattern of cytokines and surface stimulator molecules expressed that in turn defines func-tion. Studies have described effector populations within CD4+ Th1 (IFN-γ high) cells and Th17 (IL-17 high) cells (Barceló et al. 2008; Harrison et al. 2008; Chen et al. 2011; Shan et al. 2012). Although the concept of Th1 and Th17 or other subtypes of lymphocytes (and macrophages) is convenient, cytokine expression in effector populations is a stochastic process and polarization signifies a change in the statistical probability distribution profile of gene expression in populations of cells rather than the creation of distinct cellular entities. While oligoclonal expansion of CD4+ cells is documented in humans (Korn et al. 2005; Sullivan et al. 2005), the specificity of these T cells is not well-understood but is important nonetheless, because these cells may be directed against self-antigens, indica-tive of autoimmune processes, or environmental agents (e.g., viruses and bacteria) that may help to explain the

relationship between viral infection and emphysema in experimental models (Kang et al. 2008).

The retention of CD8+ T cells in the lungs of chronic smokers warrants particular attention, as it is a hallmark of COPD (O'Shaughnessy et al. 1997; Saetta et al. 1999). CD8+ T cells can kill cells through T cell-mediated cytotoxicity (Kagi et al. 1996), and these cells can activate alveolar macrophages to produce MMP-12 (Grumelli et al. 2004). MMP-12 is a potent elastin-degrading enzyme that has been linked to emphysema (Hautamaki et al. 1997). Evidence in mice exposed to cigarette smoke suggests that CD8+ T cells are required for inflammation and emphysematous destruction (Maeno et al. 2007). In mice that were chronically exposed to cigarette smoke, CD8+ T cells were oligoclonally expanded and persisted following cessation of smoke exposure (Motz et al. 2008). TCR analysis by polymerase chain reaction amplification followed by spectratyping showed preferential expansion of CD8+ T cells using Vβ7, Vβ9, and Vβ13. Similar oligoclonal expansion was observed in the lungs of smokers and persons with emphysema (Korn et al. 2005; Sullivan et al. 2005).

At present, the mechanisms responsible for this oligoclonal T cell expansion in animal models and human smokers remain unknown. It is not known whether specific antigens drive oligoclonal T cell expansions or, alternatively, whether cigarette smoke directly promotes a reduction in the breadth of the TCR repertoire. Speculatively, the decline in TCR repertoire may contribute to the increased viral infection susceptibility observed in smokers (USDHHS 2004).

Functional studies by Kalra and colleagues (2000) found that exposure to cigarette smoke induced a state of T cell anergy in rats via depletion of intracellular calcium ions. This observation critically contributes to the notion that cigarette smoke is an immunosuppressive agent (Sopori 2002). Subsequent studies in mice and humans did not confirm these observations (Zavitz et al. 2008). The impact of cigarette smoke on T cell responsiveness may be dose-dependent, as serum cotinine levels were markedly different between the two studies. Furthermore, TCR signaling may not be affected at moderate doses of cigarette smoke, and effects on innate immune cells—such as epithelial cells, macrophages, and NK cells—may predominate.

In summary, there is conclusive evidence that both CD4+ and CD8+ T cells accumulate in the lungs of smokers and persons with COPD. Although the evidence suggests that smoking has direct effects on the gene expression profiles of T cells and skews the T cell polarity toward Th1/Th17, major gaps remain in our understanding of cigarette smoke's effect on T cells. Little is known about the specificity and function of T cells accumulating in the lungs following exposure to cigarette smoke. Moreover, the mechanisms that contribute to T cell accumulation and their role in processes that contribute to the pathogenesis of smoking-related diseases remain poorly understood.

B Cells and Antibody-Mediated Autoimmunity

B cells are classically viewed as the cells that form antibodies (via plasma cells), but increasing evidence shows that B cells also regulate other immune effects through their ability to secrete cytokines (Harris et al. 2000; Lund and Randall 2010). Although dendritic cells are usually considered the main antigen-presenting cells, stimulated B cells are also highly effective antigen-presenting cells.

B cells are abundant in lungs of people with COPD, and in those of mice that have been chronically exposed to cigarette smoke (Hogg et al. 2004; Gosman et al. 2006; van der Strate et al. 2006). Immunologically, the formation of bronchial-associated lymphoid tissue is of particular interest, because it represents a tertiary lymphoid tissue. Bronchial-associated lymphoid tissue is a hallmark of Stages 3 and 4 of the COPD Global Initiative for Obstructive Lung Disease (Hogg et al. 2004). Similar structures are observed in mice following prolonged exposure to smoke, which provides an opportunity to study the immunologic structure of this function (van der Strate et al. 2006). At present, the role of bronchial-associated lymphoid tissue in the expression and progression of smoking-related diseases is not well-understood. It is also unclear whether the formation of bronchial-associated lymphoid tissue is a direct consequence of exposure to cigarette smoke or secondary to bacterial colonization of the lower respiratory tract.

Cigarette smoking decreases serum levels of all Ig classes, except for IgE (Holt 1987; Edwards 2009). Likewise, animal studies demonstrated that antibody responses to various antigens were reduced significantly as a consequence of chronic exposure to cigarette smoke. Mechanistically, cigarette smoke-exposed macrophages suppress B cell proliferation by producing secondary reactive oxidative metabolites (Hogg et al. 2004; Ishida et al. 2009).

A body of evidence asserts that COPD may be associated with pathogenic autoantibodies (Cosio et al. 2009). To date, three studies have described three autoimmune autoantibody responses: anti-elastin autoimmunity in smokers with emphysema (Lee et al. 2007b), autoantibodies to epithelium in COPD patients (Feghali-Bostwick et al. 2008), and induction of autoimmune emphysema by anti-endothelial antibodies in rats (Taraseviciene-Stewart et al. 2005). Mechanistically, evidence indicates that ciga-

rette smoke serves as an adjuvant (Trimble et al. 2008), possibly because it is a potent inducer of GM-CSF production in the lungs. The role of these autoantibodies in the pathogenesis of COPD remains disputed, because autoantibodies are common in many inflammatory conditions but they may not be pathogenic. Little evidence exists on the systemic effects, despite the fact that proposed smoking-associated autoantigens, such as elastin, are ubiquitous. It is also unclear whether B cell follicles that form in the lungs of long-term smokers are the site of these autoantibody responses.

An emerging body of literature shows that B cell subsets modulate immune responses in an antibody-independent manner by producing cytokines that direct the T cell function (Lund and Randall 2010). Mirroring the Th1/Th2 cell paradigm, B cells have been termed B effector-1 cells and B effector-2 cells based on their cytokine expression profile (Harris et al. 2000). A third subtype of B regulatory cells (Breg or B10) has also been described that produces IL-10 (Yanaba et al. 2009). The effect of cigarette smoke on these B cell subtypes has not been studied.

In summary, there is clear evidence that the number of B cells is increased in people with COPD and in experimental animals after long-term exposure to cigarette smoke. Further evidence suggests that smoking decreases most Ig classes, except for IgE. Emerging literature posits that chronic smoke exposure is associated with the presence of autoantibodies against elastin, as well as the epithelium and the endothelium. However, more experimentation is required to investigate their contribution in perpetuating smoke-induced inflammation and in the pathogenesis of COPD.

Evidence Synthesis

There is clear evidence that cigarette smoking affects innate and adaptive immunity. Smoking compromises the integrity of the respiratory epithelium and diminishes antibacterial defense proteins in the airway lumen. Smoking is associated with an increase in alveolar macrophages and affects their ability to sense microbial agents and phagocytose bacteria and apoptotic cells. Although some evidence indicates that the number of dendritic cells increases in response to exposure to cigarette smoke in humans and mice, other reports contradict these findings. Cigarette smoking is also associated with increased numbers of T and B cells in the lungs of smokers and people with COPD. Currently, there is only limited information on the function of these cells, as their antigen-specificity and effector function are not well-understood.

Summary

Two conclusions can be drawn from the current knowledge about the impact of cigarette smoke on the immune system. First, the evidence is sufficient to infer that smoking affects components of the innate and adaptive immune system. Second, evidence shows that cigarette smoke both activates and suppresses certain facets of the immune system. Of note, not every observed detrimental effect of cigarette smoke on components of the immune system will necessarily impact overall immunity. Immune cells respond in concert with other cell types and effector mechanisms; therefore, the effects on specific immune processes may be compensated by other cellular or molecular effector mechanisms. Despite compensatory mechanisms, cigarette smoke's adverse impact on innate and adaptive immune processes may compromise the ability to elicit appropriate immune inflammatory responses to clear harmful environmental agents and maintain tissue homeostasis.

Effects of Components of Cigarette Smoke on Immunity

The following discussion presents an overview of the effect of a selected few individual components of cigarette smoke on immune function. There is conclusive evidence that the particulate phase of cigarette smoke directly activates phagocytic lung cells, which accounts for some of the proinflammatory effects of smoke. Moreover, gas-phase toxins and oxidants directly damage lipids, proteins, DNA, and organelles and thereby have a proinflammatory effect. Contrasting with these proinflammatory effects, smoke may also exert immune suppressive and anti-inflammatory properties via oxidants, CO, nicotine, and some aromatic compounds. Cigarette smoke can chemically modify signaling pathways and the extracellular matrix, affecting cell activation, differentiation, and survival. While informative, the findings of studies investigating individual components to the overall effect of cigarette smoke on immunity have to be cautiously interpreted, as the net effect of cigarette smoke on the immune system ultimately reflects the sum of the interactions of all of its components exerted over time. Hence, any biological activity observed in isolation may not reflect the compound's effect within the complex mixture, but mechanistic insights are gained.

Nicotine

There is compelling evidence that nicotine affects cellular immunity, either directly by interacting with nicotinic cholinoceptors or indirectly via its effects on the nervous system. This topic is covered in Chapter 5, "Nicotine" in the section on "Health Consequences of Nicotine Exposure."

Acrolein

Acrolein is a highly reactive intermediate formed in the context of smoking by combustion and oxidation of lipids in the cell membrane. Acrolein is known for its ability to form protein adducts, bind to DNA, and induce oxidant-dependent damage to cellular structures and organelles. Lambert and colleagues (2005) found that acrolein and crotonaldehyde are the main constituents of the vapor phase that inhibit IL-2, IFN-γ, and TNF-α production by stimulated peripheral blood lymphocytes. This effect is reduced by *N*-acetylcysteine. In a study by Hristova and colleagues (2012), innate immunity was suppressed, similar to that of the direct effects of smoking, in mice exposed for 4 hours to 5 parts per million of acrolein. This effect was prominent in macrophages where impairment of NF-κB production was associated with depressed activation of c-Jun N-terminal kinase (JNK) and activation of c-Jun. Proteomic analysis revealed that acrolein was able to chemically modify recombinant JNK2 by forming protein adducts at CYS41 and CYS177, which are parts of JNK2 thought to be needed to allow activation of mitogen-activated protein kinase binding and JNK2 phosphorylation. In a similar previous study, Lambert and colleagues (2007) found that acrolein-induced suppression of cytokine release was associated with alkylation of cysteine and arginine residues on the NF-κB binding domain, which, presumptively, then reduced the ability of this transcription factor to regulate positively gene expression. Green (1985) showed that acrolein suppressed phagocytosis and antibacterial defenses by alveolar macrophages against staphylococci both in vitro and in vivo. Mechanistically, acrolein can impair primary recognition of LPS by the TLR4 receptor (Lee et al. 2008). The effects of acrolein on epithelium (e.g., suppression of beta-defensins that protect against infections) can occur at concentrations that do not cause overt oxidative stress (Lee et al. 2007c). In pathogen interaction studies, exposure to acrolein after viral infection in vivo markedly worsened the impairment of antibacterial defense caused by virus (Astry and Jakab 1983). In fractionation studies seeking to identify the factor(s) responsible for smoke-induced suppression of lymphocyte proliferation, acrolein was the most prominent cause (Lambert et al. 2005).

Broadly, acrolein has potent suppressive effects on innate and adaptive immune cells both in vitro and in vivo. The effects are observed at a physiologically relevant concentration.

Polycyclic Aromatic Hydrocarbons

Cigarette smoke contains several polycyclic aromatic hydrocarbons, notably B[*a*]P, that are known agonists of AHR (Löfroth and Rannug 1988; Meek and Finch 1999; Kitamura and Kasai 2007). AHR is a ligand-gated transcription factor that modulates gene expression and is notable for the very low concentration of ligand needed to exert effects. The receptor is widely expressed and in the immune system is prominent in Th17 and dendritic cells. The importance of AHR activation in cancer induction is strongly supported by studies showing that mice lacking this receptor are protected from B[*a*]P-induced carcinogenesis (Shimizu et al. 2000). An important part of carcinogenesis appears to be the HSP90-dependent induction of cytochrome P-450 isoforms that biotransforms the components of cigarette smoke into DNA adduct-forming carcinogens (Hughes et al. 2008).

Seemingly paradoxical, AHR-deficient mice showed enhanced inflammation in response to exposure to smoke (Thatcher et al. 2007). This appeared to result from premature degradation of REL-like, domain-containing protein, which leads to over-activity of NF-κB, a major inflammatory transcription factor. In a study by Head and Lawrence (2009), AHR stimulation in a model of respiratory viral infection using influenza A, was associated with increased neutrophilic inflammation, while the adaptive CD8+ T cell response was suppressed. The latter effects on adaptive immunity were stronger on primary than on memory responses (Lawrence et al. 2006; Neff-LaFord et al. 2007).

IL-17 is an important effector cytokine in the development of sustained neutrophilic inflammatory pathologies. Smoking exerts an adjuvant-like effect via the AHR and has been shown to promote the induction of IL-17A, CCL2, and macrophage activation that in turn promotes the formation of emphysema in mice (Chen et al. 2011). Activation of AHR is strongly implicated in smoke-induced atherosclerosis, likely reflecting dysregulated inflammation (Wu et al. 2011a).

In summary, AHR ligands contained within cigarette smoke exert both proinflammatory and immune-suppressive effects. Of interest is the link between the AHR and IL-17, an important cytokine in neutrophilic inflammatory conditions.

Carbon Monoxide

Cigarette smoke contains high concentrations of CO. A molecular machinery exists to respond to CO, considering the role of endogenously generated CO as a signaling mediator (Motterlini and Otterbein 2010). Thus, the effects of CO in smoke can be largely understood as an exaggeration of the normal physiological effects of endogenous CO.

Endogenous CO is formed during the catabolism of heme by HMOX, which exists in two forms: inducible heme oxygenase (decycling) 1 protein (HMOX1) mouse and constitutively expressed HMOX2 (Motterlini and Otterbein 2010). Oxidants strongly induce HMOX1, which is likely to play a protective role against oxidant-induced damage. Transcriptional efficiency of HMOX is regulated, in part, by the (GT)n dinucleotide repeat in the 5′-flanking region of the gene; the greater the number of repeats, the weaker the gene induction. A long dinucleotide repeat sequence has been linked to emphysema susceptibility in smokers (Yamada et al. 2000), lung adenocarcinoma (a type of cancer common among people with COPD), and decline of lung function (Kikuchi et al. 2005; Nakayama et al. 2006). Cell culture and in vivo studies showed that HMOX can protect from oxidative stress (Lee et al. 1996; Otterbein et al. 1999).

Coregulation of oxidative stress is not the only known effect of CO, which also protects cells from apoptosis and exerts weak, but real anti-inflammatory and antiproliferative effects in a range of in vivo and in vitro cell models. CO activates the soluble guanylate cyclase/guanosine monophosphate transduction pathway in many different cell types, including immune effector cells. In macrophages, CO inhibits signaling by TLR2, 4, 5, and 9 (but not TLR3) (Song et al. 2003; Nakahira et al. 2006). Here, the mechanism of action of CO is complex: it acts indirectly by suppressing the trafficking of TLRs into lipid-raft signaling complexes in the cell membrane. Evidence also indicates that CO suppresses allograft rejection (Song et al. 2003) via immune suppression, antiproliferative effects, and protection against apoptosis. These effects occur at the higher concentrations (approximately 500 parts per million) that may be encountered during exposure to smoke. Of note, the effects of soluble CO as a signaling molecule are short-lived. However, CO may exert persistent effects via protein carbonylation.

In summary, CO is abundant in cigarette smoke. Although CO protects cells from apoptosis and exerts mild anti-inflammatory and antiproliferative effects, its importance to cigarette smoke's overall effect on the immune system is not well understood.

Other Mechanisms

Protein Derivatization by Oxidants and Chemically Reactive Intermediates

Oxidants and chemically highly reactive intermediate moieties that are present in cigarette smoke frequently react with proteins (and other critical macromolecules), changing their function through derivatization and formation of consequent structures (such as polymers). Protein modification may also underlay the continuous oxidative stress that is caused by chronic exposure to smoke. Glutathione is one of the main intracellular defenses against oxidation. Under normal conditions, glutathione is reversibly oxidized and can be converted back to itself. Evidence suggests that cigarette smoke may effectively deplete glutathione by forming irreversible glutathione-aldehydes (van der Toorn et al. 2007).

In the context of smoking, *S*-glutathionylation (covalent binding of glutathione to protein thiols, which can be reversed enzymatically by glutaredoxins) and *S*-nitrosylation (modification of protein thiols by nitric oxide, which occurs in a process that can be reversed by the enzyme alcohol dehydrogenase) are common events (Kuipers et al. 2011). However, one of the most important processes of this type is carbonylation, which can be irreversible. Carbonylation is a chemical process where CO is introduced into the chemical structure of target molecules. Kuipers and colleagues (2011) extensively studied the nature of post-translational modifications caused by smoking and found that *S*-glutathionylation and *S*-nitrosylation were both decreased by smoking over a 4-week period, whereas carbonylation increased due to increased oxidative stress. This observation is consistent with the widespread occurrence of carbonylation in the lungs and also in peripheral tissues of smokers (Rahman et al. 2002; Barreiro et al. 2005). Describing the functional consequences of carbonylation for immunity, Bozinovski and colleagues (2011) associated in vitro cigarette smoke-extract mediated carbonylation—not *S*-glutathionylation and *S*-nitrosylation—with decreased TNF-α expression and phagocytosis by mouse alveolar macrophages. Carbonylation can also trigger autoantibody production as it alters the physical structure of proteins and generates neo-antigens, which is one probable link between smoking and autoimmunity (Kirkham et al. 2011). In addition to altering protein structure, carbonylation targets proteins for proteolytic destruction and may lead to pathogenic protein aggregation (Nystrom 2005).

In summary, chemically reactive moieties present in cigarette smoke carbonylate proteins and other macromolecules in smokers and experimental models. Although carbonylation caused by cigarette smoke is associated with

altered macrophage function, further studies are required to understand the biological significance of this effect and determine the specific molecular targets of carbonylation. Chemical modification of the host's proteins can generate neo-antigens, leading to the production of autoantibodies against these chemically modified molecules.

Autophagy and the Unfolded Protein Responses

Consequences of oxidative damage to protein structure include autophagy and unfolded protein responses (UPRs). Autophagy is a catabolic process during which cellular components are degraded via the lysosome (Ryter et al. 2012). Increased autophagy has been documented electromicrographically in people with COPD and by inference from the expression or activation of autophagy-associated proteins (LC3B, autophagy-related 4 [ATG4], ATG5/12, ATG7) (Chen et al. 2008). Mechanistically, autophagy has been related to smoke-induced decreases in histone deacetylase activity that in turn increase binding of early growth response-1 and E2F factors to the autophagy gene *LC3B* promoter, thus increasing *LC3B* expression. Of note, Monick and colleagues (2010) observed autophagy defects in alveolar macrophages that were isolated from smokers. These defects were associated with impaired protein aggregate clearance, dysfunctional mitochondria, and defective delivery of bacteria to lysosomes, linking autophagy to compromised bacterial host defense.

UPR is normally a homeostatic process that controls stress in the endoplasmic reticulum in response to accumulation of misfolded or unfolded proteins (Hetz 2012). UPR orchestrates the recovery of endoplasmic reticulum function, as failure to adapt to endoplasmic reticulum stress results in apoptosis. Normally the cell responds by slowing protein synthesis and increasing production of molecular chaperones needed for correct protein folding. UPR is prominently induced in the lungs of chronic cigarette smokers, as reflected by upregulation at the protein level of the UPR chaperones, GRP78, calreticulin, and calnexin (Kelsen et al. 2008). While there is evidence that acrolein, a component of cigarette smoke, induces endoplasmic reticulum stress and causes airspace enlargement (Kitaguchi et al. 2012), it is unclear whether UPR is linked to the formation of emphysema. Furthermore, despite accumulating evidence that immune responses can be adversely affected by abnormalities in the UPR (Todd et al. 2008), no formal experimental link has been established between UPR and impaired immunity caused by smoking.

In summary, autophagy and UPR are intrinsic responses to oxidative damage to proteins. Evidence suggests that cigarette smoking is associated with defective autophagy in smokers. These defects compromise bactericidal activity of alveolar macrophages and clearance of modified proteins. Despite evidence that UPR is activated in smokers, whether these processes contribute to impaired immunity is not understood.

Evidence Synthesis

A wealth of information is available to assess the impact of the individual components of cigarette smoke on immune function. Nicotine exerts both immune stimulatory and suppressive effects directly through receptors expressed on immune cells and indirectly via the nervous system. Acrolein has powerful immune-suppressive effects on innate and adaptive immune cells. Other components, such as AHR ligands, exert both proinflammatory and immune-suppressive effects, but CO has weak but significant anti-inflammatory and antiproliferation effects. Oxidants and chemically reactive intermediates can modify proteins and macromolecules, compromising their function and generating neo-antigens that may drive autoimmune processes.

Conclusion

1. The evidence is sufficient to infer that components of cigarette smoke impact components of the immune system. Some of these effects are immune activating and others are immune-suppressive.

2. While research on components of smoke is informative, it is difficult to project how an individual component's impact on the immune system relates to its effect within cigarette smoke as a whole. Furthermore, effects observed in isolation may be mitigated by or magnified in the context of exposure to the full mixture of cigarette smoke. Hence, observations made using individual components have to be interpreted cautiously.

Immunologically Mediated Diseases Associated With Smoking

Exposure to cigarette smoke is a determinant of the incidence, prevalence, and severity of a large number of diseases, whose diathesis is predicated on immunologic dysregulation (Sopori 2002; Stampfli and Anderson 2009). These diseases include diverse viral and bacterial infections, especially but not exclusively of the lungs (invasive pneumococcal disease, pneumonia, influenza, tuberculosis [TB]); periodontal disease; bacterial meningitis; postsurgical infection; rheumatic disorders, especially

rheumatoid arthritis and SLE; Crohn's disease; and cancers (USDHHS 2004, 2010).

Observational evidence shows that smoking may also reduce the incidence of several diseases known to be immunologically mediated, including ulcerative colitis, sarcoidosis, farmer's lung, pigeon breeder's disease, and Sjögren's syndrome (Sopori 2002). Although this duality may seem paradoxical, it is consistent with the complex nature of smoking as both an immunologic stimulant and suppressant. Similarly, the constituents of cigarette smoke can concurrently stimulate and suppress different components of complex immune effector networks.

Smoking, Immunity, and COPD

COPD is an umbrella term, describing a group of overlapping pathologies that lead to airflow limitation that is largely irreversible (Rabe et al. 2007) (see Chapter 7, "Respiratory Diseases"). The main pathological components of COPD are emphysema (the loss of gas-exchanging lung parenchyma), bronchiolitis (inflammation and fibrosis of small airways), and bronchitis accompanied by airway mucus hypersecretion. The causative role of smoking in the development of COPD is well-established (USDHHS 2004, 2010).

According to widely accepted research, chronic inflammation contributes to airflow limitation seen in COPD (Hogg 2004; Rabe et al. 2007), causing structural changes and narrowing of the small airways. McDonough and colleagues (2011) reported that narrowing and disappearance of small conducting airways precedes the onset of emphysematous destruction in COPD.

This discussion considers only the intersection of smoking, immunity, and COPD and does not consider the general pathobiology of COPD, a topic covered extensively in the 2010 Surgeon General's report (USDHHS 2010). Answers to several broad questions are of interest to the field: how do immune cells contribute to the pathogenesis of COPD; why is immunity persistently weakened and compromised after COPD becomes established; how does this altered immunity contribute to recurrent chest infections that provoke exacerbations; and what is the link between COPD and lung cancer?

Immune Mechanisms of Cigarette Smoke-Induced Inflammation

Extensive analysis of lungs affected by COPD has revealed that effector cells of both the innate and the adaptive immune system are present in increased numbers in the lungs and show signs of recent activation. Macrophages, neutrophils, and T and B lymphocytes are all increased in various parts of the COPD-affected lung (Finkelstein et al. 1995; Di Stefano et al. 1998, 2004; Saetta

et al. 1999; Hogg et al. 2004; Tate et al. 2009; Laws et al. 2010; Singh et al. 2010), and several mediators released by these inflammatory cells likely play a critical role in airflow obstruction by inducing mucus hypersecretion, bronchial constriction, and alveolar destruction. Surface profiling of the lymphocyte population revealed strong enrichment for CD4+ T cells and especially C8+ T cells in smokers and people with COPD (Tsoumakidou et al. 2004).

Although evidence indicates that both adaptive and innate immune components contribute to cigarette smoke-induced inflammation, animal studies using mice carrying the severe combined immunodeficiency mutation, which lack functional T and B cells, have revealed that the presence of an adaptive immune system is not required for smoke-induced inflammation and the formation of emphysema (D'hulst et al. 2005a,b). Studies using *Rag1*-deficient mice that lack functional T and B cells confirmed that innate immune processes are sufficient to elicit cigarette smoke-induced inflammation (Botelho et al. 2010). There is clear evidence that macrophage-derived proteases, such as MMP-12, a potent elastin-degrading enzyme also known as macrophage metalloelastase, and neutrophil-derived proteases, such as neutrophil elastase, contribute to emphysematous lung destruction in mice (Hautamaki et al. 1997; Shapiro et al. 2003).

Findings from other studies seemingly contrast with these findings. In a study by Maeno and colleagues (2007), CD8+ T cell-deficient mice showed a blunted inflammatory response and did not develop airspace enlargement in response to long-term exposure to cigarette smoke. Further confirming an important role for adaptive immune cells, Motz and colleagues (2010) showed that transfer of CD3+ T cells, which were isolated from the lungs of cigarette smoke-exposed mice, to T cell-deficient recipients (*Rag2*-/-) induced substantial pulmonary changes, including monocyte/macrophage and neutrophil accumulation, activation of proteases, and airspace enlargement. While these studies provide evidence that the adaptive immune system can induce disease, further research is required to determine the specificities of T cells activated by cigarette smoke, as this will provide needed information about the processes that drive adaptive immunity.

Taken together, these findings indicate that smoke-induced stimulation of innate and adaptive immunity can cause lung disease. In most affected people, both innate and adaptive immune processes likely contributed to disease, because these systems are highly entwined physiologically. Histological examination revealed that emphysematous changes correlate with macrophage and lymphocyte numbers, especially the number of CD8+ T cells (Majo et al. 2001). Mechanistically, CD8+ T cells can activate macrophages to secreted macrophage matrix MMP-12 (Grumelli et al. 2004).

Mechanisms by which cigarette smoke activates innate and adaptive immunity are less well-understood. Doz and colleagues (2008) demonstrated a critical role of TLR4/MyD88 and IL-1R1/MyD88 signaling in cigarette smoke-induced neutrophilia. While cigarette smoke contains biologically relevant levels of LPS (Hasday et al. 1999), Doz and colleagues (2008) suggested that HSP70, an endogenous TLR4 ligand, may drive smoke-induced neutrophilia. Maes and colleagues (2008) discussed whether the TLR4-dependency was reflective of the short-term exposure protocol utilized in the study by Doz and colleagues (2008).

The IL-1R1-dependency of cigarette smoke-induced inflammation has been consistently observed in several studies (Botelho et al. 2011; Pauwels et al. 2011). More specifically, Churg and colleagues (2009) demonstrated that processes associated with IL-1R1 signaling pathways contributed to the formation of emphysema; IL-1R1-deficient mice had approximately 60% reduced airspace enlargement following prolonged cigarette smoke exposure. Of note, inflammatory processes elicited by cigarette smoke required crosstalk between IL-1α+ hematopoietic and IL-1R1+ nonhematopoietic cells (Botelho et al. 2011). IL-18, another member of the IL-1 family, was also shown to contribute to cigarette smoke-induced inflammation and airspace enlargement (Kang et al. 2007). Expression of IL-1β- and IL-18-induced pulmonary inflammation and emphysema, of which the pathologies of both are associated with COPD (Lappalainen et al. 2005; Kang et al. 2007). While there is convincing evidence that members of the IL-1 family contribute to cigarette smoke-induced inflammation, it is currently not known whether components of cigarette smoke directly activate IL-1 and IL-18 expression or whether DAMPs, secondary to cigarette smoke-induced tissue damage, induce IL-1 and IL-18 expression. The latter is supported by observations from Chen and colleagues (2007a) showing that dying cells elicit inflammation through IL-1 pathways. Evidence suggests that extracellular adenosine triphosphate, a known DAMP, contributes to cigarette smoke-induced inflammation through purinergic receptor signaling in an IL-1-dependent manner (Eltom et al. 2011; Lucattelli et al. 2011; Cicko et al. 2010).

There is conclusive evidence that cigarette smoke activates innate and adaptive immune processes that contribute to the pathogenesis of COPD in susceptible people. While cellular and molecular mechanisms of the pathogenic inflammation associated with COPD are being uncovered in murine models, further research is required to delineate how cigarette smoke activates innate immune processes and target antigens of the adaptive immune response. The latter is of particular interest, because it will provide insight as to whether T and B cells that accumulate in the lungs of smokers are responding to environmental agents, such as viruses and bacteria or potentially attack host tissue.

Smoking and Respiratory Infections

Cigarette smoking is strongly associated with an increased prevalence and severity of diverse infections (Nuorti et al. 2000; Arcavi and Benowitz 2004). This is especially striking for infections of the respiratory tract where increased risks of pneumonia, invasive pneumococcal disease, influenza, and TB have been identified epidemiologically. Moreover, viral and bacterial infections are a major cause of acute exacerbation of COPD, which punctuates the natural course of this disease (Sethi and Murphy 2001; Wedzicha 2004; Sethi 2005; Donaldson and Wedzicha 2006; Papi et al. 2006; Rabe et al. 2007). Taken together, these studies show that smoking is associated with an increased incidence of microbial infection of the respiratory system, providing evidence that cigarette smoke may compromise respiratory host defense.

Smoking and Viral Infections

During epidemic influenza A, smoking significantly increased the incidence and severity of influenza in healthy young adults (MacKenzie et al. 1976; Kark et al. 1982) and suppressed vaccine responses (MacKenzie et al. 1976). Exposure to secondhand smoke as a young child was a risk factor for respiratory syncytial virus (RSV) bronchiolitis (Gurkan et al. 2000). Maternal postnatal smoking is an important risk factor for more severe bronchiolitis after RSV infection (Bradley et al. 2005).

Cigarette smoke impacts several key antiviral host defense mechanisms that likely contribute to increased risk of respiratory viral infection. For example, cigarette smoke extract suppressed in vitro antiviral immunity via oxidant-dependent processes at least in part due to hypoactivation of RIG1, an intracellular innate immune sensor that responds to virus (Wu et al. 2011b). Furthermore, cigarette smoke compromised the induction of an antiviral state by suppressing the immediate early phase and the inductive phase of the type I IFN response (Bauer et al. 2008a; Eddelston et al. 2011). Moreover, smoking suppressed T cell responses to influenza (Feng et al. 2011), although more studies are required because this effect was not consistently observed among studies (Robbins et al. 2006). Smoking also directly suppresses the activity of NK cells, weakening antiviral defenses (Mian et al. 2008). Other studies have shown similarly adverse effects of cigarette smoke on responses to viruses by peripheral blood mononuclear cells (Mian et al. 2009) and respiratory epithelial cells (Hudy et al. 2010; Eddleston et al. 2011).

In several animal models of viral infection, smoking adversely affects the normal defensive immune inflammatory response in vivo (Robbins et al. 2006; Gualano et al. 2008; Kang et al. 2008; Botelho et al. 2011). Most studies reported to date have used the influenza virus to examine the consequences of cigarette smoke to antiviral host defense. With the development of a transgenic mouse expressing human *ICAM-1* (Bartlett et al. 2008), which is the receptor for rhinovirus, studies examining the impact of cigarette smoke exposure on rhinovirus infection would be topical, given the clinical data reported for people with COPD who are also infected with rhinovirus (Mallia et al. 2011). The most noteworthy effect was the enhancement of inflammation (Robbins et al. 2006; Gualano et al. 2008; Kang et al. 2008; Botelho et al. 2011), which is associated with increased mortality (Robbins et al. 2006). Moreover, increased numbers of influenza-specific CD8+ T cells were observed in cigarette smoke-exposed mice (Gualano et al. 2008). The heightened inflammatory response was associated with increased inflammatory mediator expression, which in turn accelerated the formation of emphysema (Kang et al. 2008), providing evidence that altered immune defense to viral agents contributes to the pathogenesis of emphysema. Mechanistically, increased inflammation and remodeling was IL-18Rα-dependent, although another study (Botelho et al. 2011) suggested that IL-1R1-dependent activation of the airway epithelium contributes to the exacerbated inflammatory response elicited by influenza virus in smoke-exposed mice. In a study by Gualano and colleagues (2008), exposure to cigarette smoke was associated with a transient increase in viral burden following influenza infection, suggesting that compromised viral clearance may drive the exacerbated inflammatory response. Contrasting with these observations, studies pursued by other research groups did not show increased viral titers in cigarette smoke-exposed influenza-infected animals (Robbins et al. 2006; Kang et al. 2008; Botelho et al. 2011).

To investigate most effectively the effects of cigarette smoking on lung viral host defense, studies such as those published by Mallia and colleagues (2011) are of critical importance. Using a model of controlled rhinovirus infection among human volunteers, the study demonstrated that infection in people with COPD could induce the symptomatic, physiologic, and inflammatory features that have been previously reported in naturally occurring exacerbations of the disease. Rhinovirus infection was associated with an increased neutrophilic inflammation and deficient production of IFN-β. Although this addresses an important and highly relevant question related to acute exacerbations of COPD, the study did not include a nonsmoking control group. Hence, further stud-

ies are required to investigate the direct effects of cigarette smoke on immune and inflammatory processes elicited by experimental viral infections. This is an important consideration, as decreased type I IFN levels are not consistently observed in murine models of exposure to smoke (Robbins et al. 2006; Bauer et al. 2010), despite in vitro findings (Bauer et al. 2008a), and it is possible that decreased type I IFN levels are unique to smokers who develop COPD.

In summary, there is conclusive evidence that smoking is associated with an increased risk of respiratory viral infection. Given the complex and multilayered nature of the immune system, it is not known which of cigarette smoke's multiple adverse effects on host defense pathways affect the overall responses to viral agents. Animal studies consistently show that exposure to cigarette smoke exacerbates inflammatory processes elicited by viral infection. Mechanistic studies suggest that members of the IL-1 family, such as IL-1 and IL-18, contribute to this exacerbated inflammatory response. Further evidence suggests that cigarette smoke compromises key innate antiviral host defense mechanisms. Of particular interest are reports in which human volunteers were infected with clinically relevant viral pathogens under controlled experimental conditions. Such an approach will provide important insights into the effects of cigarette smoke antiviral host defense and its importance to the pathogenesis of smoking-related diseases, such as COPD.

Smoking and Bacterial Infections

Consistent with the increased risk of bacterial infections, cigarette smoke decreases important innate antibacterial defense proteins (Shibata et al. 2008), impairs the ability of macrophages to phagocytose and kill cellular pathogens (King et al. 1988; Berenson et al. 2006; Hodge et al. 2007, 2008), and compromises mucociliary clearance and the integrity of the epithelium (Boucher et al. 1980; Jones et al. 1980; Burns et al. 1989; Dye and Adler 1994). Where long-term smoking has caused organ disease, those organs, especially the lung, manifest further perturbed immunity. This effect relates strongly to exacerbations caused by chest infection in COPD, which can be provoked by both bacteria and viruses (Sethi and Murphy 2001; Wedzicha 2004; Papi et al. 2006).

Altered macrophage function and altered mucociliary clearance may also contribute to microbial colonization of the lungs of smokers, defined in the past by isolation of positive culture and viewed as a consequence of long-term smoking (Patel et al. 2002; Sethi and Murphy 2008). However, more recent metagenomic data have led to a revision of this concept; it is now understood that the healthy "sterile" lung has a bacterial metagenome

(Charlson et al. 2011). A similar bacterial metagenome was observed in healthy nonsmokers and smokers without COPD. In contrast, changes in the lung microbiome were observed in those with severe COPD (Charlson et al. 2010; Hilty et al. 2010; Erb-Downward et al. 2011; Sze et al. 2012). Changes in the microbiome may be confined to a specific area, as significant differences in bacterial communities were observed in people with advanced COPD between different sampling sites (Erb-Downward et al. 2011). Interestingly, metagenomic analysis revealed that smoking has a significant and independent effect on the microbiota of patients with active Crohn's disease (Benjamin et al. 2012), suggesting that the effect of cigarette smoke on the microbiota is observed at sites distant to the lungs.

Studies in animal models have demonstrated that exposure to cigarette smoke exacerbated inflammatory responses elicited by several different bacterial agents, including NTHi, *Pseudomonas aeruginosa (P. aeruginosa)* and *Streptococcus pneumoniae* (*S. pneumoniae*) (Drannik et al. 2004; Gaschler et al. 2009; Phipps et al. 2010; Harvey et al. 2011). In all studies, the cellular composition of the bacteria-exacerbated inflammatory response was neutrophilic in nature. Several of these in vivo models found increased bacterial burden, following bacterial challenge, in cigarette smoke-exposed mice compared with controlled mice (Drannik et al. 2004; Phipps et al. 2010; Harvey et al. 2011), providing evidence that compromised bacterial clearance drives these inflammatory processes. Contrasting with these observations, Gaschler and colleagues (2010) reported that the excessive inflammation observed in cigarette smoke-exposed, NTHi-infected mice was associated with a decreased bacterial burden. Mechanistically, this decrease was linked to increased titres of NTHi-specific IgA antibodies in the bronchoalveolar lavage fluid of cigarette smoke-exposed mice. NTHi-specific antibodies observed in cigarette smoke-exposed mice were likely natural antibodies against conserved bacterial targets that have been shown to protect against nasal colonization with genetically diverse NHTi strains in mice (Zola et al. 2009). Of interest, cigarette smoke-exposed mice expressed a skewed inflammatory mediator profile following NTHi challenge (Gaschler et al. 2009). This altered inflammatory mediator expression was also observed in alveolar macrophages cultured ex vivo, implying a crucial role of alveolar macrophages in mediating this skewed phenotype. Despite the different findings regarding bacterial clearance, increased cellular inflammation was consistently observed in animal models. These data suggest that cigarette smoke skews host defenses against bacteria, leading to exaggerated and possibly damaging inflammatory responses to bacteria.

There is good evidence that viral infections divert local immunity and render the host susceptible to subsequent bacterial infection. Mechanisms proposed through which viral infections predispose to bacterial superinfection include disruption of the respiratory epithelium (Avadhanula et al. 2006), impairment of ciliary function (Jakab and Green 1972; Park et al. 1993), and reduced innate antibacterial function (Jakab and Green 1976; Navarini et al. 2006; Didierlaurent et al. 2008; Shahangian 2009). While viral and bacterial co-infections are a significant cause of COPD exacerbations and are associated with greater lung function impairment and longer hospitalizations (Papi et al. 2006), the interplay between cigarette smoke, virus, and bacteria is an understudied area.

Worldwide, smoking is a leading risk factor associated with acquisition, active disease, and mortality from TB (also see "Tobacco and TB" in Chapter 7, "Respiratory Diseases") (Gajalakshmi et al. 2003; Bates et al. 2007; Slama et al. 2007). Protective immunity to *Mycobacterium tuberculosis (M. tuberculosis),* the causative agent of TB, is dependent on the coordinated innate and adaptive immune response and relies on the generation of a robust type 1 immunity (Ernst 2012). Of note, the consumption of tobacco products has markedly increased in the developing world, where TB is most prevalent. The convergence of these two epidemics makes understanding how exposure to cigarette smoke impacts TB immunity a critical health challenge. Two studies (Feng et al. 2011; Shang et al. 2011) investigated the impact of cigarette smoke on the development of type 1 immunity in the context of *M. tuberculosis* or mycobacterial infection in experimental models. These studies showed a link between exposure to cigarette smoke and impaired type 1 immunity in the lung. The experimental protocol in both studies assessed the impact of prior (discontinued) exposure to cigarette smoke on anti-TB immunity only. To date, no study has evaluated the effect of continuous exposure to cigarette smoke on host defense against pulmonary mycobacterial infection, leaving a critical knowledge gap.

In conclusion, there is clear evidence that compromised bacterial host defense is associated with an increased risk of infection by a range of different bacterial agents, including *S. pneumoniae,* NTHi, *Moraxella catarrhalis,* and *P. aeruginosa,* pathogens commonly associated with COPD exacerbation, as well as *M. tuberculosis.* A range of different immune defects contributes to the increased risk of bacterial infection, including defects in the respiratory epithelium, alveolar macrophage function, and adaptive immunity. The latter is of particular relevance, because it likely contributes to an increased risk of TB in smokers.

Smoking and Asthma

Asthma is an inflammatory disease of the airways. Conventionally, asthma is viewed as an immunologic disease, in which overactive T cell immunity, specifically Th2 immunity, leads to bronchial inflammation (Robinson et al. 1992; Coyle et al. 1995). This inflammation intersects with genetic predisposition for altered airway function, manifesting in the episodic airflow limitation that is characteristic of the condition. As for other chronic inflammatory lung diseases, patients are prone to recurrent exacerbations triggered by chest infections, which in the case of asthma are almost always caused by a virus, often rhinovirus (Busse et al. 2010). The unifying hypothesis that asthma is a disorder of Th2 immunity has been questioned in recent years, as it does not agree well with clinical observations (Anderson 2008; Holgate and Davies 2009). Asthma manifests in grades of increasing severity. Very severe and refractory asthma, which is by nature resistant to conventional anti-inflammatory therapy, may represent expression of markedly different immune effector pathways, as classical eosinophilic inflammation is less prominent. Neutrophil-rich inflammation is more prominent in severe asthma (or the group of conditions that constitute). The observation of neutrophilic inflammation in severe asthma has been interpreted as evidence of Th17 activity and also as evidence that the inflammation is triggered by innate immunity PRR effector mechanisms (Alcorn et al. 2010).

Epidemiologic studies indicate that exposure to smoke, both in utero and perinatally, increases the risk for asthma (Bouzigon et al. 2008). Noakes and colleagues (2003) associated exposure to smoke with significantly higher neonatal Th2-type responses and early onset asthma. Well-powered population association studies have demonstrated a link between risk for asthma and an asthma susceptibility locus on chromosome 17q21 (Bouzigon et al. 2008), but specific genes contributing to the increased risk and mechanisms of action are not known at present.

Asthmatic smokers are largely understudied, as smoking is often an exclusion criterion for asthma studies and, physiologically, asthmatics who smoke manifest considerable fixed airflow limitation, a disease phenotype that overlaps with COPD. Smoking unequivocally worsens asthma of all grades, accelerates the decline in lung function, and impairs the therapeutic response to corticosteroids (Kerstjens et al. 1993; Chalmers et al. 2002; Chaudhuri et al. 2003). These adverse consequences occur even though smoking suppresses sputum eosinophilia in asthmatic smokers compared with asthmatic nonsmokers (Chalmers et al. 2001). Results of most animal models of experimental asthma mirror this finding (Melgert

et al. 2004; Robbins et al. 2005; Thatcher et al. 2008; Trimble et al. 2008), although contrasting findings have been presented (Moerloose et al. 2005). Mechanisms that suppress eosinophilia are currently not well understood. Seemingly contrasting with these findings, exposure to cigarette smoke enhances sensitization to allergens and can bypass or override the normal tolerogenic response to inhaled antigen in mice (Rumold et al. 2001; Moerloose et al. 2006; Trimble et al. 2008). Experimental evidence suggests that this response is mediated, at least in part, through GM-CSF (Trimble et al. 2008). Similar processes likely contribute to the increased risk of asthma observed in young children that are exposed to cigarette smoke (Ehrlich et al. 1996; Jaakkola and Jaakkola 2002). Taken together, this is a further example of the dual nature of smoking as an immune stimulus and as a suppressor, as discussed previously.

Important parallels exist between severe asthma and the impact of cigarette smoke on the immune system. In people with COPD and in smokers without overt lung disease, asthma is associated with functional defects in macrophages (Huynh et al. 2005; Fitzpatrick et al. 2008; Naessens et al. 2012), diminishing their ability to clear and kill pathogens and to remove cellular debris. As discussed previously, compromised clearance of apoptotic cells may contribute to secondary inflammation, as intracellular DAMPs that would otherwise have been contained spill into tissue and promote secondary inflammation. Moreover, innate antiviral responses can be impaired in asthmatics (Wark et al. 2005; Contoli et al. 2006; Edwards et al. 2012). Hence, the adverse effects of cigarette smoke on antimicrobial host defenses may further weaken already compromised host defenses in people with asthma. For this reason, asthma may be more difficult to control in asthmatic smokers than in asthmatic nonsmokers (see Chapter 7).

In summary, the impact of cigarette smoke on the immune system affects multiple facets of the asthma diathesis. Cigarette smoke as an immune stimulator likely facilitates allergic sensitization early in childhood, and deficient antimicrobial host defense contributes to the increased risk of viral and bacterial infection and renders asthma more difficult to control.

Cigarette Smoke and Autoimmunity

Since the concept was first proposed by Agustí and colleagues (2003), a body of evidence has accumulated to suggest that smoking can lead to autoimmunity at least in the context of severe COPD. Autoimmunity arises when classical tolerance to self-antigens is lost or critically weakened, and T and/or B cell-mediated immune responses attack host tissues (Wing and Sakaguchi 2010).

COPD does not show striking *HLA* restriction, which is often seen for such classical T cell autoimmune diseases as multiple sclerosis and rheumatoid arthritis (Martin et al. 1992). Emerging evidence, however, suggests that the classical signs of B cell-directed autoimmunity—such as antibodies against double stranded DNA and antinuclear antigen, which occur in SLE—are observed following exposure to smoke (Bonarius et al. 2011; Nunez et al. 2011).

A measure of evidence also indicates that adaptive autoimmunity against the lung can be triggered by cigarette smoke. TCR oligoclonality was observed in lung CD4+ and CD8+ T cells of smokers and people with severe emphysema, as well as in cigarette smoke-exposed mice (Korn et al. 2005; Sullivan et al. 2005; Motz et al. 2008). Although suggestive that a narrow range of antigenic epitopes drove expansion, the specificity of these T cells was not assessed and may have included self- or pathogen-derived antigens. To date, studies elutriating MHC I- or MHC II-bound peptides from antigen-presenting cells have not been reported in either animal models or in COPD. Such studies are required to determine if the loaded peptides are self-derived, which would be indicative of an autoimmune process.

The ability of lymphocytes to mount an inflammatory attack is counterregulated by regulatory T cells whose activity is diminished by chronic smoking (Barceló et al. 2008). The number of regulatory T cells is higher in smokers with preserved lung function but diminished in people with COPD. Smoking diminishes forkhead box PC (FOXP3), a transcription factor essential to the development of competent regulatory T cells, in human airways and reduces FOXP3 in people with COPD (Isajevs et al. 2009). These data indicate that regulatory mechanisms that control the function of T cells may be restrained in people who develop COPD.

B cell proliferation and formation of germinal center-like lymphoid aggregates, where oligoclonal expansion of B cells occurs, take place in the lungs of people with COPD, as well as in mice exposed to cigarette smoke (Hogg 2004; van der Strate et al. 2006). B cells (and antibody secreting plasma cells) have been implicated in models of smoke-induced lung damage in which a number of autoantibodies against lung matrix (e.g., elastin) have been observed (Lee et al. 2007a). Lee and colleagues (2007a) ascribed the T cell phenotype as Th1, but according to Ouyang and colleagues (2008), T cell-mediated autoimmunity in other organs suggest that Th17 cells, rather than Th1 cells, are orchestrators of destructive inflammation. Kirkham and colleagues (2011) demonstrated that smoking-induced carbonylation of matrix proteins create neo-antigens that then promote the formation of self-antibodies. The presence of pathogenic complement fixing IgG1 antibodies was associated with damage to blood vessel and endothelial cells.

A concept of autoinnate immunity is emerging in which the innate immune system is inappropriately self-stimulated (Anderson 2008). More than 30 years ago, researchers recognized that lung matrix fragments generated by elastolytic enzymes, such as human neutrophil and porcine pancreatic elastases, are chemotactic for monocytes but not for mature alveolar macrophages or neutrophils (Senior et al. 1980; Hunninghake et al. 1981). A more recent study discovered that these elastin fragments directly activate chemokine receptors and contribute to macrophage accumulation and airspace enlargement following the administration of porcine pancreatic elastase in mice (Houghton et al. 2006). Moreover, evidence suggests that collagen-derived fragments exert neutrophil chemotactic properties in rats (Riley et al. 1988). Hence, proteolytic fragments generated by a net protease/antiprotease imbalance may propagate cigarette smoke-induced inflammation. Of note, IL-1R1/signaling pathways have been implicated in these processes (Couillin et al. 2009).

As discussed previously, cigarette smoke diminishes the capacity of alveolar macrophages to clear cells undergoing programmed cell death (Hodge et al. 2007). Aside from safely clearing moribund cells, efferocytosis prevents immune activation secondary to exposure to DAMPs and alarmins. In mice, clearance of apoptotic neutrophils induces a regulatory phenotype in macrophages that may regulate T cell responses (Filardy et al. 2010). In an oxidant-dependent manner, smoking suppresses efferocytosis by alveolar macrophages (Richens et al. 2009). Further evidence suggests that the accumulation of ceramides—a sphingolipid second messenger associated with cell differentiation, proliferation, and apoptosis—in the lung may contribute to inhibition of apoptotic cell clearance by alveolar macrophages (Petrusca et al. 2010). Defects in efferocytosis may also contribute to the development of autoimmunity in susceptible smokers.

In summary, chronic exposure to cigarette smoke is associated with the emergence of autoreactive T and B cells. Mechanisms that contribute to these autoimmune processes remain to be elucidated, but may include cigarette smoke's adjuvant properties, likely through innate immune stimulation and dendritic cell activation, chemical modification of self-proteins to create neo-antigens, defective clearance of apoptotic cells, and compromised regulatory functions of T cells. Although the evidence suggests that cigarette smoke induces autoimmune processes, the importance of these processes in the expression and progression of smoking-related diseases, such as COPD, remains poorly understood.

Other Diseases

Smoking cigarettes is a risk factor for developing a number of autoimmune diseases, including rheumatoid arthritis (see subsequent section in this chapter), SLE (see subsequent section in this chapter), multiple sclerosis, Graves' hyperthyroidism, and primary biliary cirrhosis, amongst others (Costenbader and Karlson 2006; Klareskog et al. 2007; Jafari and Hintzen 2011).

Multiple Sclerosis

The association of smoking with multiple sclerosis has been addressed in multiple epidemiological studies. Hernán and colleagues (2001) examined smoking as a risk factor for multiple sclerosis in the two nurses' cohorts. Current smoking was significantly associated with the relative incidence rate of multiple sclerosis (RR = 1.6; 95% CI, 1.2–2.1) (Hernán et al. 2001). The RR increased with greater cumulative exposure of smoking, and RR is not elevated in former smokers. Sundström and colleagues (2008) carried out a nested case-control study in Sweden for 109 people with multiple sclerosis and 218 matched controls. Cotinine levels were measured in samples stored at the start of an intervention study. An elevated level of cotinine was associated with the risk for multiple sclerosis, particularly in women (Sundström et al. 2008).

In a review article, Jafari and Hintzen (2011) described the findings of 14 studies on cigarette smoking and the onset of multiple sclerosis, and 3 studies on cigarette smoking and progression of multiple sclerosis. Most of the studies on cigarette smoking and onset showed a positive association, while the evidence on the 3 studies on progression was limited and mixed.

In a study by Hedström and colleagues (2009), risk for multiple sclerosis was higher in people who smoked cigarettes than in those who used Swedish snuff (snus), which points to the possible significance of reactive intermediates formed during combustion. Smoking is also associated with conversion from a relapse, remitting to a more severe and progressive clinical course (Healy et al. 2009) that is associated with larger and more damaged brain lesions (Zivadinov et al. 2009). Evidence on a potential mechanism is limited (Jafari and Hintzen 2011). In model systems, exposure to smoke directly induced microglial inflammation (Ghosh et al. 2009).

Smoking and Cystic Fibrosis

Cystic fibrosis (CF) is a heritable genetic disease caused by genetic mutations that affect the CF transmembrane conductance regulator (CFTR) (Gadsby et al. 2006). CFTR governs airway hydration and influences innate host defenses such that its impairment leads to lung inflammation, lung colonization with pathogens, recurrent chest infection, impaired lung growth in childhood, progressive decline in lung function in adulthood, impairment of pancreatic function, and reduced fertility. Smoking worsens CF and predisposes people with CF to infection (Campbell et al. 1992; Verma et al. 2001). Smoking results in ciliostasis and decreased function of the chloride channel (Campbell et al. 1992; Cohen et al. 2009), as smoking directly impairs the function of CFTR (Cantin et al. 2006). In a study by Rubin (1990), children with CF who were exposed to secondhand cigarette smoke had a markedly higher hospital admission rate for chest infections and a much worse clinical status than their counterparts. In population studies, exposure of children with CF to cigarette smoke was associated with increased use of intravenous antibiotics, suggesting more severe and possibly more frequent chest infections (Gilljam et al. 1990). As with asthma and COPD, the probable mechanism underlying such results is the suppression of antimicrobial host defenses, which is known to be compromised already in people with CF (Zheng et al. 2003). Of interest, the severity of the effect of smoking on CF is further influenced by gene variants in *TNF*-α, a proinflammatory factor, and *GSTM1*, a gene encoding the detoxifying antioxidant glutathione *S*-transferase M1 (Hull and Thomson 1998).

Smoking, HIV, and Immunity

Smoking is not associated with the progression of HIV disease, as measured by CD4+ cell counts and viral load (Galai et al. 1997; Kabali et al. 2011). However, smoking increases the risk of developing oral candidiasis and bacterial pneumonia in people who have HIV (Conley et al. 1996; Sapkota et al. 2010). Of some interest, metagenomic profiling of tobacco has revealed multiple human pathogens, and some of these can survive tobacco burning and be inhaled (Sapkota et al. 2010). Among smokers, HIV infection appears to compound the risk of developing COPD but the role of altered immunity in this association is uncertain (Petrache et al. 2008). Among human papillomavirus ([HPV] 16 and 18)-infected, HIV-positive smokers, the increased risk of cervical cancer likely relates to the increase in the replication of HPV. While compromised immune status due to HIV contributes to persistent HPV infection, higher HPV16 and HPV18 DNA load was associated with current smoking status (Palefsky et al. 1999; Xi et al. 2009), suggesting a direct effect of cigarette smoke. HIV doubles the risk of liver cancer and this risk is synergistically increased by smoking (Chuang et al. 2010), but it is not known if defective immunity is related to this association.

Smoking, Immunity, and Cancer

Exposure to cigarette smoke, both active and passive, is an established cause of lung cancer (Kuper et al. 2002; USDHHS 2004, 2010; Stewart et al. 2008) (also see "Changes in Cigarettes and the Risk of Lung Cancer Over Time" in Chapter 6). Long at issue is the extent to which the immune system contributes to this increased cancer risk.

Currently, there is evidence that the effects of cigarette smoking on immunity contribute to cancer in two main ways. First, cigarette smoke is a potent inflammatory stimuli and inflammation is a direct cancer risk (Mantovani et al. 2008; Grivennikov et al. 2010). Second, suppression of immunity by cigarette smoke likely compromises tumor immune surveillance (Stampfli and Anderson 2009).

Development of cancer is a multistage process. In the course of exposure to smoke, the epithelium acquires somatic mutations and molecular defects that culminate in oncogenic transformation. It is widely accepted that inflammatory processes play a critical role in this process (Grivennikov et al. 2010). Takahashi and colleagues (2010) demonstrated that inflammation elicited by exposure to cigarette smoke promotes tumor formation in an IκB kinase β (IKK-β) and JNK1-dependent manner. Reactive oxygen species and nitrogen intermediates, which are produced by activated inflammatory cells, may contribute to DNA damage in addition to smoke's direct DNA damaging effects. Of note, oncogenically mutated epithelium is itself markedly pro-inflammatory and less able to defend against pathogens (Anderson and Bozinovski 2003). Strong evidence indicates that as epithelial cells progressively acquire somatic mutations (e.g., in *KRAS*), inflammation and bacterial burden in the lungs increases (Anderson and Bozinovski 2003; Ji et al. 2006). These somatic mutations also increase the capacity of the epithelium to promote inflammation; for example, they concurrently decrease the ability of the epithelium to contain viral infection (Liu et al. 2008b). These observations may provide links between defects in host defense, increased inflammation, and enhanced risk for cancer.

Pioneering work from Chalmer and colleagues (1975) provided direct experimental support for defects in immune surveillance of transplanted cancers, showing that cell-mediated immune responses to transplanted tumors were inhibited in mice that were chronically exposed to cigarette smoke. Smoke exposure significantly increased the number of lung metastases following tumor challenge (Lu et al. 2007). This effect was reversible following smoking cessation and likely the consequence of impaired NK-cell function. Moreover, prenatal exposure to cigarette smoke decreased offspring resistance against transplanted tumor cells in mice (Ng et al. 2006). This phenomenon was related to decreased T cell-mediated cytotoxicity. The study did not observe an effect of prenatal exposure to cigarette smoke on the activity of NK cells.

About one-half of all surgically resectable, Stage 1 cancers of the lung removed with curative intent prove fatal, because even early stage lung cancer can be highly metastatic (Nagrath et al. 2007; Maheswaran et al. 2008). Aside from inducing cancer, inflammatory processes associated with smoking also promote metastasis from tumors, for example, by inducing matrix degrading proteases such as MMP-9 from mast cells, macrophages, and neutrophils (Alberg et al. 2005). The inflamed lung also forms a receptive field to receive metastases, especially from melanoma, breast, colon, and liver cancers.

In summary, inflammation appears to be a critical link between smoking, the immune system, and lung cancer. In experimental models, there is evidence that smoking compromises tumor immune surveillance. Affected processes include defective activity of NK cells and decreased T cell-mediated cytotoxicity.

Smoking, Immunity, and Maternal Smoking During Pregnancy

Epidemiologic studies have clearly established the links between adverse prenatal conditions and increased risk for diseases, health problems, and psychological outcomes later in life, and this forms the basis of the Developmental Origins of Health and Disease hypothesis (Gluckman et al. 2008). Maternal cigarette smoking during pregnancy remains a relatively common, but nonetheless hazardous, in utero exposure associated with a range of adverse postnatal and long-term adverse effects (Knopik et al. 2012) (see Chapter 9, "Reproductive Outcomes"). The postulated mechanism linking prenatal and early postnatal environmental exposure with adverse health outcomes later in life is epigenetic programming, such as alterations in DNA methylation (Low et al. 2011).

DNA methylation changes are detectable in blood leukocyte DNA from the umbilical cord in offspring of mothers who smoked during pregnancy. In an epigenome-wide analysis, Joubert and colleagues (2012) showed that genes involved in xenobiotic metabolism (e.g., *AHRR* and *CYP1A1*) and haematopoiesis (e.g., *GIF1, HLA-DPB2,* and *RUNX1*) display altered methylation in blood leukocyte DNA from the umbilical cord in response to maternal cigarette smoking. Such effects may be part of a wider epigenetic influence on fetal growth and child development (Knopik et al. 2012; Haworth et al. 2013). It remains to be established whether such epigenetic changes persist until

adulthood. However, the observation that grandmaternal smoking during pregnancy can result in increased risk of immune-mediated disease—such as asthma in grandchildren—independently of maternal smoking during pregnancy (Li et al. 2005), suggests that epigenetic programming of immune response in response to cigarette smoke may be inherited transgenerationally.

Direct effects on immune system function of smoking by the mother during pregnancy have also been observed. Gene expression in leucocytes from the umbilical cord is altered in response to maternal smoking. Genes showing significant modulation include those related to xenobiotic metabolism, oxidative stress, inflammation, immunity, and hematopoiesis. In particular, functional annotation of the affected genes has identified several deregulated pathways that associated with immune diseases, such as asthma, in the offspring of smokers (Votavova et al. 2011).

In an animal study, Basta and colleagues (2000) showed that rats exposed to nicotine during the gestational period exhibit decreased peripheral blood mononuclear cell proliferative responses to lipopolysaccharide or mitogen-induced activation, in both the early postnatal period and adulthood. In another animal study, involving low-dose exposure to cigarette smoke in pregnant mice, Ng and Zelikoff (2008) observed increased circulating white blood cell and lymphocyte numbers for up to 2.5 months after birth but with decreased mitogen-stimulated T cell proliferation.

In humans, several studies on cord blood have shown changes in immunological variables in smoking compared with nonsmoking mothers. Cord blood has been shown to contain significantly lower levels of polymorphonuclear leukocytes (Mercelina-Roumans et al. 1996) and higher levels of Ig (Cederqvist et al. 1984) in response to prenatal smoking. Maternal smoking also influences fetal immune function with increased fetal IgE and IgD production (Magnusson 1986) and accompanying lymphoproliferative and cytokine responses to allergens (Devereux et al. 2002; Noakes et al. 2003). In one such study, maternal smoking was associated with lower serum concentrations of IL-4 and IFN-γ in cord blood and a higher risk of wheeze at 6 years of age (Macaubas et al. 2003). Infants born to smoking mothers also showed significant attenuation of innate Toll-like-receptor responses compared with infants

of nonsmokers, with implications for the well-recognized increased risk of respiratory infections and asthma in offspring of smoking mothers (Noakes et al. 2006).

Evidence Synthesis

Collectively, the large body of available evidence reinforces the underappreciated role of cigarette smoke's adverse effects on the immune system in contributing to the causation of disease in smokers. Broadly, cigarette smoke exerts both proinflammatory and immune suppressive effects, which collectively contribute to an increased risk for diseases associated with immune diathesis.

Conclusions

1. The evidence is sufficient to infer that cigarette smoking compromises the immune system and that altered immunity is associated with increased risk for pulmonary infections.

2. The evidence is sufficient to infer that cigarette smoke compromises immune homeostasis and that altered immunity is associated with an increased risk for several disorders with an underlying immune diathesis.

Implications

The preceding discussion stresses the complex nature of smoking as both a stimulant and suppressive agent for the functioning of the immune system and outlines the disease processes, cellular effectors, and molecular mechanisms underlying these effects. A greater understanding of the multipartite nature of the effects of smoking on immunity will lead to a better understanding of the ways in which smoking causes disease. Nonetheless, smoking has documented adverse effects on the immune system that may contribute to the general morbidity experienced by smokers.

Rheumatoid Arthritis and Systemic Lupus Erythematosus

The causes of autoimmune diseases, such as rheumatoid arthritis (RA) and SLE, remain elusive despite considerable research on risk factors and mechanisms. Although there are clearly genetic factors predisposing to these diseases, environmental factors also play a key role in their development (Klareskog et al. 2011; Salliot 2011; Sestak 2011). To date, there is a considerable body of literature on the effect of smoking on RA and a smaller number of studies exploring a role for smoking in SLE. These findings are supported on a mechanistic basis by the findings of studies on smoking and the immune system (see the "Immune Function and Autoimmune Diseases" section in this chapter). This topic, smoking and autoimmune diseases, has not been reviewed previously in the reports of the Surgeon General.

Description of the Literature Review

An initial search of English publications in PubMed was performed using the key words smoking OR tobacco AND rheumatoid arthritis and then, separately, using the key words smoking OR tobacco AND systemic lupus erythematosus. Similar searches were conducted using the Ovid and Google Scholar Databases and the lists obtained from each search mechanism were compared for duplicate titles. Titles and abstracts were then reviewed for studies that addressed the association between smoking and the development, management, or severity of these diseases. All studies addressing this topic, including review articles and meta-analyses as well as small studies were assessed. In the evidence tables, only studies with more than 50 participants and those presenting original data were included. The literature search extended from 1962 through December 2012.

Rheumatoid Arthritis

RA is a chronic inflammatory disease of uncertain etiology. Deforming arthritis is the hallmark of RA, but its systemic nature is manifested by the involvement of many other organs including skin, eyes, lungs, blood vessels, and bone marrow. The estimated annual incidence of RA is approximately 40 per 100,000 persons with a prevalence of 1% (Alamanos et al. 2006). RA is more common in women and about 70% of patients are seropositive, as defined by the presence of rheumatoid factor (RF) or anti-cyclic citrullinated peptide (anti-CCP) (De Rycke 2004). RA is currently treated with a group of immunomodulatory drugs, such as corticosteroids, methotrexate, leflunomide, and inhibitors of TNF-α.

Biologic Basis

The effect of smoking as a risk factor for RA is mainly observed in RF-positive people with RA and anti-citrulline antibody (Klareskog et al. 2007). RF is a type of antibody directed against the receptor binding Fc region of IgG. As such, RF causes the formation of immune aggregates that are highly proinflammatory. Citrullination (also called deimination) refers to the amino acid arginine that is converted into the amino acid citrulline. Citrullination can alter the tertiary structure of proteins and may give rise to autoantigens that provoke the formation of anti-citrullinated protein antibodies or anti-cyclic citrullinated protein antibodies. In RA, these autoantibodies are frequently made against filaggrin and may cross-react with keratin and perinuclear factor. The direct effect of smoking on immune effector pathways is suggested by the strong association with the major histocompatibility *HLA-DRB1* allele and antibodies directed against citrullinated peptide.

Evidence Review

There is considerable evidence that smoking is one of several risk factors for the development of RA (Table 10.14*S*). This association was first identified in a study of RA among users of oral contraceptives (Vessey et al. 1987), and has now been replicated in multiple subsequent studies.

Indeed, cigarette smoking has been cited as the most conclusively established environmental risk factor for seropositive RA (Costenbader and Karlson 2006). The risk attributable to smoking among patients of European ancestry has been estimated as approaching one of six (Criswell et al. 2002) and even one of four affected people (Costenbader et al. 2006). Compared with never smokers, smoking is associated with a 1.4–4-fold increased risk of developing RA. Although there is some heterogeneity among the results of these studies, there is consistent evidence that smoking is a stronger risk factor for RA in men than in women. Some studies show that smoking is associated with a younger age at disease onset, and while both intensity and duration of cigarette exposure are associated with increased risk, duration of smoking may have

a larger effect (Costenbader and Karlson 2006). Although a small number of studies directly address risks from secondhand smoke, there is little evidence to suggest that this exposure is a risk factor for development of RA (Soderlin et al. 2013).

Sugiyama and colleagues (2010) confirmed several of these observations in a meta-analysis exploring the effect of smoking on RA. The authors pooled data from 18 studies to examine the effect of cigarette smoking on RF and anti-CCP positive disease, as well as to assess dose-response relationships of cumulative smoking with RA. The summary overall risk for developing RA was 1.4 (95% CI, 1.25–1.58) for ever smokers, 1.35 (95% CI, 1.17–1.55) for current smokers, and 1.25 (95% CI, 1.10–1.40) for past smokers in comparison with never smokers. Although 94% of the patients included in this analysis were women, the strongest risk appeared to be for men, in whom the summary overall risk for current smokers was 1.89 (95% CI, 1.56–2.34), and for RF-positive RA, in whom the overall risk was 3.91 (95% CI, 2.78–5.50). A dose-response relationship was present in women with an overall risk of 1.75 (95% CI, 1.42–2.02) for women with more than a 20-pack year exposure. There were not enough data points to assess the risk of smoking on anti-CCP positivity, but newer clinical studies support this association (Klareskog et al. 2006; Karlson et al. 2010; Kallberg et al. 2011).

There is a growing literature investigating the interaction between genotypes and environmental exposures in RA. Recent work confirms previous studies (Karlson et al. 2010; Mikuls et al. 2010) demonstrating a synergistic effect of smoking with the *HLA-DRB1 shared epitope-containing allele* in RA (Too et al. 2012). A strong association also exists supporting a synergistic effect of smoking and PTPN22, a regulatory component of T cell signaling (Costenbader et al. 2008). The association with anti-CCP positivity and smoking in some ethnic groups with this genetic predisposition is particularly notable (Pedersen et al. 2006; Klareskog et al. 2011; Salliot et al. 2011). Cigarette smoking has also been postulated to increase RA severity, but this association remains controversial. There is some support for an association of smoking with increased radiographic scores, incident rheumatoid pulmonary disease, and decreased overall physical function scores (Table 10.15*S*). For example, Manfredsdottir and colleagues (2006) demonstrated increased disease activity, as assessed by physical exam and history during 2 years of observation in smokers compared to nonsmokers, but smoking was not associated with radiographic progression of disease. Weak evidence suggests that smoking may be a risk factor for formation of rheumatoid nodules (Nyhall-Wahlin et al. 2006). Similarly, several studies showed an effect of smoking on the risk of developing extra-articular

manifestations of RA (Kim et al. 2008c; Moura et al. 2012), particularly lung disease. Finckh and colleagues (2007) showed a protective effect of heavy cigarette smoking on RA progression. Differences in patient characteristics and the recent recommendations for early aggressive treatment of RA complicate interpretation of these findings.

In contrast, there is strong evidence that smoking reduces the effectiveness of some therapies for RA (Table 10.16*S*). The response to the TNF-α inhibitory drugs, which are being increasingly used, has been most extensively studied, as drug trials included large numbers of well-characterized patients. Canhão and colleagues (2012) demonstrated that smoking was a strong predictor of a poor response (as measured by European League Against Rheumatism scores) in patients beginning their first TNF-α inhibitor. Other studies show that smoking is associated with reduced likelihood of a good response to TNF-α therapy, with response rates for former smokers falling in between those for never smokers and current smokers (Hyrich et al. 2008; Mattey et al. 2009; Abhishek et al. 2010; Soderlin et al. 2012). Westhoff and colleagues (2008) used changes in medication regimens as a surrogate for poor therapeutic response, and showed that regimen changes occurred more commonly in smokers with RA than in nonsmokers with RA. Medication changes may also occur because of side effects, and one small study of leflunomide lung toxicity demonstrated increased risk of developing lung toxicity in smokers on leflunomide (Inokuma et al. 2008). There is no association of smoking with methotrexate-induced lung toxicity (Beyeler et al. 1996; Cottin et al. 1996).

Evidence Synthesis

The available evidence supports a causal association of smoking with risk for seropositive RA. There is consistency of the findings over multiple studies involving different populations and large numbers of patients. A clear dose-response with extent of smoking is observed in the majority of studies, and the decline of risk with cessation of smoking also supports causality. There is little evidence to suggest that behaviors associated with smoking, such as alcohol and coffee intake, lower body weight, or poor physical conditioning, contribute to RA; so the association with smoking is not likely to be from confounding. The finding that patients with certain genetic backgrounds are particularly sensitive to the effects of cigarette smoke implies that particular mechanisms could underlie a causal association. Considered with the increasing evidence for a clear biological basis for alterations in the immune system, a causal association between RA and smoking is biologically plausible as well.

Evidence on smoking as a cause of increased disease severity in RA remains conflicting, and is inadequate to infer such a relationship. The studies investigating this association are heterogeneous in their design; some involved only a small numbers of patients; and there is no uniform definition of disease severity. There is sufficient evidence from large and well-designed studies to support the hypothesis that smoking is causally associated with a poor response to TNF-α inhibitors in RA patients. Dose-response relationships were found in many studies and a reduction of risk with smoking cessation further corroborates the significance of this association.

Conclusions

1. The evidence is sufficient to infer a causal relationship between cigarette smoking and rheumatoid arthritis.

2. The evidence is sufficient to infer that cigarette smoking reduces the effectiveness of the tumor necrosis factor-alpha (TNF-α) inhibitors.

Implications

Current evidence supports a causal association of smoking with RA and reduced effectiveness of the TNF-α inhibitors. Although overall attributable risk may depend on genetic factors, smoking may be one of the few known modifiable risk factors for the development of RA.

Systemic Lupus Erythematosus

SLE is an autoimmune disorder that typically affects the skin and joints, but in its most virulent form, SLE may cause severe damage of essential organs including the kidneys and the nervous system. SLE is more common in women than men and more often affects African American and Asian women. This population also tends to have more severe disease. The pathogenesis of SLE is extremely complex and remains elusive. Although deficiencies of complement component genes are associated with a higher incidence of SLE and suggest a strong genetic etiology, concordance rates for SLE in monozygotic twins are only between 25–60% (Sestak et al. 2011). The interplay between environment and genes is considered an important determinant of disease development (Tsokos 2011). A search for additional environmental factors influencing SLE development implicated smoking as a possible trigger.

Biologic Basis

Smoking is especially associated with the formation of dsDNA antinuclear autoantibodies (Freemer et al. 2006), which are known to induce many of the manifestations of SLE. The dual nature of smoking as an immune-suppressant and immune-activating agent was observed when SLE-prone MLR-*lpr/lpr* mice were exposed to cigarette smoke (Rubin et al. 2005). Antinuclear antibodies were suppressed in active smoke-exposed mice. Following smoking cessation, the suppression initially persisted but eventually greater levels of autoantibodies were observed. The study did not assess mechanisms or consequences of altered antibody levels.

Evidence Summary

Table 10.17*S* summarizes the results of studies, which included 50 or more patients and examined the association between cigarette smoking and the risk of SLE. Eight case-control studies demonstrated a positive association of current smoking with the diagnosis of SLE, while four studies showed no clear evidence of an association. Two of the studies appear to report on many of the same patients (Kiyohara et al. 2012a,b). The second of these studies also evaluated the *CYP1A1* genotype in smokers and is the first study to identify this genotype as having more than an additive effect with cigarette smoking for the development of SLE. An earlier study from the same research group reported an increased risk in a population of Japanese smokers with SLE in one city, but no increased risk in patients from another city in Japan (Washio et al. 2006). Of the two cohort studies, one found a weak association between SLE and smoking (Formica et al. 2003), while the second (Sanchez-Guerrero et al. 1996) showed no association with current or former smoking. In the studies that assessed dose-response with tobacco exposure, a relationship was found in only a single study (Hardy et al. 1998).

A meta-analysis of cigarette smoking and the risk of SLE reported in 2004, included seven case-control studies and two cohort studies (Costenbader et al. 2004). The authors reported an odds ratio of 1.5 (95% CI, 1.09–2.08) for current smokers, as compared to never smokers, for the development of SLE. A sensitivity analysis was performed excluding the study by Ghaussy and colleagues (2001) in which the effect size was much higher than the other studies. With this exclusion, the summary odds ratio was 1.31 (95% CI, 1.01–1.70). The Ghaussy and colleagues study was performed in a predominantly Hispanic population in the Southwest, and thus, may not be representative of the general population with SLE. Three of

the other positive studies included in Table 10.17*S* were carried out in Japan.

Table 10.18*S* summarizes the studies evaluating the impact of smoking on disease severity in people with SLE. It also includes several studies which explore this issue in individuals with only cutaneous lupus erythematosus. Most of the reports focus on cutaneous disease in persons with lupus, among whom smoking is clearly associated with more severe disease that is more difficult to control. The report by Ghaussy and colleagues (2003) on 111 cases demonstrates higher disease activity scores (as measured by the popular Systemic Lupus Erythematosus Disease Activity Index [SLEDAI]) in current smokers as compared to former or never smokers. In contrast, Rahman and colleagues (1998) reported no effect of smoking on SLEDAI scores in a group of 36 persons. Smoking is associated with a higher risk of thrombosis and earlier development of end-stage renal disease in patients with lupus nephritis. The finding of a significantly higher risk of autoantibodies to double-stranded DNA in current smokers suggests that alteration of self-antigens by smoking and immune activation may lead to worsening disease in current smokers. A large study of 1,346 well-characterized SLE patients in Canada reported that current smoking was associated with active SLE rash with an OR of 1.63 (95% CI, 1.07–2.48). Ever smoking was also a risk factor for cutaneous involvement, and increased risk for discoid rash (OR = 2.36; 95% CI, 1.69–3.29) and photosensitivity (OR = 1.47; 95% CI, 1.11–1.95) (Bourré-Tessier et al. 2013).

Table 10.19*S* summarizes the findings on the effect of smoking on the efficacy of treatments for SLE. In 1998, Rahman and colleagues (1998) first described the adverse effect of smoking in patients with cutaneous lupus either alone, or in the setting of SLE, on hydroxychloroquine efficacy. The study included 17 smokers and compared their responses to therapy with those of 19 nonsmokers. Nine of the nonsmokers had complete resolution of their rash within 6 months of treatment with hydroxychloroquine, while only 3 of the smokers had complete resolution. Table 10.19*S* includes two studies, which evaluated treatment in 50 or more patients. One study showed 90% of nonsmokers responded to therapy as compared to only 40% of smokers (Jewell and McCauliffe 2000). The second study evaluated the effect of smoking and *CYP* genotype on response to therapy and found that neither had a significant influence on response (Wahie et al. 2011). A report of 36 persons with cutaneous lupus supports the negative effect of smoking (Kreuter et al. 2009). The authors also reported that cessation of smoking during the observation period improved response to treatment.

Evidence Synthesis

The current mixed evidence is inadequate to support a causal association between SLE and cigarette exposure. Seven studies found an association, while four studies did not. Reflecting the relative rarity of SLE, many of the studies are small and underpowered. Genetic propensities to SLE remain poorly defined, but the observation of an interaction in risk between smoking and ethnic ancestry, particularly in persons of Hispanic and Japanese descent, suggests a biologic basis for this association. Across heterogeneous populations of SLE patients, however, the effect of smoking may be diluted by the presence of many genotypes. Dose-response relationships were not found in several studies, but sample size and power are limitations of some studies. Similarly, there is inadequate evidence to support a role for smoking as leading to greater severity of SLE. The study populations are small and heterogeneous. More importantly, variations in the definition of disease severity prevent a definitive conclusion. The best evidence supports smoking as a risk factor for cutaneous disease, and there is sparse evidence of an association with earlier renal failure and thrombosis. Similarly, studies showing higher levels of anti-dsDNA antibodies in SLE patients, who currently smoke, as compared to never and former smokers, warrant confirmation.

Finally, there is inadequate evidence supporting an effect of smoking on the response to therapy in SLE.

Conclusion

1. The evidence is inadequate to infer the presence or absence of a causal relationship between cigarette smoking and systemic lupus erythematosus (SLE), the severity of SLE, or the response to therapy for SLE.

Implications

There is intriguing evidence for an association of smoking with SLE. As few modifiable risk factors for SLE have been identified, further research on smoking and risk for SLE is warranted. Because this life-threatening disease lacks effective specific therapies and is associated with premature cardiovascular disease, continued education of SLE patients on the importance of smoking cessation is recommended.

Inflammatory Bowel Disease

The predominant forms of inflammatory bowel disease (IBD) are Crohn's disease and ulcerative colitis. Crohn's disease is characterized by transmural inflammation occurring anywhere in the luminal gastrointestinal tract predominately affecting the ileum of the small intestine and the large intestine. In contrast, inflammation associated with ulcerative colitis is generally limited to the mucosal surface of the large intestine, although backwash ileitis can occur with active disease in the cecum.

The reported incidence of IBD is greater in North America and Northern Europe than in other regions of the world where incidence has been evaluated. The incidence of Crohn's disease in North America ranges between 4–16 cases per 100,000 compared with 4–10 in Northern Europe, 1–5 in Southern Europe, and 0–4 in Africa, Asia, and Latin America.

The incidence of ulcerative colitis per 100,000 ranges between 2–16 cases in North America, 3–20 in Northern Europe, 2–11 in Southern Europe, and 1–9 in Africa, Asia, and Latin America (Molodecky et al. 2012). Using the prevalence estimates for North America and a U.S. population of 300 million, the current prevalence of IBD in the United States is estimated at 1.6–1.7 million persons (Molodecky et al. 2012).

Although the incidence of IBD increased during the last century (Binder 2004), the causes of the increase are unknown. Over 160 genetic risk factors have been associated with Crohn's disease and ulcerative colitis (Jostins et al. 2012), but genes alone cannot explain the rapid increase in incidence. While increased diagnostic sensitivity may contribute to the increase, environmental factors, including cigarette smoking, may play a role.

Risk factors for IBD may include cigarette smoking, appendectomy, diet, infections and antibiotics to treat them, and socioeconomic factors (Ng et al. 2013). The environmental factors may interact with genetic risk factors in the development and response of the immune system. Environmental factors may also alter the intestinal microbiome, which also affects IBD (Erickson et al. 2012).

A personal history of cigarette smoking is the best described risk factor for IBD in adults. The first reports of a discordant relationship between active smoking and Crohn's disease and ulcerative colitis were published in the late 1970s and early 1980s (Samuelsson 1976; Mayberry et al. 1978; Harries et al. 1982; Jick and Walker 1983; Logan et al. 1984; Somerville et al. 1984) showing that ulcerative colitis patients were less likely to smoke on or after diagnosis, compared with controls, and more likely to be former smokers than controls. Crohn's disease

patients were more likely to smoke on or after diagnosis than controls. A recent meta-analysis reported a protective association of smoking with ulcerative colitis (OR = 0.58) and an adverse association with Crohn's disease (OR = 1.75) (Mahid et al. 2006). A meta-analysis of prenatal and childhood exposure to secondhand cigarette smoke found no association with Crohn's disease or with ulcerative colitis (Jones et al. 2008). Persons with Crohn's disease, who continue to smoke, exhibit a greater need for use of immunosuppressant therapy, have higher rates of surgical resection, and greater frequency of postoperative recurrence after surgery and requirement for repeat resection (Birrenbach and Bocker 2004; Cosnes 2008). An intervention study demonstrated that Crohn's disease patients who stop smoking have a reduction in their need for immunosuppressants or surgery within the first year following cessation of cigarette smoking, when compared with those who continued to smoke. In contrast, cessation of cigarette smoking is sometimes associated with worsening disease activity in ulcerative colitis (Beaugerie et al. 2001; Cosnes 2004, 2008).

Conclusions of Previous Surgeon General's Reports

The relationship between smoking and IBD has not been assessed in previous Surgeon General's reports.

Biologic Basis

Many of the Crohn's disease and ulcerative colitis genes are associated with regions encoding immunologic cell functioning including bacterial recognition, signaling, and autophagy. For example, *NOD2* (also known as *CARD15*) genetic polymorphism located on the *IBD1* locus of chromosome 16 is associated with an increased risk of Crohn's disease, but not ulcerative colitis (Hugot et al. 1996, 2001; Ogura et al. 2001). In studies done in epithelial cell lines, cigarette smoke extract affected NOD2 expression and function (Aldhous et al. 2011).

Smoking has widespread effects on immune function. Smoking has a demonstrated role in promoting pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, IL-8, and GM-CSF, decreasing the anti-inflammatory cytokine IL-10 and activating macrophage and dendritic cell pathways (Arnson et al. 2010), all of which could play a role

in promoting an inflammatory process. Patients with IBD have been demonstrated to have a dysbiosis of the gut microbiome, characterized by a reduced bacterial diversity and a reduction in certain phylogenetic groups (Morgan et al. 2012). Studies have suggested that smoking may alter the composition of intestinal microbiome (Benjamin et al. 2012), and, through it, the risk of Crohn's disease and ulcerative colitis. Smoking may increase colonic mucin production, which may be deficient in ulcerative colitis, but there is no other strong supporting evidence for a mechanism by which smoking plays a protective role (Gibson and Muir 2005).

Despite both diseases sharing the vast majority of the genetic risk loci, the reason for the divergent effect of cigarette smoking on Crohn's disease and ulcerative colitis is unclear. In a study by Bergeron and colleagues (2012), mononuclear cells from Crohn's disease patients had an impaired response against anti-inflammatory and oxidative stress protection, partly through reduced synthesis of heat-shock protein 70. In contrast, similar cells from ulcerative colitis patients and controls did not demonstrate this impaired functioning. Similarly, the differences in the gut microbial consumption in smokers may favor the development of Crohn's disease (Benjamin et al. 2012).

Epidemiologic Evidence

Studies for the current review were compiled by searching the MEDLINE database accessed through PubMed using the search phrase (smok* or tobacco) and (crohn or "ulcerative colitis" or "inflammatory bowel disease"). The search was performed on January 25, 2013, with no restriction on the date of publication, and 1,102 articles were identified. References cited in relevant reviews and meta-analyses (Cope et al. 1986; Calkins 1989; Thomas et al. 1998; Rubin and Hanauer 2000; Birrenbach and Bocker 2004; Wolf et al. 2004; Mahid et al. 2006; Jones et al. 2008; Bastida and Beltran 2011; Hovde and Moum 2012), and the studies that met the inclusion criteria were checked to identify articles not captured by the search.

Eight studies were excluded because the controls had irritable bowel syndrome or other gastrointestinal conditions (Burns 1986; Cope et al. 1986; Silverstein et al. 1989; Martins et al. 1996; Reif et al. 2000; de Saussure et al. 2007; Mahid et al. 2007; Lopez-Serrano et al. 2010). One study was excluded because the article could not be translated into English (Bures and Fixa 1985). When several articles reported on the same group of cases, the most recent article with the largest sample size and most rigor-

ous control for confounding was included in the analysis (45 duplicates excluded).

Meta-analyses were performed using a random effects model accounting for the type of IBD, study design, and smoking definition. Smoking was classified as current at diagnosis of IBD (and corresponding age or date in controls); current at recruitment for prospective studies or when the questionnaire was administered after IBD diagnosis (or date of questionnaire administered to controls); and ever smoker at diagnosis, the time of the questionnaire, or unspecified smoking definition. Never smoker or not current smoking was used as the comparison. Former smoking was classified at the same time points as current smoking. Information on dose-response is described, but no meta-analyses were performed on dose-response relationships.

Seventy-two studies, which were reported in 75 articles, met the inclusion criteria (Table 10.20*S*). The case-control studies included hospital-based controls (often patients in orthopedic clinics or with fractures admitted through the emergency department), case-nominated controls, or controls that lived near the cases based on hospital or government records. Five prospective cohorts and 1 nested case-control study examined the incidence of Crohn's disease and ulcerative colitis by smoking status (Vessey et al. 1986; Logan and Kay 1989; Tragnone et al. 1993; Carlens et al. 2010; Higuchi et al. 2012; Chan et al. 2013). An additional case-control study enrolled only incident cases (Corrao et al. 1998). Three case series compared smoking among cases with nationally representative estimates (Srivasta et al. 1993; Tuvlin et al. 2007; van der Heide et al. 2011). The majority of studies were conducted in Europe and North America. Some studies included only women because the cases were originally collected to examine the relationship between oral contraceptives or hormone replacement therapy and disease (Vessey et al. 1986; Lashner et al. 1989, 1990; Logan and Kay 1989; Sandler et al. 1992; Katschinski et al. 1993; Boyko et al. 1994; Higuchi et al. 2012).

Current Smoking

Examining the 53 studies that reported on Crohn's disease, cases were more likely than controls to be current or ever smokers (RR = 1.6; 95% CI, 1.5–1.8). When studies that defined smoking as current at the time of recruitment into a prospective cohort or at the time of diagnosis or symptom onset in case-control studies were combined, the relationship between smoking and Crohn's disease was even greater (RR = 1.8; 95% CI, 1.6–2.2; N studies = 24; Figure 10.7); and the effect estimate did not differ meaningfully by study design. With restriction to studies assessing smoking on or before diagnosis and that adjusted for

Figure 10.7   Relationship between smoking on or before the time of diagnosis and risk of Crohn's disease

Study	Country	Number of cases		ES (95% CI)
Case-control				
Thornton et al. 1985	United Kingdom	28		5.7 (1.8–18.0)
Funakoshi et al. 1987	Japan	25		0.5 (0.2–1.4)
Tobin et al. 1987	United Kingdom	115		2.9 (1.8–4.9)
Franceschi et al. 1987	Italy	109		4.2 (2.3–7.7)
Lindberg et al. 1988	Sweden	141		2.2 (1.3–3.5)
Sandler et al. 1992	United States	167		1.6 (0.7–3.6)
Katschinski et al. 1993	Germany	79		3.0 (1.3–6.8)
Boyko et al. 1994	United States	78		2.4 (1.3–4.2)
Brignola et al. 2000	Italy	636		2.3 (1.5–3.5)
Lopez Ramos et al. 2001	Spain	134		2.8 (1.8–4.3)
Lakatos et al. 2004	Hungary	202		1.7 (1.3–2.4)
Firouzi et al. 2006	Iran	46		0.4 (0.2–1.2)
Morgan et al. 2010	New Zealand	238		2.4 (1.6–3.4)
Gearry et al. 2010	New Zealand	638		2.0 (1.5–2.7)
Andersen et al. 2011	Denmark	282		1.3 (0.9–1.8)
Pugazhendhi et al. 2011	India	200		0.8 (0.4–1.3)
Subtotal (I-squared = 70.9%, p = 0.000)				1.9 (1.5–2.4)
Prospective cohort				
Vessey et al. 1986	United Kingdom	17		3.3 (1.2–8.8)
Logan and Ray 1989	United Kingdom	42		1.8 (1.0–3.3)
Tragnone et al. 1993	Italy	35		1.5 (0.7–3.5)
Higuchi et al. 2012	United States	219		1.9 (1.4–2.5)
Subtotal (I-squared = 0.0%, p = 0.706)				1.9 (1.5–2.4)
Nested case-control				
de Silva et al. 2010	Denmark	74		1.9 (1.1–3.2)
Chan et al. 2013	Europe	75		2.0 (1.1–3.5)
Subtotal (I-squared = 0.0%, p = 0.906)				1.9 (1.3–2.8)
Case series				
Tuvlin et al. 2007	United States	351		1.3 (1.0–1.6)
van der Heide et al. 2011	Netherlands	104		1.3 (1.1–1.5)
Subtotal (I-squared = 0.0%, p = 0.904)				1.3 (1.1–1.5)
Overall (I-squared = 69.1%, p = 0.000)				1.8 (1.6–2.2)

0.2   0.5   1   2   5   10

Figure 10.7   Continued

Study	Adjustments
Case-control	
Funakoshi et al. 1987	Age
Tobin et al. 1987	Age; Gender; Location, region, or center
Franceschi et al. 1987	Age; Gender; Education or social class; Former smoking; Body mass index; Other
Lindberg et al. 1988	Age; Gender; Location, region, or center
Sandler et al. 1992	Oral contraceptives or hormone replacement therapy
Katschinski et al. 1993	Age; Oral contraceptives or hormone replacement therapy
Lopez Ramos et al. 2001	Age; Gender; Education or social class; Tonsillectomy or appendectomy; Oral contraceptives or hormone replacement therapy
Firouzi et al. 2006	Age; Gender; Tonsillectomy or appendectomy; Non-steroidal anti-inflammatory drugs; Oral contraceptives or hormone replacement therapy
Gearry et al. 2010	Age; Gender; Race or ethnicity; Education or social class; Family history of inflammatory bowel disease
Prospective cohort	
Higuchi et al. 2012	Age; Gender; Body mass index; Oral contraceptives or hormone replacement therapy
Nested case-control	
Chan et al. 2013	Age; Gender; Location, region, or center

Note: Weights are from random effects analysis. **CI** = confidence interval; **ES** = effect size.

at least one factor in a multivariable model, the association increased (RR = 2.0; 95% CI, 1.6–2.6; N studies = 11). The 2006 meta-analysis by Mahid and colleagues reported an effect estimate of 1.8 (95% CI, 1.4–2.2; N studies = 9) for current smoking combining all studies identified without restriction by timing of current smoking or confounding control.

Sixty-one studies reported on the relationship between current or ever smoking and ulcerative colitis. Ulcerative colitis cases were less likely to smoke than controls (RR = 0.54; 95% CI, 0.48–0.61). Restricting to the 28 studies that reported smoking on or before diagnosis, there was no meaningful change in the point estimate, although the CI was wider (RR = 0.56; 95% CI, 0.45–0.70) (Figure 10.8). With restriction to studies assessing smoking on or before diagnosis and adjusting for at least one factor, there was no meaningful difference compared with the unadjusted studies (RR = 0.49; 95% CI, 0.35–0.66; N studies = 16). The 2006 meta-analysis by Mahid and colleagues reported an effect estimate of 0.58 (95% CI, 0.45–0.75; N studies = 13) for current smoking among all studies identified without restriction to timing of current smoking or confounding control.

When the U.S. studies were compared separately (Jick and Walker 1983; Boyko et al. 1987, 1994; Lashner et al. 1989, 1990; Sandler et al. 1992; Silverstein et al. 1994; Minocha and Raczkowski 1997; Tuvlin et al. 2007; Higuchi et al. 2012), the Crohn's disease and ulcerative colitis results were consistent with the analyses including all countries.

The descriptive epidemiology of IBD in Asia shows rising rates of ulcerative colitis during recent decades when smoking has also increased. When the studies conducted in Asia were considered separately both Crohn's disease (RR = 0.8; 95% CI, 0.6–1.1; N studies = 8) and ulcerative colitis (RR = 0.4; 95% CI, 0.3–0.6; N studies = 13) cases were less likely to smoke than controls (Stermer et al. 1985; Funakoshi et al. 1987; Higashi et al. 1991; Epidemiology Group of the Research Committee of Inflammatory Bowel Disease in Japan [EGRCIBD-Japan] 1994; Nakamura and Labarthe 1994; Reif et al. 1995, 2000; Fich et al. 1997; Naganuma et al. 2001; Firouzi et al. 2006; Jiang et al. 2007; Pugazhendhi et al. 2011; Habashneh et al. 2012; Kayahan et al. 2012). With restriction to studies assessing smoking on or before diagnosis and adjusting

Figure 10.8   Relationship between smoking on or before the time of diagnosis and risk of ulcerative colitis

Study	Country	Number of cases		ES (95% CI)
Case-control				
Logan et al. 1984	United Kingdom	115		0.2 (0.1–0.3)
Thornton et al. 1985	United Kingdom	16		0.5 (0.1–2.0)
Funakoshi et al. 1987	Japan	105		0.5 (0.3–0.8)
Tobin et al. 1987	United Kingdom	90		0.2 (0.1–0.4)
Franceschi et al. 1987	Italy	124		0.5 (0.3–1.0)
Lindberg et al. 1988	Sweden	252		0.7 (0.4–1.0)
Higashi et al. 1991	Japan	43		0.8 (0.2–3.4)
Sandler et al. 1992	United States	130		0.9 (0.5–1.5)
Nakamura and Labarthe 1994	Japan	300		0.3 (0.2–0.5)
EGRCIBD-Japan 1994	Japan	101		0.7 (0.2–2.0)
Boyko et al. 1994	United States	152		0.9 (0.6–1.4)
Uzan et al. 2001	France	150		0.7 (0.4–1.1)
Lopez Ramos et al. 2001	Spain	153		0.3 (0.2–0.6)
Abraham et al. 2003	Australia	72		0.4 (0.2–0.9)
Lakatos et al. 2004	Hungary	468		0.3 (0.2–0.4)
Firouzi et al. 2006	Iran	382		0.2 (0.1–0.3)
Jiang et al. 2007	China	155		0.3 (0.2–0.6)
Gearry et al. 2010	New Zealand	653		0.7 (0.5–0.9)
Andersen et al. 2011	Denmark	312		0.3 (0.3–0.5)
Subtotal (I-squared = 73.9%, p = 0.000)				0.4 (0.3–0.5)
Prospective cohort				
Vessey et al. 1986	United Kingdom	26		0.7 (0.3–1.6)
Logan and Kay 1989	United Kingdom	55		1.1 (0.9–1.4)
Tragnone et al. 1993	Italy	54		1.5 (0.8–3.1)
Higuchi et al. 2012	United States	233		0.9 (0.6–1.2)
Subtotal (I-squared = 26.7%, p = 0.252)				1.0 (0.8–1.3)
Nested case-control				
Boyko et al. 1987	United States	161		0.7 (0.4–1.2)
de Silva et al. 2010	Denmark	175		1.4 (0.9–1.9)
Chan et al. 2013	Europe	177		1.4 (0.9–2.0)
Subtotal (I-squared = 56.7%, p = 0.099)				1.2 (0.8–1.7)
Case series				
Tuvlin et al. 2007	United States	309		0.6 (0.4–0.8)
van der Heide et al. 2011	Netherlands	132		0.6 (0.5–0.8)
Subtotal (I-squared = 0.0%, p = 0.709)				0.6 (0.5–0.7)
Overall (I-squared = 85.1%, p = 0.000)				0.6 (0.4–0.7)

0.1   0.2   0.5   1   2   5

Figure 10.8   Continued

Study	Adjustments
Case-control	
Logan et al. 1984	Age; Gender; Location, region, or center
Funakoshi et al. 1987	Age
Tobin et al. 1987	Age; Gender; Location, region, or center
Franceschi et al. 1987	Age; Gender; Education or social class; Former smoking; Body mass index; Other
Lindberg et al. 1988	Age; Gender; Location, region, or center
Sandler et al. 1992	Age; Gender; Education or social class
Nakamura and Labarthe 1994	Age; Gender; Alcohol
EGRCIBD-Japan 1994	Age; Gender; Location, region, or center; Alcohol
Uzan et al. 2001	Age; Gender; Location, region, or center; Tonsillectomy or appendectomy
Lopez Ramos et al. 2001	Age; Gender; Education or social class; Tonsillectomy or appendectomy; Oral contraceptives or hormone replacement therapy
Firouzi et al. 2006	Age; Gender; Tonsillectomy or appendectomy; Non-steroidal anti-inflammatory drugs; Oral contraceptives or hormone replacement therapy
Jiang et al. 2007	Age; Gender; Family history of inflammatory bowel disease; Former smoking; Tonsillectomy or appendectomy; Alcohol; Coffee or tea; Diet
Gearry et al. 2010	Age; Gender; Race or ethnicity; Education or social class; Family history of inflammatory bowel disease
Prospective cohort	
Higuchi et al. 2012	Age; Gender; Body mass index; Oral contraceptives or hormone replacement therapy
Nested case-control	
Boyko et al. 1987	Age; Gender; Alcohol; Coffee or tea
Chan et al. 2013	Age; Gender; Location, region, or center

Note: Weights are from random effects analysis. **CI** = confidence interval; **EGRCIBD-Japan** = Epidemiology Group of the Research Committee of Inflammatory Bowel Disease in Japan; **ES** = effect size.

for at least one potential confounding factor, the association with Crohn's disease became statistically significant (RR = 0.5; 95% CI, 0.2–1.0; p = 0.04; N studies = 2) and remained similar to the unadjusted estimate for ulcerative colitis (RR = 0.3; 95% CI, 0.2 – 0.5; N studies = 5) (Figure 10.9).

Former Smoking

Seventy-one studies reported on the relationship between former smoking and Crohn's disease or ulcerative colitis (Table 10.21S). The effect estimates were elevated for both Crohn's disease (RR = 1.3; 95% CI, 1.1–1.5; N studies = 28) and ulcerative colitis (RR = 1.5; 95% CI, 1.3–1.8; N studies = 43). When studies that considered former smoking on or before diagnosis and adjusted for at least one factor were examined, the relationship for Crohn's disease was no longer statistically significant (RR = 1.2; 95% CI, 0.7–1.9; N studies = 6), but the relationship with ulcerative colitis remained statistically significant (RR = 1.7; 95% CI, 1.4–2.1; N studies = 14). The increase in risk of ulcerative colitis in former smokers may persist for as long as 20 years after cessation of smoking (Higuchi et al. 2012). The 2006 meta-analysis by Mahid and colleagues found similar relationships for Crohn's disease (RR = 1.3; 95% CI, 1.0–1.8; N studies = 9) and ulcerative colitis (RR = 1.8; 95% CI, 1.4–2.3; N studies = 13).

When the U.S. and Asian studies were considered separately, the Crohn's disease and ulcerative colitis results were consistent with the analyses including all countries.

Figure 10.9   Relationship between smoking on or before the time of diagnosis and risk of Crohn's disease or ulcerative colitis among case-control studies conducted in Asia

Study	Country	Smoking definition	Number of cases		ES (95% CI)
Crohn's disease					
Funakoshi et al. 1987	Japan	Current at symptom onset	25		0.5 (0.2–1.4)
Firouzi et al. 2006	Iran	Current at diagnosis	46		0.4 (0.2–1.2)
Subtotal (I-squared = 0.0%, p = 0.771)					0.5 (0.2–1.0)
Ulcerative colitis					
Funakoshi et al. 1987	Japan	Current at symptom onset	105		0.5 (0.3–0.8)
EGRCIBD-Japan 1994	Japan	Current at diagnosis	101		0.7 (0.2–2.0)
Nakamura and Labarthe 1994	Japan	Current at symptom onset	300		0.3 (0.2–0.5)
Firouzi et al. 2006	Iran	Current at diagnosis	382		0.2 (0.1–0.3)
Jiang et al. 2007	China	Current at diagnosis	155		0.3 (0.2–0.6)
Subtotal (I-squared = 60.9%, p = 0.037)					0.3 (0.2–0.5)
Overall (I-squared = 48.7%, p = 0.069)					0.3 (0.2–0.5)

0.2   0.5   1   2

Study	Adjustments
Crohn's disease	
Funakoshi et al. 1987	Age
Firouzi et al. 2006	Age; Gender; Tonsillectomy or appendectomy; Non-steroidal anti-inflammatory drugs; Oral contraceptives or hormone replacement therapy
Ulcerative colitis	
Funakoshi et al. 1987	Age
EGRCIBD-Japan 1994	Age; Gender; Location; region or center; Alcohol
Nakamura and Labarthe 1994	Age; Gender; Alcohol
Firouzi et al. 2006	Age; Gender; Tonsillectomy or appendectomy; Non-steroidal anti-inflammatory drugs; Oral contraceptives or hormone replacement therapy
Jiang et al. 2007	Age; Gender; Family history of inflammatory bowel disease; Former smoking; Tonsillectomy or appendectomy; Alcohol; Coffee or tea; Diet

Source: Epidemiology Group of the Research Committee of Inflammatory Bowel Disease in Japan (EGRCIBD).
Note: **CI** = confidence interval; **ES** = effect size.

Dose-Response

Seven studies reported a p-value associated with a test for trend for risk with the number of cigarettes smoked per day or week or pack-years (Jick and Walker 1983; Boyko et al. 1987; Funakoshi et al. 1987; Tobin et al. 1987; Logan and Kay 1989; Nakamura and Labarthe 1994; Higuchi et al. 2012). For Crohn's disease, two studies reported that heavy smokers or current smokers with more pack-years had increased incidence of disease (Logan and Kay 1989; Higuchi et al. 2012). Among former smokers, more pack-years of cumulative smoking was also associated with an increased incidence of Crohn's disease (Higuchi et al. 2012). A dose-response relationship with ulcerative colitis was also rarely reported. Three studies

found that more cigarettes per day or pack-years among current smokers were associated with a decreased risk (Funakoshi et al. 1987; Logan and Kay 1989; Nakamura and Labarthe 1994), but two studies found that heavier current smoking was associated with an increased risk of ulcerative colitis (Jick and Walker 1983; Tobin et al. 1987). Among former smokers, heavier smoking was associated with increased risk of ulcerative colitis in two studies (Boyko et al. 1987; Nakamura and Labarthe 1994). For nine studies, the authors reported no dose-response relationship with the amount of current smoking for Crohn's disease or ulcerative colitis, but did not report a p-value from a test for trend (Boyko et al. 1987; Sorensen et al. 1987; Lindberg et al. 1988; EGRCIBD-Japan 1994; Silverstein et al. 1994; Corrao et al. 1998; Reif et al. 2000; Jiang et al. 2007; Carlens et al. 2010).

Evidence Synthesis

Smoking could plausibly affect the occurrence of IBD, a group of disorders involving immune mechanisms. However, more specific mechanistic considerations await additional research; and current understanding is insufficient to explain why smoking would increase risk for Crohn's disease and decrease risk for ulcerative colitis.

The observational findings are consistent in showing an increased risk for Crohn's disease with the exception of studies conducted in Asia. Crohn's disease cases were more likely to smoke, or be former smokers, than their comparison groups with the exception of studies conducted in Asia where Crohn's disease cases were less likely to smoke. When studies from all countries were pooled, the findings were consistent across definitions of smoking and in analyses that adjusted for at least one potential confounder. Analyses, in which the timing of smoking was established as antecedent to disease onset, provided the strongest associations, particularly when potential confounding was taken into account. In contrast, ulcerative colitis cases were less likely to be current smokers and more likely to be former smokers at the time of diagnosis, even when at least one potential confounder was accounted for in the analysis.

The associations of smoking with Crohn's disease and ulcerative colitis are moderate in strength (RR = 1.8, and 0.6, respectively), and almost uniformly consistent even when temporality is accounted for. However, the evidence was less supportive for other elements of the guidelines for causal inference. Dose-response relationships were infrequently reported, and the trends of risk were not consistently found to be statistically significant for either Crohn's disease or ulcerative colitis.

A meta-analysis of randomized trials of nicotine replacement therapy did not find that such therapies were effective treatments for ulcerative colitis, although there were issues related to tolerability and adherence in these studies (Nikfar et al. 2010). The negative evidence from trials may also be interpreted as suggesting that nicotine dosing is not the mechanism by which cigarette smoke affects risk of ulcerative colitis.

Conclusions

1. The evidence is suggestive but not sufficient to infer a causal relationship between cigarette smoking and Crohn's disease.

2. The evidence is suggestive but not sufficient to infer a causal relationship between cigarette smoking and a protective effect for ulcerative colitis.

Implications

Additional research is needed on the mechanisms by which smoking affects the risk for IBD, particularly the role of gene and smoking interactions given the large number of genetic risk factors. There is no basis for considering smoking as a potential strategy for the prevention of ulcerative colitis, given the uncertainty as to the role of smoking in the pathogenesis of the disease and the increased risk for Crohn's disease associated with smoking. Further review of the impact of smoking on the clinical course of Crohn's disease and ulcerative colitis is warranted.

Chapter Conclusions

Eye Disease: Age-Related Macular Degeneration

1. The evidence is sufficient to infer a causal relationship between cigarette smoking and neovascular and atrophic forms of age-related macular degeneration.

2. The evidence is suggestive but not sufficient to infer that smoking cessation reduces the risk of advanced age-related macular degeneration.

Dental Disease

1. The evidence is suggestive but not sufficient to infer a causal relationship between active cigarette smoking and dental caries.

2. The evidence is suggestive but not sufficient to infer a causal relationship between exposure to tobacco smoke and dental caries in children.

3. The evidence is suggestive but not sufficient to infer a causal relationship between cigarette smoking and failure of dental implants.

Diabetes

1. The evidence is sufficient to infer that cigarette smoking is a cause of diabetes.

2. The risk of developing diabetes is 30–40% higher for active smokers than nonsmokers.

3. There is a positive dose-response relationship between the number of cigarettes smoked and the risk of developing diabetes.

Immune Function and Autoimmune Disease

1. The evidence is sufficient to infer that components of cigarette smoke impact components of the immune system. Some of these effects are immune activating and others are immune-suppressive.

2. The evidence is sufficient to infer that cigarette smoking compromises the immune system and that altered immunity is associated with increased risk for pulmonary infections.

3. The evidence is sufficient to infer that cigarette smoke compromises immune homeostasis and that altered immunity is associated with an increased risk for several disorders with an underlying immune diathesis.

Rheumatoid Arthritis

1. The evidence is sufficient to infer a causal relationship between cigarette smoking and rheumatoid arthritis.

2. The evidence is sufficient to infer that cigarette smoking reduces the effectiveness of the tumor necrosis factor-alpha (TNF-α) inhibitors.

Systemic Lupus Erythematosus

1. The evidence is inadequate to infer the presence or absence of a causal relationship between cigarette smoking and systemic lupus erythematosus (SLE), the severity of SLE, or the response to therapy for SLE.

Inflammatory Bowel Disease

1. The evidence is suggestive but not sufficient to infer a causal relationship between cigarette smoking and Crohn's disease.

2. The evidence is suggestive but not sufficient to infer a causal relationship between cigarette smoking and a protective effect for ulcerative colitis.

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Appended Data Table for Figure 10.1

Study	Relative risk (95% CI)	Weight (%)
Keen et al. 1982	1.18 (0.44–3.15)	0.22
Rimm et al. 1995	1.96 (1.5–2.56)	1.78
Kawakami et al. 1997	2.51 (1.3–4.84)	0.46
Njolstad et al. 1998	0.82 (0.59–1.13)	1.42
Sugimori et al. 1998	1.42 (1.1–1.83)	1.88
Uchimoto et al. 1999	1.47 (1.13–1.92)	1.80
Manson et al. 2000	1.63 (1.5–1.77)	3.63
Nakanishi et al. 2000	2.90 (1.67–5.03)	0.63
Strandberg and Salomaa 2000	1.62 (1.01–2.59)	0.81
Hu et al. 2001	1.30 (1.15–1.47)	3.21
Wannamethee et al. 2001	1.74 (1.24–2.44)	1.34
Will et al. 2001 (females)	1.07 (1.03–1.11)	3.98
Will et al. 2001 (males)	1.19 (1.15–1.24)	3.98
Montgomery and Ekbom 2002	2.40 (1.34–4.3)	0.57
Bonora et al. 2004	0.91 (0.52–1.6)	0.61
Carlsson et al. 2004	1.06 (0.87–1.30	2.36
Eliasson et al. 2004	3.76 (1.52–9.32)	0.26
Sairenchi et al. 2004 (females)	1.39 (1.20–1.61)	2.93
Sairenchi et al. 2004 (males)	1.27 (1.16–1.39)	3.59
Foy et al. 2005	2.15 (1.20–3.86)	0.57
Lyssenko et al. 2005	1.50 (1.07–2.1)	1.33
Patja et al. 2005	1.41 (1.26–1.57)	3.35
Tenenbaum et al. 2005	1.94 (1.16–3.25)	0.70
Waki et al. 2005 (females)	1.42 (0.95–2.12)	1.05
Waki et al. 2005 (males)	1.25 (1.07–1.47)	2.80
Harding et al. 2006	1.15 (0.90–1.46)	1.98
Houston et al. 2006	1.65 (1.28–2.13)	1.88
Meisinger et al. 2006 (females)	1.38 (1.03–1.84)	1.62
Meisinger et al. 2006 (males)	1.69 (1.34–2.13)	2.07
Burke et al. 2007	2.05 (1.23–3.40)	0.72
Cugati et al. 2007	1.57 (1.03–2.40)	0.96
Dehghan et al. 2007	1.16 (0.96–1.40)	2.48
Holme et al. 2007	1.15 (0.93–1.42)	2.25
Hur et al. 2007	1.60 (1.29–1.98)	2.25
Mozaffarian et al. 2007	1.60 (1.34–1.91)	2.63
Onat et al. 2007	0.60 (0.41–0.87)	1.17
Schulze et al. 2007	1.90 (1.47–2.46)	1.85
Hayashino et al. 2008	1.99 (1.30–3.05)	0.94
Lyssenko et al. 2008	1.39 (1.23–1.57)	3.21
Magliano et al. 2008	1.66 (1.11–2.49)	1.02

Appended Data Table for Figure 10.1   **Continued**

Study	Relative risk (95% CI)	Weight (%)
Nagaya et al. 2008	1.10 (0.96–1.26)	3.06
Nichols et al. 2008	1.37 (1.22–1.54)	3.28
Park et al. 2008	1.73 (1.22–2.46)	1.25
Chien et al. 2009	1.01 (0.83–1.22)	2.46
Cho et al. 2009	2.20 (1.50–3.22)	1.12
Cullen et al. 2009	1.35 (1.20–1.51)	3.29
Hippisley-Cox et al. 2009 (females)	1.27 (1.23–1.31)	4.00
Hippisley-Cox et al. 2009 (males)	1.25 (1.21–1.29)	4.02
Mozaffarian et al. 2009	1.30 (1.04–1.63)	2.10
Laaksonen et al. 2010	1.78 (1.20–2.65)	1.06
Yeh et al. 2010	1.31 (1.04–1.65)	2.08
Overall (I-squared = 81.7%, p = 0.000)	1.37 (1.31–1.44)	100

Note: **CI** = confidence interval.

Appended Data Table for Figure 10.7

Study	Design	Country	Number of cases	Effect size (95% CI)	Adjustments
Thornton 1985	Case-control	United Kingdom	28	5.7 (1.8–18.0)	—
Funakoshi 1987	Case-control	Japan	25	0.5 (0.2–1.4)	Age
Tobin 1987	Case-control	United Kingdom	115	2.9 (1.8–4.9)	Age; gender; location, region, or center
Franceschi 1987	Case-control	Italy	109	4.2 (2.3–7.7)	Age, gender, education or social class, former smoking, body mass index, other
Lindberg 1988	Case-control	Sweden	141	2.2 (1.3–3.5)	Age; gender; location, region, or center
Sandler 1992	Case-control	United States	167	1.6 (0.7–3.6)	Oral contraceptives or hormone replacement therapy
Katschinski 1993	Case-control	Germany	79	3.0 (1.3–6.8)	Age; oral contraceptives or hormone replacement therapy
Boyko 1994	Case-control	United States	78	2.4 (1.3–4.2)	—
Brignola 2000	Case-control	Italy	636	2.3 (1.5–3.5)	—
Lopez Ramos 2001	Case-control	Spain	134	2.8 (1.8–4.3)	Age; gender; education or social class; tonsillectomy or appendectomy; oral contraceptives or hormone replacement therapy
Lakatos 2004	Case-control	Hungary	202	1.7 (1.3–2.4)	—
Firouzi 2006	Case-control	Iran	46	0.4 (0.2–1.2)	Age; gender; tonsillectomy or appendectomy; non-steroidal anti-inflammatory drugs; oral contraceptives or hormone replacement therapy
Morgan 2010	Case-control	New Zealand	238	2.4 (1.6–3.4)	—
Gearry 2010	Case-control	New Zealand	638	2.0 (1.5–2.7)	Age, gender, race/ethnicity, education or social class, family history of inflammatory bowel disease
Andersen 2011	Case-control	Denmark	282	1.3 (0.9–1.8)	—
Pugazhendhi 2011	Case-control	India	200	0.8 (0.4–1.3)	—
Subtotal: Case-control (I-squared = 70.9%; p = 0.000)				1.9 (1.5–2.4)	

Appended Data Table for Figure 10.7　　　Continued

Study	Design	Country	Number of cases	Effect size (95% CI)	Adjustments
Vessey 1986	Prospective cohort	United Kingdom	17	3.3 (1.2–8.8)	—
Logan 1989	Prospective cohort	United Kingdom	42	1.8 (1.0–3.3)	—
Tragnone 1993	Prospective cohort	Italy	35	1.5 (0.7–3.5)	—
Higuchi 2012	Prospective cohort	United States	219	1.9 (1.4–2.5)	Age, gender, body mass index, oral contraceptives or hormone replacement therapy
Subtotal: Prospective cohort (I-squared = 0.0%; p = 0.706)				1.9 (1.5–2.4)	
de Silva 2010	Nested case-control	Denmark	74	1.9 (1.1–3.2)	—
Chan 2013	Nested case-control	Europe	75	2.0 (1.1–3.5)	Age; gender; location, region, or center
Subtotal: Nested case-cohort (I-squared = 0.0%; p = 0.906)				1.9 (1.3–2.8)	
Tuvlin 2007	Case series	United States	351	1.3 (1.0–1.6)	—
van der Heide 2011	Case series	Netherlands	104	1.3 (1.1–1.5)	—
Subtotal: Case series (I-squared = 0.0%; p = 0.904)				1.3 (1.1–1.5)	
Overall (I-squared = 69.1%; p = 0.000)				1.8 (1.6–2.2)	

Note: CI = confidence interval.

Appended Data Table for Figure 10.8

Study	Design	Country	Number of cases	Effect size (95% CI)	Adjustments
Logan et al. 1984	Case-control	United Kingdom	115	0.2 (0.1–0.3)	Age; gender; location, region, or center
Thornton et al. 1985	Case-control	United Kingdom	16	0.5 (0.1–2.0)	—
Funakoshi et al. 1987	Case-control	Japan	105	0.5 (0.3–0.8)	Age
Tobin et al. 1987	Case-control	United Kingdom	90	0.2 (0.1–0.4)	Age; gender; location, region, or center
Franceschi et al. 1987	Case-control	Italy	124	0.5 (0.3–1.0)	Age, gender, education or social class, former smoking, body mass index, other
Lindberg et al. 1988	Case-control	Sweden	252	0.7 (0.4–1.0)	Age; gender; location, region, or center
Higashi et al. 1991	Case-control	Japan	43	0.8 (0.2–3.4)	—
Sandler et al. 1992	Case-control	United States	130	0.9 (0.5–1.5)	Age, gender, education or social class
Nakamura and Labarthe 1994	Case-control	Japan	300	0.3 (0.2–0.5)	Age, gender, alcohol
EGRCIBD-Japan 1994	Case-control	Japan	101	0.7 (0.2–2.0)	Age; gender; location, region or center; alcohol
Boyko et al. 1994	Case-control	United States	152	0.9 (0.6–1.4)	—
Uzan et al. 2001	Case-control	France	150	0.7 (0.4–1.1)	Age; gender; location, region or center; tonsillectomy or appendectomy
Lopez Ramos et al. 2001	Case-control	Spain	153	0.3 (0.2–0.6)	Age, gender, education or social class, tonsillectomy or appendectomy, oral contraceptives or hormone replacement therapy
Abraham et al. 2003	Case-control	Australia	72	0.4 (0.2–0.9)	—
Lakatos et al. 2004	Case-control	Hungary	468	0.3 (0.2–0.6)	—
Firouzi et al. 2006	Case-control	Iran	382	0.2 (0.1–0.3)	Age, gender, tonsillectomy or appendectomy, non-steroidal anti-inflammatory drugs, oral contraceptives or hormone replacement therapy
Jiang et al. 2007	Case-control	China	155	0.3 (0.2–0.6)	Age, gender, family history of inflammatory bowel disease, former smoking, tonsillectomy or appendectomy, alcohol, coffee or tea, diet

Appended Data Table for Figure 10.8   Continued

Study	Design	Country	Number of cases	Effect size (95% CI)	Adjustments
Gearry et al. 2010	Case-control	New Zealand	653	0.7 (0.5–0.9)	Age, gender, race/ ethnicity, education or social class, family history of inflammatory bowel disease
Andersen et al. 2011	Case-control	Denmark	312	0.3 (0.3–0.5)	—
Subtotal: Case-control (I-squared = 73.9%; p = 0.000)				0.4 (0.3–0.5)	
Vessey et al. 1986	Prospective cohort	United Kingdom	26	0.7 (0.3–1.6)	—
Logan and Kay 1989	Prospective cohort	United Kingdom	55	1.1 (0.9–1.4)	—
Tragnone et al. 1993	Prospective cohort	Italy	54	1.5 (0.8–3.1)	—
Higuchi et al. 2012	Prospective cohort	United States	233	0.9 (0.6–1.2)	Age, gender, body mass index, oral contraceptives or hormone replacement therapy
Subtotal: Prospective cohort (I-squared = 26.7%; p = 0.252)				1.0 (0.8–1.3)	
Boyko et al. 1987	Nested case-control	United States	161	0.7 (0.4–1.2)	Age, gender, alcohol, coffee or tea
de Silva et al. 2010	Nested case-control	Denmark	175	1.4 (0.9–1.9)	—
Chan et al. 2013	Nested case-control	Europe	177	1.4 (0.9–2.0)	Age; gender; location, region, or center
Subtotal: Nested case-cohort (I-squared = 56.7%; p = 0.099)				1.2 (0.8–1.7)	
Tuvlin et al. 2007	Case series	United States	309	0.6 (0.4–0.8)	—
van der Heide et al. 2011	Case series	Netherlands	132	0.6 (0.5–0.8)	—
Subtotal: Case series (I-squared = 0.0%; p = 0.709)				0.6 (0.5–0.7)	
Overall (I-squared = 85.1%; p = 0.000)				0.6 (0.4–0.7)	

Notes: CI = confidence interval; EGRCIBD-Japan = Epidemiology Group of the Research Committee of Inflammatory Bowel Disease in Japan.

Appended Data Table for Figure 10.9

Study	Disease	Country	Smoking definition	Number of cases	Effect size (95% CI)	Adjustments
Funakoshi 1987	Crohn's disease	Japan	Current at symptom onset	25	0.5 (0.2–1.4)	Age
Firouzi 2006	Crohn's disease	Iran	Current at diagnosis	46	0.4 (0.2–1.2)	Age, gender, tonsillectomy or appendectomy, non-steroidal anti-inflammatory drugs, oral contraceptives of hormone replacement therapy
Subtotal: Crohn's disease (I-squared = 0.0%, p = 0.771)					0.5 (0.2–1.0)	
Funakoshi 1987	Ulcerative colitis	Japan	Current at symptom onset	105	0.5 (0.3–0.8)	Age
EGRCIBD-Japan 1994	Ulcerative colitis	Japan	Current at diagnosis	101	0.7 (0.2–2.0)	Age; gender; location, region or center; alcohol
Nakamura 1994	Ulcerative colitis	Japan	Current at symptom onset	300	0.3 (0.2–0.5)	Age, gender, alcohol
Firouzi 2006	Ulcerative colitis	Iran	Current at diagnosis	382	0.2 (0.1–0.3)	Age, gender, tonsillectomy or appendectomy, non-steroidal anti-inflammatory drugs, oral contraceptives of hormone replacement therapy
Jiang 2007	Ulcerative colitis	China	Current at diagnosis	155	0.3 (0.2–0.6)	Age, gender, family history of inflammatory bowel disease, former smoking, tonsillectomy or appendectomy, alcohol, coffee or tea, diet
Subtotal: Ulcerative colitis (I-squared = 60.9%, p = 0.037)					0.3 (0.2–0.5)	
Overall (I-squared = 48.7%, p = 0.069)					0.3 (0.2–0.5)	

Source: Epidemiology Group of the Research Committee of Inflammatory Bowel Disease in Japan (EGRCIBD).
Note: CI = confidence interval.

Chapter 11
General Morbidity and All-Cause Mortality

Sections of this chapter on the health consequences of smoking are accompanied by evidence tables detailing the studies that were used to evaluate the evidence to assess causality. A supplement to this report is provided that contains these tables. The tables included in the supplement are indicated with an "*S*" where they are called out in the text.

Introduction

Smoking has long been known to increase mortality. Pearl's 1938 paper in *Science* showed increased mortality in users of tobacco compared to nonusers, a finding that was replicated in the 1950s by the first wave of cohort studies initiated to investigate the risks of smoking (Figure 11.1) (Pearl 1938). Previous Surgeon General's reports have commented on the increased overall risk for dying in smokers and identified smoking as the leading cause of avoidable premature mortality. The mortality risk associated with smoking has changed over time, driven by the trends in patterns of smoking in the population, as discussed in Chapters 2, "Fifty Years of Change 1964–2014," 4, "Advances in Knowledge of the Health Consequences of Smoking: From 1964–2014," and 13, "Patterns of Tobacco Use Among U.S. Youth, Young Adults, and Adults." Consequently, this chapter provides updated evidence on smoking and all-cause mortality, drawing on a pooled analysis of data from five cohorts that spans the period 2000–2010.

Other chapters in this report have addressed the causation of specific diseases by smoking. For each of these diseases, there is excess mortality attributable to smoking that is potentially avoidable through tobacco control. All-cause mortality provides a measure of the excess mortality attributable to smoking that integrates across all of these causes, as well as capturing mortality that may come from still unidentified associations of smoking with disease and through indirect pathways, such as diminished immune function.

Beyond causing specific diseases and a wide range of other adverse health effects, smoking is also associated with generally poorer health, when smokers are compared with nonsmokers. This chapter also addresses the evidence supporting such general adverse effects, which are not captured by the evidence on the many specific diseases caused by smoking. The 2004 Surgeon General's report concluded that smoking caused diminished health status, referring to a general reduction of health as

manifest, for example, by absenteeism from work and self-report (U.S. Department of Health and Human Services [USDHHS] 2004). One manifestation of the diminished health status of smokers is an increase in morbidity (i.e., illness), generally.

These general health effects of smoking contribute to increased absenteeism, loss of well-being, and have implications for health care and its costs. As a result of the specific disease burden from smoking and the diminished health status of smokers, their health care costs exceed those of nonsmokers. This chapter examines new evidence, since the 2004 report, on all-cause mortality and measures of general health status, assessing the ongoing impact of smoking on health.

Chapter 12, "Smoking-Attributable Morbidity, Mortality, and Economic Costs" discusses the relationship of smoking to several highly prevalent illnesses, and the implications these have on national health burdens. In 2003, the Centers for Disease Control and Prevention (CDC) estimated that for the year 2000, 8.6 million persons (95% confidence interval [CI], 6.9–10.5) in the United States had an estimated 12.7 million (95% CI, 10.8–15.0) serious medical conditions that were caused by smoking. The most prevalent conditions were chronic bronchitis and emphysema, which accounted for 73% of the serious medical conditions reported by smokers. As discussed in previous reports (USDHHS 2004, 2010) and in Chapter 7, "Respiratory Diseases," smoking is a primary cause of respiratory diseases. In Chapter 8, "Cardiovascular Diseases," the causal relationship between tobacco smoke from either smoking and/or exposure to secondhand smoke and cardiovascular disease is presented. Chapter 10, "Other Specific Outcomes" of this report reviews the evidence of a causal relationship between smoking and diabetes, as well as the impact that smoking has on immune function.

Figure 11.1   Survivorship lines of life tables for White males falling into three categories relative to the usage of tobacco as in Pearl, 1938
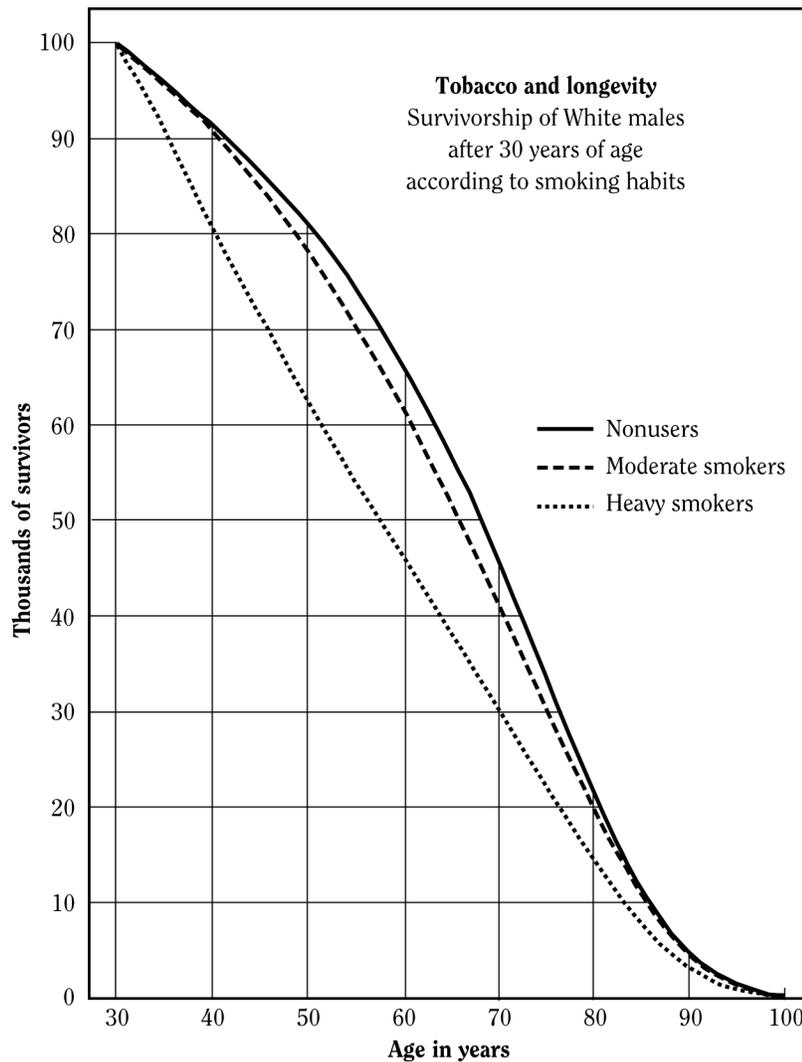
Source: Pearl 1938. Reprinted with permission from American Association for the Advancement of Science, © 1938.

Smoking and General Morbidity and Economic Costs

Disease incidence and mortality are key indicators of the effects of smoking on health, but do not capture the full impact on the health and well-being of smokers. Declines in well-being may occur well before—or even in the absence of—diagnosed disease. The goal of this section is to evaluate the effects of smoking on global measures of health and well-being. These measures were not considered in the 1964 Surgeon General's report (U.S. Department of Health, Education, and Welfare [USDHEW] 1964), but have proven to be important contributors to the overall burden of smoking-related ill health (USDHHS 2004). Smokers experience measurable declines in overall health soon after smoking initiation, and these health deficits persist through adulthood (USDHHS 2012). In contrast to the premature mortality from smoking, which begins in middle age, and the diseases caused by smoking that have

rising incidence from the fourth decade of life, the effects on general health are an immediate and current concern for smokers of all ages.

Some measures that have been used to assess the overall health impact of smoking include self-reported health status, health care utilization and costs, and workplace absenteeism. These measures are clearly interrelated, but each provides a distinct indicator of the health effects of smoking. Self-reported health status may be the most relevant measure for the individual smoker, whereas employers, who are considering implementation of smoking cessation programs, may be more interested in lost workdays due to smoking, and the use and costs of health care by smokers.

The 2004 Surgeon General's report included a comprehensive review of these topics and concluded that the evidence was sufficient to infer a causal relationship between smoking and diminished health status, a term introduced in that report. The current report updates that review, strengthening the evidence base and confirming the causal relationship. Other topics relevant to this topic are also covered in this report, including the effects of smoking on the immune system (see Chapter 10) and smoking and respiratory infections (see Chapter 7).

Biologic Basis

A conceptual model of the relationship between cigarette smoking and diminished health was described in the 2004 Surgeon General's report: smoking adversely affects health through specific disease pathogenesis—such as the development of lung cancer—or through nonspecific mechanisms, such as alterations to the immune system, systemic oxidative stress, or subclinical organ injury. Consideration of all of these pathways is necessary to capture the full effects of tobacco on health. Previous Surgeon General's reports have covered these topics in depth (USDHHS 2004). The 2010 report specifically focused on the mechanisms by which smoking causes disease concluding that "Inhaling the complex chemical mixture of combustion compounds in tobacco smoke causes adverse health outcomes, particularly cancer and cardiovascular and pulmonary diseases, through mechanisms that include DNA damage, inflammation, and oxidative stress" (USDHHS 2010, p. 9). The report also noted that there is no risk-free level of exposure to tobacco smoke. The present report adds a comprehensive review of smoking and immune function (see Chapter 10) to these previous syntheses of the evidence on how smoking causes disease and affects health.

Conclusions of Previous Surgeon General's Reports

The first comprehensive evidence synthesis on the topic of smoking and general morbidity and health status was described in the 2004 Surgeon General's report (USDHHS 2004). The conclusions of that report were as follows:

- "The evidence is sufficient to infer a causal relationship between smoking and diminished health status that may manifest as increased absenteeism from work and increased use of medical care services" (p. 29).

- "The evidence is sufficient to infer a causal relationship between smoking and increased risks for adverse surgical outcomes related to wound healing and respiratory complications" (p. 29).

In discussing the implications of these findings, the report stated "Although preventing the specific diseases caused by smoking has been a public health priority for a long time, cigarette smoking also causes a substantial and costly burden of nonspecific morbidity" (p. 677).

Epidemiologic Evidence

The current report updates some findings of the 2004 Surgeon General's report with a selective review of studies published from 2000 onward. The 2004 report established a causal relationship between smoking and diminished health; the current review builds on these findings by discussing recent results from large, longitudinal and/or nationally representative studies, such as the Health and Retirement Study (HRS) and the Behavioral Risk Factor Surveillance System (BRFSS). Emphasis was placed on larger studies, nationally representative studies, and studies that quantified the effects of smoking. These studies provide results that can be generalized to large segments of the population. Furthermore, they may provide more precise estimates of effect than smaller studies. Focusing on these studies is unlikely to produce biased conclusions because causation has already been established and studies continue to be remarkably consistent in finding poorer health among smokers. Although a few studies with null findings are highlighted in the review, the body of evidence as a whole clearly demonstrates adverse health effects of smoking.

The review of workplace absenteeism focuses on more narrowly defined populations (people who were employed, sometimes in a single industry), and here studies are included that collected adequate information about smoking (at a minimum, smoking classified as current, former, or never). In the case of health care utilization and costs, the review was restricted to studies based in the United States. Studies of smoking and specific conditions (e.g., work loss due to back pain) were not included.

Health Status

Physical, mental, and social well-being are fundamental to the concept of health and are incorporated in the World Health Organization's (WHO's) (1948) definition of health. Mental and social well-being are inherently subjective and assessed in practice by self-report of health status.

The Short Form 36 (SF-36) and Short Form 12 (SF-12), for example, are widely used instruments that collect information about eight areas of health and functioning. Lower (i.e., worse) scores on these instruments have been found to predict mortality (Dorr et al. 2006; Kroenke et al. 2008) and hospitalization (Dorr et al. 2006) in older or middle-aged adults. Other tools—including the single question, "In general, would you say your health is excellent, very good, good, fair, or poor?" have also been linked with important health outcomes (McGee et al. 1999; DeSalvo et al. 2005). The studies in Tables 11.1*S*–11.9*S* are organized by the measures of health status that were assessed. As noted, many of the studies accounted for a broad range of potential confounding factors.

Self-Reported Poor or Fair Health

In studies of population groups, ranging from adolescents and college students to the elderly, current smokers have self-reported poorer health compared with never smokers (Johnson and Richter 2002; Ostbye et al. 2002; Arday et al. 2003; Caldeira et al. 2012; Wang et al. 2012). Among respondents 18 years of age and older in BRFSS, current smokers were 70% more likely than never smokers to report poor or fair health (Strine et al. 2005). A dose-response relationship for self-reported poor or fair health was observed among current smokers in the HRS; compared with never smokers, current light smokers had a 47% increase in risk and current heavy smokers had a doubling of risk (Ostbye et al. 2002).

Former smokers also tend to be more likely to report poor or fair health than never smokers, particularly if they had only recently quit smoking at the time of assessment. Among middle-aged participants in the HRS, former smokers who quit within the last 3 years were almost twice as likely as never smokers to report poor or fair health; former smokers who had quit more than 15 years previously had a risk of fair or poor health that was similar to that of never smokers (Ostbye et al. 2002). A decline in risk for reporting poor health, with increasing time since quitting, was also observed among elderly Medicare enrollees (Arday et al. 2003). One study, using the 2006 BRFSS data, found that health-related quality of life was poorer for smokers who had tried to quit but not succeeded, compared with smokers who did not try to quit (McClave et al. 2009). Former smokers had better health-related quality of life than both groups of current smokers.

Poor Physical or Mental Function

Poor physical or mental function—assessed through SF-36 or SF-12 scores or report of difficulty with specific tasks—was evaluated in several studies. In the Nurses' Health Study (NHS) cohorts, current smokers had poorer physical and emotional functioning than never smokers. Furthermore, among current smokers, physical and emotional function declined as the number of cigarettes per day increased (Sarna et al. 2008). Current smokers also had poorer physical and emotional function than never smokers in a study of elderly or disabled Medicare enrollees (Arday et al. 2003). Among participants in the HRS, self-reported limited ability to work because of impairment or health problems was more than twice as common among current heavy smokers than among never smokers. Current light smokers had a 73% increase in risk for disability compared with never smokers (Ostbye et al. 2002). Studies conducted in other countries have also found poorer physical and/or emotional health status among current smokers compared with never smokers (Mulder et al. 2001; Sulander et al. 2005; Laaksonen et al. 2006; Myint et al. 2007; Strandberg et al. 2008; Pisinger et al. 2009; Liao et al. 2011; Vogl et al. 2012).

A study of male veterans who receive U.S. Department of Veterans Affairs (VA) health care services did not find an association between current smoking and SF-36 physical or mental component summary scores (Borzecki et al. 2005). There are several potential explanations for the difference between this study and the results of the other studies reviewed. The study of veterans had relatively high rates of nonresponse and exclusion, because of missing data. Participants who were excluded tended to have poorer physical health, mental health, and health behaviors than subjects who were included. This selection bias may have weakened the association between smoking

and health status. The effect of smoking may also have been weakened by adjustment for the number of health problems, which are likely to be on the causal pathway between smoking and self-reported poor health. The null results of this study may reflect these methodologic issues.

Decline in function was evaluated among 558 community-dwelling older women with moderate-to-severe disability at baseline (Atkinson et al. 2005). Physical decline was based on walking speed; cognitive decline was based on Mini-Mental State Examination results. During 3 years of follow-up, current smokers were over five times more likely than never smokers to experience a combination of physical and mental decline.

The status of physical and mental functioning among former smokers tends to fall in between those of current and never smokers (Sulander et al. 2005; Myint et al. 2007; Liao et al. 2011; Vogl et al. 2012), although some studies have found similar results for never and former smokers (Borzecki et al. 2005; Laaksonen et al. 2006). The association varies with time since quitting. SF-36 physical and mental component summary scores improved with longer time since quitting in the NHS cohorts (Sarna et al. 2008). In the HRS, long-term quitters were no more likely than never smokers to report limited ability to work because of health problems (Ostbye et al. 2002). These findings add to the evidence that smoking cessation improves later health outcomes.

Other Measures of General Health and Well-Being

Several other measures of health and well-being have also been evaluated in relation to smoking, including ability to walk a short distance, frailty, overall quality of life, and successful aging. In studies of middle-aged (Ostbye et al. 2002) and older people (Ostbye et al. 2002; Hardy et al. 2010), current smokers reported greater difficulty than never smokers in walking a short distance. Former smokers—particularly recent quitters—may also be at increased risk compared with never smokers (Ostbye et al. 2002).

Among participants in the Women's Health Initiative (WHI) observational study, frailty—defined on the basis of self-reported poor physical function, exhaustion, low physical activity, and unintentional weight loss—was almost three times more common among current smokers than never smokers (Woods et al. 2005). Former smokers had a 12% increase in risk of frailty compared with never smokers.

Overall quality of life (Heikkinen et al. 2008) and life satisfaction (McClave et al. 2009) also appear to be reduced by smoking, although smoking cessation may improve quality of life. Among participants in a smoking cessation trial, successful quitters reported subsequent better quality of life than those who continued to smoke (Piper et al. 2012). Similarly, in a smoking reduction trial, those who reduced their smoking by at least one-half reported better general health than those who did not reduce their smoking (Bolliger et al. 2002).

A desired outcome—successful aging—was evaluated among men and women between 42–63 years of age at baseline (Sabia et al. 2012). Successful aging was defined as having good cognitive, respiratory, and cardiovascular functioning, and the absence of disability, mental health problems, and chronic disease. Compared with people who had ever smoked, never smokers were 29% more likely to experience successful aging.

Combinations of Health Behaviors

Another, and more holistic, way of assessing the impact of smoking on health status is to consider the effect of smoking in combination with other health risk behaviors. Two cohort studies considered smoking along with other health risk behaviors in aggregate indices. Four healthy behaviors were evaluated in a large cohort of men and women between 42–63 years of age: never smoking, moderate alcohol consumption, engaging in physical activity, and daily consumption of fruits and vegetables (Sabia et al. 2012). Individuals with all four healthy behaviors were more than three times more likely than those with none of the healthy behaviors to experience successful aging (odds ratio [OR] = 3.3; 95% CI, 2.1–5.1). Similarly, a study of adults 60 years of age or older evaluated never smoking, moderate alcohol intake, 6–8 hours of sleep per night, and regular exercise. Study participants with all four healthy behaviors were 75% less likely to develop functional disability than those with none of the healthy behaviors (hazard ratio = 0.25; 95% CI, 0.11–0.57) (Liao et al. 2011). In both studies, smoking had an independent effect.

Medical Services Utilization and Cost

Medical services utilization and cost provide another measure of the overall impact of smoking on health. As described in previous sections, smoking causes a broad range of diseases and has also been linked with significant deficits in overall health. Measures of health care utilization and cost capture the medical care that is required for all of these health effects combined. Tables 11.6*S*–11.9*S* provide additional information about studies that addressed these issues.

Hospitalizations

Hospitalizations among younger smokers were evaluated in two studies conducted in military populations. Among men and women serving on active duty in the U.S. Army, hospitalization for a reason other than injury or pregnancy was 30% more common among male current smokers and 25% more common among female current smokers relative to never smokers (Robbins et al. 2000). Risk of hospitalization was also higher among former smokers than among never smokers, but to a lesser extent. In a study of female naval recruits, the likelihood of nonpregnancy-related hospitalization differed significantly by smoking status with current daily smokers having a significantly higher rate of hospitalization than other smokers and never smokers (Woodruff et al. 2010). Study results in even younger people (Johnson and Richter 2002), and much older people (Ostbye et al. 2002; Kahende et al. 2009), also suggest that smokers have higher rates of hospitalization than never smokers.

The risk of hospitalization among former smokers appears to decline with lengthening time since quitting. Compared with never smokers in the HRS, former smokers who had quit within the last 3 years had a 46% increase in risk of hospitalization, and former smokers who quit between 3–15 years previously had a 22% increase in risk (Ostbye et al. 2002). Long-term quitters (i.e., those who had quit at least 15 years previously) had a risk of hospitalization that was similar to that for never smokers. An analysis of 1999–2004 National Health and Nutrition Examination Survey (NHANES) data also indicated that the risk of hospitalization declines with time since quitting, although even long-term quitters (10 years or more) remained more likely than never smokers to be hospitalized (Kahende et al. 2009).

Outpatient Visits

Outpatient visits may occur for routine check-ups and preventive care, follow-up of ongoing illnesses (e.g., hypertension), and work-up of new symptoms or acute illness. Evidence shows that the mix of visit types differs, comparing smokers with nonsmokers, as smokers are less likely to have routine visits (USDHHS 2004). Consequently, comparisons of total visits, without disaggregation by type, are less informative as to the effects of smoking.

In the analysis of 1999–2004 NHANES data, the frequency of at least one outpatient visit in the past year was similar in current and never smokers. Current smokers, however, were more likely than never smokers to have multiple (four or more) outpatient visits in the past year (Kahende et al. 2009). Former smokers were also more likely than never smokers to have multiple outpatient visits, even among long-term quitters. In contrast, among male veterans receiving care at VA medical facilities, current smokers had fewer outpatient medical visits than never smokers (Borzecki et al. 2005).

Nursing Home Stays

Although many studies have evaluated smoking in relation to outpatient care and hospitalization, far fewer studies have addressed the relationship between smoking and nursing home stays. The available data, however, suggest that smoking increases the likelihood of a nursing home stay among both middle-aged and older individuals.

In the NHANES I Epidemiologic Follow-up Study, smoking increased the risk of a nursing home admission by 32% among those 65–74 years of age at baseline, and by 56% among those 45–65 years of age (Valiyeva et al. 2006). The comparison group included both former and never smokers, which may have led to an underestimation of the effect of smoking.

A study that included only older people (i.e., 70 years of age or older) also found an increased risk of nursing home admission among current smokers. In the Asset and Health Dynamics Among the Oldest Old Survey, current smokers were 68% more likely than never smokers to have a stay in a nursing home, convalescent home, or other long-term care health facility (Ostbye et al. 2002). The risk among former smokers was similar to the risk among never smokers.

Total Health Care Costs

A 2012 report by the Congressional Budget Office (CBO) estimated annual per capita health care spending among adults 18 years of age and older (Table 11.10*S*) (CBO 2012). Spending tended to be highest among former smokers, likely reflecting cessation following onset of an illness caused by smoking. Current smokers had greater expenditures than never smokers. Among adults 45–64 years of age, for example, annual health care spending was $7,650 for recent quitters, $5,540 for current smokers, and $5,040 for never smokers. Never smokers had the lowest spending in each age group, except the oldest; among people 75 years of age or older, spending was $1,060 less for current smokers, than for never smokers. As noted in the report, continuing smokers who survive to that age may be in good health in spite of smoking, or may have a lower propensity to use health care.

In order to account for the many ways that smokers differ from nonsmokers, the CBO analysis also compared current and former smokers with people who had never smoked, but had characteristics that were similar

to smokers. Among people who had ever smoked, between 11–16% of their health care spending was attributable to smoking.

Among former smokers in the CBO analysis, spending declined with longer time since quitting among those 45 years of age or older (Table 11.10*S*). Nevertheless, even among long-term quitters, spending remained higher than for never and current smokers.

Together, these and previous studies indicate that smoking increases the use and cost of health care (USDHHS 2004). Increases in utilization and cost are apparent in young smokers, and persist into old age. An important message for the public is that increases in utilization involve more than just physician visits; smokers are also at increased risk of hospitalization and nursing home stays, beginning at relatively young ages.

Workplace Absenteeism

Workplace absenteeism is a common and costly problem. In a 2003 analysis of the American Productivity Audit, health-related loss of productive time cost employers $225.8 billion per year, or $1,685 per employee per year (Stewart et al. 2003). The 2004 Surgeon General's report found consistent evidence that current smokers were more likely to be absent from work than never smokers (USDHHS 2004). Former smokers tended to have rates of absenteeism that were lower than current smokers and higher than never smokers, but there was some evidence that absenteeism rates varied by time since quitting; recent quitters tended to have higher absenteeism rates than long-term quitters.

A 2013 review of smoking and absence from work included several of the studies presented in the 2004 Surgeon General's report along with more recent studies (Weng et al. 2013). In a meta-analysis of 17 of the studies, current smokers were 33% more likely to have an absence from work than nonsmokers (i.e., a group that combined never smokers and former smokers).

As shown in Tables 11.11*S* and 11.12*S*, studies have assessed many different measures of absenteeism, including any absence during a specified time period (Sindelar et al. 2005), any short-term absence (Laaksonen et al. 2009), any long-term absence (Morikawa et al. 2004; Christensen et al. 2007), or total days lost (Halpern et al. 2001; Tsai et al. 2003, 2005; Bunn et al. 2006; Labriola et al. 2006; Lundborg 2007). Regardless of definition, current smokers have higher levels of absenteeism than never smokers. Amount smoked also appears to have an impact, with heavy smokers having higher levels of absenteeism than lighter smokers (Christensen et al. 2007; Laaksonen et al. 2009).

Overall, former smokers tend to have rates of absenteeism that are in between those of current smokers and those of never smokers. As for other outcomes, however, absenteeism tends to be most common among recent quitters and decrease with longer time since cessation. In a large study of U.S. workers, former smokers were 33% more likely to have had an absence in the last week than never smokers. The most recent quitters, however (i.e., those who had quit in the last 3 months), were more than three times more likely to have had an absence than never smokers. This level of absenteeism was substantially higher than in current smokers, perhaps because cessation resulted from the onset of smoking-related symptoms or disease. With longer time since quitting, absenteeism dropped below the level in current smokers, but remained higher than the level in never smokers. Former smokers who had quit at least 5 years previously were 21–24% more likely to have an absence than never smokers (Sindelar et al. 2005). A decrease in absenteeism, with longer time since quitting, was also reported in a study of U.S. petrochemical workers (Tsai et al. 2005).

Control of potential confounders varied across studies, and few of the absenteeism studies accounted for other lifestyle behaviors such as obesity, alcohol use, and physical activity. In a Swedish study (Lundborg 2007), information about obesity, alcohol use, and snuff use was available for part of the study period; a sensitivity analysis, which accounted for these factors, found that they did not substantially change the association between current smoking and absenteeism.

Evidence Synthesis

This section reviewed the evidence on smoking and general health. A broad range of health measures was considered, including self-reported health status and functional ability, health care utilization and cost, and workplace absenteeism. These measures were previously reviewed in the 2004 Surgeon General's report, and the current review updates and expands those findings. Overall, the evidence base on this broad topic has expanded and reaffirms the causal findings in the 2004 report on smoking and diminished health.

Although the measures of health assessed in this section are nonspecific and undoubtedly affected by many factors, the finding that smokers have poorer health than never smokers is highly consistent across studies and indicators. Smokers of different gender, age, and country of residence experience poorer physical and mental health and higher rates of workplace absenteeism than people who have never smoked. Similarly, studies of health care utilization and costs within the United States show that

smokers have higher rates of hospitalization, higher rates of nursing home admission, and higher total health care costs than never smokers. The strength of the associations of smoking with indicators of health status tended to be moderate with effect estimates ranging from just above unity to an approximate doubling of risk with variation by study and the measure of health used. Given the nonspecificity of the indicators considered, these associations are in a plausible and anticipated range. The nonspecificity of the outcomes considered also raises concern for potential uncontrolled confounding as underlying the observed associations. Many of the studies of smoking, in relation to general health, did adjust for a broad range of potential confounders and the associations with smoking persisted. Given the broad range of studies and the consideration of potential confounding in many, it is unlikely that confounding can completely explain the poorer health of smokers, a conclusion also reached in the 2004 report. A causal link between smoking and poorer health is further supported by the biologic plausibility of the relationship based on multiple potential mechanisms of injury reviewed in previous reports (USDHHS 2004, 2010) and evidence of a dose-response relationship. In the studies that assessed amount smoked, heavier smoking tended to be associated with a higher risk of poor health than lighter smoking.

In interpreting the evidence related to former smokers, consideration needs to be given to the temporal relationship between illness onset and the timing of cessation. Across the studies reviewed in this section, former smokers—particularly those who have recently quit—tend to have poor outcomes. This is likely the result of quitting ill; the poor health that is experienced by recent quitters often precedes—and contributes to—the decision to quit and smoking cessation. For example, among smokers enrolled in a managed care organization in Minnesota, inpatient charges, or high ambulatory care charges, were linked with subsequent quit attempts, implying that people with illness are motivated to quit (Martinson et al. 2003). Similarly, among smokers enrolled in a managed care organization in Washington state, costs among former smokers began to increase in the period prior to smoking cessation, before peaking in the quarter following cessation (Fishman et al. 2006). Among participants in a smoking cessation trial—all of whom were identified on the basis of a routine primary care visit—early costs were similar among successful quitters and continuing smokers, and costs among successful quitters dropped below those of continuing smokers by the sixth quarter post-quit (Hockenberry et al. 2012). Other studies also showed benefits for former smokers as the length of time since quitting increased (USDHHS 2004).

Conclusion

1. The evidence is sufficient to infer a causal relationship between smoking and diminished overall health. Manifestations of diminished overall health among smokers include self-reported poor health, increased absenteeism from work, and increased health care utilization and cost.

Implications

The relationship between smoking and health extends well beyond the growing number of recognized smoking-related diseases. Smokers experience diminished overall health, beginning at an early age and extending throughout adult life. The resulting health deficits affect not only smokers directly, but also their participation in the workplace and their costs to the health care system. The diminished health status of smokers has implications for multiple sectors in prevention and research.

For employers, the poorer health of smokers and the attendant costs have motivated some to stop hiring people who smoke, a strategy that has led some states to prohibit such hiring practices (Schmidt et al. 2013). Employers who have implemented such hiring practices have done so because of the increased costs of employing smokers (Schmidt et al. 2013). The ethics of such hiring bans remain a topic of debate (e.g., Schmidt et al. 2013 and Asch et al. 2013). The documented costs of hiring smokers may also be a motivation for employers to more aggressively assist their smoking employees to quit.

In general, the public has little specific awareness of the general consequences of smoking and how they begin with the onset of regular smoking. Consideration should be given as to whether, and how, the findings on the poorer health of smokers could be used to tailor messages to smokers. Any messages would need to be specific to age groups and directed at younger and older smokers. Youth should be aware that their health is affected from the start of smoking; older smokers should understand that a lifetime of smoking contributes not only to their risks for specific diseases, but also to their health, generally, and risk for nursing home admission. The effects of smoking cessation on various measures of general health warrant additional research. The poor health of recent quitters is likely explained by the phenomenon of quitting when ill, but there is little information about the health and health changes in people who quit when not ill. If health outcomes among these earlier quitters are better in both the

short- and long-term, the information would be useful in developing more powerful strategies to motivate current smokers not to delay a quit attempt.

Combinations of health behaviors and states—such as smoking, physical inactivity, and obesity—also warrant additional research attention. The magnitude of the association between combinations of high-risk behaviors and poor health can be quite large and may provide individuals with more complete information about their health risks.

Finally, incorporating information about general health into smoking prevention messages may broaden the reach of the messages. The effects of smoking on general health occur quickly after starting to smoke regularly and may be more salient—especially to younger people—than health problems that are expected to occur many years later. Even if smokers avoid a diagnosis of a smoking-caused disease, they face an increased risk of unnecessarily poor health.

All-Cause Mortality

Here, this chapter turns to mortality from all causes. This section first discusses the relationship between smoking and all-cause mortality and how the association has strengthened among current smokers during the last 50 years. It considers the fraction of all deaths among current and former smokers that may be caused by smoking, setting the stage for the attributable burden estimates provided in Chapter 12. Chapter 12 also provides estimates of the overall morbidity burden and economic costs associated with smoking in the United States.

The increased risk for all-cause mortality in smokers has been noted in multiple Surgeon General's reports with relevant conclusions (see Table 4.12*S*). Economic costs have also been addressed in previous reports, as estimated by the Smoking-Attributable Mortality, Morbidity, and Economic Costs (SAMMEC) program of the CDC (see Chapter 12).

The accelerated mortality in smokers, compared to never smokers, has been assessed in large prospective cohort studies and is usually estimated either by comparing annual death rates (per 100,000 or per 10,000 per year) across categories of smoking status controlling for age, or by contrasting the percentages of individuals who survive to various attained ages in relation to smoking behavior. Death rates in smokers can be compared with rates in never smokers using the relative risk (RR) (i.e., the age-specific or age-adjusted death rate in smokers divided by that of never smokers) and the rate difference (i.e., the age-specific or age-adjusted death rate in smokers minus that of never smokers). Alternatively, the differences in life expectancy between current, former, and never smokers can be examined using survival curves, as illustrated by Pearl's 1938 figure (Figure 11.1).

Although the discussion on all-cause mortality presented in this chapter has focused primarily on RRs, differences in death rates per 100,000 by smoking status (never and current) are also informative. Such differences show the additional burden sustained at the population level because of smoking. Both rate differences and RRs for all-cause mortality and the five main causes of death in the pooled contemporary cohort of U.S. men and women 55 years of age and older from the United States are shown in Tables 11.13 and 11.14. This pooled contemporary cohort analysis includes follow-up time from 2000–2010 from five individual U.S. cohort studies as described by Thun and colleagues (2013). The analyses shown in Tables 11.13 and 11.14 (provided to CDC's Office on Smoking and Health by investigators from the contributing cohorts) include an additional 2 years of follow-up (2009–2010) that became available from the American Cancer Society (ACS) Cancer Prevention Study II (CPS-II) Nutrition Cohort after the original publication (Thun et al. 2013), and updated outcome information from the WHI cohort.

For all-cause death rates, the rates of dying are much higher within each age stratum (55–64, 65–74, and 75 years of age and older) and smoking stratum for men than women; however, the ratios of death rates between never smokers and current smokers within each age strata are very similar for men and women. For lung cancer, the death rates for never smokers increase with age for both men and women and are comparable. However, the lung cancer death rate among current smokers increases dramatically by age, as does the RR, for both men and women. For coronary heart disease (CHD), the pattern is somewhat different. The death rates among male never smokers is much higher within each age strata in comparison with females. The death rates among current smokers also increase with age, but at a somewhat slower rate than among never smokers; hence, the RRs for CHD are slightly smaller in men and women 75 years of age and older.

Table 11.13 All-cause mortality and five main causes of death by smoking status: death rates per 100,000 among men of Cancer Prevention Study II Nutrition Cohort, Health Professional Follow-Up Study, National Household Survey, National Institutes of Health-AARP Diet and Health Study, and Women's Health Initiative, 2000–2010

	Never-smoker			Current smoker			Rate difference (/100,000)	RR (95% CI) current versus never smoker‡
	Number of deaths	Person-years	Death rate† (/100,000)	Number of deaths	Person-years	Death rate (/100,000)		
All Causes								
Age 55–64	1,182	253,125	401.81	1,170	74,157	1,409.96	1,008.15	2.92 (2.69–3.18)
Age 65–74	6,495	586,441	1,075.35	4,011	110,799	3,619.35	2,544.00	3.00 (2.89–3.13)
Age ≥75	11,312	328,189	4,988.58	1,855	26,789	10,169.60	5,181.03	2.36 (2.24– 2.48)
Lung Cancer[1]								
Age 55–64	34	253,125	12.70	232	74,157	279.94	267.24	19.03 (13.19–27.47)
Age 65–74	147	586,441	24.00	891	110,799	804.05	780.05	28.29 (23.72–33.74)
Age ≥75	190	328,189	69.97	354	26,789	1,557.64	1,487.67	22.52 (18.83–26.92)
COPD[2]								
Age 55–64	2	253,125	0.48	68	74,157	80.61	80.13	84.79 (20.65–348.23)
Age 65–74	55	586,441	9.12	367	110,799	331.13	322.01	29.70 (22.31–39.53)
Age ≥75	137	328,189	61.72	233	26,789	1,378.06	1,316.34	23.01 (18.56–28.51)
Total Stroke[3]								
Age 55–64	40	253,125	13.03	28	74,157	30.52	17.48	2.07 (1.25–3.41)
Age 65–74	310	586,441	50.42	137	110,799	123.61	73.20	2.17 (1.77–2.66)
Age ≥75	748	328,189	356.66	72	26,789	501.14	144.48	1.48 (1.16–1.88)
Coronary Heart Disease[4]								
Age 55–64	216	253,125	72.96	235	74,157	265.88	192.91	2.99 (2.47–3.62)
Age 65–74	1,256	586,441	207.26	738	110,799	665.93	458.67	2.76 (2.52–3.03)
Age ≥75	2,381	328,189	1,073.69	332	26,789	1,944.94	871.25	1.98 (1.76–2.22)
Other Heart Diseases[5]								
Age 55–64	45	253,125	14.24	38	74,157	39.25	25.01	2.50 (1.60–3.89)
Age 65–74	395	586,441	65.51	180	110,799	162.42	96.91	2.22 (1.85–2.66)
Age ≥75	883	328,189	438.57	93	26,789	565.77	127.21	1.66 (1.33–2.06)

Source: Updated analyses of the pooled contemporary cohort population described in Thun et al. 2013 provided to CDC's National Center for Chronic Disease.

Note: **CDC** = Centers for Disease Control and Prevention; **COPD** = chronic obstructive pulmonary disease; **ICD** = International Classification of Diseases.

†Rates per 100,000 person-years adjusted to the U.S. 2000 population standard within age strata.
‡Results from Cox proportional hazards models adjusted for age, cohort, race, and education.
[1]Lung cancer includes *ICD-10* codes C33, C34.
[2]COPD includes *ICD-10* codes J40–J44.
[3]Total stroke includes *ICD-10* codes I60–I69.
[4]Coronary heart disease includes *ICD-10* codes I20–I25.
[5]Other heart disease includes *ICD-10* codes I00–I09, I26–I51.

Table 11.14   All-cause mortality and five main causes of death by smoking status: death rates per 100,000 among women of Cancer Prevention Study II Nutrition Cohort, Health Professional Follow-Up Study, National Household Survey, National Institutes of Health-AARP Diet and Health Study, and Women's Health Initiative, 2000–2010

	Never smoker			Current smoker			Rate difference (/100,000)	RR (95% CI) current versus never smoker[‡]
	Number of deaths	Person-years	Death rate[†] (/100,000)	Number of deaths	Person-years	Death rate (/100,000)		
All Causes								
Age 55-64	1,542	459,118	309.45	1,023	107,168	865.82	556.37	2.64 (2.43–2.86)
Age 65-74	8,125	1,095,878	723.01	3,686	164,575	2,243.97	1,520.96	2.87 (2.76–2.99)
Age ≥75	17,029	758,352	3,024.22	2,375	50,469	6,589.07	3,564.86	2.47 (2.37–2.58)
Lung Cancer[1]								
Age 55–64	52	459,118	10.12	248	107,168	208.62	198.50	18.95 (13.99–25.66)
Age 65–74	236	1,095,878	21.24	894	164,575	544.08	522.83	23.65 (20.46–27.35)
Age ≥75	340	758,352	53.43	502	50,469	1,121.49	1,068.05	23.08 (20.07–26.55)
COPD[2]								
Age 55–64	8	459,118	1.05	56	107,168	40.13	39.08	22.58 (10.71–47.60)
Age 65–74	55	1,095,878	4.86	368	164,575	224.12	219.26	38.89 (29.24–51.73)
Age ≥75	241	758,352	44.61	285	50,469	779.15	734.55	20.96 (17.60–24.96)
Total Stroke[3]								
Age 55–64	44	459,118	9.40	34	107,168	27.89	18.49	3.27 (2.07–5.18)
Age 65–74	486	1,095,878	42.38	170	164,575	103.60	61.22	2.27 (1.90–2.72)
Age ≥75	1,560	758,352	286.94	138	50,469	443.08	156.14	1.70 (1.43–2.03)
Coronary Heart Disease[4]								
Age 55–64	132	459,118	24.90	113	107,168	91.37	66.46	3.25 (2.51–4.21)
Age 65–74	908	1,095,878	80.26	490	164,575	298.40	218.13	3.29 (2.94–3.68)
Age ≥75	2,432	758,352	456.94	287	50,469	825.95	369.00	2.25 (1.99–2.55)
Other Heart Diseases[5]								
Age 55–64	97	459,118	16.69	36	107,168	29.10	12.41	1.49 (1.00–2.20)
Age 65–74	489	1,095,878	43.10	141	164,575	85.86	42.75	1.85 (1.53–2.24)
Age ≥75	1,363	758,352	267.53	119	50,469	410.68	143.15	1.75 (1.45–2.11)

Source: Updated analyses of the pooled contemporary cohort population described in Thun et al. 2013 provided to CDC's National Center for Chronic Disease.

Note: **CDC** = Centers for Disease Control and Prevention; **COPD** = chronic obstructive pulmonary disease; **ICD** = International Classification of Diseases.

[†]Rates per 100,000 person years adjusted to the U.S. 2000 population standard within age strata.

[‡]Results from Cox proportional hazards models adjusted for age, cohort, race, and education.

[1]Lung cancer includes *ICD-10* codes C33, C34.

[2]COPD includes *ICD-10* codes J40–J44.

[3]Total stroke includes *ICD-10* codes I60–I69.

[4]Coronary heart disease includes *ICD-10* codes I20–I25.

[5]Other heart disease includes *ICD-10* codes I00–I09, I26–I51.

Temporal Trends in Relative Risk for All-Cause Mortality

The RR value for all-cause mortality associated with current cigarette smoking has increased over the last 50 years as generations of smokers who began smoking as adolescents and continued to smoke into middle and older ages have incurred the consequences of persistent life-time smoking (see Chapter 13). The 1964 Surgeon General's report discussed all-cause mortality in men, but not women (USDHEW 1964). Only two (Doll and Hill 1964; Hammond 1964) of the seven (Hammond and Horn 1958; Dunn et al. 1960, n.d.; Best et al. 1961; Doll and Hill 1964; Hammond 1964; Kahn 1966) large prospective cohort studies available at the time included substantial numbers of women. Among male smokers, the all-cause death rate was approximately 70% higher in those who smoked ciga-rettes only, and not other tobacco products, than in never smokers (RR = 1.68). The RR estimates ranged from 1.44 during the first 10 years of follow-up of the British Doc-tors Study (Doll and Hill 1964) to 1.83 during the first 22 months of follow-up of the ACS cohort study, CPS-I (Hammond, n.d.). The all-cause RR was highest in men who smoked cigarettes only and increased with daily ciga-rette consumption, duration of smoking, and earlier age at initiation; the all-cause RR decreased with the number of years since quitting.

The first systematic analysis of temporal changes in the RR for all-cause mortality associated with smok-ing was published in the 1989 Surgeon General's report (USDHHS 1989*)*. The 1989 report compared the RR val-ues for cause-specific and all-cause mortality associated with current and former smoking during the first 6 years of follow-up of CPS-I (1959–1965) to the first 4 years of CPS-II (1982–1986). The analyses were based on approxi-mately 1 million adults in CPS-I and 1.2 million in CPS-II who were 35 years of age or older. Among current male smokers, the all-cause RR increased from 1.80 (95% CI, 1.75–1.85) in CPS-I to 2.34 (95% CI, 2.26–2.43) in CPS-II. The corresponding increase in current female smokers was from 1.23 (95% CI, 1.18–1.28) in CPS-I to 1.90 (95% CI, 1.82–1.98) in CPS-II.

The RR values for all-cause mortality associated with current cigarette smoking have continued to increase into the twenty-first century. Thun and colleagues (2013) compared the risk difference and RR values associated with current and former cigarette smoking among men and women 55 years of age and older in three time peri-ods (1959–1965, 1982–1988, and 2000–2010), based on the two historical ACS cohorts, CPS-I and CPS-II, and pooled analyses of five contemporary cohorts. The latter included the National Institutes of Health-AARP Diet and Health Study (Schatzkin et al. 2001), CPS-II Nutrition Cohort (Calle et al. 2002) (a subset of the original CPS-II mortality study), WHI (Hays et al. 2003; Anderson et al. 2003), NHS (Colditz et al. 1997), and Health Professionals Follow-up Study (Rimm et al. 1995). In total, the analysis included more than 2.2 million adults 55 years of age and older. For each cohort, updated smoking information had been collected at least once during the period 2000–2010. Among women, the multivariable-adjusted rates ratio for death from all causes in current versus never smokers increased from 1.35 (95% CI, 1.30–1.40) in CPS-I to 2.08 (95% CI, 2.02–2.14) in CPS-II to 2.76 (95% CI, 2.69–2.84) in the contemporary cohorts (Table 11.1*S*). Among men, the corresponding increase in rates ratio was from 1.76 (95% CI, 1.71–1.81) in CPS-I to 2.33 (95% CI, 2.26–2.40) in CPS-II to 2.80 (95% CI, 2.72–2.88) in the contemporary cohorts. The RR values associated with current smoking were highest in middle age for men, exceeding 3.0 among men 55–74 years of age and in women 60–70 years of age. The convergence of the RR values associated with all-cause mortality for men and women, over the span of the stud-ies, was attributed to the convergence of male and female smoking patterns since the 1960s (Anderson and Burns 2001; USDHHS 2001) and the aging of birth cohorts with the heaviest lifetime smoking.

A similar temporal increase in the RR for all-cause mortality was observed in analyses of the 40-year follow-up data from the British Doctors Study, which compared the RRs associated with current versus never smokers during the first (1951–1971) and last (1971–1991) 20 years of the study (Doll et al. 1994). The all-cause RR during the first 20 years of the study was 1.62, when averaged across all ages, and increased to 2.06 in the second 20 years. Similar analyses conducted at the 50-year follow-up of the Brit-ish Doctors Study compared smoking-related mortality among doctors born in the nineteenth century (1851–1899) to those born in the twentieth century (1900–1929) (Doll et al. 2004). The all-cause RR for men who reported smoking cigarettes, exclusively, were 1.46 for those born in the nineteenth century and 2.19 for those born in the twentieth century.

The Million Women Study in the United Kingdom provides another recent assessment of the mortality risk associated with smoking. The all-cause RR associated with current smoking in the Million Women Study (Pirie et al. 2013) is similar to that in the contemporary U.S. cohorts. In this study, 1.3 million women in the United Kingdom were recruited in 1996–2001 and resurveyed by mail about 3 and 8 years later. After a median of 12 years of follow-up, women who reported current smoking at baseline had almost three times the mortality rate of never smokers (RR = 2.76; 95% CI, 2.71–2.81). The RR

was slightly higher (RR = 2.97; 95% CI, 2.71–2.81) among women who reported smoking cigarettes, both at baseline and 3 years later at resurvey, although, even among these, many would have stopped smoking during the remaining follow-up. The risks among smokers increased steeply with the amount smoked (Figure 11.2), but even those smoking 1–9 cigarettes daily at baseline (mean of 8 cigarettes per day) had twice the overall mortality rate of never smokers. For former smokers, those who stopped at 45–54, 35–44, 25–34, and under 25 years of age (corresponding to around 50, 40, 30, or 20 years of age) had progressively lower all-cause RR values (Figure 11.3). Women who quit smoking by about 30 years of age avoided approximately 95% of the excess risk compared to those who continued to smoke (Pirie et al. 2013).

In the Life Span Study of Japanese atomic bomb survivors, Sakata and colleagues (2012) reported the impact of smoking on mortality in this prospective cohort study of atomic bomb survivors and a comparison group from Hiroshima and Nagasaki. The study was initiated in 1950 and smoking status was ascertained during 1963–1992. The authors found that the overall death rate ratio for current male smokers, compared to never smokers, differed by period of birth: 1.46 (95% CI, 1.38–1.54) for men born before 1920 and 1.89 (95% CI, 1.70–2.10) for men born during 1920–1945. A similar trend was observed among female smokers (Table 11.1S). For those born during 1920–1945 and starting to smoke continuously before age 20, overall mortality was more than doubled in both genders (i.e., rate ratios vs. never smokers: men, 2.21 [95% CI, 1.97–2.48]; women, 2.61 [95% CI, 1.98–3.44]); life expectancy was reduced by almost a decade (8 years for men, 10 years for women) (Sakata et al. 2012).

Temporal Trends in Survival

Pearl (1938) found that the median survival of White males, recorded as heavy smokers in the Family History Records at Johns Hopkins, was approximately 7 years shorter than that of men recorded as nonsmokers (Figure 11.1). The 1968 Surgeon General's report on smoking and health estimated smoking-related loss of life expectancy as 8 years for heavy smokers (i.e., more than two packs per day) and 4 years for light smokers (i.e., less than ½ pack per day) (USDHEW 1968). Similar estimates were derived from the 40-year follow-up of the British Doctors Study (Doll et al. 1994) (Figure 11.4). On average during the full follow-up, median survival among men who reported being current cigarette smokers was 7.5 years shorter than among those who reported never having smoked, but the gap increased during the 40 years. Doctors who reported current smoking, during the first 20 years of the study lost an average of 5 years of life; this increased to an average loss of 8 years of life during the second 20 years of the study (Figure 11.5) (Doll et al. 2004). In the 50-year follow-up, those born in the twentieth century who smoked from an earlier age and more intensely than those born in the nineteenth century had a greater loss of life expectancy (Figure 11.5) (Doll et al. 2004).

A similar relationship between smoking and survival was reported by Jha and colleagues (2013) in an analysis of over 215,000 adults in the U.S. National Health Interview Survey during follow-up from 1997 and 2004 (Figure 11.6). Among women participating in this nationally representative survey, the estimated probability of survival to 80 years of age was 70% (99% CI, 64–76) for those who never smoked, but only 26% (99% CI, 18–33) for male current smokers. Compared to never smokers, current smokers lost an average of about 11 years for women and about 12 years of life for men. Some individual smokers will lose far more years of life than these population average figures.

Figure 11.2   Relative risk for all-cause mortality among female current versus never smoker by amount smoked at recruitment
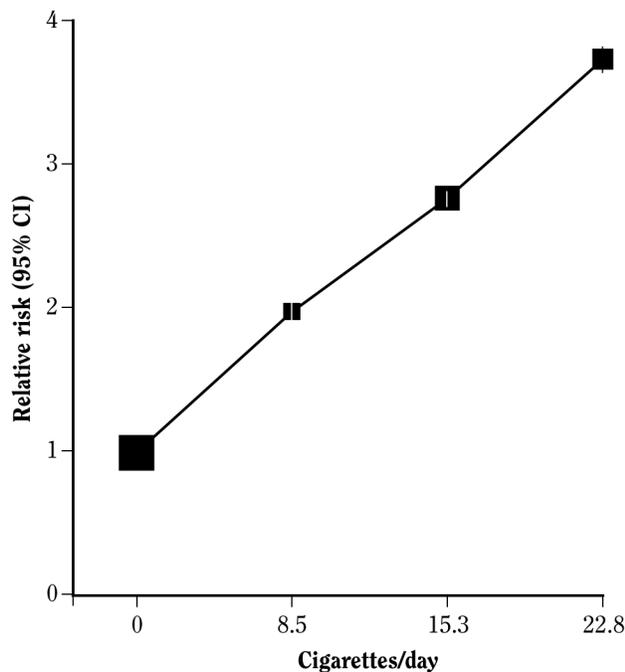
Source: Million Women Study; Pirie et al. 2013. Reprinted with permission from Elsevier, © 2013.
Note: **CI** = confidence interval.

Figure 11.3   Relative risk for all-cause mortality among female former versus current smokers by age at stopping
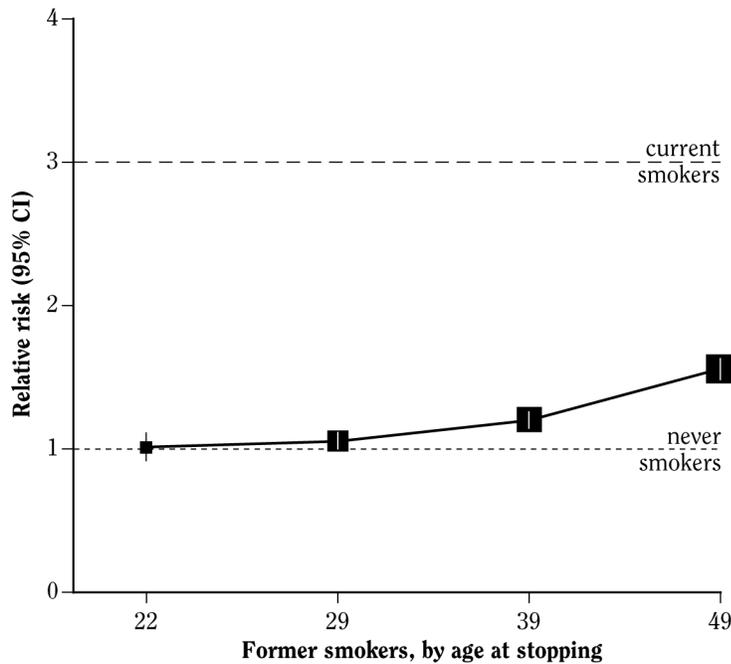
Age at stopping (mean), years	<25 (22)	25–34 (29)	35–44 (39)	45–54 (49)
Number of deaths	481	1,523	1,814	2,095
RR (95% CI)	1.01 (0.92–1.11)	1.05 (1.00–1.11)	1.20 (1.14–1.26)	1.56 (1.49–1.64)

Source: Million Women Study; Pirie et al. 2013. Reprinted with permission from Elsevier, © 2013.
Note: **CI** = confidence interval; **RR** = relative risk.

Explanation for the Temporal Trends in Relative Risk and Survival

Several factors contribute to the widening difference in survival between current and never smokers over the last 50 years. First, the death rates from lung cancer and chronic obstructive pulmonary disease (COPD), two major smoking-caused diseases, have increased among men and women who smoke, as generations of men, and later women, who began smoking in childhood and adolescence reach the ages at which the diseases caused by smoking have high incidence. The mortality risks from both diseases continue to increase in women who smoke; whereas, the lung cancer risk among male cigarette smokers appears to have plateaued at a high level since the 1980s, while COPD mortality continues to increase (Thun et al. 2013).

Second, smokers have not kept pace with the improvements in survival experienced by former and never smokers since the mid-twentieth century. For women who continue to smoke, the increasing risks from lung cancer and COPD have almost completely offset improvements in survival due to advances in prevention and treatment over the past 50 years. In male smokers, the decrease in cardiovascular mortality has been smaller, proportionately, than in never and former smokers. It is possible that some of the increase in the RR, over time, reflects changing patterns of confounding, which have not been fully accounted for in analysis. An analysis of CPS-II data for 1982–1988 showed that observed associations with smoking were only minimally altered by adjustment for a set of confounding factors compared with age-adjustment alone. This analysis, however, did not address changes in patterns of confounding over time (Malarcher et al. 2000; Thun et al. 2000; Schatzkin et al. 2001).

The premature deaths among smokers in contemporary studies result chiefly from diseases known to be caused by smoking, such as lung cancer, COPD, heart

Figure 11.4   Survival after 35 years of age among smokers and nonsmokers
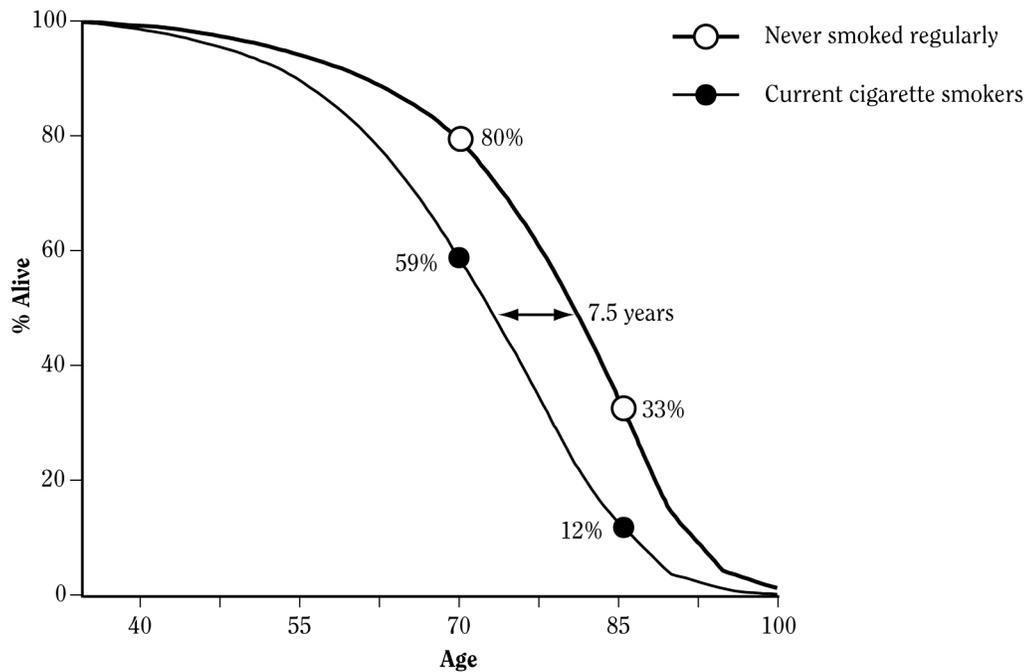
Source: Doll et al. 1994. Reprinted with permission from BMJ Publishing Group Ltd., © 1994.
Note: Overall survival after 35 years of age among British doctors recorded as cigarette smokers and nonsmokers during 40-year follow-up. Life tables are based on age-specific death rates for the entire 40-year period (Chahine et al. 2011). According to 1990 British death rates, 97% of male infants would survive from birth to 35 years of age.

disease, stroke, or other neoplastic, respiratory or vascular diseases. Studies of random samples of participants in the Million Women Study (Pirie et al. 2013) found little difference between smokers and others when potential confounding factors such as blood pressure or lipid profile were examined. Other factors, such as alcohol intake, body mass index, and socioeconomic status, were adjusted for in the analyses. Thus, most of the excess mortality associated with smoking appears to be caused directly by smoking and not by confounding. However, for some associations, such as suicide or liver cirrhosis, the association may largely reflect noncausal pathways (Doll et al. 2004).

Evidence Synthesis

Increased all-cause mortality is a well-established causal consequence of smoking (USDHHS 2004). Evidence reviewed in this report shows that the association between active cigarette smoking and death from all causes has strengthened in both men and women since the 1964 Surgeon General's report. The age-standardized RR, comparing the all-cause death rate in current smokers to that of never smokers, has more than doubled in men and more than tripled in women during this 50-year period. At some ages, the increases for current smokers compared with never smokers are far greater, at least three times higher for men 55–74 years of age and women 60–70 years of age. Life-shortening by smoking is substantial. Smokers lose an estimated decade of life. Smoking cessation by 40 years of age reduces that loss by about 90%. Even stopping by about 60 years of age reduces the loss by 40%. Reductions in the number of cigarettes smoked per day are much less effective than smoking cessation in avoiding the mortality risks from smoking (USDHHS 2004, 2010). Based on these temporal trends in risk, changes in the design of cigarettes that reduced the tar and nicotine yield of cigarettes, as measured by smoking machines, did not prevent these increases in risk (USDHHS 2004, 2010).

Figure 11.5   Survival after 60 years of age for smokers and never smokers

Doctors born 1851–1899

Doctors born 1900–1936
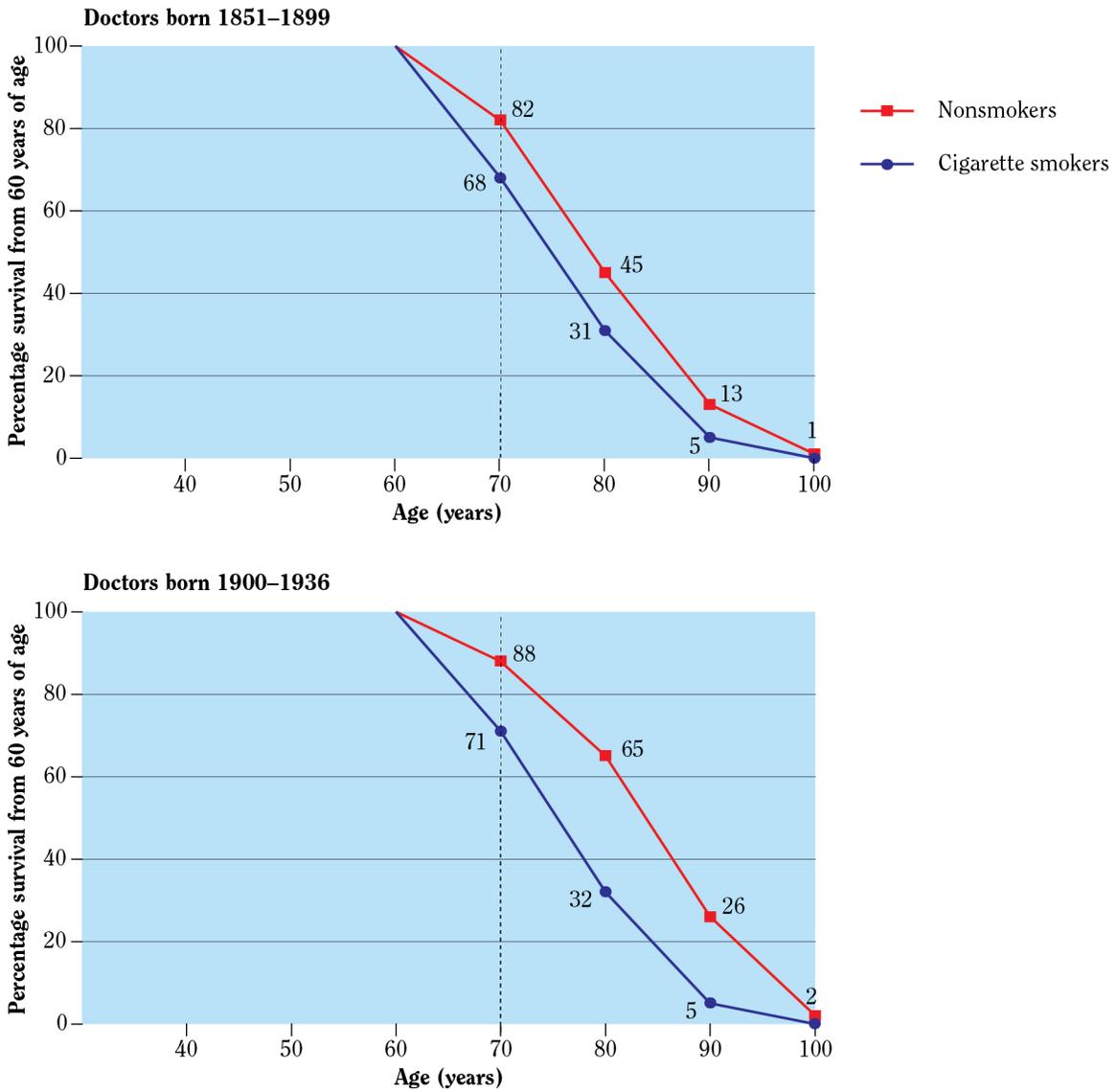
Source: Doll et al. 2004. Reprinted with permission from BMJ Publishing Group Ltd., © 2004.
Note: Survival from 60 years of age for continuing cigarette smokers and never smokers among United Kingdom male doctors born 1851–1899 (median 1889) and 1900–1930 (median 1915), with percentages alive at each decade of age (Thun et al. 1997).

Figure 11.6   Survival probabilities for current smokers and never smokers for women and men

A   Women

B   Men
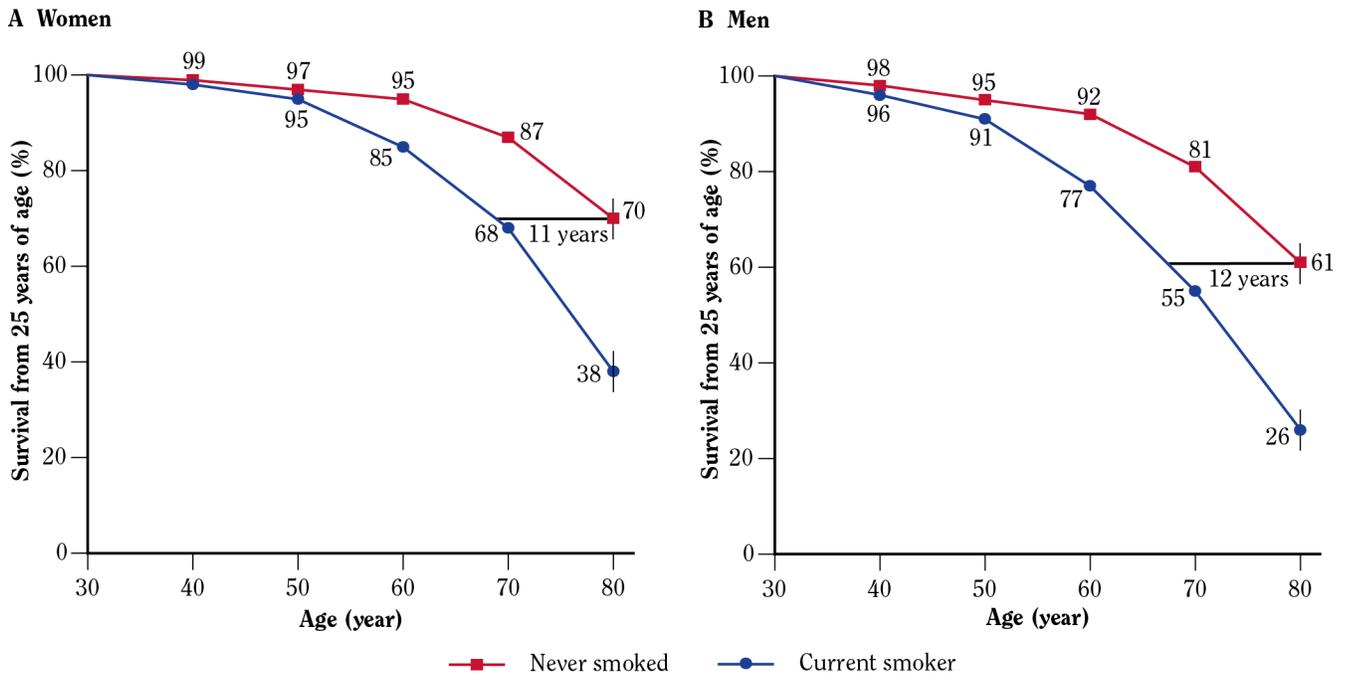
Source: Jha et al. 2013. Reprinted with permission from Massachusetts Medical Society, © 2013.
Note: Survival probabilities for current smokers and never smokers among men and women 25–80 years of age. The vertical lines at 80 years of age represent the 99% cumulative survival probabilities, as derived from the standard errors estimated with use of the jackknife procedure. Survival probabilities have been scaled from the National Health Interview Survey to the U.S. rates of death from all causes at these ages for 2004, with adjustments for differences in age, educational level, alcohol consumption, and adiposity (body mass index).

Summary

The evidence reviewed in this chapter reaffirms that smoking is a major cause of premature mortality and avoidable morbidity. Although emphasis has long been given to smoking as a cause of specific diseases, it is a powerful cause of ill-health generally, which reduces the quality of life of smokers and increases health care costs. The lives of smokers are cut short by the development of the many diseases caused by smoking and their greater risk of dying from common health events, such as complications of routine surgeries and pneumonia.

Conclusions

1. The evidence is sufficient to infer that cigarette smoking increases risk for all-cause mortality in men and women.

2. The evidence is sufficient to infer that the relative risk of dying from cigarette smoking has increased over the last 50 years in men and women in the United States.

Chapter Conclusions

1. The evidence is sufficient to infer a causal relationship between smoking and diminished overall health. Manifestations of diminished overall health among smokers include self-reported poor health, increased absenteeism from work, and increased health care utilization and cost.

2. The evidence is sufficient to infer that cigarette smoking increases risk for all-cause mortality in men and women.

3. The evidence is sufficient to infer that the relative risk of dying from cigarette smoking has increased over the last 50 years in men and women in the United States.

Implications

The increased risk of death among smokers is already a widely recognized consequence of smoking by the general public and health care professionals. This report shows that this risk is increasing, particularly among women, and threatens continuing gains in life expectancy. This information needs to be disseminated widely and effectively, reaching men and women and those who provide their health care.

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Chapter 11
General Morbidity and All-Cause Mortality

Table 11.1S   Studies on the association between smoking and all-cause mortality

Study	Design/population	Results (rate ratio 95% CI)			Findings	Comments
		Current smoker	**Former smoker**	**Never smoker**		
Sakata et al. 2012	• 27,311 men and 40,662 women born before 1945 who were atomic bomb survivors or residents of Hiroshima and Nagasaki, Japan • Smoking status obtained during 1963–1992 • Mortality status available through 2008	**Years of age started smoking** • Men born <1920: – <20: 1.66 (1.54–1.79) – 20–29: 1.42 (1.34–1.51) – ≥30: 1.17 (1.07–1.29) – Unknown: 2.85 (2.48–3.28) – All ages: 1.46 (1.38–1.54) • Men born 1920–1945: – <20: 2.21 (1.97–2.48) – 20–29: 1.71 (1.53–1.91) – ≥30: 1.48 (1.07–2.05) – Unknown: 2.04 (1.74–2.39) – All ages: 1.89 (1.70–2.10) • Women born <1920: – <20: 1.54 (1.21–1.95) – 20–29: 1.53 (1.38–1.70) – ≥30: 1.26 (1.16–1.36) – Unknown: 1.78 (1.65–1.91) – All ages: 1.51 (1.43–1.58) • Women born 1920–1945: – <20: 2.61 (1.98–3.44) – 20–29: 2.01 (1.79–2.25) – ≥30: 1.40 (1.22–1.62) – Unknown: 1.94 (1.67–2.27) – All ages: 1.81 (1.67–1.96)	**Years of age quit smoking** • Men born <1920: – <25: 1.19 (0.84–1.68) – 25–34: 1.13 (0.94–1.36) – 35–44: 1.09 (0.95–1.24) – 45–54: 1.11 (1.00–1.22) – 55–64: 1.23 (1.12–1.34) – ≥65: 1.45 (1.33–1.59) – Unknown: 1.51 (1.28–1.78) • Men born 1920–1945: – <25: 0.91 (0.58–1.42) – 25–34: 0.83 (0.66–1.05) – 35–44: 1.21 (1.02–1.44) – 45–54: 1.43 (1.23–1.68) – 55–64: 1.73 (1.45–2.06) – ≥65: 1.72 (1.16–2.57) – Unknown: 2.14 (1.70–2.69) • Women born <1920: – <25: 0.89 (0.29–2.75) – 25-34: 1.16 (0.81–1.65) – 35-44: 1.04 (0.80–1.36) – 45-54: 0.93 (0.78–1.11) – 55-64: 1.22 (1.06–1.40) – ≥65: 1.31 (1.15–1.48) – Unknown: 1.45 (1.27–1.66) • Women born 1920–1945: – <25: 1.54 (0.64–3.70) – 25-34: 1.21 (0.81–1.81) – 35-44: 1.27 (0.95–1.70) – 45-54: 1.59 (1.26–2.00) – 55-64: 1.49 (1.15–1.92) – ≥65: 1.94 (1.15–3.29) – Unknown: 1.55 (1.23–1.95)	1.0 (ref) 1.0 (ref) 1.0 (ref) 1.0 (ref) 1.0 (ref) 1.0 (ref) 1.0 (ref) 1.0 (ref) 1.0 (ref) 1.0 (ref) 1.0 (ref) 1.0 (ref) 1.0 (ref) 1.0 (ref) 1.0 (ref) 1.0 (ref) 1.0 (ref) 1.0 (ref) 1.0 (ref) 1.0 (ref) 1.0 (ref) 1.0 (ref) 1.0 (ref) 1.0 (ref) 1.0 (ref) 1.0 (ref) 1.0 (ref)	• Risk of death increased with younger age of smoking initiation, irrespective of period of birth or gender • Quitting smoking at earlier age reduced risk of death	Rate ratios presented for current vs. never smokers and for former vs. never smokers, within strata of age started/quit smoking, period of birth, and gender

Table 11.1*S*   Continued

Study	Design/population	Results (rate ratio 95% CI)			Findings	Comments
		Current smoker	**Former smoker**	**Never smoker**		

Thun et al. 2013	• CPS-I (1959–1965; 183,060 men, 355,922 women)
	
	• CPS-II (1982–1988, 293,592 men, 452,893 women)
	
	• 5 pooled contemporary cohort studies of NIH–AARP,
	
	the ACS CPS-II Nutrition Cohort (a subset of the original CPS-II
	
	mortality study), WHI, NHS, and HPFS (2000-2010; 421,702 men, 535,054 women), 55 years of age or older during follow-up
		• Men
		– CPS-I: 1.76 (1.71–1.81)
		– CPS-II: 2.33 (2.26–2.40)
		– Contemporary: 2.80
		
		• Women
		  (2.72–2.88)
		–CPS-I: 1.35 (1.30–1.40)
		–CPS-II: 2.08(2.02–2.14)
		– Contemporary: 2.76
		  (2.69–2.84)
			• Men
			– CPS-I: 1.28 (1.23–1.34)
			– CPS-II: 1.42 (1.38–1.45)
			– Contemporary: 1.47 (1.45–1.50)
			
			• Women
			–CPS-I: 1.33 (1.23–1.43)
			–CPS-II:1.33 (1.29–1.37)
			– Contemporary: 1.45 (1.43–1.48)
				1.0 (ref)
				
				1.0 (ref)
				
				1.0 (ref)
				
				1.0 (ref)
				
				1.0 (ref)
				
				1.0 (ref)
					• Absolute risks of death from smoking continue to increase among female smokers
					
					• Increased risks now nearly identical for men and women, as compared with persons who have never smoked
						Adjusted for age, race, and educational level

Note: **ACS =** American Cancer Society; **CI =** confidence interval; **CPS** = Cancer Prevention Study; **HPFS** = Health Professional Follow-up Study; **NIH-AARP** = National Institutes of Health-AARP; **NHS** = Nurses' Health Study; **WHI** = Women's Health Initiative.

Table 11.2S   Studies on the association between smoking and poor general health

Study	Design/population	Results — Current smoker	Results — Former smoker	Results — Never smoker	Findings	Comments
Johnson and Richter 2002	• 7,844 adolescents 12–17 years of age • United States	Mean self-rated health on a scale of 1 (poor) to 5 (excellent) • Total: – ≥6 days/month: 3.85 – 1–5 days/month: 3.98	• Total: 4.14	Total: 4.26	• Smokers had worse self-rated health than never smokers (p <0.01)	Adjusted for gender, age, and family income
Ostbye et al. 2002	• Health and Retirement Study (7,845 persons 51–64 years of age) • AHEAD (5,037 person ≥70 years of age) • Longitudinal studies from 1992/1993–1998 • United States	OR (95% CI) for self-reported poor or fair health • 51–64 years of age: – Heavy: 2.06 (1.80–2.36) – Light: 1.47 (1.24–1.73) • ≥70 years of age: – 1.55 (1.29–1.87)	• Time since quit: – <3 years: 1.99 (1.60–2.48) – 3–15 years: 1.28 (1.11–1.48) – >15 years: 1.07 (0.91–1.25) – 1.13 (1.01–1.27)	1.0 (ref) 1.0 (ref)	• Current smoking—particularly heavy smoking—increases risk of fair or poor health • Former smokers who have quit within the last 15 years also have an increased risk of fair or poor health • Long-term quitters (>15 years) have a risk that's similar to never smokers	Adjusted for exercise, BMI, alcohol consumption, age, race, gender, marital status, and education
Arday et al. 2003	• 134,309 elderly (≥65 years of age) and 8,640 disabled (<65 years of age) Medicare managed care enrollees	OR (95% CI) for fair or poor health • Disabled: – Daily: 1.58 (1.25–2.00) – Some days: 1.51 (0.97–2.34) • Elderly: – Daily: 1.53 (1.41–1.66) – Some days: 1.40 (1.21–1.63)	• Disabled: – ≤12 months: 1.41 (0.90–2.20) – >12 months: 1.20 (0.97–1.47) • Elderly: – ≤12 months: 2.72 (2.27–3.25) – >12 months: 1.26 (1.20–1.34)	1.0 (ref) 1.0 (ref)	• Among disabled, current daily smokers were more likely than never smokers to report fair or poor health • Among elderly, both current and former smokers were more likely than never smokers to report fair or poor health	Adjusted for age, gender, race/ethnicity, and education
Strine et al. 2005	• BRFSS • 2001–2002 • 82,918 respondents • ≥18 years of age • United States	OR (95% CI) for fair or poor general health • Total: 1.7 (1.5–1.9)	• Total: 1.4 (1.3–1.6)	1.0 (ref)	• Current and former smokers were more likely than never smokers to report fair or poor health	Adjusted for age, gender, race/ethnicity, education, employment status, and marital status

Table 11.2*S*   Continued

Study	Design/population	Results			Findings	Comments
		Current smoker	**Former smoker**	**Never smoker**		
McClave et al. 2009	• BRFSS • 2006 • 17,800 participants in 4 states • ≥18 years of age • United States	OR (95% CI) for fair or poor general health			• Frequency of fair or poor health did not vary significantly by smoking status	Adjusted for age, race/ethnicity, gender, education, marital status, employment status, chronic disease, and health care coverage
		• Total: – Nonquitter: 1.0 (ref) – Unsuccessful quitter: 1.3 (0.8– 2.1)	• Total: 1.1 (0.7–1.7)	1.1 (0.7–1.7)		
Caldeira et al. 2012	• 1,253 U.S. college students	Probability of fair or poor health status			• Compared with those who did not smoke during college, those who smoked at a high, stable level were more likely to report their health as fair or poor (p <0.05)	Adjusted for gender, race, and neighborhood income
		• Total smoked at high level throughout college: 0.28	Did not smoke during college: 0.11			
Wang et al. 2012	• 36,225 adolescents • Mean 15 years of age • Hong Kong	OR (95% CI) for poor self-rated health			• Current and former smokers were more likely than never smokers to report their health as fair or poor	Adjusted for gender, age, parental education, housing type, secondhand smoke exposure, ever drinking, physical activity, illicit drug use, and school clustering effect
		• Total: 1.52 (1.38–1.67) • Boys: 1.31 (1.13–1.53) • Girls: 1.75 (1.53–2.00)	• Total: 1.43 (1.19–1.71) • Boys: 1.43 (1.12–1.83) • Girls: 1.42 (1.08–1.85)	1.0 (ref) 1.0 (ref) 1.0 (ref)		

Note: **AHEAD** = Asset and Health Dynamics among the Oldest Old Survey; **BMI** = body mass index; **BRFSS** = Behavioral Risk Factor Surveillance System; **CI** = confidence interval; **OR** = odds ratio.

Table 11.3*S*   Studies on the association between smoking and relative risk of poor functional status

Study	Design/population	Results			Findings	Comments
		Current smoker	**Former smoker**	**Never smoker**		
Ostbye et al. 2002	• Health and Retirement Study • 7,845 persons 51–64 years of age • United States	OR (95% CI) for disability (self-reported limited ability to work because of impairment or health problems)			• Current smokers were more likely than never smokers to report limited ability to work • Former smokers were also at increased risk of limited ability to work, with the exception of long-term (>15 years) quitters	Adjusted for exercise, BMI, alcohol consumption, age, race, gender, marital status, and education
		• Total – Heavy: 2.23 (1.84–2.71) – Light: 1.73 (1.37–2.18)	• Time since quit: – <3 years: 2.45 (1.81–3.33) – 3–15 years: 1.49 (1.21–1.84) – >15 years: 1.07(0.84–1.37)	1.0 (ref)		
Atkinson et al. 2005	• 558 community-dwelling older women with moderate to severe disability • Mean age at baseline was 78 years • Followed for 3 years • United States	OR (95% CI) for experiencing both cognitive and physical decline. Physical decline based on walking speed. Mental decline based on MMSE			• Compared with never smokers, current smokers had a more than 5-fold increase in risk of cognitive and physical decline • Risk among former smokers was similar to that of never smokers	Adjusted for age, race, education, number of diseases, pulmonary disease, hemoglobin, baseline walking speed, baseline MMSE score, baseline instrumental activities of daily living, and baseline activities of daily living
		• Total: 5.66 (1.49–21.54)	• Total: 1.38 (0.48–4.00)	1.0 (ref)		
Sulander et al. 2005	• 11,793 people between 65–79 years of age • Finland	OR (95% CI) for worse functional status. Functional status scored as 0–5 (higher score reflecting worse status) based on sum of five activities of daily living: use of stairs, walking outside, bathing, dressing, and eating			• Current and former smokers had worse functional status than never smokers	Adjusted for age, alcohol, diet, physical activity, BMI, time period, occupation, and marital status
		• Men: 2.05 (1.62–2.61) • Women: 1.99 (1.47–2.68)	• Men: 1.26 (1.05–1.52) • Women: 1.67 (1.30–2.16)	1.0 (ref) 1.0 (ref)		

Table 11.3*S*
Continued

Study	Design/population	Results			Findings	Comments
		Current smoker	**Former smoker**	**Never smoker**		
Myint et al. 2007	• EPIC study • 16,678 participating men and women • 40–79 years of age at baseline (1993–1997)	OR (95% CI) for poor physical functional health (bottom 20% of population) • Men: 1.85 (1.49–2.30) • Women: 1.56 (1.30–1.87) OR (95% CI) for poor mental functional health (bottom 20% of population) • Men: 1.38 (1.12–1.70) • Women: 1.77 (1.51–2.07)	• Men: 1.18 (1.02–1.35) • Women: 1.16 (1.03–1.30) • Men: 1.18 (1.02–1.35) • Women: 1.16 (1.03–1.30)	1.0 (ref) 1.0 (ref) 1.0 (ref) 1.0 (ref)	• Current and former smokers have worse physical and mental function than never smokers	Adjusted for age, BMI, social class, education level, prevalent illness, alcohol intake, and physical activity
Liao et al. 2011	• Taiwan Longitudinal Study in Aging • 1989–2003 • 3,187 men and women ≥60 years of age without functional disability at baseline	Hazard ratio (95% CI) for functional disability. Functional disability defined as difficulty taking a bath or walking 200–300 meters independently • Total: 1.45 (1.27–1.65)	• Total: 1.23 (1.05–1.44)	1.0 (ref)	• Current and former smokers had a higher risk of functional disability than never smokers	Adjusted for alcohol, sleep, exercise, gender, marital status, education, and time-varying disease status

Table 11.3S   Continued

Study	Design/population	Results			Findings	Comments
		Current smoker	**Former smoker**	**Never smoker**		
Vogl et al. 2012	• Health Survey for England data	OR for problems with mobility			• Compared with never smokers, current heavy smokers scored worse on each of the 5 measures of health-related quality of life	Adjusted for age, gender, BMI, cardiovascular disease, number of limiting conditions, alcohol intake, physical activity, ethnicity, marital status, education, economic status, household income and size, and social capital
	• 13,241 adults ≥16 years of age	• Total – Heavy: 1.67[a] – Moderate: 1.55[a] – Light: 1.13	• Total – Ex-regular: 1.18[a] – Ex-occasional: 0.99	1.00 (ref)		
	• 2006					
	• English general population	OR for problems with self-care			• Current moderate smokers scored worse than never smokers on all of the measures except problems with usual activity	
		• Total – Heavy: 1.70[a] – Moderate: 1.45[a] – Light: 1.25	• Total – Ex-regular: 1.11 – Ex-occasional: 0.88	1.00 (ref)		
		Odds ratio for problems with usual activity			• Ex-regular smokers scored worse than never smokers on problems with mobility, pain/ discomfort, and anxiety depression	
		• Total – Heavy: 1.42[a] – Moderate: 1.37 – Light: 0.95	• Total – Ex-regular: 1.11 – Ex-occasional: 1.12	1.00 (ref)		
		Odds ratio for problems with pain/discomfort				
		• Total – Heavy: 1.46[a] – Moderate: 1.36[a] – Light: 1.34[a]	• Total – Ex-regular: 1.28[a] – Ex-occasional: 1.07	1.00 (ref)		
		Odds ratio for problems with anxiety/depression				
		• Total – Heavy: 1.86[a] – Moderate: 1.49[a] – Light: 1.43[a]	• Total – Ex-regular: 1.16[a] – Ex-occasional: 1.11	1.00 (ref)		

Note: **BMI** = body mass index; **CI** = confidence interval; **EPIC** = European Prospective Investigation into Cancer; **MMSE** = Mini-mental state examination; **OR** = odds ratio. [a]Indicates p<0.05 relative to never smokers.

Table 11.4S   Studies on the association between smoking and SF-36 or SF-12 scores[a]

Study	Design/population	Results — Current smoker	Results — Former smoker	Results — Never smoker	Findings	Comments
Mulder et al. 2001	• 9,660 men and women 20–59 years of age without a history of tobacco-related chronic disease • The Netherlands	*PCS score* • Total: 51.4 *MCS score* • Total: 46.9	• Total: 51.6 • Total: 49.2	• Total: 52.0 • Total: 49.3	• PCS was higher among never smokers than among former (p <0.05) and current (p <0.001) smokers • MCS was lower among current smokers than among former and never smokers (p <0.0001)	Adjusted for age, gender, education level, and town

Arday et al. 2003	• 134,309 elderly (≥65 years of age) and 8,640 disabled (<65 years of age) Medicare managed care enrollees	*PCS score*
		 • Disabled
		 • Daily: 29.4
		 • Some days: 27.5
		 • Elderly
		 • Daily: 40.4
		 • Some days: 41.2
		
		 MCS score
		 • Disabled
		  – Daily: 39.0
		  – Some days: 40.4
		 • Elder Daily: 51.3
		  – Some days: 51.3
			• Disabled:
			 • ≤12 months quit: 29.2
			 • >12 months quit: 29.6
			 • Elderly
			 • ≤12 months quit: 37.3
			 • >12 months quit: 40.8
			
			 • Disabled
			  – ≤12 months quit: 43.8 – >12 months quit: 43.9
			 • Elder
			  – ≤12 months quit: 49.3 – >12 months quit: 52.8
				31.8
				
				 42.4
				
				 43.5
				
				 53.0
					• Compared with never smokers, all smoking groups had worse PCS scores (p ≤0.03)
					
					 • Among disabled, current smokers—but not former smokers—had worse MCS scores than never smokers (p ≤0.01)
					
					 • Among elderly, current smokers and more recent quitters had worse MCS scores than never smokers (p <0.01)
						Adjusted for age, gender, race, education

Borzeck et al. 2005	• 1,242 male veterans • Mean 63 years of age • United States	Regression coefficients for the effect of smoking on PCS score at baseline • Total: -1.40 Regression coefficients for the effect of smoking on MCS score at baseline • Total: -0.49	• Total: -1.52 • Total: 0.84	Ref Ref	• Current smokers did not have statistically significantly worse PCS or MCS than never smokers • Former smokers had worse PCS than never smokers (p <0.05) in the cross-sectional analysis	Adjusted for age, marital status, education, employment, living alone, comorbidity, alcohol use, exercise, BMI, seat belt use, and cholesterol screening

Table 11.4*S*   Continued

Study	Design/population	Results: Current smoker	Former smoker	Never smoker	Findings	Comments
Laaksonen et al. 2006	• 8,970 employees of the city of Helsinki • 40–60 years of age	**PCS score** • Men – Heavy: 48.9 – Moderate: 50.1 • Women – Heavy: 47.8 – Moderate: 48.8	• Men: 50.5 • Women: 48.6	• Men: 50.7 • Women: 48.6	• Heavy current smokers had worse PCS and MCS than never smokers • Former smokers and never smokers had similar PCS and MCS	Adjusted for age and occupational class
		MCS score • Men – Heavy: 50.3 – Moderate: 50.1 • Women – Heavy: 49.4 – Moderate: 51.4	• Men: 52.1 • Women: 51.8	• Men: 52.0 • Women: 52.1		
Strandberg et al. 2008	• 26-year follow-up study of 1,658 White men • Finland	Compared with men who were never smokers in 1974, men who smoked more than 20 cigarettes/day in 1974 had a statistically significantly worse PCS score in 2000; there was a graded deterioration in PCS score with increasing number of cigarettes smoked daily; the relationship between smoking and the MCS score was not statistically significant			• After 26 years of follow-up, heavy smokers had worse PCS than never smokers	Age-adjusted
Sarna et al. 2008	• Nurses' Health Study cohorts • 158,736 women between 29 and 71 years of age	Regression coefficients (SE) for the effects of smoking on PCS			• Current smokers had worse PCS and MCS than never smokers (p <0.001)	Adjusted for age, BMI, physical activity, living alone, and comorbidity
		• Total: -0.55 (0.06)	• Total: -0.08 (0.05)	Ref	• Former smokers had worse MCS than never smokers (p <0.001)	
		Regression coefficients (SE) for the effects of smoking on mental component summary score (MCS)				
		• Total: -2.0 (0.07)	• Total: -0.32 (0.05)	Ref		
Pisinger et al. 2009	• 9,322 men and women between 30 and 60 years of age • Denmark	At baseline, PCS score and MCS score were highest in never smokers and lowest in daily smokers			• Smokers had worse PCS and MCS than never smokers (p <0.001)	Adjusted for gender, age, employment status, and length of vocational training

Note: BMI = body mass index; MCS = mental component summary score; PCS = physical component summary score; SE = standard error. [a]Measures of functional health and well-being; higher scores indicate better function.

Table 11.5*S*   **Studies on the association between smoking and other measures of health and function**

Study	Design/population	Results — Current smoker	Former smoker	Never smoker	Findings	Comments
Ostbye et al. 2002	• Health and Retirement Study (845 persons 51–64 years of age) • AHEAD (5,037 persons ≥70 years of age) • Longitudinal studies from 1992/1993–1998 • United States	OR (95% CI) for difficulty walking several blocks • 51–64 years of age – Heavy: 2.37 (2.05–2.74) – Light: 1.68 • (1.41–2.00) ≥70 years of age: – 2.06 (1.69–2.49)	• Time since quit: – <3 years: 2.08 (1.65–2.62) – 3–15 years: 1.34 (1.16–1.56) – >15 years: 1.09 (0.93–1.29) • ≥70 years of age: – 1.30 (1.15–1.48)	1.0 (ref) 1.0 (ref)	• Current smokers were more likely than never smokers to have difficulty walking a short distance • Former smokers were also more likely to report difficulty, although the effect varied with time since quitting; long-term quitters had a risk that was similar to never smokers	Adjusted for exercise, BMI, alcohol consumption, age, race, gender, marital status, and education
Woods et al. 2005	• 28,181 WHI observational study participants • Women 65–79 years of age and free of frailty at baseline • United States • 3 years of follow-up	OR (95% CI) for incident frailty by baseline smoking status. Frailty defined as a score of 3 or higher based on the following: poor-self reported physical function (2 points), exhaustion (1 point), low physical activity (1 point), and unintentional weight loss (1 point) • Total: 2.90 (2.35–3.57)	• Total: 1.12 (1.02–1.23)	1.0 (ref)	• Current and former smokers were more likely than never smokers to develop frailty	Adjusted for age, income, education ethnicity, BMI, alcohol, hormone therapy, self-reported health, disability, living alone, and comorbid conditions
Heikkine et al. 2008	• 8,028 persons ≥30 years of age • Mean: 51 years of age among men and 54 among women • Survey conducted 2000–2001 • Finland	Overall quality of life. Respondents were asked to rate on a scale of 0 (worst) to 10 (best) how good their present life as a whole had been within the last 30 days • Men daily smokers: 7.35 • Women daily smokers: 7.58	• Men daily smokers: 7.66 • Women daily smokers: 7.67	• Men daily smokers: 7.63 • Women daily smokers: 7.75	• Daily smokers reported worse overall quality of life than never smokers among both men (p <0.001) and women (p = 0.004) • Former smokers and never smokers had similar quality of life	Adjusted for age, education, and health-related quality of life
McClav et al. 2009	• BRFSS • 17,800 participants • 2006 in 4 states • ≥18 years of age • United States	OR (95% CI) for life dissatisfaction • Total – Nonquitter: 1.0 (ref) – Unsuccessful quitter:0.7 (0.4–1.3)	• Total: 0.5 (0.3–0.9)	• Total: 0.4 (0.2–0.7)	• Compared with current smokers who have not recently tried to quit, former smokers and never smokers are less likely to report life dissatisfaction	Adjusted for age, race/ethnicity, gender, education, marital status, employment status, chronic disease, and health care coverage

Table 11.5S Continued

Study	Design/population	Results — Current smoker	Results — Former smoker	Results — Never smoker	Findings	Comments
Hardy et al. 2010	• 9,563 community-dwelling Medicare beneficiaries ≥65 years of age	• Current smokers were more likely than never smokers to have difficulty walking ¼ mile or to be unable to walk ¼ mile • Former smokers did not differ statistically significantly from never smokers in their ability to walk a short distance			• Current smokers were more likely than never smokers to have difficulty walking a short distance or to be unable to walk a short distance (p <0.05)	Adjusted for age, gender, race, marital status, income, education, insurance status, chronic conditions, and BMI
Piper et al. 2012	• 1,504 participants in a smoking cessation trial • Average 45 years of age • United States	• During 3 years of follow-up, successful quitters experienced less of a decline in global quality of life than continuing smokers • Mean (SD) change in QOLI total at 3 years was -0.24 (1.40) in quitters and -0.47 (1.40) in continuing smokers			• Smokers who quit reported better quality of life than smokers who did not quit (p = 0.02)	
Sabia et al. 2012	• Whitehall II Study • 5,100 men and women 42–63 years of age at baseline • Followed for a median of 16.3 years • Free of cancer, coronary artery disease, and stroke at baseline	OR (95% CI) for successful aging Successful aging defined as good cognitive, physical, respiratory, and cardiovascular functioning, and absence of disability, mental health problems, and chronic disease	• Ever-smokers formed the reference group	• Total: 1.29 (1.11–1.49)	• Never smokers were more likely than ever smokers to experience successful aging	Adjusted for alcohol consumption, physical activity, daily consumption of fruits and vegetables, age, gender, education, and marital status

Note: **AHEAD =** Asset and Health Dynamics among the Oldest Old Survey; **BMI** = body mass index; **BRFSS** = Behavioral Risk Factor Surveillance System; **CI** = confidence interval; **MCS** = mental component summary score; **OR** = odds ratio; **QOLI** = Quality of Life Inventory; **SD** = standard deviation; **WHI** = Women's Health Initiative.

Table 11.6S   Studies on the association between smoking and hospitalizations

Study	Design/population	Results			Findings	Comments
		Current smoker	**Former smoker**	**Never smoker**		
Robbins et al. 2000	• 87,991 men and women serving on active duty in the U.S. Army during 1987–1998 • Average at baseline was 28.5 years of age	Rate ratio (95% CI) for hospitalization not due to injury or pregnancy			• Among both men and women, current and former smokers were more likely to be hospitalized than never smokers	Adjusted for age, race, military rank, alcohol consumption, exercise frequency, and overweight
		• Men: 1.30 (1.24–1.35) • Women: 1.25 (1.14–1.37)	• Men: 1.20 (1.14–1.26) • Women: 1.13 (1.01–1.26)	1.0 (ref) 1.0 (ref)		
Johnson and Richter 2002	•7,844 adolescents 12–17 years of age • United States	Mean number of overnight hospital stays			• Frequent smokers reported more overnight hospital stays than less frequent smokers, former smokers, or never smokers (p <0.01)	Adjusted for gender, age, and family income
		• Total – 6 or more days/month: 0.22 – 1–5 days/month: 0.04	• Total: 0.05	0.07		
Ostbye et al. 2002	• Health and Retirement Study (7,845 persons 51–64 years of age) • AHEAD (5,037 persons ≥70 years of age) • Longitudinal studies • from 1992/1993–1998 United States	OR (95% CI) for hospitalization in previous year			• Current smokers and more recent quitters were more likely to be hospitalized than never smokers • Long-term quitters (>15 years) and never smokers had a similar likelihood of hospitalization	Adjusted for exercise, BMI, alcohol consumption, age, race, gender, marital status, and education
		• 51–64 years of age – Heavy: 1.41 (1.24–1.59) – Light: 1.35 (1.16–1.56) • ≥70 years of age: – 1.28 (1.08–1.52)	• Time since quit: – <3 years: 1.46 (1.20–1.78) – 3–15 years: 1.22 (1.08–1.38) – >15 years: 0.96 (0.85–1.09) • ≥70 years of age: – 1.16 (1.04–1.29)	1.0 (ref) 1.0 (ref)		
Kahende et al. 2009	• NHANES • 1999–2004 • 15,332 adults ≥18 years of age • United States	OR for a hospitalization within the last year			• Current smokers, recent quitters (<2 years), and long-term quitters (≥10 years) were each more likely than never smokers to be hospitalized	Adjusted for gender, race/ethnicity, age, education, poverty level, and health insurance
		• Total: 1.20 (1.06–1.37)	• Total: – <2 years since quit: 2.49 (1.86–3.34) – 2–4 years since quit: 1.39 (0.98–1.97 – 5–9 years since quit: 1.17 (0.86–1.59) – ≥10 years since quit: 1.22 (1.02–1.46)	1.0 (ref)		

Table 11.6*S*   Continued

Study	Design/population	Current smoker	Former smoker	Never smoker	Findings	Comments
			Results			
Woodruff et al. 2010	• 5,503 female U.S. Navy recruits	Percent hospitalized; excludes pregnancy-related hospitalizations			• Likelihood of hospitalization did not vary by smoking status	Adjusted for time in service, education, race, and regular/ reserve status
	• Mean 19.7 years of age at entry	• Daily smoker: 13	• Former or nondaily smoker: 12	• Never smoker: 14	• Duration of hospitalization was longest among current smokers	
		Average duration of hospitalization (days)				
		• Daily smoker: 5.7	• Former or non daily smoker: 5.1	• Never smoker: 5.2		

Note: **AHEAD =** Asset and Health Dynamics among the Oldest Old Survey; **BMI** = body mass index; **CI** = confidence interval; **NHANES** = National Health and Nutrition Examination Survey; **OR** = odds ratio.

Table 11.7S   Studies on the association between smoking and outpatient visits

Study	Design/population	Results			Findings	Comments
		Current smoker	**Former smoker**	**Never smoker**		
Borzecki et al. 2005	• 1,397 male veterans • United States	Regression coefficient for the effect of smoking on physician visits			• Current smokers hadoutpatient visits than never smokers Ref (p<0.05)	Adjusted for age, marital status, education, employment, live alone, other insurance, disability, comorbidity, alcohol, exercise, BMI, seat belt use, and cholesterol screening
		Total: -0.30	Total: -0.05	Ref		
Kahende et al. 2009	• NHANES • 1999–2004 • 15,332 adults ≥18 years of age • United States	OR for at least 1 outpatient visit within the last year			• The frequency of at least 1 outpatient visit was similar in current and never smokers • Current smokers and former smokers were more likely than never smokers to have multiple (≥4) outpatient visits • Multiple outpatient visits were most common among recent quitters	Adjusted for gender, race/ethnicity, age, education, poverty level, and health insurance
		• Total: 0.94 (0.81–1.13)	• <2 years since quit: 1.75 (1.15–2.65) • 2–4 years since quit: 1.15 (0.76–1.75) • 5–9 years since quit: 1.47 (0.90–2.40) • ≥10 years since quit: 1.75 (1.42–2.14)	1.0 (ref)		
		OR for 4 or more outpatient visits within the last year				
		• Total: 1.18 (1.06–1.33)	• <2 years since quit: 1.65 (1.29–2.12) • 2–4 years since quit: 1.59 (1.17–2.18) • 5–9 years since quit: 1.34 (1.02–1.74) • ≥10 years since quit:1.17 (1.04–1.32)	1.0 (ref)		

Note: **BMI** = body mass index; **NHANES** = National Health and Nutrition Examination Survey; **OR** = odds ratio.

Table 11.8S Studies on the association between smoking and nursing home stays

Study	Design/population	Results — Current smoker	Results — Former smoker	Results — Never smoker	Findings	Comments
Ostbye et al. 2002	• AHEAD (5,037 persons ≥70 years of age) • Longitudinal study from 1993–1998 • United States	OR (95% CI) for stay in a nursing home, convalescent home, or other long-term care health facility in the previous year • ≥70 years of age: – 1.68 (1.08–2.63)	• ≥70 years of age:– 1.16 (0.85–1.58)	1.0 (ref)	• Current smokers were more likely than never smokers to have a stay in a nursing home, convalescent home, or other long-term care facility	Adjusted for exercise, BMI, alcohol consumption, age, race, gender, marital status, and education
Valiyeva et al. 2006	• NHANES I Epidemiologic Follow-up Study (NHEFS) • 6,462 people who were 45–74 years of age at baseline (1971–1975) • Followed until 1992	RR (95% CI) of a nursing home admission • 45–65 years of age at baseline:– 1.56 (1.23–1.99) • 65–74 years of age at baseline: – 1.32 (1.08–1.61)	Reference group did not smoke at baseline Reference group did not smoke at baseline		• Current smokers were more likely than people who did not smoke at baseline to be admitted to a nursing home	Adjusted for age, gender, race, BMI, major diagnoses at baseline, physical activity, blood pressure, cholesterol level, and diabetes

Note: **AHEAD** = Asset and Health Dynamics among the Oldest Old Survey; **BMI** = body mass index; **CI** = confidence interval; **NHANES** = National Health and Nutrition Examination Survey; **OR** = odds ratio; **RR** = relative risk.

Table 11.9*S* Studies on the association between smoking and costs

Study	Design/population	Results		Never smoker	Findings	Comments
		Current smoker	Former smoker			
CBO 2012 Panel	• Medical Expenditure Survey Data for 2000–2008 from the	Annual per capita spending on health care (in 2008 dollars) for former smokers, by time since quit			• Spending tended to be highest among former smokers followed by current smokers.	
	• 1998–2007 from the National Health Interview Survey	• 18–24 years of age: 2,010 • 25–44 years of age: 2,850 • 45–64 years of age: 5,540 • 65–74 years of age: 7,940 • ≥75 years of age: 8,750	• 18–24 years of age: – <5 years: 2000 – 5–14 years: NA – ≥15 years: NA	1,870		
	• ≥18 years of age				• Never smokers had the lowest spending in each age group except the oldest	
			• 25–44 years of age: – <5 years: 3,090 – 5–14 years: 2,920 – ≥15 years: 3,330	2,570		
			• 45–64 years of age: – <5 years: 7,650 – 5–14 years: 6,580 – ≥15 years: 6,290	5,040		
			• 65–74 years of age: – <5 years: 11,250 – 5–14 years: 9,760 – ≥15 years: 9,330	7,790		
			• ≥75 years of age: – <5 years: 15,530 – 5–14 years: 12,280 – ≥15 years: 11,770	9,810		

Note: **CBO** = Congressional Budget Office; **NA** = not available.

Table 11.10S Annual per capita spending on health care, by smoking status and age group (2008 dollars*)

	18–24 years	25–44 years	45–64 years	65–74 years	≥75 years
People who have never smoked	1,870	2,570	5,040	7,790	9,810
Current or former smokers	2,010	2,940	6,170	9,230	11,580
Current smokers	2,010	2,850	5,540	7,940	8,750
Former smokers					
For <5 years	2,000	3,090	7,650	11,250	15,530
For 5–14 years	n.a.	2,920	6,580	9,760	12,280
For ≥15 years	n.a.	3,330	6,290	9,330	11,770

Source: Congressional Budget Office 2012.

Note: **n.a.** = not available (because of a lack of data to produce precise estimates). Based on data for 2000 to 2008 from the Medical Expenditure Panel Survey and for 1998 to 2007 from the National Health Interview Survey.

*The numbers shown here are rounded to the nearest $10.

Table 11.11S Studies on the association between smoking and workplace absenteeism (days absent)*

		Results				
Study	**Design/population**	**Current smoker**	**Former smoker**	**Never smoker**	**Findings**	**Comments**
Halpern et al. 2001	• 292 U.S. airline employees • Mean ranged from 37 years of age among never smokers to 44 years of age among former smokers	Mean (SD) absenteeism days caused by sickness during 4-month study period • Total: 3.99 (4.86) (3.54)	• Total: 2.40	• Total: 1.33 (2.20)	• Absenteeism varied by smoking status (p = 0.0001)	
Tsai et al. 2003	• 2,203 employees of a U.S. chemical and refinery facility • Ages ranged from <30 to >60	Mean number of days lost per employee/ year • Total: 6.4	• Total: 4.8	• Total: 3.5	• Current smokers missed more days than never smokers (p-value NR)	
Tsai et al. 2005	• 2,550 regular employees at U.S. petrochemical facility • Average 46 years of age at end of study	Mean number of days lost per employee/ year • Men: 13.3 • Women: 23.3 • Total: 14.3	• Men: 8.7 • Women: 12.5 • Time since quitting – 1–9 years: 11.0 – 10–19 years: 8.8 – ≥20 years: 7.9	• Men: 7.0 • Women: 12.3 • Total: 7.6	• Among both men and women, current smokers lost almost twice as many days as never smokers (p <0.05)	

Note: **NR** = not reported; **SD** = standard deviation.

*   Absenteeism includes any absence during a specified time period, any short-term absence, any long-term absence, or total days lost.

Table 11.12S Studies on the association between smoking and relative risk (RR) of workplace absenteeism*

Study	Design/ population	Results — Current smoker	Results — Former smoker	Results — Never smoker	Findings	Comments
Morikawa et al. 2004	• 2,504 male Japanese factory workers, 35–55 years of age • 6,290 male British civil service workers, 35-55 years of age	HR (95% CI) for first long-term (>7 days) sickness absence • Japan: 1.43 (1.17–1.75) • Britain: 1.51 (1.35–1.67)	• Japan: 1.39 (1.07–1.80) Britain: 1.11 (1.02–1.21)	1.0 (ref) 1.0 (ref)	• Current and former smokers were each more likely than never smokers to have a long-term sickness absence	Age-adjusted
Sindelar et al. 2005	• 383,778 full-time U.S. workers • 18–64 years of age	OR for absence in the last week			• Current and former smokers were each more likely than never smokers to have an absence (p = 0.000 for each group) • Although risk of an absence appeared to be highest among recent quitters, each group of former smokers was more likely than never smokers to have an absence (p <0.05 for each group)	Adjusted for age, education, race, ethnicity, marital status, number of children, occupation, industry, metropolitan statistical area, state, and month and year
Labriola et al. 2006	• 3,792 Danish employees • 18–64 years of age at start of study	OR for >6 days of absence of previous year • Total: 1.61 (1.32–1.96)	• Total: 1.32 (1.03–1.68)	1.0 (ref)	• Current and former smokers were each more likely than never smokers to have more than 6 days of absence in the previous year	Adjusted for age, gender, health status, BMI, and employer and job characteristics
Christensen et al. 2007	• 5,020 Danish employees • 18–69 years of age	HR for long-term sickness absence (8 consecutive weeks) • Men – ≥15 cigarettes: 1.55 (1.00–2.40) – <15 cigarettes: 0.92 (0.50–1.73) • Women ≥15 cigarettes: – 2.05 (1.36–3.08) – <15 cigarettes: 1.21 (0.74–1.98)	• Men: 1.36 (0.85–2.19) • Women: 1.61 (1.07– 2.42)	1.0 (ref) 1.0 (ref)	• Among current smokers, only heavy smoking significantly increased risk of long-term absence • Former smoking increased risk of a long-term absence among women only	Adjusted for age, family status, SES, education, work environment, and diagnosed disease; adjustment for diagnosed disease may lead to underestimation of the smoking effect

Table 11.12S Continued

Study	Design/population	Results			Findings	Comments
		Current smoker	**Former Smoker**	**Never smoker**		
Laaksonen et al. 2009	• 5,470 female and 1,464 male Finnish city employees • 40–60 years of age	**RR for 1–3 day sickness absence**			• Heavy current smoking increased the risk of both short- and longer-term absences in men and women • Lighter current smoking was linked with short-term absences in women, and with longer-term absences in men and women • The increase in absences among former smokers was only statistically significant in women	Adjusted for age and occupational class
		• Men – >20 cigarettes: 1.71 (1.39–2.11) – ≤20 cigarettes: 1.63 (1.34–1.98)	• Men: 1.12 (0.94 to 1.33)	1.0 (ref)		
		• Women – >20 cigarettes: 1.50 (1.37–1.64) – ≤20 cigarettes: 1.23 (1.13–1.34)	• Women: 1.18 (1.10– 1.27)	1.0 (ref)		
		RR for ≥4 day sickness absence				
		• Men – >20 cigarettes: 1.66 (1.31–2.10) – ≤20 cigarettes: 1.23 (0.96–1.57)	• Men: 1.10 (0.90– 1.34)	1.0 (ref)		
		• Women: – >20 cigarettes: 1.49 (1.34–1.65) – ≤20 cigarettes: 1.32 (1.20–1.46)	• Women: 1.18 (1.08–1.29)	1.0 (ref)		

Note: **BMI** = body mass index; **CI** = confidence interval; **HR** = hazard ratio; **OR** = odds ratio; **SES** = socioeconomic status.

*Absenteeism includes any absence during a specified time period, any short-term absence, any long-term absence, or total days lost.

Chapter 12
Smoking-Attributable Morbidity, Mortality, and Economic Costs

Introduction

The preceding chapters have reviewed the extensive scientific evidence about the diverse diseases and other adverse effects caused by tobacco use. Policy actions to control tobacco use have long been motivated and informed by the knowledge that smoking causes multiple diseases and decreases life expectancy. To support policy actions and decision-making based on health evidence, quantitative estimates of the burden of disease associated with smoking in the population are made to characterize the size of the smoking epidemic and the potential benefit of tobacco control. These population-level estimates complement the epidemiologic studies that describe the risks to individuals associated with various smoking patterns.

For diseases attributable to a causal risk factor, such as smoking, epidemiologic methods can be used to estimate the disease burden associated with that risk factor for a particular population. Estimates can be based on several types of indicators, such as premature mortality, excess morbidity, disability-adjusted life years lost, changes in disability-adjusted life expectancy, quality-adjusted life years lost, years of potential life lost (YPLL), and economic costs of illness (U.S. Department of Health and Human Services [USDHHS] 2004).

The estimation of population-attributable fraction (PAF)—the percentage of the disease morbidity or mortality that is attributable to an exposure—is central to calculating burden. The calculation of PAF for a particular risk factor represents a form of quantitative risk assessment (National Research Council 1983). Risk assessment is a systematic approach that translates research findings for the purpose of guiding the implementation and evaluation of public health programs and policies (Samet et al. 2006). The elements of a risk assessment include hazard identification (does the exposure cause disease), exposure assessment (what is the population pattern of the exposure), dose-response assessment (how does risk vary with duration and amount of exposure), and risk characterization (what is the disease burden caused by the exposure). PAF was originally proposed in a classic paper by Levin (1953), and the application of this approach to smoking was described in the 1989 and 2004 Surgeon General's reports (USDHHS 1989, 2004).

Measuring changes in smoking-attributable mortality (SAM) periodically provides an ongoing indication of the burden of disease caused by tobacco use. This information can be used to reinforce the importance of comprehensive tobacco control programs at the national and state levels. For example, policymakers and decisionmakers can compare the impact of tobacco use with that of other risk factors when making decisions about resource allocation and needs (McGinnis and Foege 1993). These estimates are also useful for assessing the impact of changes in the prevalence of smoking or the risks associated with smoking over time.

This chapter first describes methods that are used to estimate the burden of disease attributable to smoking, particularly SAM, and then focuses on updates to the Smoking-Attributable Mortality, Morbidity, and Economic Costs (SAMMEC) system from the Centers for Disease Control and Prevention (CDC). These updates reflect the findings of this report which expands the list of diseases caused by smoking. SAMMEC has also been modified to incorporate recent risk estimates which are based on findings in cohort studies over the last decade (see Chapter 11, "General Morbidity and All-Cause Mortality").

The chapter then reviews past estimates of smoking-attributable morbidity and discusses how previous estimates could be updated based on the new findings presented in other chapters in this report. Next, this chapter considers approaches to updating the estimated economic costs of smoking and uses the revised SAMMEC model to estimate the economic burden from active and passive smoking in the United States. Finally, the chapter summarizes international estimates of the global burden of smoking and exposure to secondhand smoke. This chapter is limited to considering the mortality risks from cigarette smoking and does not include those of other tobacco products, either singly or in combination with cigarettes.

Prior to the estimates in this report, CDC last published estimates of smoking-attributable morbidity and mortality in 2008. For the period 2000–2004, CDC estimated approximately 393,000 annual smoking-attributable premature deaths from 19 disease categories and 4 adverse health outcomes in infants that were causally associated with smoking (CDC 2008). An additional 740 deaths from residential fires caused by smoking were counted toward that total as were 49,400 deaths from lung cancer and coronary heart disease (CHD) attributed to exposure to secondhand smoke that were computed separately from deaths caused by active smoking. For the 5-year period, the resulting annual total of attributable mortality was 444,000. Other recent estimates are described in Appendix 12.1.

Methodology Used by CDC to Compute Smoking-Attributable Mortality in the United States

The overall approach to estimating SAM includes the following components:

- Identifying those diseases caused by (cigarette) smoking;

- Developing relative risk (RR) estimates for those diseases for current and former smokers in comparison to lifetime nonsmokers;

- Developing estimates of smoking prevalence for the populations and years of interest;

- Estimating disease- and gender-specific PAFs by age group; and

- Applying the PAFs to disease-specific mortality data for the population to estimate SAM.

Understanding the parameters of PAF allows researchers to describe any uncertainties associated with the resulting PAF estimates and acknowledges the cross-sectional nature of the SAM estimates for particular calendar time points. The estimates represent the SAM for a population with a defined smoking prevalence profile and a set of disease-specific RR estimates for a given year, based on the assumption that the RR estimates accurately represent those in the population of interest.

There are several methods that have been used for calculating SAM (see Appendix 12.1). The first approach historically, the PAF calculation, is used most commonly and can be calculated as:

$$PAF = \frac{P(RR-1)}{P(RR-1)+1}$$

where P is the prevalence of exposure in the population and RR is the relative risk for disease associated with exposure assumed for the population. The formula shows that PAF varies from 0 (if either P = 0 or RR = 1) to approximately 1 at very high values for P or RR (Figure 12.1).

This approach currently underlies the SAMMEC methodology (CDC 2011). The PAF and variants have also been referred to as assigned share, excess risk, etiologic fraction, attributable proportion, attributable risk, and incidence density fraction (Levin 1953; Walter 1976;

Figure 12.1   The relationship of relative risk (RR) to the population-attributable fraction at different prevalence levels
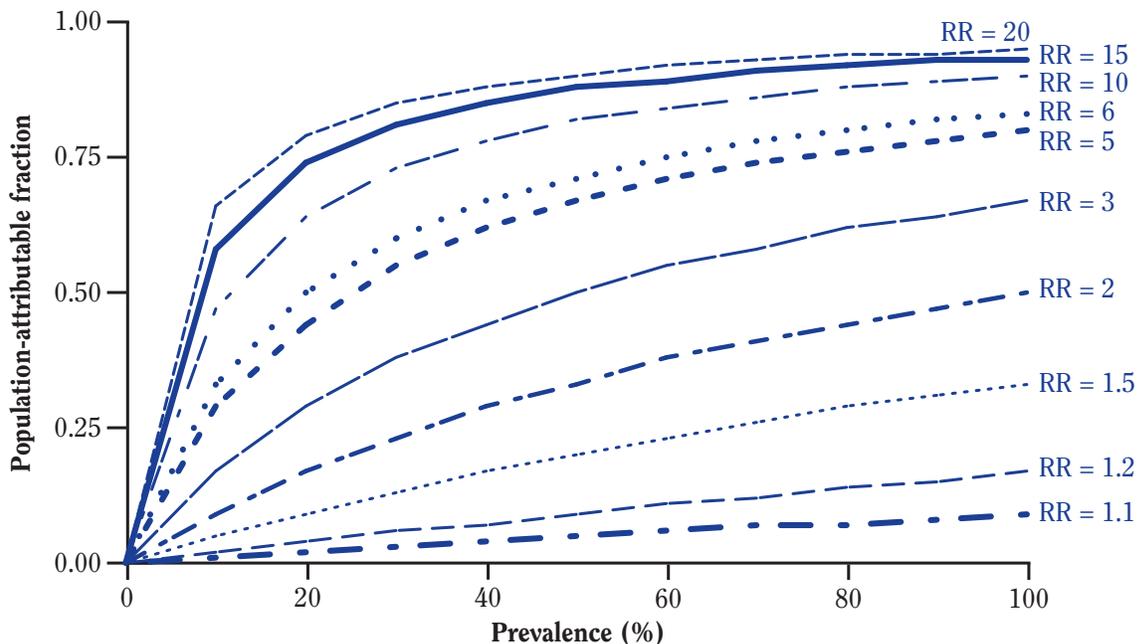
Source: Michael Thun, unpublished data.
Note: **RR** = relative risk.

incidence density fraction (Levin 1953; Walter 1976; Rothman 1986; Greenland and Robins 1988; USDHHS 1989; Greenland 1999). These measures estimate the burden (usually premature mortality) from all diseases and conditions combined or from the specific diseases attributed to smoking. When PAF is multiplied by the reported number of deaths in these disease categories, numbers of deaths for a given time period that are attributable to tobacco use can then be estimated. Based on this first application of the attributable risk calculation to available case-control data, Levin (1953) reported that 62–92% of all cases of lung cancer in study populations are caused by smoking.

Methodologic Issues in SAM Calculation

The methodology to estimate PAF for smoking—including sources of data and their limitations, potential confounding factors, sources of uncertainty, and approach to causal inference—has been reviewed and evaluated in detail in the past, including in the 2004 Surgeon General's report (USDHHS 2004), by the U.S. General Accounting Office ([USGAO] 2003) of the U.S. Congress, by an expert panel convened by CDC (SciMetrika 2010), and in the international epidemiologic literature. This section presents an overview of the general uncertainties of SAM estimates and the resulting limitations in their interpretation and application.

SAM estimates are based on assumptions that include some level of uncertainty. Not all uncertainties are encompassed by the confidence intervals (CIs), which reflect the statistical uncertainty (USDHHS 2004). Nonetheless, the estimates provide policymakers and the public with a general understanding of the magnitude of the burden imposed on the nation by cigarette smoking.

SAMMEC is not an annual surveillance system because single-year SAM calculations can be affected by small numbers of cause-specific deaths and random year-to-year variations. Also, as noted elsewhere in this chapter, when prevalence is declining, the smoking-attributable fraction (SAF) and hence the SAM will be underestimated. These effects are moderated by averaging the estimates over 5 years of prevalence data. When repeated periodically on this longer-term timeframe, SAMMEC estimates can provide insights into the consequences of the changing tobacco epidemic. The estimates are particularly useful if updated inputs are available.

Most estimates of SAM do not include mortality caused by cigar smoking, pipe smoking, or smokeless tobacco use. For example, an estimated 1,000 deaths in the United States were attributable to pipe smoking in 1991 (Nelson et al. 1996). This limitation reflects the lack of appropriate RRs related to tobacco products other than cigarettes. To date, these products cause many fewer deaths than cigarettes. However, given the dynamic nature of the tobacco-related environment, assessment of risk due to other tobacco products use is an emerging priority, particularly because of the introduction of tobacco products claiming to reduce exposure (Samet and Wipfli 2009) and increased dual use of tobacco products (Tomar et al. 2010). Dual use (i.e., use of cigarettes and another product) may complicate estimation of SAM, particularly if dual use extends to persons in age ranges where most smoking-caused deaths occur.

Confounding by such factors as alcohol consumption, education, income, blood pressure, diabetes, and other lifestyle factors has also been a concern. Generally, positive confounding has been postulated. Thun and colleagues (2000) examined the potential for confounding by lifestyle factors to bias SAM estimates and found minimal consequences of potential confounding. The representativeness of the Cancer Prevention Study II (CPS-II) cohort has also been reviewed with regard to SAMMEC estimates (Sterling and Weinkam 1987; Levy 2000). This issue has also been considered and set aside as a source of significant bias (Thun et al. 2000; USDHHS 2004). GAO (2003) reviewed CDC's assumptions, methods, and data sources for SAMMEC and concluded that SAMMEC estimates are sound, noting that appropriate attention had been paid by CDC to the issues of confounding and representativeness.

Further concerns relate to the estimation of the prevalence of smoking and the selection of RRs. The RR values used in past SAMMEC publications (Table 12.1) are based on the first 6 years of follow-up of CPS-II (1982–1988) (Thun et al. 1997b; CDC 2011). However, RR estimates associated with smoking can change over time for specific diseases (Thun and Heath 1997; Thun et al. 1997a). Patterns of smoking may change as might the toxicity and resulting risks of tobacco products. For example, compared to earlier cohorts, more recent cohorts of women began smoking at a younger age; consequently the age-specific RRs are higher (see Chapter 13, "Patterns of Tobacco Use Among U.S. Youth, Young Adults, and Adults"). Changes in tobacco product

Table 12.1 Relative risks for adult mortality from smoking-related diseases, adults 35 years of age and older, based on Cancer Prevention Study II, United States

Disease category (ICD–10 code)	Males		Females	
	Current smoker	Former smoker	Current smoker	Former smoker
Malignant neoplasms				
Lip, oral cavity, pharynx (C00–C14)	10.89	3.40	5.08	2.29
Esophagus (C15)	6.76	4.46	7.75	2.79
Stomach (C16)	1.96	1.47	1.36	1.32
Pancreas (C25)	2.31	1.15	2.25	1.55
Larynx (C32)	14.60	6.34	13.02	5.16
Trachea, lung, bronchus (C33–C34)	23.26	8.70	12.69	4.53
Cervix uteri (C53)	n/a	n/a	1.59	1.14
Kidney and renal pelvis (C64–C65)	2.72	1.73	1.29	1.05
Urinary bladder (C67)	3.27	2.09	2.22	1.89
Acute myeloid leukemia (C92.0)	1.86	1.33	1.13	1.38
Cardiovascular diseases				
Coronary heart disease (I20–I25)				
Persons 35–64 years of age	2.80	1.64	3.08	1.32
Persons ≥65 years of age	1.51	1.21	1.60	1.20
Other heart disease (I00–I09, I26–I28, I29–I51)	1.78	1.22	1.49	1.14
Cerebrovascular disease (I60–I69)				
Persons 35–64 years of age	3.27	1.04	4.00	1.30
Persons ≥65 years of age	1.63	1.04	1.49	1.03
Atherosclerosis (I70)	2.44	1.33	1.83	1.00
Aortic aneurysm (I71)	6.21	3.07	7.07	2.07
Other arterial disease (I72–I78)	2.07	1.01	2.17	1.12
Respiratory diseases				
Influenza, pneumonia (J10–J11, J12–J18)	1.75	1.36	2.17	1.10
Bronchitis, emphysema (J40–J42, J43)	17.10	15.64	12.04	11.77
Chronic airways obstruction (J44)	10.58	6.80	13.08	6.78

Source: Thun et al. 1997a; Centers for Disease Control and Prevention 2011.
Note: **ICD** = International Classification of Diseases.

composition, which could affect risk, have occurred over time (USDHHS 2010). Changing rates in the comparison population of never smokers also affect RRs. As reviewed in Chapter 8, "Cardiovascular Diseases," declining death rates from cardiovascular diseases in lifelong nonsmokers during the past half century indicate that the risk of cardiovascular death has decreased for the overall population.

Other uncertainties may also influence SAM estimates, including potential differences in the strength of association between smoking and disease or death across different racial/ethnic groups, different socioeconomic strata, and different age groups—all of which are potential modifiers of risk. A particular aspect of heterogeneity is related to the age groups for which RRs and SAM are estimated. Most deaths from cardiovascular diseases occur at older ages, and the U.S. population is aging. In 2006, 36% of all deaths from coronary heart disease occurred in persons 85 years of age and older, and 29% occurred in persons 75–84 years of age (Heron et al. 2009). At the same time, most smokers quit smoking, or die because of it, by 75 years of age. With increasing age, particularly above 60–70 years, the RR for death from cardiovascular disease declines sharply. Crude age stratification in the estimation of PAF will not adequately reflect this age-related change, potentially leading to overestimation of the PAF; however, SAMMEC originally included only two age categories (35–64 years of age and 65 years of age and older).

Another issue is that SAMMEC estimates are based on the prevalence of current and former smokers at the present time. However, the deaths that occur during a given year are primarily among persons who began smoking 30–50 years earlier. Many people quit smoking during the later decades of the twentieth century (Malarcher et al. 1997). The RRs of former smokers are lower than those of current smokers for most diseases and for any cohort; the risks for former smokers reflect the distribution of times since quitting. Unless smoking behavior (including cessation) is stable over time, cross-sectional SAM estimates do not accurately reflect the risks of past cohorts of smokers. When the prevalence of smoking is declining, as in the United States (see Chapter 13), the SAMMEC methodology will tend to understate the number of deaths caused by smoking (USDHHS 2004). Table 12.2 shows the annual prevalence of current and former smoking among adults, 35 years of age and older, from 1965–2011. The ratio of former smokers to current smokers has greatly increased over the past half-century for both men and women.

Using survey data to derive estimates of exposure (e.g., prevalence of current and former cigarette smoking) is another source of uncertainty in SAM calculations. Although population-based surveys using self-reported data provide reasonably consistent estimates of adult smoking prevalence and are generally considered to be sufficiently accurate for tracking the general pattern of tobacco use in populations, a comparison of smoking self-reports and the biomarker cotinine in National Health and Nutrition Examination Survey (NHANES) data indicates that some underestimation is likely (Caraballo et al. 2001; Brener et al. 2003; USDHHS 2004, 2006, 2010) (see Chapter 13). The ongoing decrease in the percentage of U.S. households possessing landline phones and the decreasing participation rates in telephone surveys of households with landline phones (Steeh et al. 2001; Biener et al. 2004; Delnevo and Bauer 2009) can result in an underestimation of current smoking in landline telephone-based surveys (Blumberg et al. 2008; Delnevo and Bauer 2009) because smokers are more likely to live in wireless-only households than nonsmokers (Blumberg et al. 2006, 2008) and are less likely to participate in health-related surveys (Galea and Tracy 2007). Although this issue would not affect prevalence estimates from the National Health Interview Survey (NHIS), which is based on household sampling, it could have affected state smoking prevalence estimates from the Behavioral Risk Factor Surveillance System (BRFSS) before 2011 (the year cell phone sampling was instituted); states often use BRFSS data to calculate state-specific SAM. Finally, neither NHIS nor BRFSS include institutionalized populations and persons in the military, which prevents the generalization of the results to these groups. A probable net consequence of these survey issues is some underestimation of smoking in the U.S. population in widely cited state and national surveys of smoking behavior (see Chapter 13). Any downward bias in survey estimates of smoking will lead to underestimation of SAM.

Table 12.2   Annual prevalence of current smoking and former smoking among adults, 35 years of age and older, for selected years; National Health Interview Survey (NHIS), United States, 1965–2011

	Men (years of age)								Women (years of age)							
	35–54		55–64		65–74		≥75		35–54		55–64		65–74		≥75	
Year	%CS	%FS	%CS	%FS	%CS	%FS	%CS	%FS	%CS	%FS	%CS	%FS	%CS	%FS	%CS	%FS
1965	57.1	21.2	46.6	27.1	33.1	30.1	19.3	24.2	40.8	9.4	25.0	7.6	12.4	5.1	4.5	3.6
1970	48.7	28.6	41.1	34.9	27.1	41.5	15.7	36.3	37.9	13.3	28.5	12.1	14.4	9.0	5.6	5.5
1974	48.8	30.2	37.7	40.0	29.2	43.0	15.9	38.7	37.9	14.1	30.4	16.0	16.0	12.5	5.8	7.6
1977	46.5	29.5	37.0	36.4	26.7	44.6	15.9	41.6	37.5	14.9	32.4	16.0	17.5	13.4	6.6	10.2
1980	42.7	30.9	38.5	39.4	22.2	48.0	9.0	46.3	34.3	17.9	27.9	17.6	21.8	17.6	8.9	8.8
1983	40.1	30.7	32.6	45.4	26.7	46.6	12.2	51.2	33.9	17.2	28.0	19.7	17.6	22.6	6.3	12.8
1985	36.5	34.2	31.9	47.2	21.9	53.2	15.0	51.1	31.9	20.1	27.4	22.2	17.9	23.5	7.0	17.9
1987	35.4	32.2	30.3	45.2	20.6	55.1	11.4	52.4	30.2	19.8	25.6	23.6	18.9	21.4	7.2	14.8
1988	35.6	30.9	28.0	48.4	21.4	53.9	11.4	54.5	28.3	21.0	26.2	24.4	16.7	23.8	7.3	16.3
1990	33.5	31.8	25.9	45.8	18.3	53.0	7.6	59.5	26.3	22.1	20.5	24.3	15.6	25.9	5.8	19.6
1992	34.0	31.1	25.4	45.7	19.6	53.1	10.7	52.0	27.8	20.9	22.6	23.9	14.9	23.3	7.5	24.2
1994	32.2	30.7	24.7	47.5	16.1	57.1	8.4	60.3	25.8	21.7	20.7	29.5	13.4	30.9	8.2	21.7
1995	29.7	28.1	26.9	43.3	18.1	51.5	9.6	55.2	25.9	21.2	23.7	24.4	14.4	29.7	7.9	23.1
1997[a]	31.1	26.1	24.1	45.2	16.2	56.1	7.7	56.4	25.4	20.6	19.0	27.6	15.3	28.3	7.0	22.9
1998	30.1	25.9	24.2	44.4	13.3	58.2	6.2	59.0	25.4	19.6	20.1	26.7	15.3	30.3	6.5	23.3
1999	29.1	25.2	22.3	44.8	12.6	57.8	7.5	58.1	25.0	19.4	17.7	29.5	14.0	29.6	7.1	25.9
2000	29.6	22.1	22.6	45.0	13.7	53.9	5.4	58.6	24.4	19.8	20.8	28.3	12.2	28.8	6.2	23.8
2001	27.5	23.5	24.2	44.1	14.5	55.6	7.4	55.8	24.2	18.2	19.8	27.2	12.8	28.6	5.3	25.6
2002	28.4	23.5	20.7	44.3	12.4	55.1	7.0	58.3	23.2	18.7	18.8	28.1	11.4	31.2	5.8	25.7
2003	27.0	22.1	21.2	41.8	13.3	52.8	5.9	54.1	22.9	17.6	18.2	26.4	11.0	32.4	5.6	27.9
2004	26.6	21.1	22.7	40.3	12.8	52.7	5.9	55.5	21.2	18.2	18.6	26.1	11.2	28.9	5.0	28.3
2005	27.0	19.8	21.1	41.7	11.4	52.5	5.7	56.8	21.1	17.5	16.1	26.5	10.8	30.2	5.9	26.7
2006	25.7	20.7	21.5	41.1	17.4	45.4	6.2	59.0	21.5	16.9	14.9	26.1	11.2	29.8	5.4	25.9
2007	24.0	20.6	19.6	38.6	12.5	51.8	5.1	58.3	20.9	17.0	16.2	25.1	11.9	30.2	3.2	26.0
2008	25.4	20.8	22.6	34.5	14.6	51.3	5.1	59.0	22.3	18.2	16.3	24.7	10.5	31.6	6.1	29.8
2009	26.4	20.3	20.8	40.3	12.5	52.5	5.5	56.2	21.7	16.7	16.1	26.6	12.5	33.1	6.3	25.8
2010	23.9	21.7	20.7	35.6	12.6	50.4	5.5	55.5	20.2	16.6	16.5	25.2	13.3	30.2	4.8	28.4
2011	24.2	20.5	21.4	36.1	11.7	49.9	5.0	54.9	20.8	17.0	15.0	25.5	9.9	34.6	4.0	30.6

Source: National Center for Health Statistics, public use data sets, 1965, 1970, 1974, 1977, 1980, 1983, 1985, 1987–1988, 1990, 1992, 1994–1995, 1997–2011. The NHIS sample is representative of the civilian, noninstitutionalized population of the United States.

Note: **CS** = current smokers, defined as having smoked at least 100 cigarettes and currently smoking every day or some days (the some days condition was added in 1992); **FS** = former smokers, defined as having smoked at least 100 cigarettes but not currently smoking.

[a]A questionnaire redesign of NHIS was implemented in 1997. Data preceding this year may not be directly comparable with data from 1997 and later.

2013 Update to SAMMEC Methodology

In 2013, CDC updated its SAMMEC methodology for adults to incorporate RRs based on more recent datasets. The update also refined the age ranges used in SAMMEC to more accurately capture the changes in risk with age. These changes reflect recommendations made by an expert panel convened by CDC in 2009–2010 to review its methodology for estimating SAM in the United States (SciMetrika 2010) and advise on whether updates were needed. The expert panel noted that the SAMMEC methodology had been evaluated repeatedly and was found to provide a credible indication of the mortality burden of the disease consequences of smoking. Thus, the panel did not find a need for substantive changes to the PAF methodology (SciMetrika 2010). However, the panel recommended that RRs be updated and calculated separately, to the extent possible, for individual racial/ethnic groups and older age strata. In addition, the panel noted that as sufficient evidence emerges to conclude that causal associations exist between smoking and new health conditions, data for these additional diseases should be included in future SAM estimates. The specific changes made are described below.

Age Stratification

As discussed previously, the effect of age on SAM is a particularly important consideration because death rates increase with age and the association between cardiovascular death and current smoking decreases with age. Consequently, CDC expanded the number of age strata used in SAMMEC calculations from two (35–64 years of age and 65 years of age and older) to four (35–54 years of age, 55–64 years of age, 65–74 years of age, and 75 years of age and older) and applied them to all disease categories.

Adult RR Estimates

Subsequent to the previous SAMMEC estimates, Thun and colleagues (2013) pooled data from five large contemporary cohort studies: the National Institutes of Health-AARP Diet and Health Study, the American Cancer Society's CPS-II Nutrition Cohort (a subset of the original CPS-II mortality study), the Women's Health Initiative (WHI), the Nurses' Health Study, and the Health Professionals Follow-Up Study. Each had updated smoking and endpoint information for participants 55 years of age and

older during 2000–2010. Cox proportional hazards regression was used to calculate RRs of current smokers and former smokers, with the latter group limited to those who had quit smoking at least 2 years before the start of the follow-up period. Models were adjusted for age or age plus cohort, race, and educational level. The multivariable-adjusted RR of death was similar for men and women: about 2.8 for all causes in current smokers and 1.5 for all causes in former smokers. RRs for men and women were also very similar for chronic obstructive pulmonary disease (COPD), CHD, and stroke.

Thun and colleagues (2013) compared death rates and RRs in the pooled contemporary cohort with those from previous cohorts, CPS-I (1959–1965) and CPS-II (1982–1988), when both smoking prevalence and the background death rate among never smokers were higher. Among men, RRs for current smokers increased from the 1960s to the 1980s and then plateaued, with the exception of a continuing increase in smoking-related mortality from COPD. Among women, RRs for current smokers increased across all the time periods so that they are now equal to those of men. Death rates by age and gender for lung cancer and COPD increased markedly over time from each of these cohorts to the next (Figure 12.2). Generalizability of the pooled cohort samples to the full U.S. population is a potential concern. The study populations included higher percentages of Whites and highly educated persons than are found in the general population. However, estimated RRs for participants with only a high school education or less were generally similar to, or larger than, the estimates for those with a college education; thus, the overall RRs calculated by Thun and colleagues (2013) are likely to lead to some underestimation of SAM.

Another analysis of data from a large, contemporary cohort (Jha et al. 2013) similarly found that adjusting for race/ethnicity, educational level, alcohol consumption, and adiposity had little effect on risk estimates. Jha and colleagues (2013) matched data from the National Death Index (1986–2006) to records of participants, 25 years of age and older, in the NHIS from 1997–2004. In this study, the hazard ratio for death from any cause for current smokers versus nonsmokers was 3.0 for women and 2.8 for men. The lifespan of current smokers was 11–12 years shorter than that of nonsmokers.

The analysis by Jha and colleagues (2013) also has limitations. In particular, NHIS participants are interviewed once only; thus, smoking histories are not updated in the interval between initial interview and death and

Figure 12.2   Changes over time in annual death rates from lung cancer and chronic obstructive pulmonary disease (COPD)

A. Lung cancer
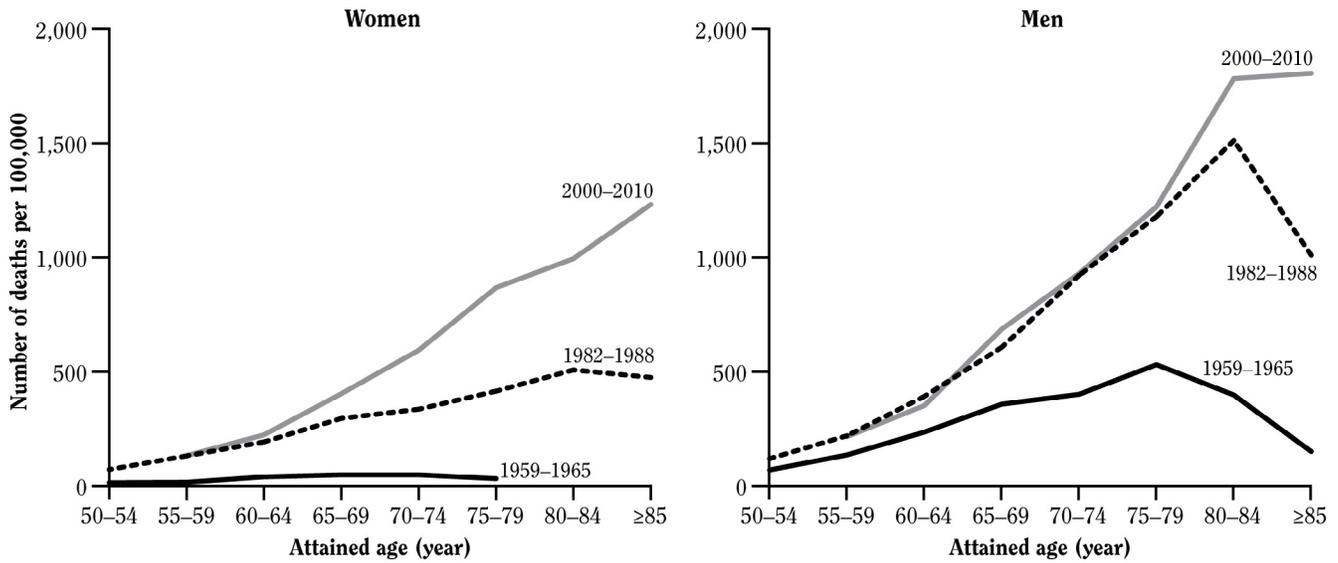
B. COPD
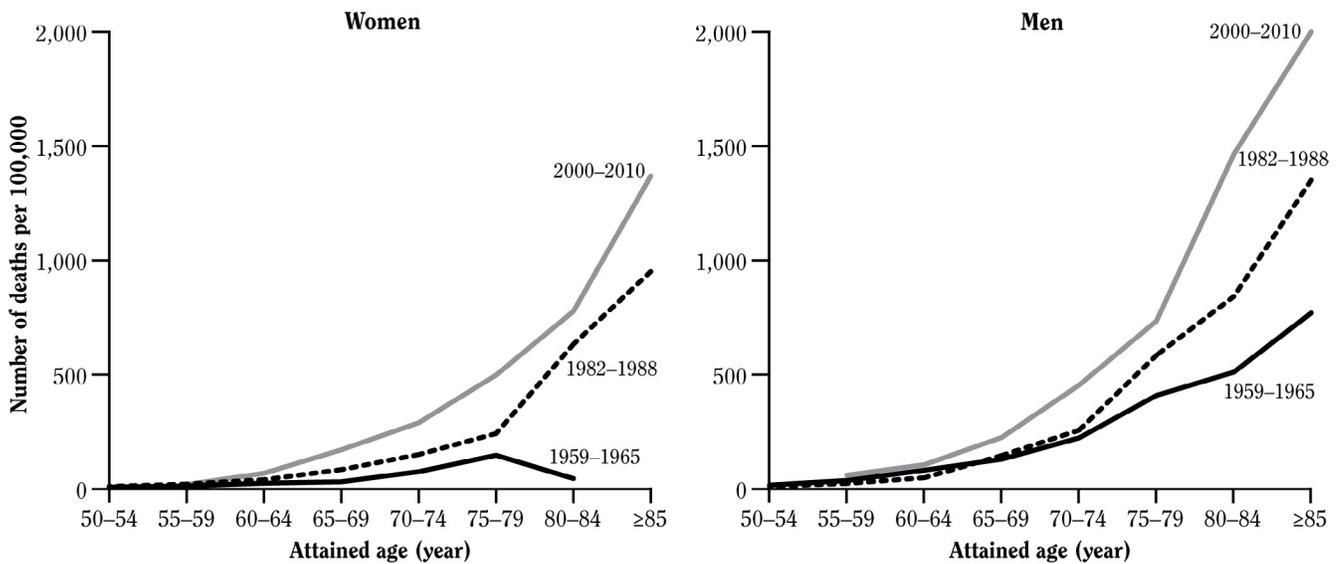
Source: Thun et al. 2013. Reprinted with permission from Massachusetts Medical Society, © 2013.
Note: Data were obtained from the first Cancer Prevention Study for the period 1959–1965, from the second Cancer Prevention Study for the period 1982–1988, and from the contemporary cohort studies for the period 2000–2010.

transitions from current smoker status to former smoker status are not captured. To avoid using outdated smoking history data, which would inevitably misclassify some former smokers as current smokers at the time of death, Jha and colleagues (2013) limited their analysis to NHIS participants from 1997–2004.

Comparable results on changes in RRs over time were found in a large cohort study carried out in the United Kingdom. Pirie and colleagues (2013) used national mortality records through 2010 to assess mortality among a cohort of women who were 52 years of age or older when recruited in 1996–2001. Participants were resurveyed 3 years after recruitment. Those who were current smokers at baseline had a 2.76 mortality rate ratio compared to nonsmokers. Those who remained current smokers at the 3-year resurvey had a mortality rate ratio of 2.97, translating to a lifespan reduction of 11 years.

These studies by Thun and colleagues (2013), Jha and colleagues (2013), and Pirie and colleagues (2013) provide compelling evidence that RRs for smoking have increased over the past decades, particularly for women. Therefore, in 2013, CDC began using RRs derived from a contemporary pooled cohort of adults 55 years of age and older in SAMMEC. This cohort is based on the one created by Thun and colleagues (2013). The original published report from this pooled cohort (Thun et al. 2013) did not include RRs for the age-specific categories needed for SAMMEC calculations (age groups 55–64, 65–74, and ≥75) or for all smoking-related causes of death now included in SAMMEC. Therefore, the investigators responsible for the datasets represented in the pooled cohort provided the RRs shown in Table 12.3 to CDC's Office on Smoking and Health. These estimates include additional data not included in the original report (Thun et al. 2013) from 2 years of follow-up (2009–2010) that became available from the CPS-II Nutrition Cohort after the original publication, as well as updated outcome information from the WHI.

Also, in women 55 years and older, the RRs for "other" vascular conditions (atherosclerosis, aortic aneurysm, other vascular conditions) were modified to exclude data from the National Heart, Lung, and Blood Institute's (NHLBI's) WHI because WHI does not ascertain these conditions. In addition, RRs for the category of smoking-attributable cancers other than lung cancer (a category which includes acute myeloid leukemia, but not other types of leukemia) were calculated excluding all leukemias from WHI because WHI did not distinguish acute myeloid leukemia from other forms of leukemia.

Comparable estimates are not available for adults younger than 55 years of age. The NHIS study by Jha and colleagues (2013) included younger adults and used a nationally representative sample. However, in constraining the dataset to only the most recent years, the study had only a limited dataset that was not sufficiently large to provide stable disease-specific RR estimates for those younger than 55 years of age. Therefore, CDC elected to continue using CPS-II as the RR source for younger adults. Since the RR estimates for populations 55 years of age and older have remained high or increased in recent years (Thun et al. 2013), it is assumed that the CPS-II RR estimates for younger adults are conservative.

Additional Adult Disease Outcomes

The evidence is now sufficient to infer a causal relationship between smoking and five additional diseases in adults: age-related macular degeneration, diabetes mellitus, tuberculosis, liver cancer, and colorectal cancer (see Chapters 6, "Cancer"; 7, "Respiratory Disease"; and 10, "Other Specific Outcomes"). Accordingly, mortality RRs were calculated for the latter four conditions using the modified pooled contemporary cohort data. Because the number of smoking-attributable deaths from these conditions is relatively low compared to conditions such as lung cancer, particularly at younger ages, RRs were calculated for these conditions combined with others (i.e., diabetes mellitus was combined with cardiovascular diseases for the youngest age groups, tuberculosis was combined with other noncancer lung diseases, and liver and colorectal cancer were combined with other cancers). The combined RRs are more stable than individual RR estimates for these conditions. Although smoking is now thought to be related to decreased immune function and survival from cancer, RRs that are needed to estimate population-attributable burden of this effect are unavailable at present.

Infant RRs

In the past, SAMMEC calculated smoking-attributable infant deaths for short gestation/low birth weight, respiratory distress syndrome, other respiratory conditions, and sudden infant death syndrome (SIDS). The four RRs were based on pooled meta-analyses by Gavin and colleagues (2001) that summarize literature from the 1980s and early 1990s. More recently, Dietz and colleagues (2010) estimated associations for prenatal smoking and preterm deliveries, term low birth weight (<2,500 grams) deliveries, SIDS, and preterm-related deaths among 3,352,756 singleton, live births using the U.S. Linked Birth/Infant Death Data Set, 2002 Birth Cohort. This analysis used a newer method of defining preterm-related deaths that had been developed by Callaghan and colleagues (2006)— an expanded definition of death from preterm delivery,

Table 12.3   Relative risks by smoking status and age group, adults 35 years of age and older, United States

	Current smokers (years of age)				Former smokers (years of age)			
	35–54[a]	55–64[b]	65–74[b]	≥75[b]	35–54[a]	55–64[b]	65–74[b]	≥75[b]
Males								
Lung cancer	14.33	19.03	28.29	22.51	4.40	4.57	7.79	6.46
Other cancers[c]	1.74	1.86	2.35	2.18	1.36	1.31	1.49	1.46
Coronary heart disease	3.88	2.99	2.76	1.98	1.83	1.52	1.58	1.32
Other heart disease[d]			2.22	1.66			1.32	1.15
Cerebrovascular disease			2.17	1.48			1.23	1.12
Other vascular diseases[e]			7.25	4.93			2.20	1.72
Diabetes mellitus			1.50	1.00			1.53	1.06
Other cardiovascular diseases[f]	2.40	2.51			1.07	1.51		
Influenza, pneumonia, tuberculosis			2.58	1.62			1.62	1.42
Chronic obstructive pulmonary disease[g]			29.69	23.01			8.13	6.55
Influenza, pneumonia, tuberculosis, chronic obstructive pulmonary disease[h]	4.47	15.17			2.22	3.98		
All causes	2.55	2.97	3.02	2.40	1.33	1.47	1.57	1.41
Females								
Lung cancer	13.30	18.95	23.65	23.08	2.64	5.00	6.80	6.38
Other cancers[c]	1.28	2.08	2.06	1.93	1.24	1.28	1.26	1.27
Coronary heart disease	4.98	3.25	3.29	2.25	2.23	1.21	1.56	1.42
Other heart disease			1.85	1.75			1.29	1.32
Cerebrovascular disease			2.27	1.70			1.24	1.10
Other vascular diseases*[e]			6.81	5.77			2.26	2.02
Diabetes mellitus			1.54	1.10			1.29	1.06
Other cardiovascular diseases[f]	2.44	1.98			1.00	1.10		
Influenza, pneumonia, tuberculosis			1.75	2.06			1.28	1.21
Chronic obstructive pulmonary disease[g]			38.89	20.96			15.72	7.06
Influenza, pneumonia, tuberculosis, chronic obstructive pulmonary disease[h]	6.43	9.00			1.85	4.84		
All causes	1.79	2.63	2.87	2.47	1.22	1.34	1.53	1.43

Source: Analyses of Cancer Prevention Study II (CPS-II) and updated analyses of the pooled contemporary cohort population described in Thun et al. 2013 provided to the Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.

[a]Relative risks for 35–54 years of age, obtained from Cancer Prevention Study.

[b]Relative risks for 54–65 years of age, 65–74 years of age, and 75 years of age and older, obtained from merged contemporary cohorts (Thun et al 2012). Relative risks for women 55 years of age and older in diseases marked with * do not include data from the NHLBI Women's Health Initiative.

[c]Other cancers consist of cancers of the lip, pharynx and oral cavity, esophagus, stomach, pancreas, larynx, cervix uteri (women), kidney and renal pelvis, bladder, liver, colon and rectum, and acute myeloid leukemia.

[d]Other heart disease comprised of rheumatic heart disease, pulmonary heart disease, and other forms of heart disease.

[e]Other vascular diseases are comprised of atherosclerosis, aortic aneurysm, and other arterial diseases.

[f]For 35–54 years of age and ages 55–64 years of age, other cardiovascular diseases are comprised of other heart disease, cerebrovascular disease, other vascular diseases, and diabetes mellitus, analyzed and reported as category. A single relative risk based on combined conditions used to compute smoking-attributable mortality. Relative risk based on combined conditions used to compute smoking-attributable mortality in these age strata.

[g]Chronic obstructive pulmonary disease comprised of bronchitis, emphysema, and chronic airways obstruction.

[h]For 35–54 years of age and 55–64 years of age, influenza, pneumonia, tuberculosis, and chronic obstructive pulmonary disease analyzed and reported as 1 category. A single relative risk based on combined conditions was used to compute smoking attributable mortality.

as opposed to using only the ICD-10 codes for disorders related to short gestation and low birth weight. This newer construct includes the codes for premature rupture of membranes, placenta previa, and placental abruption and is now used by CDC to calculate national preterm-related death rates. In addition, the analysis by Dietz and colleagues (2010) restricts infant deaths to those for which prenatal smoking has an established causal effect; the 2004 Surgeon General's report found that prenatal smoking is causally associated with SIDS, premature rupture of membranes, placenta previa, placental abruption, preterm delivery, and fetal growth restriction/low birth weight (USDHHS 2004).

Using the findings of Dietz and colleagues (2010), the new RR for SIDS is estimated at 2.7, which is somewhat higher than the 2.29 estimated by Gavin and colleagues (2001). The new RR estimate for preterm-related deaths is 1.5 (Dietz et al. 2010). This estimate replaces the former RRs for short gestation/low birth weight (1.83), respiratory distress syndrome (1.30), and other perinatal respiratory conditions (1.41).

Deaths Attributable to Exposure to Secondhand Smoke

CDC's SAM totals include estimates of deaths from lung cancer and coronary heart disease deaths due to exposure to secondhand smoke (CDC 2002, 2005, 2008). For lung cancer, calculations have been based on a method developed by the U.S. Environmental Protection Agency ([USEPA] 1992) and used estimates of the RR published by Fontham and colleagues (1994) and estimates of prevalence of nonsmokers' exposure to secondhand smoke derived from unpublished data provided by CDC's National Center for Health Statistics. Estimates were developed for California and then extended to the U.S. population, since death rates for lung cancer in California in the late 1980s were comparable in other states and California represented 12% of the U.S. population (Pierce et al. 2010). For heart disease, calculations were based on the PAF approach, using RRs that ranged from 1.2–1.68 (California Environmental Protection Agency [Cal/EPA] 1997; Ciruzzi et al. 1998), and estimates of exposure to secondhand smoke in nonsmokers came from NHANES III (1988–1994) (Pirkle et al. 1996).

This approach has now been modified based on the work of Max and colleagues (2012). In their calculations for the United States for 2006, adult exposure to secondhand smoke was determined from biomarker (serum cotinine) data from the 2003–2006 NHANES. An RR estimate for CHD from exposure to secondhand smoke of 1.32 was used based on the studies by Whincup and colleagues (2004). For lung cancer, Max and colleagues (2012) used the lower bound of the range of RR estimates for lung cancer of 1.29 from Cal/EPA (2005). These methods have now been incorporated into SAMMEC in 2013.

Smoking-Attributable Mortality in Adults and Infants, United States, 2005–2009

This section provides the SAM estimates for the United States for the period 2005–2009. The general SAM-MEC methodology has been modified as described above. The prevalence data for males and females 35 years of age and older came from NHIS for 1965–2011 (Table 12.2).

Table 12.4 provides average annual SAM for the United States for 2005–2009. The results indicate that cigarette smoking and exposure to tobacco smoke led to at least 480,000 premature deaths annually in the United States. Among adults 35 years of age and older, 163,700 smoking-attributable deaths were caused by cancer, 160,600 by cardiovascular and metabolic diseases, and 113,100 by pulmonary diseases (see Tables 12.4 and 12.5 for detailed results). Smoking during pregnancy resulted in an estimated 1,015 infant deaths annually during 2005–2009. Based on previously published estimates (Max et al. 2012), an estimated 7,330 (4.63%) lung cancer and 33,950 (8.23%) CHD deaths annually were attributable to exposure to secondhand smoke. The average annual SAM estimates also include 620 deaths from smoking-attributable residential fires based on data from the National Fire Protection Association (NFPA) and National Fire Incident Reporting System (Figure 12.3) (Hall 2012).

Smoking caused approximately 254,100 deaths in males (Table 12.5) and 183,300 deaths in females (Table 12.6), for a total of 437,400 deaths in the United States for each year from 2005–2009 from the new list of smoking-related diseases (i.e., the 19 diseases formerly used in the SAMMEC and the five diseases newly linked to smoking in

Table 12.4   Annual deaths and estimates of smoking-attributable mortality (SAM) for adults 35 years of age and older, total and by gender, United States, 2005–2009

Disease	Males Deaths	SAM	Attributable fraction (%)	Deaths	Females SAM	Attributable fraction (%)	Deaths	Total SAM	Attributable fraction (%)
Lung cancer	88,730	74,300	83.74	69,800	56,359	80.74	158,530	130,659	82.42
Other cancers[a]	102,940	26,000	25.26	75,540	10,000	13.24	178,480	36,000	20.17
Total—Cancers	**191,670**	**100,300**	**52.33**	**145,340**	**63,400**	**43.62**	**337,010**	**163,700**	**48.57**
Coronary heart disease	218,870	61,800	28.24	193,720	37,500	19.36	412,590	99,300	24.07
Other heart disease[b]	75,670	13,400	17.71	96,200	12,100	12.58	171,870	25,500	14.84
Cerebrovascular disease[c]	53,610	8,200	15.30	81,300	7,100	8.73	134,920	15,300	11.34
Other vascular disease[d]	14,480	6,000	41.43	15,510	5,500	35.47	29,990	11,500	38.35
Diabetes mellitus	35,200	6,200	17.61	35,600	2,800	7.86	70,810	9,000	12.71
Total—Cardiovascular and metabolic diseases	**397,840**	**95,600**	**24.03**	**422,330**	**65,000**	**15.39**	**820,170**	**160,600**	**19.58**
Pneumonia, influenza, tuberculosis	25,300	7,800	30.83	30,290	4,700	15.52	55,590	12,500	22.49
COPD	61,430	50,400	82.04	66,300	50,200	75.71	127,740	100,600	78.76
Total—Pulmonary diseases[e]	**86,730**	**58,200**	**67.10**	**96,590**	**54,900**	**56.84**	**183,320**	**113,100**	**61.70**
Total—Cancers, cardiovascular and metabolic diseases, pulmonary diseases	**676,240**	**254,100**	**37.58**	**664,260**	**183,300**	**27.59**	**1,340,500**	**437,400**	**32.63**
Prenatal conditions[f]	5,970	346	5.80	4,620	267	5.78	10,590	613	5.79
Sudden infant death syndrome[g]	1,370	236	17.26	950	164	17.26	2,320	400	17.26
Perinatal conditions	**7,340**	**582**	**7.93**	**5,570**	**431**	**7.74**	**12,900**	**1,013**	**7.85**
Residential fires		**336**			**284**			**620**	**-**
Secondhand smoke									
Lung Cancer	88,730	4,370	4.93	69,800	2,960	4.24	158,530	7,330	4.63
Coronary heart disease	218,870	19,150	8.75	193,720	14,800	7.64	412,590	33,950	8.23
Total—Secondhand smoke	**307,600**	**23,530**	**7.65**	**263,520**	**17,760**	**6.74**	**571,120**	**41,280**	**7.23**
TOTAL Attributable deaths		**278,540**			**201,770**			**480,320**	

Source: Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, unpublished data.

Note: **COPD** = chronic obstructive pulmonary disease.

[a]Other cancers consist of cancers of the lip, pharynx and oral cavity, esophagus, stomach, pancreas, larynx, cervix uteri (women), kidney and renal pelvis, bladder, liver, colon and rectum, and acute myeloid leukemia.

[b]Other heart disease comprised of rheumatic heart disease, pulmonary heart disease, and other forms of heart disease.

[c]Other.

[d]Other vascular diseases are comprised of atherosclerosis, aortic aneurysm, and other arterial diseases.

[e]Pulmonary diseases consists of pneumonia, influenza, emphysema, bronchitis, and chronic airways obstruction.

[f]Prenatal conditions comprised of ICD-10 codes: K550, P000, P010, P011, P015, P020, P021, P027, P070–P073, P102, P220–P229, P250–P279, P280, P281, P360–P369, P520–P523, and P77 (Dietz et al. 2010).

[g]ICD-10 code R95.

Table 12.5 Average annual smoking-attributable mortality (SAM) for males 35 years of age and older, total and by age group, United States, 2005–2009

| Disease | 35–64 years of age | | | | | | 65 years of age and older | | | | | | ≥35 years of age | |
| | 35–54 | | 55–64 | | Total[a] | | 65–74 | | ≥75 | | Total[a] | | Total[a] | |
	Deaths	SAM	Deaths	SAM	Deaths	SAM	Deaths	SAM	Deaths	SAM	Deaths	SAM	Deaths	SAM
Lung cancer	8,020	6,500	18,440	15,500	26,470	21,900	27,740	24,300	34,530	28,100	62,260	52,400	88,730	74,300
Other cancers[b]	13,370	2,800	22,540	5,400	35,900	8,200	26,380	7,900	40,660	10,300	67,040	18,200	102,940	26,000
Total—Cancers	**21,390**	**9,300**	**40,980**	**20,900**	**62,370**	**30,100**	**54,120**	**32,200**	**75,190**	**38,400**	**129,310**	**70,600**	**191,670**	**100,300**
Coronary heart disease	23,250	11,100	33,550	12,900	56,800	24,000	42,100	14,600	120,010	23,200	162,080	37,800	218,870	61,800
Other cardiovascular disease[c]	18,900	5,100	23,230	8,000	42,130	13,100								
Other heart disease[d]							12,310	3,000	45,950	5,000	58,260	8,100	75,670	13,400
Cerebrovascular disease[d]							9,390	2,000	33,800	3,000	43,190	5,000	53,610	8,200
Other vascular disease[d]							2,930	1,700	8,680	3,400	11,610	5,100	14,480	6,000
Diabetes mellitus							8,350	2,100	15,420	500	23,780	2,600	35,200	6,200
Total—Cardiovascular and metabolic diseases	**42,150**	**16,200**	**56,780**	**20,900**	**98,930**	**37,100**	**75,050**	**23,400**	**223,860**	**35,100**	**298,910**	**58,600**	**397,840**	**95,600**
Pneumonia, influenza, tuberculosis, COPD[e]	3,970	2,200	8,780	7,100	12,750	9,200								
Pneumonia, influenza, tuberculosis[f]							3,460	1,200	17,930	3,900	21,380	5,100	25,300	7,800
COPD[g]							15,040	13,300	37,560	30,600	52,600	43,900	61,430	50,400
Total—Pulmonary diseases	**3,970**	**2,200**	**8,780**	**7,100**	**12,750**	**9,200**	**18,490**	**14,500**	**55,490**	**34,500**	**73,980**	**49,000**	**86,730**	**58,200**
total—cancers, cardiovascular and metabolic diseases, pulmonary diseases	**67,500**	**27,700**	**106,540**	**48,900**	**174,050**	**76,400**	**147,660**	**70,100**	**354,540**	**108,000**	**502,190**	**178,200**	**676,240**	**254,100**
All causes	**164,750**	**52,300**	**174,350**	**64,400**	**339,100**	**116,700**	**222,100**	**79,400**	**573,910**	**134,600**	**796,010**	**214,100**	**1,135,110**	**330,800**

Source: Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, unpublished data.

Note: Estimation of SAM based on relative risks from updated analyses of the pooled contemporary cohorts described in Thun et al. 2013. **COPD** = chronic obstructive pulmonary disease; **CVD** = cardiovascular disease.

[a]Row and column totals may not add up exactly due to rounding.

[b]Cancers of the lip, pharynx and oral cavity, esophagus, stomach, pancreas, larynx, cervix uteri, kidney and renal pelvis, bladder, liver, colon and rectum, and acute myeloid leukemia were combined into 1 disease category for both analysis and presentation. A single relative risk for the combined conditions was used to compute SAM.

[c]Other cardiovascular disease consists of other heart disease, CVD, atherosclerosis, aortic aneurysm, other arterial diseases, and diabetes mellitus. For 35–54 and 55–64 years of age, the relative risk for the combined conditions was used to compute SAM. For 65–74 and ≥75 years of age, separate relative risks for other heart disease, CVD, and other vascular diseases were used to compute SAM.

[d]For 65–74 and ≥75 years of age, other heart disease, CVD, other vascular disease, and diabetes mellitus also presented as separate conditions. Other vascular disease consists of atherosclerosis, aortic aneurysm, and other arterial diseases. Separate relative risks used to compute SAM for other heart disease, CVD, and diabetes mellitus. For other vascular disease, separate relative risks used to compute SAM for each condition before summing them for presentation.

[e]For 35–54 and 55–64 years, pneumonia, influenza, bronchitis, tuberculosis, and COPD were combined into 1 disease category for analysis and presentation. COPD consists of bronchitis, emphysema, and chronic airways obstruction. A single relative risk was used to compute SAM for the entire category.

[f]For 65–74 and ≥75 years of age, pneumonia/influenza/tuberculosis and COPD analyzed and presented as separate conditions. COPD consists of bronchitis, emphysema, and chronic airways obstruction. Separate relative risks were used to compute SAM for pneumonia/influenza/tuberculosis and for COPD.

[g]For ages 65–74 years and 75 years and older, pneumonia/influenza and COPD analyzed and presented as separate conditions. COPD consists of bronchitis, emphysema, and chronic airways obstruction. Separate relative risks were used to compute SAM for pneumonia/influenza and for COPD.

Figure 12.3 Trend in civilian deaths in smoking-material home fires, United States, 1980–2010
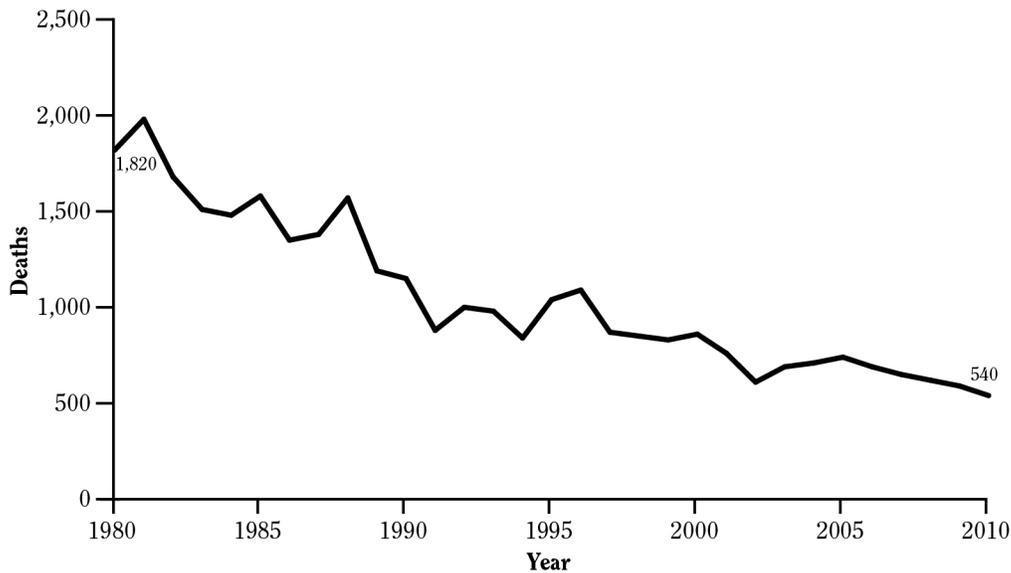
Source: Hall 2012. Reprinted with permission from NFPA's report, *"The Smoking-Material Fire Problem",* © 2013.
Note: NFPA = National Fire Protection Association.

this report). For men, 35 years of age and older, the counts of annual smoking-attributable deaths were 100,300 for cancers, 95,600 for cardiovascular and metabolic diseases, and 58,200 for pulmonary diseases (Table 12.5). For women, 35 years of age and older, the annual SAM was 63,400 for cancers, 65,000 for cardiovascular diseases, and 54,900 for pulmonary diseases (Table 12.6).

These results differ from those obtained for 2005–2009 using only CPS-II RRs for the 19 diseases included in the past (Table 12.7). Compared with CPS-II alone, the new RRs produce a higher lung cancer SAM estimate for women (53,400 vs. 48,200) and a lower lung cancer SAM estimate for men (74,300 vs. 77,200). SAM for other cancers is similar across the two methods for both men and women (36,000 with the new RRs vs. 36,900 for CPS-II alone for both genders combined). SAM for pulmonary diseases with the new RRs is also somewhat higher for both genders (113,100 vs. 108,100). The biggest difference is for cardiovascular diseases; SAM for both CHD and other cardiovascular disease SAMs are greatly increased with the new RRs. For men, cardiovascular and metabolic diseases SAM is estimated at 95,600 (vs. 70,300 with CPS-II RRs); for women, cardiovascular SAM is estimated at 65,000 (vs. 41,300 with CPS-II RRs). In total, for cancers, cardiovascular diseases, and pulmonary diseases with both genders combined, the overall annual average SAM estimate for

2005–2009 is 437,400, about 15% higher than would have been calculated using RRs from only CPS-II (382,000).

In previous infant SAMMEC calculations, the prevalence of prenatal smoking has been obtained from birth certificates. However, the 1989 version of the birth certificate and the 2003 revised birth certificate differ with respect to how smoking is ascertained. State uptake of the 2003 revised birth certificate has been gradual and it is expected that not all states will have implemented the revised birth certificate until 2014. Thus, birth certificate-based smoking data are not comparable across all states during the last decade. Therefore, for this report, the prevalence of prenatal smoking for 2005–2009 was calculated based on data from the Pregnancy Risk Assessment Monitoring System (PRAMS). PRAMS uses a self-administered questionnaire that is completed by women 2–6 months after delivering a live-born infant. Data from 34 states participating in PRAMS (Alaska, Arkansas, Colorado, Delaware, Florida, Georgia, Hawaii, Illinois, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Nebraska, New Jersey, New Mexico, New York, North Carolina, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Utah, Vermont, Washington, West Virginia, Wisconsin, and Wyoming) and New York City were included if the overall weighted response rate for a given state and year was at least 70%

Table 12.6 Average annual smoking attributable mortality (SAM) for females 35 years of age and older, total and by age group, United States, 2005–2009

Disease	35–64 years of age						65 years of age and older						≥35 years of age	
	35–54		55–64		Total[a]		65–74		≥75		Total[a]		Total[a]	
	Deaths	SAM	Deaths	SAM	Deaths	SAM	Deaths	SAM	Deaths	SAM	Deaths	SAM	Deaths	SAM
Lung cancer	6,390	4,800	12,690	10,100	19,080	14,900	20,510	16,700	30,210	21,800	50,720	38,500	69,800	53,400
Other cancers[b]	8,560	600	11,470	2,300	20,030	2,900	15,980	2,500	39,530	4,400	55,510	7,000	75,540	10,000
Total—Cancers	**14,950**	**5,400**	**24,160**	**12,400**	**39,110**	**17,800**	**36,490**	**19,200**	**69,740**	**26,200**	**106,230**	**45,500**	**145,340**	**63,400**
Coronary heart disease	7,480	3,900	12,920	3,800	20,400	7,600	23,090	7,000	150,230	22,900	173,320	29,900	193,720	37,500
Other cardiovascular disease[c]	12,320	2,900	15,800	2,400	28,120	5,300								
Other heart disease[d]							9,950	1,600	75,440	8,400	85,390	10,000	96,200	12,100
Cerebrovascular disease[d]							8,720	1,600	64,210	3,900	72,930	5,400	81,300	7,100
Other vascular disease[d]							1,900	1,000	12,270	4,200	14,160	5,200	15,510	5,500
Diabetes mellitus							7,020	900	20,990	400	28,010	1,400	35,600	2,800
Total—Cardiovascular and metabolic diseases	**19,800**	**6,800**	**28,720**	**6,200**	**48,520**	**12,900**	**50,680**	**12,100**	**323,130**	**39,800**	**373,810**	**51,900**	**422,330**	**65,000**
Pneumonia, influenza, tuberculosis, COPD[e]	3,320	1,900	7,460	5,200	10,790	7,100								
Pneumonia, influenza, tuberculosis[f]							2,780	400	24,690	2,500	27,470	2,900	30,290	4,700
COPD[f]							14,400	12,900	43,930	32,000	58,330	44,900	66,300	50,200
Total—Pulmonary diseases	**3,320**	**1,900**	**7,460**	**5,200**	**10,790**	**7,100**	**17,190**	**13,300**	**68,620**	**34,500**	**85,800**	**47,800**	**96,590**	**54,900**
Total—Cancers, cardiovascular and metabolic diseases, pulmonary diseases	**38,070**	**14,100**	**60,340**	**23,800**	**98,420**	**37,800**	**104,360**	**44,600**	**461,490**	**100,500**	**565,850**	**145,200**	**664,260**	**183,300**
All causes	**100,410**	**17,300**	**114,312**	**29,500**	**214,730**	**46,800**	**173,960**	**47,600**	**803,030**	**130,600**	**976,980**	**178,200**	**1,191,710**	**225,000**

Source: Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, unpublished data.
Note: Estimation of SAM based on relative risks from updated analyses of the pooled contemporary cohort described in Thun et al. 2013. **CVD** = cardiovascular disease; **COPD** = chronic obstructive pulmonary disease.
[a]Row and column totals may not add up exactly due to rounding.
[b]Cancers of the lip, pharynx and oral cavity, esophagus, stomach, pancreas, larynx, cervix uteri, kidney and renal pelvis, bladder, liver, colon and rectum, and acute myeloid leukemia were combined into 1 disease category for both analysis and presentation. A single relative risk for the combined conditions was used to compute SAM.
[c]Other cardiovascular disease consists of other heart disease, CVD, atherosclerosis, aortic aneurysm, other arterial diseases, and diabetes mellitus. For 35–54 and 55–64 years of age, the relative risk for the combined conditions was used to compute SAM. For 65–74 and ≥75 years of age, separate relative risks for other heart disease, CVD, and other vascular diseases were used to compute SAM.
[d]For 65–74 and ≥75 years of age, other heart disease, CVD, other vascular disease, and diabetes mellitus also presented as separate conditions. Other vascular disease consists of atherosclerosis, aortic aneurysm, and other arterial diseases. Separate relative risks used to compute SAM for other heart disease, CVD and diabetes mellitus. For other vascular disease, separate relative risks used to compute SAM for each condition before summing them for presentation.
[e]For 35–54 and 55–64 years of age, pneumonia, influenza, bronchitis, tuberculosis and COPD were combined into 1 disease category for analysis and presentation. COPD consists of bronchitis, emphysema, and chronic airways obstruction. A single relative risk was used to compute SAM for the entire category.
[f]For 65–74 and ≥75 years of age, pneumonia/influenza/tuberculosis and COPD analyzed and presented as separate conditions. COPD consists of bronchitis, emphysema, and chronic airways obstruction. Separate relative risks were used to compute SAM for pneumonia/influenza/tuberculosis and for COPD.

Table 12.7 Average annual smoking-attributable mortality (SAM) for adults 35 years of age and older, total and by gender, United States, 2005-2009: Cancer Prevention Study II (CPS-II) relative risks (RR's) vs. CPS-II/contemporary cohorts RR's

Disease	Males		Females		Total	
	CPS-II[b]	CPS-II/ contemporary cohorts[c]	CPS-II[b]	CPS-II/ contemporary cohorts[c]	CPS-II[b]	CPS-II/ contemporary cohorts[c]
Lung cancer	77,200	74,300	48,200	53,400	125,300	127,700
Other cancers[d]	27,300	26,000	9,700	10,000	36,900	36,000
Total— Cancers	**104,400**	**100,300**	**57,800**	**63,400**	**162,300**	**163,700**
Coronary heart disease	44,300	61,800	23,500	37,500	67,800	99,300
Other cardiovascular disease[e]	26,000	33,800	17,800	27,500	43,800	61,300
Total— Cardiovascular and metabolic diseases	**70,300**	**95,600**	**41,300**	**65,000**	**111,600**	**160,600**
Total— Pulmonary diseases[f]	**55,200**	**58,200**	**52,800**	**54,900**	**108,100**	**113,100**
Total— Cancers, cardiovascular and metabolic diseases, pulmonary diseases	**230,000**	**254,100**	**152,000**	**183,300**	**382,000**	**437,400**
All causes	**NA[g]**	**330,800**	**NA[g]**	**225,000**	**NA[g]**	**555,800**

Source: Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, unpublished data.

Note: **CVD** = cardiovascular disease; **NA** = not available.

[a]Row and column totals may not add up exactly due to rounding.

[b]SAM calculated using RRs from CPS-II; gender- and age-specific (35–64, ≥65 years of age) RRs and smoking status (current, former) prevalence used for estimates. [c]SAM calculated using RRs from CPS-II for 35–54 years of age and RRs from contemporary cohorts (Thun et al. 2013) for ≥55 years of age; gender- and age-specific (35–54, 55–64, 65–74, ≥75 years of age) RRs and smoking status (current, former) used for estimates.

[d]Other cancers comprised of cancers of the lip, pharynx and oral cavity, esophagus, stomach, pancreas, larynx, cervix uteri, kidney and renal pelvis, bladder, and acute myeloid leukemia. Analysis for CPS-II and contemporary cohorts also includes cancers of liver and of colon and rectum.

[e]Other cardiovascular disease comprised of other heart disease, CVD, atherosclerosis, aortic aneurysm, and other arterial diseases. Analysis for CPS-II and contemporary cohorts also includes diabetes mellitus.

[f]Pulmonary diseases consists of pneumonia, influenza, emphysema, bronchitis, and chronic airways obstruction. Analysis for CPS-II and contemporary cohorts also includes tuberculosis.

[g]All-cause SAM not computed.

Table 12.8   Average annual perinatal deaths attributable to smoking, United States, 2005–2009

Disease	Males		Females		Total	
	Deaths	SAM	Deaths	SAM	Deaths	SAM
Prenatal conditions[a]	5,970	350	4,620	270	10,590	610
Sudden infant death syndrome[b]	1,370	240	950	160	2,320	400
Total	7,340	580	5,570	430	12,900	1,020

Source: Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, unpublished data.
Note: **ICD** = International Classification of Diseases; **SAM** = smoking-attributable mortality. Column may not sum exactly due to rounding.
[a]Prenatal conditions comprised of ICD-10 codes: K550, P000, P010, P011, P015, P020, P021, P027, P070–P073, P102, P220–P229, P250–P279, P280, P281, P360–P369, P520–P523, and P77 (Dietz et al. 2010).
[b]ICD-10 code R95.

for data collected during 2005–2006 and at least 65% for data collected starting in 2007. These PRAMS states represented 70% of live births in the United States in 2009 (Martin et al. 2011). Data from these states were pooled to estimate the national prevalence of smoking during the last 3 months of pregnancy. The average prevalence of prenatal smoking during 2005–2009 was estimated at 12.3% for the 34 PRAMS states and New York City, and this estimate was used as an approximation for the national prevalence of prenatal smoking. Using this source of prevalence data and the new RRs described previously, maternal smoking was estimated to result in 1,015 infant deaths annually in 2005–2009, 582 in males and 431 in females (Table 12.8). Of these, 614 were attributed to prenatal conditions and 401 to SIDS, which is causally related to both maternal smoking during pregnancy and exposure to secondhand smoke as an infant (USDHHS 2006).

Based on the results of Max and colleagues (2012), an estimated 33,951 CHD deaths and 7,333 lung cancer deaths were due to exposure to secondhand smoke among adults, 20 years of age and older, in 2006. Table 12.9 shows the estimated deaths attributable to exposure to secondhand smoke among U.S. adults, 20 years of age and older, for 2006. Although Max and colleagues (2012) also calculated the number of infant deaths attributable to exposure to secondhand smoke, those estimates are not included here because the relevant health conditions are encompassed in the SAMMEC calculations for infants.

CDC's national smoking-attributable burden totals have also typically included an estimate of smoking-attributable deaths from residential fires (CDC 2005, 2008). NFPA publishes estimates of the average annual number of civilian deaths attributed to smoking-material fires in the United States. These estimates are based on information reported to U.S. municipal fire departments and on information obtained from surveys from the NFPA and National Fire Incidence Reporting System. The average annual number of deaths attributed to smoking-material fires in homes between 2006–2010 was 620 (336 in males, 284 in females) (Hall 2012). These fires also caused an estimated 1,570 civilian injuries and $663 million in direct property damage. As the prevalence of smoking has decreased and requirements for fire-resistant mattresses and upholstery and for "fire-safe" cigarettes have been implemented, the number of smoking-material related fires and deaths has decreased. From 1980–2010, smoking-material fires decreased by 73% and civilian deaths in home structure fires decreased by 70% (Figure 12.3) (Hall 2012).

The average annual SAM for the United States for 2010–2014 (Table 12.15) is at least 480,000 premature deaths caused by cigarette smoking and exposure to secondhand smoke; however, this estimate does not include deaths caused by use of cigars, pipes, other forms of combusted tobacco (e.g., roll-your-own cigarettes, hookah pipes, bidis; see Chapter 13 for description of these various products), nor smokeless tobacco products. As discussed in Chapter 13, the use of these products has increased in recent years; while the methodology for estimating the current population burden from the use of these tobacco products remains under discussion, the number of deaths caused by these products is expected to be in the thousands per year (Shapiro et al. 2000). Also, the estimated burden due to the new causal conclusion that exposure

Table 12.9 Deaths, years of productive life lost, and value of lost productivity from coronary heart disease and lung cancer attributable to exposure to secondhand smoke among nonsmoking adults, 20 years of age and older, United States, 2006

Cause of death	Deaths attributable to exposure to secondhand smoke	Years of productive life lost	Value of lost productivity ($ in thousands)
Coronary heart disease			
Males	19,150	256,980	3,520,660
Females	14,800	164,960	1,106,850
Total	33,950	421,940	4,627,520
Lung cancer			
Males	4,370	62,810	741,450
Females	2,960	47,830	311,690
Total	7,330	110,640	1,053,150
Totals, coronary heart disease and lung cancer			
Males	23,530	319,790	4,262,110
Females	17,760	212,790	1,418,540
Total	41,280	532,580	5,680,670

Source: Max et al. 2012. Reprinted with permission from The Sheridan Press, © 2012.
Note: Column totals may not sum exactly due to rounding.

to secondhand smoke causes stroke (see Chapter 8) has not been published. However, based upon the methodology used to compute the CHD deaths caused by exposure to secondhand smoke (Max et al. 2012), over 8,000 stroke deaths annually may be attributable to secondhand smoke.

Hence, the average annual total SAM for the United States due to smoking any combusted tobacco product or exposure to secondhand smoke is likely approaching 500,000 per year.

Projected Smoking-Related Deaths Among Youth, United States, 2012

Due to the slow decline in the prevalence of current smoking and initiation among youth and young adults (see Chapter 13, Table 13.19 and Figure 13.26), the annual burden of smoking-attributable mortality can be expected to remain at high levels for decades into the future. Although there is a trend of increasing success of quit attempts (see Chapter 13, Figure 13.17), the risks of premature death from smoking-related illness among former smokers and continuing smokers were higher in cohort study data from 2000–2012 than from earlier cohort studies (see Chapters 11 and 12).

In 1996, CDC projected the future impact of smoking on the health of children and teenagers based on the assumption that current tobacco use patterns would persist across the lives of this cohort of youth (CDC 1996). The future probability that a young adult smoker would die prematurely of a smoking-related cause was estimated to be 32% (CDC 1996). The methodology used to compute this probability of smoking-attributable mortality (PSAM) among young adult smokers is described in Appendix 12.2. The same CDC methodology was used to calculate updated estimates on the number of youth in the United States who will become future smokers and will die prematurely of a smoking-related illness (Tables 12.2.1 and 12.2.2). Because the prevalence of smoking in a birth cohort peaks during early adulthood (see Chapter 13),

the average prevalence of smoking among adults 18–30 years of age in each state during 2011–2012 was used to estimate the future prevalence of smoking during early adulthood for the 0–17-years-of-age birth cohort in 2012. The number of persons 0–17 years of age in each state in 2012 was multiplied by the state-specific prevalence of smoking among those 18–30 years of age to calculate the number of youth expected to become regular smokers in each state. Overall, the estimated number of future smokers from the 0–17-years-of-age birth cohort in 2012 in the United States was 17,371,000 (ranging from 22,300 in the District of Columbia to 1,557,800 in Texas) (Table 12.2.1).

Based on the application of PSAM (0.32) to the state-specific estimates of potential smokers, the overall number of potential future smoking-attributable deaths among youth 0–17 years of age during 2012 in the United States was 5,557,000 (ranging from 7,000 in the District of Columbia to 498,000 in Texas) (Table 12.2.1). Based on the estimated PSAM variance and the state-specific sam-

pling errors on estimates of smoking prevalence from the BRFSS, the estimated number of overall smoking-related deaths in the United States was predicted to vary on a statistical basis by less than or equal to 115,000 deaths. The CIs did not account for other sources of uncertainty, such as future changes in risk of dying from smoking or in quitting rate patterns.

These state-specific estimates were also used to calculate the proportion of youth, 0–17 years of age, who are projected to die prematurely from a smoking-related illness (Table 12.2.2). At the state level, estimates varied almost threefold, from 4.4% in Utah to 12.3% in West Virginia. Overall, 7.5% of youth from the 0–17-years-of-age birth cohort in 2012 in the United States are projected to die prematurely from a smoking-related illness if current rates of smoking and risk of disease associated with smoking persist. Therefore, an estimated 5.6 million youth currently aged 0–17 years of age will die prematurely of a smoking-related illness (Table 12.2.2).

Smoking-Attributable Morbidity Estimates

The most recent previous national estimate of smoking-attributable morbidity for the United States was published for the year 2000 (CDC 2003). For that prior report, the estimates of the prevalence of smoking-related medical conditions were obtained from NHANES III (1988–1994) for current, former, and never smokers to compute the SAFs of morbid conditions. Using the smoking prevalence estimates from BRFSS for the combined years of 1999–2001, it was estimated that 8.6 million (95% CI, 6.9–10.5 million) persons in the United States had 12.7 million (95% CI, 10.8–15.0 million) smoking-attributable serious medical conditions (CDC 2003). These estimates represent the numbers of people living with a smoking-caused disease at the time of the survey (Table 12.10). For diseases with a high mortality rate, such as lung cancer, the prevalence is low because there are few long-term survivors. For many of the conditions, the numbers of self-reported diseases were higher among former smokers than among current smokers. This pattern reflects the quitting of smoking by those who develop a smoking-caused disease, particularly later in life (USDHHS 2004).

In making these estimates, CDC noted that the self-reported data on the prevalence of the medical conditions probably substantially underestimate the true disease burden, particularly for COPD (CDC 2003). Additionally, it was noted that the scope of the medical conditions was limited to the diseases for which the NHANES had survey questions and those that previous Surgeon General's reports had concluded were caused by smoking. Finally, as reviewed in Chapter 11, smoking affects various additional acute and chronic conditions related to the quality of life, health status, and general morbidity.

In the present report, smoking and exposure to secondhand smoke have been causally linked to additional adverse health outcomes that were not considered in the 2003 estimates from CDC. These new causal associations for specific diseases link active smoking with diabetes, colorectal cancer, liver cancer, and tuberculosis, and exposure to secondhand smoke and stroke. For each of these diseases, there is an excess burden attributable to smoking and is potentially avoidable through tobacco control. Additionally, Chapter 11 reviews the evidence regarding the excess morbidity attributable to smoking as reflected

Table 12.10   Number and percentage of cigarette smoking-attributable conditions[a] among current and former smokers[b], by condition, United States[c], 2000

Disease	Current smokers Number	%	Former smokers Number	%	Overall total Number	%
Chronic bronchitis	2,633,000	49	1,872,000	26	4,505,000	35
Emphysema	1,273,000	24	1,742,000	24	3,016,000	24
Heart attack	719,000	13	1,755,000	24	2,474,000	19
All cancer except lung cancer	358,000	7	1,154,000	16	1,512,000	12
Stroke	384,000	7	637,000	9	1,021,000	8
Lung cancer	46,000	1	138,000	2	184,000	1
Total[d]	5,412,000	100	7,299,000	100	12,711,000	100

Source: Centers for Disease Control and Prevention 2003.

[a]Cigarette smoking-attributable conditions considered are stroke, heart attack, emphysema, chronic bronchitis, and cancer of the lung, bladder, mouth/pharynx, esophagus, cervix (women), kidney, larynx, and pancreas.

[b]Current smokers were defined as persons who reported smoking ≥100 cigarettes during their lifetime and who now smoke some days or every day. Former smokers were defined as persons who reported having smoked ≥100 cigarettes during their lifetime but did not smoke at the time of the interview.

[c]Results are adjusted for age, race, gender, and state/area of residence and rounded to the nearest 1,000.

[d]Numbers might not add to total because of rounding.

in overall health status and general morbidity that may come from still unidentified associations between smoking and disease and through indirect pathways, such as diminished immune function. For the cancers, respiratory and cardiovascular diseases, and other adverse health outcomes, issues that merit attention in future updates of the estimates of smoking-attributable morbidity are outlined below.

Cancer

In this report, smoking has been causally linked to colorectal and liver cancer. Both of these cancer sites are among the most common for men and women (see Chapter 6). The previously reported estimates of 1,696,000 (1,512,000 + 184,000) persons in the year 2000 with a history of cancer due to current or past smoking were limited to lung, bladder, mouth/pharynx, esophagus, cervix, kidney, larynx, and pancreas sites. For cancer sites with a high mortality rate, such as the lung, the number of persons surviving is low because there are few long-term survivors. Although liver cancer has a low 5-year survival rate similar to lung cancer (i.e., 14% for liver and 16% for lung), the 5-year survival rate for persons with colorectal cancer is much higher (64%) (American Cancer Society 2013). Hence, an updated estimate of the number of

persons surviving with cancer caused by smoking would be expected to increase with the inclusion of liver and colorectal cancer sites.

COPD

Previous Surgeon General's reports and Chapter 7 of this report document the very high level of risk for COPD due to active smoking. A very high proportion of COPD is attributable to current and past smoking (CDC 2008). Based on self-reports, 12–13 million U.S. adults report having COPD (American Lung Association 2013). However, self-reports of COPD likely substantially underestimate the true disease burden from smoking-attributable chronic respiratory diseases (CDC 2002, 2003). Analyses of data from NHANES III, which was the basis for the 2003 report from CDC, indicated that 63% of the respondents with a documented low level of lung function (forced expiratory volume in 1 second) <80% of the predicted value did not self-report a diagnosis of obstructive lung disease (CDC 2002). Using impaired lung function to estimate the prevalence of disease, approximately 24 million U.S. adults would be classified as having COPD (CDC 2002). Based on the estimate that 85–90% of these potential cases would be attributable to current or former smoking (USDHHS 2010), the total smoking-attributable burden of

COPD prevalence could be estimated to be between 20.4–21.6 million persons. This range of estimated prevalence of COPD is substantially higher than the 2003 estimate of 7,521,000 for chronic bronchitis and emphysema combined (CDC 2003).

Cardiovascular Diseases

In the United States, there is a high prevalence of persons living with a cardiovascular disease condition (see Table 8.4 in Chapter 8). In 2008, the estimated numbers of people in the United States with prevalent cardiovascular disease related to smoking were: history of acute myocardial infarction, 7.9 million; angina pectoris, 9 million; stroke, 7 million; heart failure, 5.7 million; atrial fibrillation, 2.2 million; and peripheral arterial disease (PAD), 8.3 million (NHLBI 2012). In 2000, it was estimated that among persons living with serious medical conditions, smoking caused approximately 2.5 million of the heart attacks and more than 1 million of the strokes (CDC 2003). Additionally, these estimates did not include the cardiovascular disease morbidity attributable to exposure to secondhand smoke.

However, in this and other reports (USDHHS 2004, 2010, 2012), the evidence has been reviewed showing that even brief exposures to tobacco smoke, from either smoking or exposure to secondhand smoke, can cause acute cardiovascular events and the progression of chronic vascular diseases. As reviewed in Chapter 8, the evidence is now sufficient to conclude that exposure to secondhand smoke causes stroke, and that the implementation of smokefree policies can reduce the incidence of acute coronary events. Additionally, the evidence reviewed in Chapter 10 leads to a conclusion that smoking causes diabetes. Since prior Surgeon General's reports have shown smoking causes PAD, the increasing evidence regarding the high RR of smoking in the development of symptomatic PAD (e.g., RR = 21 among women who smoked 15 or more cigarettes per day) (Conen et al. 2011) suggest that a high proportion of the prevalent PAD conditions could be attributable to smoking. Internationally, it has been estimated that approximately 15% of acute myocardial infarction events could be caused by exposure to secondhand smoke (Teo et al. 2006). Thus, the previous estimates of the cardiovascular disease morbidity burden attributable to smoking are most likely significant underestimates of the total, if these additional causes and the effects of secondhand smoke were to be included.

Additionally, the impact of smoking on progression of atherosclerotic disease may not have been adequately estimated in earlier estimates of SAM. Previous reports reviewed the evidence on the mechanisms by which smoking and exposure to secondhand smoke contribute to the early onset, progression, and severity of the atherosclerotic disease (USDHHS 2010, 2012). In 2010, the number of cardiovascular surgery procedures performed included: 1 million cardiac catheterizations, 500,000 balloon angioplasties or atherectomies, 454,000 insertions of coronary artery stent, and 395,000 coronary artery bypass graft procedures (CDC 2013). Thus, the prevalence of persons who have had such cardiovascular surgery procedures—which could have been due to the atherosclerotic disease caused by smoking—could be similar to the proportion of deaths from CHD caused by smoking (i.e., about 28% for men and almost 20% for women).

As the U.S. population ages, the number of persons who have been diagnosed with congestive heart failure (CHF) has increased (NHLBI 2012). In 2008, it was estimated that 5.7 million people have CHF in the United States. Evidence indicates that CHD is the underlying cause for approximately 65% of CHF cases and that smoking is a major contributing factor in the atherosclerotic disease process that leads to CHD (USDHHS 2004). According to the 19-year follow-up from the first NHANES Epidemiologic Follow-up Study, approximately 17.1% of the incident CHF could be attributed to tobacco smoking (He et al. 2001).

Thus, the previous estimate that about 3.5 million persons are living with a cardiovascular disease condition caused by smoking or exposure to secondhand smoke (CDC 2003) would appear to be a substantial underestimate of the total burden due to not only survivors of acute coronary events and strokes caused by smoking but also the number of persons with PAD, CHF, and a history of cardiovascular surgery procedures that could be attributed to smoking.

Diabetes

The present report concludes that smoking causes diabetes (see Chapter 10). As discussed in that chapter, the prevalence of diabetes in the United States has been increasing; in 2011, 25.6 million adults, 20 years of age and older, had diabetes. In the annual estimated smoking-attributable mortality for 2010–2014, approximately 13% of annual deaths due to diabetes were caused by current and former smoking (Table 12.4). Thus, the proportion of cases of diabetes attributable to smoking should be addressed when calculating smoking-attributable morbidity as well as mortality.

Summary

Approximately 8.6 million persons in the United States had an estimated 12.7 million smoking-attributable serious medical conditions in 2000 (CDC 2003). As noted previously, the updated evidence on diseases caused by smoking and exposure to secondhand smoke indicate that this estimate is likely a substantial underestimation of the true disease burden. Due to the increased burden of liver cancer and colorectal cancer, the various aspects of cardiovascular disease morbidity, which were not included in previous estimates, and the addition of diabetes cases attributed to smoking, the number of serious medical conditions caused by smoking could be much larger. For COPD alone, the updated estimate of the burden caused by smoking could be more than double the existing estimate.

Smoking-Attributable Economic Costs

This section covers smoking-attributable economic costs resulting from lost productivity and health care expenditures.

Loss of Productivity

The productivity losses calculated here only represent the present value of future earnings (PVFE) from paid labor and of foregone future imputed earnings from unpaid household work that is unrealized as a consequence of early mortality. Past estimations of PVFE values to use for productivity loss calculations were based on values for the United States in 2000 (Haddix et al. 2003) and an assumed 1% productivity rate and 3% discount rate. Estimates of PVFE for later years were estimated by applying annual changes in the non-seasonally-adjusted employment cost index for total compensation for civilian workers (U.S. Bureau of Labor Statistics n.d.). Male-specific PVFEs were used for both males and females, to account for historical gender bias in compensation.

Productivity losses were estimated by multiplying age-specific YPLL by age-specific PVFE, with total productivity determined by adding subtotals across age and disease categories. Estimates are based on deaths in adults 35–79 years of age.

YPLLs are calculated by multiplying age-specific SAM for each disease category by age group-specific years of life remaining. Years of life remaining are based on

U.S. life table data published by the National Center for Health Statistics at CDC. For this report, U.S. life tables were current through 2008; for these calculations, years of life remaining for 2009 were considered equal to those for 2008. Total YPLL is determined by adding subtotals across age and disease categories.

Grosse and colleagues (2009) published updated estimates of PVFE for the United States for 2007. PVFEs for total production for both genders combined were used for estimating productivity losses for 2005–2009, with 2007 values serving as the baseline and values for earlier and later years estimated by annual change in the employment cost index. Due to the use of different assumptions and parameters, the PVFE values published by Grosse and colleagues (2009) were conservative compared to the PVFE estimates published by Haddix and colleagues (2003).

Table 12.11 lists estimated average annual smoking-attributable productivity loss by disease category and gender for the United States from 2005–2009. For 2005–2009, the value of lost productivity attributable to premature death from smoking, based on the 19 diseases used in prior SAMMEC estimates (CDC 2008), was $107.6 billion—$69.6 billion in men and $38 billion in women. Cancers accounted for $44.5 billion of lost productivity costs, and cardiovascular and metabolic diseases accounted for $44.7 billion, and pulmonary diseases accounted for $18.4 billion. Using all-cause mortality, the value of lost SAM would be $150.7 billion—$105.6 billion in men and $45.1 billion in women. Additionally, the value of lost productivity due to premature deaths caused by exposure to secondhand smoke was estimated to be $5.7 billion (Table 12.9). Because these figures account only for lost productivity due to premature mortality and not for lost productivity due to morbidity they significantly underestimate the full value of lost productivity costs due to smoking.

Updated Estimates of Smoking-Attributable Health Care Expenditures

The smoking-attributable health care expenditure is one important component of smoking-attributable economic costs. Although the prevalence of smoking continues to decline in the United States, smoking-related health care expenditures still account for an estimated 5–14% of the total health care expenditures in the United States (Levy and Newhouse 2011; Congressional Budget Office [CBO] 2012). The analytical approaches used to estimate attributable expenditures vary depending on the methodology adopted and the time horizon considered in the analysis. In terms of the former, some studies use a

Table 12.11 Average annual value of lost productivity attributable to death from cigarette smoking, adults 35–79 years of age, United States, 2005–2009

Disease	Value of lost productivity ($ in thousands)[a]		
	Males	**Females**	**Total**
Lung cancer	20,326,794	14,084,073	34,410,868
Other cancers[b]	7,434,058	2,614,451	10,048,509
Total—Cancers	**27,760,852**	**16,698,524**	**44,459,376**
Coronary heart disease	20,646,966	7,420,262	28,067,228
Other cardiovascular disease[c]	11,209,038	5,454,808	16,663,845
Total—Cardiovascular and metabolic diseases	**31,856,004**	**12,875,069**	**44,731,073**
Total—Pulmonary diseases[d]	**9,963,054**	**8,402,054**	**18,365,108**
Total—Cancers, cardiovascular and metabolic diseases, pulmonary diseases	**69,579,910**	**37,975,647**	**107,555,557**
Total—All causes	**105,641,174**	**45,085,339**	**150,726,514**

Source: Centers for Diease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, unpublished data.

[a]Value of lost productivity calculated based on potential value of future earnings in the United States in 2007, published by Grosse et al. 2009.

[b]Other cancers comprised of cancers of the lip, pharynx and oral cavity, esophagus, stomach, pancreas, larynx, cervix uteri, kidney and renal pelvis, bladder, colon and rectum, liver, and acute myeloid leukemia.

[c]Other cardiovascular disease comprised of other heart disease, cardiovascular disease, atherosclerosis, aortic aneurysm, other arterial diseases, and diabetes mellitus.

[d]Pulmonary diseases consist of pneumonia, influenza, tuberculosis, emphysema, bronchitis, and chronic airways obstruction.

disease-specific approach, in which the attributable expenditure for each major smoking-related disease is estimated as the product of the total health care expenditure for the disease and the share of attributable expenditure. The sum of these disease-specific attributable expenditures provides the total health care expenditure that is attributable to smoking. Other studies take a regression approach, in which health care expenditures are compared by smoking status while controlling for other factors that may differ among current, never, and former smokers. In terms of time horizons, most previous studies on smoking-attributable health care expenditures have taken a cross-sectional approach, in which attributable expenditures were calculated for a point in time. A few took a lifetime approach, in which the attributable expenditures were considered over an individual's life expectancy (Manning et al. 1991; Sloan et al. 2004).

In order to account for the methodologic differences and to provide a reasonable range of smoking-attributable health care expenditures, this section presents estimated attributable expenditures obtained from three different approaches: (1) updated estimates by type of medical services based on the expenditure SAFs in the SAMMEC,

(2) updated estimates by age and gender based on an approach originated by Solberg and colleagues (2006), and (3) national estimates by source of fund from a regression analysis using the data from the Medical Expenditure Panel Survey (MEPS) (Xu et al. in press). Although these approaches are not the only ways to estimate the smoking-attributable health care expenditures, they are commonly used. To be consistent with SAM, all of these estimates are cross-sectional. Use of these approaches explores the sensitivity of estimates to the method selected.

Smoking-Attributable Health Care Expenditures by Type of Medical Services

The approach published by Miller and colleagues (1999) involves estimation of expenditure smoking-attributable fractions for five categories of personal health care expenditures—ambulatory care, hospital care, prescriptions, nursing home care, and other care (including home health care, durable and nondurable medical equipment, and other professional services) while accounting for potential confounders. The expenditure SAFs are calculated based on a 2-stage econometric model. Estimates of smoking-attributable health care expenditures are for

adults 19 years of age and older and exclude dental expenditures. Values for category-specific health care expenditures are based on data from the Centers for Medicare & Medicaid Services ([CMS] 2012c).

Based on this approach, smoking-attributable medical expenditures were estimated to be $75.5 billion for 1998 (CDC 2002), and $96 billion for 2004 (CDC 2008). Updated estimates for the United States in 2009 were produced based on this approach, using expenditure SAFs for 2004 (CDC n.d.). Expenditures for persons 19 years of age and younger were excluded using 2004 age-specific expenditure data published by CMS (2012a). Updated overall and category-specific expenditure estimates are presented in Table 12.12. Overall, an estimated $132.5 billion of health care expenditures in adults 19 years of age and older were attributable to smoking in 2009, an approximate 38% increase over the 2004 figure. This accounts for 7.6% of all health care expenditures (excluding dental expenditures) in adults ages 19 years and older, consistent with the 6–8% range reported by Warner and colleagues (1999). This figure excludes costs attributable to exposure to second-hand smoke.

Table 12.12   Aggregate health care expenditures attributable to cigarette smoking by type of service among adults, 19 years of age and older, United States, 2009

Type of service	Smoking attributable fraction (%)[a]	Expenditures ($ in billions)
Hospitals	10.3	67.0
Ambulatory care	4.9	21.0
Nursing home care	7.9	10.6
Prescription drugs	9.5	25.5
Other services[b]	3.3	8.2
Total	7.6	132.5[c]

Source: Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, unpublished data.
Note: Based on the approach by Miller and colleagues 1999. Expenses are presented in 2009 dollars.
[a]Smoking-attributable fractions for 2004 in the United States are available at https://apps.nccd.cdc.gov/sammec/exp_comp.asp.
[b]Other expenditures include home health care, durable and nondurable medical equipment, and other professional services.
[c]Sum of individual categories does not equal the total due to rounding.

Smoking-Attributable Health Care Expenditures by Age and Gender

This approach, using the latest evidence-based RRs of smoking-related disease events, presents an option to distribute smoking-attributable health care expenditures by age, gender, and smoking status. The major advantage of this approach is that it can create estimates closely reflecting the known epidemiologic risks of smoking and benefits of cessation by age and gender. In this approach, per capita health care expenditures by smoking status are first estimated based on the projected 2012 per capita personal health care expenditures for 19 years of age and older from CMS (2012b) and relative cost ratios of health care expenditures for current and former smokers compared to never smokers. These cost ratios are calculated from per-person relative health care costs by smoking status reported by Musich and colleagues (2003). In that study, costs were calculated controlling for age, gender, and the presence of chronic diseases (Musich et al. 2003). With the estimated per capita health care expenditures by smoking status, the national smoking-attributable health care expenditures and expenditure SAFs can be obtained using national prevalence figures for current, former, and never smokers. The national smoking-attributable health care expenditures are then apportioned by age and gender group according to the distribution of hospitalization days for smoking-related diseases.

Specifically, for each smoking-related disease h, age group i, and gender j, hospitalization days are distributed by smoking status using algebraic manipulation of the formula:

$$DAYST_{h,i,j} = \sum_{k \epsilon S} DAYSN_{h,i,j,k} * RR_{h,i,j,k}$$

where DAYST and DAYSN are the number of hospitalization days for all smokers, including both current and former smokers, and never smokers, respectively, and the smoking status s is defined by three values for k representing never, current, and former smokers. $RR_{h,i,j,k}$ is the RR of hospitalization for smoking status k, age group i, and gender j relative to never smokers from the same demographic group (RR = 1.0 for never smokers). After solving for DAYSN, RRs are used to calculate days of hospitalization for current and former smokers. The portion of days across all smoking-related diseases for each age, gender, and smoking status group ($PD_{i,j,k}$) is then:

$$PD_{i,j,k} = \frac{\sum_h DAYSN_{h,i,j,k} * RR_{h,i,j,k}}{\sum_h \sum_{k \epsilon s} DAYSN_{h,i,j,k} * RR_{h,i,j,k}}$$

In practice, the RR for hospitalizations is replaced by the proxy, the RR of mortality. Finally, the resulting proportions can be applied along with estimates of smoking prevalence and national smoking-attributable health care expenditures to estimate the distribution of expenditures by age, gender, and smoking status that reflect relative disease risk.

The number of hospitalization days comes from the 2010 National Hospital Discharge Survey. Hospitalization days are weighted to a nationally representative sample and standard errors on counts and percentages are tabulated using the generalized variance curves provided by the National Hospital Discharge Survey (NHDS) in the public use data set. The prevalence figures for current smokers, former smoker and never smokers are estimated from the 2012 NHIS.

Results from this approach suggest that smoking accounted for 8.66% of total annual health care expenditures in the United States in 2012. The projected personal health care expenditure is $2,031.2 billion in 2013, after excluding dental expenditures and expenditures for persons 19 years of age or younger based on 2004 age specific expenditure data published by CMS (2012a,b). Consequently, the smoking-attributable health care expenditure in 2013 is estimated around $175.9 billion. Of the total, $94.2 billion was contributed by current smokers and $81.7 billion was contributed by former smokers. Table 12.13 presents smoking-attributable health care expenditures by age and gender.

Smoking-Attributable Health Care Expenditures by Source of Funds

This regression approach is based on a two-part model to calibrate the impact of smoking independently from the impact of other factors that are correlated with smoking and may affect health care expenditures. The data used in the analysis come from the MEPS. The MEPS is a nationally representative survey of the civilian non-institutionalized U.S. population that provides detailed information on health care use and medical expenditures. MEPS respondents can be directly linked to the NHIS, as they are drawn from the NHIS household samples within the preceding 2 years. The NHIS, designed to be a major source of information on the health of the civilian noninstitutionalized U.S. population, collects detailed smoking history information from respondents. Therefore, respondents' smoking status in the analysis comes from the NHIS. The final data set contains approximately 41,000 observations from the 2006–2010 MEPS that are linked to the 2004–2009 NHIS.

The two-part model, a standard statistical technique for analyzing health care spending data (Finkelstein et

Table 12.13   Aggregate health care expenditures ($ in billions) attributable to cigarette smoking among adults, 35 years of age and older, by age group and gender, United States, 2012

| Age group | Former smokers | | | Current smokers | | | Total |
	Males	Females	Subtotal	Males	Females	Subtotal	
35–44 years	0.5	0.3	0.8	3.0	2.4	5.4	6.2
45–54 years	2.9	1.1	4.0	10.7	8.8	19.4	23.4
55–64 years	8.6	5.5	14.1	17.4	12.8	30.2	44.3
65–74 years	15.4	11.2	26.7	15.0	10.0	25.0	51.7
≥75 years	18.6	17.6	36.2	5.9	8.3	14.2	50.4
All ages	46.0	35.7	81.7	52.0	42.2	94.2	175.9

Source: Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, unpublished data.
Note: Based on the approach by Solberg and colleagues 2006. Expenditures presented in 2013 dollars. Since relative risks of mortality of smoking-related diseases do not differ by smoking status for those between 19 and 34 years of age, the approach assigns no smoking-attributable health care expenditures to that particular age group.

al. 2009; CBO 2012), separately estimates the probability of having any medical expenditure in the first part and then estimates annual medical expenditure conditional on having positive expenditures in the second part. The estimates from each part are then combined to estimate annual smoking-attributable health care expenditures.

In each component of the model, health care expenditures excluding dental are considered as a function of the respondent's smoking status and individual sociodemographic and health characteristics. Each respondent in the analysis was categorized as a current smoker, a recent quitter (quit smoking within the last 5 years), a long-term quitter (quit smoking for more than 5 years), or a never smoker. Studies have found that former smokers, and particularly recent quitters, might have higher expenditures than continuing smokers (Fishman et al. 2003, 2006; Hockenberry et al. 2012), as quits are often prompted by symptoms of disease that continue to cause care utilization in the years following quitting. This issue has been addressed in different ways in the existing literature, by excluding recent quitters (Solberg et al. 2006), categorizing recent quitters as current smokers (Sloan et al. 2004; Jha et al. 2013), or mathematically smoothing over expenditure increases in the period after successfully quitting in a way that effectively excludes recent quitters from the analysis of spending (CBO 2012). This analysis includes an independent group of recent quitters to address this issue.

In order to account for differences in sociodemographic and health characteristics by smoking status, all of the regressions included controls for age (18–24 years of age, 25–44 years of age, 45–64 years of age, 65–74 years of age, and 75 years of age and older), gender, race/ethnicity (Whites, Blacks, Hispanics, Others), education (less than high school, high school, some college, college and above), marital status (married or cohabitating, never married, not cohabitating, divorced/separated/widowed), family income as percent of federal poverty level (<100%, 100–124%, 125–200%, 200–399%, 400% and above), indicators of alcohol consumption (excessive drinkers, nonexcessive drinkers, and nonusers), indicators of body weight (underweight, normal weight, overweight, and obese), an indicator of health insurance coverage (when applicable), the receipt of flu shots, use of seatbelt, taking more risks than average person, and belief in own ability to overcome illness without medical help (yes vs. no), and geographic location (four census regions), and the year fixed effect.

A linear probability model was used for the first part. Based on the specification tests, a generalized linear model with a log link and gamma distribution was used in the second part (Manning and Mullahy 2001). In addition to the total health care expenditure, separate two-part models were also performed by source of fund (out-of-

pocket, private, Medicaid, and Medicare, other federal, and others). In all analyses, bootstrapped standard errors were obtained.

Smoking-attributable fractions of health care expenditures are estimated using the following formula:

$$SAFE_{ij} = \frac{EXPS_{ij} - EXPNS_i}{EXPNS_i}$$

where $EXPS_{ij}$ is the predicted level of expenditures given individual i's smoking status j (current smokers, recent quitters, or long term quitters), whereas $EXPNS_i$ is the predicted level of expenditures if individual i had never been a smoker and $SAFE_{ij}$ represents the various attributable fractions. Specifically, using the estimated model, each individual's $EXPS_{ij}$ is obtained as the product of the predicted probability of having an expenditure given the smoking status and the predicted expenditure conditional on the expenditure being positive. The calculation for $EXPNS_i$ is the same except that the smoking indicator is set to never smoking. The $SAFE_{ij}$ of the population is obtained by averaging over the population for each current or former smoker.

One limitation, however, is that the MEPS expenditure estimates have been shown to be 38% lower than comparable estimates from the Personal Health Care Expenditures reported by CMS, since the MEPS sample is limited to noninstitutionalized civilians and it does not include costs for some services such as long-term care stays longer than 45 days (Sing et al. 2006).

Therefore, the annual expenditures presented are estimated based on the 2010 National Health Expenditures by health insurance enrollment from CMS (2012b) and SAFs by source of fund estimated from the MEPS. Specifically, these expenditures are calculated as the product of SAFs estimated via MEPS by total health care expenditures for the corresponding category reported.

The estimates from the NHIS-linked MEPS data suggest that 8.7% of total health care expenditure was attributable to cigarette smoking between 2006–2010. Based on the 2010 Personal Health Care Expenditures report by CMS, smoking contributed to more than $170 billion in health care expenditures in total (Table 12.14). In particular, roughly 3.4% of out-of-pocket health care expenditure (approximately $8.5 billion), 4.4% of private health insurance expenditure (approximately $33.7 billion), 15.2% of Medicaid expenditure (approximately $40.1) billion, or 9.6% of Medicare expenditure (approximately $45 billion) was smoking attributable. In other words, more than 60% of annual health care expenditures associated with smoking in the United States were reimbursed by public funds, either Medicaid, Medicare, or other federal funds.

Table 12.14   **Smoking-attributable fraction (SAF) and aggregate health care expenditures attributable to cigarette smoking by source of fund, National Health Expenditure Accounts (NHEA), United States, 2010**

Source of fund	SAF (%)		Expense ($ in billions)	
	Estimated SAF	95% CI	NHEA	95% CI
Self-paid	3.4	0.6–6.0	8.5	1.5–15.2
Private insurance	5.4	1.0–9.9	33.7	6.4–61.3
Medicaid	15.2	6.2–27.4	40.1	16.7–66.3
Medicare	9.6	4.4–15.6	45.0	20.5–73.1
Other federal	32.8	21.3–46.3	24.5	15.9–34.6
Others	11.8	0.0–23.9	17.9	0.0–36.2
Total	8.7	5.1–12.6	170.6	92.9–228.2

Source: Xu et al., in press.
Note: Expenditures presented in 2010 dollars. Expenditures associated with dental services are excluded from the total national health expenditures by source of fund. Expenditures for persons under 19 years of age were also excluded using 2004 age-specific expenditure data published by the Centers for Medicare & Medicaid Services. The sum of individual categories does not equal the total due to rounding. **CI** = confidence interval.

Synthesis of Findings

In the preceding sections, smoking-attributable health care expenditures have been estimated based on three different approaches providing a range of figures. None of the total smoking-attributable health care expenditures estimated from these approaches is dependent on a list of specific smoking-attributable conditions. Annual smoking-attributable estimated health care expenditures are between $132.5 billion in 2009 to $175.9 billion in 2013. These estimates are far higher than the $95.9 billion estimate for 2004 by CDC (2008). In comparison, if the CDC estimate for 2004 had been simply adjusted using the Consumer Price Index (all items and medical care-specific) to 2012, the resulting estimates would have been $116.56 billion (all items) or $128.32 billion (medical care-specific).

These estimated attributable expenditures also suggest that smoking has accounted for approximately 7–9% of total annual health care spending in the United States during recent years. In addition to total smoking-attributable health care expenditures, each approach provides specific estimates for different subpopulations in the United States. Results in Table 12.13 suggest that annual attributable health care expenditures may vary by age, from $6.2 billion for those between 35–44 years of age to approximately $50 billion for both those between 65–74 years of age and those 75 years of age and above, while estimates in Table 12.14 imply that more than 60% of the attributable health care expenditures are likely paid by public funds. Based on expenditure SAFs in the SAMMEC, Table 12.12 indicates that smoking contributes $67 billion in expenditures for hospitals, $21 billion in ambulatory care, $10.6 billion in nursing home care, $25.5 billion in prescription drugs, and $8.2 billion in other services.

These three approaches each have their own limitations. The updated SAMMEC approach depends on SAFs for expenditures estimated in 2004 and the data used for the estimation comes from the 2000–2004 MEPS. These attributable fractions are likely outdated and thus may cause an underestimation of smoking-attributable health care expenditures.

Although the second approach originated by Solberg and colleagues (2006) can closely reflect the known epidemiologic risks of smoking and the benefits of cessation by age and gender, the estimated attributable expenditures depend on the relative cost ratios of health care expenditures for current and former smokers compared to never smokers. In addition, the use of mortality RRs as a proxy for the RR of hospitalizations implicitly assumes that the event-fatality rate is constant across smoking status. If instead, for example, current smokers have a lower event-fatality rate than former smokers for a particular smoking-related disease, then the RRs of death for former

smokers compared to current smokers would be higher than the RR of events. Consequently, the calculations might overestimate the economic benefits of quitting. Second, if there are differences in case-events by smoking status and those differences are not constant with respect to age, then the distribution of expenditures by age group could also be impacted by using mortality RRs as a proxy. Differences in disease cases by smoking status have not been systematically studied in detail and, therefore, it is difficult to predict the direction and extent of any biases introduced to those estimates.

Finally, although a two-part model is commonly used to model health expenditures, the robustness of the estimates depends on the extent to which all of the factors of health care spending and mortality are accounted for. For example, in an analysis using a similar approach, the CBO (2012) concluded that differences in demographic characteristics account for $130 (12%) of the gap in annual expenditures between current or former smokers and nonsmokers who otherwise resemble smokers in the 45–64 age group, $380 (26%) of the gap in the 65–74 age group, and $460 (26%) of the gap in the 75-and-over age group. In the regression approach, an extensive set of factors are included, in addition to the regional fixed effects. After controlling for similar factors, Jha and colleagues (2013) concluded that additional adjustments did not materially affect their estimated smoking impacts on hazard ratios of mortality. This finding provides indirect evidence to support the specification used in the analysis.

Summary

The estimated SAFs of health care expenditures from all three approaches (7.6%, 8.7%, and 8.7%) are within the range of findings from existing cross-sectional studies which extend from 6.54% in Miller and colleagues (1999) to 14% in Warner and colleagues (1999). Particularly, these estimates are very close to the most recent estimated SAFs reported in the CBO's report (2012), which concluded that 7% of total annual spending on health care in the United States between 2002–2008 was attributable to cigarette smoking. Thus, the various estimates, coming from different data sets and methodologies, are consistent in showing that smoking has continued to cause a significant portion of health care expenditures in the United States.

Total Smoking-Attributable Mortality, 1965–2014

Table 12.15 provides the estimated smoking-attributable mortality for the period 1965–2014. The 2004 Surgeon General's report provided an estimated cumulative total for SAM for 1965–1999 (USDHHS 2004, Chapter 7 and Appendix). The total SAM estimates for 1965–1999 were derived from annual population-attributable risk estimates for the period beginning with the publication of the first Surgeon General's report on the health consequences of smoking in 1964.

Specific details on the methodology used to compute the population-attributable risk estimates for 1965–1999 were provided in the 2004 Surgeon General's report (USDHHS 2004, Chapter 7 and Appendix). Deaths from cigar smoking, pipe smoking, and smokeless tobacco use were not included in these estimates, nor were deaths from fires and exposure to secondhand smoke for the period of 1965–1999. The mortality RR estimates for the 19 disease categories among adults causally associated with smoking were obtained from data from CPS-I and CPS-II: CPS-I data (1959–1965) were used for 1965–1971; CPS-II data (1982–1988) for 1982–1999; and the midpoint RRs between CPS-I and CPS-II were used for 1972–1981.

The average annual SAM estimates for the United States from 2000–2004 have been published (CDC 2008) and briefly described above. For the period 2000–2004, CDC estimated the annual SAM for 19 disease categories based on the mortality RR estimates from CPS-II (1982–1988). Annual estimates of smoking-attributable premature deaths for four health outcomes in infants, deaths from residential fires caused by smoking, and deaths from lung cancer and CHD attributed to exposure to secondhand smoke also were published (CDC 2008).

The 2013 update to SAMMEC methodology was discussed earlier in this chapter. Estimates for 2005–2009 for men and women are shown in Tables 12.5 and 12.6. Updated estimates of infant deaths and deaths attributable to exposure to secondhand smoke for 2005–2009 are shown in Tables 12.8 and 12.9. The average annual SAM for the United States for 2005–2009 are provided in Table 12.7.

From 1965–2009, smoking caused an estimated 5.8 million cancer deaths, 7.0 million cardiovascular and metabolic disease deaths, 3.2 million respiratory disease deaths, and 103,355 infant deaths (Table 12.15). Since

Table 12.15   Smoking-attributable mortality,[a] total and by gender, United States, 1965–2014

Disease	Males 1965–1999	Males 2000–2004	Males 2005–2009	Males 2010–2014	Females 1965–1999	Females 2000–2004	Females 2005–2009	Females 2010–2014	Total 1965–1999	Total 2000–2004	Total 2005–2009	Total 2010–2014	Total 1965–2009	Total 1965–2014
Lung cancer	2,286,800	393,400	371,500	371,500	812,000	234,210	267,000	267,000	3,099,000	627,610	638,500	638,500	4,365,110	5,004,000
Other cancers[b]	804,800	128,960	130,000	130,000	241,500	47,670	50,000	50,000	1,046,400	176,630	180,000	180,000	1,403,030	1,583,000
Total—Cancers	**3,091,600**	**522,360**	**501,500**	**501,500**	**1,053,700**	**281,880**	**317,000**	**317,000**	**4,145,400**	**804,240**	**818,500**	**818,500**	**5,768,140**	**6,587,000**
Coronary heart disease	2,517,200	254,420	309,000	309,000	981,800	145,610	187,500	187,500	3,499,000	400,030	496,500	496,500	4,395,530	4,892,000
Other cardiovascular disease[c]	1,336,000	141,280	169,000	169,000	704,000	101,190	137,500	137,500	2,040,000	242,460	306,500	306,500	2,588,960	2,895,000
Total—Cardiovascular and metabolic diseases	**3,853,200**	**395,700**	**478,000**	**478,000**	**1,685,800**	**246,790**	**325,000**	**325,000**	**5,539,000**	**642,490**	**803,000**	**803,000**	**6,984,490**	**7,787,000**
Total—Pulmonary diseases[d]	**1,440,700**	**268,980**	**291,000**	**291,000**	**715,800**	**247,720**	**274,500**	**274,500**	**2,156,500**	**516,690**	**565,500**	**565,500**	**3,238,690**	**3,804,000**
Total—Cancers, cardiovascular and metabolic diseases, pulmonary diseases	**8,385,500**	**1,187,030**	**1,270,500**	**1,270,500**	**3,455,300**	**776,390**	**916,500**	**916,500**	**11,840,900**	**1,963,420**	**2,187,000**	**2,187,000**	**15,991,320**	**18,178,000**
Perinatal conditions[e]	**54,200**	**2,230**	**2,910**	**2,910**	**40,200**	**1,660**	**2,160**	**2,160**	**94,400**	**3,880**	**5,080**	**5,080**	**103,360**	**108,000**
Residential fires[f]	**41,930**	**2,080**	**1,680[f]**	**1,680[f]**	**33,820**	**1,600**	**1,420[f]**	**1,420[f]**	**75,750**	**3,680**	**3,100**	**3,100**	**82,530**	**86,000**
Secondhand smoke														
Lung cancer	74,590	10,660	21,870	21,870	44,410	6,350	14,800	14,800	172,670	17,000	36,670	36,670	172,670	263,000
Coronary heart disease	779,100	146,280	95,760	95,760	445,900	83,720	74,000	74,000	1,624,760	230,000	169,760	169,760	1,624,760	2,194,000
Total—Secondhand smoke	**853,690**	**156,940**	**117,630**	**117,630**	**490,310**	**90,060**	**88,790**	**88,790**	**1,797,420**	**247,000**	**206,420**	**206,420**	**1,797,420**	**2,457,000**
TOTAL—Attributable deaths	**8,439,700**	**1,348,280**	**1,407,840**	**1,407,840**	**3,495,500**	**869,700**	**1,021,650**	**1,021,650**	**13,808,470**	**2,217,980**	**2,401,600**	**2,401,600**	**17,974,620**	**20,830,000**

Source: Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, unpublished data.

Note: **CPS** = Cancer Prevention Study; **ICD** = International Classification of Diseases; **RR** = relative risk; **SAM** = smoking-attributable mortality. SAM calculated using RRs from CPS-II; gender- and age-specific (35–64, ≥65 years of age) RRs and smoking status (current, former) prevalence used for estimates. SAM calculated using RRs from CPS-II for adults 35–54 years of age and RRs from contemporary cohorts (Thun et al. 2013) for adults 55 years of age and older; gender- and age-specific (35–54, 55–64, 65–74, ≥75 years of age) RRs and smoking status (current, former) used for estimates. All-cause SAM not computed.

[a]Row and column totals may not add up exactly due to rounding.

[b]Other cancers comprised of cancers of the lip, pharynx and oral cavity, esophagus, stomach, pancreas, larynx, cervix uteri (women), kidney and renal pelvis, bladder and acute myeloid leukemia. Data for 2005–2009 also include cancers of liver and of colon and rectum.

[c]Other cardiovascular disease comprised of other heart disease cardiovascular disease, atherosclerosis, aortic aneurysm, and other arterial diseases. Data for 2005–2009 also include diabetes mellitus.

[d]Pulmonary diseases consists of pneumonia, influenza, emphysema, bronchitis and chronic airways obstruction. Data for 2005–2009 also includes tuberculosis.

[e]Prenatal conditions comprised of ICD-10 codes: K550, P000, P010, P011, P015, P020, P021, P027, P070–P073, P102, P220–229, P250–P279, P280, P281, P360–P369, P520–P523, and P77 (Dietz et al. 2010).

[f]Based on average annual deaths, 2006–2010, reported by Hall 2012.

1980, there have been an estimated 32,530 smoking-attributable residential fire-related deaths (Figure 12.3). Since Hall (2012) reports that smoking-material fires dropped by more than one-half when smoke detectors became more widely used in the late 1970s, it can be conservatively estimated that the number of residential fire deaths from 1965–1979 was at least 50,000 (e.g., 2,000 per year). Thus, for the period 1965–2009, the total number of smoking-attributable residential fire-related deaths can be estimated to be about 82,530 (50,000 + 32,530). Deaths attributable to exposure to secondhand smoke have not been estimated for 1965–1990; however, since 1990 the total number of deaths attributable to exposure to secondhand smoke is estimated to be about 3,400 annually for lung cancer and 35,000 for CHD (Steenland 1992; USEPA 1992; CDC 2005, 2008). Since exposures to secondhand smoke were much higher in nonsmokers in earlier decades (USDHHS 2006), it can be estimated that the

deaths attributable to exposure to secondhand smoke back to 1965 could be estimated to be about at similar rates for the 35-year period (1965–1999). Thus, for the period 1965–2009, the total number of premature deaths attributable to exposure to secondhand smoke can be estimated to be about 1.8 million. Hence, for 1965–2009, the total estimated deaths attributable to smoking and exposure to secondhand smoke was about 18.0 million.

From 2010–2014, the number of deaths caused by smoking and exposure to secondhand smoke is estimated to continue at levels similar to that from 2005–2009—namely, about 480,000 per year. Therefore, the estimated total for the years 2010–2014 would be approximately 2.4 million additional deaths caused by smoking and exposure to secondhand smoke, and the total estimate for the 50-year period, from 1965–2014, would be approximately 20.4 million deaths caused by smoking and exposure to secondhand smoke.

Summary

Cigarette smoking remains the single leading cause of preventable mortality in the United States and causes a high morbidity burden. The costs of health care are substantial. This chapter reviewed various methods for assessing the disease burden of smoking-related illnesses, including epidemiologic calculations, indirect estimates, and model-based approaches for assessing SAM. These estimates are not strongly biased by potential confound-

ing factors, even though smokers and nonsmokers tend to have different profiles for a number of lifestyle-related risk factors for disease. Economic disease burden estimates assess the costs of smoking to governments and society in general. Both types of assessments provide compelling evidence that programs and policies are needed to continue the progress toward ending the tobacco epidemic.

Conclusions

1. Since the first Surgeon General's report on smoking and health in 1964, there have been more than 20 million premature deaths attributable to smoking and exposure to secondhand smoke. Smoking remains the leading preventable cause of premature death in the United States.

2. Despite declines in the prevalence of current smoking, the annual burden of smoking-attributable mortality in the United States has remained above 400,000 for more than a decade and currently is estimated to be about 480,000, with millions more living with smoking-related diseases.

3. Due to the slow decline in the prevalence of current smoking, the annual burden of smoking-attributable mortality can be expected to remain at high levels for decades into the future, with 5.6 million youth currently 0 to 17 years of age projected to die prematurely from a smoking-related illness.

4. Annual smoking-attributable economic costs in the United States estimated for the years 2009–2012 were between $289–332.5 billion, including $132.5–175.9 billion for direct medical care of adults, $151 billion for lost productivity due to premature death estimated from 2005–2009, and $5.6 billion (in 2006) for lost productivity due to exposure to secondhand smoke.

Implications

Estimates of the attributable burden of disease from smoking have value for policy formulation and decision-making. They may be useful for motivating action and for assigning priorities. For smoking, the enormity of the estimates is a powerful impetus for action. In addition, economic cost-of-illness studies on tobacco-related diseases can help inform policymakers about the economic benefits of supporting comprehensive tobacco use prevention and control programs, and implementing effective policies and regulations to reduce tobacco use in the United States. The estimates of expenditures are essential for cost-effectiveness and cost-benefit analyses. Uniformly, such analyses provide a strong basis for implementing effective tobacco control strategies. Additionally, these estimates may be useful in estimating SAM in other countries (Appendix 12.1).

Acknowledgment

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Appended Table 12.2 **Annual prevalence of current smoking and former smoking among adults, 35 years of age and older, for selected years; NHIS, United States, 1965–2011**

A. Men

Year	35–54 years of age: % CS	35–54 years of age: % FS	55–64 years of age: % CS	55–64 years of age: % FS	65–74 years of age: % CS	65–74 years of age: % FS	75 years of age and older: % CS	75 years of age and older: % FS
1965	57.1	21.2	46.6	27.1	33.1	30.1	19.3	24.2
1970	48.7	28.6	41.1	34.9	27.1	41.5	15.7	36.3
1974	48.8	30.2	37.7	40.0	29.2	43.0	15.9	38.7
1977	46.5	29.5	37.0	36.4	26.7	44.6	15.9	41.6
1980	42.7	30.9	38.5	39.4	22.2	48.0	9.0	46.3
1983	40.1	30.7	32.6	45.4	26.7	46.6	12.2	51.2
1985	36.5	34.2	31.9	47.2	21.9	53.2	15.0	51.1
1987	35.4	32.2	30.3	45.2	20.6	55.1	11.4	52.4
1988	35.6	30.9	28.0	48.4	21.4	53.9	11.4	54.5
1990	33.5	31.8	25.9	45.8	18.3	53.0	7.6	59.5
1992	34.0	31.1	25.4	45.7	19.6	53.1	10.7	52.0
1994	32.2	30.7	24.7	47.5	16.1	57.1	8.4	60.3
1995	29.7	28.1	26.9	43.3	18.1	51.5	9.6	55.2
1997[a]	31.1	26.1	24.1	45.2	16.2	56.1	7.7	56.4
1998	30.1	25.9	24.2	44.4	13.3	58.2	6.2	59.0
1999	29.1	25.2	22.3	44.8	12.6	57.8	7.5	58.1
2000	29.6	22.1	22.6	45.0	13.7	53.9	5.4	58.6
2001	27.5	23.5	24.2	44.1	14.5	55.6	7.4	55.8
2002	28.4	23.5	20.7	44.3	12.4	55.1	7.0	58.3
2003	27.0	22.1	21.2	41.8	13.3	52.8	5.9	54.1
2004	26.6	21.1	22.7	40.3	12.8	52.7	5.9	55.5
2005	27.0	19.8	21.1	41.7	11.4	52.5	5.7	56.8
2006	25.7	20.7	21.5	41.1	17.4	45.4	6.2	59.0
2007	24.0	20.6	19.6	38.6	12.5	51.8	5.1	58.3
2008	25.4	20.8	22.6	34.5	14.6	51.3	5.1	59.0
2009	26.4	20.3	20.8	40.3	12.5	52.5	5.5	56.2
2010	23.9	21.7	20.7	35.6	12.6	50.4	5.5	55.5
2011	24.2	20.5	21.4	36.1	11.7	49.9	5.0	54.9

Appended Table 12.2   **Continued**

B. Women

Year	35–54 years of age: % CS	35–54 years of age: % FS	55–64 years of age: % CS	55–64 years of age: % FS	65–74 years of age: % CS	65–74 years of age: % FS	75 years of age and older: % CS	75 years of age and older: %FS
1965	40.8	9.4	25.0	7.6	12.4	5.1	4.5	3.6
1970	37.9	13.3	28.5	12.1	14.4	9.0	5.6	5.5
1974	37.9	14.1	30.4	16.0	16.0	12.5	5.8	7.6
1977	37.5	14.9	32.4	16.0	17.5	13.4	6.6	10.2
1980	34.3	17.9	27.9	17.6	21.8	17.6	8.9	8.8
1983	33.9	17.2	28.0	19.7	17.6	22.6	6.3	12.8
1985	31.9	20.1	27.4	22.2	17.9	23.5	7.0	17.9
1987	30.2	19.8	25.6	23.6	18.9	21.4	7.2	14.8
1988	28.3	21.0	26.2	24.4	16.7	23.8	7.3	16.3
1990	26.3	22.1	20.5	24.3	15.6	25.9	5.8	19.6
1992	27.8	20.9	22.6	23.9	14.9	23.3	7.5	24.2
1994	25.8	21.7	20.7	29.5	13.4	30.9	8.2	21.7
1995	25.9	21.2	23.7	24.4	14.4	29.7	7.9	23.1
1997[a]	25.4	20.6	19.0	27.6	15.3	28.3	7.0	22.9
1998	25.4	19.6	20.1	26.7	15.3	30.3	6.5	23.3
1999	25.0	19.4	17.7	29.5	14.0	29.6	7.1	25.9
2000	24.4	19.8	20.8	28.3	12.2	28.8	6.2	23.8
2001	24.2	18.2	19.8	27.2	12.8	28.6	5.3	25.6
2002	23.2	18.7	18.8	28.1	11.4	31.2	5.8	25.7
2003	22.9	17.6	18.2	26.4	11.0	32.4	5.6	27.9
2004	21.2	18.2	18.6	26.1	11.2	28.9	5.0	28.3
2005	21.1	17.5	16.1	26.5	10.8	30.2	5.9	26.7
2006	21.5	16.9	14.9	26.1	11.2	29.8	5.4	25.9
2007	20.9	17.0	16.2	25.1	11.9	30.2	3.2	26.0
2008	22.3	18.2	16.3	24.7	10.5	31.6	6.1	29.8
2009	21.7	16.7	16.1	26.6	12.5	33.1	6.3	25.8
2010	20.2	16.6	16.5	25.2	13.3	30.2	4.8	28.4
2011	20.8	17.0	15.0	25.5	9.9	34.6	4.0	30.6

Sources: National Center for Health Statistics, public use data sets, 1965, 1970, 1974, 1977, 1980, 1983, 1985, 1987–1988, 1990, 1992, 1994–1995, 1997–2011. The NHIS sample is representative of the civilian, noninstitutionalized population of the United States.
Notes: CS = Current smokers, defined as having smoked at least 100 cigarettes and currently smoking every day or some days (the some days condition was added in 1992); FS = former smokers, defined as having smoked at least 100 cigarettes but not currently smoking; **NHIS =** National Health Interview Survey.
[a]A questionnaire redesign of NHIS was implemented in 1997. Data preceding this year may not be directly comparable with data from 1997 and later.

Appended Table 12.3   **Relative risks by smoking status and age group, adults 35 years of age and older, United States**

A. Males

	Current smokers (years of age)				Former smokers (years of age)			
	35–54[a]	55–64[b]	65–74[b]	≥75[b]	35–54[a]	55–64[b]	65–74[b]	≥75[b]
Lung cancer	14.33	19.03	28.29	22.51	4.40	4.57	7.79	6.46
Other cancers[c]	1.74	1.86	2.35	2.18	1.36	1.31	1.49	1.46
Coronary heart disease	3.88	2.99	2.76	1.98	1.83	1.52	1.58	1.32
Other heart disease[d]			2.22	1.66			1.32	1.15
Cerobrovascular disease			2.17	1.48			1.23	1.12
Other vascular diseases[e]			7.25	4.93			2.20	1.72
Diabetes mellitus			1.50	1.00			1.53	1.06
Other cardiovascular diseases[f]	2.40	2.51			1.07	1.51		
Influenza, pneumonia, tuberculosis			2.58	1.62			1.62	1.42
Chronic obstructive pulmonary disease[g]			29.69	23.01			8.13	6.55
Influenza, pneumonia, tuberculosis, chronic obstructive pulmonary disease[h]	4.47	15.17			2.22	3.98		
All causes	2.55	2.97	3.02	2.40	1.33	1.47	1.57	1.41

B. Females

	Current smokers (years of age)				Former smokers (years of age)			
	35–54[a]	55–64[b]	65–74[b]	≥75[b]	35–54[a]	55–64[b]	65–74[b]	≥75[b]
Lung cancer	13.30	18.95	23.65	23.08	2.64	5.00	6.80	6.38
Other cancers[c]	1.28	2.08	2.06	1.93	1.24	1.28	1.26	1.27
Coronary heart disease	4.98	3.25	3.29	2.25	2.23	1.21	1.56	1.42
Other heart disease			1.85	1.75			1.29	1.32
Cerebrovascular disease			2.27	1.70			1.24	1.10
Other vascular diseases*[e]			6.81	5.77			2.26	2.02
Diabetes mellitus			1.54	1.10			1.29	1.06
Other cardiovascular diseases[f]	2.44	1.98			1.00	1.10		
Influenza, pneumonia, tuberculosis			1.75	2.06			1.28	1.21
Chronic obstructive pulmonary disease[g]			38.89	20.96			15.72	7.06
Influenza, pneumonia, tuberculosis, chronic obstructive pulmonary disease[h]	6.43	9.00			1.85	4.84		
All causes	1.79	2.63	2.87	2.47	1.22	1.34	1.53	1.43

Source: Analyses of Cancer Prevention Study II (CPS-II) and updated analyses of the pooled contemporary cohort population described in Thun et al. 2013 provided to the Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.

[a]Relative risks for 35–54 years of age, obtained from Cancer Prevention Study.

[b]Relative risks for 54–65 years of age, 65–74 years of age, and 75 years of age and older, obtained from merged contemporary cohorts (Thun et al 2012). Relative risks for women 55 years of age and older in diseases marked with * do not include data from the NHLBI Women's Health Initiative.

[c]Other cancers consist of cancers of the lip, pharynx and oral cavity, esophagus, stomach, pancreas, larynx, cervix uteri (women), kidney and renal pelvis, bladder, liver, colon and rectum, and acute myeloid leukemia.

[d]Other heart disease comprised of rheumatic heart disease, pulmonary heart disease, and other forms of heart disease.

[e]Other vascular diseases are comprised of atherosclerosis, aortic aneurysm, and other arterial diseases.

Appended Table 12.3   Continued

[f]For 35–54 years of age and ages 55–64 years of age, other cardiovascular diseases are comprised of other heart disease, cerebrovascular disease, other vascular diseases, and diabetes mellitus, analyzed and reported as category. A single relative risk based on combined conditions used to compute smoking-attributable mortality. Relative risk based on combined conditions used to compute smoking-attributable mortality in these age strata.

[g]Chronic obstructive pulmonary disease comprised of bronchitis, emphysema, and chronic airways obstruction.

[h]For 35–54 years of age and 55–64 years of age, influenza, pneumonia, tuberculosis, and chronic obstructive pulmonary disease analyzed and reported as 1 category. A single relative risk based on combined conditions was used to compute smoking attributable mortality.

Table 12.5 **Average annual smoking-attributable mortality (SAM) for males 35 years of age and older, total and by age group, United States, 2005–2009**

Disease	35–54 years of age		55–64 years of age		35–64 years of age		65–74 years of age		≥75 years of age		65 years of age and older: Total[a]		≥35 years of age: Total[a]	
	Deaths	SAM	Deaths	SAM	Deaths	SAM	Deaths	SAM	Deaths	SAM	Deaths	SAM	Deaths	SAM
Lung cancer	8,020	6,500	18,440	15,500	26,470	21,900	27,740	24,300	34,530	28,100	62,260	52,400	88,730	74,300
Other cancers[b]	13,370	2,800	22,540	5,400	35,900	8,200	26,380	7,900	40,660	10,300	67,040	18,200	102,940	26,000
Total—Cancers	**21,390**	**9,300**	**40,980**	**20,900**	**62,370**	**30,100**	**54,120**	**32,200**	**75,190**	**38,400**	**129,310**	**70,600**	**191,670**	**100,300**
Coronary heart disease	23,250	11,100	33,550	12,900	56,800	24,000	42,100	14,600	120,010	23,200	162,080	37,800	218,870	61,800
Other cardiovascular disease	18,900	5,100	23,230	8,000	42,130	13,100								
Other heart disease[d]							12,310	3,000	45,950	5,000	58,260	8,100	75,670	13,400
Cerebrovascular disease[d]							9,390	2,000	33,800	3,000	43,190	5,000	53,610	8,200
Other vascular disease[d]							2,930	1,700	8,680	3,400	11,610	5,100	14,480	6,000
Diabetes mellitus							8,350	2,100	15,420	500	23,780	2,600	35,200	6,200
Total—Cardiovascular and metabolic diseases	**42,150**	**16,200**	**56,780**	**20,900**	**98,930**	**37,100**	**75,050**	**23,400**	**223,860**	**35,100**	**298,910**	**58,600**	**397,840**	**95,600**
Pneumonia, influenza, tuberculosis, COPD[e]	3,970	2,200	8,780	7,100	12,750	9,200								
Pneumonia, influenza, tuberculosis[f]							3,460	1,200	17,930	3,900	21,380	5,100	25,300	7,800
COPD[g]							15,040	13,300	37,560	30,600	52,600	43,900	61,430	50,400
Total—Pulmonary diseases	**3,970**	**2,200**	**8,780**	**7,100**	**12,750**	**9,200**	**18,490**	**14,500**	**55,490**	**34,500**	**73,980**	**49,000**	**86,730**	**58,200**
total—cancers, cardiovascular and metabolic diseases, pulmonary diseases	**67,500**	**27,700**	**106,540**	**48,900**	**174,050**	**76,400**	**147,660**	**70,100**	**354,540**	**108,000**	**502,190**	**178,200**	**676,240**	**254,100**
All causes	**164,750**	**52,300**	**174,350**	**64,400**	**339,100**	**116,700**	**222,100**	**79,400**	**573,910**	**134,600**	**796,010**	**214,100**	**1,135,110**	**330,800**

Source: Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, unpublished data.

Note: Estimation of SAM based on relative risks from updated analyses of the pooled contemporary cohorts described in Thun et al. 2013. **COPD** = chronic obstructive pulmonary disease; **CVD** = cardiovascular disease.

[a] Row and column totals may not add up exactly due to rounding.

[b] Cancers of the lip, pharynx and oral cavity, esophagus, stomach, pancreas, larynx, cervix uteri, kidney and renal pelvis, bladder, liver, colon and rectum, and acute myeloid leukemia were combined into 1 disease category for both analysis and presentation. A single relative risk for the combined conditions was used to compute SAM.

[c] Other cardiovascular disease consists of other heart disease, CVD, atherosclerosis, aortic aneurysm, other arterial diseases, and diabetes mellitus. For 35–54 and 55–64 years of age, the relative risk for the combined conditions was used to compute SAM. For 65–74 and ≥75 years of age, separate relative risks for other heart disease, CVD, and other vascular diseases were used to compute SAM.

[d] For 65–74 and ≥75 years of age, other heart disease, CVD, other vascular disease, and diabetes mellitus also presented as separate conditions. Other vascular disease consists of atherosclerosis, aortic aneurysm, and other arterial diseases. Separate relative risks used to compute SAM for other heart disease, CVD, and diabetes mellitus. For other vascular disease, separate relative risks used to compute SAM for each condition before summing them for presentation.

[e] For 35–54 and 55–64 years, pneumonia, influenza, bronchitis, tuberculosis, and COPD were combined into 1 disease category for analysis and presentation. COPD consists of bronchitis, emphysema, and chronic airways obstruction. A single relative risk was used to compute SAM for the entire category.

[f] For 65–74 and ≥75 years of age, pneumonia/influenza/tuberculosis and COPD analyzed and presented as separate conditions. COPD consists of bronchitis, emphysema, and chronic airways obstruction. Separate relative risks were used to compute SAM for pneumonia/influenza/tuberculosis and for COPD.

[g] For ages 65–74 years and 75 years and older, pneumonia/influenza and COPD analyzed and presented as separate conditions. COPD consists of bronchitis, emphysema, and chronic airways obstruction. Separate relative risks were used to compute SAM for pneumonia/influenza and for COPD.

Appended Table 12.6   Average annual smoking-attributable mortality (SAM) for females 35 years of age and older, total and by age group, United States, 2005–2009

A. 35–64 years of age

Disease	35–54 years of age: Deaths	35–54 years of age: SAM	55–64 years of age: Deaths	55–64 years of age: SAM	35–64 years of age: Total[a] Deaths	35–64 years of age: Total[a] SAM
Lung cancer	6,390	4,800	12,690	10,100	19,080	14,900
Other cancers[b]	8,560	600	11,470	2,300	20,030	2,900
Total—Cancers	**14,950**	**5,400**	**24,160**	**12,400**	**39,110**	**17,800**
Coronary heart disease	7,480	3,900	12,920	3,800	20,400	7,600
Other cardiovascular disease[c]	12,320	2,900	15,800	2,400	28,120	5,300
Other heart disease[d]						
Cerebrovascular disease[d]						
Other vascular disease[d]						
Diabetes mellitus						
Total—Cardiovascular and metabolic diseases	**19,800**	**6,800**	**28,720**	**6,200**	**48,520**	**12,900**
Pneumonia, influenza, tuberculosis, COPD[e]	3,320	1,900	7,460	5,200	10,790	7,100
Pneumonia, influenza, tuberculosis[f]						
COPD[g]						
Total—Pulmonary diseases	**3,320**	**1,900**	**7,460**	**5,200**	**10,790**	**7,100**
Total—Cancers, cardiovascular and metabolic diseases, pulmonary diseases	**38,070**	**14,100**	**60,340**	**23,800**	**98,420**	**37,800**
All causes	100,410	17,300	114,312	29,500	214,730	46,800

Appended Table 12.6   Continued
B. 65 years of age and older

Disease	65–74 years of age: Deaths	65–74 years of age: SAM	75 years of age and older: Deaths	75 years of age and older: SAM	65 years of age and older: Total[a] Deaths	65 years of age and older: Total[a] SAM
Lung cancer	20,510	16,700	30,210	21,800	50,720	38,500
Other cancers[b]	15,980	2,500	39,530	4,400	55,510	7,000
Total—Cancers	**36,490**	**19,200**	**69,740**	**26,200**	**106,230**	**45,500**
Coronary heart disease	23,090	7,000	150,230	22,900	173,320	29,900
Other cardiovascular disease[c]						
Other heart disease[d]	9,950	1,600	75,440	8,400	85,390	10,000
Cerebrovascular disease[d]	8,720	1,600	64,210	3,900	72,930	5,400
Other vascular disease[d]	1,900	1,000	12,270	4,200	14,160	5,200
Diabetes mellitus	7,020	900	20,990	400	28,010	1,400
Total—Cardiovascular and metabolic diseases	**50,680**	**12,100**	**323,130**	**39,800**	**373,810**	**51,900**
Pneumonia, influenza, tuberculosis, COPD[e]						
Pneumonia, influenza, tuberculosis[f]	2,780	400	24,690	2,500	27,470	2,900
COPDg	14,400	12,900	43,930	32,000	58,330	44,900
Total—Pulmonary diseases	**17,190**	**13,300**	**68,620**	**34,500**	**85,800**	**47,800**
Total—Cancers, cardiovascular and metabolic diseases, pulmonary diseases	**104,360**	**44,600**	**461,490**	**100,500**	**565,850**	**145,200**
All causes	**173,960**	**47,600**	**803,030**	**130,600**	**976,980**	**178,200**

Appended Table 12.6   Continued

C. Total: 35 years of age and older

Disease	Deaths	SAM
Lung cancer	69,800	53,400
Other cancers[b]	75,540	10,000
Total—Cancers	**145,340**	**63,400**
Coronary heart disease	193,720	37,500
Other cardiovascular disease[c]		
Other heart disease[d]	96,200	12,100
Cerebrovascular disease[d]	81,300	7,100
Other vascular disease[d]	15,510	5,500
Diabetes mellitus	35,600	2,800
Total—Cardiovascular and metabolic diseases	**422,330**	**65,000**
Pneumonia, influenza, tuberculosis, COPD[e]		
Pneumonia, influenza, tuberculosis[f]	30,290	4,700
COPD[g]	66,300	50,200
Total—Pulmonary diseases	**96,590**	**54,900**
Total—Cancers, cardiovascular and metabolic diseases, pulmonary diseases	**664,260**	**183,300**
All causes	**1,191,710**	**225,000**

Source: Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, unpublished data.

Note: Estimation of SAM based on relative risks from updated analyses of the pooled contemporary cohort described in Thun et al. 2013. **CVD** = cardiovascular disease; **COPD** = chronic obstructive pulmonary disease.

[a]Row and column totals may not add up exactly due to rounding.

[b]Cancers of the lip, pharynx and oral cavity, esophagus, stomach, pancreas, larynx, cervix uteri, kidney and renal pelvis, bladder, liver, colon and rectum, and acute myeloid leukemia were combined into 1 disease category for both analysis and presentation. A single relative risk for the combined conditions was used to compute SAM.

[c]Other cardiovascular disease consists of other heart disease, CVD, atherosclerosis, aortic aneurysm, other arterial diseases, and diabetes mellitus. For 35–54 and 55–64 years of age, the relative risk for the combined conditions was used to compute SAM. For 65–74 and ≥75 years of age, separate relative risks for other heart disease, CVD, and other vascular diseases were used to compute SAM.

[d]For 65–74 and ≥75 years of age, other heart disease, CVD, other vascular disease, and diabetes mellitus also presented as separate conditions. Other vascular disease consists of atherosclerosis, aortic aneurysm, and other arterial diseases. Separate relative risks used to compute SAM for other heart disease, CVD and diabetes mellitus. For other vascular disease, separate relative risks used to compute SAM for each condition before summing them for presentation.

[e]For 35–54 and 55–64 years of age, pneumonia, influenza, bronchitis, tuberculosis and COPD were combined into 1 disease category for analysis and presentation. COPD consists of bronchitis, emphysema, and chronic airways obstruction. A single relative risk was used to compute SAM for the entire category.

[f]For 65–74 and ≥75 years of age, pneumonia/influenza/tuberculosis and COPD analyzed and presented as separate conditions. COPD consists of bronchitis, emphysema, and chronic airways obstruction. Separate relative risks were used to compute SAM for pneumonia/influenza/tuberculosis and for COPD.

Chapter 12 Appendices

Appendix 12.1

Other Methods Used to Calculate Smoking-Attributable Mortality

Several alternative methods have been developed for estimating the number of deaths attributable to smoking. The indirect method developed by Peto and colleagues (1992, 1994), often referred to as the "Peto-Lopez approach," has been used in countries where the data needed to estimate the population-attributable fraction (PAF) directly are not available. This approach uses the death rate for lung cancer in the country of interest as an indirect indicator of the cumulative risk of smoking. It calculates a smoking impact ratio that represents the absolute excess of lung cancer mortality in a population relative to the lung cancer mortality rate in a known group of nonsmokers, specifically the population from the Cancer Prevention Study II (CPS-II). This method does not require data on the prevalence of current or former smoking in the country of interest; this is inferred from the lung cancer mortality excess using the country-specific death rates for lung cancer and the age- and gender-specific death rates for lung cancer among never smokers in CPS-II. Because age-specific death rates among smokers in CPS-II tended to be twice those of nonsmokers, excess risks for all other diseases considered causally related to tobacco use are halved to produce conservative estimations for non-U.S. settings, and the smoking impact ratio is applied to these deaths to estimate the total smoking-attributable mortality (SAM).

Other researchers (Sterling et al. 1993; Malarcher et al. 2000; Thun et al. 2000a) have used model-based approaches to compute PAF. These approaches essentially expand the formula for PAF to include adjustments for potential confounding factors, including education, alcohol consumption, hypertension, diabetes, occupational risk factors, and income. These approaches were developed in part in response to methodologic concerns raised about possible confounding by differences in risk factors for tobacco-caused disease other than cigarettes across smoking groups (Sterling et al. 1993). However, the work by Malarcher and colleagues (2000) and Thun and colleagues (2000b) indicated that confounding affects SAM estimates only slightly (<1% difference in SAM with and without confounder adjustment) in the United States.

Leistikow (2004) and colleagues (2005, 2006, 2008) proposed estimating SAM based on the correlation between the trend in the national lung cancer mortality rate and the corresponding trend in mortality from all other cancers combined. To estimate SAM, this approach uses linear regression, age-adjusted rates from the Surveillance, Epidemiology, and End Results database, and the following formula:

$$Smoking\text{-}attributable\ fraction = 1 - \frac{rate\ in\ the\ unexposed}{rate\ in\ the\ exposed}$$

This approach attributes any change in the total rate of cancer to tobacco use and ignores co-temporal changes in other factors. Therefore, the approach may not accurately reflect the number of deaths from all types of cancers attributable to smoking.

Preston and colleagues (2010) developed a model-based approach to estimate SAM in high income countries. Like Peto and colleagues (1992, 1994), they used the lung cancer mortality rate as an indicator of the impact of smoking on the mortality from all other causes. But instead of applying relative risks (RRs) for lung cancer and other diseases from a previous study, such as CPS-II, they modeled the relationship between mortality from causes other than lung cancer as a function of lung cancer mortality and other variables within a macro-level statistical model, allowing the data to determine the lung-cancer mortality/all other cause mortality relationship for each country. Model outputs were used to compute SAFs for all-cause mortality. With one exception (Japan), the estimates of smoking-attributable fractions (SAFs) for the 20 countries studied were consistent with the findings of Peto and colleagues (1992, 1994). Rostron (2010) proposed refining this model with the addition of an interaction term for age and calendar year to better reflect mortality changes over time in causes other than lung cancer and produce female-specific results closer to those of Peto and colleagues (1992, 1994). Rostron (2010) also compared findings from the modified model-based method to findings computed using a modified Peto-Lopez indirect approach in which adjusted RRs based on mortality follow-up for participants from 1997–2003. Although RRs from the National Health Interview Survey (NHIS) Linked Mortality Files were used in place of RRs from CPS-II, the study found that the modified approaches produced comparable findings for the 20 countries studied.

Rostron (2011) also proposed a new method that considers potential confounding and uses finer age stratification than that of smoking-attributable mortality, morbidity, economic costs (SAMMEC). With this method, hazard ratios for all-cause mortality stratified by smoking

status are derived by matching NHIS participant records to the National Death Index. Smoking status is defined per responses to the NHIS, with current smokers categorized as light, medium, or heavy smokers based on the number of cigarette packs smoked per day (<1 pack, 1–1.9 packs, ≥2 packs). Hazard ratios are computed for 10-year age groups using a Cox proportional hazards model, fitting both unadjusted models and adjusted models that control for race, Hispanic ethnicity, marital status, education, family income, alcohol consumption, and body mass index.

Oza and colleagues (2011) proposed another method to compute SAM. The method is based on the indirect method developed by Peto and colleagues (1992) but also accounts for declining RRs due to widespread reduction in tobacco use. Declining RRs in former smokers produced somewhat smaller estimates than the indirect method. However, both approaches produced larger SAM estimates than those produced by the PAF approach.

Recent Estimates of Smoking-Attributable Mortality in the United States

Estimates by CDC (2008, 2009)

The Centers for Disease Control and Prevention ([CDC] 2008) published updated calculations of SAM and years of potential life lost (YPLL) calculations, covering the period 2000–2004. CDC estimated approximately 393,000 annual deaths from the 19 disease categories among adults and the four adverse infant health outcomes for which there was sufficient evidence to infer a causal relationship with smoking (National Cancer Institute 1999; U.S. Department of Health and Human Services [USDHHS] 2004). The 19 adult diseases included neoplasms (of the lip, oral cavity, and pharynx; esophagus; stomach; pancreas; larynx; trachea, bronchus, and lung; cervix; bladder; kidney and other urinary tract; and acute myeloid leukemia), cardiovascular diseases (coronary heart disease, other heart disease, cerebrovascular disease, atherosclerosis, aortic aneurysm, and other arterial disease), and respiratory diseases (pneumonia and influenza, bronchitis and emphysema, and chronic airways obstruction). The perinatal conditions included short gestation and low birth weight, respiratory distress syndrome, other respiratory conditions in newborns, and sudden infant death syndrome.

Calculations of SAFs and SAMs were based on RRs for smoking-related diseases and smoking prevalence estimates for current and former smokers, 35 years of age and older, and for maternal smokers. Age-adjusted RR data were obtained from CPS-II (1982–1988); gender-specific smoking prevalence data for adults, 35 years of age and older, were obtained from NHIS. RR estimates for the death of infants whose mothers smoked during pregnancy were obtained from studies by McIntosh (1984) and Gavin and colleagues (2001). Data on the prevalence of maternal smoking were obtained from birth certificates for most states for 2000–2004 (National Center for Health Statistics [NCHS] n.d.). Age- and gender-specific mortality data were also obtained from the NCHS (Minino et al. 2007). YPLL for persons 35 years of age and older were calculated using remaining life expectancy—that is, life expectancy at any given age of death minus age at death and for infants, from birth.

Based on these data, annual SAM for men 35 years of age and older was approximately 104,500 for cancers, 79,100 for cardiovascular diseases, and 53,800 for respiratory diseases. For women 35 years of age and older, the annual SAM was 56,400 for cancers, 49,400 for cardiovascular diseases, and 49,500 for respiratory diseases. The largest numbers of smoking-attributable deaths were from lung cancer, coronary heart disease, and chronic obstructive pulmonary disease (COPD) (124,800, 82,000, and 64,700, respectively, for men and women combined). SAM based on these 19 conditions was responsible for the total annual YPLL of 3,319,000 for males and 2,152,600 for females. Smoking during pregnancy was estimated to result in 560 deaths in infant males and 410 deaths in infant females annually.

CDC also estimated that approximately 740 deaths are attributable to residential fires caused by smoking (Hall 2012) and 49,400 deaths in adults from lung cancer and coronary heart disease due to exposure to second-hand smoke (California Environmental Protection Agency 2005), for an overall total of approximately 444,000 premature deaths annually from active smoking and exposure to tobacco smoke.

CDC also published state-based SAM calculations for 2000–2004 (CDC 2009). The average annual number of smoking-attributable deaths ranged from 492 (Alaska) to 36,687 (California), with a median of 5,534. In all states, the number of smoking-attributable deaths was higher for males than females. SAM rates per 100,000 population were lowest in Utah (138.3), Hawaii (167.6), and Minnesota (215.1) and highest in Kentucky (370.6), West Virginia (344.3), and Nevada (343.7). The median average annual SAM rate for 2000–2004 was 263.3 deaths per 100,000. These rates reflect differences in smoking prevalence and in population and mortality distributions among states. In general, lower SAM rates were observed in states with lower prevalence of smoking.

Estimates by Rogers (2005)

Rogers and colleagues (2005) estimated excess deaths attributable to cigarette smoking in the United States in 2000 by using discrete-time hazard models and life tables with covariates to take into account smoking status and multiple demographic and lifestyle covariates. Data regarding baseline smoking and demographic and lifestyle variables were obtained from the Health Promotion and Disease Prevention supplement to the 1990 NHIS. Death rates were based on mortality follow-up for 1990–1997 in the linked NHIS-Multiple Cause of Death files. Categorization of smoking was based on both status (current, former, and never) and amount smoked daily by current smokers and former smokers before they quit. Covariates in the models included age, gender, race, marital status, family income, employment status, education, drinking status, seatbelt use, stress, physical activity, and body mass index. Rogers and colleagues (2005) estimated that 338,000 deaths attributable to smoking could have been averted in the United States in 2000 if current and former smokers had the same mortality experience as never smokers. They estimated about 57,000 fewer smoking-attributable deaths than reported by CDC for 2001 (CDC 2002), a gap they attributed to differences in methods, time periods, subpopulations, and assumptions. They also noted that controlling confounding factors had a modest impact on the relationship between smoking and mortality, which was consistent with previous studies (Malarcher et al. 2000; Thun et al. 2000b).

Estimates by Danaei and Colleagues (2009)

Danaei and colleagues (2009) estimated mortality attributable to 12 modifiable dietary, lifestyle, and metabolic risk factors in the United States. These risk factors included high blood glucose, low-density lipoprotein, cholesterol, blood pressure, overweight-obesity, high dietary trans fatty acid intake, dietary salt intake, low dietary polyunsaturated fatty acid intake, omega-3 fatty acid intake, fruit and vegetable intake, physical activity, alcohol use, and smoking. The study used the smoking impact ratio (Peto et al. 1992) as the metric for tobacco exposure and incorporated 18 diseases and conditions having a smoking-attributable component. These diseases and conditions corresponded closely to the conditions used in SAMMEC, but Danaei and colleagues (2009) also included diabetes mellitus, colorectal cancer, tuberculosis, and hypertensive disease. RRs for most smoking-attributable conditions were derived primarily from CPS-II, but RRs for diabetes and tuberculosis were obtained from meta-analyses of large prospective cohorts (for diabetes) or cohort, case-control, and cross-sectional studies (for tuberculosis).

According to Danaei and colleagues, tobacco smoking accounted for an estimated 467,000 deaths (95% confidence interval, 436,000–500,000) in the United States in 2005.

Estimates by Preston and Colleagues (2010) and Rostron (2010)

Using their model-based approach, Preston and colleagues (2010) estimated that 24% of deaths among persons 50 years of age and older in the United States were attributable to smoking in 2003. This result translates to about 26,000 fewer smoking-attributable deaths in males and about 97,000 more smoking-attributable deaths in females in the United States in 2003 than that estimated by CDC for adults, 35 years of age and older (CDC 2008). Rostron (2010)—noting differences in both the totals and the age distribution of smoking-attributable deaths for females when comparing the approach of Peto and colleagues (1992, 1994) with that of Preston and colleagues (2010)—modified the model-based approach by adding an age-by-year interaction term. Results for females using the modified approach (166,000 smoking-attributable deaths in 2003 among women 50 years of age and older) were more consistent with the results from CDC (174,000 smoking-attributable deaths per year in 2000–2004 among women 35 years of age and older).

Estimates by Rostron (2011, 2013)

Rostron (2011) used a survival analysis approach to compute adult SAM for 2002–2006 in the United States. The RR estimates were based on mortality follow-up of adults in the NHIS from 1997–2004 to 2006. Overall, the study estimated that 291,000 men and 229,000 women died annually from 2002–2006 as a result of smoking. This approach avoided the issue of changing RRs over time by using RRs based on observations of smoking behavior made in a cohort that was followed during the period for which SAM was estimated. This approach produced somewhat higher estimates of SAM than those published in 2008 using SAMMEC, particularly for women, which the author postulated was due to using a more recent data source for estimating smoking exposure. In a subsequent study, Rostron (2013) used CDC's SAMMEC methodology with RRs derived from mortality follow-up using public use data from 1997–2004 from NHIS Linked Mortality Files. The public use files contained perturbed data, in which date and underlying cause of death are replaced with synthetic data for selected decedents to reduce the risk of respondent identification. Although this technique is considered unlikely to cause large changes in results, caution should be used when interpreting results for

specific causes of death. Rostron (2011) used these data to calculate RRs adjusted for race/ethnicity, educational attainment, alcohol consumption, and body mass index. Deaths related to exposure to secondhand smoke were not included. With this approach, Rostron estimated about 380,000 smoking-attributable adult deaths in the United States in 2004.

Estimates by Oza and Colleagues (2011)

Oza and colleagues (2011) performed a comparative analysis of methods to compute SAM for the United States in 2005. They used three methods: (1) the Peto-Lopez approach; (2) the Peto-Lopez approach modified to account for lower RRs for many diseases in former smokers; and (3) the PAF method. RRs for smoking-attributable diseases were obtained from CPS-II. For the PAF method, current and former smoking prevalence was computed using data from the National Health and Nutrition Examination Survey for 2003–2004 and 2005–2006. Based on the unmodified Peto-Lopez method, smoking-attributable estimates of deaths reported by Oza and colleagues (2011) were 254,700 and 227,000 for males and females, respectively. Accounting for lower RRs for many diseases in former smokers produced a small reduction in the number of smoking-attributable deaths: 251,900 and 221,100, respectively. The PAF method produced the smallest estimates of SAM, with estimates of 225,800 for males and 163,700 for females.

The four sets of estimates share PAF as the common conceptual base. However, differing methods were used to develop the RRs used for the calculations. Rostron (2011, 2013) used estimates obtained from the NHIS follow-up from 1997–2004, and other estimates were directly (CDC 2008) or indirectly (Danaei and colleagues 2009; Oza and colleagues 2011) from CPS-II. Nonetheless, the resulting estimates spanned a relatively narrow range from about 440,000–500,000.

Recent Estimates of Smoking-Attributable Mortality in Other Countries

The World Health Organization (WHO 2012) published a global report regarding mortality attributable to tobacco. WHO reported that in 2004, about 5 million deaths attributable to tobacco use (combustible and noncombustible) occurred in adults, 30 years of age and older, worldwide, or 1 death about every 6 seconds. These 5 million deaths represented about 12% of global deaths in this age range, with 16% of deaths in men and 7% of deaths

in women being attributable to tobacco use. The Americas and European WHO regions had the highest proportion of deaths attributable to tobacco use (16% for both), while the Eastern Mediterranean (7%) and African (3%) regions had the lowest proportion of deaths (WHO 2012). Worldwide, 5% of deaths from communicable diseases and 14% of deaths from noncommunicable diseases are attributable to tobacco use. Within communicable diseases, lower respiratory infections and tuberculosis have the highest proportions of deaths attributable to tobacco use (12% and 7%, respectively). Noncommunicable diseases with the highest proportions of deaths attributable to tobacco use are respiratory diseases (36%), cancers (22%), and cardiovascular diseases (10%). Globally, 71% of deaths from lung cancer and 42% of deaths from COPD are attributable to tobacco use (WHO 2012).

Lim and colleagues (2012) systematically reviewed and synthesized published and unpublished data to estimate deaths and disability-adjusted life years (DALYs) attributable to the independent effects of 67 risk factors and clusters of risk factors for 21 regions in 1990 and 2010. The Peto-Lopez approach was used to estimate the burden from smoking. In this comprehensive study, tobacco smoking, including exposure to secondhand smoke, was among the top three contributors to global disease burden in both years, accounting for more than 5 million deaths in 1990 and more than 6 million in 2010, and above 150 million DALYs in both years. In 2010, tobacco smoking accounted for 8.4% of the global disease burden among men and was the leading risk factor, and accounted for 3.7% of disease burden among women (fourth highest risk factor); it was the second leading cause of disease for both genders combined (Lim et al. 2012).

Öberg and colleagues (2011) examined burden of disease from exposure to secondhand smoke in 2004 for 192 counties, computing attributable deaths and DALYs for children and nonsmoking adults. They estimated that globally, 33% of nonsmoking males, 35% of nonsmoking females, and 40% of children were exposed to secondhand smoke. They reported that about 603,000 deaths, or 1% of global mortality, were attributable to exposure to secondhand smoke—with 47% of deaths occurring in women, 26% in men, and 28% in children. The most common causes of death worldwide attributable to exposure to secondhand smoke were coronary heart disease, lower respiratory infections, asthma, and lung cancer. In addition, about 10.9 million DALYs (0.7% of global burden of disease in DALYS) were attributable to exposure to secondhand smoke. Of these DALYs, 61% were in children; the highest burdens of disease were for lower respiratory infections (children <5 years of age), coronary heart disease (adults), and asthma (adults and children).

Thun and colleagues (2013) published estimates of mortality attributable to tobacco for 41 medium and high resource countries for 1950 through the most recent time for which data were available (typically 2005–2009). This was done in context of a four-stage model, as first proposed by Lopez and colleagues (1994), that was developed to describe the tobacco epidemic and explain the lengthy delay between widespread adoption of smoking by a population and the full effects on mortality. The analysis was undertaken in part to examine predictions derived from the model in light of recent past declines in smoking prevalence. They reported that over the past two decades, SAM for males, which had peaked in the 1960s to 1980s in many of the counties examined, was level or declining in most of the countries. The largest declines were observed in Finland and England, but not much of a decline was observed in Bulgaria, Greece, Hungary, Japan, Norway, Portugal, Romania, and Spain. However, during that same time, SAM in females was increasing or plateauing, and even increasing rapidly in some countries (e.g., The Netherlands). Projecting the model to 2025, the authors expect both the prevalence of smoking and SAM to decline in parallel in most developed countries. They also noted that the four-stage model seemed generalizable to men in developing countries, but not women, particularly in predicting widespread uptake of smoking—suggesting that developing gender-specific models may be more appropriate for these countries (Thun et al. 2013).

Appendix 12.2

Methodology

In 1996, the Centers for Disease Control and Prevention (CDC) projected the future impact of smoking on the health of children and teenagers if then current tobacco use patterns persisted across the lives of this cohort of youth. Among the 68.7 million youth 0–17 years of age in 1995, CDC estimated that 16.6 million of them would become smokers as young adults and that 5.3 million of them would die prematurely from a smoking-related illness. For this model in 1996, the number of future adult smokers was calculated by projecting the future number of smokers from this cohort that would continue to smoke throughout their lives. The future total of smoking-related deaths among youth smokers was calculated by estimating the number of future adult smokers from the 68.7 million youth. The model then applied estimates of premature death attributable to smoking among continuing smokers (Peto and Lopez 1994) and among those who quit smoking after the age of 35 years (Mattson et al. 1987). Based on data from the 1986 National Mortality Followback Survey, 55% (95% confidence interval [CI] ± 1%) of persons who had ever smoked at least 100 cigarettes during their lifetimes continued to smoke until 1 year before their deaths, and 45% (95% CI ± 1%) quit smoking earlier in their adult lives (CDC, unpublished data). Based on data from long-term cohort studies, an estimated 50% of deaths among continuing smokers were attributable to smoking (Peto and Lopez 1994). Although estimates of the number of smoking-attributable deaths among former smokers ranged from 10% to 37%, a conservative estimate of 10% was used in the 1996 analysis (Mattson et al. 1987; CDC 1996; CDC unpublished data). The future probability of smoking-attributable mortality (PSAM) among youth was computed to be 0.32 ([0.55 x 0.5] + [0.45 x 0.1]). Estimates for the variance of the two smoking-attributable fractions (50% and 10%) within the PSAM were computed from the American Cancer Society's Cancer Prevention Study II (Thun et al. 1995). These two variances were combined with the variances for the probabilities of continued smoking or quitting smoking using a Taylor Series approximation method, which yielded an estimate of 0.00422 for the relative error of the PSAM. To reflect the uncertainty of the multiple assumptions about future smoking and mortality patterns, this error estimate for the PSAM was increased by a factor of 2.5, yielding an estimated standard error of 0.0106.

However, as reviewed in this report, input data have changed since this model was used in 1996. For example, the relative risks for major diseases caused by smoking—including lung cancer and chronic obstructive pulmonary disease (see Chapter 12, particularly Table 12.3)—were higher for 2000–2012 than those obtained from the two cohort studies from the American Cancer Society, which examined data from 1959 to 1986 (see Chapters 11 and 12). As reviewed in Chapter 13, patterns of quitting smoking are improving in the United States (see Figure 13.17). Furthermore, in 2012, approximately 40% of adult smokers quit smoking before 45 years of age and approximately 57% did so before 65 years of age (see Table 13.9). However, about 60% of adult smokers continue to smoke beyond 40 years of age. Although data indicate benefits to quitting smoking even later in life, the proportion of the excess risk that can be prevented declines with age

(Jha et al. 2013; Thun et al. 2013). Approximately one in six young adult smokers who do not quit until 40 years of age still may die prematurely from a smoking-related disease, but the excess risk more than doubles among former smokers who do not quit before 55 years of age (Jha et al. 2013). Among continuing smokers in the United States, an estimated 60% of premature deaths are attributable to smoking (Jha et al. 2013). An updated estimate of the PSAM based on these recent patterns of quitting and new risks reviewed in this report has not been computed. This uncertainty is not reflected in the CI.

Findings

Although the patterns of quitting smoking are improving, the risk of premature death from smoking-related illness among former smokers and continuing smokers is higher than that calculated in 1996. The model used by CDC in 1996 was used to calculate updated estimates on the number of youth in the United States who will become future smokers and will die prematurely of a smoking-related illness (Tables 12.1.1 and 12.1.2). State-specific data on the prevalence of current smoking among adults, 18–30 years of age, in each state and the District of Columbia, were obtained from the Behavioral Risk Factor Surveillance System (BRFSS) for 2011–2012. Current smokers were respondents who reported having smoked at least 100 cigarettes during their lifetimes and who reported currently smoking. Because the prevalence of smoking in a birth cohort peaks during early adulthood (see Chapter 13), the average prevalence of smoking among adults 18–30 years of age in each state during 2011–2012 was used to estimate the future prevalence of smoking during early adulthood for the 0–17-years-of-age

birth cohort in 2012. The number of persons 0–17 years of age in each state in 2012 was obtained from the National Center for Health Statistics (2013). This figure was multiplied by the state-specific prevalence of smoking among those 18–30 years of age to calculate the number of youth anticipated to become regular smokers in each state. Overall, the estimated number of future smokers from the 0–17-years-of-age birth cohort in 2012 in the United States was 17,371,000 (ranging from 22,300 in the District of Columbia to 1,557,800 in Texas) (Table 12.2.1).

Based on the application of PSAM (0.32) to the state-specific estimates of potential smokers, the overall number of potential future smoking-attributable deaths among youth 0–17 years of age during 2012 in the United States was 5,557,000 (ranging from 7,000 in the District of Columbia to 498,000 in Texas) (Table 12.2.1). Based on the estimated PSAM variance and the state-specific sampling errors on estimates of smoking prevalence from the BRFSS, the estimated number of overall smoking-related deaths in the United States was predicted to vary on a statistical basis by less than or equal to 115,000 deaths. The CIs did not account for other sources of uncertainty, such as future changes in risk of dying from smoking or a greater quitting rate earlier in life in the future.

These state-specific estimates were also used to calculate the proportion of youth, 0–17 years of age, who are projected to die prematurely from a smoking-related illness (Table 12.2.2). At the state level, estimates varied almost threefold, from 4.4% in Utah to 12.3% in West Virginia. Overall, 7.5% of youth from the 0–17-years-of-age birth cohort in 2012 in the United States are projected to die prematurely from a smoking-related illness if current rates of smoking and risk of disease associated with smoking persist.

Table 12.2.1 Prevalence of current smoking among adults, 18–30 years of age,[a] and projected number of persons, 0–17 years of age, who will become smokers and die prematurely as adults because of a smoking-related illness, by state—United States, 2012

State	Prevalence (%) of current smoking 18–30 years of age (± 95% CI)	Population, 0–17 years of age[b]	Projected number of smokers 0–17 years of age (± 95% CI)	Projected number of deaths 0–17 years of age
Alabama	29.9 (2.9)	1,124,406	336,200 (303,600–368,800)	108,000
Alaska	23.3 (3.1)	187,100	43,600 (37,800–49,400)	14,000
Arizona	22.2 (3.5)	1,620,894	359,800 (303,100–416,600)	115,000
Arkansas	30.2 (4.0)	710,881	214,700 (186,300–242,400)	69,000
California	14.9 (1.3)	9,240,219	1,376,800 (1,256,700–1,496,900)	441,000
Colorado	23.0 (2.0)	1,231,358	283,200 (258,600–307,800)	91,000
Connecticut	22.1 (2.8)	793,558	175,400 (153,200–197,600)	56,000
Delaware	26.2 (3.4)	205,050	53,700 (46,800–60,700)	17,000
District of Columbia	20.4 (3.7)	109,480	22,300 (18,300–26,400)	7,000
Florida	21.1 (2.6)	4,002,480	844,500 (740,500–944,600)	270,000
Georgia	25.6 (2.7)	2,490,125	637,500 (570,200–704,700)	204,000
Hawaii	22.1 (2.7)	303,011	67,000 (58,800–74,800)	21,000
Idaho	22.1 (3.5)	426,653	94,300 (79,400–108,800)	30,000
Illinois	23.5 (3.3)	3,064,065	720,100 (618,900–818,100)	230,000
Indiana	29.6 (2.5)	1,591,477	471,100 (431,300–509,300)	151,000
Iowa	23.8 (2.5)	722,953	172,100 (154,000–189,400)	55,000
Kansas	26.4 (1.7)	724,304	191,200 (178,900–204,300)	61,000
Kentucky	36.5 (2.8)	1,018,238	371,700 (343,100–401,200)	119,000

Table 12.2.1 Continued

State	Prevalence (%) of current smoking 18–30 years of age (± 95% CI)	Population, 0–17 years of age[b]	Projected number of smokers 0–17 years of age (± 95% CI)	Projected number of deaths 0–17 years of age
Louisiana	27.5 (2.8)	1,117,803	307,400 (276,100–338,700)	98,000
Maine	31.7 (2.5)	265,918	84,300 (77,600–91,200)	27,000
Maryland	21.5 (2.7)	1,343,800	288,900 (252,600–325,200)	92,000
Massachusetts	23.0 (1.8)	1,401,415	322,300 (297,100–349,000)	103,000
Michigan	29.4 (2.5)	2,266,870	666,500 (609,800–723,100)	213,000
Minnesota	25.0 (2.0)	1,276,148	319,000 (293,500–343,300)	102,000
Mississippi	28.7 (2.6)	745,333	213,900 (194,500–234,000)	68,000
Missouri	28.4 (2.9)	1,403,475	398,600 (357,900–440,700)	128,000
Montana	26.6 (2.4)	221,980	59,000 (53,700–64,200)	19,000
Nebraska	25.6 (1.5)	463,405	118,600 (111,700–125,600)	38,000
Nevada	19.4 (2.9)	663,583	128,700 (109,500–147,300)	41,000
New Hampshire	24.7 (3.3)	274,840	67,900 (58,800–77,000)	22,000
New Jersey	22.0 (2.1)	2,026,384	445,800 (403,300–486,300)	143,000
New Mexico	24.2 (2.2)	514,442	124,500 (113,200–135,300)	40,000
New York	20.5 (2.4)	4,263,154	873,900 (771,600–976,300)	280,000
North Carolina	24.6 (2.2)	2,286,528	562,500 (512,200–612,800)	180,000
North Dakota	28.1 (3.1)	154,608	43,400 (38,700–48,200)	14,000
Ohio	30.4 (2.5)	2,663,674	809,800 (743,200–876,300)	259,000
Oklahoma	29.4 (2.6)	937,363	275,600 (251,200–300,900)	88,000

Table 12.2.1 Continued

State	Prevalence (%) of current smoking 18–30 years of age (± 95% CI)	Population, 0–17 years of age[b]	Projected number of smokers 0–17 years of age (± 95% CI)	Projected number of deaths 0–17 years of age
Oregon	24.8 (3.0)	860,624	213,400 (187,600–239,300)	68,000
Pennsylvania	27.8 (2.1)	2,739,386	761,500 (704,000–821,800)	244,000
Rhode Island	22.5 (3.1)	216,474	48,700 (42,000–55,400)	16,000
South Carolina	29.9 (2.3)	1,080,090	322,900 (298,100–347,800)	103,000
South Dakota	32.2 (3.2)	204,169	65,700 (59,200–72,500)	21,000
Tennessee	26.2 (4.1)	1,494,016	391,400 (330,200–452,700)	125,000
Texas	22.3 (2.1)	6,985,639	1,557,800 (1,411,100–1,704,500)	498,000
Utah	13.6 (1.4)	887,972	120,800 (108,300–132,300)	39,000
Vermont	25.4 (3.1)	123,951	31,500 (27,600–35,200)	10,000
Virginia	25.3 (2.8)	1,856,737	469,800 (417,800–521,700)	150,000
Washington	20.5 (1.9)	1,584,967	324,900 (294,800–356,600)	104,000
West Virginia	38.5 (3.4)	384,041	147,900 (134,800–160,500)	47,000
Wisconsin	25.2 (3.2)	1,317,557	332,000 (289,900–374,200)	106,000
Wyoming	27.9 (3.2)	135,490	37,800 (33,500–42,100)	12,000
Total		73,728,088	17,371,900 (15,604,600–19,133,800)	5,557,000

Source: Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, unpublished data.

Note: **CI** = confidence interval.

[a]Prevalance data were obtained from the Behavioral Risk Factor Surveillance System.

[b]Population estimates were obtained from the National Center for Health Statistics 2013.

Table 12.2.2 Proportion (%) of persons, 0–17 years of age, who are projected to become smokers and die prematurely as adults because of smoking-related illness, by state—United States, 2012

State	Population, 0–17 years of age[a]	Projected number of deaths	Proportion (%) of population projected to die prematurely
Alabama	1,124,406	108,000	9.6
Alaska	187,100	14,000	7.5
Arizona	1,620,894	115,000	7.1
Arkansas	710,881	69,000	9.7
California	9,240,219	441,000	4.8
Colorado	1,231,358	91,000	7.4
Connecticut	793,558	56,000	7.1
Delaware	205,050	17,000	8.4
District of Columbia	109,480	7,000	6.5
Florida	4,002,480	270,000	6.8
Georgia	2,490,125	204,000	8.2
Hawaii	303,011	21,000	7.1
Idaho	426,653	30,000	7.1
Illinois	3,064,065	230,000	7.5
Indiana	1,591,477	151,000	9.5
Iowa	722,953	55,000	7.6
Kansas	724,304	61,000	8.4
Kentucky	1,018,238	119,000	11.7
Louisiana	1,117,803	98,000	8.8
Maine	265,918	27,000	10.1
Maryland	1,343,800	92,000	6.9
Massachusetts	1,401,415	103,000	7.4
Michigan	2,266,870	213,000	9.4
Minnesota	1,276,148	102,000	8.0
Mississippi	745,333	68,000	9.2
Missouri	1,403,475	128,000	9.1
Montana	221,980	19,000	8.5
Nebraska	463,405	38,000	8.2
Nevada	663,583	41,000	6.2
New Hampshire	274,840	22,000	7.9
New Jersey	2,026,384	143,000	7.0
New Mexico	514,442	40,000	7.7
New York	4,263,154	280,000	6.6
North Carolina	2,286,528	180,000	7.9

Table 12.2.2   Continued

State	Population, 0–17 years of age[a]	Projected number of deaths	Proportion (%) of population projected to die prematurely
North Dakota	154,608	14,000	9.0
Ohio	2,663,674	259,000	9.7
Oklahoma	937,363	88,000	9.4
Oregon	860,624	68,000	7.9
Pennsylvania	2,739,386	244,000	8.9
Rhode Island	216,474	16,000	7.2
South Carolina	1,080,090	103,000	9.6
South Dakota	204,169	21,000	10.3
Tennessee	1,494,016	125,000	8.4
Texas	6,985,639	498,000	7.1
Utah	887,972	39,000	4.4
Vermont	123,951	10,000	8.1
Virginia	1,856,737	150,000	8.1
Washington	1,584,967	104,000	6.6
West Virginia	384,041	47,000	12.3
Wisconsin	1,317,557	106,000	8.1
Wyoming	135,490	12,000	8.9
Total	73,728,088	5,557,000	7.5

Source: Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, unpublished data.

[a]Population estimates were obtained from the National Center for Health Statistics 2013.

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Chapter 13
Patterns of Tobacco Use Among U.S. Youth, Young Adults, and Adults

Introduction

In the United States, the widespread use of tobacco began more than a century ago, and the epidemic of tobacco-caused diseases and premature mortality associated with tobacco use has continued to the present day. The purpose of the current chapter is to document key patterns and trends in tobacco use in the United States among youth (12–17 years of age), young adults (18–25 years of age), and adults age 26 years of age or older. The chapter indicates overall progress in the United States, but describes the persistence of a high prevalence of tobacco use among segments of the population. Historically, reports of the Surgeon General have focused almost exclusively on cigarette smoking, but the shifting patterns of tobacco use have necessitated the consideration of other products, both those that are noncombustible and others that deliver nicotine. Accordingly, this chapter includes critical information about cigars and smokeless tobacco, and it highlights changing patterns of tobacco use. Information about new and emerging products, such as e-cigarettes, is also included. Clearly, the effective characterization of key patterns and trends in tobacco use is critical to the development and maintenance of programs designed to reduce the burden of tobacco-caused morbidity and mortality.

Data Sources

In the United States, a variety of national surveillance systems collect tobacco-specific data for youth, young adults, and adults. These systems typically assess behaviors related to cigarette smoking and, sometimes, the use of other tobacco products; some also collect information on important aspects of tobacco use (e.g., quit attempts). These surveys have differing methods and provide comparable, but not identical, measures of tobacco use. Because each survey provides unique information, monitoring the results of all of them is necessary to fully understand behaviors and trends. The principal surveys used in this chapter are described in Appendix 13.1, and additional information about data sources for adolescents is available in the 2012 Surgeon General's report, *Preventing Tobacco Use Among Youth and Young Adults* (U.S. Department of Health and Human Services [USDHHS] 2012). For this chapter, specific national surveillance systems were selected to serve as primary data sources based on the salience of their content, the timeliness of their data, the completeness with which they cover the populations they are intended to represent, and the strength of their methodology.

In this chapter, cross-sectional data are presented from three national surveillance systems: Youth Risk Behavior Surveillance System (YRBSS), National Survey on Drug Use and Health (NSDUH), and National Health Interview Survey (NHIS). Each of these population-based systems uses anonymous or confidential self-reported surveys to gather data. Generally, self-reported data are considered to be sufficiently accurate for tracking the general pattern of tobacco use in populations (Brener et al. 2003; USDHHS 2004). Table 13.1 and Appendix 13.1 describe the three data sources in detail, and Appendix 13.2 defines the survey items and terms used in the present report.

YRBSS includes both state and local surveys and a national survey. The National Youth Risk Behavior Survey (YRBS) uses probability samples of public and private high school students who fill out questionnaires administered anonymously in schools. This survey is representative of the U.S. high school population. National YRBS data are available from 1991–2011 and are used in this report to illustrate trends over time. In contrast to YRBS, NSDUH, which is conducted under the direction of the federal Substance Abuse and Mental Health Services Administration (SAMHSA) employs household-based sampling, which is designed to represent the entire civilian, noninstitutionalized population of the United States from 12 years of age and older. A major strength of NSDUH is that the national sample is allocated equally across three age-specific population groups that were defined earlier in this chapter: youth, young adults, and adults. In addition, NSDUH includes youth who have dropped out of school or are frequently absent, which are two groups more likely to smoke. NSDUH is the only national surveillance system that has a wide repertoire of tobacco-use measures that can be compared across the three priority populations. Questionnaires for NSDUH are completed confidentially in the home with audio computer-assisted self-interviewing so that only the respondent is aware of the questions being asked. Unless otherwise indicated, all NSDUH data presented in this chapter are from the 2012 survey. Last, NHIS, which has been a primary source of health data on the U.S. adult population since the 1950s, is an annual cross-sectional household interview survey of the adult (18

Table 13.1   Sources of national survey data on tobacco use, United States

	NSDUH	National YRBS	NHIS
Sponsoring agency or organization	SAMHSA	CDC	CDC
Type of survey	Cross-sectional	Cross-sectional	Cross-sectional
Years	2012	1991, 1993, 1995, 1997, 1999, 2001, 2003, 2005, 2007, 2009, and 2011	1965–2012 (various years)
Mode of survey administration	Audio computer-assisted self-administered personal interview	School-based, self-administered questionnaire	Computer-assisted personal interview
Response rate	2012: 86.1% for household screening; 73.0% for interviewing	2011: 81% for schools; 87% for students; 71% overall	2010: 60.8% for household adults 2012: 61.2% for household adults
Sample size	2012: 68,309 persons ≥12 years of age, including 45,836 adults ≥18 years of age	2011: 15,425 9th–12th grade students	2010: 27,157 adults ≥18 years of age 2012: 34,525 adults ≥18 years of age
Type of tobacco use examined	Cigarettes, smokeless tobacco (chewing tobacco, snuff), cigars, and pipe tobacco	Cigarettes, smokeless tobacco, and cigars	Cigarettes (annually), smokeless tobacco, and cigars (selected years)

Note: **CDC** = Centers for Disease Control and Prevention; **NHIS** = National Health Interview Survey; **NSDUH** = National Survey on Drug Use and Health; **SAMHSA** = Substance Abuse and Mental Health Services Administration; **YRBS** = National Youth Risk Behavior Survey.

years of age and older) U.S. civilian noninstitutionalized population. NHIS data on tobacco use are available for the period 1965–2011 and are used in this report to illustrate trends over time. In addition, data from NHIS were pooled into a combined dataset and analyzed to obtain estimates of changes in the patterns of use of cigarettes over time by gender, calendar year, and birth cohorts from 1890–1990 (Holford et al. in press).

Key Epidemiologic Measures

This chapter covers a variety of epidemiologic measures, including the age when cigarette smoking begins, current prevalence of daily and intermittent cigarette smoking, indicators of smoking cessation, current prevalence of smokeless tobacco use and cigar smoking, and current prevalence of polytobacco use (i.e., the use of multiple tobacco products). Data from the survey or surveys best suited to address the issue were selected for presentation in the text and accompanying tables and figures. The most recent estimates (i.e., those for 2012) use data from NSDUH, while estimates of cessation indicators rely on data from NHIS. Trends over time among youth are based on data from the National YRBS, and trends over time among adults use data from NHIS. These trends are presented both as annual cross-sectional survey results and as pooled data across birth cohorts from annual surveys.

Historical Trends in Tobacco Use

Trends in Tobacco Use Consumption: 1900–2011

Numerous Surgeon General's reports have reviewed patterns of tobacco use in the twentieth century (USDHHS 1989, 1994, 1998, 2000, 2012). In the earliest decade of the last century, Americans consumed tobacco primarily in the form of chewing tobacco and cigars, but cigarette use grew rapidly after that period, increasing sharply between the 1910s and the mid-1960s, first in men and then in women (Figure 13.1) (USDHHS 2000). Additionally, during this period, tobacco users shifted away from chewing tobacco, inhaling snuff, and smoking cigars and pipes (USDHHS 2000; Giovino 2002) to the smoking of cigarettes. Although cigarette consumption has been declining since the mid-1960s, cigarettes remain by far the most commonly used tobacco product in the United States. In the context of declining cigarette consumption, however, the consumption of moist snuff, cigars, and pipe/roll-your-own tobacco slightly increased during the first decade of the twenty-first century (Figure 13.2).

Changing Patterns in the Consumption of Tobacco Products Other Than Cigarettes, by Type

The increase in use of roll-your-own/pipe tobacco has largely been attributed to cigarette smokers seeking less expensive cigarettes (Stehr 2005). In fact, roll-your-own cigarettes are typically less expensive than factory-made cigarettes, and loose tobacco for roll-your-own cigarettes is often taxed at a lower rate than manufactured cigarettes at both the federal and state levels (Morris and Tynan 2012; Young et al. 2012).

Smokeless Tobacco

After decades of limited use of smokeless tobacco, consumption rose between 1970 and the mid-1980s because of aggressive marketing to youth and young adult males (National Cancer Institute [NCI] 1992; USDHHS 2000, 2012). From the mid-1980s to 2000, the overall consumption of smokeless tobacco (i.e., chew and moist

Figure 13.1   Per capita consumption of different forms of tobacco in the United States, 1880–2011
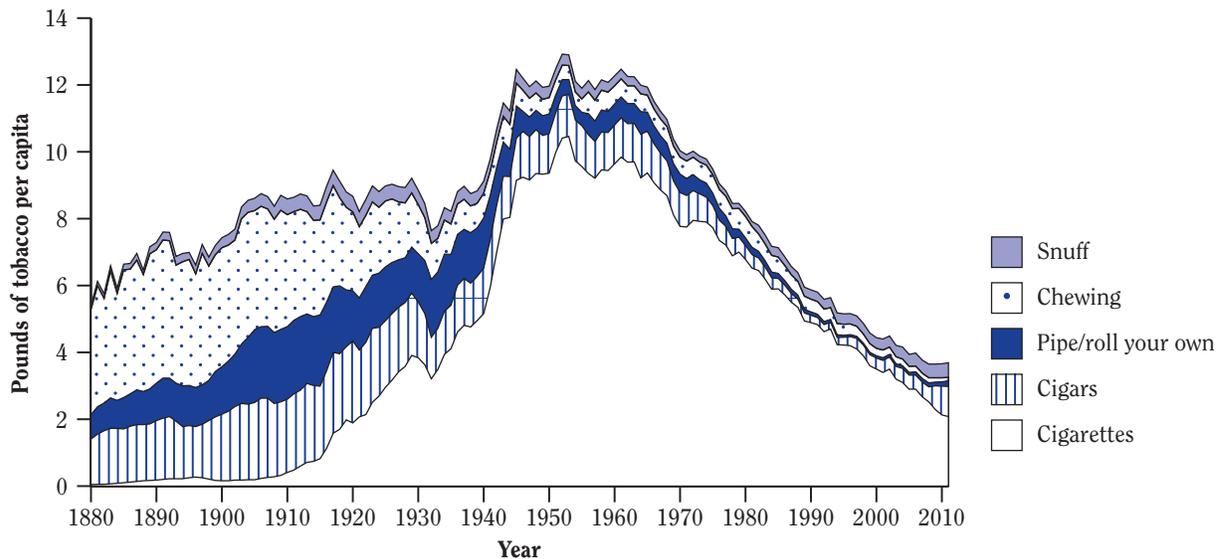
Source: U.S. Department of Treasury 2012.

Figure 13.2   Per capita consumption of noncigarette products in the United States, 1970–2011
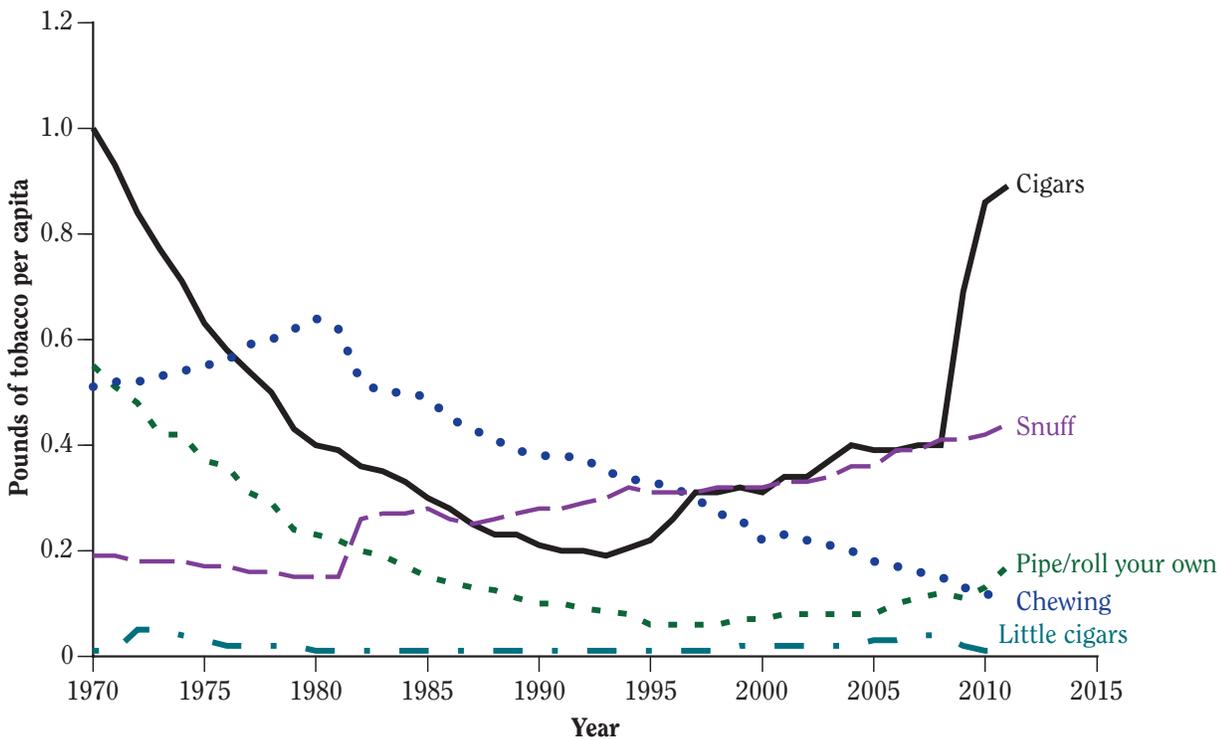
Source: U.S. Department of Treasury 2012.
Note: A "little cigar" is defined in the *Federal Cigarette Labeling and Advertising Act of 1965* as "any roll of tobacco wrapped in leaf tobacco or any substance containing tobacco (other than any roll of tobacco which is a cigarette within the meaning of subsection (1)) and as to which one thousand units weigh not more than three pounds."

snuff) declined. Although consumption of moist snuff increased rapidly between 1990 and 2011, decreases in chewing tobacco since the mid-1980s produced a net negative effect in the smokeless tobacco consumed until 2000 when growth in consumption of moist snuff contributed to a net increase in smokeless tobacco. This resulted in a consistent growth in total consumption of smokeless tobacco since 2004. The growth in moist snuff use came as both Reynolds American, Inc. and Altria Group, Inc., purchased the major smokeless tobacco companies in the United States (Conwood and U.S. Smokeless Tobacco Company, respectively) and launched smokeless tobacco products under the brand names of cigarettes (e.g., Camel Snus and Marlboro Snus) between 2006–2010. Factors found to contribute to the continued growth of moist snuff use include increased tobacco company expenditures to promote moist snuff use (Federal Trade Commission 2012), the initiation of snuff use among cigarette smokers (current or former) in the face of increasing cigarette prices and smoking bans, as well as the use of

targeted marketing (Ohsfeldt et al. 1997; Delnevo et al. 2012). Indeed, advertising for some moist snuff products, often cobranded with cigarette names, has consistently included messages aimed explicitly at smokers and has positioned the products as modern and acceptable tobacco alternatives to use in places where smoking is banned or otherwise inconvenient (Delnevo et al. 2012).

Cigars

Cigars were a common form of tobacco use for much of the twentieth century, but after peaking around 1950, per capita consumption has shrunk dramatically (Figure 13.1). This measure reached its lowest level in 1993, but since then per capita consumption has more than tripled (U.S. Department of Agriculture 2007; U.S. Department of Treasury 2012). The increase in cigar consumption in the mid-1990s was attributed to large cigars, but as shown in Figure 13.3, which presents per capita consumption in "sticks" rather than pounds of tobacco (as shown in Figures 13.1 and 13.2), the rapid increase in the 2000s

up to 2008 was primarily attributable to the consumption of small cigars, which resemble cigarettes (Delnevo 2006). Traditionally, cigar smoking in the United States was a behavior of older men (NCI 1998), but the industry's increased marketing of cigars to targeted groups such as youth, young adults, and women (NCI 1998) reversed the low rates of use typically seen among these groups. By the early 2000s, some surveys suggested that the cigar boom was over (Gilpin and Pierce 2001; Nyman et al. 2002), but consumption more than doubled from 2000–2012 (U.S. Department of Treasury 2012). In 2009, the reauthorization of the State Children's Health Insurance Program included an increase in the federal excise tax on various tobacco products, and while the new law closed some loopholes by equalizing the tax on little cigars with cigarettes, it created other exceptions that the tobacco industry was quick to exploit. Around that time, the industry slightly increased the weight of some of its cigar products, shifting them from the "little cigar" into the more favorable "cigar" category (over 3 pounds per 1,000 cigars) for tax classification purposes. This shift allowed for a lower retail price and the presentation of a new product on the market, the "filtered cigar," which is slightly larger than the little cigar but is taxed as a large cigar (U.S. Department of Treasury 2012). Consumption of little cigars dropped significantly in 2009, but the total consumption of cigars continued to increase annually (Figure 13.3).

Figure 13.3   Cigar consumption in the United States, 2000–2012
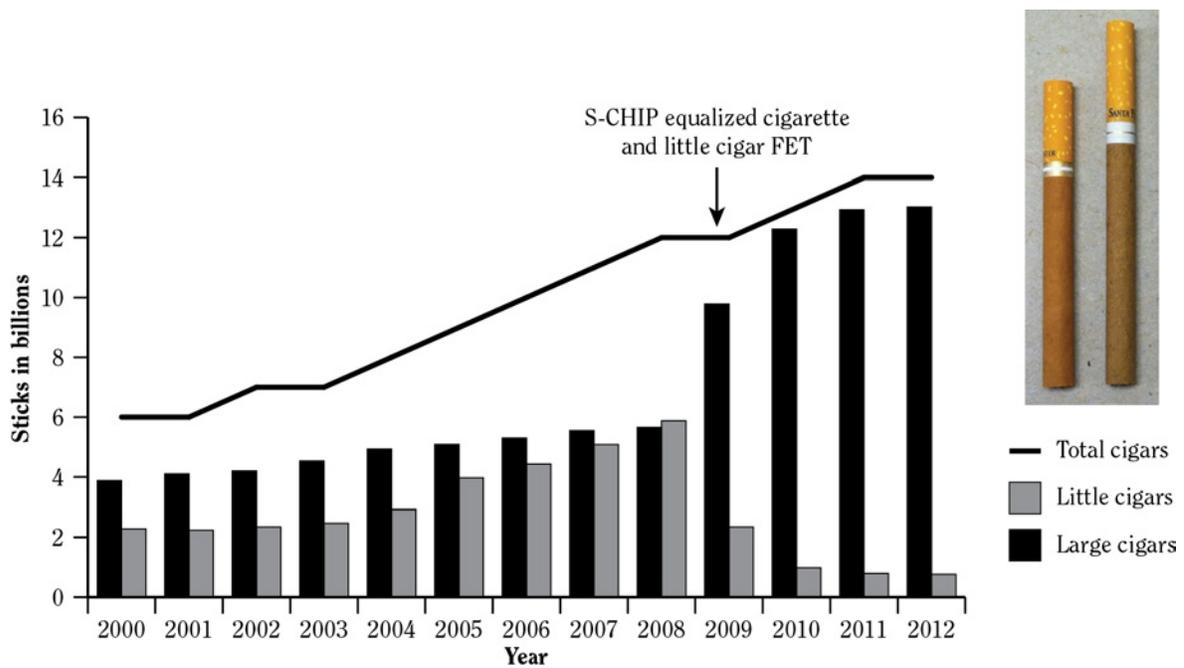
Source: U.S. Department of Treasury 2012.
Note: A "little cigar" is defined in the *Federal Cigarette Labeling and Advertising Act of 1965* as "any roll of tobacco wrapped in leaf tobacco or any substance containing tobacco (other than any roll of tobacco which is a cigarette within the meaning of subsection (1)) and as to which one thousand units weigh not more than three pounds." **FET** = federal excise tax; **S-CHIP** = State Children's Health Insurance Program.

Cigarette Smoking

Age When Smoking Begins

One of the most important—and widely cited—findings from the 1994 and 2012 Surgeon General's reports on smoking and health was that virtually all cigarette smoking begins before 18 years of age (USDHHS 1994, 2012). An examination of the birth cohort data indicates that, historically speaking, this is true for males born after 1950 and for females born after 1960. Table 13.2, which uses 2012 NSDUH data in an analysis parallel to that conducted for the 1994 and 2012 Surgeon General's reports, further illustrates and updates this finding. In the 2012 NSDUH, adult smokers 30–39 years of age were asked about their first experience with cigarette smoking. Among adults who had ever smoked cigarettes daily, the mean age (in years) of smoking initiation was 15.3, and the mean age of beginning to smoke daily was 18.2. Among adults who had ever smoked cigarettes daily, 86.9% had tried their first cigarette by the time they were 18 years of age, while an additional 11.5% did so by 26 years of age. About two-thirds (64.3%) of adults who had ever smoked daily began to do so by 18 years of age, and almost one-third of adults who had ever smoked (22.7%) began to smoke daily between 18–26 years of age. Virtually no initiation of cigarette smoking (<1.5%) and few transitions to daily smoking (<4.3%) actually occurred in adulthood—that is, after 26 years of age. Of note, initiation of cigarette smoking often occurred early in adolescence (before 18 years of age); 13.6% of adults who had ever smoked daily began smoking by age 14, before entering high school.

Current Prevalence of Smoking

Current cigarette smoking is the measure most commonly used to describe the prevalence of cigarette smoking, but surveillance systems offer different definitions of current smoking (Delnevo and Bauer 2009). NHIS defines current smoking among adults as having smoked at least 100 cigarettes during one's lifetime and smoking every day or some days. NSDUH defines current smoking for youth, young adults, and adults as having smoked part or all of a cigarette during the past 30 days. Thus, SAMHSA does not use 100 lifetime cigarettes as a threshold when making estimates of the prevalence of current cigarette smoking from NSDUH data. This chapter continues to use the criterion of smoking part or all of a cigarette during the past 30 days for youth and young adults. To facilitate

Table 13.2   Cumulative percentages of recalled age at which a respondent who had ever smoked daily first used a cigarette and began smoking daily,[a] by smoking status among adults (30–39 years of age); National Survey on Drug Use and Health 2012; United States

	Persons who had ever smoked daily	
Recalled age (years)	First tried a cigarette % (95% CI)	Began smoking daily % (95% CI)
≤10	7.2 (6.01–8.54)	1.2 (0.78–1.83)
≤11	10.4 (8.93–11.99)	2.3 (1.63–3.21)
≤12	19.1 (17.33–21.10)	4.6 (3.70–5.72)
≤13	29.6 (27.43–31.95)	8.6 (7.37–9.97)
≤14	42.5 (40.07–44.91)	13.6 (12.06–15.22)
≤15	58.0 (55.48–60.52)	23.3 (21.12–25.53)
≤16	70.3 (67.96–72.61)	36.4 (33.98–38.88)
≤17	77.3 (75.08–79.31)	47.9 (45.44–50.43)
≤18	86.9 (85.09–88.58)	64.3 (61.79–66.80)
≤19	90.3 (88.68–91.76)	72.2 (69.75–74.48)
≤20	93.3 (91.97–94.41)	79.2 (76.99–81.16)
≤21	95.3 (94.10–96.27)	83.6 (81.58–85.48)
≤22	96.2 (95.01–97.04)	86.7 (84.79–88.40)
≤23	96.8 (95.67–97.59)	88.7 (86.83–90.30)
≤24	97.4 (96.33–98.11)	90.3 (88.49–91.78)
≤25	98.1 (97.16–98.75)	93.3 (91.74–94.53)
≤26	98.4 (97.46–99.00)	94.9 (93.49–95.96)
≤27	99.0 (98.24–99.43)	95.6 (94.31–96.65)
≤28	99.4 (98.85–99.69)	96.3 (95.00–97.21)
≤29	99.5 (98.92–99.75)	97.2 (96.09–98.03)
≤30	99.9 (99.64–99.96)	99.2 (98.58–99.50)
≤31–39	100.0	100.0
Mean age (years)	15.3	18.2

Source: 2012 NSDUH: Substance Abuse and Mental Health Services Administration.

Note: **CI** = confidence interval.

[a]Based on responses to the following questions: "Have you ever smoked part or all of a cigarette?" "How old were you the first time you smoked part or all of a cigarette?" "Has there ever been a period in your life when you smoked cigarettes every day for at least 30 days?" "How old were you when you first started smoking cigarettes every day?"

comparisons with NHIS, however, data in selected tables on all adults (18 years of age or older) incorporate the 100-cigarette threshold, as noted in the footnotes. Last, YRBSS defines current smoking for students as smoking on at least 1 day during the 30 days before the survey, but it does not require current smokers to have smoked at least 100 cigarettes in their lifetime (see Appendix 13.2).

Adolescents and Young Adults

According to the 2012 NSDUH survey, the prevalence of current cigarette smoking among youth 12–17 years of age (Table 13.3) was 6.6% and was similar among males (6.8%) and females (6.3%). By race or ethnicity, the prevalence was highest among White youth (8.2%). Current cigarette smoking increased with age among youth, with a rate of 1.2% for the youngest group (12–13 years of age) and 13.6% for the oldest (16–17 years of age). A higher prevalence of smoking was noted among youth living below the poverty level (7.6%) than in those living at or above this threshold (6.2%). Last, the prevalence was highest in the Midwest and South.

Of the three age groups of interest in this chapter, young adults 18–25 years of age had the highest prevalence of current cigarette smoking (31.8% for this group vs. 6.6% for youth) (Table 13.3). Among young adults, prevalence was higher for males (36.6%) than for females (27.1%), and this pattern held for all racial/ethnic groups. Also among young adults, Whites had the highest prevalence of current smoking (36.6%), followed by Blacks (26.2%) and Hispanics (25.0%). When gender and race/ethnicity among young adults are combined, White males had the highest prevalence (40.6%) and Hispanic females the lowest (18.6%). Prevalence also varied by region, with the rate highest in the Midwest and lowest in the West. Although there was little variation in prevalence by age among young adults, the increase in prevalence from the oldest group among young people (16–17 years of age) to the youngest group among young adults (18–20 years of age) was dramatic—from 13.6% to 28.2%. Through its advertising and promotional campaigns, the tobacco industry markets heavily to its youngest legal target: young adults (Katz and Lavack 2002; Ling and Glantz 2002; Biener and Albers 2004); at 18 years of age, the purchase of cigarettes is legal in most states in the United States.

Adults

The 2012 prevalence of current cigarette smoking for all adults (i.e., those 18 years of age or older)

was 22.0% according to NSDUH (Table 13.4). This estimate is higher than the 18.1% reported using NHIS in 2012 (Figure 13.4). Factors contributing to this difference and other differences between the two surveys are discussed in Appendix 13.2. Per the 2012 NSDUH, adult males had a higher prevalence (24.8%) of current smoking than adult females (19.3%). By race/ethnicity, prevalence was highest among American Indians/Alaska Natives, at 38.5%. The prevalence was similar for Whites (23.9%) and Blacks (22.6%) and lowest among Hispanics (15.2%) and Asians (8.3%). Males had a higher prevalence than females for all racial/ethnic groups other than American Indians/Alaska Natives for whom data are lacking. The differential by gender was most pronounced among Asians, where the ratio was about 3 (males) to 1 (female).

As noted earlier, the measurements of the prevalence of adult smoking for NSDUH are based on smoking at least 100 cigarettes in a lifetime (plus smoking in the last 30 days); the difference between this standard and the NSDUH standard for young adults (smoked all or part of a cigarette in the past 30 days) explains the differences for adults 18–25 years of age between Table 13.3 and Table 13.4.

Adults 18–25 and 26–44 years of age had the highest prevalence estimates for current smoking, 24.6% and 27.3%, respectively. The prevalence of smoking then declined with age. Current cigarette smoking and the level of education were inversely associated. In 2012, 10.4% of those with at least a college degree were current cigarette smokers, compared with 31.5% of those who had less than a high school education. Lastly, the prevalence of current smoking was higher among those living below the poverty line (32.5%) than among those living at or above the poverty line (20.0%).

Daily Versus Intermittent Smoking

Research suggests that as many as one-fifth of current smokers do not smoke on a daily basis (Trinidad et al. 2009); moreover, the frequency of daily use varies considerably between youth, young adults, and adults. This section examines patterns of daily smoking among youth, young adult, and adult current smokers and also presents the prevalence of intermittent and daily smoking for adults. NSDUH defines daily cigarette smoking as smoking on all 30 days of the previous month. Intermittent smoking is defined as smoking in the past month, but not daily, among current smokers.

Figure 13.4 **Trends in prevalence (%) of current cigarette smoking among adults, 18 years of age and older, by gender; National Health Interview Survey (NHIS) 1965–2012; United States**
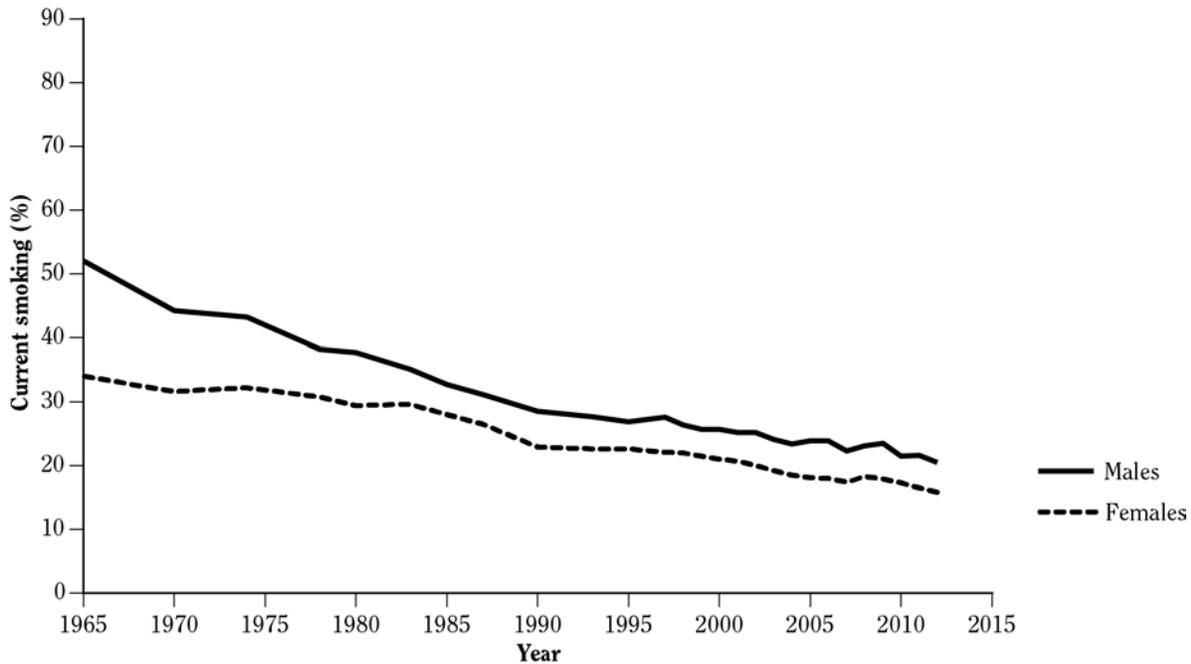
Source: 1965–2012 NHIS, National Center for Health Statistics, public use data tapes.

Adolescents and Young Adults

Table 13.5 presents the prevalence of daily smoking among 12- to 17-year-olds who had smoked cigarettes during the previous month. Overall, 22.0% of youth cigarette smokers were daily smokers. As a percentage, daily smoking among youth smokers was not significantly different between males and females; however, it was more common among Whites than Blacks or Hispanics. The prevalence of daily smoking increased with greater age. By region, the prevalence of daily smoking did not vary significantly by region.

For all variables on which comparisons can be made, the prevalence of daily smoking among past-month smokers was higher for young adults (18–25 years of age) than for youth (12–17 years of age) (Table 13.5). Overall, 45.1% of young adult smokers were daily smokers. Females had a higher rate than males, and as among youth, the highest rate by race/ethnicity was among Whites (52.8%). Daily smoking increased with age, with the rate rising from 37.3% for those 18–20 years of age to 51.9% for the 24–25 years of age group. Regionally, the highest rate was observed in the Midwest and the lowest in the West.

Adults

In 2012, an estimated 61.9% of adult current cigarette smokers were daily smokers; conversely, 38.1% had smoked only on some days during the previous month (Table 13.6). Daily smoking was higher for females (64.9%) than males (59.3%). By race/ethnicity, Whites had the highest rate of daily smoking (68.6%). Notably, lower rates of daily smoking were found among Asians, Blacks, and Hispanics. In general, daily smoking was inversely related to educational status. Current smokers living at or above the poverty line had a higher rate of daily smoking (62.6%) than those below the poverty line (60.4%). By region, the highest rates of daily smoking were observed in the Midwest (68.3%).

In contrast to the data reported above showing that female smokers had a higher prevalence of daily smoking than males when female and male current smokers were used for the corresponding denominators, the prevalence of daily smoking in 2012 was higher among males (15.8%) than females (13.7%) (Table 13.7). This is because adult males had a higher prevalence of current smoking than adult females (26.7% vs. 21.1%).

Table 13.3 **Prevalence of current cigarette smoking[a] among young people, by selected characteristics; National Survey on Drug Use and Health (NSDUH) 2012; United States**

Characteristic	12–17 years of age % (95% CI)	18–25 years of age % (95% CI)
Overall	6.6 (6.1–7.0)	31.8 (30.9–32.7)
Gender		
Male	6.8 (6.2–7.4)	36.6 (35.3–37.9)
Female	6.3 (5.8–6.9)	27.1 (25.9–28.2)
Race/ethnicity		
White, non-Hispanic	8.2 (7.6–8.8)	36.6 (35.4–37.8)
Male	8.3 (7.5–9.2)	40.6 (38.9–42.2)
Female	8.1 (7.3–9.0)	32.5 (30.9–34.2)
Black or African American, non-Hispanic	4.1 (3.2–5.1)	26.2 (24.1–28.4)
Male	4.8 (3.6–6.3)	30.9 (27.8–34.3)
Female	3.3 (2.2–4.9)	21.9 (19.1–24.9)
Hispanic or Latino	4.8 (4.0–5.8)	25.0 (23.1–27.0)
Male	5.2 (4.1–6.6)	30.9 (27.9–34.1)
Female	4.4 (3.5–5.6)	18.6 (16.5–20.9)
Other[b]	4.5 (3.5–5.8)	26.4 (23.3–29.7)
Male	4.4 (3.0–6.4)	33.1 (28.3–38.3)
Female	4.7 (3.4–6.4)	20.0 (16.6–23.9)
Age (in years)		
12–13	1.2 (0.9–1.5)	NA
14–15	4.6 (4.1–5.2)	NA
16–17	13.6 (12.6–14.6)	NA
18–20	NA	28.2 (26.8–29.7)
21–23	NA	33.8 (32.4–35.3)
24–25	NA	34.5 (32.7–36.2)
Poverty status		
At or above poverty level	6.2 (5.8–6.7)	31.3 (30.2–32.3)
Below poverty level	7.6 (6.7–8.7)	34.3 (32.5–36.0)
Unknown[c]	NA	22.1 (15.9–29.8)
Region		
Northeast	5.7 (5.0–6.5)	31.7 (29.7–33.8)
Midwest	7.8 (7.0–8.6)	35.6 (33.8–37.5)
South	7.2 (6.4–8.0)	32.4 (30.9–33.8)
West	5.1 (4.3–6.0)	27.7 (25.8–29.7)

Source: 2012 NSDUH: Substance Abuse and Mental Health Services Administration.
Note: **CI** = confidence interval; **NA** = not applicable.
[a]Based on responses to the question "During the past 30 days, have you smoked part or all of a cigarette?" Respondents who chose "Yes" were classified as current smokers.
[b]Includes Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and persons of 2 or more races.
[c]Respondents 18–22 years of age currently living in a college dormitory were included in the Unknown category.

Table 13.4   **Prevalence of current cigarette smoking[a] among adults 18 years of age and older, by selected characteristics; National Survey on Drug Use and Health (NSDUH) 2012; United States**

Characteristic	Male % (95% CI)	Female % (95% CI)	Total % (95% CI)
Total	24.8 (23.9–25.7)	19.3 (18.5–20.2)	22.0 (21.3–22.6)
Race/ethnicity			
White, non-Hispanic	25.6 (24.5–26.8)	22.2 (21.1–23.3)	23.9 (23.0–24.7)
Black, non-Hispanic	28.9 (25.9–32.0)	17.4 (15.2–19.8)	22.6 (20.6–24.6)
Hispanic	19.2 (17.1–21.6)	11.2 (9.7–12.9)	15.2 (13.8–16.7)
American Indian/Alaska Native, non-Hispanic	—[b]	—[b]	38.5 (30.6–47.2)
Asian, non-Hispanic	13.1 (9.3–18.2)	4.3 (2.8–6.4)	8.3 (6.3–10.9)
Education			
Less than high school	36.2 (33.4–39.1)	26.5 (24.0–29.1)	31.5 (29.5–33.5)
High school graduate	31.3 (29.5–33.1)	23.6 (22.1–25.3)	27.4 (26.2–28.6)
Some college	25.9 (24.1–27.8)	21.4 (19.9–22.9)	23.4 (22.2–24.7)
College graduate	11.1 (9.8–12.5)	9.7 (8.6–10.9)	10.4 (9.5–11.3)
Age group (years)			
18–25	28.4 (27.1–29.6)	20.7 (19.7–21.8)	24.6 (23.7–25.5)
26–44	31.6 (30.0–33.1)	23.2 (21.9–24.5)	27.3 (26.2–28.4)
45–64	23.7 (21.9–25.7)	20.8 (19.2–22.4)	22.2 (20.9–23.5)
≥65	9.9 (7.9–12.3)	9.4 (7.7–11.4)	9.6 (8.3–11.2)
Poverty status			
At or above poverty level	22.9 (21.9–23.8)	17.3 (16.4–18.2)	20.0 (19.3–20.8)
Below poverty level	37.8 (35.1–40.6)	28.9 (26.8–31.0)	32.5 (30.8–34.3)
Unknown[c]	8.9 (5.2–14.8)	6.1 (3.9–9.4)	7.5 (5.0–11.1)
Region			
Northeast	23.2 (21.1–25.3)	18.3 (16.6–20.0)	20.6 (19.3–22.0)
Midwest	26.5 (24.9–28.2)	23.7 (22.1–25.4)	25.1 (23.8–26.4)
South	26.2 (24.6–27.9)	19.8 (18.4–21.3)	22.9 (21.7–24.0)
West	22.2 (20.1–24.4)	15.4 (13.7–17.1)	18.7 (17.3–20.2)

Source: 2012 NSDUH: Substance Abuse and Mental Health Services Administration.

Note: **CI** = confidence interval.

[a]Current smoking is defined as smoking in the 30 days preceding the survey and having used 100 cigarettes or more in lifetime. Respondents with unknown lifetime number of cigarettes consumed were excluded from the analysis.

[b]Low precision; no estimate reported.

[c]Respondents 18–22 years of age currently living in a college dormitory are included in the Unknown category.

Table 13.5   **Prevalence of intermittent[a] and daily[b] cigarette smoking among young people who are past-month cigarette users[c], by selected characteristics; National Survey on Drug Use and Health (NSDUH) 2012; United States**

Characteristic	12–17 years of age		18–25 years of age	
	Intermittent[a] % (95% CI)	Daily[b] % (95% CI)	Intermittent[a] % (95% CI)	Daily[b] % (95% CI)
Overall	78.0 (75.3–80.5)	22.0 (19.5–24.7)	54.9 (53.1–56.6)	45.1 (43.4–46.9)
Gender				
Male	79.0 (75.2–82.4)	21.0 (17.6–24.8)	57.4 (55.2–59.5)	42.6 (40.5–44.8)
Female	76.9 (72.9–80.4)	23.1 (19.6–27.1)	51.5 (49.0–53.9)	48.5 (46.1–51.0)
Race/ethnicity				
White, non-Hispanic	74.3 (71.1–77.3)	25.7 (22.7–28.9)	47.2 (45.1–49.2)	52.8 (50.8–54.9)
Male	76.1 (71.5–80.1)	23.9 (19.9–28.5)	48.9 (46.2–51.6)	51.1 (48.4–53.8)
Female	72.4 (67.3–77.0)	27.6 (23.0–32.7)	45.0 (42.1–47.9)	55.0 (52.1–57.9)
Black or African American, non-Hispanic	86.7 (77.3–92.6)	13.3 (7.4–22.7)	65.5 (61.3–69.5)	34.5 (30.5–38.7)
Male	—[d]	—[d]	66.8 (61.5–71.7)	33.2 (28.3–38.5)
Female	—[d]	—[d]	63.9 (56.5–70.6)	36.1 (29.4–43.5)
Hispanic or Latino	86.7 (79.2–91.8)	13.3 (8.2–20.8)	75.9 (72.0–79.5)	24.1 (20.5–28.0)
Male	—[d]	—[d]	80.9 (76.6–84.5)	19.1 (15.5–23.4)
Female	89.1 (79.6–94.4)	10.9 (5.6–20.4)	67.2 (60.6–73.1)	32.8 (26.9–39.4)
Other[e]	84.3 (74.9–90.6)	15.7 (9.4–25.1)	59.9 (52.5–66.8)	40.1 (33.2–47.5)
Male	—[d]	—[d]	58.0 (49.3–66.2)	42.0 (33.8–50.7)
Female	—[d]	—[d]	62.7 (52.7–71.8)	37.3 (28.2–47.3)
Age (in years)				
12–13	—[d]	—[d]	NA	NA
14–15	86.8 (82.6–90.0)	13.2 (10.0–17.4)	NA	NA
16–17	74.1 (70.5–77.3)	25.9 (22.7–29.5)	NA	NA
18–20	NA	NA	62.7 (60.0–65.4)	37.3 (34.6–40.0)
21–23	NA	NA	52.5 (49.9–55.1)	47.5 (44.9–50.1)
24–25	NA	NA	48.1 (45.1–51.1)	51.9 (48.9–54.9)
Poverty status				
At or above poverty level	78.1 (74.9–81.0)	21.9 (19.0–25.1)	53.6 (51.7–55.5)	46.4 (44.5–48.3)
Below poverty level	77.7 (72.2–82.4)	22.3 (17.6–27.8)	55.5 (52.1–58.9)	44.5 (41.1–47.9)
Unknown[f]	NA	NA	89.4 (84.3–93.0)	10.6 (7.0–15.7)
Region				
Northeast	75.5 (68.3–81.6)	24.5 (18.4–31.7)	55.1 (51.1–59.0)	44.9 (41.0–48.9)
Midwest	76.3 (71.6–80.4)	23.7 (19.6–28.4)	47.2 (44.1–50.3)	52.8 (49.7–55.9)
South	77.5 (72.8–81.7)	22.5 (18.3–27.2)	54.9 (52.1–57.8)	45.1 (42.2–47.9)
West	83.3 (75.9–88.7)	16.7 (11.3–24.1)	63.3 (59.7–66.9)	36.7 (33.1–40.3)

Source: 2012 NSDUH: Substance Abuse and Mental Health Services Administration.
Note: **CI** = confidence interval; **NA** = not applicable.
[a]Intermittent smoking is defined as smoking in the past month but not daily, among current smokers.
[b]Daily smokers are defined as smoking daily among current smokers.
[c]Based on responses to the question "During the past 30 days, have you smoked part or all of a cigarette?" Respondents who chose "Yes" were classified as current smokers.
[d]Low precision; no estimate reported.
[e]Includes Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and persons of 2 or more races.
[f]Respondents 18–22 years of age currently living in a college dormitory are included in the Unknown category.

Table 13.6 **Prevalence of intermittent[a] and daily[b] cigarette smoking among adults 18 years of age and older among past-month cigarette users[c], by selected characteristics; National Survey on Drug Use and Health (NSDUH) 2012; United States**

Characteristic	Intermittent[a] % (95% CI)	Daily[b] % (95% CI)
Overall	38.1 (36.7–39.6)	61.9 (60.4–63.3)
Gender		
Male	40.7 (38.8–42.7)	59.3 (57.3–61.2)
Female	35.1 (33.2–37.1)	64.9 (62.9–66.8)
Race/ethnicity		
White, non-Hispanic	31.4 (29.9–33.0)	68.6 (67.0–70.1)
Black, non-Hispanic	51.9 (47.5–56.3)	48.1 (43.7–52.5)
Hispanic	62.2 (57.6–66.6)	37.8 (33.4–42.4)
American Indian/Alaska Native, non-Hispanic	_[d]	_[d]
Asian, non-Hispanic	47.2 (35.8–59.0)	52.8 (41.0–64.2)
Education		
Less than high school	34.0 (31.1–37.1)	66.0 (62.9–68.9)
High school graduate	34.0 (31.8–36.3)	66.0 (63.7–68.2)
Some college	39.4 (36.8–42.0)	60.6 (58.0–63.2)
College graduate	52.4 (48.5–56.3)	47.6 (43.7–51.5)
Age (in years)		
18–25	54.9 (53.1–56.6)	45.1 (43.4–46.9)
26–44	38.2 (36.1–40.4)	61.8 (59.6–63.9)
45–64	30.5 (27.8–33.4)	69.5 (66.6–72.2)
≥65	27.4 (21.4–34.3)	72.6 (65.7–78.6)
Poverty status		
At or above poverty level	37.4 (35.8–39.1)	62.6 (60.9–64.2)
Below poverty level	39.6 (36.7–42.5)	60.4 (57.5–63.3)
Unknown[e]	89.4 (84.3–93.0)	10.6 (7.0–15.7)
Region		
Northeast	39.4 (36.4–42.4)	60.6 (57.6–63.6)
Midwest	31.7 (29.4–34.0)	68.3 (66.0–70.6)
South	39.0 (36.6–41.5)	61.0 (58.5–63.4)
West	43.1 (39.6–46.7)	56.9 (53.3–60.4)

Source: 2012 NSDUH: Substance Abuse and Mental Health Services Administration.

Note: **CI** = confidence interval.

[a]Intermittent smoking is defined as smoking in the past month but not daily, among current smokers.

[b]Daily smokers are defined as smoking daily among current smokers.

[c]Based on responses to the question "During the past 30 days, have you smoked part or all of a cigarette?" Respondents who chose "Yes" were classified as current smokers.

[d]Low precision; no estimate reported.

[e]Respondents 18–22 years of age currently living in a college dormitory are included in the Unknown category.

Table 13.7 **Prevalence of intermittent[a] and daily[b] cigarette smoking among adults 18 years of age and older, by selected characteristics; National Survey on Drug Use and Health (NSDUH) 2012; United States**

Characteristic	Intermittent[a] % (95% CI)	Daily[b] % (95% CI)
Overall	9.1 (8.7–9.5)	14.7 (14.1–15.3)
Gender		
Male	10.9 (10.3–11.5)	15.8 (15.0–16.6)
Female	7.4 (6.9–7.9)	13.7 (13.0–14.4)
Race/ethnicity		
White, non-Hispanic	7.9 (7.5–8.4)	17.2 (16.5–18.0)
Black, non-Hispanic	13.2 (11.8–14.8)	12.2 (10.8–13.8)
Hispanic	11.6 (10.4–12.9)	7.0 (6.1–8.2)
American Indian/Alaska Native, non-Hispanic	19.8 (14.0–27.4)	22.3 (16.3–29.8)
Asian, non-Hispanic	4.8 (3.7–6.2)	5.4 (3.7–7.8)
Education		
Less than high school	11.5 (10.3–12.8)	22.3 (20.7–23.9)
High school graduate	10.0 (9.3–10.8)	19.4 (18.4–20.6)
Some college	10.0 (9.3–10.8)	15.4 (14.4–16.5)
College graduate	6.0 (5.4–6.7)	5.5 (4.8–6.2)
Age (in years)		
18–25	17.5 (16.7–18.2)	14.4 (13.7–15.1)
26–44	11.0 (10.3–11.8)	17.9 (16.9–18.8)
45–64	6.9 (6.2–7.7)	15.7 (14.7–16.8)
≥65	2.7 (2.1–3.6)	7.3 (6.1–8.7)
Poverty status		
At or above poverty level	8.1 (7.6–8.5)	13.5 (12.9–14.1)
Below poverty level	14.1 (13.0–15.4)	21.6 (20.1–23.2)
Unknown[c]	19.7 (14.6–26.1)	2.3 (1.2–4.4)
Region		
Northeast	8.8 (8.0–9.7)	13.6 (12.5–14.8)
Midwest	8.4 (7.7–9.1)	18.1 (17.0–19.3)
South	9.7 (9.0–10.4)	15.1 (14.2–16.1)
West	8.9 (8.0–9.9)	11.7 (10.6–13.0)

Source: 2012 NSDUH: Substance Abuse and Mental Health Services Administration.

Note: **CI** = confidence interval.

[a]Intermittent smoking is defined as smoking in the past month but not daily.

[b]Daily smokers are defined as smoking daily.

[c]Respondents 18–22 years of age currently living in a college dormitory are included in the Unknown category.

American Indians/Alaska Natives and Whites had the highest prevalence of daily smoking. For intermittent smoking, Blacks had about the same prevalence (13.2%) as they did for daily smoking (12.2%). In contrast, among Hispanics there were more intermittent smokers (11.6%) than daily smokers (7.0%), but for Whites and American Indians/Alaska Natives the opposite was true, with the rates for Whites being 17.2% for daily and just 7.9% for intermittent. Education was inversely related to daily smoking, but by age there was no clear trend under 65 years of age (those 65 years of age or older had the lowest rate of daily smoking by far, 7.3%). The 18–25 years of age group was the only age category in which the estimate for intermittent smoking was higher than the estimate for daily smoking, a pattern that is consistent with the evolving smoking behavior of young adults. In 2012, intermittent smoking decreased steadily with age. Regarding poverty status, the prevalence of daily smoking was much higher among those below the poverty level (21.6%) than among those at or above this level (13.5%). Similarly, the prevalence of intermittent smoking was higher for those below the poverty level than among those at or above this standard. Last, by region the Midwest and South had the highest prevalence of daily smoking.

Cessation

Attempts to Quit Smoking in the Past Year

Attempts to quit cigarette smoking ("quit attempts") are considered an important intermediate step to increasing rates of cessation and, thereby, reducing the overall prevalence of smoking. In the 2012 NHIS, adult participants who were current daily smokers were asked whether they had stopped smoking for more than 1 day in the past 12 months because they were trying to quit. As reported in Table 13.8, an estimated 42.7% of daily smokers in 2012 had attempted to quit smoking in the past year. The prevalence of quit attempts did not differ significantly by gender. Black (49.3%) and Hispanic (51.8%) daily smokers had a higher prevalence of quit attempts than did their White counterparts (40.9%). In general, education was associated with attempting to quit, with the college-educated group having the highest percentage (49.0%). There was an inverse association with age, as young adults had the highest prevalence of attempting to quit (48.5%) and those 65 years of age or older had the lowest rate (34.6%). Last, the prevalence of attempting to quit did not differ significantly by poverty status.

Interest in Quitting Smoking

According to the 2010 NHIS, 68.9% of current adult daily smokers in that year were interested in quitting smoking (Table 13.8). As was the case among smokers who attempted to quit, estimates for interest in quitting did not differ significantly by gender or poverty status. In contrast, estimates differed significantly by race/ethnicity, with Whites and Blacks having the highest absolute estimates. In general, those with higher levels of education had more interest in quitting, although those with at least 9 years of education but no diploma had an estimate of 71.1%, quite similar to the estimates for those with some college education (72.1%) and those with at least a college degree (72.5%). Beginning with the 25–44 years of age group, the estimates for interest in quitting decreased with each age group.

Quit Ratio

In 2012, the overall quit ratio (i.e., the percentage of ever smokers who had quit smoking) among U.S. adults was 55.1% (Table 13.9), which means that in that year there were more former smokers than there were current smokers in the United States. The quit ratio was almost the same for men and women. By race/ethnicity, Whites (57.1%) and Asians (51.8%) had the highest quit ratios, and Blacks (44.1%) and American Indians/Alaska Natives (48.2%) had the lowest. Beginning with the group that had at least 9 years of education but no high school diploma, the quit ratio increased as level of education rose. Both greater age and not living in poverty were positively correlated with the quit ratio.

Trends Over Time in the Quit Ratio

The percentage of ever smokers who had quit increased sharply in both genders between 1965 and the early 1990s, but for males this rate has changed little since then (Figure 13.5). Furthermore, although for a long time males had a substantially higher quit ratio than females, females did not experience the same plateau as males, with the ratio for females substantially higher in 2011 than in the early 1990s. By 2005, the difference between the genders was trivial. Regardless, although the quit ratio is a useful indicator, analyses of changes over time in this ratio for a group, or for the entire U.S. population, needs to be interpreted in light of changes in the age distribution of the population of interest. As shown in Figure 13.7, the percentage of ever smokers who quit smoking increased over time for all age groups except for young adults

Table 13.8   Percentage of current adult daily cigarette smokers 18 years of age and older who attempted to quit smoking during the past year or had an interest in quitting smoking, by selected characteristics; National Health Interview Survey (NHIS) 2010 and 2012; United States

Characteristic	Attempted to quit smoking (2012) % (95% CI)	Had an interest in quitting smoking (2010) % (95% CI)
Total	42.7 (40.9–44.5)	68.9 (67.1–70.8)
Gender		
Male	43.1 (40.6–45.6)	67.8 (65.2–70.4)
Female	42.2 (39.7–44.7)	70.1 (67.6–72.7)
Race/ethnicity		
White, non-Hispanic	40.9 (38.7–43.1)	69.4 (67.1–71.6)
Black, non-Hispanic	49.3 (45.0–53.6)	74.1 (69.6–78.5)
Hispanic	51.8 (45.7–57.9)	58.4 (52.8–64.0)
American Indian/Alaska Native, non-Hispanic	—[a]	52.1 (31.1–73.2)
Asian, non-Hispanic	39.4 (29.2–49.6)	63.3 (53.5–73.1)
Education[b]		
≤8 years	35.5 (27.9–43.1)	64.5 (56.7–72.4)
9–11 (including 12 years, no diploma)	39.0 (34.3–43.6)	71.1 (66.9–75.3)
High school diploma	40.0 (36.9–43.1)	66.5 (63.4–69.6)
Some college	44.3 (41.3–47.2)	72.1 (69.0–75.1)
≥College	49.0 (43.3–54.6)	72.5 (67.4–77.6)
Age group (years)		
18–24	48.5 (41.9–55.1)	65.8 (59.8–71.8)
25–44	46.8 (44.0–49.6)	74.3 (71.7–76.9)
45–64	38.8 (36.2–41.4)	68.3 (65.6–71.0)
≥65	34.6 (29.6–39.7)	52.7 (46.7–58.6)
Poverty status		
At or above poverty level	43.8 (41.6–46.0)	69.9 (67.7–72.1)
Below poverty level	40.4 (36.9–43.9)	66.6 (62.8–70.4)
Unknown[c]	39.1 (32.7–45.5)	66.1 (60.0–72.2)
Region		
Northeast	44.2 (39.6–48.8)	70.6 (65.2–76.0)
North Central	42.6 (38.9–46.3)	69.9 (66.2–73.6)
South	42.1 (39.4–44.8)	68.6 (65.7–71.5)
West	42.9 (39.2–46.7)	66.8 (63.3–70.2)

Source: 2010 and 2012 NHIS: National Center for Health Statistics, public use data tapes.
Note: **CI** = confidence interval.
[a]Low precision; no estimate reported.
[b]Education is reported for adults ≥25 years of age only.
[c]Respondents 18–22 years of age currently living in a college dormitory were included in the Unknown category.

Table 13.9   Percentage of ever cigarette smokers 18 years of age and older who have quit smoking (i.e., the quit ratio), by selected characteristics; National Health Interview Survey (NHIS) 2012; United States

Characteristic	Quit ratio % (95% CI)
Overall	55.1 (54.0–56.2)
Gender	
Male	55.3 (53.8–56.8)
Female	54.8 (53.2–56.3)
Race/ethnicity	
White, non-Hispanic	57.1 (55.8–58.4)
Black, non-Hispanic	44.1 (41.0–47.3)
Hispanic	53.6 (50.4–56.8)
American Indian/Alaska Native, non-Hispanic	48.2 (35.7–60.6)
Asian, non-Hispanic	51.8 (46.2–57.4)
Education[a]	
≤8 years	57.6 (52.9–62.3)
9–11 (including 12 years, no diploma)	43.5 (40.2–46.8)
High school diploma	50.9 (48.8–53.0)
Some college	57.1 (55.0–59.1)
≥College	73.9 (71.9–75.9)
Age group (years)	
18–24	26.5 (22.4–30.5)
25–44	40.7 (38.8–42.6)
45–64	56.9 (55.0–58.7)
≥65	82.1 (80.5–83.7)
Poverty status	
At or above poverty level	57.5 (56.2–58.8)
Below poverty level	34.5 (31.9–37.0)
Unknown[b]	64.7 (61.7–67.7)
Region	
Northeast	59.0 (55.9–62.0)
North Central	51.2 (49.1–53.4)
South	52.3 (50.3–54.3)
West	61.1 (59.1–63.1)

Source: 2012 NHIS: National Center for Health Statistics, public use data tapes.
Note: **CI** = confidence interval.
[a]Education is reported for adults ≥25 years of age only.
[b]Respondents 18–22 years of age currently living in a college dormitory were included in the Unknown category.

(18–24 years of age) whose quit ratio has changed little over 45 years. The greatest gains were observed among those 65 years of age and older; this age group continued its gains even during the 1990s and beyond when the quit ratio leveled out for all other age groups. Thus, to more fully appreciate the changes seen over time in the quit ratio by gender or another classification, one would have to look at changes within specific age groups and, moreover, changes in the relative size of these different age groups.

In terms of race/ethnicity, as shown in Figure 13.6, for decades Whites had a higher quit ratio than Hispanics and Blacks, but by 2010 the gap between Whites and Hispanics was negligible, underscoring the fact that the quit ratio among Hispanics had increased considerably over time. The quit ratio for Black smokers, in contrast, did not move closer to Whites over time. Still, as noted above, one would have to examine the changes in age distribution over the years within a racial/ethnic group to more fully understand the trends in the quit ratio by that classification.

Trends Over Time in Smoking

Adolescents

National YRBS data (Figure 13.8) indicate that the decline in the prevalence of current cigarette smoking among students was nonlinear during the past two decades, highlighting the decline in the prevalence of current smoking among youth that began after the Master Settlement Agreement (MSA) in 1998. Figure 13.8 illustrates that the prevalence of cigarette smoking increased among high school students from 1991–1997, hit a peak in 1997 before the MSA in 1998, and then began a steep decline (Nelson et al. 2008; Centers for Disease Control and Prevention [CDC] 2010) from 1997–2003 and then a more gradual decline from 2003–2011. In 1991, about one-quarter (27.6% of males, 27.3% of females) of high school students were current smokers (Figure 13.8A). By 1997, the prevalence of current smoking had increased to more than one-third (37.7% males, 34.7% females) of high school students. Nonetheless, current cigarette smoking among students was at its lowest point in 2011 with less than one in five high school students smoking (19.9% males, 16.1% females). These trends in current cigarette smoking were reasonably consistent across racial/ethnic subgroups (Figure 13.8B).

Figure 13.5   Percentage of ever cigarette smokers 18 years of age and older who had quit smoking (i.e., the quit ratio), by gender; National Health Interview Survey (NHIS) 1965–2012; United States
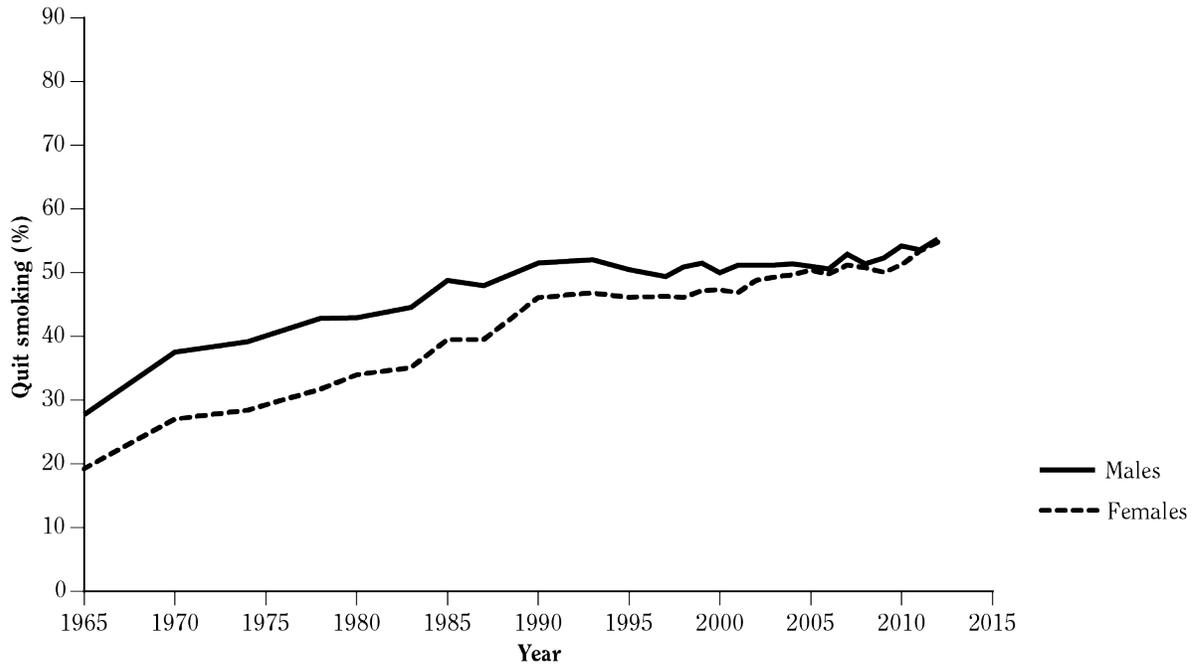
Source: 1965–2012 NHIS, National Center for Health Statistics, public use data tapes.

Figure 13.6   Percentage of ever cigarette smokers 18 years of age and older who had quit smoking (i.e., the quit ratio), by age group; National Health Interview Survey (NHIS) 1965–2012; United States
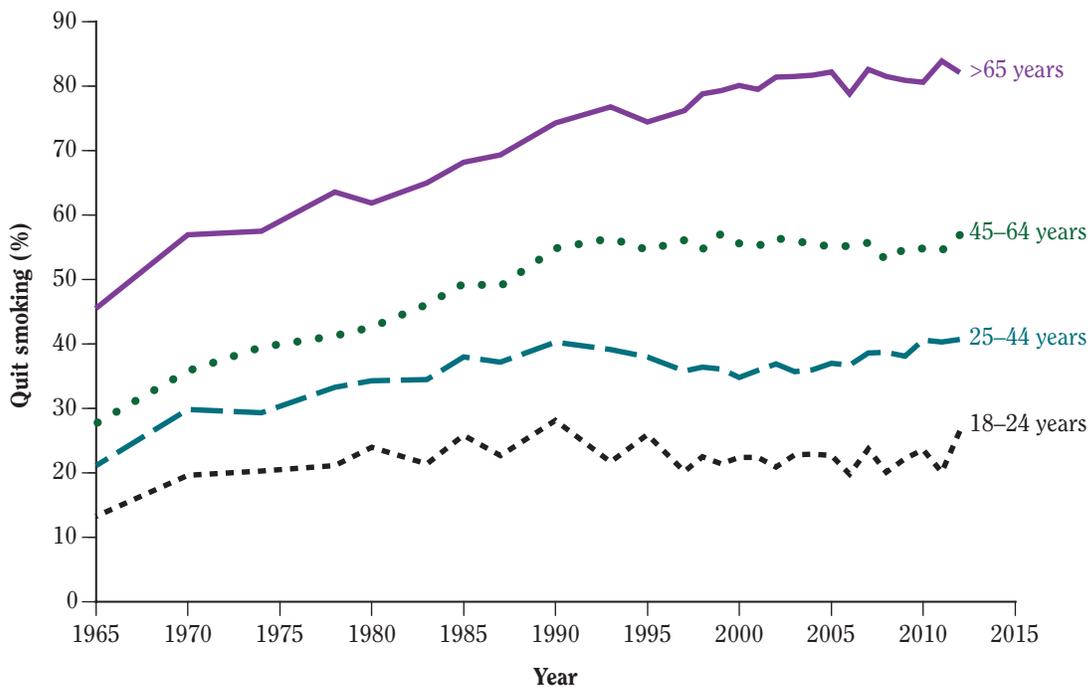
Source: 1965–2012 NHIS, National Center for Health Statistics, public use data tapes.

Figure 13.7   Percentage of ever cigarette smokers 18 years of age and older who had quit smoking (i.e., the quit ratio), by race/ethnicity; National Health Interview Survey (NHIS) 1965–2012; United States
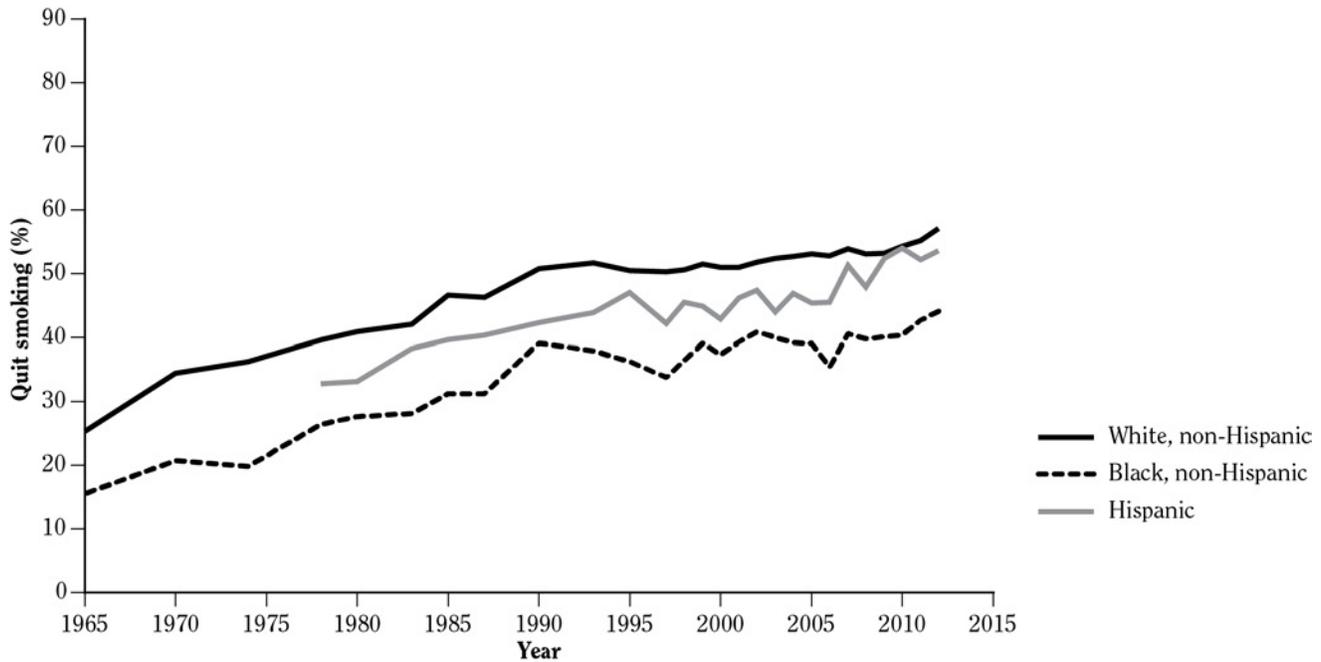
Source: 1965–2012 NHIS, National Center for Health Statistics, public use data tapes.

Adults

In the years before the 1964 Surgeon General's report, the prevalence of cigarette smoking was already declining among men but was still rising among women (Figure 13.9) (Warner and Murt 1982). Figures 13.4, 13.10, and 13.11 display long-term trends in current cigarette smoking using NHIS data from 1965–2012. Among all adults (18 years of age or older), the prevalence of current cigarette smoking declined steadily over time from 1965 (42.4%) to 2012 (18.1%). Most of this decline reflected reductions in current smoking among males (Figure 13.4). In 1965, just over one-half (51.9%) of males were current cigarette smokers—in 2011, less than one-fifth (19.0%) were. The decline for females was steady but less dramatic: in 1965, about one-third (33.9%) of females were current cigarette smokers—in 2011, less than one-fifth (17.3%) were. Although trends in current smoking among Blacks, Whites, and Hispanics varied over time (Figure 13.10), current smoking declined among all three groups from 1965–2011. Similarly, the prevalence of current cigarette smoking from 1965–2011 declined for all four age groups (Figure 13.11). From 2005–2011, the most marked decline was seen in those 18–24 years of age (from 24.4 to 18.9%).

Using data from NHIS for 1991–2012, Figures 13.12, 13.13, and 13.14 show trends in the prevalence of daily cigarette smoking by gender, race/ethnicity, and age group, respectively. As noted earlier in this chapter, most adult current smokers smoke daily. Figure 13.12 shows that the prevalence of daily smoking among adults 18 years of age or older declined slowly but steadily over time for both genders, but by 2007, this trend flattened out. Overall, the prevalence of daily smoking declined by 7.8% for males and 6.8% for females from 1991–2011 (Figure 13.12). The trends over time by racial/ethnic group from 1991–2011 were more diverse (Figure 13.13); among Whites, the prevalence declined by 6.3%, while among Blacks the rate declined 8.5%. Among Hispanics, however, the prevalence dropped over one-half, going from 14.4% in 1991 to 7% in 2011, or a 7.4% decline. Among all three racial/ethnic groups, the declines slowed and/or stalled between 2007–2011. Figure 13.14 shows all four age groups had a lower prevalence at the end of the period than at the beginning, with the greatest decline noted among smokers 25–44 years of age whose prevalence of daily smoking declined by 9.5%. The youngest group (18–24 years of age) differed from the other three age groups by experiencing a notable increase in daily smoking during part of the period; its

Figure 13.8   Trends over time in the prevalence of current cigarette smoking among high school students, by gender and race/ethnicity; National Youth Risk Behavior Survey (YRBS) 1991–2011; United States

A. Gender
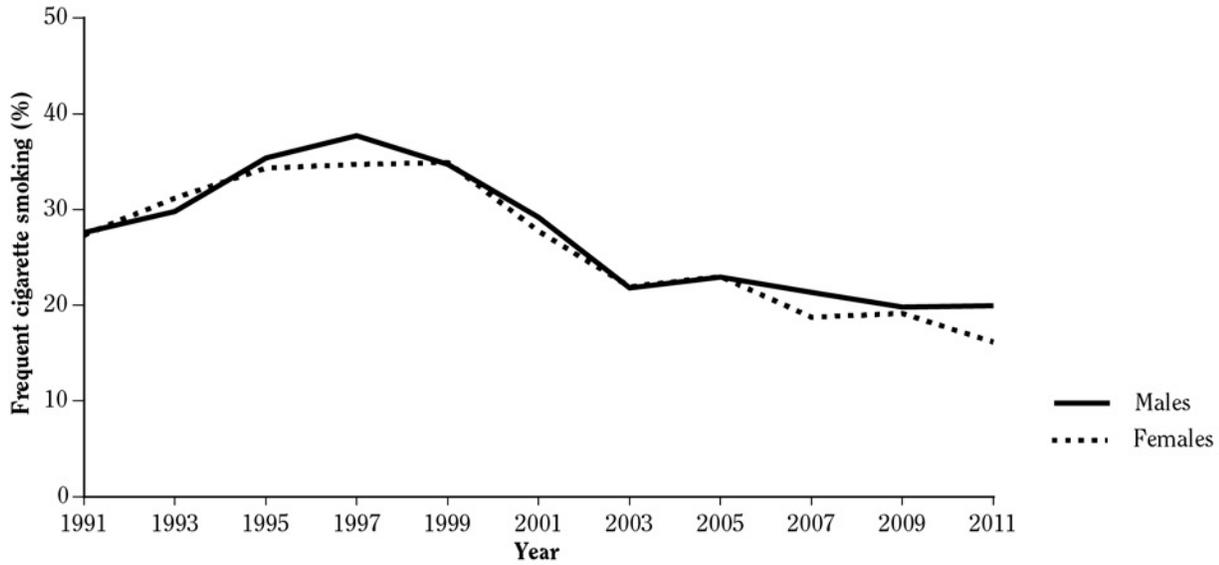
B. Race/ethnicity
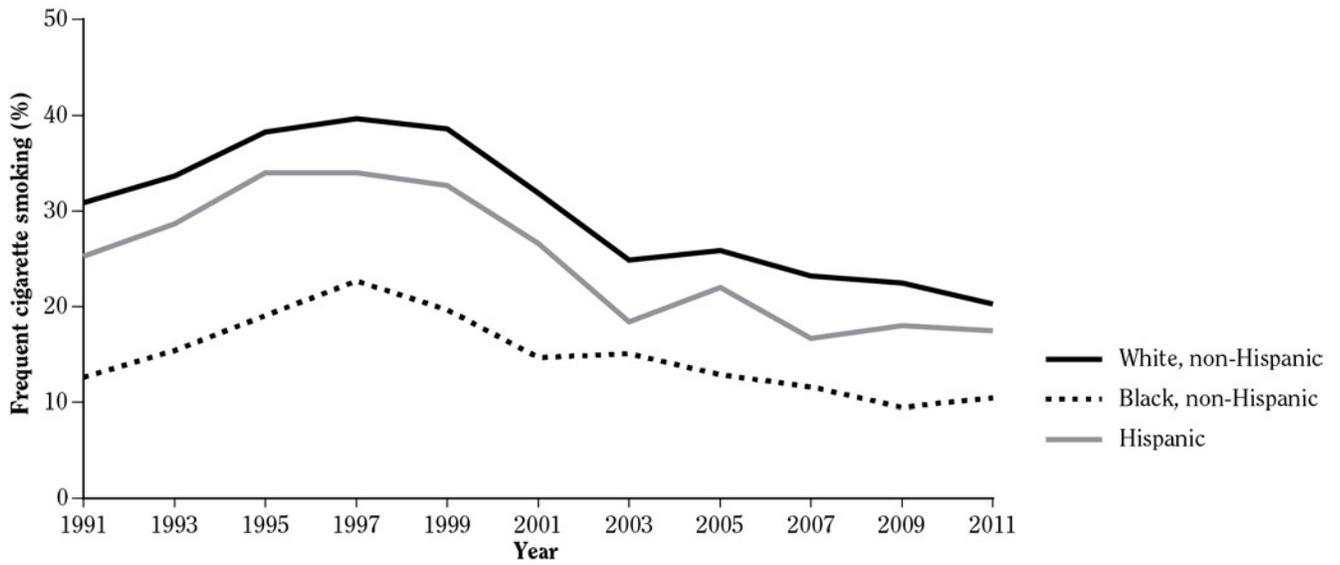
Source: 1991–2011 National YRBS, Centers for Disease Control and Prevention.
Note: Prevalence based on responses to the question "During the past 30 days, on how many days did you smoke cigarettes?" Respondents who reported that they had smoked cigarettes on at least 1 day during the 30 days before the survey were classified as current smokers.

Figure 13.9   Prevalence of current cigarette smokers, by gender, calendar year, and birth cohort
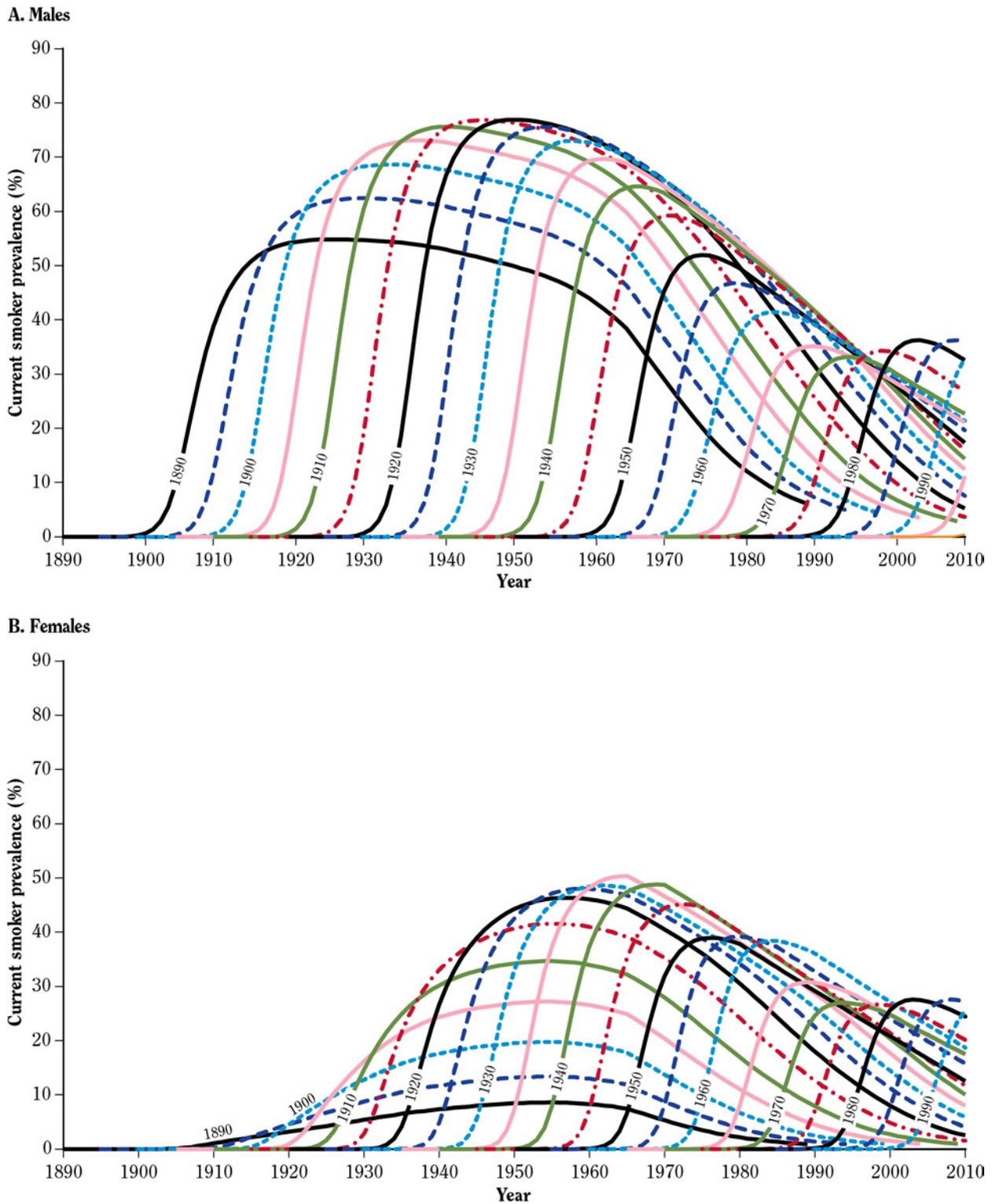
A. Males

B. Females

Source: Holford et al. in press. *American Journal of Preventive Medicine.* February 2014; online only.

Figure 13.10 Trends in prevalence (%) of current cigarette smoking among adults 18 years of age and older, by race/ethnicity; National Health Interview Survey (NHIS) 1965–2012; United States
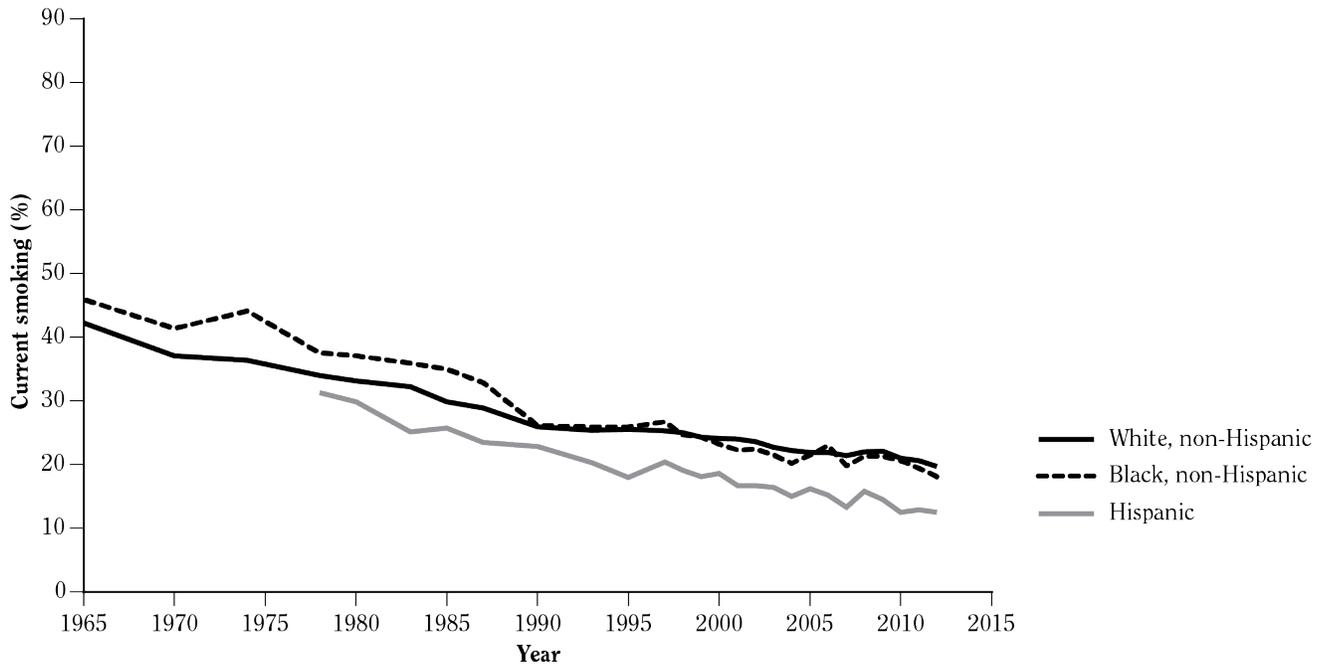
Source: 1965–2012 NHIS, National Center for Health Statistics, public use data tapes.

Figure 13.11 Trends in prevalence (%) of current cigarette smoking among adults, by age group; National Health Interview Survey (NHIS) 1965–2012; United States
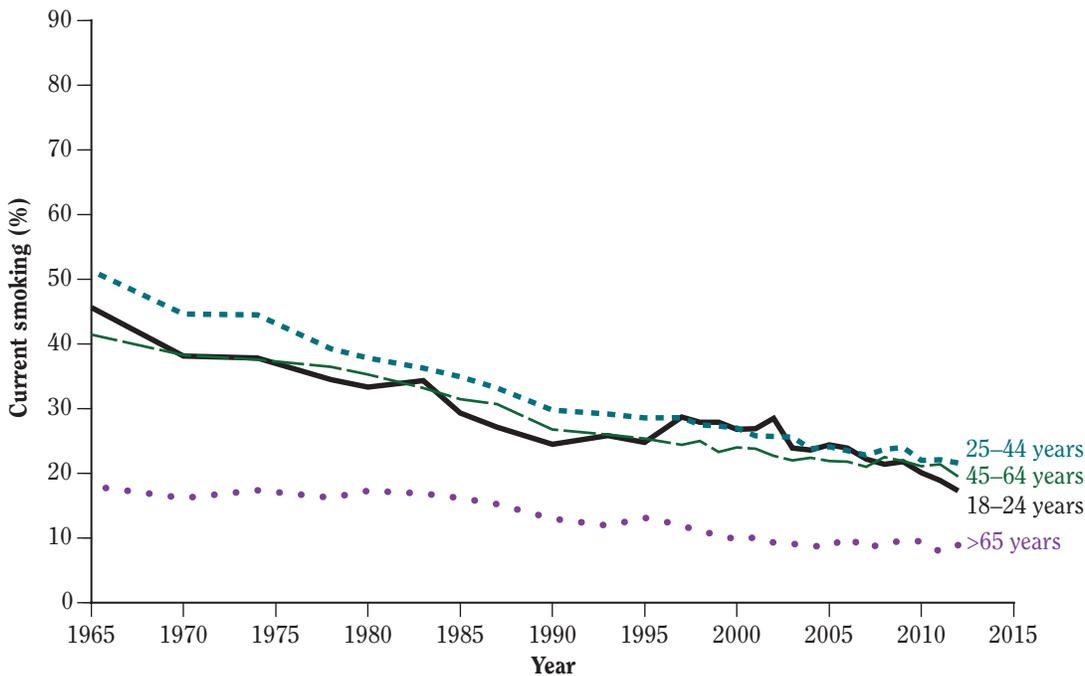
Source: 1965–2012 NHIS, National Center for Health Statistics, public use data tapes.

Figure 13.12 Trends in prevalence (%) of daily cigarette smoking[a] among adults 18 years of age and older, by gender; National Health Interview Survey (NHIS) 1991–2012[b]; United States
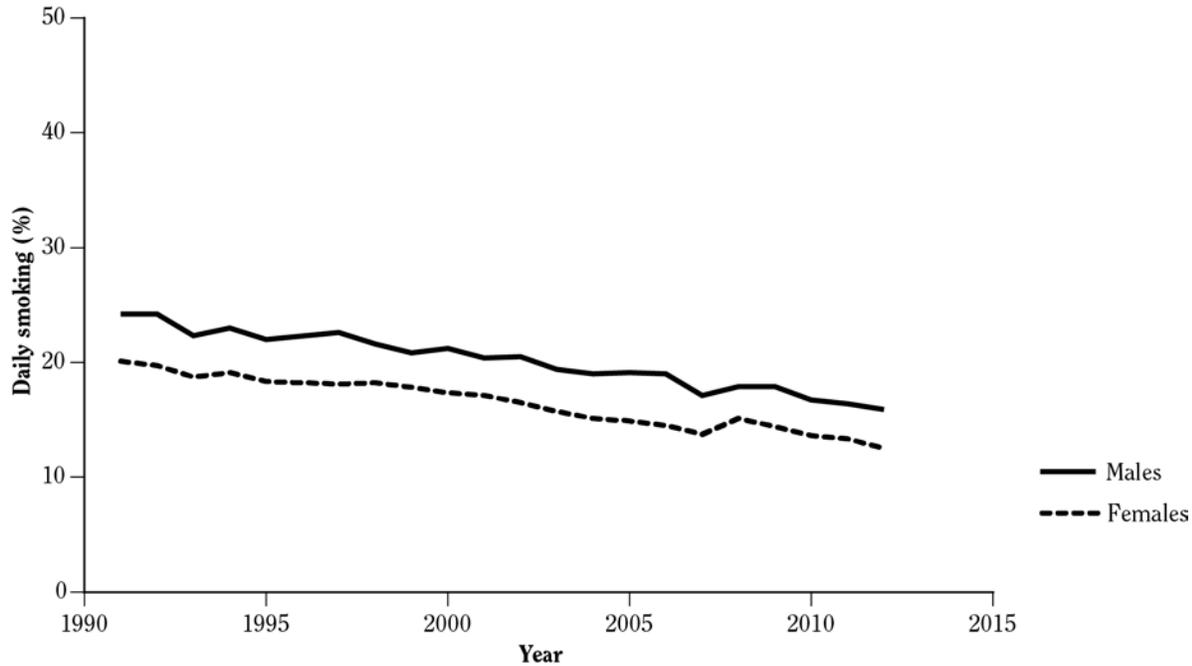
Source: 1991–2012 NHIS, National Center for Health Statistics, public use data tapes.
[a]Current daily smokers in NHIS included adult respondents who reported smoking ≥100 cigarettes in their lifetime and specified currently smoking "every day."
[b]Data for daily smoking were not available before 1991 or in 1996.

rate rose from 18.2% in 1991 to 21.4% in 2002 before declining sharply to 13.2% in 2011. The other three age groups have experienced a slowing of their declines in the prevalence of daily smoking since 2007, no longer increasing for smokers 45–64 years of age.

Smoking History by Birth Cohorts

Previous Surgeon General's reports have presented cross-sectional survey data when discussing historical trends in cigarette smoking (USDHHS 1989, 1994, 1998, 2000, 2012), but the present report will examine historical trends by using a different approach, one that is based on pooling and modeling the existing cross-sectional NHIS data. Specific details about the methodology used to generate these curves can be examined elsewhere (Anderson et al. 2012; Holford et al. in press).

Figure 13.9 provides estimates of the prevalence of current smoking by birth cohort and year for males (A) and females (B). Figures 13.15A (males) and 13.15B

(females) show probabilities of smoking initiation by birth cohort and age, and Figures 13.16A (males) and 13.16B (females) provide estimates of the mean number of cigarettes smoked per day by birth cohort and year. Finally, Figures 13.17A (males) and 13.17B (females) present annual probabilities of cigarette smoking cessation by age and birth cohort.

The birth cohort curves for males and females allow for a much more detailed presentation of the history of cigarette smoking since the early twentieth century than was possible in early Surgeon General's reports. Past discussions of this history have focused primarily on the decline in the prevalence of adult current smoking since 1965 (Figure 13.4), with some estimates presented of higher smoking prevalence during the 1940s and 1950s (USDHHS 1989, 1994, 1998, 2000, 2012). As shown in Figure 13.9A, for males, each birth cohort curve rises sharply, reaches a peak, and then declines more slowly over time—indicating that developmental patterns of cigarette smoking among males have been relatively stable across generations. The rise in each curve for males that represents the initiation of smoking is illustrated in more detail

Figure 13.13 Trends in prevalence (%) of daily cigarette smoking[a] among adults 18 years of age and older, by race/ethnicity[b]; National Health Interview Survey (NHIS) 1991–2012[c]; United States
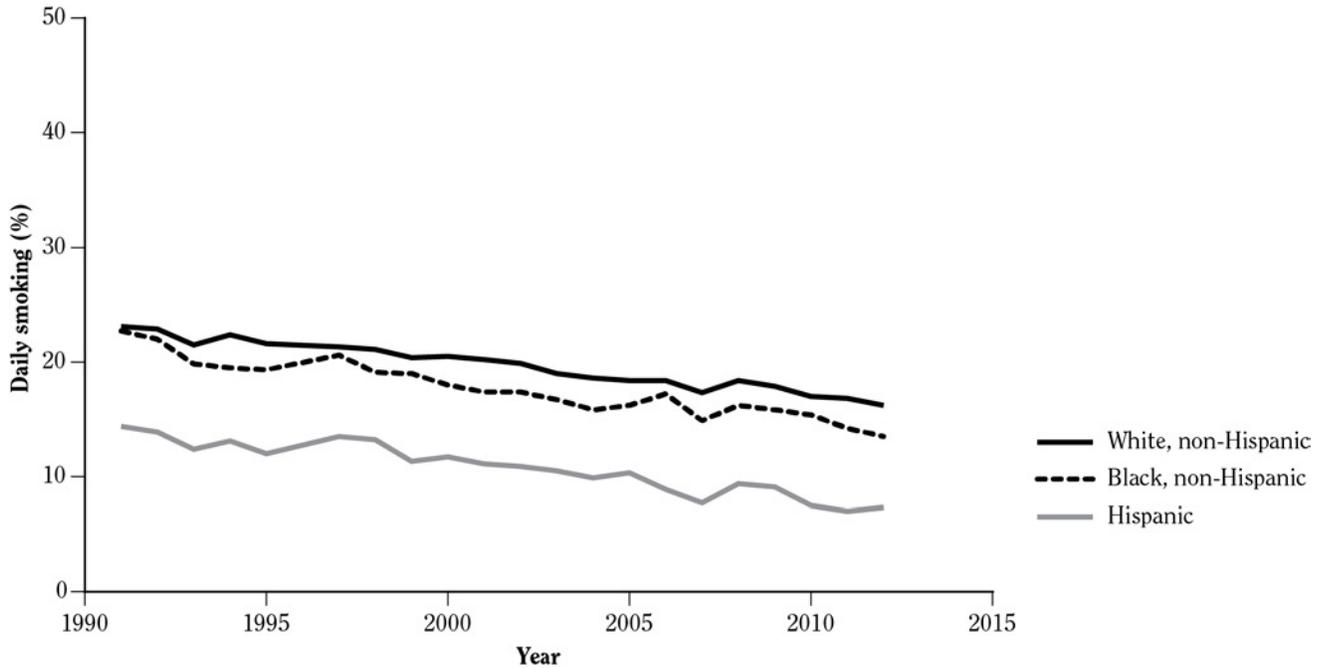
Source: 1991–2012 NHIS, National Center for Health Statistics, public use data tapes.
[a]Current daily smokers in NHIS included adult respondents who reported smoking ≥100 cigarettes in their lifetime and specified currently smoking "every day."
[b]In 1999, NHIS began reporting race according to the 1997 Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity. Before 1999, data were reported according to the 1977 Standards and are not strictly comparable to later years. In 2000, NHIS began reporting Hispanic ethnicity (which includes persons of Hispanic, Latino, or Spanish descent).
[c]Data for daily smoking were not available before 1991 or in 1996.

in Figure 13.15A. For all birth cohorts, earliest smoking initiation began at about 10 years of age, with the probability of starting to smoke rising before peaking at about 17 years of age and then declining to almost nothing by about 30 years of age. This pattern for males was more prominent in the most recent birth cohorts.

Males who served in World War II or entered adolescence during the war years had the highest rates of smoking initiation (Figure 13.15A), with a peak in late adolescence of about 14–16% starting to smoke annually. As a result, among males born between 1915 and 1925, the curves show that over three-fourths of these men were current smokers by 30 years of age (Figure 13.9A). Among men born after 1925, the peak prevalence of smoking began to fall, slowly at first, but more rapidly up through males born around 1970. For males born from 1970 to 1994, the analyses indicate that the peak prevalence of current smoking in young adulthood has stopped declining and remains at about 30% (Holford et al. in press).

Among females, current smoking curves are distinctly different from those of males (Figure 13.9B). For females, the highest peak prevalence of current smoking was reached by those born between 1935–1939. Although the rate of smoking initiation (Figure 13.15B) and the rise in the current prevalence of smoking among females born from about 1930 to 1960 was more similar to those among males born between 1915–1925 than to those born in 1930–1960, the peak prevalence of current smoking reached by females, at about 45–50%, was lower than it was for males. But similar to the case with males, the curves of current smoking declined from these peak years down to the birth cohorts for 1980 and then for some time after, but they have stopped declining in recent birth cohorts (Holford et al. in press).

The curves describing the estimated probability of smoking initiation by age across the birth cohorts for males and females provide a more detailed picture of these patterns of initiation (Figures 13.15A and 13.15B). As

Figure 13.14 Trends in prevalence (%) of daily cigarette smoking[a] among adults, by age group; National Health Interview Survey (NHIS) 1991–2012[b]; United States
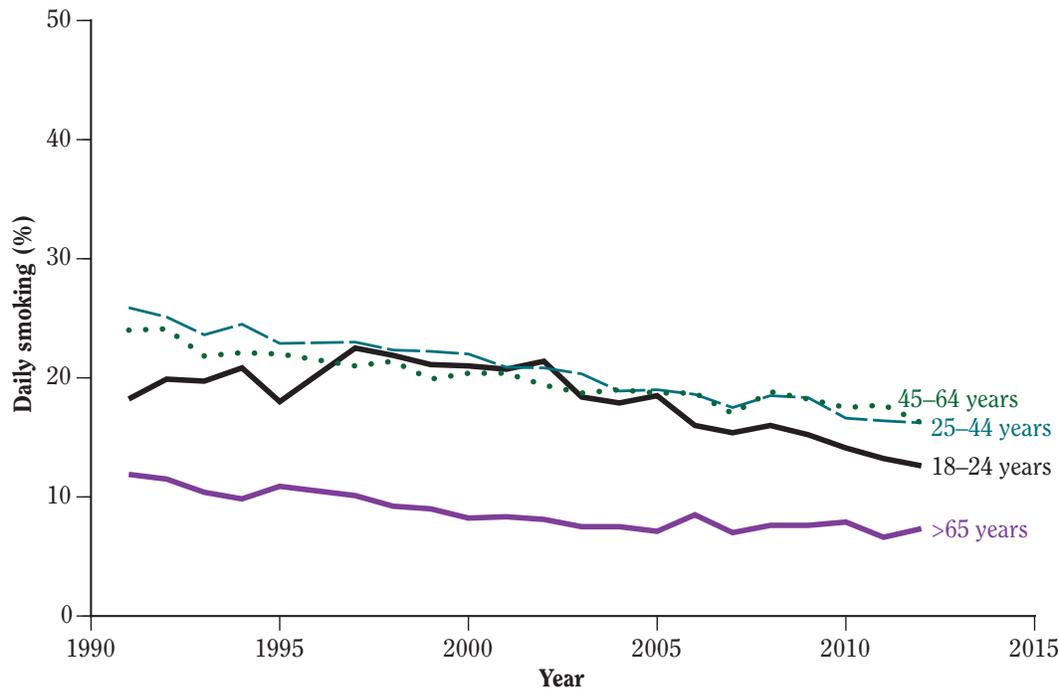
Source: 1991–2012 NHIS, National Center for Health Statistics, public use data tapes.
[a]Current daily smokers included adult respondents who reported smoking ≥100 cigarettes in their lifetime and specified currently smoking "every day."
[b]Data for daily smoking were not available before 1991 or in 1996.

noted in this chapter, among males across birth cohorts, the curve rises sharply, reaches a peak in late adolescence, and then declines, with little initiation beyond 30–35 years of age. By comparison, for females, initiation curves rise more slowly with age and extend into later ages, particularly among females born in 1980 and later. As shown in Figure 13.15B, among females, the peak annual initiation rates were lower than among males, particularly in comparisons of birth cohorts before 1920. In birth cohorts from 1920–1950, initiation rates among females became much higher and closer to those seen among males, but it was not until the 1960 birth cohorts that the actual rates became similar by gender (at about 6–8% per year in late adolescence), largely due to the sharp decline in peak initiation rates among men. Since the 1960s, initiation rates among males and females have been more similar (Holford et al. in press).

The decline in current smoking by calendar year in each birth cohort curve (Figure 13.9A for males and Figure 13.9B for females) represents the impact of smoking cessation as a particular birth cohort ages and reflects the higher mortality of smokers. This later part of these curves

shows larger differences across birth cohorts than the inclines that describe smoking initiation. In more recent birth cohorts, the decline in current smoking has been steeper and less protracted than in earlier birth cohorts, suggesting that smoking cessation now occurs at an increased frequency earlier in the life course. This interpretation is reinforced by data presented in Figure 13.17A for males and Figure 13.17B for females. At all ages, the probability of smoking cessation in the most recent birth cohorts exceeds that of earlier birth cohorts.

Larger differences across birth cohorts can also be observed with regard to daily consumption of cigarettes, illustrated in Figure 13.16A (males) and Figure 13.16B (females). In more recent birth cohorts, consumption has flattened greatly across the developmental life course, compared with earlier birth cohorts. The mean number of cigarettes smoked reached its highest level at about 25 cigarettes per day for males and about 20 cigarettes per day for females from 1970–1990. Since then, total consumption has fallen to its lowest levels and today remains at less than 10 cigarettes per day (Holford et al. in press).

Figure 13.15 Annual probabilities of initiating cigarette smoking, by gender, birth cohort, and age
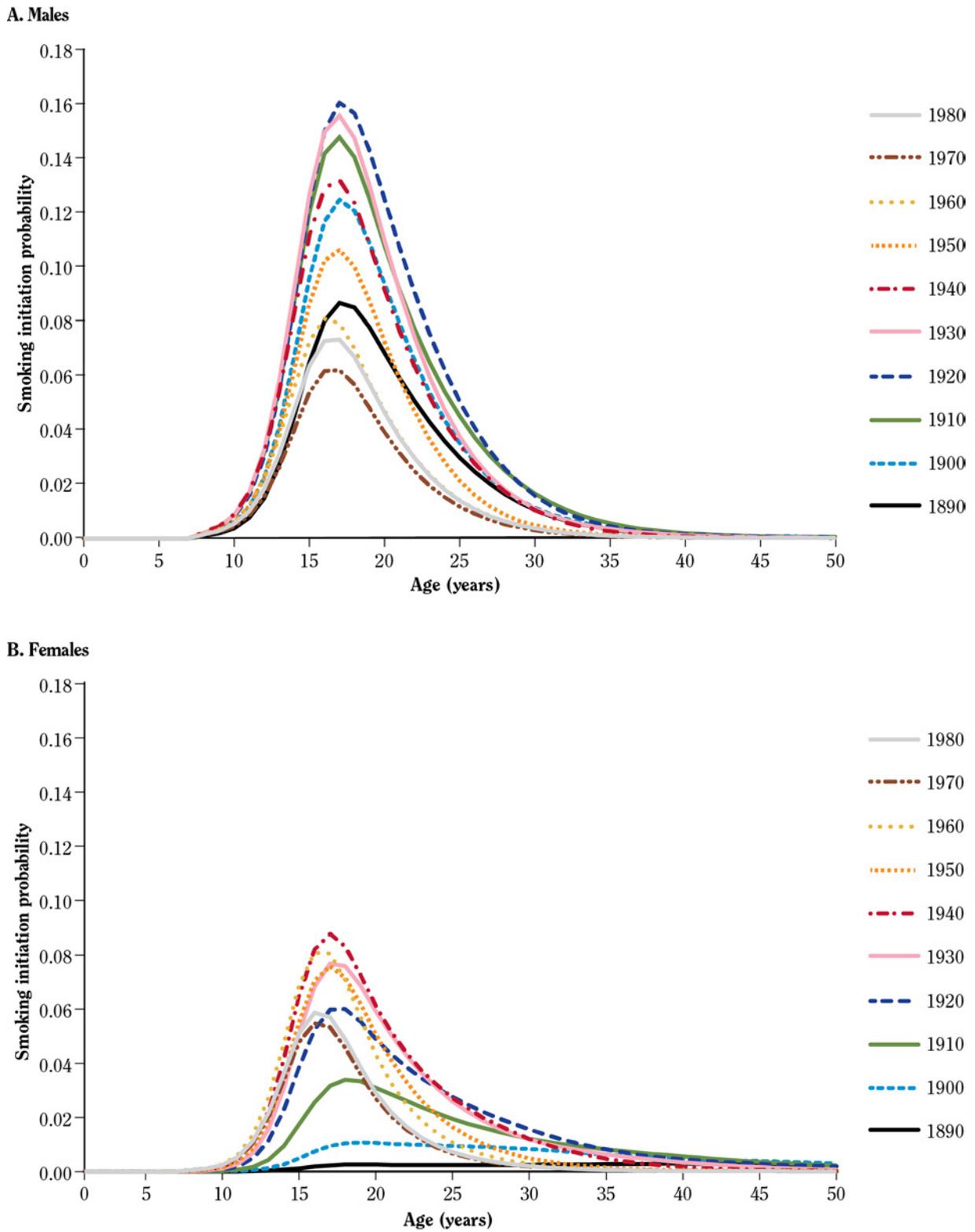
A. Males

B. Females

Source: Holford et al. in press. *American Journal of Preventive Medicine.* February 2014; online only.

Figure 13.16 Mean number of cigarettes smoked per day, by gender, year, and birth cohort
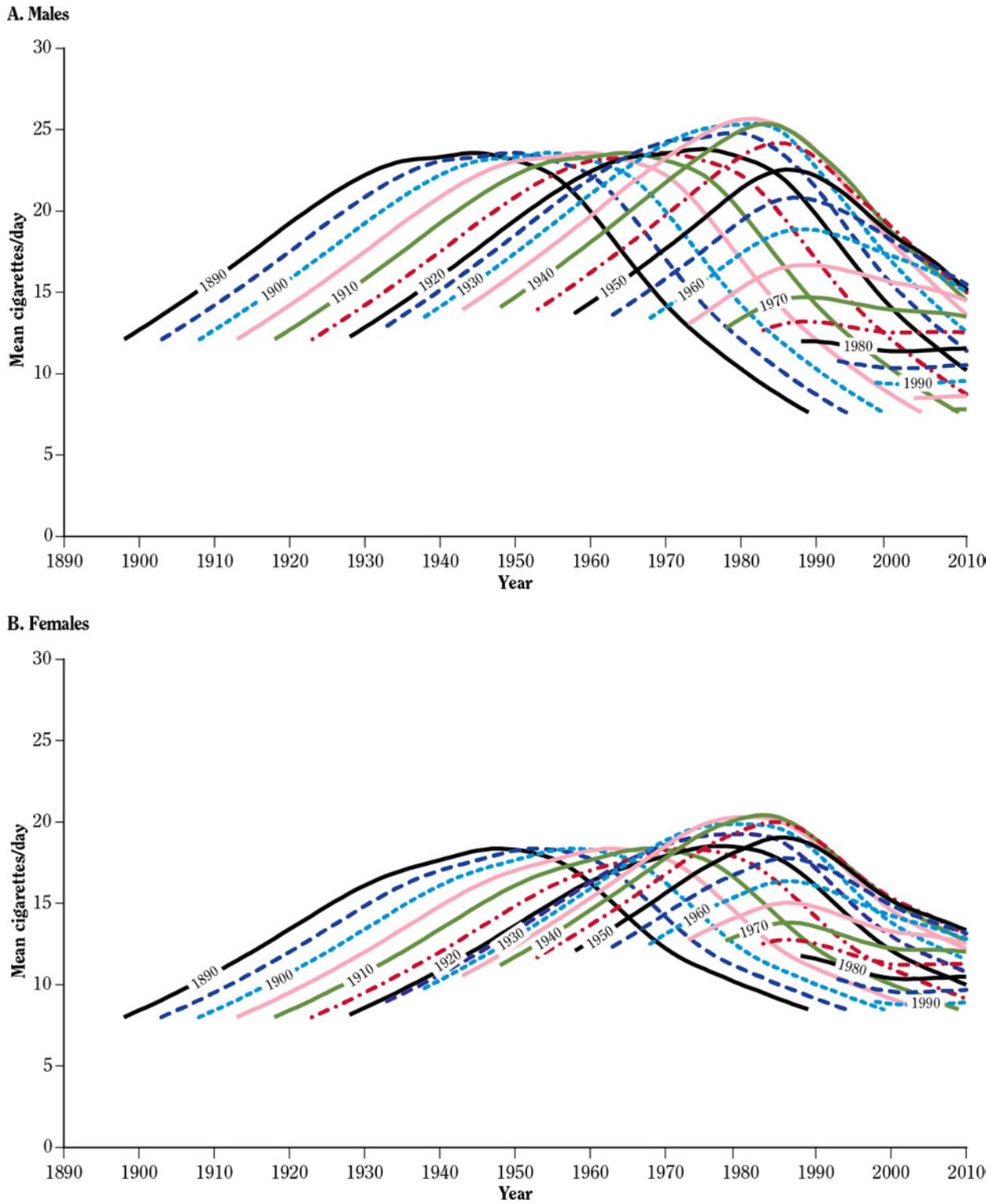
A. Males

B. Females

Source: Holford et al. in press. *American Journal of Preventive Medicine.* February 2014; online only.

Figure 13.17 Annual probabilities of cigarette smoking cessation, by gender, age, and birth cohort
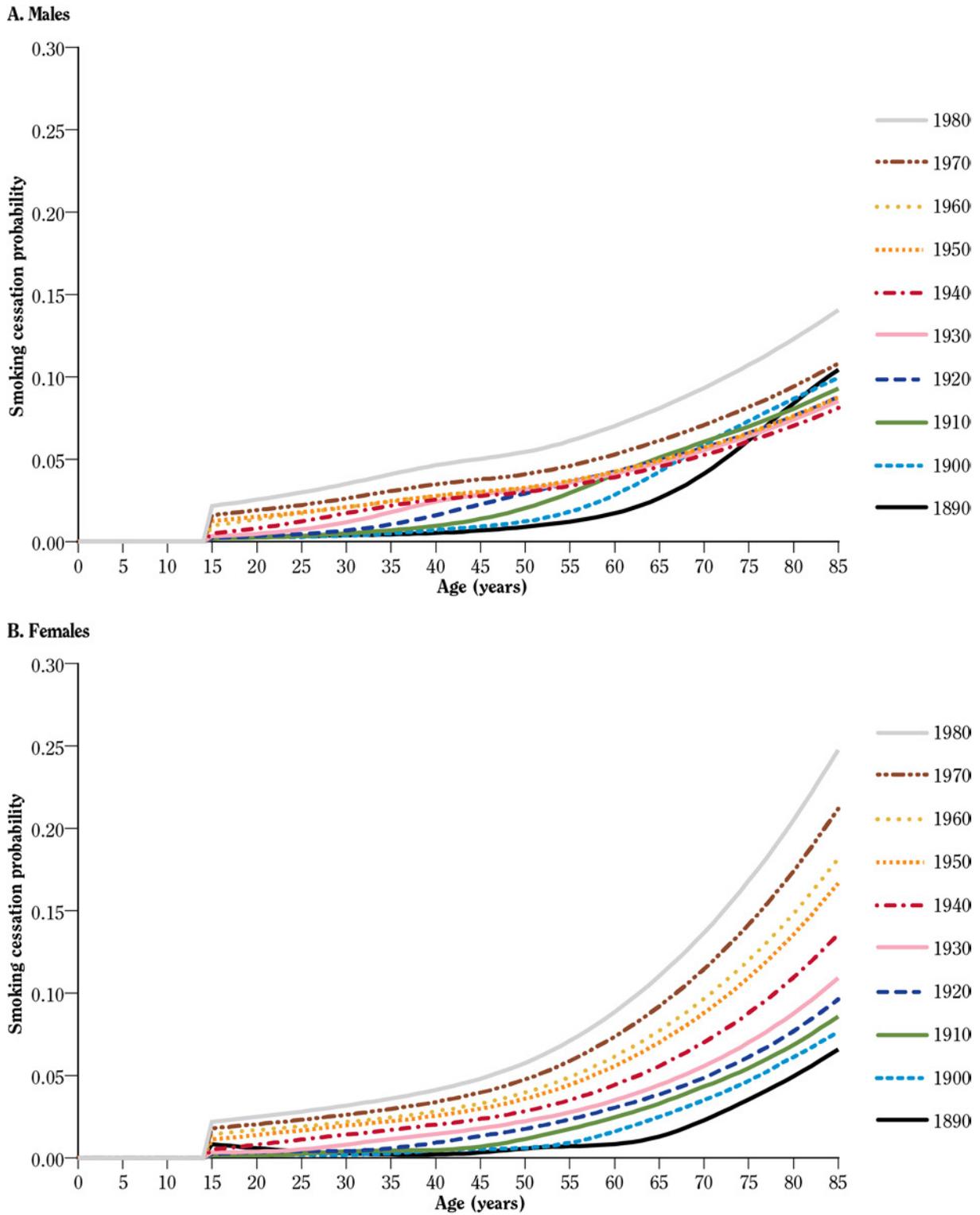
A. Males

B. Females

Source: Holford et al. in press. *American Journal of Preventive Medicine.* February 2014; online only.

Other Tobacco Products

Although cigarettes remain the most prevalent form of tobacco use in the United States, the use of other tobacco products, such as cigars and smokeless tobacco, is still common. Data from the U.S. Department of Agriculture and trade data reported by industry indicate that although cigarette consumption has declined substantially, both the consumption and sale of moist snuff and cigars have risen (Maxwell 2012a,b,c). Moreover, some tobacco users consume more than one product, while others switch from one product to another (prompted by perceived harm reduction, differential prices, and/or smokefree air policies).

Patterns of Smokeless Tobacco Use

Historically, the use of smokeless tobacco in the United States has been highest among White males (Bhattacharyya 2012). In the United States, smokeless tobacco is usually consumed in one of two forms: chewing tobacco, which is made up of long strands of tobacco; and snuff tobacco, a fine-grain tobacco that comes in either a moist blend or a dry or nasal form. Moist snuff is the most popular form of snuff and, indeed, is the most popular smokeless tobacco product. The amount of nicotine and nitrosamine varies widely in chewing tobacco and moist snuff, as it does between the different brands within each type (Richter and Spierto 2003; McNeill et al. 2006; Stepanov et al. 2006).

Current Prevalence Among Youth and Young Adults

Per NSDUH, the overall prevalence in 2012 of current use of smokeless tobacco was 2.1% for youth 12–17 years of age (Table 13.10). Current use was substantially more common among males (3.7%) than females (0.4%). In addition, the prevalence of current use of smokeless tobacco was significantly higher among White youth than Black, Hispanic, or "Other" youth; when gender and race/ethnicity are considered, the highest prevalence was among White males (5.8%). The percentage of youth who were current users of smokeless tobacco increased with age; no differences were observed by poverty status.

Patterns of smokeless tobacco use among young adults (18–25 years of age) usually mirrored those of youth (12–17 years of age). The overall prevalence was 5.5% (Table 13.10), and current use was far more common among males (10.5%) than females (0.5%). In addition,

Whites had a significantly higher prevalence of use than Blacks, Hispanic, or "Other" young adults. The prevalence of current use varied little by age among young adults. However, the higher rates for young adults compared with youth are notable. By region, the highest rate of current use among young adults was in the Midwest.

Current Prevalence Among Adults

In 2012, according to NSDUH, the national prevalence of current smokeless tobacco use was 3.6% for all adults (i.e., men and women 18 years of age or older) (Table 13.11). Current use was substantially higher among males (7.1%) than females (0.4%). This significant difference by gender was found for Whites, Hispanics, American Indians/Alaska Natives, and Asians. In addition, there were significant gender differences for every category within educational attainment, age, and poverty status. Because of the extremely low rates of use among females, the patterns by demographic characteristics described below will cover males only. Among racial/ethnic groups, use was highest among American Indians/Alaska Natives (16.2%), a finding that was reported previously (CDC 1987; Schinke et al. 1987; Kaplan et al. 1997). In addition, the use of smokeless tobacco was significantly higher among Whites (9.3%) than Blacks, Hispanics, or Asians. A higher prevalence was found in the groups that were not college graduates. The lowest was among those 65 years of age or older (1.5%). By region, the highest rate of use was in the Midwest and the South.

Trends Over Time in the Use of Smokeless Tobacco

Figure 13.18 shows trend data on the use of smokeless tobacco among youth from 1995–2011 that were derived from the National YRBS. Data on use of smokeless tobacco were first measured by YRBS in 1995, but data from other surveys indicate that the use of smokeless tobacco among youth rose sharply in the early 1990s and peaked around 1995 (USDHHS 2012). As shown in Figure 13.18A, the use of smokeless tobacco by female students was very low throughout the 1995–2011 period. Among male students, use declined from 1995–2003, and was stable from 2003–2011. Use differed by race/ethnicity with White male students having consistently higher rates of use than their Hispanic or Black counterparts (Figure 13.18B). However, due to a decrease in smokeless tobacco use among White males from 1995–2003, the gap between White male students and Black and Hispanic male students

Table 13.10   Prevalence of current smokeless tobacco use[a] among young people, by selected characteristics; National Survey on Drug Use and Health (NSDUH) 2012; United States

Characteristic	12–17 years of age % (95% CI)	18–25 years of age % (95% CI)
Overall	2.1 (1.8–2.3)	5.5 (5.1–5.9)
Gender		
Male	3.7 (3.3–4.2)	10.5 (9.8–11.3)
Female	0.4 (0.3–0.5)	0.5 (0.4–0.7)
Race/ethnicity		
White, non-Hispanic	3.2 (2.9–3.6)	8.6 (8.0–9.2)
Male	5.8 (5.1–6.6)	16.2 (15.1–17.4)
Female	0.5 (0.4–0.8)	0.8 (0.6–1.1)
Black or African American, non-Hispanic	0.4 (0.2–0.8)	0.4 (0.2–0.8)
Male	0.7 (0.4–1.4)	0.9 (0.4–1.6)
Female	0.1 (0.0–0.5)	0.1 (0.0–0.5)
Hispanic or Latino	0.5 (0.3–0.9)	1.7 (1.3–2.3)
Male	0.9 (0.6–1.6)	3.1 (2.2–4.3)
Female	0.1 (0.1–0.4)	0.2 (0.1–0.6)
Other[b]	1.3 (0.8–2.0)	3.2 (2.2–4.6)
Male	2.2 (1.3–3.6)	6.3 (4.3–9.0)
Female	0.3 (0.1–0.8)	0.3 (0.1–1.1)
Age (in years)		
12–13	0.4 (0.3–0.7)	NA
14–15	1.7 (1.4–2.1)	NA
16–17	4.0 (3.5–4.5)	NA
18–20	NA	5.4 (4.8–6.0)
21–23	NA	5.7 (5.1–6.4)
24–25	NA	5.5 (4.7–6.3)
Poverty status		
At or above poverty level	2.2 (2.0–2.5)	6.2 (5.7–6.7)
Below poverty level	1.5 (1.1–2.1)	3.9 (3.3–4.6)
Unknown[c]	NA	5.7 (3.2–10.0)
Region		
Northeast	1.4 (1.1–1.9)	4.1 (3.5–4.9)
Midwest	2.7 (2.3–3.1)	7.6 (6.7–8.6)
South	2.5 (2.0–3.0)	6.2 (5.5–6.9)
West	1.3 (1.0–1.8)	3.7 (3.0–4.5)

Source: 2012 NSDUH: Substance Abuse and Mental Health Services Administration.
Note: **CI** = confidence interval; **NA** = not applicable.
[a]Current smokeless tobacco use is defined as using smokeless tobacco in the 30 days preceding the survey.
[b]Includes Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and persons of 2 or more races.
[c]Respondents 18–22 years of age currently living in a college dormitory are included in the Unknown category.

Table 13.11 Prevalence of current smokeless tobacco use[a] among adults 18 years of age and older, by selected characteristics; National Survey on Drug Use and Health (NSDUH) 2012; United States

Characteristic	Male % (95% CI)	Female % (95% CI)	Total % (95% CI)
Total	7.1 (6.6–7.6)	0.4 (0.3–0.6)	3.6 (3.4–3.9)
Race/ethnicity			
White, non-Hispanic	9.3 (8.7–10.0)	0.3 (0.2–0.4)	4.7 (4.3–5.0)
Black, non-Hispanic	2.3 (1.4–4.0)	1.6 (0.7–3.4)	1.9 (1.2–3.0)
Hispanic	2.3 (1.6–3.3)	0.1 (0.0–0.5)	1.2 (0.9–1.7)
American Indian/Alaska Native, non-Hispanic	16.2 (10.7–23.7)	2.6 (1.2–5.6)	9.3 (6.3–13.5)
Asian, non-Hispanic	0.9 (0.4–1.9)	0.0 (0.0–0.1)	0.4 (0.2–0.9)
Education			
Less than high school	6.4 (5.4–7.6)	1.4 (0.7–3.0)	4.0 (3.3–4.8)
High school graduate	8.7 (7.7–9.7)	0.3 (0.2–0.6)	4.4 (3.9–4.9)
Some college	8.5 (7.5–9.5)	0.3 (0.1–0.5)	3.9 (3.5–4.4)
College graduate	4.7 (4.0–5.5)	0.1 (0.1–0.3)	2.3 (2.0–2.7)
Age group (years)			
18–25	10.5 (9.8–11.3)	0.5 (0.4–0.7)	5.5 (5.1–5.9)
26–44	9.9 (8.9–10.9)	0.3 (0.2–0.5)	5.0 (4.6–5.6)
45–64	5.0 (4.2–5.9)	0.3 (0.2–0.7)	2.6 (2.2–3.1)
≥65	2.7 (1.9–3.8)	0.6 (0.2–1.8)	1.5 (1.0–2.1)
Poverty status			
At or above poverty level	7.2 (6.7–7.7)	0.3 (0.1–0.5)	3.7 (3.4–4.0)
Below poverty level	6.5 (5.4–7.8)	1.0 (0.6–1.8)	3.2 (2.7–3.9)
Unknown[b]	11.1 (6.1–19.2)	0.2 (0.1–0.8)	5.7 (3.2–10.0)
Region			
Northeast	4.2 (3.5–4.9)	0.2 (0.1–0.3)	2.1 (1.7–2.4)
Midwest	9.0 (8.0–10.1)	0.5 (0.2–1.5)	4.6 (4.1–5.3)
South	8.4 (7.6–9.4)	0.5 (0.3–0.9)	4.3 (3.9–4.8)
West	5.5 (4.5–6.6)	0.3 (0.1–0.5)	2.8 (2.4–3.3)

Source: 2012 NSDUH: Substance Abuse and Mental Health Services Administration.
Note: **CI** = confidence interval.
[a]Current smokeless tobacco use is defined as using smokeless tobacco in the 30 days preceding the survey.
[b]Respondents 18–22 years of age currently living in a college dormitory are included in the Unknown category.

Figure 13.18 Trends over time in prevalence (%) of current smokeless tobacco use among high school students, by gender and race/ethnicity (males only); National Youth Risk Behavior Survey (YRBS) 1995–2011; United States

A. Gender
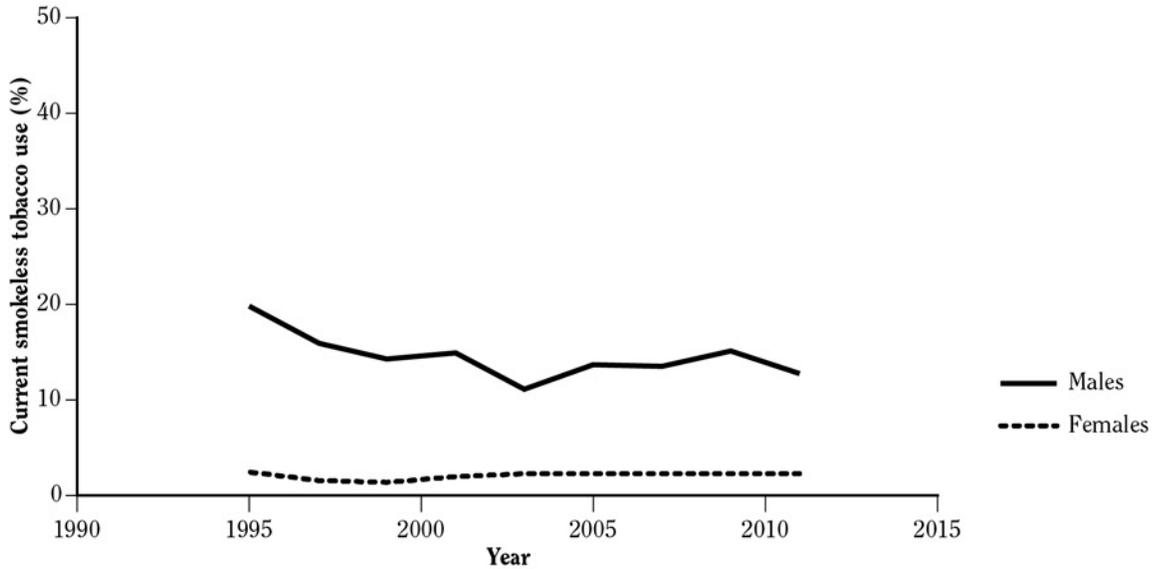
B. Race/ethnicity (males only)
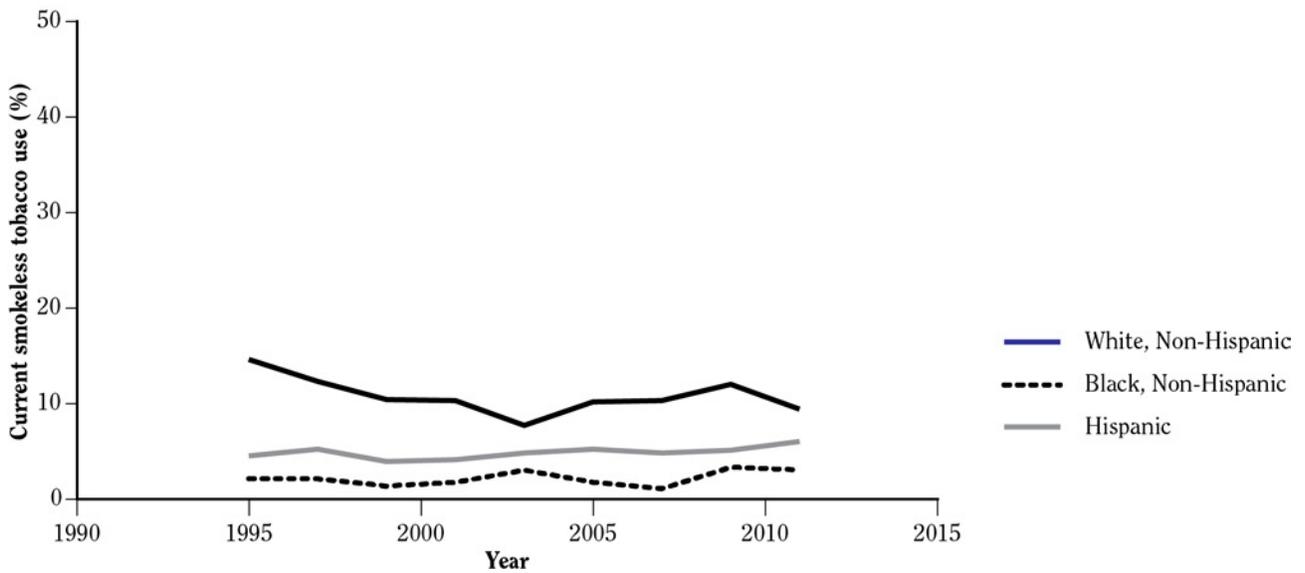
Source: 1995–2011 National YRBS: Centers for Disease Control and Prevention.
Note: Based on responses to the question "During the past 30 days, on how many days did you use chewing tobacco, snuff, or dip, such as Red Man, Levi Garrett, Beech Nut, Skoal, Skoal Bandits, or Copenhagen?" Respondents who reported that they used chewing tobacco, snuff, or dip on at least 1 day during the 30 days before the survey were classified as current smokeless tobacco users.

Figure 13.19 Trends in prevalence (%) of smokeless tobacco use[a] among adults 18 years of age and older, by gender and selected survey years[b]; National Health Interview Survey (NHIS) 1987–2010; United States

Source: 1987–2010 NHIS, National Center for Health Statistics, public use data tapes.
[a]Current users of smokeless tobacco included respondents who reported currently using snuff or chewing tobacco. From 1987 to 1992, this group included those who reported ever using snuff or chewing tobacco or using snuff or chewing tobacco at least 20 times and who specified currently using snuff or chewing tobacco. In 1998, this group included those who reported using snuff or chewing tobacco at least 20 times and who specified currently using snuff or chewing tobacco every day or some days. From 2000 to 2010, this category included those who reported ever using snuff or chewing tobacco or using snuff or chewing tobacco at least 20 times and who specified currently using snuff or chewing tobacco every day or some days.
[b]Data are plotted for 1987, 1991, 1992, 1998, 2000, 2005, and 2010.

has decreased over time. As revealed in Figure 13.18B, the use of smokeless tobacco among Black and Hispanic male students was stable from 1995–2011.

Trend data on the use of smokeless tobacco among adults have been derived from the NHIS; questions on smokeless tobacco use were asked on that survey in 1987, 1991, 1992, 1998, 2000, 2005, and 2010. Across these years (Figure 13.19), use was extremely low among females. For males, prevalence decreased from 1986–2000 but has been increasing since then. Concerning race/ethnicity, a decrease followed by an increase was seen for White males who have had, historically, higher rates of current use of smokeless tobacco than Black or Hispanic males. The prevalence among Black and Hispanic males (Figure 13.20) varied over time, but the erratic trend line among Hispanics should be viewed with caution, given the small sample. Last, three of the four male age groups (i.e., all but the 25–44 years of age group), experienced declines in the use of smokeless tobacco between 1987–2000, but an upward trend was documented for males 18–24 years of

age beginning in 2000 and in the other three age groups from 2005 (Figure 13.21).

Patterns of Cigar Use

The *Excise Tax Reduction Act of 1965* defines a cigar as "any roll of tobacco wrapped in leaf tobacco or in any substance containing tobacco". There are many different types of cigars, including large cigars, cigarillos, and small or little cigars. Small or little cigars closely resemble cigarettes. Despite the wide variety of cigar products, however, a single classification system has not been accepted universally (Baker et al. 2000). Historically, cigar smoking in the United States has been a behavior of older men, but the industry's increased marketing of cigars during the 1990s to targeted groups reversed the low rates of use among adolescents (USDHHS 1998). Correspondingly, the rise in the prevalence of cigar use during the mid-1990s was not limited to adults. Instead, as documented

Figure 13.20 Trends in prevalence (%) of smokeless tobacco use[a] among adult males 18 years of age and older, by race/ethnicity[b] and selected survey years[c]; National Health Interview Survey (NHIS) 1987–2010; United States

Source: 1987–2010 NHIS, National Center for Health Statistics, public use data tapes.

[a]Current users of smokeless tobacco included respondents who reported currently using snuff or chewing tobacco. From 1987 to 1992, this group included those who reported ever using snuff or chewing tobacco or using snuff or chewing tobacco at least 20 times and who specified currently using snuff or chewing tobacco. In 1998, this group included those who reported using snuff or chewing tobacco at least 20 times and who specified currently using snuff or chewing tobacco every day or some days. From 2000 to 2010, this category included those who reported ever using snuff or chewing tobacco or using snuff or chewing tobacco at least 20 times and who specified currently using snuff or chewing tobacco every day or some days.

[b]In 1999, NHIS began reporting race according to the 1997 Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity. Before 1999, data were reported according to the 1977 Standards and thus are not strictly comparable to later years. In 2000, NHIS began reporting Hispanic ethnicity (which includes persons of Hispanic, Latino, or Spanish descent).

[c]Data are plotted for 1987, 1991, 1992, 1998, 2000, 2005, and 2010.

[d]Data for Hispanics were statistically unreliable (relative standard error >30%) for 1987, 1992, 2000, and 2005.

by numerous local, state, and national surveys, cigar use and experimentation was widespread among both male and female adolescents (CDC 1997; Delnevo et al. 2002; Marshall et al. 2006).

Current Prevalence Among Youth and Young Adults

NSDUH data indicate that 2.6% of 12- to 17-year-olds were current smokers of cigars in 2012 (Table 13.12), with current use defined as smoking cigars in the preceding 30 days. Use differed by gender, with males (3.5%) having smoked cigars at slightly over twice the rate of females (1.6%); this gender pattern also held for Whites, Hispanics, and others. By race/ethnicity, White youth had the highest prevalence. Current cigar use rose with increasing age.

In 2012, 10.7% of young adults (18–25 years of age) were current cigar smokers (Table 13.12), and the patterns of use generally mirrored those of youth. Current use among males (16.4%) was over three times that of females (5.1%). Use among females, however, was not inconsequential; in fact, the estimate for Black females was 8.5% in 2012. For young adults overall, the highest prevalence by race/ethnicity was among Whites and Blacks. Notably, despite a large difference in the prevalence of cigar use between 16- to 17-year-olds (5.6%) and 18- to 20-year-olds (11.9%), the prevalence of cigar use among young adults (18–20 years of age) was significantly lower than use among 21- to 23-year-olds and 24- to 25-year-olds. Current use varied by region with the lowest prevalence in the West.

Figure 13.21 Trends in prevalence (%) of smokeless tobacco use[a] among adult males 18 years of age and older, by age group and selected survey years[b]; National Health Interview Survey (NHIS) 1987–2010; United States

Source: 1987–2010 NHIS, National Center for Health Statistics, public use data tapes.
[a]Current users of smokeless tobacco included respondents who reported currently using snuff or chewing tobacco. From 1987 to 1992, this group included those who reported ever using snuff or chewing tobacco or using snuff or chewing tobacco at least 20 times and who specified currently using snuff or chewing tobacco. In 1998, this group included those who reported using snuff or chewing tobacco at least 20 times and who specified currently using snuff or chewing tobacco every day or some days. From 2000 to 2010, this category included those who reported ever using snuff or chewing tobacco or using snuff or chewing tobacco at least 20 times and who specified currently using snuff or chewing tobacco every day or some days.
[b]Data are plotted for 1987, 1991, 1992, 1998, 2000, 2005, and 2010.

Current Prevalence Among Adults

For 2012, the estimated prevalence for current cigar use among adults was 5.4% (Table 13.13). The estimate for males (9.1%) was more than four times that for females (2.0%). These gender differences persisted for all racial/ethnic groups as well as by educational status, age, and poverty status, but the magnitude of the difference by gender, when expressed as a ratio, was notably less for young adults than for adults 45–64 or 65 years of age and older. By race/ethnicity, the prevalence was highest among American Indians/Alaska Natives (7.9%), followed by Blacks (7.6%), Whites (5.5%), Hispanics (4.2%), and Asians (1.7%). This pattern was fairly consistent in both genders. The prevalence of cigar use varied little by educational status, except that lower use was observed among those who were college graduates (4.6%). Age and current cigar use were inversely related, with an estimate of 10.7% for those 18–25 years of age and just 1.6% for those 65 years of age or older. Use was more likely among those living below the poverty level (6.6%) than it was for those at

or above the poverty level (5.2%). It is useful to highlight here that some research suggests that when faced with higher cigarette prices as a result of increases in the cigarette excise tax, cigarette smokers switch to cigars (Delnevo et al. 2004; Delnevo and Hrywna 2007), and those living below the poverty level are more price sensitive. Regionally, the highest prevalence was in the Northeast (5.9%) and in the West (4.4%).

Trends Over Time in the Use of Cigars

Data from 1997–2011 obtained from the National YRBS indicate that current cigar use among male high school students declined from 1997–2005 and then remained stable from 2005–2011 (Figure 13.22A). Among female students, current cigar use declined from 1997–2011. Current use declined among all three racial/ethnic groups presented in Figure 13.22B. Among White students, current cigar use declined from 1997–2003 and then remained stable from 2003–2011. Among Black students, current cigar use declined from 1997–2007 and

Table 13.12 Prevalence of current cigar use[a] among young people, by selected characteristics; National Survey on Drug Use and Health (NSDUH) 2012; United States

Characteristic	12–17 years of age % (95% CI)	18–25 years of age % (95% CI)
Overall	2.6 (2.3–2.9)	10.7 (10.2–11.3)
Gender		
Male	3.5 (3.1–3.9)	16.4 (15.5–17.3)
Female	1.6 (1.4–2.0)	5.1 (4.6–5.7)
Race/ethnicity		
White, non-Hispanic	3.2 (2.9–3.6)	12.1 (11.4–12.9)
Male	4.4 (3.9–5.1)	19.0 (17.8–20.2)
Female	1.9 (1.5–2.4)	5.2 (4.5–5.9)
Black or African American, non-Hispanic	1.9 (1.4–2.6)	11.8 (10.5–13.4)
Male	2.3 (1.6–3.3)	15.5 (13.4–18.0)
Female	1.5 (0.8–2.7)	8.5 (7.0–10.2)
Hispanic or Latino	1.8 (1.4–2.3)	7.3 (6.3–8.5)
Male	2.2 (1.6–3.1)	11.6 (9.7–13.8)
Female	1.3 (0.9–1.9)	2.7 (2.1–3.6)
Other[b]	1.8 (1.2–2.7)	8.0 (6.3–10.2)
Male	2.6 (1.6–4.3)	12.0 (9.0–15.7)
Female	1.0 (0.5–1.7)	4.2 (2.6–6.8)
Age (in years)		
12–13	0.4 (0.2–0.6)	NA
14–15	1.7 (1.4–2.1)	NA
16–17	5.6 (5.0–6.2)	NA
18–20	NA	11.9 (11.1–12.8)
21–23	NA	10.5 (9.7–11.4)
24–25	NA	9.2 (8.3–10.2)
Poverty status		
At or above poverty level	2.6 (2.4–3.0)	10.8 (10.2–11.5)
Below poverty level	2.4 (1.9–2.9)	10.1 (9.1–11.2)
Unknown[c]	NA	14.3 (11.4–17.8)
Region		
Northeast	2.8 (2.3–3.5)	11.1 (9.8–12.5)
Midwest	2.9 (2.5–3.4)	11.8 (10.8–12.9)
South	2.7 (2.2–3.2)	11.3 (10.4–12.2)
West	2.0 (1.6–2.6)	8.8 (7.6–10.0)

Source: 2012 NSDUH: Substance Abuse and Mental Health Services Administration.
Note: **CI** = confidence interval; **NA** = not applicable.
[a]Current cigar use is defined as smoking cigars in the 30 days preceding the survey.
[b]Includes Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and persons of 2 or more races.
[c]Respondents 18–22 years of age currently living in a college dormitory are included in the Unknown category.

Table 13.13 Prevalence of current cigar use[a] among adults 18 years of age and older, by selected characteristics; National Survey on Drug Use and Health (NSDUH) 2012; United States

Characteristic	Male % (95% CI)	Female % (95% CI)	Total % (95% CI)
Total	9.1 (8.5–9.7)	2.0 (1.8–2.3)	5.4 (5.1–5.8)
Race/ethnicity			
White, non-Hispanic	9.5 (8.8–10.3)	1.7 (1.5–2.0)	5.5 (5.1–5.9)
Black, non-Hispanic	12.3 (10.4–14.5)	3.8 (3.1–4.8)	7.6 (6.7–8.7)
Hispanic	6.7 (5.3–8.5)	1.7 (1.2–2.5)	4.2 (3.5–5.2)
American Indian/Alaska Native, non-Hispanic	—[b]	2.5 (1.1–5.5)	7.9 (4.4–13.7)
Asian, non-Hispanic	2.7 (1.4–5.4)	0.7 (0.3–2.0)	1.7 (0.9–2.9)
Education			
Less than high school	10.1 (8.6–11.8)	2.8 (2.1–3.7)	6.5 (5.7–7.5)
High school graduate	8.4 (7.5–9.3)	2.0 (1.6–2.4)	5.1 (4.6–5.6)
Some college	10.7 (9.5–12.0)	2.3 (1.9–2.9)	6.1 (5.5–6.7)
College graduate	8.0 (7.0–9.2)	1.4 (1.0–1.8)	4.6 (4.1–5.2)
Age group (years)			
18–25	16.4 (15.5–17.3)	5.1 (4.6–5.7)	10.7 (10.2–11.3)
26–44	10.3 (9.3–11.4)	2.2 (1.8–2.7)	6.2 (5.7–6.8)
45–64	7.6 (6.5–8.8)	1.4 (1.0–1.9)	4.4 (3.8–5.0)
≥65	3.1 (2.2–4.4)	0.5 (0.2–1.1)	1.6 (1.2–2.2)
Poverty status			
At or above poverty level	8.6 (8.0–9.3)	1.8 (1.5–2.0)	5.2 (4.8–5.5)
Below poverty level	11.6 (10.2–13.3)	3.1 (2.5–3.9)	6.6 (5.9–7.4)
Unknown[c]	23.3 (17.8–29.8)	5.2 (3.4–7.8)	14.3 (11.4–17.8)
Region			
Northeast	10.2 (8.8–11.7)	1.9 (1.4–2.5)	5.9 (5.1–6.7)
Midwest	9.2 (8.2–10.3)	2.3 (1.9–2.8)	5.6 (5.1–6.2)
South	9.6 (8.6–10.7)	2.2 (1.8–2.6)	5.7 (5.2–6.3)
West	7.4 (6.3–8.8)	1.6 (1.2–2.1)	4.4 (3.8–5.2)

Source: 2012 NSDUH: Substance Abuse and Mental Health Services Administration.

Note: **CI** = confidence interval.

[a]Current cigar use is defined as smoking cigars in the 30 days preceding the survey.

[b]Low precision; no estimate reported.

[c]Respondents 18–22 years of age currently living in a college dormitory are included in the Unknown category.

Figure 13.22 Trends over time in prevalence (%) of current cigar smoking among high school students, by gender and race/ethnicity; National Youth Risk Behavior Survey (YRBS) 1997–2011; United States

A. Gender
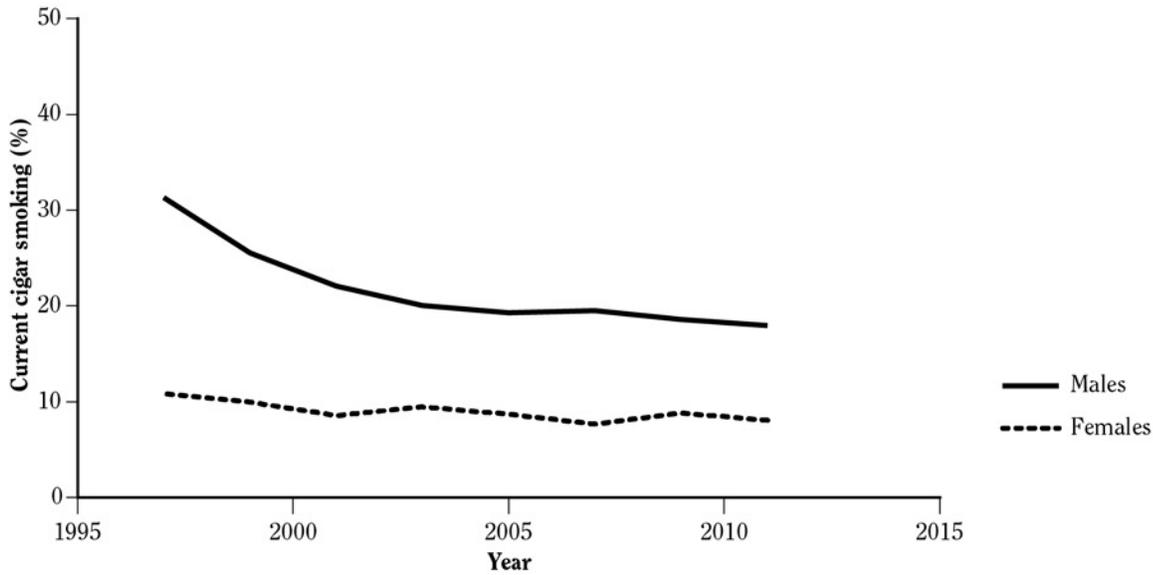
B. Race/ethnicity
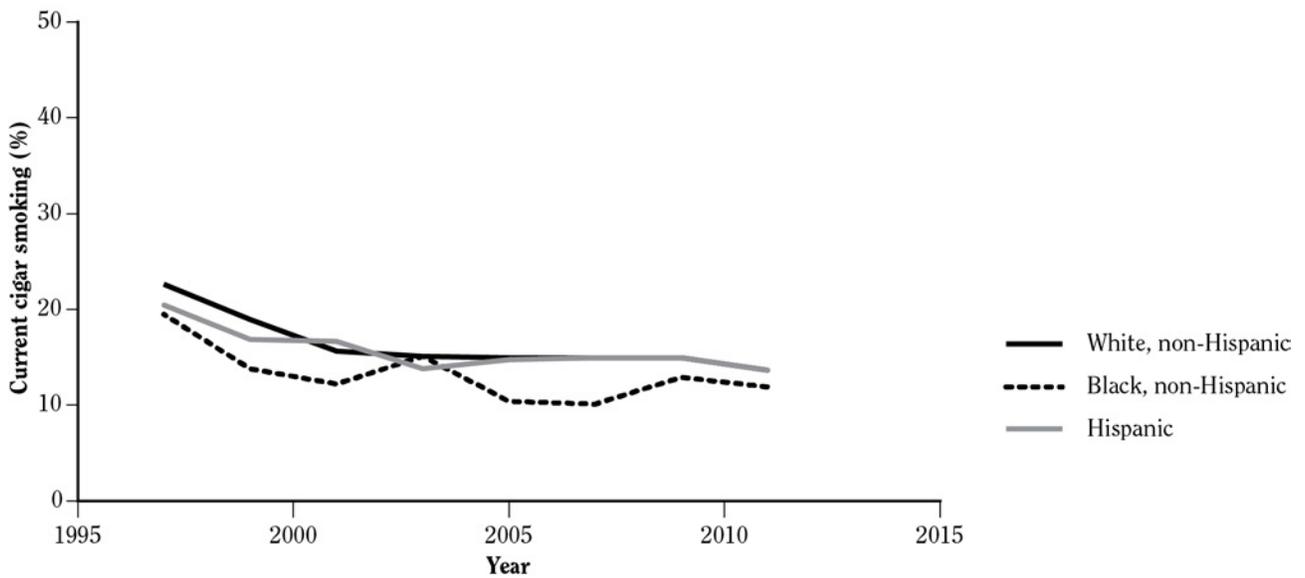
Source: 1997–2011 National YRBS: Centers for Disease Control and Prevention.
Note: Based on responses to the question "During the past 30 days, on how many days did you smoke cigars, cigarillos, or little cigars?" Respondents who reported that they had smoked cigars, cigarillos, or little cigars on at least 1 day during the 30 days before the survey were classified as current cigar users.

then remained stable from 2007–2011. Among Hispanic students, current cigar use declined from 1997–2011.

Trend data on adult cigar smoking are derived from NHIS; questions on cigar use were asked on that survey in 1987, 1991, 1992, 1998, 2000, 2005, and 2010. Per Figure 13.23, the prevalence of cigar use was extremely low among females across the period of interest. Among adult males, prevalence decreased from 1986–1992, then increased through 1998 and was essentially stable thereafter. When examined by racial/ethnic groups (Figure 13.24), there was no clear trend among Hispanic and Black non-Hispanic males. Figure 13.25 highlights trends in adult male cigar use by age groups. Cigar use declined among all age groups from 1987–1992 and then began to rise for all groups, except those 65 years of age and older. The increase peaked in 1998 and then remained relatively flat through 2010 for 18- to 24-year-olds and 25- to 44-year-olds. However, cigar use among 45- to 64-year-olds increased slightly from 1998–2010.

Patterns of Polytobacco Use

The use of multiple tobacco products—also called polytobacco use, dual use, or concurrent use—is common among some tobacco users (Backinger et al. 2008). In 2012, per NSDUH (Table 13.14), an estimated 8.6% of youth (12–17 years of age), 38.1% of young adults, and 27.0% of adults (26 years of age or older) were current users of one or more tobacco products. Most users used only one tobacco product (predominantly cigarettes), but 2.6% of youth, 10.1% of young adults, and 3.7% of adults used more than one product. The most common combination in all three age groups was cigarettes and cigars; for roughly one-half of polytobacco users, this was the combination employed.

Figure 13.23 Trends in prevalence (%) of current cigar use[a] among adults 18 years of age and older, by gender and selected survey years[b]; National Health Interview Survey (NHIS) 1987–2010; United States
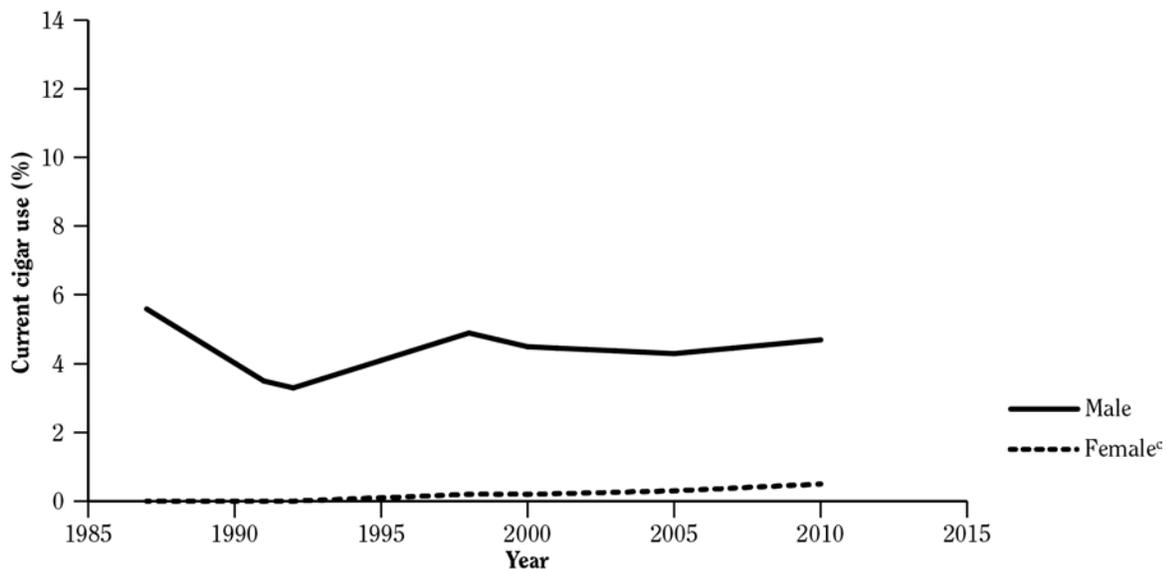
Source: 1987–2010 NHIS, National Center for Health Statistics, public use data tapes.
[a]Current users of cigars included respondents who reported currently using cigars. From 1987 to 1992, this group included those who reported ever smoking cigars and who specified smoking cigars now. From 1998 to 2010, this group included those who reported ever smoking cigars and who specified currently smoking cigars every day or some days.
[b]Data are plotted for 1987, 1991, 1992, 1998, 2000, 2005, and 2010.
[c]Data for females were statistically unreliable (relative standard error >30%) for 1987, 1991, and 1992.

Figure 13.24 Trends in prevalence (%) of current cigar use[a] among adult males 18 years of age and older, by race/ethnicity[b] and selected survey years[c]; National Health Interview Survey (NHIS) 1987–2010; United States

Source: 1987–2010 NHIS, National Center for Health Statistics, public use data tapes.

[a]Current users of cigars included respondents who reported currently using cigars. From 1987 to 1992, this group included those who reported ever smoking cigars or smoking at least 50 cigars and who specified smoking cigars now. From 1998 to 2010, this category included those who reported ever smoking cigars or smoking at least 50 cigars and who specified currently smoking cigars every day or some days.

[b]In 1999, NHIS began reporting race according to the 1997 Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity. Before 1999, data were reported according to the 1977 Standards and thus are not strictly comparable to later years. In 2000, NHIS began reporting Hispanic ethnicity (which includes persons of Hispanic, Latino, or Spanish descent).

[c]Data are plotted for 1987, 1991, 1992, 1998, 2000, 2005, and 2010.

[d]Data for Hispanics were statistically unreliable (relative standard error >30%) for 1992.

Current Prevalence Among Youth and Young Adults

Among youth, polytobacco use in 2012 (Table 13.15) was higher among males (3.7%) than females (1.5%), primarily because smokeless tobacco and cigar use are more common among males. Polytobacco use was higher among White youth (3.6%) than Hispanic (1.6%) or Black (1.1%) youth. Consistent with other prevalence trends, polytobacco use increased with age. No discernible trend was observed by region.

The prevalence of polytobacco use among young adults (18–25 years of age) was four times that of youth (Table 13.15). Among young adults, the difference between males (16.1%) and females (3.9%) was more pronounced than it was among youth. Racial/ethnic differences in polytobacco use mirrored that of youth. Moreover, polytobacco use was higher among White young adult males (20.7%) than any other group. Use of more than one tobacco prod-

uct was highest at 18–20 years of age (10.6%) and 21–23 years of age (10.2%). Regionally, the highest prevalence of polytobacco use was observed in the Midwest and South.

Current Prevalence Among Adults

Among adults (18 years of age or older), the prevalence of polytobacco use in 2012 was much higher among males (7.9%) than females (1.6%) (Table 13.16). The prevalence varied by race/ethnicity. It was highest among American Indians/Alaska Natives (6.8%) and Blacks (5.3%) and lowest among Asians (1.0%). Polytobacco use increased as educational level decreased. The patterns by age group reflect those described previously for cigarettes, cigars, and smokeless tobacco, with prevalence inversely related to age group. Last, polytobacco use among those below the poverty level (7.0%) was almost twice that of those at or above the poverty level (4.1%).

Figure 13.25 Trends in prevalence (%) of current cigar use[a] among adult males 18 years of age and older, by age group and selected survey years[b], National Health Interview Survey (NHIS) 1987–2010; United States

Source: 1987–2010 NHIS, National Center for Health Statistics, public use data tapes.

[a]Current users of cigars included respondents who reported currently using cigars. From 1987 to 1992, this group included those who reported ever smoking cigars or smoking at least 50 cigars and who specified smoking cigars now. From 1998 to 2010, this category included those who reported ever smoking cigars or smoking at least 50 cigars and who specified currently smoking cigars every day or some days.

[b]Data are plotted for 1987, 1991, 1992, 1998, 2000, 2005, and 2010.

[c]Data for adults 18–24 years of age were statistically unreliable (relative standard error >30%) for 1992.

Patterns of New and Emerging Products Use

Current Prevalence Among Youth and Young Adults

An analysis of data from the 2011 and 2012 National Youth Tobacco Survey (NYTS) provided an updated definition of current tobacco use, in which hookah, snus, dissolvable tobacco, and electronic cigarettes were added to take into account nonconventional products that are either new to the market and/or are increasing in popularity. The previous definition for current tobacco use included only cigarettes, cigars, smokeless tobacco, pipes, bidis, and kreteks, thus yielding slightly lower estimates of current tobacco use. For example, in 2011, the previous definition for overall current tobacco use resulted in estimates of 7.1% for middle school and 23.2% for high school students, whereas the new definition resulted in 2011 estimates of 7.5% for middle school and 24.3% for high school students (Tables 13.17–13.18). In 2012, the prevalence of current tobacco use among middle and high

school students was 6.7% and 23.3%, respectively. After cigarettes, cigars were the second most commonly used tobacco product at 2.8% and 12.6%, respectively.

Data for four tobacco products—hookah, snus, dissolvable tobacco, and electronic cigarettes, were first collected in the NYTS in 2011. During 2011–2012—current use of electronic cigarettes nearly doubled among both middle school (0.6% to 1.1%) and high school (1.5% to 2.8%) students, and hookah use increased among high school students (4.1% to 5.4%). During the same period, significant decreases occurred in current use of bidis and kreteks among both middle and high school students, as well as in dissolvable tobacco use among high school students. A substantial proportion of youth tobacco use occurs with products other than cigarettes, so monitoring and prevention of youth tobacco use needs to incorporate other products, including those that are new or emerging.

Electronic Cigarettes

During 2011–2012, data from the NYTS suggested a doubling of electronic cigarette use among U.S. middle

Table 13.14   Prevalence of current use of multiple tobacco products by age group; National Survey on Drug Use and Health (NSDUH) 2012; United States

Tobacco products[a]	12–17 years of age % (95% CI)		18–25 years of age % (95% CI)		≥26 years of age % (95% CI)	
No tobacco use	91.4	(90.9–91.8)	61.9	(61.0–62.9)	73.0	(72.2–73.8)
User, any tobacco products	8.6	(8.2–9.1)	38.1	(37.1–39.0)	27.0	(26.2–27.8)
Cigarettes only	4.1	(3.8–4.5)	22.5	(21.7–23.3)	19.0	(18.3–19.8)
Smokeless tobacco only	0.9	(0.7–1.0)	1.7	(1.5–2.0)	2.0	(1.8–2.3)
Cigars only	0.8	(0.7–1.0)	3.4	(3.1–3.7)	1.9	(1.7–2.2)
Pipe only	0.2	(0.1–0.3)	0.4	(0.3–0.6)	0.3	(0.2–0.4)
Multiple tobacco products	2.6	(2.4–2.9)	10.1	(9.6–10.6)	3.7	(3.4–4.0)
Cigarettes + smokeless only	0.6	(0.5–0.8)	2.1	(1.9–2.3)	0.8	(0.7–0.9)
Cigarettes + cigars only	1.1	(0.9–1.2)	5.1	(4.7–5.5)	2.0	(1.8–2.2)
Cigarettes + pipe only	0.2	(0.1–0.3)	0.5	(0.4–0.6)	0.2	(0.2–0.3)
Smokeless + cigars only	0.1	(0.1–0.2)	0.5	(0.4–0.6)	0.2	(0.1–0.3)
Smokeless + pipe only	_[b]		0.0	(0.0–0.1)	0.0	(0.0–0.1)
Cigars + pipe only	0.0	(0.0–0.1)	0.2	(0.1–0.3)	0.1	(0.1–0.2)
Cigarettes + smokeless + cigars only	0.3	(0.2–0.4)	1.0	(0.9–1.2)	0.2	(0.1–0.2)
Cigarettes + smokeless + pipe only	0.0	(0.0–0.1)	0.0	(0.0–0.1)	0.1	(0.0–0.2)
Cigarettes + cigars + pipe only	0.1	(0.1–0.2)	0.5	(0.4–0.6)	0.1	(0.1–0.2)
Cigars + smokeless + pipe only	0.0	(0.0–0.0)	0.0	(0.0–0.0)	_[b]	
Cigarettes + cigars + smokeless + pipe	0.1	(0.0–0.1)	0.1	(0.1–0.2)	0.0	(0.0–0.0)

Source: 2012 NSDUH: Substance Abuse and Mental Health Administration.
Note: **CI** = confidence interval.
[a]Tobacco products include cigarettes, smokeless tobacco (i.e., chewing tobacco and snuff), cigars, and pipe tobacco.
[b]Low precision; no estimate reported.

and high school students. Among all students in grades 6–12, ever use of electronic cigarettes increased from 3.3% to 6.8% (Tables 13.17–13.18); current electronic cigarette use increased from 1.1% to 2.1%, and current use of both electronic-cigarettes and conventional cigarettes increased from 0.8% to 1.6%. In 2012, among ever electronic cigarette users, 9.3% reported never smoking conventional cigarettes; among current electronic cigarette users, 76.3% reported current conventional cigarette smoking.

Among middle school students, ever electronic cigarette use increased from 1.4% to 2.7% during 2011–2012 (Tables 13.17–13.18); current electronic cigarette use increased from 0.6% to 1.1% (p <0.05), and current use of both electronic cigarettes and conventional cigarettes increased from 0.3% to 0.7%. In 2012, among middle school ever electronic cigarette users, 20.3% reported never smoking conventional cigarettes; among middle school current electronic cigarette users, 61.1% reported current conventional cigarette smoking.

Among high school students, ever electronic cigarette use increased from 4.7% to 10.0% during 2011–2012 (Tables 13.17–13.18); current electronic cigarette use increased from 1.5% to 2.8%, and current use of both electronic cigarettes and conventional cigarettes increased from 1.2% to 2.2%. In 2012, among high school ever electronic cigarette users, 7.2% reported never smoking conventional cigarettes; among high school current electronic cigarette users, 80.5% reported current conventional cigarette smoking. Patterns of use by race/ethnicity are shown in Table 13.18.

Current Prevalence Among Adults

Given the range of tobacco products currently being used by adults, including new and emerging tobacco products that have been heavily marketed, definitions of overall current tobacco use for adults should incorporate a range of products. NSDUH provides data on several tobacco products in addition to cigarettes, including smokeless tobacco, cigars, and pipe tobacco (Table 13.19).

Table 13.15   **Prevalence of current use of multiple tobacco products[a] among young people, by selected characteristics; National Survey on Drug Use and Health (NSDUH) 2012; United States**

Characteristic	12–17 years of age % (95% CI)	18–25 years of age % (95% CI)
Overall	2.6 (2.4–2.9)	10.1 (9.6–10.6)
Gender		
Male	3.7 (3.3–4.1)	16.1 (15.3–17.0)
Female	1.5 (1.2–1.8)	3.9 (3.5–4.4)
Race/ethnicity		
White, non-Hispanic	3.6 (3.2–4.0)	12.7 (12.0–13.5)
Male	5.2 (4.6–5.9)	20.7 (19.5–21.9)
Female	1.9 (1.5–2.3)	4.7 (4.1–5.4)
Black or African American, non-Hispanic	1.1 (0.7–1.8)	6.8 (5.7–8.0)
Male	1.3 (0.7–2.3)	9.6 (7.8–11.7)
Female	0.9 (0.4–2.0)	4.2 (3.1–5.7)
Hispanic or Latino	1.6 (1.2–2.1)	5.8 (4.8–6.8)
Male	2.1 (1.5–2.9)	9.4 (7.8–11.3)
Female	1.1 (0.8–1.7)	1.8 (1.3–2.6)
Other[b]	1.4 (0.9–2.2)	8.1 (6.3–10.4)
Male	1.9 (1.0–3.4)	13.1 (9.9–17.0)
Female	0.9 (0.5–1.7)	3.4 (1.9–6.0)
Age (in years)		
12–13	0.5 (0.3–0.7)	NA
14–15	1.7 (1.4–2.1)	NA
16–17	5.5 (4.9–6.1)	NA
18–20	NA	10.6 (9.8–11.5)
21–23	NA	10.2 (9.4–11.0)
24–25	NA	9.0 (8.0–10.0)
Poverty status		
At or above poverty level	2.7 (2.4–3.0)	10.4 (9.8–11.0)
Below poverty level	2.5 (1.9–3.1)	9.1 (8.2–10.2)
Unknown[c]	NA	11.3 (8.2–15.3)
Region		
Northeast	1.8 (1.4–2.3)	9.3 (8.1–10.5)
Midwest	3.1 (2.7–3.6)	11.7 (10.6–12.8)
South	3.0 (2.5–3.6)	11.0 (10.2–11.9)
West	2.1 (1.7–2.7)	7.8 (6.8–8.9)

Source: 2012 NSDUH: Substance Abuse and Mental Health Services Administration.

Note: **CI** = confidence interval; **NA** = not applicable.

[a]Multiple use is defined as using 2 or more tobacco products. Tobacco products include cigarette, smokeless tobacco (i.e., chewing tobacco and snuff), cigars, and pipe tobacco.

[b]Includes Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and persons of 2 or more races.

[c]Respondents 18–22 years of age currently living in a college dormitory are included in the Unknown category.

Table 13.16   Prevalence of current use of multiple toba   cco products[a] among adults 18 years of age and older, by selected characteristics; National Survey on Drug Use and Health (NSDUH) 2012; United States

Characteristic	Male % (95% CI)	Female % (95% CI)	Total % (95% CI)
Total	7.9 (7.4–8.4)	1.6 (1.4–1.8)	4.6 (4.4–4.9)
Race/ethnicity			
White, non-Hispanic	8.7 (8.1–9.3)	1.5 (1.3–1.8)	5.0 (4.7–5.3)
Black, non-Hispanic	9.3 (7.6–11.3)	2.0 (1.5–2.8)	5.3 (4.5–6.3)
Hispanic	4.8 (3.7–6.1)	1.5 (1.0–2.2)	3.1 (2.5–3.9)
American Indian/Alaska Native, non-Hispanic	12.0 (7.3–19.2)	1.8 (0.8–4.0)	6.8 (4.2–10.8)
Asian, non-Hispanic	1.1 (0.7–1.8)	0.9 (0.4–2.3)	1.0 (0.6–1.7)
Education			
Less than high school	10.9 (9.5–12.5)	2.9 (2.2–3.8)	7.0 (6.2–8.0)
High school graduate	9.0 (8.1–10.0)	1.5 (1.2–1.9)	5.2 (4.7–5.7)
Some college	9.1 (8.2–10.2)	1.8 (1.4–2.2)	5.1 (4.6–5.6)
College graduate	4.0 (3.3–4.8)	0.9 (0.6–1.3)	2.4 (2.0–2.8)
Age group (years)			
18–25	16.1 (15.3–17.0)	3.9 (3.5–4.4)	10.1 (9.6–10.6)
26–44	10.2 (9.2–11.2)	1.8 (1.5–2.3)	5.9 (5.4–6.5)
45–64	5.2 (4.3–6.3)	1.0 (0.7–1.4)	3.1 (2.6–3.6)
≥65	1.2 (0.7–1.9)	0.5 (0.2–1.1)	0.8 (0.5–1.2)
Poverty status			
At or above poverty level	7.0 (6.5–7.6)	1.3 (1.1–1.5)	4.1 (3.9–4.4)
Below poverty level	12.8 (11.3–14.5)	3.0 (2.3–3.7)	7.0 (6.2–7.8)
Unknown[b]	19.9 (14.1–27.3)	2.5 (1.4–4.5)	11.3 (8.2–15.3)
Region			
Northeast	6.5 (5.6–7.4)	1.3 (1.0–1.9)	3.8 (3.3–4.3)
Midwest	8.2 (7.3–9.1)	1.9 (1.6–2.4)	5.0 (4.5–5.5)
South	9.5 (8.6–10.5)	1.7 (1.4–2.1)	5.4 (5.0–5.9)
West	6.1 (5.1–7.3)	1.3 (0.9–1.8)	3.7 (3.1–4.3)

Source: 2012 NSDUH: Substance Abuse and Mental Health Services Administration.
Note: **CI** = confidence interval.
[a]Multiple use is defined as using 2 or more tobacco products. Tobacco products include cigarette, smokeless tobacco (i.e., chewing tobacco and snuff), cigars, and pipe tobacco.
[b]Respondents 18–22 years of age currently living in a college dormitory are included in the Unknown category.

Table 13.17 **Percent current use[a] of tobacco by product, school level, and gender; National Youth Tobacco Survey 2011 and 2012; United States**

	Total				Female				Male			
	2011		2012		2011		2012		2011		2012	
	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)
Middle School												
Tobacco[b]	7.5	(6.5–8.8)	6.7	(5.8–7.7)	5.9	(4.7–7.4)	5.6	(4.7–6.7)	9.0	(7.9–10.3)	7.8	(6.7–9.0)
Both combustible & noncombustible tobacco[c]	1.9	(1.5–2.5)	2.0	(1.6–2.5)	1.6	(1.2–2.1)*	1.6	(1.2–2.1)*	2.2	(1.7–3.0)	2.5	(2.0–3.1)
Only combustible[d]	4.5	(3.7–5.5)	3.7	(3.2–4.3)	3.8	(2.8–5.0)	3.5	(2.8–4.4)	5.2	(4.3–6.2)[†]	3.9	(3.4–4.5)[†]
Only noncombustible[e]	1.1	(0.8–1.4)	1.0	(0.7–1.3)	0.5	(0.3–0.9)	0.5	(0.3–0.8)	1.6	(1.2–2.3)	1.4	(1.0–2.0)
Cigarettes	4.3	(3.5–5.2)	3.5	(2.8–4.3)	4.0	(3.1–5.2)	3.2	(2.5–4.0)	4.5	(3.7–5.5)	3.8	(3.0–4.7)
Cigars	3.5	(2.8–4.2)	2.8	(2.4–3.4)	2.5	(1.9–3.4)	2.4	(1.9–3.2)	4.3	(3.4–5.4)	3.2	(2.7–3.8)
Smokeless tobacco	2.2	(1.8–2.7)	1.7	(1.3–2.1)	1.4	(1.0–2.0)	1.2	(0.8–1.6)	3.0	(2.3–3.8)	2.2	(1.7–2.9)
Pipes	2.2	(1.7–2.9)	1.8	(1.4–2.3)	1.8	(1.3–2.5)	1.7	(1.3–2.3)	2.7	(2.1–2.5)	1.9	(1.4–2.4)
Bidis	1.7	(1.3–2.2)[†]	0.6	(0.5–0.7)[†]	1.4	(1.0–1.9)[†]	0.4	(0.3–0.7)[†]	1.9	(1.4–2.6)[†]	0.7	(0.5–1.0)[†]
Kreteks	1.1	(0.9–1.4)[†]	0.5	(0.4–0.7)[†]	0.9	(0.6–1.3)[†]	0.4	(0.3–0.7)[†]	1.3	(1.0–1.6)[†]	0.6	(0.4–0.9)[†]
Hookah	1.0	(0.8–1.4)	1.3	(1.0–1.7)	1.0	(0.6–1.6)	1.0	(0.7–1.4)	1.1	(0.7–1.5)	1.5	(1.1–2.2)
Snus	0.9	(0.6–1.2)	0.8	(0.6–1.0)	0.8	(0.5–1.2)	0.6	(0.4–0.9)	1.0	(0.6–1.4)	1.0	(0.7–1.4)
Dissolvable tobacco	0.3	(0.2–0.4)*	0.5	(0.4–0.8)*	0.3	(0.2–0.5)*	0.4	(0.2–0.6)*	0.3	(0.1–0.5)*	0.7	(0.4–1.1)*
Electronic cigarettes	0.6	(0.4–0.9)[†]	1.1	(0.9–1.5)[†]	0.4	(0.2–0.7)[†]	0.8	(0.6–1.1)[†]	0.7	(0.4–1.3)[†]	1.5	(1.1–2.1)[†]
High School												
Tobacco	24.3	(22.1–26.6)	23.3	(21.6–25.2)	19.0	(17.0–21.1)	18.1	(16.2–20.1)	29.4	(26.6–32.4)	28.3	(26.2–30.6)
Both combustible & noncombustible tobacco	6.2	(5.1–7.5)	6.8	(5.9–7.9)	2.0	(1.5–2.6)[†]	3.4	(2.8–4.2)[†]	10.3	(8.4–12.4)	10.1	(8.6–11.7)
Only combustible	15.7	(14.6–16.8)	14.4	(13.2–15.6)	16.3	(14.4–18.3)	14.2	(12.6–15.9)	15.0	(13.8–16.3)	14.6	(13.3–15.9)
Only noncombustible	2.4	(1.8–3.2)	2.1	(1.7–2.7)	0.7	(0.4–1.1)	0.5	(0.3–0.7)	4.1	(3.1–5.5)	3.7	(2.9–4.8)
Cigarettes	15.8	(13.7–18.1)	14.0	(12.5–15.7)	13.8	(11.7–16.2)	11.7	(10.2–13.4)	17.7	(15.2–20.4)	16.3	(14.5–18.3)
Cigars	11.6	(10.5–12.7)	12.6	(11.4–13.9)	7.4	(6.3–8.6)	8.4	(7.2–9.8)	15.7	(14.3–17.2)	16.7	(15.0–18.5)
Smokeless tobacco	7.3	(5.9–9.0)	6.4	(5.5–7.5)	1.6	(1.2–2.2)	1.5	(1.1–2.1)	12.9	(10.4–15.9)	11.2	(9.5–13.0)
Pipes	4.0	(3.4–4.6)	4.5	(4.0–5.2)	2.8	(2.2–3.4)	3.2	(2.7–3.9)	5.1	(4.3–6.0)	5.8	(5.0–6.7)

Table 13.17   Continued

	Total				Female				Male			
	2011		2012		2011		2012		2011		2012	
	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)
Bidis	2.0	(1.6–2.5)[†]	0.9	(0.7–1.1)[†]	1.0	(0.7–1.4)[†]	0.5	(0.3–0.7)[†]	2.9	(2.3–3.7)[†]	1.3	(1.0–1.7)[†]
Kreteks	1.7	(1.4–2.0)[†]	1.0	(0.8–1.2)[†]	0.8	(0.6–1.2)[†]	0.5	(0.3–0.7)[†]	2.4	(1.9–2.9)[†]	1.5	(1.1–1.9)[†]
Hookah	4.1	(3.4–5.0)[†]	5.4	(4.6–6.3)[†]	3.5	(2.8–4.4)	4.5	(3.7–5.4)	4.8	(3.7–6.1)	6.2	(5.3–7.3)
Snus	2.9	(2.3–3.7)	2.5	(2.0–3.0)	0.8	(0.5–1.1)	0.9	(0.7–1.3)	5.1	(3.9–6.6)	3.9	(3.2–4.9)
Dissolvable tobacco	2.0	(1.6–2.5)[†]	0.8	(0.6–1.0)[†]	0.1	(0.1–0.4)*	0.6	(0.4–0.9)*	0.6	(0.4–1.0)	1.0	(0.8–1.4)
Electronic cigarettes	1.5	(1.2–2.0)[†]	2.8	(2.3–3.5)[†]	0.7	(0.5–1.0)[†]	1.9	(1.5–2.4)[†]	2.3	(1.7–3.1)[†]	3.7	(2.9–4.8) [†]

Source: National Youth Tobacco Survey 2011–2012.

Note: **CI** = confidence interval.

[a]Current use of cigarettes was determined by asking, "During the past 30 days, on how many days did you smoke cigarettes?"; Current use of cigars was determined by asking, "During the past 30 days, on how many days did you smoke cigars, cigarillos, or little cigars?"; Current use of smokeless tobacco was determined by asking, "During the past 30 days, on how many days did you use chewing tobacco, snuff, or dip?"; Current use of pipe was determined by asking, "During the past 30 days, on how many days did you smoke tobacco in a pipe?"; In 2011, current use of bidis and kreteks were determined by asking, "During the past 30 days, on how many days did you smoke bidis?" and "During the past 30 days, on how many days did you smoke kreteks?"; In 2012, current use of bidis and kreteks were determined by asking, "During the past 30 days, which of the following products have you used on at least one day?"; Current use of hookah, snus, dissolvable tobacco, and electronic cigarettes were deteremined by asking, "During the past 30 days, which of the following products have you used on at least one day?"

[b]Tobacco is use of cigarettes or cigars or smokeless tobacco or tobacco pipes or bidis or kreteks or hookah or snus or dissolvable tobacco or electronic cigarettes on ≥1 day in the past 30 days.

[c]Both combustible & noncombustible tobacco is use of cigarettes or cigars or tobacco pipes or bidis or kreteks or hookah and smokeless tobacco or snus or dissolvable tobacco or electronic cigarettes on ≥1 day in the past 30 days.

[d]Only combustible tobacco is use of cigarettes or cigars or tobacco pipes or bidis or kreteks or hookah on ≥1 day in the past 30 days and no use of smokeless tobacco, snus, dissolvable tobacco, and electronic cigarettes in the past 30 days.

[e]Only noncombustible tobacco is use of smokeless tobacco or snus or dissolvable tobacco or electronic cigarettes on ≥1 day in the past 30 days and no use of cigarettes, cigars, tobacco pipes, bidis, kreteks, and hookah in the past 30 days.

*Data statistically unreliable due to sample size <50 OR relative standard error >0.3 on at least 1 year's data; thus, no t-test was done.

[†]p-value of the t-test for difference between 2011 and 2012 prevalences is <0.05.

Table 13.18 Percent current use[a] of tobacco by product, school level, and race/ethnicity; National Youth Tobacco Survey 2011 and 2012; United States

	White, non-Hispanic				Black, non-Hispanic				Hispanic				Other, non-Hispanic			
	2011		2012		2011		2012		2011		2012		2011		2012	
	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)
Middle School																
Tobacco[b]	6.2	(5.1–7.4)	5.1	(4.2–6.3)	8.5	(6.6–10.9)	7.7	(5.9–10.1)	11.5	(10.2–13.1)	10.5	(8.6–12.8)	6.1	(3.8–9.9)	3.1	(1.7–5.4)
Both combustible & noncombustible tobacco[c]	2.0	(1.4–2.6)	1.7	(1.3–2.2)	0.9	(0.4–1.8)*	1.4	(1.0–2.0)*	2.8	(2.1–3.7)	3.4	(2.5–4.6)	2.0	(1.1–3.6)*	1.2	(0.5–2.8)*
Only combustible[d]	3.0	(2.2–4.0)	2.5	(2.0–3.1)	7.0	(5.3–9.0)	5.6	(4.3–7.3)	7.8	(6.8–9.1)†	6.1	(4.9–7.5)†	2.8	(1.5–5.0)*	1.4	(0.7–2.7)*
Only noncombustible[e]	1.2	(0.8–1.7)	1.0	(0.7–1.4)	0.7	(0.4–1.3)*	0.7	(0.3–2.0)*	0.9	(0.6–1.4)	1.0	(0.6–1.8)	1.3	(0.6–3.2)*	0.5	(0.2–1.3)*
Cigarettes	3.8	(2.8–5.1)	3.1	(2.4–4.0)	3.6	(2.6–5.0)	2.6	(1.7–4.0)	6.7	(5.6–8.0)	5.4	(4.2–7.1)	3.4	(2.0–5.8)*	1.7	(0.8–3.6)*
Cigars	2.3	(1.7–3.0)	1.6	(1.2–2.0)	5.7	(4.3–7.4)	5.0	(3.8–6.6)	6.1	(4.9–7.4)	4.9	(3.8–6.4)	1.6	(0.8–3.2)*	1.5	(0.7–3.1)*
Smokeless tobacco	2.3	(1.8–2.9)	1.6	(1.1–2.2)	1.0	(0.5–2.1)*	0.6	(0.3–1.3)*	2.9	(2.3–3.6)	2.4	(1.7–3.4)	2.4	(1.2–4.8)*	1.4	(0.7–3.1)*
Pipes	1.5	(1.1–2.2)	1.2	(0.8–1.7)	1.3	(0.8–2.1)*	1.2	(0.6–2.2)*	5.0	(4.2–6.1)	3.7	(2.7–5.1)	2.5	(1.2–5.0)*	0.5	(0.2–1.1)*
Bidis	1.0	(0.7–1.5)*	0.3	(0.2–0.5)*	1.9	(1.1–3.2)*	0.6	(0.4–1.0)*	3.5	(2.6–4.6)†	1.2	(0.8–1.8)†	1.2	(0.5–2.8)*	0.7	(0.2–2.4)*
Kreteks	0.6	(0.4–0.6)	0.3	(0.2–0.5)	0.9	(0.5–1.6)*	0.2	(0.1–0.7)*	2.5	(2.0–3.3)†	1.0	(0.6–1.7)†	1.8	(0.7–4.3)*	0.7	(0.2–2.4)*
Hookah	0.9	(0.6–1.4)	0.8	(0.6–1.2)	0.9	(0.5–1.7)*	0.9	(0.4–1.8)*	1.7	(1.2–2.3)†	3.0	(2.2–4.1)†	0.1	(0.0–0.5)*	0.3	(0.1–1.6)*
Snus	1.0	(0.7–1.4)	0.7	(0.5–1.0)	0.6	(0.2–1.3)*	0.4	(0.1–0.9)*	1.0	(0.6–1.5)	1.1	(0.7–1.7)	0.7	(0.2–2.5)*	0.4	(0.1–2.8)*
Dissolvable tobacco	0.2	(0.1–0.5)*	0.4	(0.2–0.7)*	0.4	(0.1–1.2)*	0.5	(0.2–1.5)*	0.2	(0.1–0.5)*	1.0	(0.6–1.6)*	0.4	(0.1–2.4)*	0.1	(0.0–0.5)*
Electronic cigarettes	0.6	(0.4–1.0)*	0.9	(0.6–1.3)*	0.4	(0.2–1.0)*	1.1	(0.6–2.2)*	0.6	(0.4–1.1)*	2.0	(1.4–2.9)*	0.7	(0.2–2.6)*	0.3	(0.1–0.8)*
High School																
Tobacco	26.6	(23.6–29.8)	24.6	(22.3–27.0)	18.9	(15.6–22.8)	22.6	(19.7–25.8)	23.8	(21.2–26.5)	22.5	(19.5–25.6)	13.9	(10.5–18.3)	13.7	(9.9–18.8)
Both combustible & noncombustible tobacco	7.5	(6.1–9.3)	8.2	(6.9–9.6)	2.3	(1.2–4.2)*	2.3	(1.6–3.2)*	5.4	(4.3–6.6)	6.4	(5.0–8.1)	3.4	(2.0–5.7)	4.4	(2.9–6.5)
Only combustible	15.8	(14.5–17.3)†	13.6	(12.2–15.0)†	15.7	(13.1–18.6)	19.2	(16.4–22.4)	16.9	(15.2–18.3)	14.8	(13.0–16.8)	9.1	(6.1–13.3)	8.3	(5.7–12.0)
Only noncombustible	3.2	(2.4–4.2)	2.8	(2.2–3.6)	1.0	(0.4–2.3)*	1.1	(0.6–1.9)*	1.5	(1.0–2.3)	1.3	(0.9–1.9)	1.5	(0.6–3.5)*	1.1	(0.5–2.4)*
Cigarettes	17.6	(14.7–20.9)	15.4	(13.2–17.8)	10.6	(7.6–14.6)	9.6	(7.6–12.0)	15.8	(13.9–17.8)	14.3	(12.0–16.9)	8.9	(6.2–12.5)	8.7	(5.9–12.5)

Table 13.18   Continued

	White, non-Hispanic				Black, non-Hispanic				Hispanic				Other, non-Hispanic			
	2011		2012		2011		2012		2011		2012		2011		2012	
	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)
Cigars	12.1	(10.7–13.6)	12.2	(10.8–13.8)	11.7	(9.8–13.9)[†]	16.7	(14.4–19.3)[†]	11.3	(9.8–13.1)	12.4	(10.6–14.4)	5.7	(4.0–8.1)	6.3	(4.4–9.0)
Smokeless tobacco	9.2	(7.4–11.5)	8.1	(6.9–9.5)	3.0	(1.8–5.1)	2.2	(1.5–3.2)	5.1	(3.8–6.8)	5.1	(3.8–6.8)	4.0	(2.4–6.6)	3.4	(2.3–5.2)
Pipes	3.5	(2.9–4.4)	4.5	(3.8–5.4)	2.4	(1.5–3.8)	2.9	(1.8–4.5)	6.3	(5.2–7.7)	6.2	(5.2–7.4)	3.4	(1.7–6.6)*	2.4	(1.4–3.9)*
Bidis	1.4	(1.0–2.0)[†]	0.7	(0.5–1.0)[†]	2.0	(1.2–3.2)*	0.8	(0.4–1.7)*	3.7	(2.9–4.8)[†]	1.4	(0.9–2.2)[†]	1.8	(1.0–3.4)*	0.4	(0.2–1.1)*
Kreteks	1.4	(1.0–2.0)	1.1	(0.8–1.5)	1.3	(0.8–2.2)*	0.6	(0.3–1.1)*	2.5	(1.9–3.3)[†]	0.9	(0.6–1.4)[†]	2.0	(1.0–4.0)*	0.3	(0.1–0.7)*
Hookah	4.3	(3.4–5.4)[†]	6.1	(5.2–7.2)[†]	1.7	(0.9–3.0)	2.1	(1.6–2.9)	5.1	(4.1–6.3)	6.6	(5.1–8.5)	4.8	(2.5–9.0)*	2.5	(1.5–4.1)*
Snus	3.7	(2.8–4.9)	3.3	(2.6–4.2)	0.7	(0.3–1.5)*	0.6	(0.3–1.1)*	2.3	(1.7–3.1)	1.8	(1.3–2.5)	1.7	(0.7–3.8)*	0.8	(0.4–1.6)*
Dissolvable tobacco	0.3	(0.1–0.5)*	0.7	(0.5–0.9)*	0.3	(0.1–1.2)*	0.8	(0.4–1.3)*	0.8	(0.5–1.3)	1.4	(1.0–2.1)	0.6	(0.1–2.9)*	0.5	(0.2–1.2)*
Electronic cigarettes	1.8	(1.3–2.4)[†]	3.4	(2.7–4.2)[†]	0.8	(0.3–1.7)*	1.1	(0.7–1.9)*	1.3	(0.8–2.1)[†]	2.7	(1.9–3.8)[†]	0.6	(0.3–1.2)*	2.2	(0.9–5.8)*

Source: National Youth Tobacco Survey 2011–2012.

Note: **CI** = confidence interval.

[a]Current use of cigarettes was determined by asking, "During the past 30 days, on how many days did you smoke cigarettes?"; Current use of cigars was determined by asking, "During the past 30 days, on how many days did you smoke cigars, cigarillos, or little cigars?"; Current use of smokeless tobacco was determined by asking, "During the past 30 days, on how many days did you use chewing tobacco, snuff, or dip?"; Current use of pipe was determined by asking, "During the past 30 days, on how many days did you smoke tobacco in a pipe?"; In 2011, current use of bidis and kreteks were determined by asking, "During the past 30 days, on how many days did you smoke bidis?" and "During the past 30 days, on how many days did you smoke kreteks?"; In 2012, current use of bidis and kreteks were determined by asking, "During the past 30 days, which of the following products have you used on at least one day?"; Current use of hookah, snus, dissolvable tobacco, and electronic cigarettes were deteremined by asking, "During the past 30 days, which of the following products have you used on at least one day?"

[b]Tobacco is use of cigarettes or cigars or smokeless tobacco or tobacco pipes or bidis or kreteks or hookah or snus or dissolvable tobacco or electronic cigarettes on ≥1 day in the past 30 days.

[c]Both combustible & noncombustible tobacco is use of cigarettes or cigars or tobacco pipes or bidis or kreteks or hookah and smokeless tobacco or snus or dissolvable tobacco or electronic cigarettes on ≥1 day in the past 30 days.

[d]Only combustible tobacco is use of cigarettes or cigars or tobacco pipes or bidis or kreteks or hookah on ≥1 day in the past 30 days and no use of smokeless tobacco, snus, dissolvable tobacco, and electronic cigarettes in the past 30 days.

[e]Only noncombustible tobacco is use of smokeless tobacco or snus or dissolvable tobacco or electronic cigarettes on ≥1 day in the past 30 days and no use of cigarettes, cigars, tobacco pipes, bidis, kreteks, and hookah in the past 30 days.

*Data statistically unreliable due to sample size <50 OR relative standard error >0.3 on at least 1 year's data; thus, no t-test was done.

[†]p-value of the t-test for difference between 2011 and 2012 prevalences is <0.05.

Table 13.19   Percentage of tobacco product use in the past month among persons 18 years of age and older, 2002–2012

Substance	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Total tobacco products[a]	30.8[b]	30.2[b]	29.6[b]	29.9[b]	30.1[b]	29.2[b]	28.8[b]	28.1	27.8	26.9	27.3
Cigarettes[c]	25.8[b]	25.2[b]	24.7[b]	24.7[b]	24.8[b]	24.1[b]	23.7[b]	23.0[d]	22.6	21.7	22.0
Smokeless tobacco	3.5	3.4	3.1[b]	3.3	3.5	3.3	3.6	3.5	3.6	3.3	3.6
Cigars	5.5	5.5	5.8	5.8	5.7	5.5	5.5	5.4	5.4	5.2	5.4
Pipe tobacco	0.8	0.7[b]	0.8[d]	0.9	1.0	0.8	0.8[d]	0.8	0.9	0.8	1.0
Cigarettes[c] or cigars	28.5[b]	27.9[b]	27.6[b]	27.7[b]	27.7[b]	27.0[b]	26.4[b]	25.8[d]	25.5	24.6	24.8
Cigarettes,[c] cigars, or pipe tobacco	28.8[b]	28.2[b]	27.9[b]	28.0[b]	28.0[b]	27.3[b]	26.7[b]	26.1	25.8	24.9	25.2

Source: Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health, 2002–2012.
[a]Tobacco products include cigarettes, smokeless tobacco (i.e., chewing tobacco or snuff), cigars, or pipe tobacco.
[b]The difference between estimate and 2012 estimate is statistically significant at the 0.01 level.
[c]Past-month cigarette use is defined as smoking during the 30 days preceding the survey and smoking 100 cigarettes or more in a lifetime. Respondents with an unknown lifetime number of cigarettes smoked were excluded from the analysis.
[d]The difference between this estimate and 2012 estimate is statistically significant at the 0.05 level.

Data from the 2012 NSDUH show that the prevalence of combustible (cigarettes, cigar, or pipe tobacco) tobacco product use among adults 18 years of age or older was 25.2% and the prevalence of overall tobacco product use (cigarettes, cigars, pipe tobacco, and smokeless) was 27.3%, both of which were significantly higher than the 22.0% prevalence of cigarette smoking (Table 13.19). In addition, NSDUH data suggest that declines in cigarette smoking may be masking persistently high cigarette initiation rates (Figure 13.26). Overall, 2.3 million persons 12 years of age or older initiated cigarette use in 2012, a level equivalent to that observed in 2005. These data on persistently high cigarette initiation rates are not inconsistent with data shown in Table 13.2; however, data in Figure 13.26 focus on somewhat different and more recent aspects of the problem. Table 13.2 shows the age of smoking initiation among adults 30–39 years of age who had ever smoked daily. Figure 13.26 shows the recent patterns of ever smoking even a single cigarette. The proportion of adults (18 years of age or older) who initiated cigarette use in the previous year was greater than prior years. If this pattern continues and is also reflected in those who ever become daily smokers by 30 years of age, the high rates of

initiation below 18 years of age shown in Table 13.2 could improve in the future.

Electronic Cigarettes

Although NSDUH did not measure electronic cigarette use in 2012 and other nationally representative surveillance data on the awareness and use of electronic cigarettes remains limited, all available data show rapid increases in recent years. Data from the HealthStyles Survey show that awareness of electronic cigarettes among adults 18 years of age or older increased from 40.9% in 2010 to 57.9% in 2011 (King et al. 2013). Ever use of electronic cigarettes also nearly doubled among all adults during 2010–2011, from 3.3% to 6.2% (Table 13.20). During the same period, the prevalence of ever electronic cigarette use among current cigarette smokers increased from 9.8% to 21.2%, while the prevalence among former cigarette smokers increased from 2.5% to 7.4%. Prevalence remained unchanged among never cigarette smokers (1.3%). Other studies described in Table 13.20 are consistent with these results.

Figure 13.26 Cigarette initiation during the past year among persons 12 years of age and older, by age at first use, 2002–2012
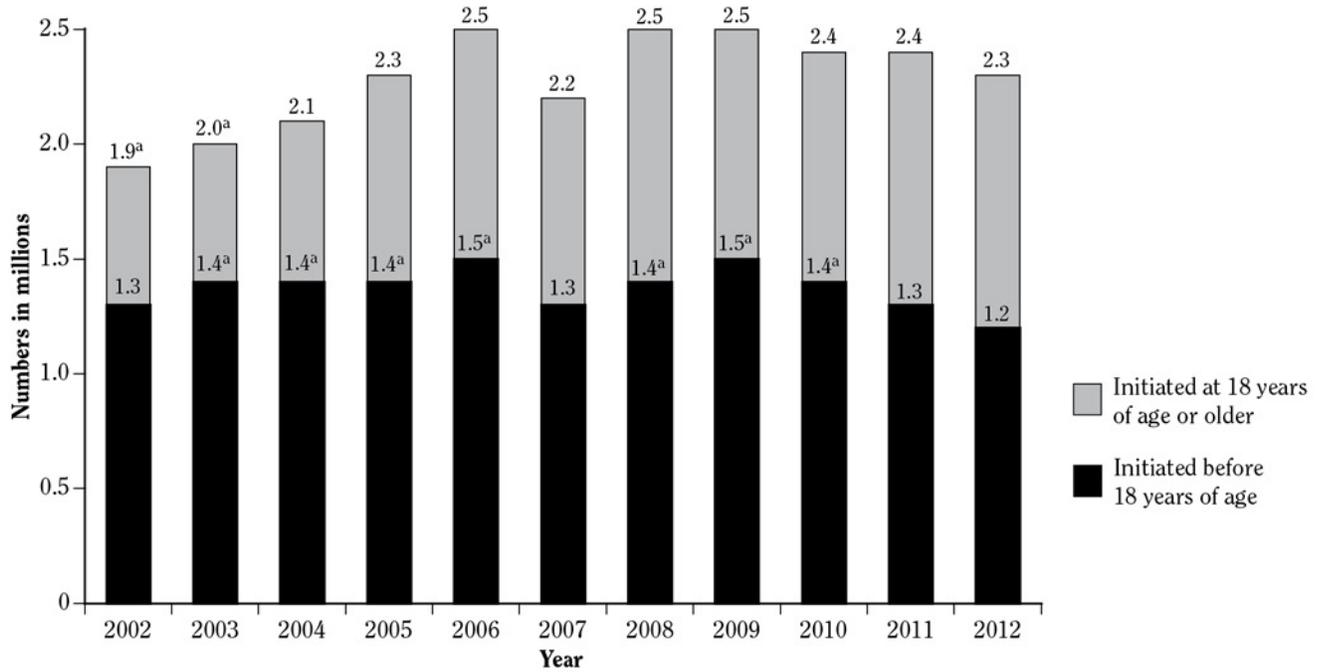
Source: Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health, 2002–2012.
[a]Difference between this estimate and the 2012 estimate is statistically significant at the .05 level.

Table 13.20   Sources of data and prevalence of electronic nicotine delivery systems (ENDS); United States, 2012–2013

Study	Study design/population	Findings
McMillen et al. 2012	• Social Climate Survey of Tobacco Control • 3,240 online surveys and telephone interviews • 2010 • United States	**Ever use of ENDS (%)** • Overall: 1.8 • Smoking status: – Never: 0.3 – Former: 1.5 – Nondaily: 8.2 – Daily: 6.2 • Region:[a] – Northeast: 2.7 – Midwest: 1.4 – South: 1.6 – West: 1.9 • Race: – White: 1.7 – Black: 1.9 – Other: 1.8 • Years of age: – 18–24: 2.5 – ≥25: 1.6 • Education: – <High school diploma: 0.7 – High school diploma: 1.7 – Some college: 3.7 – College degree: 0.5

Table 13.20 Continued

Study	Study design/population	Findings
Pearson et al. 2012	• Legacy Longitudinal Smoker Cohort (LLSC) (n = 3658) • Knowledge Networks' KnowledgePanel (n=2,649) • 2010 online surveys and telephone interviews • United States	**Prevalence of ENDS use among Knowledge Networks' KnowledgePanel** • Ever use of ENDS: – Never smoker: 0.8% (0.4–1.7) – Former smoker: 2.0% (1.0–3.8) – Current smoker: 11.4% (9.3–14.0) • Use for current smokers, % (95% CI): – Overall: 11.4 (9.2–14.0) – Gender: o Male: 12.6 (9.2–16.9) o Female: 10.3 (7.7–13.7) – Race/ethnicity: o White: 11.8 (9.4–14.7) o Black: 8.2 (3.6–17.7) o Hispanic: 10.2 (5.1–19.6) o Other: 18.1 (8.4–34.6) – Education: o <High school diploma: 11.6 (6.5–19.8) o High school diploma or GED: 8.5 (6.0–11.9) o Some college: 13.6 (9.8–18.5) o College degree: 13.7 (8.4–21.6) **Prevalence of ENDS use among LLSC** • Ever use of ENDS: – Never smoker: Not reported – Former smoker: 3.1% (1.3–7.1) – Current smoker: 6.4% (5.3–7.7) • Use for current smokers, % (95% CI): – Overall: 6.4 (5.3–7.7) – Gender: o Male: 7.3 (5.6–9.5) o Female: 5.3 (4.2–6.7) – Race/ethnicity: o White: 7.4 (6.1–9.1) o Black: 0.8 (0.3–2.0) o Hispanic: 5.5 (3.2–9.5) o Other: 6.0 (2.5–13.6) – Education: o <High school diploma: 3.4 (2.0–7.7) o High school diploma or GED: 7.0 (5.3–9.1) o Some college: 7.4 (5.2–10.4) o College degree: 9.4 (5.6–15.5)
Adkison et al. 2013	• Wave 8 of the International Tobacco Control Four-Country Survey: – Canada: n = 1,581 – United States: n = 1,520 – UK: n = 1,325 – Australia: n = 1,513 • July 2010–June 2011 • Online surveys and telephone interviews	• Current ENDS user, United States: 1.08% (95% CI, 0.52–2.12)

Table 13.20   Continued

Study	Study design/population	Findings
King et al. 2013	• HealthStyles Survey • 4,184 adults (≥18 years of age) • 2010 mail survey • United States	**Ever use of ENDS[b], % (95% CI)** • Gender: – Male: 2.3 (1.3–3.4) – Female: 1.9 (1.3–2.6) • Years of age: – 18–24: —[c] – 25–34: 2.9 (1.1–4.7) – 35–44: 3.4 (2.0–4.8) – 45–54: 1.9 (1.0–2.8) – 55–64: 2.2 (0.9–3.4) – ≥65: 0.8 (0.2–1.4) • Race/ethnicity: – White, non-Hispanic: 2.4 (1.6–3.2) – Black, non-Hispanic: —[c] – Other, non-Hispanic: 1.8 (0.4–3.2) – Hispanic: 2.3 (0.9–3.7) • Education: – <High school: —[c] – High school graduate: 3.1 (1.3–5.0) – Some college: 2.3 (1.4–3.2) – College graduate: 1.5 (0.7–2.2) • Annual household income: – <$15,000: 1.1 (0.3–1.9) – $15,000–$24,999: 1.6 (0.4–2.9) – $25,000–$39,999: 2.9 (0.6–5.2) – $40,000–$59,999: 1.9 (0.7–3.1) – ≥$60,000: 2.4 (1.5–3.3) • Region:[a] – Northeast: 1.1 (0.3–1.9) – Midwest: 3.3 (1.5–5.1) – South: 1.4 (0.8–2.0) – West: 3.0 (1.7–4.2) • Smoking status: – Current smoker: 6.8 (4.6–8.9) – Former smoker: 0.6 (0.2–1.1) – Never smoker: 1.2 (1.5–2.7) • Total: 2.1 (1.5–2.7)

Table 13.20 Continued

Study	Study design/population	Findings

King et al. 2013	• HealthStyles Survey
	• 2,505 adults (≥18 years of age)
	• 2010 Web survey
	• United States
		Ever use of ENDS[b], % (95% CI)
		• Gender:
		  – Male: 3.0 (1.9–4.2)
		  – Female: 3.7 (2.4–4.9)
		• Years of age:
		  – 18–24: 7.0 (3.0–10.9)
		  – 25–34: 3.1 (1.4–4.8)
		  – 35–44: 3.2 (1.4–5.0)
		  – 45–54: 3.2 (1.3–5.2)
		  – 55–64: 2.9 (1.1–4.8)
		  – ≥65: —[c]
		• Race/ethnicity:
		  – White, non-Hispanic: 3.8 (2.7–4.9)
		  – Black, non-Hispanic: —[c]
		  – Other, non-Hispanic: —[c]
		  – Hispanic: 3.0 (1.0–5.1)
		• Education:
		  – <High school: 4.3 (1.7–6.9)
		  – High school graduate: 4.0 (2.2–5.7)
		  – Some college: 3.6 (2.0–5.1)
		  – College graduate: 2.0 (0.8–3.2)
		• Annual household income:
		  – <$15,000: 3.5 (1.5–5.6)
		  – $15,000–$24,999: —[c]
		  – $25,000–$39,999: 3.5 (1.3–5.8)
		  – $40,000–$59,999: 2.5 (1.1–3.8)
		  – ≥$60,000: 3.5 (2.1–4.9)
		• Region:[a]
		  – Northeast: —[c]
		  – Midwest: 5.4 (3.1–7.6)
		  – South: 2.5 (1.4–3.6)
		  – West: 3.7 (2.0–5.5)
		• Smoking status:
		  – Current smoker: 9.8 (6.9–12.6)
		  – Former smoker: 2.5 (0.8–4.2)
		  – Never smoker: 1.3 (0.5–2.0)
		• Total: 3.3 (2.5–4.2)

Table 13.20   Continued

Study	Study design/population	Findings
King et al. 2013	• HealthStyles Survey • 4,050 adults (≥18 years of age) • 2011 Web survey • United States	**Ever use of ENDS[b], % (95% CI)** • Gender: – Male: 5.8 (4.4–7.2) – Female: 6.6 (5.1–8.2) • Years of age: – 18–24: 8.1 (4.0–12.2) – 25–34: 6.6 (3.9–9.3) – 35–44: 5.7 (3.6–7.7) – 45–54: 8.0 (5.5–10.5) – 55–64: 5.5 (3.4–7.5) – ≥65: 3.7 (1.9–5.4) • Race/ethnicity: – White, non-Hispanic: 6.8 (5.6–8.1) – Black, non-Hispanic: 4.5 (1.6–7.3) – Other, non-Hispanic: 6.1 (1.8–10.4) – Hispanic: 3.9 (1.1–6.7) • Education: – <High school: 7.4 (3.4–11.4) – High school graduate: 7.5 (5.4–9.7) – Some college: 6.1 (4.6–7.7) – College graduate: 4.4 (2.9–5.9) • Annual household income: – <$15,000: 7.5 (4.3–10.7) – $15,000–$24,999: 5.7 (1.9–9.4) – $25,000–$39,999: 9.4 (5.7–13.0) – $40,000–$59,999: 4.9 (2.9–6.9) – ≥$60,000: 5.6 (4.3–7.0) • Region:[a] – Northeast: 5.6 (3.5–7.7) – Midwest: 7.7 (5.3–10.1) – South: 6.2 (4.4–8.0) – West: 5.3 (3.3–7.3) • Smoking status: – Current smoker: 21.2 (17.0–25.4) – Former smoker: 7.4 (5.0–9.7) – Never smoker: 1.3 (0.7–1.8) • Total: 6.2 (5.2–7.3)

Table 13.20   Continued

Study	Study design/population	Findings

Regan et al. 2013	• ConsumerStyles Survey
	• 2009: n = 21,240
	• 2010: n = 20,000
	• United States
		Ever use ENDs (n = 249): % (95% CI)[d]
		• Gender:
		  – Male: 6.5 (4.9–8.0)
		  – Female: 10.5 (7.9–13.2)
		• Years of age:
		  – 18–24: 10.1 (3.1–17.0)
		  – 25–34: 9.2 (6.2–12.2)
		  – 35–44: 6.9 (4.9–9.0)
		  – 45–54: 9.2 (7.1–11.3)
		  – 55–64: 5.9 (3.4–8.4)
		  – ≥65: 7.9 (4.8–11.1)
		• Race/ethnicity:
		  – White, non-Hispanic: 8.3 (6.4–10.1)
		  – Black, non-Hispanic: 8.9 (4.9–12.9)
		  – Other, non-Hispanic: 8.2 (4.6–11.7)
		  – Hispanic: 8.9 (4.5–13.3)
		• Education:
		  – <High school: 17.8 (5.4–30.2)
		  – High school graduate: 9.5 (6.2–12.7)
		  – Some college: 8.0 (5.9–10.1)
		  – ≥College graduate: 7.0 (4.3–9.6)
		• Annual household income:
		  – <$15,000: 12.9 (5.8–20.0)
		  – $15,000–$24,999: 12.6 (6.7–18.5)
		  – $25,000–$39,999: 8.1 (4.7–11.4)
		  – $40,000–$59,999: 9.3 (5.1–13.5)
		  – ≥$60,000: 6.0 (4.7–7.4)
		• Region:
		  – Northeast: 9.5 (4.9–14.2)
		  – Midwest: 8.6 (5.5–11.8)
		  – South: 8.1 (6.0–10.3)
		  – West: 7.3 (5.1–9.6)
		• Smoking status:
		  – Current smoker: 18.2 (13.8–22.7)
		  – Former smoker: 6.2 (4.0–8.3)
		  – Never smoker: 3.8 (2.7–4.9)
		• Tobacco use:
		  – Uses tobacco: 17.2 (13.6–20.8)
		  – Uses one tobacco product: 14.7 (10.6–18.7)
		  – Uses >1 tobacco product: 21.1 (14.3–28.0)
		  – Does not use tobacco: 3.6 (2.6–4.6)

Table 13.20   Continued

Study	Study design/population	Findings

Regan et al. 2013	• ConsumerStyles Survey
	• 2009: n = 21,240
	• 2010: n = 20,000
	• United States
		Ever use ENDs (n = 249): OR (95% CI)[d]
		• Gender
		  – Male: 0.59 (0.40–0.86)[*]
		  – Female: 1
		• Years of age:
		  – 18–24: 1.30 (0.54–3.14)
		  – 25–34: 1.17 (0.67–2.05)
		  – 35–44: 0.87 (0.51–1.48)
		  – 45–54: 1.18 (0.71–1.93)
		  – 55–64: 0.73 (0.39–1.36)
		  – ≥65: 1
		• Race/ethnicity:
		  – White, non-Hispanic: 1
		  – Black, non-Hispanic: 1.08 (0.62–1.89)
		  – Other, non-Hispanic: 0.99 (0.58–1.68)
		  – Hispanic: 1.09 (0.60–1.97)
		• Education:
		  – <High school: 2.90 (1.13–7.45)[*]
		  – High school graduate: 1.41 (0.81–2.45)
		  – Some college: 1.17 (0.71–1.92)
		  – ≥College graduate: 1
		• Annual household income:
		  – <$15,000: 2.24 (1.25–4.02) [*]
		  – $15,000–$24,999: 1.36 (0.82–2.28)
		  – $25,000–$39,999: 1.59 (0.92–2.77)
		  – $40,000–$59,999: 2.30 (1.17–4.51)[*]
		  – ≥$60,000: 1
		• Region:
		  – Northeast: 1.33 (0.71–2.51)
		  – Midwest: 1.19 (0.71–2.01)
		  – South: 1.11 (0.72–1.72)
		  – West: 1
		• Smoking status:
		  – Current smoker: 5.71 (3.72–8.76) [*]
		  – Former smoker: 1.68 (1.03–2.72) [*]
		  – Never smoker: 1
		• Tobacco use:
		  – Uses tobacco: 5.55 (3.80–8.11) [*]
		  – Uses one tobacco product: 4.59 (3.00–7.04) [*]
		  – Uses >1 tobacco product: 7.17 (4.36–11.78) [*]
		  – Does not use tobacco: 1

Table 13.20   Continued

Study	Study design/population	Findings

Regan et al. 2013	• ConsumerStyles Survey
	• 2009: n = 21,240
	• 2010: n = 20,000
	• United States
		Past month use of ENDS (n = 115): % (95% CI)[d]
		• Gender:
		  – Male: 3.6 (2.4–4.9)
		  – Female: 3.5 (2.5–4.6)
		• Years of age:
		  – 18–24: —[e]
		  – 25–34: 3.7 (1.6–5.7)
		  – 35–44: 2.9 (1.7–4.1)
		  – 45–54: 4.8 (3.2–6.4)
		  – 55–64: 3.1 (1.2–5.0)
		  – ≥65: 5.2 (2.5–7.9)
		• Race/ethnicity:
		  – White, non-Hispanic: 3.3 (2.3–4.3)
		  – Black, non-Hispanic: 5.8 (2.4–9.3)
		  – Other, non-Hispanic: 3.1 (1.1–5.2)
		  – Hispanic: 4.3 (0.9–7.8)
		• Education:
		  – <High school: —[e]
		  – High school graduate: 4.1 (1.9–6.3)
		  – Some college: 3.4 (2.2–4.5)
		  – ≥College graduate: 2.9 (1.8–4.1)
		• Annual household income:
		  – <$15,000: 4.6 (1.7–7.5)
		  – $15,000–$24,999: 4.1 (1.6–6.6)
		  – $25,000–$39,999: 4.3 (1.9–6.8)
		  – $40,000–$59,999: 3.7 (1.3–6.1)
		  – ≥$60,000: 3.0 (1.9–4.0)
		• Region:
		  – Northeast: 4.2 (1.7–6.6)
		  – Midwest: 2.8 (1.2–4.4)
		  – South: 3.5 (2.3–4.8)
		  – West: 4.2 (2.5–6.0)
		• Smoking status:
		  – Current smoker: 6.3 (4.1–8.6)
		  – Former smoker: 2.9 (1.4–4.5)
		  – Never smoker: 2.2 (1.3–3.1)
		• Tobacco use:
		  – Uses tobacco: 7.1 (5.0–9.1)
		  – Uses one tobacco product: 4.3 (2.6–6.0)
		  – Uses >1 tobacco product: 11.4 (6.9–15.9)
		  – Does not use tobacco: 1.8 (1.1–2.5)

Table 13.20   Continued

Study	Study design/population	Findings

Regan et al. 2013	• ConsumerStyles Survey
	• 2009: n = 21,240
	• 2010: n = 20,000
	• United States
		Past month use of ENDS (n = 115): OR (95% CI)[d]
		• Gender:
		  – Male: 1.03 (0.64–1.67)
		  – Female: 1
		• Years of age:
		  – 18–24: 0.46 (0.12–1.74)
		  – 25–34: 0.69 (0.31–1.53)
		  – 35–44: 0.54 (0.27–1.10)
		  – 45–54: 0.91 (0.47–1.74)
		  – 55–64: 0.59 (0.25–1.35)
		  – ≥65: 1
		• Race/ethnicity:
		  – White, non-Hispanic: 1
		  – Black, non-Hispanic: 1.79 (0.89–3.61)
		  – Other, non-Hispanic: 0.94 (0.45–1.99)
		  – Hispanic: 1.32 (0.55–3.19)
		• Education:
		  – <High school: 3.47 (1.15–10.46)[e]
		  – High school graduate: 1.42 (0.70–2.85)
		  – Some college: 1.15 (0.67–1.99)
		  – ≥College graduate: 1
		• Annual household income:
		  – <$15,000: 1.40 (0.68–2.89)
		  – $15,000–$24,999: 1.48 (0.74–2.97)
		  – $25,000–$39,999: 1.25 (0.58–2.69)
		  – $40,000–$59,999: 1.57 (0.73–3.35)
		  – ≥$60,000: 1
		• Region:
		  – Northeast: 0.98 (0.46–2.09)
		  – Midwest: 0.65 (0.31–1.35)
		  – South: 0.83 (0.47–1.47)
		  – West: 1
		• Smoking status:
		  – Current smoker: 3.06 (1.72–5.42)[e]
		  – Former smoker: 1.36 (0.68–2.73)
		  – Never smoker: 1
		• Tobacco use:
		  – Uses tobacco: 4.21 (2.53–7.01)[e]
		  – Uses one tobacco product: 2.48 (1.40–4.40)[e]
		  – Uses >1 tobacco product: 7.10 (3.89–12.98)[e]
		  – Does not use tobacco: 1

Note: GED = general education development; **OR** = odds ratio; **CI** = confidence interval.

[a]Regions are taken from U.S. Census Bureau: Northeast (Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont); Midwest (Indiana, Illinois, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin); South (Alabama, Arkansas, Delaware, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and West Virginia); West (Alaska, Arizona, California, Colorado, Hawaii, Idaho, New Mexico, Montana, Oregon, Nevada, Utah, Washington, and Wyoming).

[b]Defined as a response of "electronic cigarettes or e-cigarettes" to the question, "Have you tried any of the following products, even just one time?"

[c]Relative standard error ≥40%.

[d]Among those who had heard of ENDS.

[e]Unreliable estimate; data censored because relative standard error >45%.

*Significant at p <0.05.

Conclusions

Extensive national surveys document the rise and subsequent decline of cigarette use, the current heterogeneity of cigarette use across subgroups of the population, and the changing patterns of tobacco product use. Such data are requisite for continually evaluating and reshaping tobacco control strategies. The data reviewed support the following conclusions:

In the United States, the prevalence of current cigarette smoking among adults has declined from 42% in 1965 to 18% in 2012.

1. The prevalence of current cigarette smoking declined first among men (between 1965 and the 1990s), and then among women (since the 1980s). However, declines in the prevalence of smoking among adults (18 years of age and older) have slowed in recent years.

2. Most first use of cigarettes occurs by 18 years of age (87%), with nearly all first use by 26 years of age (98%).

3. Very large disparities in tobacco use remain across racial/ethnic groups and between groups defined by educational level, socioeconomic status, and region.

4. In the United States, there are now more former smokers than there are current smokers. More than half of all ever smokers have quit smoking.

5. The rate of quitting smoking among recent birth cohorts has been increasing, and interest in quitting is high across all segments of society.

6. Patterns of tobacco use are changing, with more intermittent use of cigarettes and an increase in use of other products.

Summary and Implications

Cigarette smoking among both youth and adults has declined since 1964. However, declines in the prevalence of cigarette smoking among adults have slowed in recent years. Survey data indicate that tobacco control efforts need to not only address the population generally but also to focus on subpopulations with a higher prevalence of tobacco use and lower rates of quitting. Some of the highest prevalence rates have been observed among persons of lower socioeconomic status, sexual minorities (including individuals who are gay, lesbian, bisexual and transgender, and individuals with same-sex relationships and/or attraction), high school dropouts (Fagan et al. 2007; Lee et al. 2009; Garrett et al. 2011, 2013; SAMSHA 2013) and in Appalachia and the South (Pickle and Su 2002) as well as among vulnerable populations with complex comorbid medical illness (e.g. HIV/AIDS and cardiovascular disease) (Crothers et al. 2009; Hoffman et al. 2009; Marshall et al. 2009; Vidrine 2009; Levine et al. 2010; Tesoriero et al. 2010; Pines et al. 2011; Rahmanian et al. 2011), mental illness, and alcohol and substance abuse disorders (CDC 2013; Prochaska et al. 2008; Schroeder and Morris 2010; Villanti et al. 2012). Additionally, polytobacco use is now very common, especially among youth and young adults, and a recent upsurge in the use of cigars has also occurred. Limited national surveillance data are available to monitor the use of nonconventional tobacco products, particularly electronic cigarettes and hookah pipes, suggesting the need for sustained and expanded efforts to capture all forms of tobacco use. Given the rapid increase in electronic cigarette use among both adults and adolescents, rigorous surveillance of these products is particularly important, including their impact on the initiation and cessation of conventional tobacco use and concurrent use with other conventional tobacco products. Without question, data collection systems need the capacity to monitor the patterns of both conventional and nonconventional tobacco use across all segments of our society. The tables in this chapter provide the prevalence of use of cigarettes and other tobacco products stratified by gender, race/ethnicity, education, age groups, poverty status, and region of the United States; however, the high prevalence of smoking in some other segments of society suggests the need for national data collection systems which have the capacity to provide surveillance of tobacco use patterns in other segments of society where higher prevalence of tobacco use has been observed.

Appendix 13.1: Sources of Data

Data in this chapter were obtained from three national surveys: National Health Interview Survey (NHIS), National Survey on Drug Use and Health (NSDUH), and the Youth Risk Behavior Survey (YRBS) (Table 13.1).

National Health Interview Survey

NHIS is a multipurpose survey conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) and is the principal source of information on the health of the civilian, noninstitutionalized population of the United States. The NHIS has been conducted continuously since 1957. Questions on smoking have been included in selected survey years since 1965, and detailed items allowing classification by race and ethnicity have been included since 1978. Detailed questions on tobacco use are included in a Cancer Control Supplement to the NHIS, which was initiated in 1987 and subsequently conducted in 1992, 2000, 2005, and 2011. Face-to-face interviews are used to collect confidential data from a representative sample of the population at the respondent's place of residence (NCHS 2008).

The sampling plan follows a multistage area probability design that permits the representative sampling of households and noninstitutional group quarters (e.g., college dormitories) in all 50 states and the District of Columbia. Non-Hispanic African American or Black, Hispanic or Latino, and Asian persons are oversampled. For each family in NHIS, one sample child (younger than 18 years of age) and one sample adult are randomly selected, and information on each is collected. For children and those adults not at home during the interview, information is provided by a knowledgeable adult family member. Since 1974, only self-reports of cigarette smoking and use of other tobacco products have been used, and thus no proxy data have been employed since 1974 on questions of import to this report. Since 1997, NHIS has been conducted using computer-assisted personal interviewing by interviewers from the U.S. Census Bureau; sampling and interviewing are continuous throughout each year (NCHS 2008).

National Survey on Drug Use and Health

NSDUH is an annual survey of the civilian, noninstitutionalized population 12 years of age and older in the United States. Before 2002, this survey, which has been conducted by the federal government since 1971, was called the National Household Survey on Drug Abuse. NSDUH is the primary source of statistical information on the use of illegal drugs by the U.S. population; face-to-face interviews are used to collect confidential data from a representative sample of the population at the respondent's place of residence. The survey is sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA) of the U.S. Department of Health and Human Services and is planned and managed by SAMHSA's Center for Behavioral Health Statistics and Quality.

Data are collected using audio computer-assisted self-interviewing, and respondents are given a US$30 incentive payment for participation. The total targeted sample size for 1 year of 67,500 participants is allocated equally across three age groups: 12–17, 18–25, and 26 years of age and older. The NSDUH sampling frame includes residents of noninstitutional group quarters (e.g., shelters, rooming houses, dormitories, and group homes), residents of the 50 states and the District of Columbia, and civilians living on military bases. The sample excludes persons with no fixed household address (e.g., homeless transients not in shelters) and long-term residents of institutional group quarters (e.g., prisons and hospitals).

Youth Risk Behavior Surveillance System

Developed in 1990 by CDC, the YRBSS monitors priority health risk behaviors, including tobacco use, among high school students in the United States. In addition to the surveys that are conducted by state, local, territorial, and tribal health and education agencies, there is a national YRBS conducted by CDC. The current report includes data from the national YRBS only, which has a sampling frame

of all public and private school students in grades 9–12 in the 50 states and the District of Columbia. A three-stage cluster sample design is used to sample (1) large-sized counties or groups of smaller adjacent counties, (2) public and private schools with a probability proportional to the schools' enrollment, and (3) one or two randomly selected classes in each grade. Examples of classes include homerooms, classes of a required discipline (e.g., English or social studies), and all classes meeting during a required period (e.g., second period). All students in a sampled class are eligible to participate. Oversampling is used to achieve sufficiently large subsamples of Black or African American and Hispanic or Latino students to enable separate analyses of these subgroups. Schools that decline to participate in the original sample are not replaced. Students complete self-administered, paper-and-pencil questionnaires and record their answers directly in the questionnaire booklet or on a separate computer-scannable answer sheet (CDC 2013). Local procedures to obtain the permission of parents are followed. Trained personnel administer the questionnaires to students in their classrooms for the national survey and for most state and local surveys. The participation of students is both voluntary and anonymous (CDC 2013).

Appendix 13.2: Measures of Tobacco Use

Validity of Measures of Tobacco Use Among Youth

All of the data on tobacco use among youth that are presented in this report are based on retrospective, self-reported responses to questionnaires. Because of the retrospective nature of data collection, and because tobacco use is viewed by many as a socially undesirable behavior, there is a risk of inaccurate or dishonest responses. Because it was not feasible to verify the self-reported data included here, it is important for researchers to interpret these data with some caution and an understanding of possible sources of inaccuracy. Many factors can affect the validity of self-reported data—factors that can be categorized as cognitive or situational. Cognitive processes that affect responses include comprehension of the question, retrieval of relevant information from memory, decision making about the adequacy of the information retrieved, and the generation of a response (Brener et al. 2003). Each of these processes can contribute to errors in responses and, subsequently, to problems with validity.

Situational factors that affect the validity of self-reported data refer to characteristics of the external environment in which the survey is being conducted. These include the setting (i.e., school or home based), the method (i.e., self-administered questionnaire or in-person interview), the social desirability of the behavior being reported, and the perception of privacy and/or confidentiality of responses (U.S. Department of Health and Human Services [USDHHS] 1994; Brener et al. 2003).

Many studies have found that youth report a higher number of sensitive behaviors when a survey is completed in a school setting rather than in their homes (Gfroerer et al. 1997; Hedges and Jarvis 1998; Kann et al. 2002). For example, Kann and colleagues (2002) compared the school-based National Youth Risk Behavior Survey (YRBS) with the household-based YRBS supplement to the National Health Interview Survey (NHIS). The study found that the school-based survey produced a significantly higher reporting of many sensitive behaviors, such as driving after drinking alcohol, binge drinking, and currently using marijuana and cocaine. Four measures of various stages of the smoking uptake process were higher in the school-based survey, but estimates of current cigarette use and frequent cigarette use, while elevated in the school-based survey, were not significantly different from estimates generated in the household-based survey. Few differences in nonsensitive behaviors were observed. Two other studies (Gfroerer et al. 1997; Brener et al. 2003) indicate that although self-reported estimates of current use of alcohol and illicit drugs were higher in the school-based versus household-based surveys, estimates of current cigarette smoking were quite similar across settings. All three of these studies used self—rather than interviewer—administered interviews/questionnaires. Nevertheless, the provision of privacy that school surveys provide is important, especially if smoking becomes more socially unacceptable over time. Notably, household-based surveys are more likely to include youth who drop out of school or are frequently absent from school, and these groups are more likely to smoke.

Self-administered methods of data collection have generally produced higher reporting of sensitive behaviors, including tobacco use, than have interviewer-administered methods (Turner et al. 1992; Aquilino 1994; Brittingham et al. 1998). For example, Turner and colleagues (1992) found that the prevalence of current smoking among 12- to 17-year-olds based on reports in the self-administered version of the National Survey on Drug Use and Health (NSDUH) home-based survey was considerably higher (by 10–30%) than it was using the interviewer-administered version. The absence of personal interaction with an interviewer on self-administered surveys may reduce the reporting biases associated with perceived privacy and the social desirability of a behavior (Brener et al. 2003).

Another situational influence is the use of the "bogus pipeline" (Brener et al. 2003). This method has been used to improve the validity of self-reported measures of smoking, especially in school-based surveys. Respondents are told that a biochemical test will be used to accurately evaluate their smoking behavior after the questionnaire is completed, although in fact such a test will not be used. This method has been associated with higher reported smoking prevalence (Aguinis et al. 1993). None of the surveys used in this report make use of the bogus pipeline, but each survey has taken alternative steps to ensure that the survey setting is private and that the data collected are at least confidential if not anonymous.

In conclusion, the factors described above may affect the point estimate of smoking prevalence. However, if these factors remain stable over the years, they should not affect the trends seen over time.

Validity of Measures of Tobacco Use Among Adults

All of the data on tobacco use among adults that were presented in this report were based on retrospective self-reported responses to questionnaires. Biochemical validation studies suggest that data on self-reported cigarette smoking are generally valid, except in certain situations, such as in conjunction with intense smoking cessation programs and with certain populations, such as pregnant women or adolescents (Velicer et al. 1992; Kendrick et al. 1995; USDHHS 2012). Misclassification may also be more common among intermittent smokers. Additionally, smokers may misreport the number of cigarettes smoked per day because of digit preference (preference for multiples of 10) (Klesges et al. 1995). Regardless, a meta-analysis of 26 validation studies found that self-reported smoking status is generally accurate (Patrick et al. 1994), particularly when interviewer-administered questionnaires are used. It should be noted here that much of the research literature on the validity of self-reported data is restricted to cigarette smoking—cigars and smokeless tobacco are rarely addressed. As such, a discussion of the factors that may affect validity is warranted so that the data presented in the present report are interpreted with some caution and an understanding of possible sources of inaccuracy. Clearly, many factors can affect the validity of self-reported data, such as response biases and methodologic features of surveys.

Methodologic differences in survey administration—including, but not limited to, timing, survey question order, sampling, data collection mode (e.g., computer-assisted personal interviewing vs. computer-assisted telephone interviewing), participation rates, and operational definitions—can affect prevalence estimates of tobacco use (Ryan et al. 2012). NHIS and NSDUH both use computer-assisted personal interviewing, which is done in the home. NSDUH differs from NHIS, however, with respect to the operational definition of cigarette smoking (Delnevo and Bauer 2009). NHIS defines current smoking among adults as smoking at least 100 cigarettes during one's lifetime and smoking every day or on some days. In contrast, NSDUH defines current smoking for youth, young adults, and adults as smoking part or all of a cigarette during the past 30 days. The Substance Abuse and Mental Health Services Administration, which sponsors NSDUH, does not use the 100 cigarettes-in-a-lifetime threshold when making estimates of cigarette smoking prevalence from NSDUH data. This likely contributes to the consistently higher estimates from NSDUH noted throughout this report (see "Measures of Tobacco Use" section below) (Ryan et al. 2012). Tables in this chapter continue the criteria described above for youth and young adults. To facilitate comparisons with NHIS, however, data in selected tables on all adults 18 years of age or older incorporate the 100-cigarette threshold, as noted in the footnotes to the tables. Ryan and colleagues (2012) discuss these differences in the definitions of current smoking and how they could affect smoking estimates, particularly in some subpopulations. However, with the use of a modified NSDUH current smoking definition that incorporated the 100-cigarettes-in-a-lifetime threshold, Ryan and colleagues (2012) observed that a notable number of subpopulation estimates (e.g., 26–34 years of age group, Asians, and Hispanics groups) became comparable between the NSDUH and NHIS surveys for the year 2008.

Ryan and associates (2012) also noted other methodologic differences between the surveys beyond the current smoking definition that may contribute to the consistently higher estimates in NSDUH, including survey mode, setting, context, and incentives. The NSDUH interview mode is strictly in person using computer-assisted personal interviewing that is thought to provide respondents with an enhanced sense of privacy. Although NHIS is interviewer administered, some interviews that cannot be fully conducted in person are completed by telephone. Ryan and coworkers (2012) also note that the context of the survey and question placement could be a factor contributing to higher self-report of smoking in NSDUH. Within the NHIS survey context, smoking may be viewed as one of the most serious health behaviors that respondents are asked about. Within NSDUH, in contrast, the survey content focuses almost entirely on substance-use behaviors, both licit and illicit, and respondents may perceive smoking to be one of the more socially acceptable behaviors they are being asked about. Finally, since 2002, NSDUH began paying respondents a US$30 incentive upon completion of the survey, while NHIS remains uncompensated. Although these factors may affect the point estimates of various tobacco use indicators, if the factors remain stable over the years they should not affect the trends seen over time within a given survey. Still, direct comparisons of point estimates across surveys are not advised because of methodologic differences between them. Instead, readers should consider consistency in patterns across years for the same survey.

Measures of Tobacco Use

Measures of tobacco use differ slightly among surveys and by the target population. For each tobacco use measure, the definitions used in the various surveys are summarized below.

Current Smoking: Youth

YRBS defines current smoking among students as having smoked cigarettes on at least 1 day during the 30 days before the survey. NSDUH asks whether the respondent has smoked "part or all of a cigarette" during the past 30 days to determine current usage.

Current Smoking: Adult

For NHIS from 1965–1991, current smokers were defined as respondents who had smoked at least 100 ciga-

rettes and who answered "yes" to the question "Do you smoke cigarettes now?" Beginning in 1992, NHIS assessed whether respondents smoked every day, some days, or not at all. Persons who smoked every day or some days were classified as current smokers. In contrast, NSDUH defines a current cigarette smoker as a person who has smoked all or part of a cigarette during the past 30 days. The 100-cigarettes-in-a-lifetime threshold is not traditionally used by NSDUH in reporting the prevalence of current cigarette smoking. This difference, in part, contributes to the consistently higher estimates from NSDUH data than from other surveys. However, the 100-cigarettes-in-a-lifetime threshold question was collected and used in the present report when giving estimates of prevalence for adults.

Intermittent and Daily Smoking

In NSDUH, participants who reported that they had smoked on every day during the past 30 days were classified as daily smokers; those who smoked on 1–29 days were classified as intermittent smokers. In NHIS, intermittent smokers were those who report currently smoking "some days," while daily smokers were those who report currently smoking "every day."

Attempts to Quit Smoking

An attempt to quit smoking was defined in this chapter as having quit smoking for more than 1 day during the previous year. Depending on the year of the survey, NHIS asked about attempts to quit during the past year or in a lifetime. Examples of questions were "During the past 12 months, have you quit smoking for one day or longer?" and "Have you ever stopped smoking for one day or longer?" In the 1998 NHIS, the question was revised to "During the past 12 months, have you stopped smoking for more than one day because you were trying to quit smoking?"

Current Use of Smokeless Tobacco

NSDUH defines current use of smokeless tobacco as having used it during the 30 days before the survey. To determine current usage, NSDUH asks whether the respondent has "used snuff, even once" and/or "used chewing tobacco, even once" during the past 30 days. An affirmative answer to either question categorizes that respondent as a current user. YRBS defines current use of smokeless tobacco as using chewing tobacco, snuff, or dip on at least 1 day during the 30 days before the survey. NHIS defines current use of smokeless tobacco as use on every day or some days.

Current Cigar Use

NSDUH defines current cigar use as having smoked cigars during the 30 days before the survey. Cigars are defined as "big cigars, cigarillos, and even little cigars that look like cigarettes." To determine current usage, NSDUH asks whether the respondent has smoked "part or all of a cigar" during the past 30 days. An affirmative answer to either question categorizes that respondent as a current user. NHIS first asks "Have you ever used a cigar?" Those providing an affirmative response are asked "Do you currently smoke cigars every day, some days or not at all?" Those responding "every day" or "some days" are defined as current cigar smokers. YRBS defines current cigar use as smoking cigars, cigarillos, or little cigars on at least 1 day during the 30 days before the survey.

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Table 13.17   Percent current use[a] of tobacco by product, school level, and gender, National Youth Tobacco Survey 2011 and 2012, United States A. Middle school

	Total, 2011: % (95% CI)	Total, 2012: % (95% CI)	Females, 2011: % (95% CI)	Females, 2012: % (95% CI)	Males, 2011: % (95% CI)	Males, 2012: % (95% CI)
Tobacco[b]	7.5 (6.5–8.8)	6.7 (5.8–7.7)	5.9 (4.7–7.4)	5.6 (4.7–6.7)	9.0 (7.9–10.3)	7.8 (6.7–9.0)
Both combustible & noncombustible tobacco[c]	1.9 (1.5–2.5)	2.0 (1.6–2.5)	1.6 (1.2–2.1)*	1.6 (1.2–2.1)*	2.2 (1.7–3.0)	2.5 (2.0–3.1)
Only combustible[d]	4.5 (3.7–5.5)	3.7 (3.2–4.3)	3.8 (2.8–5.0)	3.5 (2.8–4.4)	5.2 (4.3–6.2)[†]	3.9 (3.4–4.5)[†]
Only noncombustible	1.1 (0.8–1.4)	1.0 (0.7–1.3)	0.5 (0.3–0.9)	0.5 (0.3–0.8)	1.6 (1.2–2.3)	1.4 (1.0–2.0)
Cigarettes	4.3 (3.5–5.2)	3.5 (2.8–4.3)	4.0 (3.1–5.2)	3.2 (2.5–4.0)	4.5 (3.7–5.5)	3.8 (3.0–4.7)
Cigars	3.5 (2.8–4.2)	2.8 (2.4–3.4)	2.5 (1.9–3.4)	2.4 (1.9–3.2)	4.3 (3.4–5.4)	3.2 (2.7–3.8)
Smokeless tobacco	2.2 (1.8–2.7)	1.7 (1.3–2.1)	1.4 (1.0–2.0)	1.2 (0.8–1.6)	3.0 (2.3–3.8)	2.2 (1.7–2.9)
Pipes	2.2 (1.7–2.9)	1.8 (1.4–2.3)	1.8 (1.3–2.5)	1.7 (1.3–2.3)	2.7 (2.1–2.5)	1.9 (1.4–2.4)
Bidis	1.7 (1.3–2.2)[†]	0.6 (0.5–0.7)[†]	1.4 (1.0–1.9)[†]	0.4 (0.3–0.7)[†]	1.9 (1.4–2.6)[†]	0.7 (0.5–1.0)[†]
Kreteks	1.1 (0.9–1.4)[†]	0.5 (0.4–0.7)[†]	0.9 (0.6–1.3)[†]	0.4 (0.3–0.7)[†]	1.3 (1.0–1.6)[†]	0.6 (0.4–0.9)[†]
Hookah	1.0 (0.8–1.4)	1.3 (1.0–1.7)	1.0 (0.6–1.6)	1.0 (0.7–1.4)	1.1 (0.7–1.5)	1.5 (1.1–2.2)
Snus	0.9 (0.6–1.2)	0.8 (0.6–1.0)	0.8 (0.5–1.2)	0.6 (0.4–0.9)	1.0 (0.6–1.4)	1.0 (0.7–1.4)
Dissolvable tobacco	0.3 (0.2–0.4)*	0.5 (0.4–0.8)*	0.3 (0.2–0.5)*	0.4 (0.2–0.6)*	0.3 (0.1–0.5)*	0.7 (0.4–1.1)*
Electronic cigarettes	0.6 (0.4–0.9)[†]	1.1 (0.9–1.5)[†]	0.4 (0.2–0.7)[†]	0.8 (0.6–1.1)[†]	0.7 (0.4–1.3)[†]	1.5 (1.1–2.1)[†]

Table 13.17 Continued B. High school

	Total, 2011: % (95% CI)	Total, 2012: % (95% CI)	Females, 2011: % (95% CI)	Females, 2012: % (95% CI)	Males, 2011: % (95% CI)	Males, 2012: % (95% CI)
Tobacco[b]	24.3 (22.1–26.6)	23.3 (21.6–25.2)	19.0 (17.0–21.1)	18.1 (16.2–20.1)	29.4 (26.6–32.4)	28.3 (26.2–30.6)
Both combustible & noncombustible tobacco[c]	6.2 (5.1–7.5)	6.8 (5.9–7.9)	2.0 (1.5–2.6)[†]	3.4 (2.8–4.2)[†]	10.3 (8.4–12.4)	10.1 (8.6–11.7)
Only combustible[d]	15.7 (14.6–16.8)	14.4 (13.2–15.6)	16.3 (14.4–18.3)	14.2 (12.6–15.9)	15.0 (13.8–16.3)	14.6 (13.3–15.9)
Only noncombustible[e]	2.4 (1.8–3.2)	2.1 (1.7–2.7)	0.7 (0.4–1.1)	0.5 (0.3–0.7)	4.1 (3.1–5.5)	3.7 (2.9–4.8)
Cigarettes	15.8 (13.7–18.1)	14.0 (12.5–15.7)	13.8 (11.7–16.2)	11.7 (10.2–13.4)	17.7 (15.2–20.4)	16.3 (14.5–18.3)
Cigars	11.6 (10.5–12.7)	12.6 (11.4–13.9)	7.4 (6.3–8.6)	8.4 (7.2–9.8)	15.7 (14.3–17.2)	16.7 (15.0–18.5)
Smokeless tobacco	7.3 (5.9–9.0)	6.4 (5.5–7.5)	1.6 (1.2–2.2)	1.5 (1.1–2.1)	12.9 (10.4–15.9)	11.2 (9.5–13.0)
Pipes	4.0 (3.4–4.6)	4.5 (4.0–5.2)	2.8 (2.2–3.4)	3.2 (2.7–3.9)	5.1 (4.3–6.0)	5.8 (5.0–6.7)
Bidis	2.0 (1.6–2.5)[†]	0.9 (0.7–1.1)[†]	1.0 (0.7–1.4)[†]	0.5 (0.3–0.7)[†]	2.9 (2.3–3.7)[†]	1.3 (1.0–1.7)[†]
Kreteks	1.7 (1.4–2.0)[†]	1.0 (0.8–1.2)[†]	0.8 (0.6–1.2)[†]	0.5 (0.3–0.7)[†]	2.4 (1.9–2.9)[†]	1.5 (1.1–1.9)[†]
Hookah	4.1 (3.4–5.0)[†]	5.4 (4.6–6.3)[†]	3.5 (2.8–4.4)	4.5 (3.7–5.4)	4.8 (3.7–6.1)	6.2 (5.3–7.3)
Snus	2.9 (2.3–3.7)	2.5 (2.0–3.0)	0.8 (0.5–1.1)	0.9 (0.7–1.3)	5.1 (3.9–6.6)	3.9 (3.2–4.9)
Dissolvable tobacco	2.0 (1.6–2.5)[†]	0.8 (0.6–1.0)[†]	0.1 (0.1–0.4)*	0.6 (0.4–0.9)*	0.6 (0.4–1.0)	1.0 (0.8–1.4)
Electronic cigarettes	1.5 (1.2–2.0)[†]	2.8 (2.3–3.5)[†]	0.7 (0.5–1.0)[†]	1.9 (1.5–2.4)[†]	2.3 (1.7–3.1)[†]	3.7 (2.9–4.8)[†]

Source: National Youth Tobacco Survey 2011–2012.

Note: **CI =** confidence interval.

[a]Current use of cigarettes was determined by asking, "During the past 30 days, on how many days did you smoke cigarettes?"; Current use of cigars was determined by asking, "During the past 30 days, on how many days did you smoke cigars, cigarillos, or little cigars?"; Current use of smokeless tobacco was determined by asking, "During the past 30 days, on how many days did you use chewing tobacco, snuff, or dip?"; Current use of pipe was determined by asking, "During the past 30 days, on how many days did you smoke tobacco in a pipe?"; In 2011, current use of bidis and kreteks were determined by asking, "During the past 30 days, on how many days did you smoke bidis?" and "During the past 30 days, on how many days did you smoke kreteks?"; In 2012, current use of bidis and kreteks were determined by asking, "During the past 30 days, which of the following products have you used on at least one day?"; Current use of hookah, snus, dissolvable tobacco, and electronic cigarettes were deteremined by asking, "During the past 30 days, which of the following products have you used on at least one day?"

[b]Tobacco is use of cigarettes or cigars or smokeless tobacco or tobacco pipes or bidis or kreteks or hookah or snus or dissolvable tobacco or electronic cigarettes on >1 day in the past 30 days.

cBoth combustible & noncombustible tobacco is use of cigarettes or cigars or tobacco pipes or bidis or kreteks or hookah and smokeless tobacco or snus or dissolvable tobacco or electronic cigarettes on ≥1 day in the past 30 days.

dOnly combustible tobacco is use of cigarettes or cigars or tobacco pipes or bidis or kreteks or hookah on ≥1 day in the past 30 days and no use of smokeless tobacco, snus, dissolvable tobacco, and electronic cigarettes in the past 30 days.

eOnly noncombustible tobacco is use of smokeless tobacco or snus or dissolvable tobacco or electronic cigarettes on ≥1 day in the past 30 days and no use of cigarettes, cigars, tobacco pipes, bidis, kreteks, and hookah in the past 30 days.

*Data statistically unreliable due to sample size <50 OR relative standard error >0.3 on at least 1 year's data; thus, no t-test was done.

†p-value of the t-test for difference between 2011 and 2012 prevalences is <0.05.

Table 13.18   Percent current use[a] of tobacco by product, school level, and race/ethnicity, National Youth Tobacco Survey 2011 and 2012, United States A. Middle school

	White, non-Hispanic, 2011: % (95% CI)	White, non-Hispanic, 2012: % (95% CI)	Black, non-Hispanic, 2011: % (95% CI)	Black, non-Hispanic,, 2012: % (95%CI)	Other, non-Hispanic, 2011: % (95% CI)	Other, non-Hispanic, 2012: % (95% CI)
Tobacco[b]	6.2 (5.1–7.4)	5.1 (4.2–6.3)	8.5 (6.6–10.9)	7.7 (5.9–10.1)	11.5 (10.2–13.1)	10.5 (8.6–12.8)
Both combustible & noncombustible tobacco[c]	2.0 (1.4–2.6)	1.7 (1.3–2.2)	0.9 (0.4–1.8)*	1.4 (1.0–2.0)*	2.8 (2.1–3.7)	3.4 (2.5–4.6)
Only combustible[d]	3.0 (2.2–4.0)	2.5 (2.0–3.1)	7.0 (5.3–9.0)	5.6 (4.3–7.3)	7.8 (6.8–9.1)[†]	6.1 (4.9–7.5)[†]
Only noncombustible[e]	1.2 (0.8–1.7)	1.0 (0.7–1.4)	0.7 (0.4–1.3)*	0.7 (0.3–2.0)*	0.9 (0.6–1.4)	1.0 (0.6–1.8)
Cigarettes	3.8 (2.8–5.1)	3.1 (2.4–4.0)	3.6 (2.6–5.0)	2.6 (1.7–4.0)	6.7 (5.6–8.0)	5.4 (4.2–7.1)
Cigars	2.3 (1.7–3.0)	1.6 (1.2–2.0)	5.7 (4.3–7.4)	5.0 (3.8–6.6)	6.1 (4.9–7.4)	4.9 (3.8–6.4)
Smokeless tobacco	2.3 (1.8–2.9)	1.6 (1.1–2.2)	1.0 (0.5–2.1)*	0.6 (0.3–1.3)*	2.9 (2.3–3.6)	2.4 (1.7–3.4)
Pipes	1.5 (1.1–2.2)	1.2 (0.8–1.7)	1.3 (0.8–2.1)*	1.2 (0.6–2.2)*	5.0 (4.2–6.1)	3.7 (2.7–5.1)
Bidis	1.0 (0.7–1.5)*	0.3 (0.2–0.5)*	1.9 (1.1–3.2)*	0.6 (0.4–1.0)*	3.5 (2.6–4.6)[†]	1.2 (0.8–1.8)[†]
Kreteks	0.6 (0.4–0.6)	0.3 (0.2–0.5)	0.9 (0.5–1.6)*	0.2 (0.1–0.7)*	2.5 (2.0–3.3)[†]	1.0 (0.6–1.7)[†]
Hookah	0.9 (0.6–1.4)	0.8 (0.6–1.2)	0.9 (0.5–1.7)*	0.9 (0.4–1.8)*	1.7 (1.2–2.3)[†]	3.0 (2.2–4.1)[†]
Snus	1.0 (0.7–1.4)	0.7 (0.5–1.0)	0.6 (0.2–1.3)*	0.4 (0.1–0.9)*	1.0 (0.6–1.5)	1.1 (0.7–1.7)
Dissolvable tobacco	0.2 (0.1–0.5)*	0.4 (0.2–0.7)*	0.4 (0.1–1.2)*	0.5 (0.2–1.5)*	0.2 (0.1–0.5)*	1.0 (0.6–1.6)*
Electronic cigarettes	0.6 (0.4–1.0)*	0.9 (0.6–1.3)*	0.4 (0.2–1.0)*	1.1 (0.6–2.2)*	0.6 (0.4–1.1)*	2.0 (1.4–2.9)*

Table 13.18 Continued B. High school   *Surgeon General's Report*

	White, non-Hispanic, 2011: % (95% CI)	White, non-Hispanic, 2012: % (95% CI)	Black, non-Hispanic, 2011: % (95% CI)	Black, non-Hispanic,, 2012: % (95% CI)	Other, non-Hispanic, 2011: % (95% CI)	Other, non-Hispanic, 2012:% (95% CI)
Tobacco[b]	26.6 (23.6–29.8)	24.6 (22.3–27.0)	18.9 (15.6–22.8)	22.6 (19.7–25.8)	23.8 (21.2–26.5)	22.5 (19.5–25.6)
Both combustible & noncombustible tobacco[c]	7.5 (6.1–9.3)	8.2 (6.9–9.6)	2.3 (1.2–4.2)*	2.3 (1.6–3.2)*	5.4 (4.3–6.6)	6.4 (5.0–8.1)
Only combustible[d]	15.8 (14.5–17.3)[†]	13.6 (12.2-15.0)[†]	15.7 (13.1–18.6)	19.2 (16.4–22.4)	16.9 (15.2–18.3)	14.8 (13.0–16.8)
Only noncombustible	3.2 (2.4–4.2)	2.8 (2.2–3.6)	1.0 (0.4–2.3)*	1.1 (0.6–1.9)*	1.5 (1.0–2.3)	1.3 (0.9–1.9)
Cigarettes	17.6 (14.7–20.9)	15.4 (13.2–17.8)	10.6 (7.6–14.6)	9.6 (7.6–12.0)	15.8 (13.9–17.8)	14.3 (12.0–16.9)
Cigars	12.1 (10.7–13.6)	12.2 (10.8–13.8)	11.7 (9.8–13.9)	16.7 (14.4–19.3)	11.3 (9.8–13.1)	12.4 (10.6-14.4)
Smokeless tobacco	9.2 (7.4–11.5)	8.1 (6.9–9.5)	3.0 (1.8–5.1)	2.2 (1.5–3.2)	5.1 (3.8–6.8)	5.1 (3.8–6.8)
Pipes	3.5 (2.9–4.4)	4.5 (3.8–5.4)	2.4 (1.5–3.8)	2.9 (1.8–4.5)	6.3 (5.2–7.7)	6.2 (5.2–7.4)
Bidis	1.4 (1.0–2.0)[†]	0.7 (0.5–1.0)[†]	2.0 (1.2–3.2)*	0.8 (0.4–1.7)*	3.7 (2.9–4.8)[†]	1.4 (0.9–2.2)
Kreteks	1.4 (1.0–2.0)	1.1 (0.8–1.5)	1.3 (0.8–2.2)*	0.6 (0.3–1.1)*	2.5 (1.9–3.3)[†]	0.9 (0.6–1.4)[†]
Hookah	4.3 (3.4–5.4)[†]	6.1(5.2-7.2)	1.7 (0.9–3.0)	2.1 1.6-2.9)	5.1 (4.1–6.3)	6.6(5.1–8.5)
Snus	3.7 (2.8–4.9)	3.3 (2.6–4.2)	0.7(0.3–1.5)*	0.6 (0.3–1.1)*	2.3 (1.7–3.1)	1.8 (1.3–2.5)
Dissolvable tobacco	0.3 (0.1–0.5)*	0.7 (0.5–0.9)*	0.3 (0.1–1.2)*	0.8 (0.4–1.3)*	0.8 (0.5–1.3)	1.4(1.0–2.1)
Electronic cigarettes	1.8 (1.3–2.4)†	3.4 (2.7–4.2)[†]	0.8 (0.3–1.7)*	1.1 (0.7–1.9)*	1.3 (0.8–2.1)[†]	2.7 (1.9–3.8)[†]

Source: National Youth Tobacco Survey 2011–2012. *Note:* **CI** = confidence interval.

[a]Current use of cigarettes was determined by asking, "During the past 30 days, on how many days did you smoke cigarettes?"; Current use of cigars was determined by asking, "During the past 30 days, on how many days did you smoke cigars, cigarillos, or little cigars?"; Current use of smokeless tobacco was determined by asking, "During the past 30 days, on how many days did you use chewing tobacco, snuff, or dip?"; Current use of pipe was determined by asking, "During the past 30 days, on how many days did you smoke tobacco in a pipe?"; In 2011, current use of bidis and kreteks were determined by asking, "During the past 30 days, on how many days did you smoke bidis?" and "During the past 30 days, on how many days did you smoke kreteks?"; In 2012, current use of bidis and kreteks were determined by asking, "During the past 30 days, which of the following products have you used on at least one day?"; Current use of hookah, snus, dissolvable tobacco, and electronic cigarettes were deteremined by asking, "During the past 30 days, which of the following products have you used on at least one day?"

[b]Tobacco is use of cigarettes or cigars or smokeless tobacco or tobacco pipes or bidis or kreteks or hookah or snus or dissolvable tobacco or electronic cigarettes on ≥1 day in the past 30 days.

[c]Both combustible & noncombustible tobacco is use of cigarettes or cigars or tobacco pipes or bidis or kreteks or hookah and smokeless tobacco or snus or dissolvable tobacco or electronic cigarettes on ≥1 day in the past 30 days.

[d]Only combustible tobacco is use of cigarettes or cigars or tobacco pipes or bidis or kreteks or hookah on ≥1 day in the past 30 days and no use of smokeless tobacco, snus, dissolvable tobacco, and electronic cigarettes in the past 30 days.

[e]Only noncombustible tobacco is use of smokeless tobacco or snus or dissolvable tobacco or electronic cigarettes on ≥1 day in the past 30 days and no use of cigarettes, cigars, tobacco pipes, bidis, kreteks, and hookah in the past 30 days.*

[†]p-value of the t-test for difference between 2011 and 2012 prevalences is <0.05.
Data statistically unreliable due to sample size <50 OR relative standard error >0.3 on at least 1 year's data; thus, no t-test was done.

Chapter 14
Current Status of Tobacco Control

Introduction

The overall purpose of this chapter is to identify the tobacco control measures that have worked up to now as the basis for subsequent considerations in Chapters 15 and 16 ("The Changing Landscape of Tobacco Control: Current Status and Future Directions" and A Vision for Ending the Tobacco Epidemic: A Society Free of Tobacco-Related Death and Disease," respectively), which look forward to how to reduce and even end the tobacco epidemic. Previous Surgeon General's reports on smoking and health have articulated a vision for ending the tobacco epidemic through a variety of methods, including sustained use of successful interventions, a comprehensive approach, and continued support to build the scientific foundation for action (U.S. Department of Health and Human Services [USDHHS] 2000, 2004, 2006, 2010, 2012). Recent recommendations made by expert groups also emphasize comprehensive coordinated approaches to reducing tobacco use and its harms (Bonnie et al. 2007; USDHHS 2010; World Health Organization [WHO] 2008b). The potentially relevant literature is vast and, consequently, coverage in this chapter is analytic and synthetic without providing an exhaustive review of all relevant evidence (supporting reviews are provided online at www.surgeongeneral.gov in Appendices 14.1–14.5).

This chapter first considers the shifting public image of tobacco use during the past 50 years, which has been critical to driving the decline of tobacco smoking (see Chapter 2, "Fifty Years of Change 1964–2014"). Tobacco use has serious economic and social implications for the population, and is intimately tied to collective images and attitudes that can positively or negatively impact use. As scientific knowledge about the disease effects of smoking has advanced, and as research on tobacco industry documents and litigation have uncovered the deceptive and covert activities of tobacco companies, attitudes toward tobacco use and smoking in public places have changed from accepting to increasingly unfavorable.

In the second part of this chapter, the changing nature of tobacco products is reviewed and a brief overview is provided of current efforts to regulate tobacco manufacturing, marketing, and use. Tobacco and other commercial tobacco products that contain nicotine cover a wide range, including not only conventional cigarettes, cigars, and smokeless tobacco but dissolvable tobacco products (DTPs), electronic delivery systems, low nitrosamine smokeless tobacco, and water pipes. The emergence of such new products has become increasingly germane to the formulation of tobacco control policies.

The third section covers two key tobacco control measures—tobacco taxes and clean indoor air laws, which both have a large span and size of population impact (USDHHS 2000). Other legal strategies, including restrictions on advertising and access to tobacco by minors, are also briefly reviewed. It concludes with a brief review of litigation as a tobacco control strategy.

The fourth section in this chapter focuses on clinical, educational and community-wide strategies and approaches for tobacco cessation. It reviews the evidence that tobacco use is a chronic condition of addiction with remission and relapse, requiring repeated interventions and, often, multiple attempts to quit successfully for the long-term. A series of interventions and treatments are briefly reviewed, including counseling, quitlines, and medications. Approaches for tobacco dependence treatment through the health care delivery system are also reviewed (e.g., a national network of quitlines, supporting the "5A's model").

The comprehensive educational and community-wide strategies acknowledge that individual behavioral choices occur in a larger, complex context: a social setting of family, schools, community, and culture; a complex economic and physical environment; formal and informal government policies; and the prevailing legal atmosphere. The review covers a mix of programs developed as large-scale research and demonstration studies (e.g., the National Cancer Institute's [NCI's] American Stop Smoking Intervention Study [ASSIST], the Community Intervention Trial for Smoking Cessation [COMMIT]), and comprehensive state programs often carried out by state and local public health agencies.

The final section of this chapter briefly reviews international tobacco control activities and related issues, including trade policies.

The Changing Public Image of Tobacco

The level of social acceptability of smoking was a major contributing factor in the rising prevalence of smoking up to the middle of the twentieth century, and then to the declining prevalence of smoking during the past 50 years (Cummings 2009). The importance of the changing public image of tobacco is discussed in greater detail in Chapter 2, as well as in previous Surgeon General's reports (U.S. Department of Health, Education, and Welfare [USDHEW] 1979; USDHHS 2000, 2006, 2012), and in several histories of tobacco control (Kluger 1996; Brandt 2007; Proctor 2011).

When the first Surgeon General's report was issued in 1964, up to 60–70% of young and middle-aged men were current smokers, and almost 50% of young women were smokers as well (see Chapter 13, "Patterns of Tobacco Use Among U.S. Youth, Young Adults, and Adults," Figure 13.9A and 13.9B). In the 1960s and even into the 1970s and 1980s, smoking was permitted nearly everywhere—smokers could light up at work; in hospitals, school buildings, bars, and restaurants; and on buses, trains, and airplanes. In the mid-1960s, the culture of smoking was so accepted that even the Surgeon General's Advisory Committee had ashtrays on the table, when they met to discuss the evidence that would eventually conclude that cigarette smoking is a cause of cancer and other life-threatening diseases (Figure 14.1).

For anyone growing up in the 1950s and 1960s, it was common to see doctors; athletes; radio, movie, and television celebrities; and popular cartoon characters advertising various cigarette brands (Figure 14.2). In fact, the marketing of cigarettes was so commonplace that the 1967 Federal Trade Commission (FTC) report commented "…that it is virtually impossible for Americans of almost any age to avoid cigarette advertising" (FTC 1967). In 1964, tobacco companies were major sponsors of popular television shows on all three television networks (Pollay 1994). These companies also arranged for product placements in movies, and other entertainment media, to increase the social image of smoking as popular, sophisticated, and classy (Mekemson and Glantz 2002; USDHHS 2012). As reviewed in previous reports, the tobacco companies have viewed the movie industry as an opportunity for advertising as far back as the Nickelodeon era when movies were silent, cost only a nickel, and ad slides played between reels (USDHHS 2012).

Although comprehensive historical tracking of portrayals of tobacco use in U.S. films is only available since 2002, a study of a random sample of major movies released between 1950–2002 found that smoking incidents declined from 10.7 incidents per hour in 1950 to a minimum of 4.9 in 1980–1982 but increased to 10.9 in 2002 (see USDHHS 2012, Figure 5.11). Despite declining

Figure 14.1   Meeting of the 1964 Surgeon General's Advisory Committee

Source: © Fred Ward–1964–www.AwardAgency.com

Figure 14.2   Cigarette advertisements

Source: Richard Pollay Tobacco Advertising Collection at Roswell Park Cancer Institute, Buffalo, NY.

tobacco use and increasing public understanding of the dangers of smoking in the real world, by 2002 smoking in movies had returned to levels observed in 1950, when smoking was nearly twice as prevalent in reality as it was in 2002 (Glantz et al. 2004). Beginning in 2002, Thumbs Up Thumbs Down!, a project of Breathe California of Sacramento-Emigrant Trails, has collected data on every film that was in the Top 10 theatrical box office for at least 1 week (which includes 83% of all films released in the United States and 96% of tickets sold) (Centers for Disease Control and Prevention [CDC] 2011c; Polansky et al. 2012). These data show that the number of tobacco incidents increased between 2002–2005, then declined from 2005–2010 and rebounded in 2011 and 2012 (Figure 14.3A).

Based on these data on tobacco incidents, population exposure to smoking incidents in movies can be estimated from box office attendance data (one impression equals one tobacco incident on screen viewed by one audience member one time) (CDC 2011c; Polansky et al. 2012). Theatrical impressions substantially underestimate total exposure because they include only in-theater exposure, not viewing on home media: broadcast, cable, satellite, and on-demand; on DVD and Blu-ray and on streaming media. Youth-rated movies delivered 20.4 billion impressions to domestic theatrical audiences in 2005

(Figure 14.3B). This exposure dropped by 73%, to 5.5 billion in 2010, then rebounded to 14.9 billion impressions in 2012. Of the youth-rated impressions that year, 99% (14.8 billion/14.9 billion) were delivered by PG-13 movies. While R-rated films on average include more smoking than PG-13 films, youth are much less likely to view R-rated films than PG-13 films; as a result, youth receive about three times the absolute exposure to smoking images from PG-13 films than R-rated films (Sargent et al. 2012). In 2012, impressions delivered by youth-rated movies comprised 56% (14.9 billion/26.5 billion) of all in-theater tobacco impressions (Polansky et al. 2012).

The 2012 Surgeon General's report concluded that there is a causal relationship between depictions of smoking in movies and initiation of smoking among young people (USDHHS 2012). The report based this conclusion on a large body of epidemiologic, behavioral, and experimental data. Subsequently, additional evidence shows a dose-response relationship between frequency of exposure to onscreen smoking images in movies and increased risk of smoking initiation (Dal Sin et al. 2011; Hanewinkel et al. 2012; Sargent et al. 2012; Morgenstern et al. 2011, 2013a, b). Additionally, based on the actual mix of films that adolescents viewed, it has been estimated that reducing in-theater exposures from a current median of about 275 annual exposures per adolescent from PG-13 movies

Figure 14.3A Total tobacco incidents in top-grossing U.S. movies, by Motion Picture Association of America rating
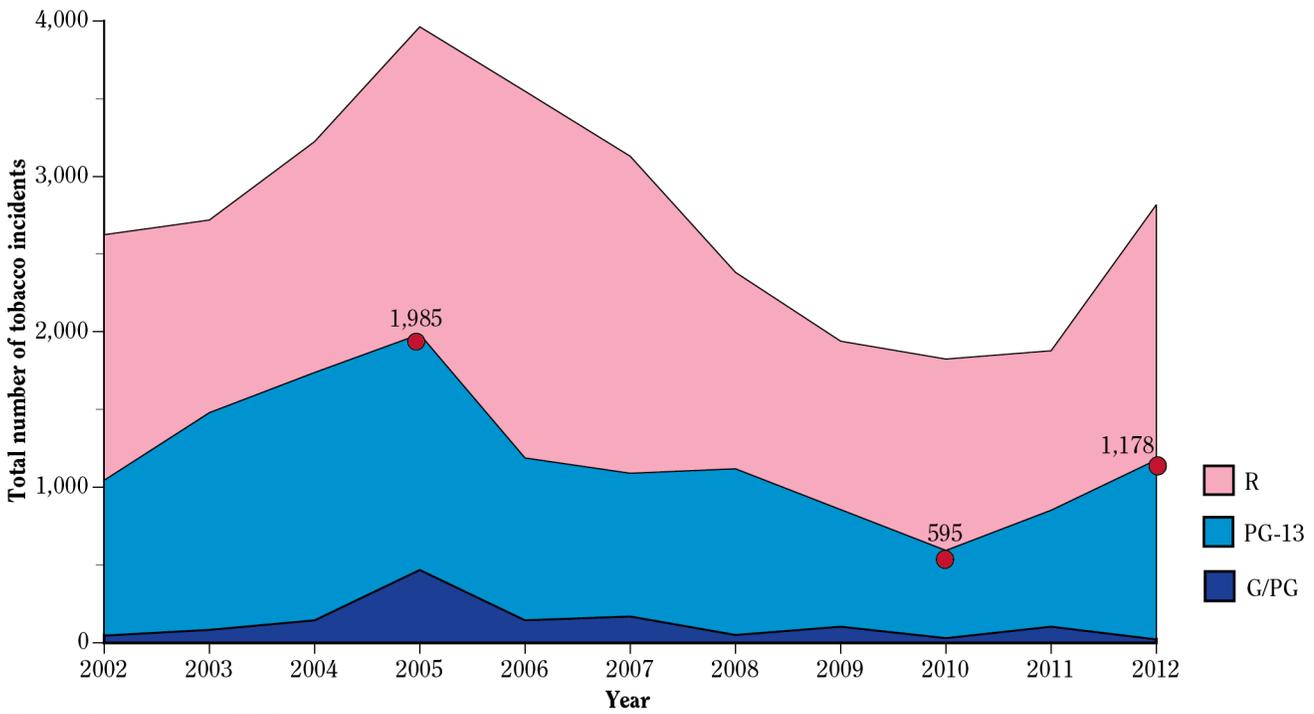
Source: Polansky et al. 2012.

Figure 14.3B Tobacco impressions[a] delivered by top-grossing U.S. movies, by Motion Picture Association of America rating
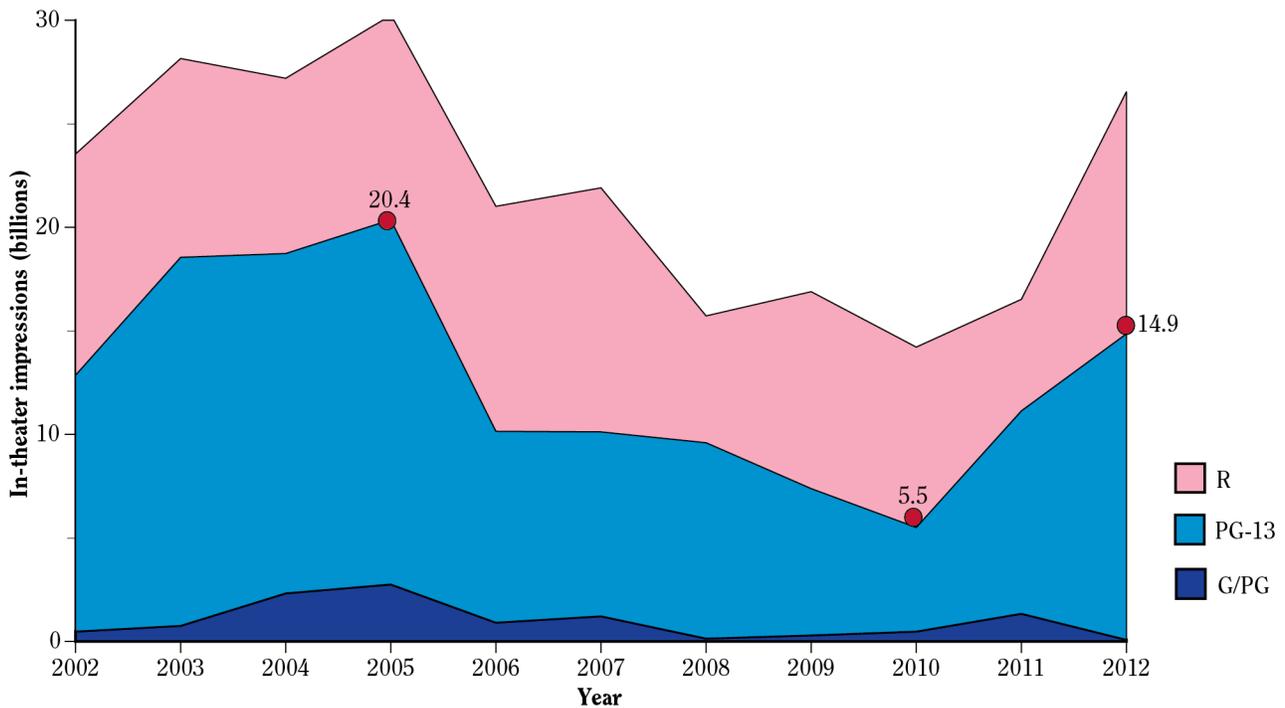
Source: Polansky et al. 2012.
[a]One impression equals one tobacco use incident on screen viewed by one audience member.

down to approximately 10 or less would reduce the prevalence of adolescent smoking by 18% (95% CI, 14–21%) (Sargent et al. 2012).

Reports on the health risks of cigarette smoking were published with increasing frequency from the 1920s, but it was not until the 1950s and 1960s that medical research on smoking and cancer began to receive widespread media attention and the public began to recognize the adverse consequences (see Chapter 2) (Brandt 2007). In a 1966 Harris poll, only 40% recognized smoking as a major cause of lung cancer, 27% considered it a minor cause, and one-third were uncertain, saying that "science has not yet determined the relation between smoking and lung cancer" (Saad 2002). One explanation for people not believing that smoking was a health risk is the aggressive actions of the tobacco industry in suggesting scientific uncertainty and controversy about the findings (e.g., the "Frank Statement" on smoking issued in 1954 [Pollay Advertising Collection, n.d.]) (Brandt 2007). Over time, the public's perception of smoking gradually shifted from viewing smoking as a minor health concern to increasing acceptance that there are serious health risks associated with smoking. Smoking became increasingly less acceptable as a social practice (Sadd 1998). In 2001, Gallup asked this question again and found that 71% of Americans identified smoking as a major cause of cancer, 11% said it was a minor cause, and 16% were unsure (Sadd 2002).

The first large-scale national counter-advertising campaign to educate the public about the health risks of tobacco use was launched in 1967, under the Fairness Doctrine, which required broadcasters to provide free media time for antismoking public service announcements in response to cigarette commercials (Cummings 2002). Several studies have concluded that the antismoking messages mandated by the Fairness Doctrine resulted in a sharp reduction in smoking, which rebounded after the antismoking ads went off the air in 1971, as a result of the broadcast advertising ban (O'Keefe 1971; Warner 1989; Simonich 1991). Beginning in 2000, the American Legacy Foundation launched the truth® campaign, a broadcast counter-advertising campaign which primarily targeted teens and young adults (Healton 2001). This extensively evaluated campaign was found to have been successful in creating a high level of awareness of its messages among the intended target audience, and to have been effective in discouraging youth from smoking (Farrelly 2002; Richardson et al. 2010). Additional evidence in support of the effectiveness of paid counter-advertising campaigns comes from the sharp declines in cigarette consumption observed in localities that have invested heavily in mass media campaigns (Farrelly et al. 2008; NCI 2008).

Smokefree Policies

Today, the adverse health effects of exposure to secondhand smoke are well understood, and firm causal conclusions have been reached on its risk to the health of nonsmokers (USDHHS 2006). The growth of laws regulating smoking in public locations such as schools, health care facilities, public transportation, government buildings, elevators, and restaurants has been a clear indicator of the changing social acceptability of smoking. However, in 1964, there were no laws regulating smoking in public locations. Evidence regarding the health consequences of exposure to secondhand smoke emerged in the 1970s and 1980s. This evidence supported the start of the nonsmokers' rights movement, which became a critical force in tobacco control efforts. This movement was largely responsible for motivating policies limiting where people could smoke (USDHHS 2006). Currently, federal laws prohibit smoking on buses, trains, and domestic airline flights. The U.S. military continues to extend the number of tobacco-free areas. In 1994, the U.S. Congress outlawed smoking in most of the nation's public schools and federally funded programs that serve children, including Head Start centers, day care centers, and community health centers (USDHHS 2000). In 1993, the Joint Commission on the Accreditation of Health Care organizations required hospitals to ban smoking indoors, but did not require restrictions on smoking in any other parts of the campus. By 1994, more than 96% of hospitals were smokefree, and 40% had tighter restrictions than were required (Institute of Medicine [IOM] 2013). By 2012, the majority of states and hundreds of individual communities in the United States had adopted comprehensive smokefree laws that prohibit smoking in nonhospitality workplaces, restaurants, and bars (CDC 2012c). Most hospitals, many private businesses, and hundreds of colleges and universities have now voluntarily prohibited tobacco use on their campuses, as a way to establish a smokefree norm that discourages people from using tobacco (CDC 2012d). The policies restricting where people can smoke have made cigarette use less socially acceptable and less convenient, and thus, have encouraged cessation and discouraged uptake of smoking (Gilpin 2004; Bauer 2005; Siegel 2008).

The progress in implementing comprehensive smokefree laws has been one of the major public health accomplishments since 1964; however, as reviewed later in this chapter, wide geographic, occupational, and demographic disparities remain and only about one in three residents of the United States lives under state or local laws that make worksites, restaurants, and bars completely smokefree (CDC 2008b, 2010).

Smoking in the Military

As discussed in Chapter 13, the males who were involved in World War II, or who were in adolescence during this era, initiated smoking at the highest rates and had the highest birth cohort prevalence of current smoking as young men. Smoking had been viewed as acceptable and even a positive in the U.S. military. As public opinion about smoking has changed and knowledge of the health effects of smoking has grown, tobacco control policies in the military have also changed. Appendix 14.1, online at www.surgeongeneral.gov, provides a more complete discussion of this topic.

During the past 50 years, the Department of Defense's (DoD's) stance on tobacco has markedly shifted. However, although tobacco use was supported in the middle of the twentieth century (e.g., mini-packs of cigarettes in ration accessory packs until 1975) (Smith et al. 2007) and tolerated well into the 1980s, the antitobacco use tide turned in the late 1990s as evidence of the immediate health and readiness consequences of smoking started to emerge. Cigarettes were banned from all military rations in 1975 (Smith and Malone 2009), and smoking was restricted in DoD facilities in 1977 (Executive Order No. 13058 1977). Between 1985–2001, both DoD and the U.S. Congress attempted to increase commissary cigarette prices, but these efforts were largely thwarted by the tobacco industry (Smith et al. 2007). Finally in 2001, DoD Directive 1330.9 established that tobacco prices on U.S. bases should be "no lower than 5 percent below the most competitive commercial price in the local community" (Smith et al. 2007, pp. 42–3). Even with this policy, a recent investigation of pricing differences between 145 matched Walmart stores and Military Exchanges found that the average retail price at an Exchange was 25.4% lower (Jahnke et al. 2011).

Despite the continued struggles with pricing, many DoD installations have expanded tobacco control policies extending the number of tobacco-free installations (Joseph et al. 2005). For example, the Air Force has prohibited tobacco use, virtually everywhere, on an Air Force installation with the exception of designated tobacco areas. Tobacco use outside of designated tobacco areas, including when walking outside of the designated tobacco areas, is prohibited (Air Force Instruction 40-102 2012).

Tobacco use is still prevalent in the military, despite the official DoD policy of strongly discouraging tobacco use, including prolonged and efficacious total tobacco bans during training (Klesges et al. 1999, 2006). However, the tobacco industry continues to reach this vulnerable military population by such methods as the placement of a coupon inside the cigarette carton when external coupons and/or promotions were prohibited (Stirlen 1994). Additionally, the industry has sent smokeless tobacco to Marines in Iraq, while maintaining that it was not a violation of the policy against distribution of free tobacco product samples, because they "responded to direct requests from troops" (Elliott 2003). Further, in response to tobacco advertising regulations, the tobacco industry has turned to promotional opportunities in adult-only venues such as bars and pubs (Katz and Lavack 2002), particularly those near military bases as stated in one marketing report, "...it seems the venues located in close proximity to the bases attract a large crowd of demographically desirable consumers" (National Field Report 1992).

Advocacy Efforts

As the public image of smoking and tobacco use has changed to become increasingly less favorable over the past half-century, advocacy efforts to restrict tobacco use have intensified. An extensive review of tobacco control advocacy was provided in Chapter 2, "A Historical Review of Efforts to Reduce Smoking in the United States" of the 2000 Surgeon General's report (USDHHS 2000). This chapter provides a short overview of some important milestones in tobacco control advocacy, which has played a critical role in motivating tobacco control at levels extending from local to national.

Many different groups have been active in tobacco control advocacy. Since 1964, the campaign to reduce smoking can be considered as "the entirety of changes in the social environment spawned by scientific and social interest in the hazards of smoking" (Warner 1989, p. 144); this movement covers not only specific activities, but also "the changing social norms that have accompanied them" (p. 144). Given this broad view, the span of activities involves persons, private organizations, and government agencies, all with different motivations: those ideologically committed to a movement to reduce smoking, those who operate profit-making businesses, those seeking public office, and those in public office who mandate laws and regulations. Critical contributions have come from national health organizations, public health and medical researchers, organized medicine through various professional organizations, government regulatory agencies and health departments, school officials, voluntary organizations in health, foundations, lobbying groups, private firms dealing with the health or insurance needs of employees, smoking cessation clinics, and individual medical practitioners.

These wide-ranging advocacy efforts, loosely organized and networked at best, faced the formidable challenge of opposing the responses of the well-funded and highly centralized tobacco industry. In an analysis of tobacco industry tactics, the Advocacy Institute defined nine areas of activity: intimidation, alliances, front groups, campaign funding, lobbying, legislative action, buying expertise, philanthropy, and advertising and public relations (Advocacy Institute 1996). In its discussion of well over 100 instances in these areas, which were documented largely from media reports, the Advocacy Institute (1996) does not accuse the tobacco industry of illegal activity, but rather, of far-ranging and systematic efforts to ensure the continued use of tobacco products. One critical advocacy effort for responding to these diverse industry counters to tobacco control has been tobacco industry denormalization. For example, a focus on the industry has been well integrated into the California Tobacco Control Program, since its inception as part of educating the public about disease risks (e.g., "The tobacco industry is making a killing off you"), and into several national youth nonsmoking campaigns. There is now considerable literature suggesting that denormalization has independent effects on reducing tobacco use (Malone et al. 2012).

Taken together, and backed by the enormous resources of the industry, efforts by the tobacco companies have had considerable impact in promoting tobacco use and slowing efforts to reduce or prevent it. Against this well-funded industry, advocacy efforts have played a critical role and proved effective in denormalizing smoking and portraying the truth about the industry and the dangers of its products. As described later in this chapter, other approaches have also proved effective in countering the tobacco industry, including litigation and enhanced awareness of the industry's efforts to mislead the public.

As public health efforts to discourage tobacco use evolved to become broader and stronger over the past half-century, the tobacco industry's strategies changed in parallel in an effort to sustain sales and protect its financial interests. To an extent, these efforts were successful; the companies continue to have millions of individual purchases every day of the year, with most consumers being brand-loyal, specifying a preferred brand by name (Maxwell 2010; FTC 2012). The summary of the 1981 FTC report documents the success of the industry's public relations efforts. The report found that by the early 1980s, although most Americans were generally aware that smoking was hazardous, many in the public, especially smokers, did not have sufficient information about the health risks of smoking to understand just how dangerous smoking was for them (Myers 1981). So egregious were the actions of the tobacco industry that U.S. District Judge Gladys Kessler found the companies guilty of violations under the *Racketeer Influenced and Corrupt Organizations* (*RICO*) *Act* (1994) (*U.S. v. Philip Morris USA, Inc.,* 449 F. Supp. 2d 1 (D.D.C. 2006)). In her findings of fact, affirmed on appeal, Judge Kessler concluded the evidence revealed that the companies had participated in a "scheme to defraud smokers and potential smokers in order to maximize their profits by preserving and enhancing the market for cigarettes, to avoid costly liability judgments, to derail attempts to make smoking socially unacceptable, and to sustain the cigarette industry" (*Philip Morris* 449 F. Supp. 2d at 852; *U.S. v. Philip Morris USA Inc.,* 449 F. Supp. 2d 1, 852 (D.D.C. 2006), *aff'd in relevant part by U.S. v. Philip Morris, Inc.,* 566 F. 3d 1095 (D.C. Cir. 2009 (per curiam)).

Changes in the Tobacco Industry, Products, and Product Regulations

In 1964, the evidence on tobacco and health focused on cigarettes since most tobacco users in the United States were cigarette smokers, and most tobacco consumption per person was in the form of cigarettes (USDHEW 1964). Subsequent reports of the Surgeon General were mandated by the U.S. Congress to address the health consequences of cigarettes. The rise of smokeless tobacco use in the 1970s and 1980s led Surgeon General C. Everett Koop to request a report on these products by the National Institutes of Health (NIH) (USDHHS 1986). The 2010 Surgeon General report provided some discussion of the changing tobacco industry and products (USDHHS 2010), but other than that report, most Surgeon General's reports on the health consequences of smoking have provided little discussion of the health effects of tobacco products other than cigarettes. The current report includes information on tobacco products other than cigarettes, because of the rapidly changing nature of tobacco products, trends

in new product use, and the tobacco industry itself, since the turn of the twenty-first century. Such information is becoming increasingly relevant to future tobacco control approaches, as the array of products is becoming increasingly diverse.

The tobacco industry's strategies have evolved, and are continuing to evolve, in ways that will influence attitudes towards it and the use of tobacco products. Over the past two decades, there have been several mergers and acquisitions of tobacco-related businesses in what may be a response to the new international regulations on tobacco products, a declining domestic cigarette market, and a growing international tobacco business. In 1994, the American Tobacco Company exited the tobacco business by selling off its cigarette brands to British American Tobacco (BAT). Starting in 1994, popular American brands such as Lucky Strike, Pall Mall, Carlton, and Misty were marketed in the United States by the BAT subsidiary, Brown & Williamson, which in 2004 was acquired by R.J. Reynolds (RJR) forming a new publicly-traded holding company called Reynolds American, Inc. (RAI). In 2008, RAI acquired Conwood Smokeless Tobacco Company and changed the name of the company to American Snuff Company. In 2009, RAI launched Camel Snus and, the following year, RJR introduced Camel DTPs. RAI also acquired the rights to market ZONNIC nicotine replacement products and purchased Niconovum AB, a Swedish company making oral nicotine replacement products. In 2003, Philip Morris changed its name to Altria and, in 2009, acquired U.S. Smokeless Tobacco Company. Shortly after, Altria began to market Marlboro Snus along with other smokeless tobacco products, such as Skoal and Copenhagen, in the United States. The international cigarette business continued through a new entity, Philip Morris International. In 2012, Lorillard acquired Blu Electronic Cigarettes, the manufacturer of Blu electronic cigarettes. In 2013, RJR announced that it will introduce VUSE electronic cigarettes and Altria announced that it will introduce MarkTen electronic cigarettes, thus, all three major cigarette manufacturers plan to have electronic cigarettes on the market (Sizemore 2013).

Some of the new products, such as electronic nicotine delivery systems (ENDS), marketed as "electronic cigarettes," were developed and/or are marketed by companies that had little or no experience in developing and marketing traditional tobacco products (WHO 2009c; Henningfield and Zaatari 2010; Cobb and Abrams 2011). Additionally, other tobacco products, such as bidis and waterpipes, have long histories of extensive use in other countries, but have been more recently marketed and adopted in the United States (WHO 2006; CDC 2012c). Given the level of evidence linking tobacco product use to ill health, all products containing tobacco and nicotine should be assumed to be both harmful and addictive, although the risk from the use of tobacco products depends not only on the type of product but also on how they are used (i.e., the actual doses of toxins that are taken in, and whether the product is used in addition to other products, promotes initiation of tobacco use, or delays smoking cessation) (WHO 2006, 2007). Thus, establishing a meaningful rank order of actual risk per product is not possible (Gray and Henningfield 2006; WHO 2006, 2008a).

Table 14.1 provides a summary of these products. It is meant to be illustrative, rather than comprehensive, because the nature of the products and their marketing is changing rapidly and an expanding array of products and manufacturers are being discussed in the trade literature. The products are categorized by their general form and mode of use, and not necessarily with reference to their definition by the U.S. Food and Drug Administration (FDA), or WHO, or statutory definitions by the U.S. Congress, FTC, or the Bureau of Alcohol, Tobacco, Firearms and Explosives. Together, the modified novel products, summarized in Table 14.1, pose challenges to research, surveillance, health policy, and regulation because they vary so widely in form, mode of use, apparent contents, designs and emissions, and potential health effects, including addictiveness, and marketing claims, implicit and explicit. Moreover, following introduction into the market, many products have been rapidly modified, perhaps in response to consumer feedback and market testing. For example, ENDS have grown from a category of novelty products in 2005 to an extensively marketed and increasingly accessible category, with awareness of ENDS doubling from 16.4% in 2009 to 32.2% in 2010 and ever use of ENDS more than quadrupling from 2009 (0.6%) to 2010 (2.7%) (American Legacy Foundation 2012; Regan et al. 2013). Studies and assessments by FDA and independent scientists have demonstrated enormous variability in design, operation, and contents and emissions of carcinogens, other toxicants, and nicotine from ENDS (Westenberger 2009; WHO 2009c; Henningfield and Zaatari 2010; Cobb and Abrams 2011; American Legacy Foundation 2012). The marketing claims for ENDS also vary widely and have included claims of safety, use for smoking cessation, and statements that they are exempt from clean air policies that restrict smoking (WHO 2009c; Cobb et al. 2010; Henningfield and Zaatari 2010; American Legacy Foundation 2012; Cheah et al. 2012).

Another less prevalent, but expanding and diversifying group of products is categorized by FDA as DTPs, which were evaluated by FDA's Tobacco Products Scientific Advisory Committee (TPSAC) in 2012 (TPSAC 2012). Extensive TPSAC deliberation and public

Table 14.1   Modified traditional tobacco products and novel tobacco products

Product type	Mode of use and operation	Developers and marketers	Health opportunities, concerns, and other comments
DTPs	Orally used films, tablets, and other systems that rapidly dissolve to provide buccal and some GI absorption[a]	Major tobacco companies developed or market with common apparent intent for use "when you can't smoke"	Some of these products appear to blur the distinction between tobacco and drug products but by not making explicit drug claims they have thus far avoided regulation as drug products. Product marketing generally appears to position the products as alternatives to cigarettes for when smoking is prohibited
ENDS[b]	Inhalation of vapors produced by heating contains nicotine and other substances. Some brands can be refilled by solutions made by the same or different companies	Chinese consumer product companies developed and dominate the global market. Many of the ENDS made in the United States are less cigarette-like in appearance	Products vary widely as to contents, emissions, and claims, thus reducing the relevance of categorical generalizations about their benefits and harms. Tobacco is not necessary for operation although some products include tobacco extracts to enhance sensory experience. These products are banned in some countries as unapproved drug products
Cigarette substitutes that heat tobacco with less tobacco combustion than cigarettes	RJR products burn carbon fuel; Philip Morris product electrically heats a small amount of tobacco per puff	Major cigarette companies	This category is distinguished from ENDS, and it is possible that it will be displaced by ENDS
Low nitrosamine smokeless tobacco including "snus" and pouches	Oral use with absorption and exposure primarily buccal along with GI exposure	Traditional smokeless companies and new companies, and more recently developed and acquired by major tobacco companies	This category varies widely from products that appear similar to conventional snuff and snus to those that appear more similar to pharmaceutical products
Low nicotine content cigarettes with low addiction risk	Inhalation of combustion products as with conventional cigarettes	Tobacco companies have tried to market such products over the past 20 years but presently are made primarily for research	Could enable cessation and reduce risk of addiction in those who initiated use. Not expected to be widely adopted unless all cigarettes were required not to exceed nicotine product standard by FDA (Teng et al. 2005; Hatsukami et al. 2010, 2012)
Waterpipes, also known as hookah and shisha	Inhalation of heated vapors drawn through water; often in 30–60 minute sessions with other persons sharing device	Traditional devices from India, Middle East, and Southeast Asia with many new companies in United States and elsewhere	Traditional and most widely used forms burn carbon material and produce high levels of user and environmental carbon monoxide and other toxic substances. More recent electronically heated systems have not been well studied. Some marketing claims include smoking cessation and exemption from clean air laws

Note: **DTP** = dissolvable tobacco products; **ENDS** = electronic nicotine delivery systems; **FDA** = U.S. Food and Drug Administration; **GI** = gastrointestinal; **RJR** = R.J. Reynolds.

[a]Dissolvable tobacco products have not been statutorily defined or defined by FDA or other agencies, and the term is used to include products that appear likely to dissolve in less than 1 minute, unlike traditional lozenges which are intended to dissolve over 10–30 minutes. The analysis provided for DTPs also applies to some new nondissolvable tobacco-free products such as "Verve," introduced in 2012.

[b]Electronic Nicotine Delivery Systems is the term recommended by the World Health Organization (2009c).

comments, including from public health organizations and the tobacco industry, led to conclusions that reveal great uncertainty as to whether these products are likely to contribute positively or negatively to public health (TPSAC 2012). The products were generally found to be lower in toxicants than traditional tobacco products, and lower in their likelihood of delivering comparable levels of disease-causing toxins as traditional tobacco products. TPSAC found that such products could confer potential health benefits at the individual and population levels if they were adopted as total substitutes for cigarettes by cigarette smokers who would not have otherwise quit. On the other hand, many of the products have apparently been developed and marketed to undermine smoking cessation efforts, by enabling cigarette smokers to manage restrictions on smoking by using them "for when you can't smoke" (TPSAC 2012). Another concern was the possibility that these products would emerge as initiation products and, thus, lead to initiation in persons who would not have otherwise done so. People who initiate nicotine exposure with DTPs might also be at risk for subsequent use of more toxic products, including cigarettes. Consequently, TPSAC concluded that the health risks of this category of products will be strongly determined by how they are marketed and how they are actually used (TPSAC 2012).

As discussed by WHO, tobacco products vary widely in form, content, and emissions, but virtually all types are primarily represented by products that are designed and manufactured to be addictive (WHO 2006). Earlier reports of the Surgeon General have described the addictive properties of tobacco products and the role of nicotine (e.g., USDHHS 1986, 1988, 1989, 2010), as have other authoritative agencies (Royal College of Physicians [RCP] of London 2000; National Institute of Drug Abuse [NIDA] 2012; WHO 2006, 2007, 2012b). This report does not review this foundational evidence, but does address some factors contributing to product addictiveness that are relevant to consideration of these emerging products for nicotine delivery. As discussed in the 2010 Surgeon General report, the ongoing research is contributing to further improvements in the understanding of the neurobiology and role of tobacco product design factors in tobacco addiction, as well as advances in the diagnosis and treatment of addiction and withdrawal as described in the fifth edition of the American Psychiatric Association's *Diagnostic and Statistical Manual* (American Psychiatric Association 2013). In addressing the public health consequences of these products, consideration needs to be given to ingredients and design features that can contribute to product addictiveness, and marketing approaches that can contribute to use patterns leading to addiction (WHO 2006; NCI 2008; USDHHS 2010, 2012).

Cigarettes carry the highest risk of addiction following initiation, due to cigarette designs that facilitate efficient and tolerable inhalation of nicotine-laden toxic smoke deep into the lung (RCP 2000; WHO 2001; USDHHS 2010). Although focused largely on cigarettes and conventional smokeless tobacco products, NCI Monographs 13 and 19 (NCI 2001, 2008) and an IOM report (Stratton et al. 2001) describe how product characteristics may be reflected in marketing, in order to stimulate initiation and foster continued use that leads to the development and maintenance of addiction. For example, cigarettes were designed to make smoke more easily inhalable and to provide low-tar and nicotine yields in smoking machine tests (NCI 2001). Smokeless tobacco products were designed with nicotine delivery and flavor characteristics targeted to certain populations, such as low-dose nicotine delivery fruit-flavored products for initiation by youth and higher dosage products targeted to tolerant longer term users (USDHHS 1994; *Federal Register* 1995, 1996). Similarly, FDA's TPSAC found that menthol in cigarettes was a design feature that produced physiological effects, including sensory effects contributing to tobacco use; and marketing and product branding of menthol and its effects also contributed to initiation and persistence of cigarette smoking (TPSAC 2011).

Menthol

Menthol is an organic compound, either derived from natural sources or synthesized, that is widely used in consumer and medicinal products, including cigarettes. It has cooling, analgesic, and irritative properties, reflecting its interactions with specific neuronal biological receptors that can modulate pain and communicate to areas of the brain concerned with taste and other sensations. The use of menthol in cigarettes followed the accidental discovery that menthol provided cooling properties to the smoke (Proctor 2011). Menthol brands entered the market in the 1930s and their use greatly expanded in the 1950s when aggressive marketing to African Americans began. It has been noted that the widespread marketing of menthol cigarette brands in Black communities covered "…literally every aspect of life, from Black-owned publications and jazz concerts through civil rights groups, to massive billboards throughout the Black community" (Gardiner and Clark 2010, p. S88). The manner in which the aggressive marketing of menthol cigarettes within Black communities resulted in persisting high rates of use of these brands among this group has been reviewed (Yerger and Malone 2002; Gardiner 2004; Sutton and Robinson 2004; Yerger et al. 2007). More recent analyses of marketing campaigns in

racial/ethnic communities have shown similar aggressive patterns of marketing of menthol cigarettes have continued (Cruz et al. 2010; Gardiner and Clark 2010). At present, menthol is a "characterizing flavor" for about 30% of cigarettes in the United States and it is present in most cigarettes at concentrations lower than in those labeled as menthol cigarettes (TPSAC 2011). Beyond being the predominant cigarette product smoked by African Americans, menthol cigarettes are popular among adolescents. In analyses of nationally representative survey data from 2004 to 2010, youth and young adults were heavy consumers of mentholated cigarettes, with menthol use particularly associated with being younger, female, and of non-White race/ethnicity (Giovino et al. 2013). Further, the survey data indicated that use of mentholated cigarettes has either remained constant or increased from 2004–2010 in youth and young adults while rates of use of nonmenthol cigarettes has been declining. Based upon these data, the authors suggested that progress in reducing youth smoking rates in recent years likely has been attenuated by the sale and marketing of mentholated cigarettes, including brands such as Camel Menthol and Marlboro Menthol (Giovino et al. 2013).

The *Family Smoking Prevention and Tobacco Control Act* (*Tobacco Control Act* 2009) banned the use of all characterizing flavors except menthol in cigarettes and cigarette tobacco. It explicitly required TPSAC to complete a report during its first year of existence on the public health impact of menthol in cigarettes. That report was released in July 2011 (USFDA 2011). It offers a comprehensive review of patterns of use of menthol cigarettes, the pharmacology and toxicity of menthol, and the risks of menthol cigarettes, including toxicologic and epidemiologic findings. To address the public health impact of having menthol in cigarettes, TPSAC modeled scenarios of smoking in the U.S. population, comparing the public health consequences of smoking with and without the presence of menthol cigarettes. TPSAC's review found evidence indicating that menthol cigarettes promoted experimentation and regular smoking and increased the likelihood of addiction in youth smokers. With regard to cessation, TPSAC concluded that among African Americans, smokers of menthol cigarettes were less likely to quit successfully. TPSAC did not find evidence that the presence of menthol in cigarettes increased the disease risks in smokers of menthol cigarettes compared to nonmenthol cigarettes.

Modeling carried out by TPSAC showed that the availability of menthol cigarettes increased the number of smokers in the population and led to additional excess mortality from smoking. Modeling by Levy and colleagues (2011) provided similar results. Based on its qualitative evaluation of the literature and the modeling results, TPSAC offered the overall conclusion that: "Removal of menthol cigarettes from the marketplace would benefit public health in the United States" (TPSAC 2011, p. 225). In July 2013, FDA issued an Advance Notice of Proposed Rulemaking to obtain additional information related to potential regulatory options on menthol cigarettes (*Federal Register* 2013). At the same time, FDA also released its own preliminary independent scientific evaluation of existing data and research on menthol cigarettes that addressed the association between menthol cigarettes and various outcomes, including initiation, addiction, and cessation (USFDA 2013c).

Overview of the *Tobacco Control Act*

The history of efforts to regulate tobacco has been reviewed in previous Surgeon General reports (USDHHS 2000, 2010, 2012) and books on tobacco control (Kluger 1996; Brandt 1997; Kessler 2001; Proctor 2011). The *Tobacco Control Act* (2009) gives FDA broad authority to regulate tobacco products. One of the unique features of the statute is that it creates a new regulatory framework by which tobacco products are now regulated. FDA is empowered to regulate in a manner that is "appropriate for the protection of the public health" (*Tobacco Control Act* 2009, §907(a)(3)(A)), an important departure from the standard of safety and efficacy that governs the regulation of human drugs and medical devices. The U.S. Congress also commanded FDA to consider the individual- and population-level health effects of regulatory actions, including the impact on initiation, cessation, and reinitiation by those who had quit (*Tobacco Control Act* 2009, §907(a)(3)(B)). FDA's efforts are funded by a fee levied on tobacco manufacturers and importers (*Tobacco Control Act* 2009, §919).

Over time, effective implementation of the powerful regulatory tools contained in the *Tobacco Control Act* will serve as a key component of a comprehensive national tobacco control plan to reduce the death and disease from tobacco use (Zeller 2012, 2013). The most significant of the provisions in the law include:

- *Authority to Issue Product Standards*: Section 907 of the *Tobacco Control Act* empowers FDA to issue standards to control the allowable levels of chemicals or chemical compounds, or ingredients in tobacco products or smoke to reduce the toxicity, addictiveness, or appeal of tobacco products. This

provision includes the power to reduce the amount of nicotine that can be delivered to nonaddictive levels as long as the standard does not reduce nicotine levels to zero (*Tobacco Control Act* 2009, §907(d)(3)). FDA will have to consider the impact of a proposed standard on population-level risks and benefits, including both users and nonusers of tobacco products; and the likelihood of current users stopping tobacco use or nonusers starting tobacco use (*Tobacco Control Act* 2009, §907(a)(3)).

- *Authority to Issue Orders for the Marketing of New Products*: Historically, the tobacco industry was free to introduce new products and modify marketed products in any way they chose. Section 910 of the *Tobacco Control Act* now requires a manufacturer to obtain an order from FDA, prior to the marketing of a new product or making a modification to an existing product including constituent, smoke constituent, content, delivery or form of nicotine, additive or ingredient (*Tobacco Control Act* 2009, §910(c)). Applications for new products will be reviewed by FDA under the public health standard, using the mandatory individual- and population-level criteria as considerations.

- *Authority to Issue Orders for "Modified Risk Tobacco Products"*: To prevent consumers from being misled by claims and descriptors on tobacco packaging and advertisement such as "light" or "low-tar" on tobacco packaging and advertisement (NCI 2001), Section 911 of the *Tobacco Control Act* states that no one may introduce into interstate commerce any modified-risk tobacco product unless FDA issues a risk modification or exposure modification order permitting such introduction. In order to qualify for a risk modification order, manufacturers must demonstrate, among other things, that the product, as actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users and benefit the population as a whole. In order to qualify for an exposure modification order, manufacturers must demonstrate that the overall reductions in exposure are substantial and that the product is expected to benefit the health of the population as a whole and also that consumers will not be misled into believing that the product presents a lower risk for disease or is less harmful than other commercially marketed tobacco products (*Tobacco Control Act* 2009, §911(g)(2)).

- *Authority to Demand Health Information from Manufacturers*: Under Section 904(b) of the *Tobacco Control Act*, FDA may require tobacco companies to submit information on the health, toxicological, behavioral, or physiological effect of any tobacco products and their constituents, including smoke constituents, ingredients, components, and additives (*Tobacco Control Act* 2009, §904(b)). The information includes documents related to research activities and findings, as well as marketing and research activities.

Until implementation of the *Tobacco Control Act* in 2009, FDA had no authority to address product formulation issues, and there was little federal oversight of tobacco product designs that might contribute to addictiveness. Since the mid-1990s' release of the tobacco industry documents, it has been increasingly evident how extensive were the research, manufacturing, and marketing efforts by the industry to make products more acceptable and addictive (*Federal Register* 1995, 1996; Kessler 2001; WHO 2001, 2007, 2012b; USDHHS 2010). These examples illustrate that the risk, severity, and persistence of addiction to tobacco, like addiction to other substances, are influenced by many factors beyond the pharmacology of the addicting drug. These include social factors; perceptions of harm, cost, and access (USDHHS 1988; O'Brien 2010;); and the formulation of the drug itself (*Controlled Substances Act of 1970;* Compton and Volkow 2006; Cone 2006; Schuster 2006; Dart 2009; Dasgupta and Schnoll 2009; O'Brien 2010; USFDA 2010a, 2013b; NIDA 2012). In fact, changes in drug form, such as the introduction of free-base and smokeable cocaine in the 1980s, and easily tampered and abused prescription opioids in the 1990s, are considered major factors contributing to the escalation of stimulant and opioid abuse, respectively (Compton and Volkow 2006; Koob and Le Moal 2006; O'Brien 2010). Similarly, many changes in tobacco product form and marketing have been documented as efforts by the tobacco industry to contribute to tobacco use and addiction by fostering initiation among young people; making products easier and more acceptable to use; making and marketing products so as to address health concerns; and making and marketing products to perpetuate addiction through the use of alternate products, when smoking is not allowed or is socially unacceptable (*Federal Register* 1995, 1996; Kessler 2001; *Philip Morris* 449 F. Supp. 2d at 908; WHO 2001, 2007, 2012b; USDHHS 2012). These concerns contributed to the rationale and support for the development and implementation of tobacco regulation in the United

States through the *Tobacco Control Act* (2009), and globally through the WHO Framework Convention on Tobacco Control (FCTC) (WHO 2013).

The *Tobacco Control Act* gives FDA the authority to set standards ("product standards") for products, so as to contribute to the improvement of the public health and reduction of tobacco product use. To support FDA's efforts, NIH and FDA are collaborating to foster research on tobacco product addictiveness, toxicity, appeal, and other characteristics that will provide additional scientific foundation for developing a regulatory framework, including potential tobacco product standards (NIH and FDA 2012). The research findings could lead to product standards that will not only curtail the efforts of the tobacco industry to enhance addictiveness and attractiveness, but may also contribute to standards that will contribute to reducing their potential to cause and sustain addiction, thus supporting tobacco control prevention and cessation efforts. Globally, WHO is working through the WHO FCTC with member states, and its expert advisory committee, to assess the evidence and support efforts to develop recommendations for tobacco product regulation that will contribute to reduced use and addiction (WHO 2012b, 2013). Nationally and internationally, the challenge of changes in tobacco product form, patterns of use, and the industry, are being addressed by these regulatory frameworks and guided by continuing research.

Significant FDA Actions to Date

FDA has taken a number of significant actions, as it creates the regulatory framework to oversee tobacco products and implement the broad provisions of the *Tobacco Control Act* (USFDA 2013a). Among the key steps the agency has taken are the following.

Reissuance of FDA's 1996 final rule that restricts the sale and distribution of tobacco products to minors (21 CFR *Part 1140 March 2010)*

The key provisions of this rule include prohibiting the sale of cigarettes or smokeless tobacco to people younger than 18 years of age; prohibiting the sale of cigarette packages with fewer than 20 cigarettes; prohibiting the sale of cigarettes and smokeless tobacco in vending machines, self-service displays, or other impersonal modes of sales, except in very limited situations; prohibiting free samples of cigarettes, and limiting the distribution of free samples of smokeless tobacco products. The final rule also contains restrictions on marketing, including prohibiting tobacco brand name sponsorship of any

athletic, musical, or other social or cultural event, or any team or entry in those events; and prohibiting the sale or distribution of items, such as hats and tee shirts, with cigarette and smokeless tobacco brands or logos (*Federal Register* 2010).

Regulation requiring graphic warning labels on cigarette packages and in advertisements (June 2011)

The key provisions of this final rule mandated nine new warnings on cigarette packages and cigarette advertisements covering 50% of the front and back panels of all cigarette packs, and at least 20% of all cigarette advertising (*Federal Register* 2011). The rule contained a separate image for each of the nine new text warnings mandated in the *Tobacco Control Act* (2009, §201(a)).

Litigation was filed against FDA by the tobacco industry in the case of *R.J. Reynolds Tobacco Co. v. U.S. Food and Drug Administration*, No. 11-1482 (D.D.C.), *on appeal*, No. 11-5332 (D.C. Cir. 2012). Although the U.S. Court of Appeals for the Sixth Circuit upheld FDA's authority to require graphic health warnings, the D.C. Circuit, in a separate challenge, ruled that the warnings promulgated by FDA were unconstitutional (violated the 1st amendment) and remanded the issue back to the agency. FDA has announced it will undertake research to support new rulemaking on graphic warning labels consistent with the *Tobacco Control Act*. Larger warnings on smokeless tobacco products have already been implemented.

In addition, FDA has issued a series of guidance documents on topics that, although not legally binding, represent FDA's current thinking on a subject matter. The subject areas of the most significant guidance documents include:

- Implementing the Congressionally mandated ban on labeling and advertising containing misleading descriptors such as "light" and "low-tar" (June 2010) (USFDA 2010b). The *Tobacco Control Act* prohibits the use of descriptors such as "light" and "low-tar" as unapproved modified tobacco product claims. The basis for this provision is that consumers mistakenly believe products bearing these descriptors are safer or less harmful than other tobacco products. The FDA guidance document provided clarification on the prohibited use of these terms.

- Demonstrating "substantial equivalence" for tobacco products (January 2011) (USFDA 2011c). In addition to pre-market evaluation of new tobacco products, the statute details another pathway to market under

section 905(j) of the *Tobacco Control Act*. This guidance document contains important information for tobacco product manufactures who wish to try to demonstrate substantial equivalence. In June 2013, the Center for Tobacco Products at FDA issued the first orders allowing the marketing of new tobacco products, after the agency determined the products to be "substantially equivalent" to specific predicate products. FDA also issued the first orders denying marketing for other new tobacco products after finding that the products had different characteristics than their predicate products and the applicant did not adequately show that the new products do not raise different questions of public health (and therefore were "not substantially equivalent" to the predicate product) (USFDA 2013e). FDA continues to review product submissions and to make decisions about whether the products are substantially equivalent (and can therefore be legally marketed) or not substantially equivalent (in which case the product cannot be marketed in the United States).

- Applications for premarket review of new tobacco products (September 2011) (USFDA 2011a). As previously mentioned, the statute envisions that manufacturers will file applications with FDA for orders authorizing the marketing of new tobacco products. This guidance specifies information that should be contained in such an application including full reports on health risks; statement of all components, ingredients, additives, properties, and principles of operation; description of methods of manufacturing and processing; explanation of how the product complies with applicable product standards; and proposed labeling. The guidance interprets and expands on several key provisions in Section 910 of the *Tobacco Control Act*, including reports on investigations of health risks associated with the product; providing information on ingredients, additives, and other properties of the product; and providing information on methods of manufacturing and processing.

- Establishment of a list of harmful and potentially harmful constituents in tobacco products. The *Tobacco Control Act* obligated FDA to create a list of harmful and potentially harmful constituents in tobacco products (HPHCs) (*Tobacco Control Act* 2009, §904(a)(3)). In April 2012, FDA published a list of 90 HPHCs. Additionally, Section 904(a)(3) requires tobacco product manufacturers to submit a list of HPHCs by brand and by quantity in each brand and subbrand. Section 904(d) of the *Tobacco Control Act* also requires FDA to publish the HPHC list in a way that is understandable and not misleading to a layperson [904(d)(1)]. FDA is undertaking an experimental study to determine the best way to present such data.

- Applications for designation as a "modified risk tobacco product (April 2012)" (USFDA 2012b). This is one of the most extensive guidance documents issued by FDA. It elucidates what manufacturers should include in applications in order to market modified-risk tobacco products that could bear claims touting either a reduction in exposure to harmful compounds or claims that risk has actually been reduced. Importantly, guidance is provided on the types of studies companies should consider conducting and including in their applications.

Given that FDA regulates tobacco products based on a public health standard that needs to consider the product's impact on the population as a whole, including users and nonusers, tobacco regulatory science serves as the critical bridge between tobacco products and public health by enabling FDA to assess various products' inherent risks, how they are used, and impact on individual and population health in order to regulate them appropriately. Tobacco regulatory science supports the evaluation of the risks and benefits of tobacco regulatory decisions and provides a robust scientific foundation for regulatory policies regarding the manufacture, marketing, and distribution of tobacco products and educating the public about the harms.

Although there is a vast and sound science base with regard to numerous provisions within the *Tobacco Control Act,* new research will not only help assess the impact of FDA regulatory authority over tobacco products, but inform future regulatory activities. The agency took several actions to ensure that sound science will exist with which to inform regulatory actions. In 2011, it collaborated with NIDA to launch a major longitudinal study of tobacco use and behavior (Population Assessment of Tobacco and Health Study) (USFDA 2011b). The study, which started in September 2013, expects to invite 59,000 people 12 years of age and older to participate and will examine behavioral changes over time in tobacco product use and subsequent biological and health outcomes. In 2012, FDA issued a statement of research priorities designed to communicate its priority regulatory science research questions (USFDA 2012a). In September 2013, FDA and NIH announced the

funding of 14 research projects to establish the Tobacco Centers of Regulatory Science, a first-of-its-kind program designed to generate research to inform the regulation of tobacco products to protect public health and train the next generation of tobacco regulatory scientists (USFDA 2013d). In addition, FDA is funding numerous research projects via collaborations with NIH, CDC, FDA's National Center for Toxicological Research and research contracts in order to better understand the risks associated with tobacco use.

Challenges to Full Implementation of the *Tobacco Control Act*

FDA has faced a number of challenges as it implements the extensive provisions of the *Tobacco Control Act*. An entire center needed to be established at the same time that the agency was confronted with a series of mandatory deadlines in the law. From 2009–2012, the agency succeeded both in building this new center and meeting all of the deadlines imposed by the U.S. Congress.

A second challenge was the successful litigation commenced by the tobacco industry around preventing the final graphic warning label rule from going into effect (*R.J. Reynolds v. Food and Drug Administration* 2012). On April 22, 2013 the Supreme Court of the United States declined to hear the appeal of the March 2012 ruling by the U.S. Court of Appeals for the Sixth Circuit (Bayer et al. 2013; Orentlicher 2013). There is the ongoing possibility of litigation from the tobacco industry (Thomas and Gostin 2013).

Evidence-based regulation of the manufacture, sale, and marketing of tobacco products is an essential component of a comprehensive national effort to reduce the death and disease resulting from tobacco use. The tools to control product introduction, claims, and product performance were intended by the U.S. Congress to place oversight of the tobacco products marketplace within FDA, an independent agency whose mission is to protect public health.

Potential Impact of Implementation of the *Tobacco Control Act*

Continuing actions include regulating existing products and their constituents; reviewing and allowing the marketing of new products; evaluating modified risk claims and products and requiring premarket testing and postmarket surveillance to evaluate unintended consequences of introducing these products to the market; evaluating substantial equivalence reports before the products are introduced into the market; and educating the public with accurate information to correct misleading messages (Zeller 2012, 2013). These actions will benefit from FDA's application of the public health standard and population-level behavioral criteria as they relate to proposed regulatory action (Villanti et al. 2011; Zeller 2012).

FDA authority over tobacco products has the potential to be a key policy lever to reduce tobacco use and its harms at the population level (Zeller 2012). For example, a simulation model of multiple influences projected a sizeable benefit of a mentholated cigarette ban with 323,000 deaths averted from 2011–2050, a third of them among African Americans, assuming an impact on initiation and cessation of 10% (Levy et al. 2011). Experts have also outlined strategies for tobacco harm reduction (Zeller et al. 2009), such as nicotine reduction (Henningfield et al. 2004; Hatsukami et al. 2010, 2013; Benowitz and Henningfield 2013) and product standards (Hatsukami 2013), as avenues for FDA to dramatically reduce population harm. FDA has a variety of potential options including considering ways to reduce the harm and addiction liability of all tobacco products, ways to enhance the use of noncombustible and less addictive tobacco-derived nicotine products, and carefully evaluating modified risk/reduced harm forms of delivery (Hatsukami 2013). The lines between the recreational use of emerging tobacco-derived nicotine products and the therapeutic use of nicotine replacement products for smoking cessation are changing (e.g., in the form of using e-cigarettes, dissolvables, or snus; or in promoting more flexible therapeutic use of medicinal nicotine products for cessation in current users).

Tobacco Control Policies

Public health efforts to control tobacco use have been bolstered by policies at the national, state, and local levels. This section briefly examines the effectiveness of selected regulatory approaches (e.g., taxes and smokefree indoor air policies) to prevent tobacco use, encourage cessation, and reduce exposure to secondhand smoke among nonsmokers. This section also includes a brief discussion of advertising and restricted access for minors. Several of these policies are among the most effective tobacco control strategies of the past 50 years (e.g., taxation and smokefree indoor air policies) and are the cornerstone of state and local tobacco control efforts covered in a later section in this chapter. These strategies are reviewed here, however, since over the history of tobacco control, they have commonly been applied individually.

Taxes

In the United States, the federal government, all 50 states, the District of Columbia, and many local governments tax tobacco products. Although many factors affect the final price of cigarettes and other tobacco products, the most important policy-related determinant of tobacco prices is excise taxes on tobacco products. Taxes on tobacco provide revenue to governments at a relatively low administrative cost, making these taxes especially appealing. Moreover, higher taxes have decreased consumption of tobacco products, especially cigarettes, and thereby improved public health (USDHHS 2012). This combination of increasing revenues and improving public health has made tobacco taxation a valuable and effective policy lever in recent decades. In 2012, the federal tax rate was $1.01 per pack (Orzechowski and Walker 2012) and the mean state tax rate was $1.53 per pack (Campaign for Tobacco-Free Kids 2013). The average price, nationally, for a pack of cigarettes in 2012 was $6.00 (Campaign for Tobacco-Free Kids 2012b).

Figure 14.4 shows that the inflation-adjusted retail price of cigarettes in the United States had remained relatively low for much of the twentieth century, and then increased by over 70% from 1997–2002. This large increase was partly the result of two federal tax increases (from $0.24 to $0.34 in 2000 and from $0.34 to $0.39 per pack in 2002) and the numerous increases in state excise taxes; it also reflected the significant increases in the wholesale price of cigarettes. In fact, between 1998–2003, wholesale prices for cigarettes increased 122% (Capehart

2004), largely as a result of the increased costs associated with expenses for individual state tobacco settlements and expenses related to the Master Settlement Agreement (MSA). The more recent sharp increases in the inflation-adjusted retail price of cigarettes are due to another federal tax increase (from $0.39 to $1.01 in 2009) and numerous increases in state and local taxes. Since January 1, 2002, 47 states, the District of Columbia, and several U.S. territories have increased their cigarette excise taxes a total of 105 times. Even Kentucky, North Carolina, and Tennessee—tobacco-producing states that have long resisted raising tobacco taxes—have increased tax rates on cigarettes. As of March 31, 2013, the rates ranged from $0.17 per pack in Missouri to $4.35 per pack in New York (Table 14.2).

Moreover, hundreds of municipalities impose taxes on cigarettes, but the rates are generally relatively small when compared with state taxes. However, in recent years, several cities and counties have implemented large increases. For example, in 2002, New York City increased its tax on cigarettes from $0.08 per pack to $1.50 per pack. Similarly, both the city of Chicago and Cook County, Illinois (Cook County includes Chicago as well as many other jurisdictions), raised taxes on cigarettes. Combining federal, state, and local taxes, individuals purchasing cigarettes in New York City and Chicago, Illinois, paid the highest cigarette excise taxes in the country at $5.85 and $5.66 per pack, respectively, as of December 12, 2012 (Campaign for Tobacco-Free Kids 2013).

Another kind of tax, the general sales tax, is also quite common. In 2013, 45 states and the District of Columbia imposed general sales taxes on cigarettes; as of November 1, 2012, these taxes added between $0.14 and $0.43 to the price of a pack of cigarettes (Table 14.2). In addition, 9 states currently apply excise taxes on tobacco products other than cigarettes; these taxes are predominantly ad valorem. Finally, in most states the general sales tax is applied to other tobacco products as well as to cigarettes.

Previous Surgeon General's reports (USDHHS 2000, 2012) have concluded that increases in cigarette prices, including those that result from increases in excise taxes, reduce the initiation, prevalence, and intensity of smoking among youth and adults. Additionally, two comprehensive reviews of the literature summarize the evidence on the impact of price on tobacco consumption; one is included in the International Agency for Research on Cancer (IARC) Handbooks of Cancer Prevention in Tobacco Control

Figure 14.4   Annual retail tobacco price index and per capita (18+) cigarette consumption—United States 1900–2012
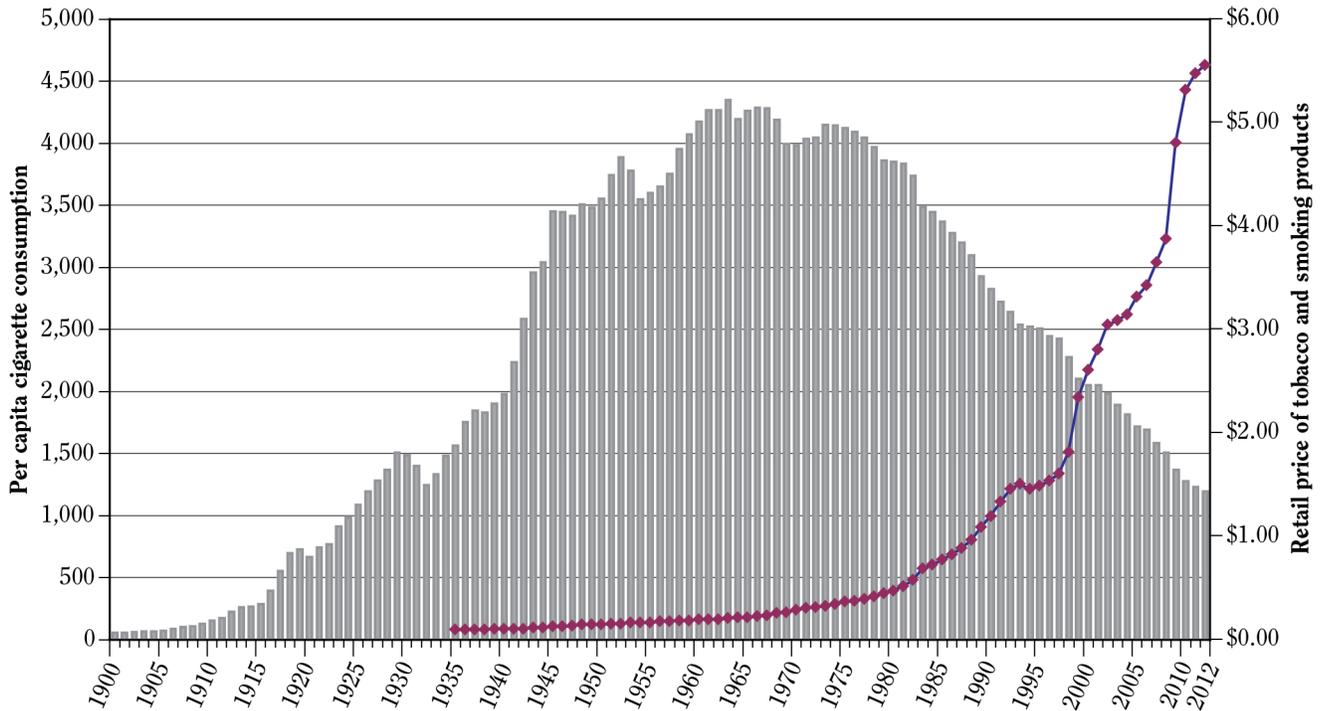
Source: Orzechowski and Walker 2013; U.S. Bureau of Labor Statistics (BLS) 2013; U.S. Department of Agriculture 2013; U.S. Department of the Treasury 2013.
Note: U.S. Bureau of Labor Statistics (BLS) Tobacco and Smoking Product Index was converted to average retail price per pack using BLS Fiscal Year (July–June) 2011 Index (825.49) and Orzechowski and Walker (2013) average annual price for 2011 ($5.55) values.

(IARC 2011), and the second a summary of key findings by Chaloupka and colleagues (2011). Five general conclusions can be drawn from these reviews (Chaloupka 2011; IARC 2011). First, increases in cigarette prices can lead to substantial reductions in cigarette smoking. The consensus estimate from the two reviews is that a 10% increase in cigarette price will result in a 3–5% reduction in overall cigarettes consumed. Second, increases in cigarette prices will decrease not only the prevalence of smoking but also the average number of cigarettes smoked by smokers. Third, much previous research on cigarette consumption among youth suggests that both youth and young adults are more responsive than adults to changes in cigarette prices, with several studies finding youth and young adults to be two to three times as responsive to changes in price as adults (see USDHHS 2012 for a complete review). Fourth, there is greater price responsiveness among lower income populations (IARC 2011). Finally, state excise tax increases create revenues for states.

In 2009, the *Children's Health Insurance Program Reauthorization Act* increased the federal tax rate on cigarettes from 39 cents per pack to 100.66 cents per pack. For the first time, it also applied the same tax rate to cigarette-like small cigars (from 3.7 cents per pack to 100.66 cents per pack) and roll-your-own tobacco (from 4.5 cents per pack to 100.66 cents per pack) (Campaign for Tobacco-Free Kids 2009). However, there remain substantial differences in the federal taxes on these products (cigarettes, small cigars, and roll-your-own tobacco) and other tobacco products, including regular cigars, pipe tobacco, and smokeless tobacco, which are taxed at much lower rates. In addition, the industry manipulated the weight of some small cigars by adding a few grams of filler to make them qualify as large cigars, thus avoiding the tax increase (CDC 2012a). This change in classification resulted in a dramatic, immediate increase in large cigar use over a 2-month period. The industry also began repackaging and marketing pipe tobacco to be used for roll-your-own

Table 14.2   State cigarette excise taxes (dollars per pack) and sales tax rate applied to cigarettes

State	Excise tax March 31, 2013 (in dollars)	Sales tax rate November 1, 2012 (%)	State	Excise tax March 31, 2013 (in dollars)	Sales tax rate November 1, 2012 (%)
Alabama	0.425	4	Montana	1.70	0
Alaska	2.00	0	Nebraska	0.64	5.5[d]
Arizona	2.00	6.6	Nevada	0.80	6.85[a,b]
Arkansas	1.15	6	New Hampshire	1.68	0
California	0.87	7.25[a,b]	New Jersey	2.70	7
Colorado	0.84	2.9	New Mexico	1.66	5.125
Connecticut	3.40	6.35	New York	4.35	4[d]
Delaware	1.60	0	North Carolina	0.45	4.75[d]
District of Columbia	2.50	6[c]	North Dakota	0.44	5
Florida	1.339	6	Ohio	1.250	5.5
Georgia	0.37	4[d]	Oklahoma	1.03	4.5[d]
Hawaii	3.20	4	Oregon	1.18	0
Idaho	0.57	6	Pennsylvania	1.60	6
Illinois	1.98	6.25	Rhode Island	3.50	7
Indiana	0.995	7	South Carolina	0.57	6
Iowa	1.36	6	South Dakota	1.53	4
Kansas	0.79	6.3[d]	Tennessee	0.62	7
Kentucky	0.60	6	Texas	1.41	6.25[d]
Louisiana	0.36	4[d]	Utah	1.70	4.65[b,d]
Maine	2.00	5	Vermont	2.62	6
Maryland	2.00	6	Virginia	0.30	5
Massachusetts	2.51	6.25	Washington	3.025	6.5
Michigan	2.00	6	West Virginia	0.55	6
Minnesota[e]	1.23	6.875[d]	Wisconsin	2.52	5[b]
Mississippi	0.68	7	Wyoming	0.60	4[b]
Missouri	0.17	4.225[d]			

Mean state excise tax: $1.478   Mean sales tax rate: 5.05%
Median state excise tax: $1.339   Median sales tax rate: 6%

Source: Sales tax data from Orzechowski and Walker 2012. Excise tax data from Centers for Disease Control and Prevention, Office on Smoking and Health, State Tobacco Activities Tracking and Evaluation System, unpublished data.
Note: The states of Alaska, Delaware, Montana, New Hampshire, and Oregon do not have a state general sales tax.
[a]Includes that portion of state-collected local sales tax rates where local rates are uniform and statewide.
[b]Additional local taxes that are not uniform are collected by the state and are not included here.
[c]The District of Columbia exempted cigarettes from the sales and use tax in October of 2011 and replaced it with a surtax of 36¢ per 20 pack. The tax listed in the table is the cigarette excise tax of $2.50 plus the cigarette surtax of 36¢.
[d]Certain cities and/or counties impose general sales and/or excise taxes that are collected by the state (not included here).
[e]Minnesota sells stamps for $1.586 per pack. It is a composite of the 48¢ per pack excise tax, a 75¢ per pack health impact fee, and a 35.6¢ per pack wholesale sales tax assessed in lieu of a general sales tax.

cigarette production. Evidence indicates that despite continued decreases in cigarette consumption in the United States, consumption of re-engineered pipe tobacco and large cigars has increased substantially since the federal tobacco excise tax was increased in 2009 (CDC 2012a).

As discussed in previous Surgeon General's reports, several significant challenges have impeded the effectiveness of excise tax increases. As the differential levels of taxation have widened between states, tax avoidance and evasion practices have increased. Tax avoidance and evasion, also known as illicit trade, occurs along a continuum of individual and group behaviors. Tax avoiders at both the individual and group levels pay some local, state, and federal taxes, whereas tax evaders do not. Tax avoidance activities include individual cross-border, Internet, and untaxed purchases on tribal lands, as well as consumer behaviors such as product switching, carton purchases, and using cheaper outlets. Individuals and small-scale organizations also bootleg cigarettes in low tax jurisdictions for resale in high tax jurisdictions. Tax evasion includes illegal activities often conducted by large-scale organizations, such as organized smuggling, counterfeiting, and illegal manufacturing. In states and municipalities with the highest taxes, such as New York and Chicago, as many as 40% of cigarettes consumed were purchased in a lower-tax jurisdiction (Merriman 2010; Virginia State Crime Commission 2013). More than one-half (55.4%) of smokers report using at least one price-minimization strategy when purchasing cigarettes—including carton purchasing, Indian reservation purchase, generic brands, coupon use, and Internet purchase—with an average reduction of $1.27 per pack (22%) (Xu et al. 2013). In addition, the tobacco industry has developed extremely sophisticated mechanisms to blunt and mitigate the effects of price increases. These include Web-based, mail-order, brand repositioning, and store-based discounting that is timed to scheduled price increases.

Tax avoidance and evasion undermine the efficacy of high prices in reducing consumption and initiation, especially among price-sensitive groups (IARC 2011). However, IARC concluded that there is sufficient evidence that tax avoidance and evasion reduce, but do not eliminate, the public health and revenue impact of tobacco tax increases (IARC 2011).

Selected state experience suggests that all levels of government can enhance revenue collection and minimize tax avoidance and evasion through several promising policy approaches. For instance, California and Massachusetts have both implemented a high-tech cigarette tax stamp, which includes encrypted information on payments that is reported electronically to the state's revenue collection entity. Electronic data collection and reporting allows for more consistent monitoring of tax and MSA payments, improves tobacco licensure management, and makes the stamps harder to counterfeit. California has found that this tax stamp, combined with enhanced tobacco tax payment enforcement, has helped reduce state tax evasion by 37% since its implementation in 2005 (McIntosh 2007). The state estimates that an additional 101 million packs per year are sold through legal retail distribution channels instead of illegally, valued at $87.7 million per year (Bartolo and Kimsey 2013). Improved tax stamping technology appears to be a promising state tobacco control practice.

It has been suggested that this promising state practice could also be expanded to the national level with a national track and trace system. A track and trace system, in the tobacco control context, is a system that can track goods from manufacture to distribution to sale, identifying points in the supply chain where taxes should be paid and confirm payment. WHO's FCTC includes establishing a national track and trace system and recommends that system include, at a minimum: nonpredictable serialization of all tobacco products to the level of the smallest saleable unit, with each unique code linked to a secure database of information on that product; common numbering standards for serialization, which should include information about the manufacturer, date of manufacture, and brand; human-readable printing/labeling of serialization of numbers on all traded units; establishment of parent-child relationships between different packaging units so individual cartons and cases can be separated from master cases during shipping; recordkeeping along the supply chain; maintenance of relevant data by supply-chain partners; query interfaces between the databases of supply-chain partners and enforcement authorities; and a standard protocol for transferring queries and data (WHO 2010).

The *Tobacco Control Act* authorizes the FDA to implement a national track and trace system (15 *U.S.C.* §920(b)(3)). The Department of the Treasury's Alcohol Tobacco Tax and Trade Bureau, which is responsible for collecting federal tobacco excise taxes, while not authorized to implement a national track and trace system, has authority over product markings (e.g., tax stamps) to facilitate this tax collection (26 *U.S.C.* §5723(b)). These two agencies would benefit from working together to develop a track and trace system that could meet their two complementary goals: to collect federal tobacco excise taxes and to control tobacco product regulations (Department of the Treasury 2010).

Data from France indicate that price increases can be a win-win scenario for tobacco control and the government. From 1990–2005, cigarette prices tripled, consumption was cut in half, and government revenue from

tobacco doubled, adjusted for inflation (Peto 2013; Jha and Peto, in press). The 2009 U.S. federal tax increase on cigarettes and subsequent tax increases at the state and local levels represent recent successes in tobacco control. However, a substantial range persists in the levels of cigarette excise taxes across states, and cigarettes and noncigarette tobacco products are not similarly taxed. Another issue is that current tax levels are static and do not account for inflation. Increasing the federal tax for noncigarette products, implementing systems to control for tax avoidance and evasion (e.g., high-tech tax stamps and track and trace systems), shrinking the tax disparity between states and localities, and establishing a taxation system that accounts for inflation, would likely improve the impact of taxes on the prevalence of tobacco use, especially among young smokers most sensitive to price. Closing the gap in these federal tax rates would further reduce tobacco use and increase tobacco revenues at the federal level.

Finally, there is concern that the dramatic drop in funding for tobacco control programs, which has occurred concurrently with a dramatic increase in tax-related revenue to states, may not be entirely coincidental. Although increases in price from excise taxes still make money for a state despite decreased consumption, fiscal agencies in states may not perceive the same relationship between increased funding for effective tobacco control programs and state revenues. Although long-term reductions in smoking may lower state expenditures for health care, this is a much less tangible effect than the immediate loss of tax and MSA revenue from a significant decline in cigarette consumption due to a tobacco control program effect. For example, some state governors raised concerns about the 2009 federal tax increase because they thought the resulting consumption drop would lower their tax and MSA revenues.

Smokefree and Tobacco-Free Legislation

As discussed later in this chapter, smokefree legislation at the state and local levels is a key component of a comprehensive tobacco control strategy (Task Force on Community Preventive Services 2005; CDC 2007; USDHHS 2012). Although progress has been made to increase the protection of nonsmokers in the United States from exposure to secondhand smoke since the release of the 1986 Surgeon General's report on the health consequences of involuntary exposure to tobacco smoke (USDHHS 1986a), biomonitoring of exposure indicates that about 40% of nonsmokers, and about one-half of

young children 3–11 years of age, continue to be exposed (CDC 2010). Wide geographic, occupational, and demographic disparities remain (CDC 2008b,c, 2010). In 2008, it was estimated that only about one in three residents of the United States live under state or local laws that make worksites, restaurants, and bars completely smokefree (CDC 2008b, 2010).

As described in Chapters 6–10 and previous reports, exposure to secondhand smoke has been linked to a wide variety of adverse health effects affecting the fetus, infants and children, and adults (USDHHS 2006, 2010). The primary purpose of laws and policies on secondhand smoke is to protect nonsmokers from exposure to secondhand smoke. However, a growing body of evidence suggests that these policies have the additional benefit of lowering smoking rates among youth and young adults. There are several pathways for this effect including lower visibility of role models who smoke, fewer opportunities to smoke alone or with others, and diminished social acceptability and social advantage for smoking (Alesci et al. 2003; Eisenberg and Forster 2003; Wakefield and Forster 2005). One study, Dinno and Glantz (2009), indicated that although the prevalence of smoking and cigarette consumption was higher in people with low education and income (using the 2002 Tobacco Use Supplement to the Current Population Survey), a cross-sectional analysis found that this group exhibited the same reductions in smoking associated with the presence of clean indoor air laws and tax increases on tobacco products as did people in higher education and income groups.

Policies on clean indoor air take the form of legislation and/or regulations at the federal, state, local, and institutional levels that prohibit smoking in specified locations, such as workplaces, public places, restaurants, bars and casinos, schools, day care centers, and health care facilities (USDHHS 1989, 2000). Although there have been laws on clean indoor air for 40 years, their coverage has expanded dramatically in recent years (Hyland et al. 2012). As of May 31, 2013, 24 states, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands have laws that prohibit smoking in all workplaces, including bars and restaurants (American Nonsmokers' Rights Foundation [ANRF] 2013a). As noted earlier in this chapter, the movement for laws on clean indoor air largely began at the local level, and many states without comprehensive laws have cities or counties with such laws. The spread of these local laws is shown in Figure 14.5. The ANRF (2013a) estimated that as of May 31, 2013, comprehensive local and/or state laws on clean indoor air covered 49% of the U.S. population. Figure 14.6 provides a map of the implementation of these laws (ANRF 2013b).

Figure 14.5   Number of municipalities and local laws covering smoking in workplaces, restaurants, and enclosed public places, generally, 1978–2013
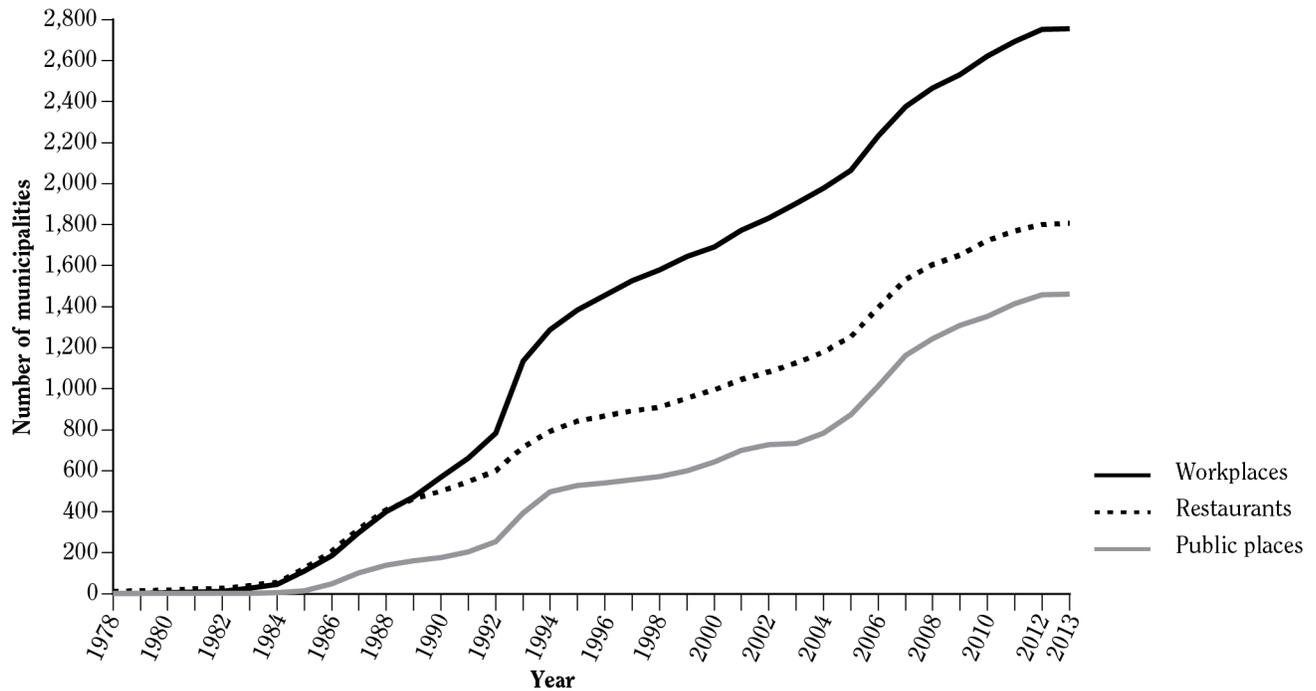
Source: American Nonsmokers' Rights Foundation 2013a.

Many locations are smokefree because they are environments oriented towards youth. According to the CDC School Health Policies and Programs Study for 2006, in that year 70% of states and 95% of school districts, included in a nationally representative sample, prohibited smoking by students in school buildings, grounds, vehicles, and off-campus school-sponsored events (Jones et al. 2007). However, only 47% of the states, but 78% of the school districts, had smoke-free schools in which the same restrictions applied to staff (Jones et al. 2007). At least 1,178 U.S. colleges and universities were completely smokefree as of July 8, 2013, which includes having 100% smokefree residential housing policies (ANRF 2012d). On the basis of data from the Tobacco Use Supplement of the Current Population Survey, CDC reported that in 2009 the median proportion (by state) of households with smokefree policies for everyone living in or entering the home was 81% (King et al. 2013). Finally, smoking has been prohibited in vehicles, when children younger than certain ages are present, in nine U.S. cities or counties, six states, Puerto Rico, nine Canadian provinces/territories, and six Australian states (Global Advisors Smokefree Policy 201).

Relatively little evidence is available about sociodemographic disparities in the coverage of smokefree policies in public and private locations. In one study, Skeer and coworkers (2004) examined differences in community characteristics in relation to the strength of their local policies on clean indoor air in public places; they found that towns with higher education levels and greater per capita income were more likely to have the most restrictive policies. Gonzalez and colleagues (2013) found that Hispanics and Asians have benefited more from the rapid spread of clean indoor air laws and non-Hispanic Blacks have benefited less. A CDC report, using 1999–2004 National Health and Nutrition Examination Survey data, found that youth were three to four times as likely as adults to be exposed to secondhand smoke in the home (CDC 2008a). In this study, non-Hispanic Blacks were the most likely and Mexican Americans the least likely to be exposed to secondhand smoke at home (17.9%; 95% CI, 15.2–21.0), and members of low-income families were three times as likely to be exposed, as their counterparts in the highest income group (5.9%; 95% CI, 5.1–7.0). Poverty income ratio was defined as the ratio of family income to the U.S. Census Bureau poverty threshold

Figure 14.6 Map of 100% smokefree laws, United States, May 31, 2013

American Nonsmokers' Rights Foundation

As of April 5, 2013

Note: American Indian and Alaska Native sovereign tribal laws are not reflected on this map.

Territories and Commonwealths

Commonwealth of Northern Mariana Islands

Guam

American Samoa

Puerto Rico

U.S. Virgin Islands

Locality Type with a 100% Smokefree Law

▲ City
● County

State and Commonwealth/Territory Law Type

■ 100% Smokefree in Non-Hospitality Workplaces, Restaurants, and Bars

■ 100% Smokefree in one or two of the above

□ No 100% Smokefree State Law
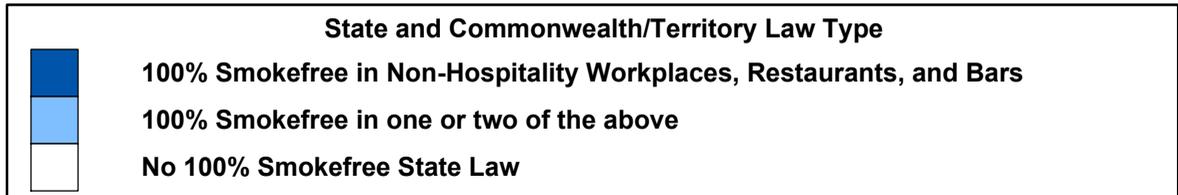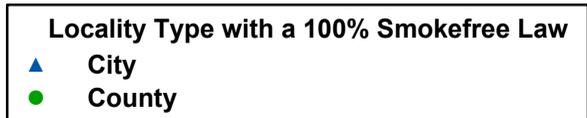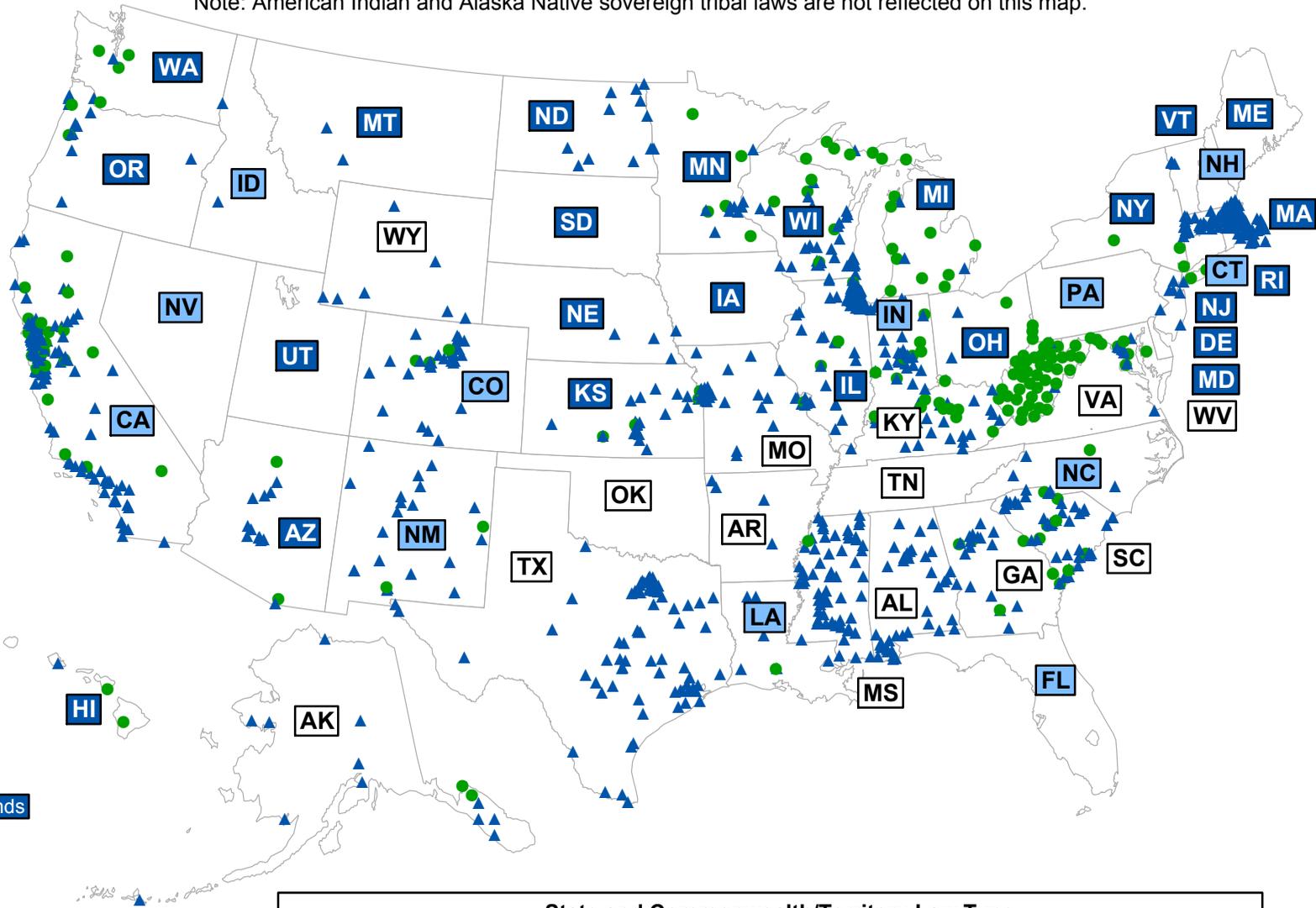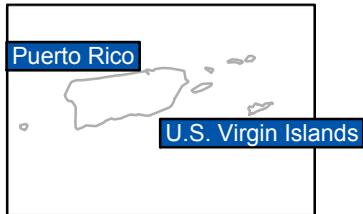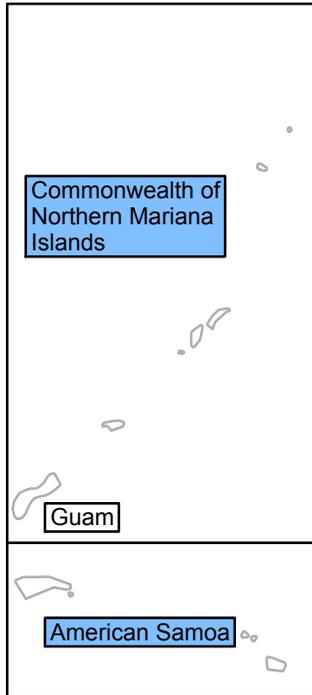
In addition to reducing exposure to secondhand smoke, smokefree policies and laws have also been found to reduce active smoking. The 2006 Surgeon General's report concluded that workplace smoking restrictions lead to less smoking. The 2012 Community Guide's conclusion on the effects of smokefree policies found that these policies reduce the prevalence of tobacco use, increase the number of tobacco users who quit, and reduce tobacco use initiation among young people (Community Preventive Services Task Force 2012). IARC (2009) concluded that there is strong evidence that smokefree workplaces lead to increased successful cessation among smokers and that smokefree policies reduce tobacco use among youth. A 2010 systematic review by the Community Preventive Services Task Force found that smokefree policies were associated with a median 3.4% reduction in tobacco use prevalence and a median 6.4% increase in tobacco use cessation (Hopkins et al. 2010; Task Force on Community Preventive Services 2010). The 2010 Cochrane review found that there is limited evidence about the impact of smokefree laws on active smoking, but that the trend is downward (Callinan et al. 2010).

As of 2013, a summary of progress in implementing smokefree policies includes:

- Smokefree legislation had been adopted by 36 states and over 3,500 municipalities (ANRF 2013b).

- 2,311 states, commonwealths, territories, cities, and counties had a law that restricted smoking in one or more outdoor areas (Americans for Nonsmokers' Rights [ANR] 2012b).

- 4 states prohibit smoking in privately owned vehicles when a child is present (ANR 2012a; CDC 2012d).

- The state of Maine and the city of Boston, Massachusetts, enacted smoking bans in public housing beginning in 2012.

- As of March 31, 2013, there were a total of 19 states with smokefree policies on public school campuses (K–12) (CDC STATE System, unpublished data). Seven of the 19 states also had smokefree policies on private school campuses (K–12). Three states (Arkansas, Iowa, and Oklahoma) banned smoking on public college campuses; and Iowa also had a smokefree policy for private college campuses. Iowa was the only state with smokefree policies for all four types of campuses: private and public schools (K–12) and colleges.

- In 2008, 45% of U.S. hospitals had a smokefree campus policy, with an additional 15% of hospitals pursuing smokefree policies (Williams et al. 2009). As of 2012, 4 national hospitals, clinics, insurers, and health service companies had adopted smokefree policies nationwide that extend to all sites; 3,419 local and/or state hospitals, health care systems, or clinics had adopted smokefree campus grounds; and 105 psychiatric hospitals had adopted smokefree indoor air policies (ANRF 2013f). A total of 34 states banned smoking in hospitals (CDC 2012d). Of these, three states (Arkansas, Illinois, and North Dakota) have designated smoking areas on hospital campuses. Eight states or territories and 154 municipalities have enacted smokefree indoor air laws in nursing homes, in addition to 64 individual nursing homes across the country (ANRF 2013e).

- In 2004, the Federal Bureau of Prisons made all federal facilities 100% smokefree, restricting smoking by correctional facility inmates, employees, and visitors. Nearly all states have adopted smokefree and/or tobacco-free policies in correctional facilities also. Correctional facilities in 19 states are smokefree and tobacco-free indoors and outdoors, 15 states are smokefree and tobacco-free indoors, 1 state and 1 territory are smokefree indoors and outdoors, and 12 states are smokefree indoors only (ANRF 2013c).

- DoD and all of the armed forces except the Coast Guard have set goals to increase tobacco-free areas, but have yet to achieve them despite promoting tobacco-free lifestyles through public education campaigns, commander training, the banning of all tobacco use during basic training, and the prohibition of tobacco use by instructors in the presence of students. A report by IOM, *Combating Tobacco in Military and Veteran Populations* (IOM 2009), provides an update on these efforts to promote tobacco-free environments in the military.

- Reviews by CDC (2010) have shown where the greatest levels of disparity in exposure to secondhand smoke remain. These areas of disparity include many states without comprehensive smokefree legislation, and among lower socioeconomic status populations, and service and hospitality workers.

Regulations on Youth Access

One component in a comprehensive strategy to prevent smoking among youth is restricting the supply of cigarettes to minors (CDC 2007a; USDHHS 2012). Youth can obtain cigarettes in two ways: commercially (from a store or vending machine) and socially (borrowing, buying, or stealing them from other youth or adults). A variety of strategies aim at restricting commercial access, and these strategies, in turn, can limit social access by reducing the total number of cigarettes accessible to youth (USDHHS 2012).

The three possible strategies for encouraging compliance with age-of-sale laws are taking appropriate steps in the retail environment, educating merchants, and actively enforcing the laws. Taking appropriate steps in the retail environment includes requiring tobacco products to be located behind the counter, posting signage informing customers that it is illegal for minors to purchase tobacco, and banning vending machines and self-service sales (Forster and Wolfson 1998). Taking these steps possibly reduces the likelihood that youth will obtain cigarettes, even if the store's clerk is inattentive. Education of merchants is an attempt to inform retailers of the laws; it is assumed that educated retailers would be less likely to sell cigarettes to minors (Rigotti 1999). Self-enforcement and education of merchants are not enough, however, to prevent minors from purchasing tobacco from commercial establishments (USDHHS 2012); penalties and improved enforcement of laws are needed. Penalties for selling tobacco to minors include revoking store licenses, and fining merchants and clerks who sell to youth, both of which are usually done after a random compliance check.

The IOM report recommends requiring state licensing of all retail outlets that sell tobacco products to verify the age of purchasers, including banning the use of self-service displays and vending machines, restricting direct access to tobacco products, and selling products only in a face-to-face exchange (Bonnie et al. 2007). During the past 10 years, two states have adopted tobacco retail outlet licensing requirements (CDC 2012d). In March 2010, FDA published a final regulation restricting the sale and distribution of cigarettes, cigarette tobacco, and smokeless tobacco. Requirements in this regulation included: prohibition of the sale of tobacco products to children younger than 18 years of age; a need for proof of age by photo identification for purchasers younger than 27 years of age; prohibition of the sale of tobacco products in vending machines, self-service displays, or other impersonal modes of sale, except in very limited circumstances; prohibition of free samples of cigarettes and limitation on the distribution of free samples of smokeless tobacco

products to certain facilities; and prohibition of the sale of cigarettes in packets of fewer than 20 cigarettes (USFDA 2010c). FDA is enforcing these provisions through state contracts and other enforcement activities. Retailer penalties can include warning letters, civil money penalties (fines), and no-tobacco sales order.

The 2012 Surgeon General's report reviewed the efficacy of interventions to prevent the sale of tobacco products to underage youth in detail and concluded that the data are mixed on whether interventions to restrict access can lead to a reduction in the number of retailers selling tobacco to minors. However, it was noted that the Community Preventive Services Task Force (2005) concluded that community mobilization, combined with additional interventions—such as stronger local laws directed at retailers, active enforcement of retailer sales laws, and retailer education with reinforcement—are recommended. A comprehensive review also supports the efficacy of enforced reductions in the sales of cigarettes to minors (DiFranza 2011).

Bans and Restrictions on Advertising and Promotion

In discussing advertising, it is important to clarify what it is and what it is not (Richards and Curran 2002). Advertising is a type of marketing that uses the media to create positive product imagery or associations or to connect the product with desirable personal traits, activities, or outcomes (Richards and Curran 2002). Marketing can be defined as the mix of all activities designed to increase sales (including both advertising and promotional activities). Advertising, for example, could take the form of ads in print; such an ad might show attractive couples smoking cigarettes in an appealing environment. Promotional activities usually do not rely on advertising and can take a variety of forms, including reducing the price paid by consumers. Price promotion may take the form of coupons, merchandise add-ons, and free samples. Another form would be allowances paid to retailers to increase their profit margins; in return, the retailer places the tobacco products in favorable places within the store. The retailer could pass the promotional allowance on to consumers in the form of lower prices. Other types of promotion include sponsoring events, selling or distributing branded items, and contests that encourage user participation in exchange for prizes.

According to FTC (2012), in 2010 more than $8 billion was spent on cigarette advertising and promotion in the United States. This sum spent on advertising and

promotions threatens public health, as it increases overall smoking and encourages youth to begin to smoke (NCI 2008; USDHHS 2012). The tobacco industry and consultant researchers (e.g., Heckman et al. 2008) contend that there is no definitive research showing that advertising increases smoking; however, this claim is countered by longitudinal research (NCI 2008) and strong empirical evidence, including the tobacco industry's own internal documents and trial testimony, that there is a consistent dose-response relationship between the marketing and promotional efforts by tobacco companies and the initiation and progression of tobacco use among young people (USDHHS 2012). Also, from a cost-benefit point of view, the potential public health advantages and associated economic gains (such as in long-term worker productivity) of banning cigarette advertising are far greater than the private costs to tobacco companies and advertisers of any lost revenues; consequently, it has been suggested that an advertising ban would be sensible from an economic perspective (NCI 2008). As concluded in NCI Monograph 19: "The studies of tobacco advertising bans in various countries show that comprehensive bans reduce tobacco consumption. Non-comprehensive restrictions generally induce an increase in expenditures for advertising in 'non-banned' media and for other marketing activities, which offset the effect of the partial ban so that any net change in consumption is minimal or undetectable" (NCI 2008, p. 281).

Although the evidence reviewed in NCI Monograph 19 supports the efficacy of comprehensive bans on advertising, other evidence continues to emphasize the importance of reducing existing levels of advertising and promotions in this country, particularly in any form or setting where young people can be exposed. Specifically, the 2012 Surgeon General's report concluded that "the evidence is sufficient to conclude that there is a causal relationship between advertising and promotional efforts of the tobacco companies and the initiation and progression of tobacco use among young people" (p. 602). This report reviewed the evidence that the tobacco industry has used a mixture of actions to alter the prices of their products, including a variety of price-reducing promotions, and that these actions attract price-sensitive populations such as youth to their products, as well as soften the price impact on consumers of increases in federal and state tobacco excise taxes. In addition to pricing policies, the report reviewed the evidence that tobacco manufacturers have employed a wide range of advertising, marketing, and promotional initiatives which have been shown to be key factors in initiation and progression of tobacco use among youth and young adults. The report reviewed the evidence that tobacco advertising and promotion, particularly those initiatives containing imagery which associates

positive qualities with tobacco use and impacts attitudes about smoking, intentions to smoke, and actual smoking behavior among youth. Finally, in addition to advertising and promotions, the 2012 report cited evidence that the tobacco industry has invested heavily in packaging design and brand imagery on packages, which is especially influential during adolescence and young adulthood when smoking behavior and brand preferences are being developed.

At present, the tobacco retail environment serves unique roles in industry marketing and promotional activities. The 2012 Surgeon General's report (USDHHS 2012) found that the presence of heavy cigarette advertising in convenience stores, especially in predominately ethnic and low-income neighborhoods, increases the likelihood of exposing youth to prosmoking messages, which can increase initiation rates among those exposed, particularly if stores are near schools. Therefore, based upon the findings in the 2012 report, local policies and approaches to reduce point-of-purchase advertising and promotions have increased.

As many forms of direct advertising and promotion of tobacco products have been curtailed, it has been noted that the entertainment media are among the few remaining channels for transmission of aspirational images of smoking to large audiences (Kline 2000). The billions of impressions of tobacco use that movies deliver (Figure 14.3B), combined with the fact that conventional cigarette advertising on television and radio has been banned since 1971, and billboards banned and other forms of cigarette advertising directed at youth severely restricted since 1999 by the MSA, emphasizes the importance of onscreen smoking in the movies as one of the largest remaining unrestricted traditional media channels promoting smoking and tobacco use to youth. The 2012 Surgeon General's report reviewed the historical links between the tobacco companies and the movie industry. Evidence from tobacco company documents has provided confirmation of a commercial relationship between the tobacco industry and film studios that began in the 1920s and continued into the 1970s after cigarette advertising was banned on television (Mekemson and Glantz 2002; Lum et al. 2008). As reviewed in the 2012 report, it appeared that voluntary policies by three of the major motion picture studios had all but eliminated smoking from their youth-rated films. It has been suggested that controlling for rating, budget and other factors, on average movies with smoking make less money than smokefree movies (Glantz and Polansky 2011). However, data from 2011 and 2012 (Figure 14.3A) suggest that this decline has reversed (Glantz et al. 2012; McAfee and Tynan 2012). Based on the findings in the 2012 Surgeon General's report that there is a causal relationship between the depictions of smoking in the movies

and initiation of smoking among young people, actions that would eliminate depiction of tobacco use in movies that are produced and rated as appropriate for children and adolescents could have a significant effect toward preventing youth from becoming tobacco users.

The *2009 Prevent All Cigarette Trafficking* (PACT) *Act* closed a loophole enabling individuals to purchase tobacco products via the Internet or mail without paying the appropriate taxes. The PACT Act ensures the collection of federal, state, and local tobacco taxes on cigarettes and smokeless tobacco products sold via the Internet or other mail-order sales and makes tobacco products not mailable by the U.S. Postal Service (Campaign for Tobacco-Free Kids 2010). It also restricts youth access to tobacco products via Internet and mail-order sales by requiring age verification prior to sale and upon delivery.

Tobacco Product Litigation

When the nation's first Surgeon General's report on smoking and health was released in 1964, litigation against cigarette manufacturers concerning the health effects of their products had been ongoing for 10 years. It would take an additional 30 years until tobacco litigation began to have a deep impact on the landscape of tobacco control. This history of tobacco product litigation is described in more detail online at www.surgeongeneral.gov in Appendix 14.2. Additionally, a summary of major tobacco litigation cases is also provided online in Appendix 14.3.

Litigation against tobacco companies has proven to be a tool for advancing the fundamental public health goal of tobacco control—reducing the morbidity and mortality caused by tobacco products. It can contribute to tobacco control in several ways:

- Tobacco litigation has offered an opportunity to shed light on the practices of tobacco manufacturers by exposing once-secret internal documents and giving a voice to former industry insiders (Bero 2003).

- The media coverage of tobacco litigation serves to educate and reinforce messaging about the health risks associated with the use of tobacco products (Dunlop and Warner 2010).

- Litigation, when successful, can lead to increases in price due to the high cost of verdicts or settlements to manufacturers, which results in reduced consumption of tobacco products, particularly among youth (Chaloupka and Pacula 2001).

- Very large punitive damages have the potential to encourage manufacturers to examine their practices and change behaviors that could trigger such monetary sanctions (Table 14.3) (Guardino and Daynard 2005).

- Settlements may include provisions that restrict marketing practices that might be difficult to achieve through legislation (Jacobson and Warner 1999).

- Litigation complements other tobacco control efforts and can serve as a public reminder of the need for state and federal policy interventions (Vernick et al. 2007).

- By focusing on the conduct of the manufacturers and their role in the injuries at issue, tobacco litigation plays an important role in denormalizing the industry and its practices that contribute to the toll of tobacco use on public health (Vernick et al. 2007).

State Attorney General Cases

The 2000 Surgeon General's report and Appendix 14.2 (found online at www.surgeongeneral.gov) provide a summary of several of the most influential cases, including the State Attorney General cases, which started in 1994. The first four of these lawsuits against the tobacco industry to recover health care expenditures for treating tobacco-related ailments of Medicaid recipients were brought by Mississippi, Minnesota, Florida, and Texas. In each of these first four cases, the tobacco industry settled separately with the state. All together, the four settlements resulted in the tobacco industry agreeing to pay a total of $35.3 billion over a 25-year period (Miura et al. 2006).

Shortly after settling separately with Mississippi, Minnesota, Florida, and Texas, the tobacco industry sought to resolve the outstanding state-brought Medicaid reimbursement lawsuits by entering into a comprehensive settlement agreement. On November 23, 1998, the four largest tobacco companies (Brown & Williamson, Lorillard, Philip Morris, and R.J. Reynolds) entered into the MSA with the remaining 46 states and five territories. They entered into this agreement after failing to reach a congressionally brokered global settlement, which would have given the tobacco industry certain immunities from liability going forward (Givel and Glantz 2004).

Under the MSA, the tobacco industry agreed to make annual payments to the states for a 25-year period in return for each state abandoning its Medicaid reimbursement claim. By 2012, the participating tobacco companies

Table 14.3   Punitive damages in tobacco litigation

Case name	State	Verdict year	Punitive damages award	Final status of award
Henley v. Philip Morris	CA	1999	$50 million	$9 million
Williams v. Philip Morris	OR	1999	$79.5 million	$79.5 million
Whiteley v. RJR, Philip Morris	CA	2000	$250,000	$250,000
Engle v. R.J. Reynolds, et al.	FL	2000	$144.8 billion	$0
Boeken v. Philip Morris	CA	2001	$3 billion	$50 million
Burton v. Philip Morris	KS	2002	$15 million	$0
Schwarz v. Philip Morris	OR	2002	$150 million	$25 million*
Bullock v. Philip Morris	CA	2002	$28 billion	$28 million
Boerner v. Brown and Williamson Corp.	AR	2003	$15 million	$15 million
Price v. Philip Morris	IL	2003	$3 billion	$0
Frankson v. Brown and Williamson Corp.	NY	2004	$20 million	$5 million
Smith v. Brown and Williamson Corp.	MO	2005	$20 million	$1.5 million
Evans v. Lorillard	MA	2010	$81 million	$81 million*

*On appeal as of December 2012.

had paid the states approximately $87 billion in MSA payments, not including payments to the four states that settled separately (National Association of Attorneys General 2012). On average, the tobacco industry pays each participating state and territory about $120 million in MSA payments annually. After the initial 25-year period elapses, the tobacco industry will continue to make annual payments to the states based on domestic cigarette sales.

The MSA, however, did not require states to earmark the tobacco industry's payments for tobacco control programs; the attorneys general who negotiated the settlement did not have the power to do so. As a result, most states use their MSA payments for general purposes, unrelated to public health. In 1999, CDC published guidelines recommending the amount states should spend on tobacco cessation and prevention efforts (CDC 1999, 2012e). Only a few states spend the CDC's recommended amount on tobacco control (CDC 2007a; American Lung Association 2012). The MSA also specifies that at least $1.65 billion of the states' recovery would be directed to create an independent public health foundation to conduct programs to reduce youth tobacco use. This foundation, which became the American Legacy Foundation (Legacy), was established in 1999. Starting in 2000, Legacy implemented the national truth® campaign—a mass media countermarketing effort focused on preventing youth smoking.

Legacy also provided over $120 million in grant funding to support state and local tobacco control efforts.

In addition to the monetary payments, the MSA included provisions directly benefiting the public health, such as prohibitions or restrictions on: outdoor advertising, distribution of promotional merchandise, sponsorship of public events, targeting underage smoking, and political lobbying. The MSA also improved access to the tobacco industry's documents by requiring the companies to fund, and update for 10 years, a searchable Web site containing millions of documents produced in litigation; however, in practice, the availability of the documents was only practical when Legacy established the Legacy Tobacco Documents Library at the University of California at San Francisco.

It has been suggested that one of the greatest public health consequences of the MSA was the tobacco industry's decision to increase cigarette prices after execution of the MSA (Cutler et al. 2002). To cover the initial payments to the states and payments for the tobacco control programs under the MSA, the tobacco industry had to increase the price of cigarettes. The increase in cigarette retail prices created a decline in cigarette sales of about 10% over the next couple of years, with the most significant decrease in consumption by younger adults (Daynard et al. 2001; Sloan and Trogdon 2004). Although the MSA

was not able to earmark payments to states for tobacco control programs, it appears to have had a large overall impact on tobacco control and public health through payments to states, restrictions on marketing methods, and substantial funding of tobacco control and public health programs. More specifically, the landmark settlement also included the establishment of a national public health education foundation with resources dedicated exclusively to reducing the tobacco epidemic, and thus, is widely recognized as one of MSA's lasting legacies. That entity—the American Legacy Foundation—has been a leader in using national mass media to help increase antitobacco-related knowledge, attitudes, beliefs, and behaviors among youth and adults. In its first 2 years alone (2000–2002), 22% of the overall decline in youth smoking was attributed to Legacy's bold truth® campaign (Farrelly et al. 2005, 2009). Legacy's national efforts have been particularly important in states which failed to invest even the minimum expenditures recommended by CDC in 1999 for tobacco control and prevention programs.

United States v. Philip Morris, Inc. (Department of Justice Case)

On September 22, 1999, the U.S. Department of Justice (DOJ) filed a civil suit against the major U.S. tobacco companies in the U.S. District Court for the District of Columbia (Douglas et al. 2006; Guardino et al. 2007). The 11 defendants in this case were: Philip Morris, Inc., now Philip Morris USA, Inc. ("Philip Morris"); R.J. Reynolds Tobacco Co., now Reynolds American ("R.J. Reynolds" or "RJR"); Brown & Williamson Tobacco Co., now part of Reynolds American ("Brown & Williamson" or "B&W"); Lorillard Tobacco Company ("Lorillard"); the Liggett Group, Inc. ("Liggett"); American Tobacco Co., merged with Brown & Williamson, which is now part of Reynolds American ("American Tobacco"); Philip Morris Cos., now Altria ("Altria"); B.A.T. Industries p.l.c. ("BAT Ind."), now part of BATCo, British American Tobacco (Investments) Ltd. ("BATCo"); The Council for Tobacco Research—U.S.A., Inc. ("CTR"); The Tobacco Institute, Inc. ("TI"). In the suit, DOJ alleged that the tobacco industry conspired to defraud the public by knowingly producing harmful and addictive products and by deliberately misrepresenting the risks of their products, in violation of the *RICO* Act (Douglas et al. 2006; Guardino et al. 2007). DOJ also originally sought to recover tobacco-related medical costs paid by the federal government; but in 2000 the district court dismissed the medical-recovery claims (*U.S. v. Philip Morris Inc.,* 116 F. Supp. 2d 131 (D.D.C. 2000)). The relief the government sought under the *RICO* statute included a permanent injunction to restrain the tobacco industry from committing future fraud and misrepresen-

tation; and an order compelling the cigarette manufacturers to disgorge the ill-gotten profits from their unlawful conduct. During the trial an appellate court ruled in 2005 that disgorgement of the defendants' proceeds was not permitted as a remedy under the civil provisions of the *RICO* Act (*U.S. v. Philip Morris USA Inc., 39*6 F.3d 1190 (D.C. Cir. 2005)). The appellate court later ruled, based on the 2005 disgorgement decision, that other monetary remedies, such as smoker cessation programs and a counter-marketing campaign, were also not available under the civil provisions of the *RICO* statute (*U.S. v. Philip Morris USA Inc.,* 566 F.3d 1095 (D.C. Cir. 2009) (per ciriam)).

The trial was split into a liability phase, which began on September 21, 2004, nearly 5 years after DOJ had filed the suit, and a remedies phase, which began on May 2, 2005 (Guardino et al. 2007). Presentation of evidence ended on June 2, 2005, and closing arguments ended on June 9, 2005 (Guardino et al. 2007). Not including subsequent appeals, the case involved "the exchange of millions of documents, the entry of more than 1,000 Orders, and a trial which lasted approximately 9 months with 84 witnesses testifying in open court" (*Philip Morris* 449 F. Supp. 2d at 1).

U.S. District Court Judge Gladys Kessler entered her final opinion and order on August 17, 2006, and found that the tobacco industry defendants violated the *RICO* Act by lying, misrepresenting, and deceiving the public "including smokers and the young people they avidly sought as 'replacement smokers,' about the devastating health effects of smoking and environmental tobacco smoke" (*Philip Morris* 449 F. Supp. 2d at 1). Based on the trial evidence Judge Kessler found that the tobacco industry established an enterprise "to accomplish the following goals: counter the growing scientific evidence that smoking causes cancer and other illnesses, avoid liability verdicts in the growing number of plaintiffs' personal injury lawsuits against Defendants, and ensure the future economic viability of the industry" (*Philip Morris* 449 F. Supp. 2d at 34).

Judge Kessler found the tobacco industry liable for perpetrating seven fraudulent schemes. The findings of this case have had a profound and continuing impact on public opinion and public policy. The *Tobacco Control Act* incorporates as congressional findings of fact Judge Kessler's determinations that "the major United States cigarette companies continue to target and market to youth," that the companies sought to "encourage youth to start smoking subsequent to the signing of the Master Settlement Agreement in 1998," and that they "have designed their cigarettes to precisely control nicotine delivery levels and provide doses of nicotine sufficient to create and sustain addiction while also concealing much of their nicotine-related research" (*Tobacco Control Act* 2009, §2(47)

– (49)). The Sixth Circuit cited Judge Kessler's findings of facts extensively in its 2012 decision upholding the constitutionality of several key provisions (although striking down other provisions) of the statute (*Discount Tobacco City & Lottery, Inc. v. United States,* 674 F.3d 509 (6th Cir. 2012, *cert. denied,* 133 S. Ct. 1966 (2013)). A summary of Judge Kessler's monumental 1,700-page Opinion has been completed, primarily using a compilation of select quotes from the Opinion (Tobacco Control Legal Consortium 2006). Specifically, Judge Kessler found that the tobacco industry defendants had:

- The tobacco industry defendants have *"Publicly denied, distorted, and minimized the hazards of smoking for decades"* (*Philip Morris* 449 F. Supp. 2d at 146). In this section of the Opinion, Judge Kessler explains that the evidence shows that the Defendants (see footnote[a]) knew for fifty years or more that cigarette smoking caused disease, but repeatedly denied that smoking caused adverse health effects ("The Hazards of Smoking," Tobacco Control Legal Consortium 2006).

- *"Since the 1950s, Defendants have researched and recognized, decades before the scientific community did, that nicotine is an addictive drug, that cigarette manufacturers are in the drug business, and that cigarettes are drug delivery devices."* In this section of the Opinion, Judge Kessler discusses the evidence that for over 40 years, the Defendants' research had shown that the nicotine in tobacco causes cigarette smoking to be addictive. Judge Kessler addresses the evidence that the Defendants not only publicly denied that smoking is addictive but also withheld information about their research from the American public, the government, and the public health community, including the United States Surgeon General. Judge Kessler explains that the evidence shows the Defendants acted this way to maintain profits by keeping people smoking and attracting new consumers, to avoid liability, and to prevent regulation of the industry ("Addiction," Tobacco Control Legal Consortium 2006) (*Philip Morris* 449 F. Supp. 2d at 208).

- *"Defendants have designed their cigarettes to precisely control nicotine delivery levels and provide doses of nicotine sufficient to create and sustain addiction."* In this section of the Opinion, Judge Kessler discusses evidence showing that the Defendants control the nicotine levels in cigarettes to ensure that smokers become addicted and stay addicted. Judge Kessler explains that, although the Defendants deny publicly that they manipulate or control the nicotine levels, the facts prove otherwise ("Nicotine Levels," Tobacco Control Legal Consortium 2006) (*Philip Morris* 449 F. Supp. 2d at 309).

- Defendants falsely marketed and promoted low tar/light cigarettes as less harmful than full flavor cigarettes in order to keep people smoking and sustain corporate revenues" (*Philip Morris* 449 F. Supp. 2d at 430). In this section of the Opinion, Judge Kessler explains that, since the 1970s, Defendants have misled consumers into believing that so-called "low tar" and "light" cigarettes are healthier than other cigarettes and are an acceptable alternative to quitting. The Defendants do this even though they have known for decades that light cigarettes offer no clear health benefit. Judge Kessler describes how the Defendants dramatically increased their sales by exploiting consumers' belief that light cigarettes are less harmful, while claiming falsely that their marketing is based only on smokers' preference for a lighter taste. Judge Kessler finds that the Defendants are continuing to make these false and misleading claims in order to reassure smokers and dissuade them from quitting ("Light Cigarettes," Tobacco Control Legal Consortium 2006).

- *"The evidence is clear and convincing – and beyond any reasonable doubt – that Defendants have marketed to young people twenty-one and under while consistently, publicly, and falsely, denying they do so"* (*Philip Morris* 449 F. Supp. 2d at 391). In this section of the Opinion, Judge Kessler discusses the evidence showing that the Defendants tracked youth behavior and used the information to create highly sophisticated marketing campaigns to get young people to start smoking and continue smoking. Judge Kessler explains that the Defendants sought to remain profitable by bringing new, young smokers into the market to replace those who die or quit ("Marketing to Youth," Tobacco Control Legal Consortium 2006).

- Defendants' statements about secondhand smoke sought "to deceive the public, distort the scientific record, avoid adverse findings by government agencies, and forestall indoor air restrictions" (*Philip Morris* 449 F. Supp. 2d at 693). In this section of the Opinion, Judge Kessler explains that the evidence shows that the Defendants have long known that secondhand smoke, or environmental tobacco

smoke, is hazardous to nonsmokers and that Defendants have understood how this information could affect the tobacco industry's profitability. Judge Kessler describes the steps the Defendants took, after promising to support objective research on the issue, to undermine independent research efforts, to fund industry-friendly research, and to suppress and trivialize unfavorable research results. Judge Kessler emphasizes that the evidence shows that the Defendants continue to deny the extent to which secondhand smoke is hazardous to nonsmokers ("Secondhand Smoke," Tobacco Control Legal Consortium 2006) (*Philip Morris* 449 F. Supp. 2d at 208).

- *"Defendants attempted to and, at times, did prevent/stop ongoing research, hide existing research, and destroy sensitive documents in order to protect their public positions on smoking and health, avoid or limit liability for smoking and health related claims in litigation, and prevent regulatory limitations on the cigarette industry"* (*Philip Morris* 449 F. Supp. 2d at 801). In this section of the Opinion, Judge Kessler discusses the evidence that for over 50 years, the Defendants tried to protect themselves from litigation and regulation by (1) suppressing and concealing scientific research, (2) destroying documents, and (3) shielding other documents from public view by asserting that they were "privileged" and protected by law. Judge Kessler explains that the Defendants' destruction of documents makes it impossible to know what materials once existed ("Suppression of Information," Tobacco Control Legal Consortium 2006).

Based on these findings, Judge Kessler determined that they were reasonably likely to continue engaging in fraud and deceit, and accordingly ordered a number of remedies (*Philip Morris* 449 F. Supp. 2d at 908). The specific remedies included prohibiting them from using brand descriptors (such as light, low-tar, mild, ultra light, and natural), which portray a healthier cigarette; requiring them to issue public "corrective statements" on the health consequences of smoking, cigarette addiction, industry manipulation of cigarettes as nicotine delivery devices, and the hazards of light and low-tar cigarettes; extending the defendants' obligation to maintain the Minnesota depository and their online document web/sites for tobacco documents for 15 additional years; and permanently enjoining (i.e., prohibiting) the defendants from "making, or causing to be made in any way, any material, false, misleading, or deceptive statement or representa-

tion. . . that is disseminated to the United States public and that misrepresents or suppresses information concerning cigarettes" (*Philip Morris* 449 F. Spp. 2d at 938). On May 22, 2009, the D.C. Circuit upheld Judge Kessler's findings of fact, her determination of liability, and the majority of the remedies she ordered, and on June 28, 2010, the Supreme Court declined to accept review of the case, exhausting the cigarette companies' appeals (*Philip Morris* 566 F.3d, 2009, *cert. denied*, 130 S. Ct. 3501).

The Court of Appeals affirmed Judge Kessler's determinations that the cigarette manufacturers engaged in deliberate deception, with "specific intent" to defraud consumers (*Philip Morris* 566 F.3d, 2009, *cert. denied*, 130 S. Ct. 3501). In rejecting the companies' claims that their deliberately false and misleading statements were protected First Amendment "free speech," the D.C. Circuit stressed that the companies "knew of their falsity at the time and made the statements with the intent to deceive," and observed, "we are not dealing with accidental falsehoods, or sincere attempts to persuade; Defendants' liability rests on deceits perpetrated with knowledge of their falsity" (*Philip Morris* 566 F.3d, 2009, *cert. denied*, 130 S. Ct. 3501). Based on the cigarette companies' demonstrated "proclivity for unlawful conduct," the D.C. Circuit substantially affirmed Judge Kessler's remedies (*Philip Morris* 566 F.3d, 2009, *cert. denied*, 130 S. Ct. 3501).

In 2011, the cigarette companies asked the district court to vacate its findings of fact and remedies (*Philip Morris* 449 F. Supp. 2d at 1), claiming that due to the *Tobacco Control Act* (2009), future fraud and deception was no longer possible. The lower court decisively rejected this motion, observing that "FDA rulemaking is not designed to prevent future racketeering activity covered by *RICO*" (*U.S. v. Philip Morris USA, Inc.,* 787 F. Supp. 2d 68 (D.D.C.) *aff'd,* 686 F. 3d 832 (D.C. Cir. 2012)). The Court of Appeals affirmed, observing that because the possibility of *RICO* liability had not deterred the tobacco companies from engaging in fraud and conspiracy, "the district court reasonably found the defendants were not likely to be deterred by the *Tobacco Control Act* either" (*U.S. v. Philip Morris USA, Inc.,* 686 F.3d 832, 837 (D.C. Cir. 2012) ("Vacatur Opinion")). Thus in 2012, the D.C. Circuit affirmed Judge Kessler's 2011 determination that the cigarette companies remain reasonably likely to continue engaging in fraud and deception (*Philip Morris* 686 F.3d 832). The cigarette companies did not seek Supreme Court review.

Also in 2012, the district court ordered specific text for the tobacco companies to disseminate as "corrective statements" (*U.S. v. Philip Morris USA, Inc.,* 907 F. Supp. 2d 1 (D.D.C. 2012) ("Corrective Statement

Decision"), *appeal docketed,* No. 13-5028 (D.C. Cir. Jan. 30, 2013)). The statements address five specific subjects. As samples, the addiction and nicotine-manipulation statements read:

> A Federal Court has ruled that the Defendant tobacco companies deliberately deceived the American public about the addictiveness of smoking and nicotine, and has ordered those companies to make this statement. Here is the truth:
>
> - Smoking is highly addictive. Nicotine is the addictive drug in tobacco.
> - Cigarette companies intentionally designed cigarettes with enough nicotine to create and sustain addiction.
> - It's not easy to quit.
> - When you smoke, the nicotine actually changes the brain—that's why quitting is so hard. (*Philip Morris,* 686 F.3d 832).
>
> A Federal Court has ruled that the Defendant tobacco companies deliberately deceived the American public about designing cigarettes to enhance the delivery of nicotine, and has ordered those companies to make this statement. Here is the truth:

> - Defendant tobacco companies intentionally designed cigarettes to make them more addictive.
> - Cigarette companies control the impact and delivery of nicotine in many ways, including designing filters and selecting cigarette paper to maximize the ingestion of nicotine, adding ammonia to make the cigarette taste less harsh, and controlling the physical and chemical make-up of the tobacco blend.
>
> When you smoke, the nicotine actually changes the brain—that's why quitting is so hard (*U.S. v. Philip Morris USA, Inc.,* 787 F. Supp. 2d 68 (D.D.C. 2011), *aff'd,* 686 F.3d 832 (D.C. Cir. 2012)). The statements are to be disseminated via print and online newspaper advertisements; TV spots; package "onserts"; and the companies' websites (*Philip Morris USA* 449 F. Supp. 2d at 938). They may also be delivered through countertop and header point-of-sale displays, although this would be limited to "participating retailers" in the cigarette companies' retailer-incentive programs (*Philip Morris,* 566 F.3d 1095 (D.D. Cir. 2009) (per curiam)). The cigarette companies have filed an appeal from the corrective-statement decision, contending that it violates their First Amendment free-speech rights.

Clinical and Educational Approaches for Tobacco Cessation

This section reviews the current status of clinical and educational approaches for tobacco cessation. These interventions are reviewed in greater detail within Appendix 14.4 and the efficacy of various pharmaceutical treatments are reviewed in Appendix 14.5 (both available online at www.surgeongeneral.gov). Although the health benefits of smoking cessation have long been documented (USDHEW 1979; USDHHS 1990, 2004; Doll 2004; Doll et al. 2004; Jha et al. 2013), the 2006 NIH State-of-the-Science Conference on Tobacco Use singled out the need to build consumer demand for and more widespread use of proven cessation services as having untapped potential for increasing their reach, use, and impact (Backinger and O'Connell 2007). The 2007 IOM report (Bonnie et al. 2007) emphasized the need to expand treatment use by aligning cessation treatments and the policies that support their use and delivery across all levels of health care and public health systems, and calls for a coordinated, comprehensive strategy to dramatically increase the number of smokers who quit each year (Abrams 2007). The IOM report further stated "systems integration is arguably the single most critical missing ingredient needed to maximize the as yet unrealized potential to significantly increase population cessation rates" (Bonnie et al. 2007, p. 376). Appendix 14.4 of this report provides a review of the current status of efforts to implement these recommendations for a more coordinated and comprehensive strategy for population-based smoking cessation. As reviewed in Appendix 15.1, recent studies model the impact on population quit rates with an integrated implementation of the multiple recommended policies (Levy et al. 2010). Based on a set of assumptions and the implementation of all five policies in combination, this model projected an increase in the baseline population quit rate by 150% (e.g., from about 4.3% baseline up to about 10.9%) (Levy et al. 2010). Although this projected increase has been viewed as optimistic, the

model results suggest that more complete implementation of evidence-based cessation interventions could have large population impacts.

Health Care Policies

In 2009, the U.S. Congress passed the *American Recovery and Reinvestment Act,* which included the *Health Information Technology Economic and Clinical Health (HITECH) Act.* One of the major goals of the HITECH Act was to accelerate the adoption of electronic health records (EHR) through the creation of Medicaid and Medicare EHR Incentive Programs with payments totaling $27 billion over 10 years to "meaningful EHR users" (Office of the National Coordinator for Health Information Technology 2011). In line with the 2008 U.S. Public Health Service recommendations (Fiore et al. 2008), one of the 15 core objectives comprising "meaningful use" in Stage 1 is to "record smoking status for patients 13 years or older" (CMS 2012a). Currently, few studies address the influence of EHR tobacco screening on health care provider and patient behaviors related to smoking cessation (Boyle et al. 2011), but some have shown increases in delivery of the "5A's" (Szpunar et al. 2006; Bentz et al. 2007) or other provider counseling (Spencer et al. 1999), referrals to a quitline (Bentz et al. 2007; Sherman et al. 2008; Linder et al. 2009), and in the proportion of patients setting a quit date (McCullough et al. 2009). Since January 2011, 47 states and territories have launched their Medicaid EHR Incentive Programs (CMS 2012b).

More recent policy changes have focused on improving coverage of tobacco cessation treatment to prevent tobacco-related disease. The 2010 *Patient Protection and Affordable Care Act* included tobacco cessation in several sections related to disease prevention, including prohibiting states from excluding coverage for tobacco-cessation drugs from their Medicaid programs, providing coverage without cost-sharing of tobacco dependence treatment for pregnant women covered by Medicaid, and eliminating copayments for Medicare preventive services that are rated A or B by the U.S. Preventive Services Task Force (USPSTF), including tobacco use counseling for all adults (Koh and Sebelius 2010). An example of this shift to prevention is also evident in the August 2010 Medicare expansion of coverage of smoking and tobacco use cessation counseling to beneficiaries who use tobacco and who do not have signs or symptoms of tobacco-related disease (CMS 2011).

Implementation of the expanded coverage of cessation treatment mandated by Affordable Care Act varies significantly across private health insurance contracts. A 2012 report highlights conflicting language within individual insurance contracts on coverage of tobacco cessation, lack of specificity in scope of coverage in many contracts, inconsistency with USPSTF recommendations, cost-sharing for tobacco cessation counseling, and access restrictions (Kofman et al. 2012).

Although the importance of programs and policies to increase the access to evidence-based cessation assistance and to more fully implement the USPSTF recommendations have been noted in several major reviews (Backinger and O'Connell 2007; Bonnie et al. 2007; Backinger et al. 2010), concerns have been raised that the public resources needed to implement these recommendations could be more efficiently and cost-effectively used to promote successful cessation in other ways such as supporting community-based advocacy efforts to reduce the social acceptability of smoking (Chapman and Mackenzie 2010). In raising these concerns, it has been noted that the importance of increasing the success rate in unaided quitting should be recognized in the discussion of the most effective approaches to reduce smoking rates (Chapman and Mackenzie 2010; Chapman and Wakefield 2013). In the National Tobacco Cessation Collaborative's Consumer Demand Roundtable (Backinger et al. 2010), the important role of combining implementation of the USPSTF recommendations with public policy (McGoldrick and Boonn 2010) efforts, including excise taxes, smoke-free policies (Hyland and Cummings 2010), and media campaigns (Czarnecki et al. 2010) were recognized. This combined and comprehensive approach is considered in more detail in the following section.

Comprehensive Statewide Tobacco Control Programs

Educational and community-wide approaches have long been used in tobacco control to reduce and prevent the initiation of tobacco use (USDHHS 2000). Over time, these initiatives have evolved in their approach, moving toward more comprehensive programs. Comprehensive tobacco control programs are funded as ongoing public health efforts to implement and coordinate evidence-based population-level interventions, (1) prevent initiation of tobacco among youth and young adults, (2) promote quitting among adults and youth (3) eliminate exposure to secondhand smoke (4) identify and eliminate tobacco-related disparities among population groups (CDC 1999, 2007a). A comprehensive approach—one that optimizes synergies from applying a mix of educational, clinical, regulatory, economic, and social strategies—has

been established as the guiding principle for controlling tobacco use. In the United States, comprehensive tobacco control programs are typically organized and funded at the state level, with capabilities such as administrative support, surveillance, and program monitoring and evaluation (CDC 1999, 2007a).

Concurrent with the implementation of multiple community-based intervention trials, a broad national movement to reduce tobacco use began to emerge in the 1980s (USDHHS 2000). However, unlike the community-based intervention trials, the movement and the large-scale interventions that developed from it were not structured around research hypotheses and preplanned evaluation designs. Instead, the movement was characterized by community mobilization at the national, state, and local levels. In addition, the idea that multiple educational (including paid media), taxation, legislative, and regulatory approaches are needed to address the social, economic, and environmental influences on tobacco use was underpinned by established theories and principles of health promotion (Kickbusch 1989; Allison and Rootman 1996; Downie et al. 1996; Nutbeam 1998).

Following the establishment of statewide tobacco control programs in Minnesota in 1985 and California in 1989, comprehensive tobacco control programs began to develop during the 1990s (USDHHS 1994). ASSIST was established in 17 states in 1991 (NCI 2005), and the SmokeLess States coalitions, funded by the Robert Wood Johnson Foundation, were established in 19 states during 1993–2004 (Gerlach and Larkin 2005; NCI 2005). In 1994, CDC funded 32 non-ASSIST states and the District of Columbia through its Initiatives to Mobilize for the Prevention and Control of Tobacco Use (IMPACT) program (USDHHS 2000). In 1999, CDC launched the National Tobacco Control Program, which provides financial support and technical assistance for tobacco control programs in all 50 states, the District of Columbia, 8 U.S. territories, 6 national networks, and 8 tribal support centers (CDC 2007). From 2000–2012, Legacy funded a range of competitive grant initiatives including Youth Empowerment (19 states), Priority Populations (over 84 funded programs in over 40 States), Legacy Evaluation Research Network grants, Small Innovative Grants, CDC Match Grants, and Cessation Quitline Grants totaling approximately $120 million. Many of these grants directly supported comprehensive state and local tobacco control programs.

All 50 states and the District of Columbia currently have state tobacco control programs that are funded through various revenue streams, including tobacco excise tax revenues, tobacco industry settlement payments, state general funds, the federal government, and nonprofit organizations (CDC 2012e). Increases in the excise tax

on cigarettes from either voter initiatives or state legislation were the mechanism to fund early statewide tobacco control programs. California's program was funded by voter initiatives (1989), as were programs in Massachusetts (1993), Arizona (1994), and Oregon (1996). Many states have also used MSA and other settlement funds to finance statewide programs. In 1997, Florida began a comprehensive program paid for, in part, by funding from the state's settlement with the tobacco industry. Similarly, Mississippi, Texas, and Minnesota used some funds from their individual settlements with the tobacco industry for tobacco control programs. Many of the 46 other states that signed the 1998 MSA also used some settlement funds to finance state-level tobacco control programs; however, this was not specified in the agreement (Campaign for Tobacco-Free Kids 2012a).

States that have made larger investments in comprehensive tobacco control programs have seen larger declines in cigarettes sales than the nation as a whole, and the prevalence of smoking among adults and youth has declined faster, as spending for tobacco control programs has increased (CDC 2007). Figure 14.7 shows the total funding for state tobacco control programs and the prevalence of current smoking among U.S. high school students during 1986–2009. In Florida, a comprehensive program reduced the prevalence of smoking during 1998–2003 among middle and high school students by 50% and 35%, respectively (Bauer et al. 2000). Similarly, during 2001–2010, declines in the prevalence of both adult and youth smoking in New York state outpaced declines nationally, resulting in smoking-attributable personal health care expenditures in 2010 that were $4.1 billion less than they would have been had the prevalence remained unchanged (RTI International 2011). Experience also shows that the longer the states invest in comprehensive tobacco control programs, the greater and faster the impact. In California, which has the nation's first and longest-running comprehensive state tobacco control program, the prevalence of cigarette smoking among adults declined from 22.7% in 1988 to 11.9% in 2010 (California Department of Public Health 2011).

Evidence reviews in prior reports (USDHHS 2000, 2006, 2012), the Community Preventive Services Task Force (Task Force on Community Preventive Services 2005), and IARC Handbooks on Cancer Prevention (IARC 2009; 2011) have documented the efficacy of many of the individual interventions which are combined within comprehensive state tobacco control programs. As noted above in the section on "Tobacco Control Policies," taxation, smokefree indoor air policies, and other policies are among the most effective tobacco control strategies. However, in the evaluation of individual state tobacco control

Figure 14.7   Total funding for state tobacco control programs, 1986–2009 (adjusted to fiscal year 2010 dollars)
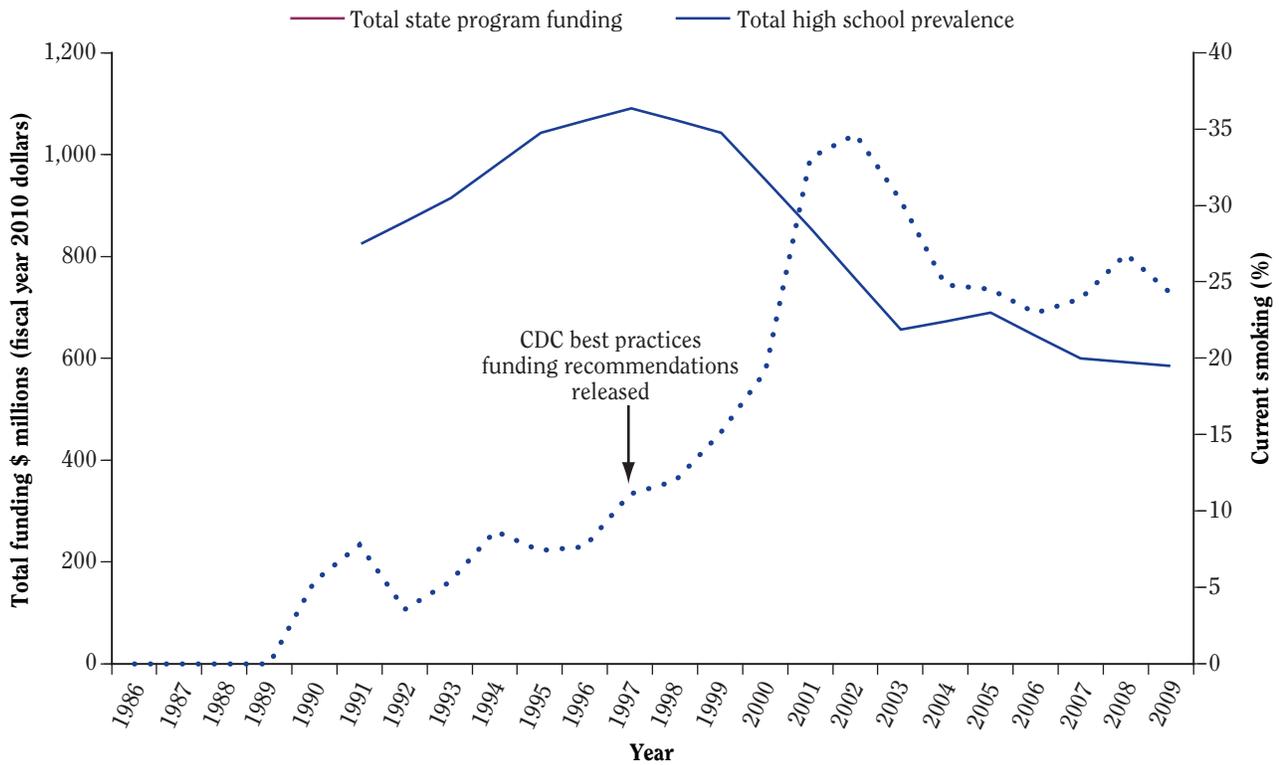
Source: Project ImpacTEEN; University of Illinois at Chicago; CDC, Youth Risk Behavior Survey, 1991–2009. Current smoking defined as high school students who smoked on ≥1 of the past 30 days—United States.
Note: **CDC** = Centers for Disease Control and Prevention.

programs where multiple policies and program initiatives are combined, it is often difficult to assess the relative contribution of each one. Nonetheless, several studies have quantified the impact of the policies and programs implemented in these comprehensive tobacco control programs. Table 14.4 summarizes available outcome data for some notable statewide programs, including Arizona, California, Maine, Massachusetts, Minnesota, New York, and Oregon. Additionally, many state programs have experienced, and are facing, substantial cuts to tobacco control funding, resulting in the near elimination of tobacco control programs in those states. In 2010, states were appropriating only 2.4% of their state tobacco revenues for tobacco control, and reaching the CDC's *Best Practices for Comprehensive Tobacco Control Programs* (*Best Practices 2007*) funding goal would have required an additional 13% of tobacco revenues, or $3.1 billion of the $24 billion collected (CDC 2012e). Table 14.5 shows the level of tobacco-related revenues and appropriations, by state, during 1998–2010. In fiscal year 2013, Alaska

was the only state to fund its tobacco control program at the CDC-recommended level (Campaign for Tobacco-Free Kids 2012a).

Best Practices 2007 outlined the elements of an evidence-based comprehensive state tobacco control program (CDC 2007). The report recommended four goals for comprehensive statewide tobacco control programs: (1) preventing initiation among youth and young adults; (2) promoting quitting among adults and youth; (3) eliminating exposure to secondhand smoke; and (4) identifying and eliminating tobacco-related disparities among population groups. *Best Practices 2007* also described an integrated programmatic structure for implementing interventions proven to be effective, which includes the following overarching intervention components—state and community interventions, health communication interventions, and cessation interventions. Although these individual intervention components are effective, evidence from the most effective statewide programs indicates that these interventions can have greater impact when they work in concert

Table 14.4   Summary of selected state program components and outcomes

State	Program	Funding	Components	Outcome	Citation
Arizona	• Tobacco Education and Prevention • Program 1997–Present	Proposition 200 in 1994 increased cigarette tax	• Mass media and sponsorships • Local lead agency grants for school education, cessation, protection from environmental tobacco smoke • Quitlin • Statewide projects and evaluation	• Prevalence of current smoking decreased from 23.1% in 1996 to 18.3%in 1999 (p≤0.05) • Prevalence of smokers asked about smoking status by health care provider increased from 30.9% in 1996 to 43.7%in 1999 (p≤0.05) • Percentage of smokers reporting being asked about smoking status and advised to quit increased from 25.1% in 1996 to 36.7% in 1999 (p≤0.05)	Wakefield and Chaloupka 2000; CDC 2001
Arizona	• FCP • 1996–2001 • Tucson only	Robert Wood Johnson Foundation	• Community-wide comprehensive program aimed at youth tobacco prevention	• 27% reduction in adolescent smoking between 1996–1999	Levy et al. 2006
California	• California Tobacco Control Program • 1988–Present	1988 California passed Proposition 99 mandating establishment of California Tobacco Control Program; funded by an increased excise tax on cigarettes	• Cessation tools • Mass media campaign • Community program • Smokefree policies	• Per capita cigarette consumption decreased 61% in fiscal years 1989–1990 and 2006–2007 • Adult smoking prevalence decreased from 26.7% in 1987 to 16.7% in 1995; prevalence in 2010 was 11.9% • 2000–2010 youth smoking prevalence decreased from 21.6–13.8% • Lung and bronchus cancer rates declined almost 4 times faster than nationwide rates 1988–2004	USDHHS 2000; Wakefield and Chaloupka 2000; "California Tobacco Control Program Priorities" 2010; Riordan 2012
Maine	• Maine Tobacco Prevention and Control • Program 1997–Present	Funded by legislative bill, H.P. 1357, which increased state excise taxes for cigarettes	• Counter-marketing and public awareness tobacco treatment programs • Community programs • Enforcement programs • School programs • Smokefree policies • Evaluation	• High school smoking prevalence decreased from 39.2% in 1997 to 15.2%in 2011	USDHHS 2000; "History of the Partnership For a Tobacco-Free Maine" 2008; "Maine Policies and Programs" 2008; Riordan 2012

Table 14.4 Continued

State	Program	Funding	Components	Outcome	Citation
Massachusetts	• Tobacco Cessation and Prevetion Program • 1993–Present	1993 voter-approved initiative increased cigarette excise tax by $0.25 and $0.25 increase on wholesale price of smokeless tobacco	• Mass media • School programs • Community programs, including cessation and protection from environmental tobacco smoke • Statewide services, including quitline	• Per capita cigarette consumption decreased by 36% between 1992–2000, compared to 16% nationwide • High school student prevalence of current smoking decreased 27% in 1995–2001 • Prevalence of adult current smoking decreased from 22.6% in 1993 to 17.9% in 2000	USDHHS 2000; Wakefield and Chaloupka 2000; Riordan 2012
Minnesota	• Minnesota Tobacco Use Prevent and Local Endowment • 1975–Present	Portion of funding from the Master Settlement Agreement and increased excise taxes		• Adult smoking prevalence decreased from 22.1% in 1999 to • 16.1% in 2010 High school students reporting any tobacco use in the past 30 days decreased from 38.7% in 2000 to 27.0% in 2010 • No change in prevalence of cigar use or smokeless tobacco use in 2000–2008, among high school students	USDHHS 2000; Results from the Minnesota Youth Tobacco and Asthma Survey" 2008; "Teens and Tobacco in Minnesota the View from 2008; "Tobacco Use in Minnesota: 2010 Update" 2011
New York	• New York State Department of Health Tobacco Control Program • 2000–Present	Funding generated from tax revenue and the Master Settlement Agreement	• Cessation tools • Mass media campaigns • Community programs	• 53.5% reduction in high school current smoking in 2000–2010 • Adult smoking decreased from 21.6% in 2000 to 15.5% in 2010	"Youth Prevention and Adult Smoking in New York" 2011; Riordan 2012; USDHHS 2012
Oregon	• Tobacco Prevention and Education Program • 1996–Present	Measure 44 increased excise tax on cigarettes	• School programs • Statewide and community • Quitline projects	• Adult smoking prevalence decreased from 23.4% in 1996 to 21.9% in 1998	USDHHS 2000; Wakefield and Chaloupka 2000; Tobacco Prevention and Education Program 2010

Note: **CDC** = Centers for Disease Control and Prevention; **FCP** = Full Court Press; **USDHHS** = U.S. Department of Health and Human Services.

Table 14.5   Total state tobacco-related revenues (in millions of dollars)—United States, 1998–2010

State	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	Total (1998 2010 −
Alabama	68.3	65.4	227.7	167.3	176.2	153.9	166.1	252.6	245.3	243.0	247.8	252.9	229.9	**2,496.3**
Alaska	28.4	58.7	62.7	61.6	64.1	60.0	62.4	70.1	77.4	84.2	98.6	99.8	92.4	**920.5**
Arizona	166.1	163.1	308.3	247.8	264.0	299.3	366.9	376.1	379.1	440.8	504.5	489.8	427.9	**4,433.7**
Arkansas	83.3	81.5	79.3	222.6	134.2	131.5	180.1	179.8	179.8	172.3	183.0	207.3	251.9	**2,083.7**
California	61.2.1	1,431.6	1,856.1	1,884.2	1,977.9	1,783.7	1,823.7	1,837.8	1,837.8	1,773.6	1,787.0	1,826.6	1,601.2	**21,966.3**
Colorado	59.6	122.8	137.3	141.4	151.1	133.5	139.7	202.4	202.4	285.3	299.5	302.0	269.5	**2,530.2**
Connecticut	120.6	204.5	215.2	227.6	282.6	357.9	392.9	372.4	372.4	366.9	470.8	462.3	509.2	**4,358.8**
Delaware	22.7	42.5	47.1	50.3	55.2	58.1	96.2	106.4	106.4	110.5	147.4	156.2	157.0	**1,157.5**
District ofColumbia	17.5	45.5	52.0	53.2	58.3	55.5	59.6	59.0	59.0	58.6	66.0	80.5	70.9	**734.7**
Florida	1,000.0	959.5	1,059.3	1,163.1	1,192.0	966.9	785.8	815.8	815.8	819.2	803.1	808.6	1,598.9	**12,788.7**
Georgia	85.1	199.1	224.2	230.8	246.5	222.3	370.5	382.9	382.9	366.8	370.6	380.1	340.4	**3784.8**
Hawaii	32.4	66.7	72.5	88.3	105.6	106.0	115.4	121.5	121.5	125.3	157.6	164.8	170.8	**1,447.8**
Idaho	25.0	41.0	45.3	45.4	48.6	45.3	68.6	68.3	68.3	69.4	74.7	74.9	65.5	**739.3**
Illinois	457.2	700.7	745.6	752.9	786.7	912.6	1,021.0	934.8	934.8	884.9	904.5	902.8	833.6	**10,742.6**
Indiana	118.1	210.6	230.4	233.9	251.6	456.5	458.0	458.0	458.0	477.9	653.1	655.7	583.4	**5,245.6**
Iowa	94.6	132.5	141.0	142.2	148.2	138.5	141.6	142.9	142.9	174.6	304.9	297.4	274.7	**2,273.3**
Kansas	52.6	89.5	97.5	99.5	105.6	164.6	172.7	170.9	170.9	165.7	178.9	179.8	160.5	**1,805.3**
Kentucky	18.1	98.9	112.0	123.5	142.0	123.3	131.2	162.2	16.2.2	284.4	292.9	321.1	390.6	**2,462.0**
Louisiana	83.5	187.0	216.1	215.5	254.3	240.7	272.1	282.8	282.8	263.0	288.6	299.3	260.4	**3,113.7**
Maine	71.7	112.4	119.2	121.1	147.4	139.0	141.0	141.0	141.0	199.7	202.0	201.0	190.9	**1,982.7**
Maryland	128.3	234.0	327.6	335.1	359.3	392.5	406.1	411.6	411.6	405.6	506.7	575.5	546.5	**5,031.7**
Massachusetts	293.1	466.2	491.2	508.7	557.8	675.6	676.6	670.2	670.2	662.8	707.2	877.2	820.3	**8,068.1**
Michigan	525.0	798.3	829.0	846.7	888.5	1,072.7	1,124.6	1,367.4	1,367.4	1,358.7	1,330.3	1,314.8	1,223.3	**14,059.2**
Minnesota	420.6	398.1	500.0	524.0	544.0	428.2	343.9	335.8	335.8	592.5	574.4	560.3	544.9	**6,338.6**
Mississippi	280.0	157.0	245.7	276.1	273.0	213.5	155.4	160.2	160.2	166.1	197.1	184.8	247.0	**2,691.8**
Missouri	106.1	105.0	104.0	487.2	251.7	229.8	242.4	244.3	244.3	235.0	250.4	262.8	231.5	**2,982.6**
Montana	13.5	32.4	36.5	37.5	41.1	41.2	68.9	83.7	83.7	107.9	118.9	117.1	108.4	**913.6**
Nebraska	46.5	47.8	77.7	75.4	84.7	94.0	105.0	104.9	104.9	102.8	113.3	113.8	101.2	**1,194.7**

Table 14.5 Continued

State	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	Total 2010) 1998–
Nevada	55.7	87.3	94.3	98.2	101.0	97.4	160.5	167.9	167.9	166.6	172.5	160.1	143.4	**1,670.6**
New Hampshire	74.0	102.8	129.9	127.9	130.2	134.4	141.0	135.9	135.9	179.0	209.6	243.6	273.9	**2,063.0**
New Jersey	302.2	409.7	793.8	621.8	659.3	815.4	991.7	1027.7	1027.7	999.3	1025.7	1014.2	978.2	**10,653.4**
New Mexico	22.0	48.7	54.8	56.2	60.8	55.0	97.1	98.1	98.1	97.5	105.6	107.5	96.4	**995.0**
New York	656.9	1,226.6	1,421.2	1,775.8	1,965.3	1,744.3	1,764.3	1,749.5	1,749.5	1,709.4	1,792.9	2,244.5	2,061.8	**21,796.9**
North Carolina	44.3	149.6	166.6	180.1	205.5	176.1	186.4	188.0	188.0	376.5	388.8	395.2	391.0	**3,150.0**
North Dakota	22.4	37.9	42.2	42.0	44.4	39.2	41.1	41.5	41.5	43.4	57.3	59.7	52.8	**566.0**
Ohio	275.0	502.0	551.3	568.8	606.2	830.9	847.3	875.8	875.8	1,231.0	1,245.5	1,239.1	1,145.8	**11,234.9**
Oklahoma	65.2	112.1	121.0	124.1	128.8	116.9	121.4	170.9	170.9	264.4	310.1	333.6	310.7	**2,432.5**
Oregon	183.5	226.4	225.9	227.5	237.0	289.5	312.2	290.9	290.9	309.8	312.5	313.4	284.2	**3,512.5**
Pennsylvania	336.5	456.9	771.2	669.4	731.0	1,166.1	1,319.0	1,395.3	1,395.3	1,362.3	1,396.8	1,403.4	1,424.9	**13,801.9**
Rhode Island	61.8	93.5	99.9	102.1	127.9	134.5	156.1	175.5	175.5	161.0	165.3	179.3	182.2	**1,804.5**
South Carolina	31.3	81.9	94.4	96.3	106.9	93.1	99.4	101.7	101.7	98.0	110.0	116.6	102.4	**1,228.4**
South Dakota	19.9	35.6	38.7	39.8	41.6	40.6	48.2	48.6	48.6	65.2	84.8	89.9	81.8	**681.6**
Tennessee	80.8	78.7	334.7	224.6	244.4	246.7	263.6	267.7	267.7	275.3	417.3	463.4	422.1	**3,577.0**
Texas	926.9	1,543.1	1,360.6	1,455.0	1,502.0	1,195.0	966.4	990.7	990.7	1,518.1	1,987.2	1,687.6	1,691.3	**17,832.0**
Utah	42.6	67.1	71.4	67.9	77.9	75.1	81.6	82.7	82.7	82.9	97.4	95.5	90.4	**1,018.0**
Vermont	24.8	42.7	45.8	49.5	53.9	67.6	75.7	72.3	72.3	85.0	95.9	103.3	101.2	**887.9**
Virginia	15.7	109.9	133.0	139.3	156.7	13.8	144.6	241.9	241.9	295.2	298.9	315.2	280.0	**2,555.7**
Washington	258.5	347.0	371.6	361.4	448.8	455.3	453.4	459.3	459.3	542.2	592.9	579.6	545.5	**5,959.3**
West Virginia	34.2	74.3	83.4	86.0	94.0	94.3	153.6	154.5	154.5	159.9	180.9	190.0	175.1	**1,639.6**
Wisconsin	247.7	353.1	359.4	369.1	436.9	415.7	421.6	426.4	426.4	421.9	604.9	714.2	780.6	**5,973.9**
Wyoming	5.8	17.1	18.8	20.5	22.8	21.1	29.5	37.6	37.6	39.2	44.7	46.1	39.6	**379.8**
Total	**8,817.7**	**13,483.2**	**16,044.2**	**16,868.1**	**17,775.9**	**18,134.6**	**18,964.3**	**19,716.3**	**19,716.3**	**21,510.7**	**23,501.5**	**24,264.3**	**23,958.0**	**243,762.5**

Source: Centers for Disease Control and Prevention 2012a.
Note: Adjusted to fiscal year ending June 30. Revenues include state settlement revenues and net state cigarette tax collections. Revenues not reported include excise taxes collected on smokeless tobacco products, local excise taxes, and state or local sales taxes.

with additional components, such as surveillance and evaluation, as well as administration and management, to produce the synergistic effects of a comprehensive tobacco control program.

State and Community Interventions

The history of successful public health practice has demonstrated that the active and coordinated involvement of a wide range of societal and community resources is the foundation of sustained solutions to pervasive problems, like tobacco use (Green and Kreuter 2000; IOM 2002; NCI 2005; CDC 2007; USDHHS 2012). In an evidence-based review of population-based tobacco prevention and control efforts, the Task Force on Community Preventive Services confirmed the importance of coordinated and combined intervention efforts (Zaza et al. 2005). The strongest evidence, demonstrating the effectiveness of many of the population-based approaches that were most highly recommended by the Task Force, comes from studies in which specific strategies for smoking cessation, preventing tobacco use initiation, and eliminating exposure to secondhand smoke are combined with efforts to mobilize communities and integrate these strategies into synergistic and multicomponent efforts (Zaza et al. 2005). Additionally, research has shown the importance of community support, and involvement at the grassroots level, in implementing several of the most highly effective policy interventions, including increasing the unit price of tobacco products and creating smokefree environments (CDC 2007). This community-based intervention model to create a social and legal climate, which cultivates changes in social norms around tobacco use, has now become a core element of comprehensive statewide tobacco control programs (USDHHS 2000, 2012; Mueller et al. 2006; NCI 2006; CDC 2007). The CDC-recommended community-based model to produce durable changes in social norms is based on evidence that strategies with the greatest span will have the largest population impact (USDHHS 2000; Wisotzky et al. 2004; NCI 2005; Bonnie et al. 2007; CDC 2007). Recommendations from evidence-based reviews indicate that more individual focused educational and clinical approaches, with a smaller span of impact, should be combined with population-based efforts at the state and community levels (USDHHS 2000; NCI 2005; Bonnie et al. 2007; CDC 2007).

Statewide programs can provide the skills, resources, and information needed for the coordinated, strategic implementation of effective community programs. For example, educating local community coalitions about the legal and technical aspects of smokefree air ordinances and enforcement can be provided most efficiently through statewide partners, who have experience in providing these services (CDC 2007). Direct funding provided to statewide organizations can also be used to mobilize their organizational assets to strengthen community resources (CDC 2007). Each state's financial and social demographic characteristics have a significant role in their tobacco prevention and control efforts. Statewide efforts can include establishing a strategic plan for comprehensive tobacco control with appropriate partners at the state and local levels; implementing evidence-based policy interventions to decrease tobacco initiation, increase cessation, and protect people from exposure to secondhand smoke; collecting data; and developing and implementing culturally appropriate interventions (CDC 2007).

In addition to statewide programs, communities can also engage in strategies to address the way tobacco is promoted; the time, manner, and place in which it is sold; and how and where it is used, while also changing the knowledge, attitudes, and practices of tobacco users and nonusers (NCI 2005; CDC 2007). Effective community programs involve and influence people in their daily environment (Eriksen 2005; Minkler 2005; NCI 2005; CDC 2007). Therefore, community engagement and mobilization are essential to programs addressing tobacco control, and changing policies that can impact societal organizations, systems, and networks necessitates the involvement of community partners. For example, family and school-based programs when coordinated with community-wide efforts may be useful in the prevention of smoking initiation (USDHHS 2012). During the 1990s, three nationally funded programs—two by the federal government and one by a private foundation—and one federally funded research project helped communities mobilize to reduce tobacco use. The ASSIST, IMPACT, and SmokeLess States programs are examples of community-based interventions that have been successful in achieving tobacco control outcomes among adults and youth (USDHHS 2000, 2004, 2012).

Following the publication of the 2000 Surgeon General's report, Carson and colleagues (2011) published a Cochrane Review on community interventions in tobacco control. This review concluded that community interventions may be effective in preventing the initiation of smoking, and recommended five principles that should be implemented when conducting a community intervention, which are presented in Table 14.6. The 2012 Surgeon General's report also highlighted COMMIT as a community-wide intervention. The COMMIT intervention was a multiyear, randomized control trial, in 10-paired communities across the United States and 1-paired community in Ontario, to assess if community-wide comprehensive programs were effective in increasing, cessation among smokers (COMMIT Research Group, 1995a,b). The

Table 14.6   Five principles for community interventions

1. Use and build upon the knowledge of existing effective programs rather than repeating methods that have had limited success
2. Build flexible programs that can adapt to the variation between communities
3. Pre-test program with members of the target population prior to implementation of the full program
4. Use theoretical constructs to guide development of programs
5. Ensure intended audience is being reached by program

Source: Sowden et al. 2003.

COMMIT program was effective in increasing quit rates in intervention communities for light and moderate smokers, but not for heavy smokers (COMMIT Research Group, 1995a,b). COMMIT demonstrated no differences in smoking behavior, over time, for youth in the intervention communities compared to youth in the control communities; however, the intervention focus was primarily on adults (USDHHS 2012).

In addition to strategies associated with statewide and community-based policies and programs, essential components of a comprehensive tobacco control program also include disparity elimination initiatives and interventions specifically aimed at influencing youth (CDC 2007). Because some populations experience a disproportionate health and economic burden from tobacco use, a focus on eliminating such tobacco-related disparities is necessary. To ultimately eliminate tobacco-related disparities, equity in tobacco prevention and control must be achieved by removing avoidable structural and social barriers and equally implementing tobacco control programs and policies. State capacity and infrastructure, including clear leadership and dedicated resources, are essential to the development and implementation of a strong strategic plan that encompasses the identification and elimination of tobacco-related disparities (CDC 2007). Similarly, because most people who start smoking are younger than 18 years of age, intervening during adolescence is critical (USDHHS 2012). Community programs and interventions should be part of a comprehensive effort, coordinated, and implemented in conjunction with efforts to create tobacco-free social norms, including increasing the unit price of tobacco products, sustaining antitobacco media campaigns, and making environments smokefree (USDHHS 1994, 2012; Bonnie et al. 2007; CDC 2007).

The conceptual framework for state and community interventions, outlined in *Best Practices 2007,* has been used to develop the current generation of statewide comprehensive tobacco control programs (CDC 2007).

However, it is important to note that most comprehensive programs currently in place have not been able to fully implement all recommended components. Policy and regulation components are especially hampered, because many state and local actions are limited by federal mandates and preemptions. Moreover, only two states, California and Massachusetts, have implemented comprehensive tobacco control programs for sufficient time to provide evaluation data on the overall efficacy of the emerging comprehensive model (CDC 2007; USDHHS 2012).

Health Communication Interventions

Mass-reach health communication interventions can be powerful tools for preventing the initiation of tobacco use, promoting and facilitating cessation, and shaping social norms related to tobacco use and exposure to secondhand smoke (CDC 2007). Typically, effective health communication interventions and countermarketing strategies employ a wide range of efforts: paid television, radio, out-of-home (e.g., billboard, transit), print, and digital advertising at the state and local levels; media advocacy through public relations/earned media efforts, such as press releases/conferences, social media, and local events; health promotion activities, such as working with health care professionals and other partners promoting quitlines, and funding permitting, offering free nicotine replacement therapy such as nicotine patches, gums, or lozenges; and efforts to reduce or replace tobacco industry sponsorship and promotion as well as to decrease movie smoking imagery (CDC 2007). Innovations in health communication interventions include the ability to target and engage specific audiences through multiple communication channels such as online video, mobile Web site, and smartphone and tablet applications. However, these platforms should be considered complements to, not substitutes for, traditional mass media (NCI 2008; USDHHS 2012). Evaluation of each digital media effort must be conducted to determine effectiveness and to help build an evidence base.

Effective messages that are targeted appropriately can stimulate public support for tobacco control interventions and create a supportive climate for policy and programmatic community efforts (USDHHS 2000). Young people are particularly vulnerable to social and environmental influences to use tobacco; messages and images that make tobacco use appealing to them are everywhere (USDHHS 2000; McAfee and Tynan 2012). For example, youth and young adults see smoking in their social circles, movies, video games, Web sites, and throughout the communities where they live. Nonsmoking adolescents exposed to tobacco advertising and promotional campaigns are significantly more likely to become young adult smokers (Lovato et al. 2003; Gilpin et al. 2007). Moreover, youth who are exposed to images of smoking in movies are more likely to smoke; those who get the most exposure to onscreen smoking are about twice as likely to begin smoking as those who get the least exposure (USDHHS 2012). Furthermore, evidence indicates adults are also influenced by tobacco promotion, particularly at the point of purchase (Clattenburg et al. 2012). Because youth and young adults continue to be heavily exposed to protobacco media—including images of smoking in movies, advertising, and promotion—public education campaigns are needed to prevent tobacco use initiation and to promote cessation (CDC 2007; USDHHS 2012).

In addition, because smoking in movies is such a major source of protobacco media exposure, if smoking in PG-13-rated movies was reduced to the fifth percentile of exposure, youth smoking rates could be reduced by 18% (Sargent et al. 2012). The magnitude of this effect would be similar to an increase in the price of cigarettes from about $6.00 per pack to over $7.50 average price. However, since onscreen smoking imagery continues in home media (e.g., broadcast, cable, satellite, and on-demand; on DVD and Blu-ray and on streaming media), there is a continuing need for public education campaigns to prevent tobacco use initiation.

Although the relative effectiveness of specific message concepts and strategies varies by target audience, research shows that countermarketing and other media approaches must have sufficient reach, frequency, and duration to be successful (Terry-McElrath et al. 2005; CDC 2006). Mass media campaigns have been a particularly successful component of prevention efforts in tobacco control for decades; able to reach large proportions of the population, mass media messages have the potential to influence not only individual behaviors but also social norms and institutional policies, which in turn can shape patterns of population-wide tobacco use (Hopkins et al. 2001; Hornick 2002). The first example of a successful campaign resulted from a legal challenge based on the Fairness Doctrine, which required countermarketing antitobacco ads to be aired to balance the protobacco advertising by the tobacco industry (USDHHS 2000). The Fairness Doctrine campaign of 1967–1970, which was the first sustained nationwide tobacco control media effort, documented that an intensive mass media campaign can produce significant declines in smoking rates among both adults and youth (Hamilton 1972).

As discussed above in the Tobacco Products Litigation section, one of the positive impacts of the MSA settlement between the states and the tobacco industry was the establishment of the Legacy Foundation. From this funding, Legacy implemented a national youth prevention media intervention—the truth® campaign, which employs an industry manipulation messaging strategy to help youth and young adults reject tobacco. Findings from numerous studies demonstrate that exposure to truth® campaign messages is associated with increases in antitobacco attitudes and beliefs, as well as a lower likelihood of initiating tobacco use (Farrelly 2002; Farrelly et al. 2005, 2009).

In 2008, Legacy, together with the National Alliance for Tobacco Cessation, launched EX, the first national adult cessation campaign since the Fairness Doctrine. This campaign was found to increase quit attempts, particularly among low-socioeconomic and minority smokers (Vallone et al. 2011a,b).

More recently, CDC aired "Tips from Former Smokers" (TIPS) during March–June 2012, the first federally funded, nationwide, paid-media tobacco education campaign in the United States (CDC 2012b; McAfee et al. 2013). The TIPS campaign featured former smokers talking about their experiences living with diseases caused by smoking, and included advertising on national and local cable television, local radio, online media, and billboards, and in movie theaters, transit venues, and print media. A subsequent evaluation of the campaign found that the number of weekly calls to the telephone quitline portal 1-800-QUIT-NOW from the 50 states, the District of Columbia, Guam, and Puerto Rico increased 132% (207,519 additional calls) during the TIPS campaign, and the number of unique visitors to the NCI smoking cessation Web site (NCI 2013) increased 428% (510,571 additional unique visitors) (CDC 2012b). Quit attempts among smokers increased from 31.1–34.8% (12% relative increase) (McAfee et al. 2013); 13.4% of these quit attempters reported not smoking at follow-up. Nationally, an estimated 1.6 million additional smokers made a quit attempt, and 220,000 remained abstinent at follow-up. Cessation recommendations made by nonsmokers increased from 2.6–5.1%, while talking with friends and family about dangers of smoking increased from 31.9–35.2%, resulting in

an estimated 4.5 million additional nonsmokers recommending cessation services to family members or friends and an additional 6 million talking about the dangers of smoking. As a result of the success of the first TIPS campaign, a second series of TIPS ads were released by CDC in March 2013.

The experience of tobacco control campaigns in many states, including Arizona, California, Florida, Massachusetts, Minnesota, and Oregon, as well as the national TIPS campaign, suggests that message content is very important (CDC 2007). Influential and successful campaigns contain a number of essential elements, including optimized themes, appropriate emotional tone, appealing format, clear messages, intensity, and adequate repetition (Pechmann 2001; Siegel 2002; Farrelly et al. 2003; Wakefield et al. 2003; Schar et al. 2006; Richardson et al. 2007; Angus et al. 2008; NCI 2008). Mass media campaigns lacking these elements have been shown to be less effective. In addition, messages that elicit strong emotional response, such as personal testimonials and viscerally negative content, produce stronger and more consistent effects on audience recall (Terry-McElrath et al. 2005).

Prior reports and reviews have shown that mass media campaigns are an effective tool to reduce the prevalence of tobacco and prevent initiation of tobacco use. The 1994 Surgeon General's report concluded that mass media campaigns are cost-effective. NCI Monograph 19 concluded mass media campaigns designed to discourage tobacco use can change youth attitudes about tobacco use, curb smoking initiation, and encourage adult cessation, and their effects are greater when mass media campaigns are combined with other prevention efforts, such as school and/or community-based programs (NCI 2008). In 2012, the U.S. Surgeon General's report included a systematic review of mass media campaigns and youth to update the NCI Monograph 19 review. The 2012 report noted that mass media campaigns are often a part of larger tobacco control programs; therefore, it is difficult to assess individual effects. Nevertheless, the report concluded that the evidence is sufficient to infer a causal relationship between adequately funded antismoking media campaigns and a reduced prevalence of smoking among youth, and that the evidence suggests a dose-response relationship between exposure to antismoking media messages and reduced smoking behavior among youth (USDHHS 2012).

Since the review conducted in the 2012 Surgeon General's report, there have been a few studies that examined the effects of mass media campaigns on tobacco use, cessation, behavior, attitudes, knowledge, intentions, or cessation. Summaries of these studies are shown in Table 14.7. Overall, these studies demonstrate that mass-reach health communications interventions are effective in reducing the prevalence of smoking (Davis et al. 2012; Emery et al. 2012); increasing cessation, quit attempts, or intentions to quit (Vallone et al. 2011; Davis et al. 2012; Emery et al. 2012); and increasing appropriate knowledge, beliefs, and attitudes regarding tobacco use (Murphy-Hoefer et al. 2010; Richardson et al. 2010). Further, Richardson and colleagues (2010) and Delva and colleagues (2009) provide evidence that mass media campaigns should be targeted toward specific populations (Delva et al. 2009; Richardson et al. 2010). However, it is difficult to assess the outcomes of mass media campaigns, because many do not reach CDC's recommended levels of funding, or they are components of other statewide or national programs.

Cessation Interventions

Quitting smoking is beneficial to health at any age, and cigarette smokers who quit before 35 years of age have mortality rates similar to those who never smoked (Doll et al. 2004; CDC 2011a). From 1965–2011, the prevalence of cigarette smoking among adults in the United States decreased from 42.4% to 19.0%, in part, because of an increase in the number who quit smoking (CDC 2011b). In 2011, 68.9% of adult smokers wanted to stop smoking, and 42.7% had made a quit attempt in the past year (see Table 13.8).

To increase tobacco use cessation, CDC's *Best Practices 2007* recommends that state action on tobacco use treatment should include both health care system-based interventions and population-based interventions, such as quitlines and reducing cost barriers for treatment. The report specifically recommends the following elements: (1) sustaining, expanding, and promoting the services available through population-based counseling and treatment programs, such as cessation quitlines; (2) covering treatment for tobacco use under both public and private insurance, including individual, group, and telephone counseling and all FDA-approved tobacco cessation medication; (3) eliminating cost and other barriers to treatment for underserved populations, particularly the uninsured and populations disproportionately affected by tobacco use; and (4) making the health care system changes recommended by the Public Health Service guidelines (Fiore et al. 2008), such as implementing a system of tobacco use screening and documentation and linking tobacco users to quitline services (CDC 2007). However, it is important to note that the cessation landscape has changed considerably since *Best Practices 2007,* with the enactment of Affordable Care Act, the implementation of the Meaning-

Table 14.7   **Summary of studies examining effects of mass media campaigns on youth and adult smoking behavior, attitudes, knowledge, intentions, or cessation**

Study	Design/population	Intervention description/ measures	Findings	Strengths, limitations, and comments
Davis et al. 2012	• New York Behavioral Risk Factor Surveillance system and National Health Interview Survey • Repeated cross-sectional surveys • 8,608 New York adult smokers • 2003–2009 • Data weighted to be representative of state	• New York Tobacco Control Program included mass media campaign focused on cessation • Used graphic images and focused on health consequences	• Significant increases in people reporting intentions to quit, seriously considering quitting, self-report exposure to advertisements, and people who made at least attempt to quit • Significant decreases in prevalence of current smoking and daily cigarette consumption • Decrease in prevalence of smoking steeper in New York compared to national data	Mass media campaign part of a larger program; difficult to assess individual effects; mass media campaign largest intervention within statewide program
Emery et al. 2012	• Combined with Nielsen data from Current Population Surveys Tobacco Use Supplement • Cross-sectional • 433,232 adults ≥18 years of age • 1999–2007	• Assessed relationship between U.S. adult smoking and exposure to state-sponsored antitobacco advertisements	• Increased exposure to antitobacco advertisements associated with less smoking, positively associated with intentions to quit, and made past year quit attempts • Increased exposure to tobacco advertising associated with increased smoking	Repeated cross-sectional data, cannot determine direct causal inference; difficult to assess if people saw advertisements; exposure of antitobacco messages was below CDC recommended levels
Richardson et al. 2010	• Multiple cross-sectional surveys from Legacy Media Tracking Surveys • 19,701 young adults 18–24 years of age • 2000–2004 • United States	• "Truth"—a nationally aired antitobacco media campaign, which focused on manipulation of tobacco industry	• Awareness of the campaign was associated with various attitudes and beliefs • No significant associations between awareness of campaign and intentions	Data were not very recent; included exposure to antitobacco sentiment as a covariate to account for young adults with pre-existing antismoking attitudes and beliefs
Delva et al. 2009	• Cross-sectional • 2,374 adults (51% had children) • Florida	• A mass media campaign, targeted at youth, was part of Florida's tobacco prevention program • Sought to determine if the youth-targeted campaign reached adults independent of having children	• More adults with children were aware of campaign compared to those without children • Awareness of tobacco industry manipulation was associated with all smokers' intentions to quit, independent of having children	Majority white non-Hispanic population; small sample size, when only smokers selected; mass media campaigns need to be targeted at specific audiences, but may have an effect on other populations

Table 14.7   Continued

Study	Design/population	Intervention description/ measures	Findings	Strengths, limitations, and comments
Murphy-Hoefer et al. 2010	• Quasi-experimental • 1,020 18–24 years of age (2 public 4-year arts and sciences colleges; 1 in a northern state and 1 in a southern state)	• Classes were randomly assigned 1 of 3 types of antitobacco messages (social norms, health consequences, and tobacco industry manipulation) • Pretest given and collected, then two 30-second messages from assigned group shown twice, posttest administered • Tested influence of the social norms, health consequences, and tobacco industry manipulation on knowledge, attitudes, and beliefs	• Health consequences antitobacco messages were only type of advertisement that increased college students' knowledge, attitudes, and beliefs	Not generalizable to other populations; scales need to be validated for this population; link to behavioral outcomes unknown
Vallone et al. 2011	• Longitudinal analyses • 4,067 adults 18–49 years of age • United States	• Baseline data collected prior to mass media campaign • The Ex Campaign: national mass media campaign to promote cessation in adults interested in quitting • Follow-up conducted 6 months after the launch	• Awareness of the campaign was significantly associated with increase in cessation-related cognitions index score among both Hispanics and smokers with less than a high school education • Increased awareness associated with quit attempts among Blacks • No significant associations in White, non-Hispanics	No control group; mass media campaign reach was at lower levels than CDC recommendations; mass media campaigns effectively reach minority and underserved populations

Note: **CDC** = Centers for Disease Control and Prevention.

ful Use initiative, the widespread adoption of EHRs, the creation of the Centers for Medicare and Medicaid Innovation, the introduction of new voluntary Joint Commission hospital performance measures, the increasing shift to managed care plans in state Medicaid programs, changes in the organization of private health care, and the emphasis on establishing linkages between public health interventions and clinical interventions. These changes have presented significant new opportunities to institutionalize tobacco use screening and intervention and to increase the availability of evidence-based cessation treatments within health care systems (Koh 2012).

Quitlines are telephone-based tobacco cessation services that help tobacco users quit. Services offered by quitlines include coaching and counseling, referrals, mailed materials, training to health care providers, web-based services, and in some instances, free medications such as

nicotine replacement therapy (North American Quitline Consortium [NAQC] 2012). Services are usually provided by a contractor, which can be a public or private organization; the specific services provided typically vary by state and eligibility. There are multiple advantages to telephone counseling, when compared to other smoking cessation interventions (Zhu et al. 1996; Lichtenstein et al. 2010). First, quitlines are convenient; telephone counseling decreases logistical barriers to treatment and increases service utilization. Second, the semi-anonymous nature of phone counseling allows for candid discussion and faster progression of initial counseling sessions. Third, quitlines promote accountability and social support, while reducing the likelihood of attrition. Finally, quitlines allow for the use of a structured protocol, which can dictate minimum acceptable content per session. Moreover, a structured protocol ensures quality control: that every call is com-

prehensive, yet brief, thus increasing its utility for population-based application (Zhu et al. 1996; Lichtenstein et al. 2010).

The history and growth of quitlines have been summarized by Anderson and Zhu (2007) and Lichtenstein and colleagues (2010). In the early 1980s, NCI introduced the first telephone-based smoking cessation service as a component of the Cancer Information Service. The effectiveness of a reactive quitline that provided services through client-initiated calls was subsequently established, and the American Lung Association adopted the approach (Ossip-Kelin et al. 1991; Lichtentstein et al. 2010) for several years. In 1992, Group Health Cooperative of Puget Sound, a health maintenance organization, introduced the Free & Clear quitline service for its members, which utilized a proactive approach with counselor-initiated calls after clients first phoned the quitline. Concurrently, California established the first publicly funded statewide quitline using a similar proactive approach. Massachusetts (1994), Arizona (1996), and Oregon (1998) instituted proactive quitlines in the ensuing years, and by 2005, 44 U.S. states had sponsored some form of quitline (Lichtenstein et al. 2010). As of 2013, all 50 states and the District of Columbia had their own quitlines (NAQC N.D.). Callers to the national 1-800-QUIT-NOW portal are transferred to their state quitlines. The quitline network is supported by NCI, which manages the national portal, and by CDC, which provides supplemental funding to state quitlines as part of its support for comprehensive state tobacco control programs, as well as providing funding to the NAQC (CDC 2012b; NAQC N.D.). A critical factor in the rapid and widespread adoption of quitlines in the United States has been state public health programs, which saw the value of quitlines as an accessible and cost-effective clinical service, as well as an integral component of population-based approaches to smoking cessation (Anderson and Zhu 2007; Lichtenstein et al. 2010).

Quitlines have been shown to significantly increase rates of smoking cessation, when compared with minimal interventions, self-help, or no counseling; a meta-analysis of nine studies estimated the odds of quitting as 1.6 to 1 (95% CI, 1.4–1.8) (Fiore et al. 2008). However, state quitlines currently reach only 1–2% of smokers, largely because most state tobacco control programs lack sufficient funding to provide and promote quitline services to more callers (Anderson and Zhu 2007; Keller et al. 2010). CDC recommends that state quitlines reach 6–8% of the state's smokers (CDC 2007). In the United States, some consistently funded state quitlines have reached 4–5% of their smoking populations in 1 year (Woods and Haskins et al. 2007; Woods et al. 2007), and some large cities have reached 4% of their smokers in just 1 month by publicizing free nicotine patches available from the quitline (Cummings et al. 2006a,b).

In addition to quitlines, CDC's *Best Practices 2007* also recommends that statewide comprehensive tobacco control programs include health care system-based interventions (CDC 2007). The report specifically recommends that system-based initiatives ensure that all tobacco users, who are seen in the health care system, are screened for tobacco use. Additionally, all tobacco users should receive advice to quit and should be offered brief, or more intensive, counseling service and FDA-approved cessation medication (CDC 2007). Counseling and behavioral support for the treatment of tobacco use and dependence are described in more detail elsewhere in this chapter. In summary, the Public Health Service's evidence-based clinical practice guidelines on cessation state that brief advice by medical providers to quit smoking is an effective intervention (Fiore et al. 2008). More intensive interventions (e.g., individual, group, or telephone) that provide social support and coaching on problem-solving skills are even more effective. Combining counseling with FDA-approved medication for smoking cessation is most effective. The Public Health Service guideline also stresses that health care system changes are needed, such as covering treatment for tobacco use under both public and private insurance and eliminating cost and other barriers to treatment for underserved populations (Fiore et al. 2008). Model programs in large managed care plans show that full implementation of health care system changes, quitline services, comprehensive insurance coverage, and promotion of the services increases the use of proven treatments and decreases the prevalence of smoking (CDC 2007; Fiore et al. 2008).

International Tobacco Control

Increasingly, innovations in tobacco control programs and policies are occurring outside of the United States. Therefore, the history of international tobacco control is reviewed in this chapter since it provides a context for considering progress in the United States, and examples of what types of future efforts could be undertaken here. Previous Surgeon General's reports have reviewed the history of international tobacco control efforts. Although this chapter focuses primarily on the United States, this section briefly describes key global tobacco policy changes over the past half-century. Before the 1964 Surgeon General's report, significant scientific work was being conducted in other countries linking smoking with major health effects. In 1962, Royal College of Physicians (RCP) published the report, *Smoking and Health* (RCP 1962). In 1967, the first World Conference on Smoking and Health was held in New York City to convene international scientists and advocates to consider the findings of the 1962 RCP report and the 1964 Surgeon General's report. Since 1967, periodic (every 2–4 years) world conferences have been held to mobilize and coordinate international tobacco control efforts (see Table 14.8 for a listing of the years and locations of these conferences). Following a 1970 resolution at the World Health Assembly calling on governments to take action in the field of smoking control, WHO (1970) has had a commitment to antismoking action. WHO Expert Committees were convened in 1974 and 1979 to advise WHO in the field of smoking control. Beginning with the Third World Conference on Smoking and Health in 1975, WHO has cosponsored the world conferences and, increasingly, has taken a leadership role in activities. The WHO Technical Report, No. 636, *Controlling the Smoking Epidemic: Report of the WHO Expert Committee on Smoking Control* (WHO 1979), provided a comprehensive blueprint of the types of economic, policy, and regulatory interventions, which are very consistent with the established evidence-based best practices now defined in the WHO FCTC treaty and the MPOWER components: **M**onitor tobacco use and prevention policies; **P**rotect people from tobacco smoke; **O**ffer help to quit tobacco use; **W**arn about the dangers of tobacco; **E**nforce bans on tobacco advertising, promotion and sponsorship; and **R**aise taxes on tobacco. This is discussed in greater detail later in this chapter.

The activities at the World Conferences on Smoking and Health (and, since 1990, called the World Conference on Tobacco or Health) (Table 14.8) have been a forum to share and discuss scientific findings; however, since the early conferences, there has been a strong emphasis on mobilizing country efforts to promote social and legislative changes, engaging the leadership in health ministries and major voluntary health organizations into the tobacco control effort, and creating strong alliances among tobacco control leaders from across the world. Between the conferences, a network of tobacco control experts provided technical assistance to small regional groups or individual countries to maintain these same themes. This network was led by Nigel Gray of the Anti-Cancer Council of Victoria in Australia, who was head of the Union for International Cancer Control (UICC) Tobacco Program from 1974–1990, and included staff and volunteers from the American Cancer Society (ACS) and other UICC member organizations (e.g., Hong Kong Anti-Cancer Society), international leaders from other medical and professional groups (e.g., International Union Against Tuberculosis and Lung Disease, World Lung Foundation), and groups such as the United Kingdom's Action on Smoking and Health and Norway's National Council on Smoking and Health. Advocacy organizations in the United States, such as Doctors Ought to Care and ANR, drew upon the experience of similar groups such as the United Kingdom's Action on Smoking and Health, the Australian Council on Smoking and Health, and the Australian BUGA UP, in adopting stronger anti-industry campaigns and strategies (Chapman 1996, 2007).

By the 1990s, the tobacco epidemic was recognized as a rapidly growing international cause of premature death. In 1993, Ruth Roemer, lawyer and public health researcher, began to raise support for an international legal approach to address the global tobacco epidemic (Roemer et al. 2005; WHO 2009a). The process of creating an international instrument for tobacco control was formally initiated in May 1995 at the 48th World Health Assembly (WHO 1995), but the enterprise was not formally launched until 1999. In 1998, the newly elected WHO Director-General, Gro Harlem Brundtland, established the Tobacco Free Initiative as a special cabinet project and championed the concept of a framework convention on tobacco control (WHO 2009a).

The history of WHO FCTC has been documented (WHO 2009a). FCTC was the first international health treaty negotiated under the WHO treaty-making constitutional authority. In May 2000, the 53rd World Health Assembly accepted the provisional text, which had been prepared by an intergovernmental technical working group, and called for the treaty negotiations to begin

Table 14.8   Years and locations for the World Conferences on Smoking and Health

Year	Number	Conference	Location
1967	1	World Conference on Smoking & Health	New York City
1971	2	World Conference on Smoking & Health	London
1975	3	World Conference on Smoking & Health	New York City
1979	4	World Conference on Smoking & Health	Stockholm
1983	5	World Conference on Smoking & Health	Winnipeg
1987	6	World Conference on Smoking & Health	Tokyo
1990	7	World Conference on Tobacco or Health	Perth
1992	8	World Conference on Tobacco or Health	Buenos Aires
1994	9	World Conference on Tobacco or Health	Paris
1997	10	World Conference on Tobacco or Health	Beijing
2000	11	World Conference on Tobacco or Health	Chicago
2003	12	World Conference on Tobacco or Health	Helsinki
2006	13	World Conference on Tobacco or Health	Washington, D.C.
2009	14	World Conference on Tobacco or Health	Mumbai
2012	15	World Conference on Tobacco or Health	Singapore
2015	16	World Conference on Tobacco or Health	Abu Dhabi

(WHO 2000). Following six Intergovernmental Negotiating Body sessions between October 2000 and March 2003, the treaty was adopted by the 56th World Health Assembly in May 2003 (WHO 2003). It became one of the most rapidly and widely embraced treaties in the United Nations (UN) history. By June 29, 2004, 168 UN member states had signed the WHO FCTC expressing their willingness to become a Party to the Convention. Ninety days after the 40th state had acceded to, ratified, accepted, or approved the FCTC, the treaty entered into force on February 27, 2005. Together with UN Member States and regional economic integration organizations, there are now 176 Parties to the Convention. The United States signed the Convention on October 5, 2004, but the treaty has not been ratified by the U.S. Senate.

The articles of FCTC provide a scientific basis for coordinating world tobacco control efforts. Based on these FCTC treaty articles, and the scientific evidence on effective strategies to control the tobacco epidemic, WHO developed the six component MPOWER format to evaluate the implementation of tobacco control in all countries (WHO 2008b).

- **M**onitor tobacco use and prevention policies. Articles 20 and 21 of FCTC

- **P**rotect people from tobacco smoke. Article 8 of FCTC

- **O**ffer help to quit tobacco use. Article 14 of FCTC

- **W**arn about the dangers of tobacco. Articles 11 and 12 of FCTC

- **E**nforce bans on tobacco advertising, promotion and sponsorship. Article 13 of FCTC

- **R**aise taxes on tobacco. Articles 6 and 15 of FCTC

Using specific indicators based on each of these MPOWER components, global progress in tobacco control has been monitored (see the text box "MPOWER Success: Turkey" for one example). The key findings of the status of tobacco control in 2008 are shown in Table 14.9.

In 2009, an update report was released focusing on the implementation of smokefree environments (WHO 2009b). In 2011, the third global report provided data on the level of countries' achievement of the six MPOWER measures, updated through 2010, and additional data collected on warning the public about the dangers of tobacco

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MPOWER Success: Turkey

Turkey was the first country to implement all MPOWER measures within 6 years. Turkey's MPOWER successes included:

- **M**onitor: Surveillance and monitoring through Global Adult Tobacco Surveys and Global Youth Tobacco Surveys
- **P**rotect: 100% smokefree laws with regulations to ensure compliance
- **O**ffer Help: National quitline and free cessation services (including nicotine replacement therapy)
- **W**arn: Mass media campaigns and graphic health warnings that cover 65% of tobacco packaging
- **E**nforce: Total ban on tobacco advertising, promotion and sponsorship
- **R**aise taxes: Increase in tobacco taxes (80.3% of retail price)

The results of implementing all MPOWER measures in Turkey:

- A 13.7% decline in smoking prevalence after comprehensive tobacco control measures were put into place (2008–2012)

Smoking prevalence by gender, Turkey, 1993–2012

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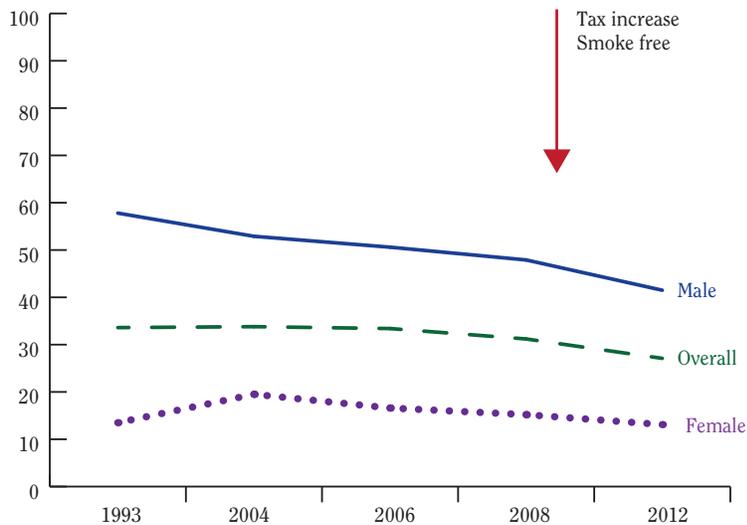
(WHO 2011). The report examines in detail the two primary strategies to provide health warnings—labels on tobacco product packaging and antitobacco mass media campaigns. It provides a comprehensive overview of the evidence base for warning people about the harms of tobacco use as well as country-specific information on the status of these measures. The fourth and most recent global report, released in 2013, examines the enforcement of bans on tobacco advertising, promotion, and sponsorship, in addition to providing data updates on MPOWER achievements through 2012, at the country level (WHO 2013b). The updated status report on global tobacco control on key indicators is shown in Figure 14.8.

As tobacco control gained greater priority under WHO Director-General Dr. Gro Harlem Brundtland, several international collaborations were expanded. In 1998, CDC and WHO created the Global Youth Tobacco Survey to address the need for surveillance of tobacco use among adolescents across the world (Warren et al. 2006, 2008). Additional surveillance surveys have been added, includ-

Table 14.9   Global tobacco control MPOWER key findings, 2008

Monitor tobacco use and prevention policies
- Good monitoring tracks the extent and evolution of the epidemic and indicates how best to tailor policies.
- Currently, half of countries – two in three in the developing world – do not have even minimal information about tobacco use.

Protect people from tobacco smoke
- Every person has a right to breathe air free of tobacco smoke. In addition to protecting the health of non-smokers, smoke-free environments encourage smokers to quit.
- Evidence from pioneering countries shows that smoke-free laws do not harm businesses and are popular with the public.
- Permitting smoking in designated areas undermines the benefit of smoke-free environments.
- Only 5% of the global population is protected by comprehensive national smoke-free legislation.

Offer help to quit tobacco use
- Among smokers who are aware of the dangers of tobacco, three out of four want to quit. Counseling and medication can double the chance that a smoker who tries to quit will succeed.
- National comprehensive services supporting cessation are available only in 9 countries, representing 5% of the world population.

Warn about the dangers of tobacco use
- Relatively few tobacco users fully grasp the health dangers. Hard-hitting anti-tobacco ads and graphic pack warnings reduce the number of children who begin smoking and increase the number of smokers who quit.
- Pictures are more powerful deterrents than words on tobacco packaging warnings, but only 15 countries, representing 6% of the world's population, mandate pictorial warnings.
- Just five countries, with 4% of the world's population, meet the highest standards for pack warnings.

Enforce bans on tobacco advertising, promotion and sponsorship
- Widespread advertising falsely associates tobacco with desirable qualities.
- Studies have found that advertising bans can lower tobacco consumption.
- Only 5% of the world's population currently lives in countries with comprehensive national bans on tobacco advertising, promotion and sponsorship.
- About half the children of the world live in countries that do not ban free distribution of tobacco products.

Raise taxes on tobacco
- Tobacco taxes are the most effective way to reduce tobacco use, especially among young people and the poor.
- Increasing tobacco taxes by 10% generally decreases tobacco consumption by 4% in high-income countries and by about 8% in low- and middle-income countries.
- Tobacco tax increases also increase government revenues.
- Only four countries, representing 2% of the world's population have tax rates greater than 75% of the retail price.
- In countries with available information, tobacco tax revenues are more than 500 times higher than spending on tobacco control. In low- and middle-income countries, tobacco tax revenues are more than 9000 and 4000 times higher than spending on tobacco control, respectively.

Source: World Health Organization (WHO) 2008b.
Note: A follow-up report was released in 2009 focusing on the implementation of smoke-free environments (WHO 2009b).

ing the Global School Personnel Survey, the Global Health Professions Student Survey, and the Global Adult Tobacco Survey (GATS) (Warren et al. 2009). Tobacco Questions for Surveys: a subset of key questions from GATS was introduced to promote standard use of tobacco questions in surveys. Results from the GATS component were recently published showing the tobacco use rates in 14 low- and middle-income countries (LMICs) compared with data from the United Kingdom and United States (Giovino et al 2012).

Leading up to the FCTC negotiations, the Framework Convention Alliance (FCA) was created in 1999 (WHO 2013). FCA was formally established in 2003, and now includes over 350 organizations from more than 100 countries. FCA has a mission to work on the development, ratifications, and implementation of the FCTC. FCA produces policy papers supporting the implementation of FCTC articles (e.g., on price and tax; product regulation; packaging and labeling; education and training; advertising, promotion, and sponsorship; cessation, illicit

Figure 14.8   World Health Organization (WHO) selected key indicators for tobacco control policies, 2012
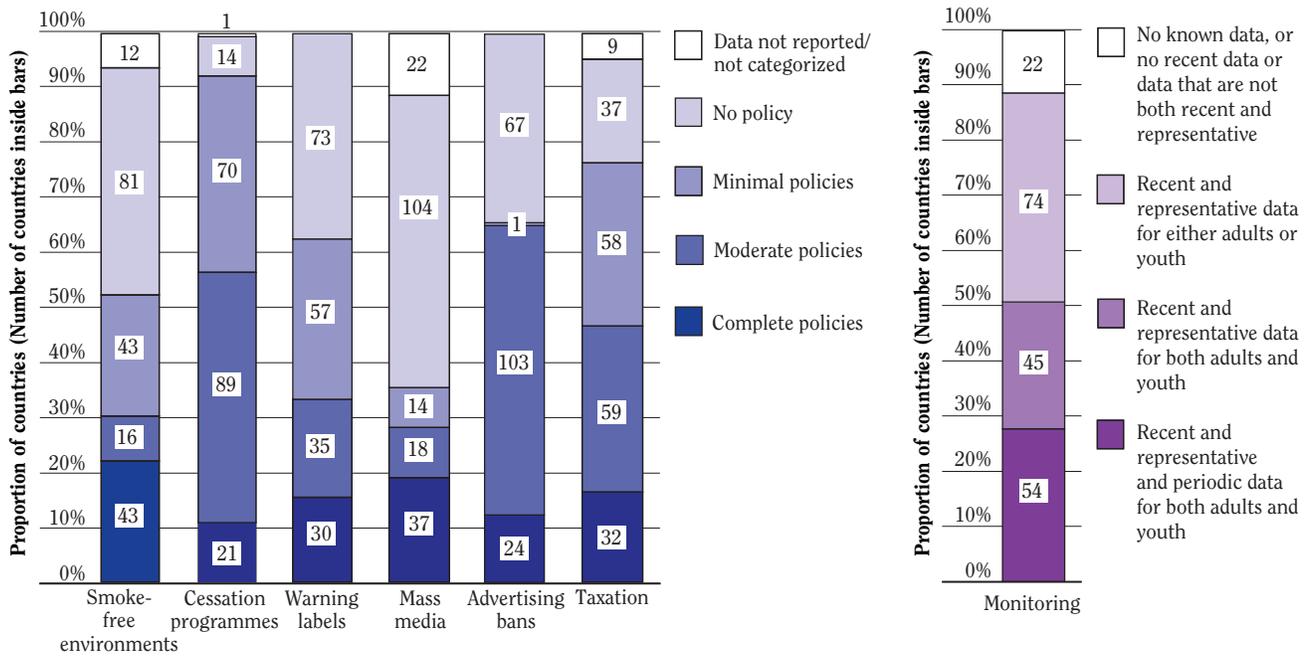
Source: WHO 2013.

trade, alternative livelihoods, and environments; liability; reporting on treaty implementation; and technical and financial assistance). FCA also organizes public events, workshops, and media campaigns to support the development, ratification, and implementation of the FCTC treaty and related tobacco control activities.

The Global Smokefree Partnership ([GSP] 2013) was formed to promote the implementation of smokefree air policies worldwide. The GSP currently is hosted by the International Union against Tuberculosis and Lung Diseases and FCA. GSP works together with the civil society and nongovernmental organizations within countries to gain the support of universities, intergovernmental organizations, ministries of health, corporations, and civic and medical leaders to support smokefree air policies and legislation. The pace at which comprehensive smokefree policies—such as policies that ban smoking in all enclosed public places and workplaces (no designated smoking rooms allowed), including bars, restaurants, and public transportation—have spread across the world has been cited as one of the most visible products of policy changes following a country's joining FCTC (Hyland et al. 2012). Ireland passed comprehensive smokefree legislation even before ratifying FCTC. Similarly, shortly after

signing FCTC, both New Zealand and Norway implemented comprehensive smokefree policies. As of 2012, 28 countries had national comprehensive smokefree laws, which required 100% coverage of bars, restaurants, and nonhospitality workplaces (Table 14.10) and an additional 27 countries had national smokefree laws, which were not as fully comprehensive (Hyland et al. 2012).

Funding for global tobacco control has dramatically increased in recent years, primarily due to foundation support. In 2007, the Bloomberg Initiative to Reduce Tobacco Use was started to address the lack of global resources to implement FCTC (Bloomberg Philanthropies 2013). In 2009, the Bloomberg Philanthropies joined forces with The Bill & Melinda Gates Foundation to broaden the global tobacco control movement, particularly in China, India, Southeast Asia, and Africa, with a commitment of $125 million. The initial Bloomberg Initiative to Reduce Tobacco Use commitment of $600 million was increased by an additional $220 million in 2012 (Bloomberg Philanthropies 2012). The Initiative continues to fund five institutions with global reach in tobacco control advocacy and public health: Campaign for Tobacco-Free Kids, National Foundation for the Centers for Disease Control and Prevention, the Johns Hopkins Bloomberg School of

Public Health, WHO, and the World Lung Foundation/ International Union Against Tuberculosis and Lung Disease. GATS, described above, is one major component of the Initiative (Giovino et al. 2012). A short list of the accomplishments, as of 2013, among LMICs that the Bloomberg Initiative (2013) has supported since 2007 are shown below:

- 32 countries successfully supported to implement national smokefree legislation, providing protection from exposure to second-hand smoke to over 1.3 billion people.

- 24 countries successfully supported to implement legislative bans on tobacco advertising, protecting nearly 1 billion people from tobacco advertising.

- 31 countries successfully supported to implement pictorial health warnings to warn about the dangers of tobacco use to over 2.7 billion people.

- 12 countries successfully supported increased tobacco taxes.

- In total, 46 countries representing over 4.5 billion people, have made critical legislative improvements supported by the grants program (Bloomberg Philantrophies 2013).

The majority of the accomplishments in tobacco control reviewed in this chapter have focused on the United States. However, as the brief summary above shows, the tobacco control activities occurring within the United States, since 1964, have happened within a dramatic global context. Following the first World Conference on Smoking and Health in 1967, there has been an active flow of tobacco control efforts between the United States and its global partners. For example, as an ACS volunteer, Dr. Joseph W. Cullen was an active member of the UICC Tobacco Program technical assistance teams before joining NCI in 1982, where he established NCI's Smoking Tobacco and Cancer Program (Greenwald and Cullen 1984). As described above, STCP was a major funder of tobacco control research and programs in the 1980s, including the ASSIST program that was the foundation of comprehensive statewide tobacco control efforts (Cullen 1989; USDHHS 2000). Several of the international tobacco control innovations, particularly those related to media and public health advocacy, were integrated into ASSIST intervention activities (NCI 2005). Another member of the UICC Tobacco Program technical assistance teams, Michael Pertschuk, was an important advisor to ASSIST and other U.S. tobacco control program efforts

on media advocacy strategies, including ACS's S*moke Signals: The Smoking Control Media Handbook* (ACS 1987). In addition to these several examples, there have been many international links and contributions across many of the tobacco control activities reviewed in this chapter.

International Trade and Tobacco Control

Tobacco and tobacco products are widely traded international goods and subject to the agreements that govern international trade (see Chapter 2) (Bettcher et al. 2001; WHO 2012a). Increasingly, international trade agreements have become relevant to tobacco control in the United States (Jarman et al. 2012). The intersection between international trade and tobacco control dates to the 1970s and the expansion of free trade areas through global, regional, and bilateral trade agreements (Bettcher et al. 2001; WHO 2012a). This history was reviewed in previous Surgeon General's reports, particularly in the 2000 report (see Chapter 6, USDHHS 2000). As reviewed in that report, various U.S. policies and programs have been used to help domestic tobacco growers and cigarette companies expand into foreign markets, particularly starting with trade cases initiated under Section 301 of the *Trade Act of 1974*. Four Section 301 cases in the late 1980s dealt with cigarettes: against Japan (1985), Taiwan (1986), South Korea (1988), and Thailand (1989). Threats of retaliatory sanctions under Section 301 led to agreements with each country, which permitted U.S. cigarette firms access to their markets. In the 1990s, multinational trade agreements became the basis for opening foreign markets to U.S. tobacco products. The Uruguay Round of negotiations under the General Agreement on Tariffs and Trade, concluded in 1994, established the World Trade Organization (WTO) and initiated an overhaul of the international trade regime. The agreement included, for the first time, the liberalization of trade in unmanufactured tobacco and facilitated the expansion of trade in tobacco products through significant reductions in tariff and non-tariff barriers to trade. Regional trade agreements and free trade areas, such as the North American Free Trade Agreement, the European Union, and the Association of South-East Asian Nations acted in synergy with events at the global level by further mandating trade liberalization in goods and services.

Early on, it was recognized that trade liberalization may stimulate demand for tobacco products, especially in traditionally closed tobacco markets in LMICs (Chaloupka et al. 1998; Taylor et al. 2000; Bettcher et al. 2001).

Table 14.10   Global tobacco control MPOWER key findings, countries 100% smokefree, 2009

Country[a]	Local law approval[b]	Additional coverage
Australia	• First State 2006 (Tasmania) • Last State 2010 (Northern Territory)	In some states, vehicles with children
Bermuda	2006	
Bhutan	2005	
British Virgin Islands	2006	
Canada	• First Territories 2004 (Northwest and Nunavut) • Last Territory 2009 (Prince Edward Island)	In some territories, vehicles with children. Outdoor seating and patios are smokefree as well
Cyprus	2010	Vehicles with children
England	2006	
France	2007	
Guatemala	2008	
Honduras	2010	
Hong Kong	2006	Public transport interchanges
Iceland	2007	
Iran	2007	All roofed areas
Ireland	2004	
Lithuania	2007	
Maldives	2009	
New Zealand	2003	Prisons
Northern Ireland	2007	
Norway	2004	
Panama	2008	
Paraguay	2010	
Peru	2006	
Scotland	2006	
Singapore	2009	All roofed areas
Spain	2011	
Turkey	2008	
Uruguay	2006	
Wales	2006	

Source: Hyland et al. 2012. Reprinted with permission from BMJ Publishing Group, Ltd., © 2012.
[a]Countries were considered 100% smokefree if the national law banned smoking in nonhospitality workplaces, restaurants, and bars (no designated smoking rooms allowed), according to the American Nonsmoker's Rights Foundation. 3 countries with all subnational entities having this type of policies were also considered 100% smokefree, such as Canada and Australia.
[b]Law implementation and not law enforcement is described. Definitions and specifications of indoor workplaces might vary according to local law.

Where trade agreements require parties to lower tariffs on tobacco or tobacco products, savings may be passed on to consumers, reducing the retail cost of tobacco products and stimulating demand. Liberalization may also facilitate greater competition in the tobacco sector, which can place downward pressure on prices, stimulate advertising of tobacco products, and lead to brand and product innovation designed to attract new consumers. Fortunately, following the lead of Thailand in its initial challenge, the political awareness around the region was increased and has remained strong on this issue (Mackay et al. 2013).

Since the late 1990s, a number of economic studies have been carried out to empirically examine the relationship between cigarette consumption and trade liberalization (Chaloupka et al. 1998; Taylor et al. 2000; Bettcher et al. 2001; WHO 2012a). These studies largely support the conclusion that past free trade agreements have increased tobacco consumption in LMICs. However, liberalization has not been found to increase the cigarette market in high-income countries, such as in the United States (Taylor et al. 2000). Moreover, it has been suggested that implementation of evidence-based tobacco control policies can reduce the impact of trade liberalization on consumption (WHO 2012a).

As more markets have been opened to transnational tobacco companies, the most significant risk posed by international trade agreements to tobacco control has shifted to rules governing so-called nontariff barriers to trade, (such as regulatory measures) which may restrict the regulatory autonomy of domestic authorities (WHO 2012a). International trade and investment litigation has increasingly become part of a global strategy by the tobacco industry to undermine tobacco control measures, including commitments contained in the FCTC (WHO 2012a). These disputes are occurring through WTO, regional and bilateral trade dispute settlement mechanisms, and international investment arbitration (Jarman et al. 2012; Gleeson and Friel 2013). Unlike past experiences with trade liberalization, the implications of these recent legal disputes directly concern domestic tobacco control efforts in high-income countries, including the United States (Jarman et al. 2012; WHO 2012a).

The Role of FCTC in Trade and Investment

Notably, the word trade never appears in the final FCTC (Mamudu et al. 2011). Throughout the negotiations, an alliance of LMICs and nongovernmental organizations fought to secure specific language prioritizing public health and tobacco control over trade agreements. Although the final text does not include any specific reference to health over trade, the first line of the Convention's preamble states, "The Parties to this Convention, determined to give priority to their right to protect public health." The general objective of FCTC, and this wording in particular, could be interpreted as intending to allow strong domestic tobacco control measures, even if there are adverse consequences that affect trade and may make international trade and investment agreements more sensitive to tobacco control (WHO 2012a). In addition, Article 5.3 of the Convention and its implementation guidelines provide that Parties should not grant the tobacco industry incentives for investment and should restrict their dealings with the industry. This could be interpreted as barring countries from taking tobacco industry-related claims to international trade bodies, including WTO. FCTC also sets out rules governing conflicts between itself and other treaties, including trade and investment agreements. The Punta del Este Declaration on Implementation of FCTC reinforces the flexibility that Parties have in implementing tobacco control measures (Lieberman 2012). In addition to FCTC, Resolution WHA 59.26 on international trade and health highlighted the need for WHO Member States to seek coherence in their trade and health policies. Also, the Doha Declaration on the Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement and Public Health has helped clarify the flexibilities that permit WTO Members to protect health under TRIPS (Lieberman 2012).

Tobacco-Related Trade Disputes in WTO

There are 141 countries that are Members of WTO and also Parties to FCTC and are, therefore, bound to both sets of commitments. Since FCTC came into force in 2005, seven tobacco control policies adopted by FCTC Parties and one FCTC-consistent tobacco control policy adopted by a non-Party (United States) have been the subject of discussions within WTO committees. Four of these policies have been subject to formal WTO dispute settlement proceedings. Although some of these cases do not have wide-ranging implications for tobacco control, some may prove to be significant, including the *U.S. Clove Cigarettes* case, in which the Appellate Body of WTO held that parts of the *Tobacco Control Act* are inconsistent with WTO obligations (Jarman et al. 2012). In this case, Indonesia requested a WTO dispute resolution panel in June 2010 based on the U.S. ban on characterizing flavors (other than tobacco or menthol) in cigarettes included in the *Tobacco Control Act*. Indonesia argued to the panel that the law was discriminatory because imported clove

cigarettes were banned, although domestic menthol cigarettes are allowed to remain in the market. Alternatively, the United States argued that excluding menthol from the cigarette flavor ban was justified under WTO obligations because banning menthol cigarettes (which are regularly smoked by tens of millions of adults) presented different public health issues and potential consequences compared to banning other flavored cigarettes (which were used regularly by very few adults). The WTO found that the distinctions on what flavors were banned in the United States were based upon health considerations; however, the WTO appellate body was not persuaded that there was a legitimate regulatory reason to ban clove cigarettes but not menthol cigarettes and held that the ban on clove cigarettes was inconsistent with the WTO obligation to treat imported products no less favorably than similar domestic products. On July 23, 2013, the United States announced that it had come into compliance with the WTO rulings. However, on August 23, 2013, Indonesia requested a special WTO Dispute Settlement Body meeting to request WTO authorization to impose countermeasures based on Indonesia's allegation that the United States has not come into compliance. The United States objected to Indonesia's request, referring the matter to arbitration.

Australia–Plain Packaging disputes are also significant WTO dispute settlement cases currently under way. In those disputes, a number of WTO Members are challenging Australia's right to implement plain packaging of tobacco products (Gleeson and Friel 2013). Various claims have been made, including that the measure unlawfully interferes with trademark rights and is more trade restrictive than necessary to protect human health. Those cases raise the question of how much authority any government has over the content and look of tobacco product packaging. A number of additional countries, which are considering plain packaging polices, are closely watching the outcome of the case, although New Zealand has announced that it will move forward with plans to introduce unbranded, standardized packaging with large health warnings for all tobacco products.

Bilateral Trade and Investment Agreements

In addition to these high-profile WTO disputes, tobacco companies have also brought recent claims directly against countries under other international financial agreements. Regional and bilateral trade and investment agreements, which have become increasingly common in the past decade, have provided another avenue through which tobacco control laws may be challenged.

For example, such agreements often include investor-state settlement provisions that grant investors the right to initiate dispute settlement proceedings against foreign governments in their own right under international law. Similar provisions are currently being used by a tobacco company to challenge tobacco control policies in Australia and Uruguay.

Confronting the Tobacco Epidemic in a New Era of Trade and Investment Liberalization reviews the ways in which the tobacco industry exploits international trade and investment agreements (WHO 2012a). This report provides an overview of the challenges posed by the ways that countries have been coordinating their trade, investment, and health policies. The specialized areas of law point to the need for greater capacity within tobacco control to address these challenges.

Summary

The past 50 years has witnessed a dramatic shift in attitudes among Americans toward tobacco products and the use of tobacco. This shift, from tobacco products being a widely accepted element of daily life to an addiction viewed unfavorably, has been driven by public health interventions and policies that discourage tobacco use and by the steps taken to regulate tobacco products and protect the population. We now have multiple examples of successful interventions, policies, and regulatory approaches, and these should guide future efforts to reduce tobacco use among youth and adults. Although there has been significant progress, much remains to be done in applying what is known to control tobacco use and in adapting these approaches to the new challenges for tobacco control as the industry diversifies its product lines.

This chapter expands and updates prior reviews in this series of reports on intervention approaches to reduce tobacco use in the population. As documented in previous reviews of a diverse and substantial body of research and evaluation literature, the evidence base documents the efficacy and effectiveness of a suite of tobacco control interventions and policy measures. These approaches, along with the regulatory authority of FDA, will be the foundation for designing strategies for further speeding the decline of tobacco use in the United States.

Conclusions

1. The evidence is sufficient to conclude that there are diverse tobacco control measures of proven efficacy at the population and individual levels.

2. The evidence is sufficient to conclude that advertising and promotional activities by the tobacco companies cause the onset and continuation of smoking among adolescents and young adults.

3. Tobacco product regulation has the potential to contribute to public health through reductions in tobacco product addictiveness and harmfulness, and by preventing false or misleading claims by the tobacco industry of reduced risk.

4. The evidence is sufficient to conclude that litigation against tobacco companies has reduced tobacco use in the United States by leading to increased product prices, restrictions on marketing methods, and making available industry documents for scientific analysis and strategic awareness.

5. The evidence is sufficient to conclude that increases in the prices of tobacco products, including those resulting from excise tax increases, prevent initiation of tobacco use, promote cessation, and reduce the prevalence and intensity of tobacco use among youth and adults.

6. The evidence is sufficient to conclude that smokefree indoor air policies are effective in reducing exposure to secondhand smoke and lead to less smoking among covered individuals.

7. The evidence is sufficient to conclude that mass media campaigns, comprehensive community programs, and comprehensive statewide tobacco control programs prevent initiation of tobacco use and reduce the prevalence of tobacco use among youth and adults.

8. The evidence is sufficient to conclude that tobacco cessation treatments are effective across a wide population of smokers, including those with significant mental and physical comorbidity.

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Appended Table 14.2   State cigarette excise taxes (dollars per pack) and sales tax rate applied to cigarettes

State	Excise tax March 31, 2013 (in dollars)	Sales tax rate November 1, 2012 (%)
Alabama	0.425	4
Alaska	2.00	0
Arizona	2.00	6.6
Arkansas	1.15	6
California	0.87	7.25[a,b]
Colorado	0.84	2.9
Connecticut	3.40	6.35
Delaware	1.60	0
District of Columbia	2.50	6[c]
Florida	1.339	6
Georgia	0.37	4[d]
Hawaii	3.20	4
Idaho	0.57	6
Illinois	1.98	6.25
Indiana	0.995	7
Iowa	1.36	6
Kansas	0.79	6.3[d]
Kentucky	0.60	6
Louisiana	0.36	4[d]
Maine	2.00	5
Maryland	2.00	6
Massachusetts	2.51	6.25
Michigan	2.00	6
Minnesota[e]	1.23	6.875[d]
Mississippi	0.68	7
Missouri	0.17	4.225[d]
Montana	1.70	0
Nebraska	0.64	5.5[d]
Nevada	0.80	6.85[a,b]
New Hampshire	1.68	0
New Jersey	2.70	7
New Mexico	1.66	5.125
New York	4.35	4[d]
North Carolina	0.45	4.75[d]
North Dakota	0.44	5
Ohio	1.250	5.5
Oklahoma	1.03	4.5[d]
Oregon	1.18	0
Pennsylvania	1.60	6
Rhode Island	3.50	7

State	Excise tax March 31, 2013 (in dollars)	Sales tax rate November 1, 2012 (%)
South Carolina	0.57	6
South Dakota	1.53	4
Tennessee	0.62	7
Texas	1.41	6.25[d]
Utah	1.70	4.65[b,d]
Vermont	2.62	6
Virginia	0.30	5
Washington	3.025	6.5
West Virginia	0.55	6
Wisconsin	2.52	5[b]
Wyoming	0.60	4[b]
Mean	1.478	5.05
Median	1.339	6

Source: Sales tax data from Orzechowski and Walker 2012. Excise tax data from Centers for Disease Control and Prevention, Office on Smoking and Health, State Tobacco Activities Tracking and Evaluation System, unpublished data.

Note: The states of Alaska, Delaware, Montana, New Hampshire, and Oregon do not have a state general sales tax. [a]Includes that portion of state-collected local sales tax rates where local rates are uniform and statewide. [b]Additional local taxes that are not uniform are collected by the state and are not included here.

[c]The District of Columbia exempted cigarettes from the sales and use tax in October of 2011 and replaced it with a surtax of 36¢ per 20 pack. The tax listed in the table is the cigarette excise tax of $2.50 plus the cigarette surtax of 36¢.

[d]Certain cities and/or counties impose general sales and/or excise taxes that are collected by the state (not included here).

[e]Minnesota sells stamps for $1.586 per pack. It is a composite of the 48¢ per pack excise tax, a 75¢ per pack health impact fee, and a 35.6¢ per pack wholesale sales tax assessed in lieu of a general sales tax.

Appended Data Table for Figure 14.6

State	City or county	100% workplaces	100% restaurants	100% bars
Alaska	Anchorage	Yes	Yes	Yes
Alaska	Barrow	—	Yes	—
Alaska	Dillingham	—	Yes	—
Alaska	Fairbanks	Yes	—	—
Alaska	Haines Borough	Yes	Yes	Yes
Alaska	Juneau	—	Yes	Yes
Alaska	Klawock	Yes	Yes	Yes
Alaska	Koyuk	Yes	Yes	—
Alaska	Nome	Yes	Yes	Yes
Alaska	Palmer	Yes	Yes	Yes
Alaska	Petersburg	—	Yes	Yes
Alaska	Sitka	Yes	Yes	—
Alaska	Skagway Borough	Yes	Yes	Yes
Alaska	Unalaska	—	Yes	Yes
Alabama	Albertville	Yes	Yes	Yes
Alabama	Alexander City	Yes	Yes	—
Alabama	Atmore	Yes	Yes	Yes
Alabama	Auburn	—	Yes	Yes
Alabama	Bay Minette	—	Yes	—
Alabama	Bayou La Batre	Yes	Yes	Yes
Alabama	Bessemer	Yes	Yes	—
Alabama	Birmingham	Yes	Yes	Yes
Alabama	Center Point	Yes	—	—
Alabama	Citronelle	Yes	Yes	Yes
Alabama	Clay	Yes	Yes	Yes
Alabama	Cottonwood	Yes	Yes	Yes
Alabama	Daphne	Yes	Yes	—
Alabama	Decatur	Yes	Yes	Yes
Alabama	East Brewton	Yes	Yes	Yes
Alabama	Fairfield	—	Yes	Yes
Alabama	Fairhope	Yes	Yes	—
Alabama	Flomaton	Yes	Yes	Yes
Alabama	Foley	Yes	Yes	—
Alabama	Fort Payne	—	Yes	—
Alabama	Fultondale	Yes	Yes	Yes
Alabama	Geneva	Yes	—	—
Alabama	Gulf Shores	Yes	Yes	Yes
Alabama	Headland	—	Yes	Yes
Alabama	Homewood	—	Yes	Yes
Alabama	Jasper	Yes	Yes	Yes

Appended Data Table for Figure 14.6   Continued

State	City or county	100% workplaces	100% restaurants	100% bars
Alabama	Lanett	Yes	Yes	Yes
Alabama	Luverne	—	Yes	Yes
Alabama	Midfield	Yes	Yes	Yes
Alabama	Mobile	Yes	Yes	—
Alabama	Northport	—	Yes	—
Alabama	Opelika	Yes	Yes	—
Alabama	Opp	—	Yes	—
Alabama	Orange Beach	Yes	Yes	Yes
Alabama	Oxford	Yes	Yes	Yes
Alabama	Phenix City	Yes	Yes	Yes
Alabama	Prichard	Yes	Yes	—
Alabama	Robertsdale	Yes	Yes	—
Alabama	Saraland	—	Yes	Yes
Alabama	Spanish Fort	Yes	Yes	—
Alabama	Talladega	Yes	Yes	Yes
Alabama	Tuskegee	Yes	Yes	—
Alabama	Vestavia Hills	Yes	Yes	Yes
Arkansas	Fairfield Bay	Yes	Yes	Yes
Arkansas	Fayetteville	—	Yes	—
Arkansas	Highfill	Yes	Yes	—
Arkansas	Pine Bluff	—	Yes	—
Arizona	Chandler	Yes	—	—
Arizona	Coconino County	Yes	Yes	—
Arizona	Cottonwood	Yes	—	—
Arizona	Flagstaff	Yes	Yes	Yes
Arizona	Gilbert	Yes	Yes	Yes
Arizona	Goodyear	Yes	—	—
Arizona	Guadalupe	Yes	Yes	Yes
Arizona	Nogales	Yes	—	—
Arizona	Prescott	Yes	Yes	Yes
Arizona	Santa Cruz County	Yes	—	—
Arizona	Sedona	Yes	Yes	Yes
Arizona	Surprise	Yes	—	—
Arizona	Tempe	Yes	Yes	Yes
Arizona	Youngtown	Yes	Yes	Yes
California	Alameda County	Yes	Yes	Yes
California	Albany	Yes	Yes	Yes
California	Auburn	Yes	—	—
California	Belmont	Yes	Yes	Yes
California	Belvedere	Yes	—	Yes

Appended Data Table for Figure 14.6   Continued

State	City or county	100% workplaces	100% restaurants	100% bars
California	Berkeley	Yes	Yes	Yes
California	Blue Lake	Yes	Yes	Yes
California	Burlingame	Yes	—	—
California	Butte County	Yes	—	—
California	Calabasas	Yes	Yes	Yes
California	Calexico	Yes	Yes	—
California	Calistoga	Yes	—	—
California	Campbell	—	Yes	Yes
California	Capitola	Yes	—	—
California	Carpinteria	Yes	Yes	Yes
California	Ceres	Yes	—	—
California	Chico	Yes	Yes	Yes
California	Chino Hills	Yes	—	—
California	Colfax	Yes	—	—
California	Contra Costa County	Yes	Yes	Yes
California	Cotati	Yes	—	—
California	Cupertino	Yes	—	—
California	Davis	Yes	Yes	Yes
California	Del Mar	Yes	Yes	Yes
California	Dublin	—	Yes	Yes
California	El Cajon	—	Yes	Yes
California	El Cerrito	—	Yes	Yes
California	Emeryville	—	Yes	Yes
California	Eureka	Yes	Yes	Yes
California	Fairfax	Yes	Yes	Yes
California	Fort Bragg	Yes	—	—
California	Fremont	Yes	Yes	—
California	Galt	—	Yes	Yes
California	Gilroy	—	Yes	Yes
California	Glendale	Yes	Yes	Yes
California	Goleta	Yes	—	—
California	Hayward	—	Yes	Yes
California	Hughson	Yes	—	—
California	Imperial Beach	Yes	Yes	Yes
California	Laguna Hills	Yes	Yes	Yes
California	Laguna Woods	Yes	Yes	Yes
California	Larkspur	Yes	Yes	Yes
California	Lathrop	Yes	—	—
California	Loma Linda	Yes	Yes	Yes
California	Long Beach	Yes	Yes	Yes

State	City or county	100% workplaces	100% restaurants	100% bars
California	Mammoth Lakes	Yes	Yes	Yes
California	Marin County	Yes	Yes	Yes
California	Martinez	Yes	Yes	Yes
California	Mendocino County	Yes	—	—
California	Menlo Park	—	Yes	Yes
California	Merced	Yes	—	—
California	Mill Valley	Yes	Yes	Yes
California	Millbrae	Yes	Yes	Yes
California	Mission Viejo	—	Yes	Yes
California	Modesto	Yes	Yes	—
California	Monterey	Yes	Yes	Yes
California	Monterey County	Yes	Yes	Yes
California	Moorpark	Yes	Yes	Yes
California	Morgan Hill	Yes	Yes	Yes
California	Morro Bay	Yes	Yes	Yes
California	Mountain View	Yes	Yes	Yes
California	Murrieta	—	Yes	Yes
California	Napa	—	Yes	Yes
California	Napa County	Yes	—	—
California	Newark	Yes	Yes	Yes
California	Novato	Yes	Yes	Yes
California	Oakland	Yes	—	—
California	Ojai	Yes	—	—
California	Paradise	Yes	—	—
California	Pasadena	Yes	Yes	Yes
California	Patterson	Yes	—	—
California	Petaluma	Yes	—	—
California	Pinole	—	Yes	Yes
California	Pittsburg	—	Yes	Yes
California	Pleasant Hill	Yes	Yes	Yes
California	Pleasanton	—	Yes	—
California	Rancho Cucamonga	—	Yes	Yes
California	Richmond	Yes	Yes	Yes
California	Rohnert Park	Yes	Yes	Yes
California	Roseville	Yes	—	—
California	Ross	Yes	Yes	Yes
California	Sacramento	Yes	—	—
California	Sacramento County	Yes	—	—
California	Salinas	—	Yes	Yes
California	San Anselmo	Yes	Yes	Yes

Appended Data Table for Figure 14.6 **Continued**

State	City or county	100% workplaces	100% restaurants	100% bars
California	San Bernardino County	Yes	—	—
California	San Carlos	—	Yes	Yes
California	San Diego	—	Yes	Yes
California	San Francisco	Yes	Yes	—
California	San Jose	Yes	Yes	Yes
California	San Juan Bautista	Yes	Yes	—
California	San Luis Obispo	Yes	Yes	Yes
California	San Mateo	Yes	Yes	Yes
California	San Mateo County	Yes	—	—
California	San Rafael	Yes	Yes	Yes
California	San Ramon	Yes	—	—
California	Santa Barbara	Yes	Yes	Yes
California	Santa Barbara County	Yes	—	—
California	Santa Clara	Yes	Yes	
California	Santa Clara County	Yes	Yes	Yes
California	Santa Clarita	Yes	—	—
California	Santa Cruz	Yes	—	—
California	Santa Cruz County	Yes	—	—
California	Santa Rosa	Yes	—	—
California	Saratoga	Yes	—	—
California	Sausalito	Yes	Yes	Yes
California	Scotts Valley	Yes	Yes	
California	Sebastopol	Yes	Yes	Yes
California	Shafter	Yes	Yes	—
California	Shasta County	Yes	Yes	Yes
California	Sierra Madre	—	Yes	Yes
California	Solana Beach	—	Yes	Yes
California	Solano County	Yes	—	—
California	Sonoma County	Yes	Yes	Yes
California	South Pasadena	Yes	Yes	Yes
California	Stanislaus County	Yes	—	—
California	Sunnyvale	—	Yes	—
California	Temecula	Yes	Yes	Yes
California	Tiburon	Yes	Yes	Yes
California	Tracy	Yes	—	—
California	Tuolumne County	Yes	—	—
California	Ukiah	Yes	—	—
California	Union City	Yes	Yes	Yes
California	Vallejo	Yes	—	—
California	Ventura	Yes	—	—

Appended Data Table for Figure 14.6   Continued

State	City or county	100% workplaces	100% restaurants	100% bars
California	Ventura County	Yes	—	—
California	Visalia	Yes	Yes	—
California	Watsonville	Yes	—	—
California	Yountville	Yes	—	—
Colorado	Alamosa	—	Yes	—
Colorado	Arvada	Yes	Yes	Yes
Colorado	Avon	Yes	Yes	Yes
Colorado	Boulder	Yes	Yes	Yes
Colorado	Boulder County	Yes	Yes	Yes
Colorado	Breckenridge	—	Yes	Yes
Colorado	Brighton	—	Yes	Yes
Colorado	Central City	—	Yes	Yes
Colorado	Dillon	—	Yes	Yes
Colorado	Eagle County	Yes	Yes	Yes
Colorado	Edgewater	Yes	Yes	Yes
Colorado	Firestone	Yes	—	—
Colorado	Fort Collins	Yes	Yes	Yes
Colorado	Frisco	—	Yes	Yes
Colorado	Golden	—	Yes	Yes
Colorado	Grand Junction	—	Yes	Yes
Colorado	Greeley	—	Yes	Yes
Colorado	Lakewood	—	Yes	Yes
Colorado	Longmont	—	Yes	Yes
Colorado	Louisville	—	Yes	Yes
Colorado	Loveland	—	Yes	Yes
Colorado	Monte Vista	—	Yes	Yes
Colorado	Pueblo	Yes	Yes	Yes
Colorado	Rifle	—	Yes	Yes
Colorado	San Luis	Yes	Yes	Yes
Colorado	Silverthorne	—	Yes	Yes
Colorado	Snowmass Village	Yes	Yes	Yes
Colorado	Steamboat Springs	—	Yes	—
Colorado	Summit County	—	Yes	Yes
Colorado	Superior	—	Yes	Yes
Colorado	Telluride	Yes	Yes	Yes
Colorado	Timnath	Yes	Yes	Yes
Colorado	Winter Park	—	Yes	Yes
District of Columbia	Washington	Yes	Yes	Yes
Georgia	Athens/Clarke County	—	Yes	Yes
Georgia	Berkeley Lake	Yes	Yes	—

Appended Data Table for Figure 14.6   Continued

State	City or county	100% workplaces	100% restaurants	100% bars
Georgia	Buena Vista	Yes	Yes	Yes
Georgia	Chatham County	Yes	Yes	Yes
Georgia	Columbia County	Yes	Yes	—
Georgia	Cordele	Yes	—	—
Georgia	Decatur	Yes	Yes	—
Georgia	DeKalb County	Yes	—	—
Georgia	Douglas	Yes	Yes	—
Georgia	Douglas County	Yes	—	—
Georgia	Douglasville	Yes	—	—
Georgia	Dunwoody	Yes	—	—
Georgia	Effingham County	—	Yes	Yes
Georgia	Gainesville	—	Yes	Yes
Georgia	Loganville	Yes	Yes	—
Georgia	Madison	—	Yes	—
Georgia	Morrow	Yes	Yes	Yes
Georgia	Peachtree City	—	Yes	—
Georgia	Savannah	Yes	Yes	Yes
Georgia	Snellville	—	Yes	Yes
Georgia	Tift County	—	Yes	Yes
Georgia	Tifton	—	Yes	—
Georgia	Valdosta	Yes	Yes	—
Hawaii	Hawaii County	Yes	Yes	—
Hawaii	Honolulu	Yes	Yes	—
Hawaii	Maui County	—	Yes	—
Idaho	Glenwood	Yes	Yes	Yes
Idaho	Boise	Yes	Yes	Yes
Idaho	Moscow	—	—	Yes
Illinois	Arlington Heights	Yes	Yes	—
Illinois	Barrington	Yes	Yes	Yes
Illinois	Batavia	Yes	Yes	Yes
Illinois	Bedford Park	Yes	Yes	Yes
Illinois	Benton	Yes	Yes	Yes
Illinois	Berwyn	Yes	—	—
Illinois	Bloomington	Yes	Yes	Yes
Illinois	Buffalo Grove	Yes	Yes	Yes
Illinois	Burr Ridge	Yes	Yes	Yes
Illinois	Calumet City	Yes	—	—
Illinois	Carbondale	—	Yes	Yes
Illinois	Centralia	Yes	Yes	Yes
Illinois	Chicago	Yes	Yes	Yes

Appended Data Table for Figure 14.6   Continued

State	City or county	100% workplaces	100% restaurants	100% bars
Illinois	Chicago Heights	Yes	—	—
Illinois	Cook County	Yes	Yes	Yes
Illinois	Countryside	Yes	Yes	Yes
Illinois	Deerfield	Yes	Yes	Yes
Illinois	DeKalb	Yes	Yes	Yes
Illinois	East Moline	Yes	Yes	Yes
Illinois	East Peoria	Yes	Yes	Yes
Illinois	Elk Grove Village	Yes	Yes	Yes
Illinois	Elmwood Park	Yes	Yes	Yes
Illinois	Evanston	Yes	Yes	Yes
Illinois	Frankfort	Yes	Yes	Yes
Illinois	Galesburg	Yes	Yes	Yes
Illinois	Hanover Park	Yes	Yes	—
Illinois	Hawthorn Woods	Yes	Yes	Yes
Illinois	Highland Park	Yes	Yes	Yes
Illinois	Hinsdale	Yes	Yes	Yes
Illinois	Hoffman Estates	Yes	Yes	—
Illinois	Indian Head Park	Yes	—	—
Illinois	Justice	Yes	—	—
Illinois	La Grange	Yes	Yes	—
Illinois	La Grange Park	Yes	—	Yes
Illinois	Lake Bluff	Yes	Yes	Yes
Illinois	Lake County	Yes	Yes	Yes
Illinois	Lake Forest	Yes	Yes	Yes
Illinois	Lemont	Yes	Yes	Yes
Illinois	Libertyville	Yes	Yes	Yes
Illinois	Lincolnshire	Yes	—	—
Illinois	Lincolnwood	Yes	Yes	Yes
Illinois	Lindenhurst	Yes	Yes	Yes
Illinois	Long Grove	Yes	—	—
Illinois	Mclean County	Yes	Yes	—
Illinois	Milan	Yes	Yes	Yes
Illinois	Morton Grove	Yes	Yes	Yes
Illinois	Naperville	Yes	Yes	Yes
Illinois	New Lenox	Yes	Yes	Yes
Illinois	Niles	Yes	—	—
Illinois	Normal	Yes	Yes	Yes
Illinois	Norridge	Yes	Yes	Yes
Illinois	North Aurora	Yes	Yes	Yes
Illinois	Northbrook	Yes	Yes	—

Appended Data Table for Figure 14.6   Continued

State	City or county	100% workplaces	100% restaurants	100% bars
Illinois	Oak Lawn	Yes	—	—
Illinois	Oak Park	Yes	Yes	Yes
Illinois	Orland Park	Yes	Yes	Yes
Illinois	Palatine	Yes	Yes	Yes
Illinois	Palos Hills	Yes	Yes	Yes
Illinois	Park Forest	Yes	Yes	Yes
Illinois	Park Ridge	Yes	Yes	Yes
Illinois	Plainfield	Yes	Yes	Yes
Illinois	Prospect Heights	Yes	Yes	Yes
Illinois	Riverside	Yes	Yes	—
Illinois	Rochelle	Yes	Yes	Yes
Illinois	Rolling Meadows	Yes	Yes	Yes
Illinois	Sangamon County	Yes	Yes	Yes
Illinois	Schaumburg	Yes	Yes	—
Illinois	Skokie	Yes	—	—
Illinois	South Beloit	Yes	Yes	Yes
Illinois	Springfield	—	Yes	Yes
Illinois	Steger	Yes	—	—
Illinois	Taylor Springs	Yes	Yes	Yes
Illinois	Tinley Park	Yes	Yes	Yes
Illinois	Urbana	Yes	Yes	Yes
Illinois	Vernon Hills	Yes	Yes	Yes
Illinois	Villa Grove	Yes	Yes	Yes
Illinois	Wamac	Yes	Yes	Yes
Illinois	Washington	Yes	Yes	Yes
Illinois	Westchester	Yes	—	—
Illinois	Wheaton	Yes	Yes	—
Illinois	Wheeling	Yes	—	—
Illinois	Wilmette	Yes	Yes	Yes
Illinois	Worth	Yes	Yes	Yes
Indiana	Allen County	Yes	Yes	—
Indiana	Avon	Yes	Yes	—
Indiana	Bloomington	Yes	Yes	Yes
Indiana	Carmel	Yes	Yes	—
Indiana	Chesterton	Yes	—	—
Indiana	Crawfordsville	—	—	Yes
Indiana	Crown Point	Yes	Yes	—
Indiana	Cumberland	Yes	Yes	Yes
Indiana	Delaware County	Yes	Yes	Yes
Indiana	Elkhart	Yes	Yes	Yes

Appended Data Table for Figure 14.6   Continued

State	City or county	100% workplaces	100% restaurants	100% bars
Indiana	Evansville	Yes	Yes	Yes
Indiana	Fort Wayne	Yes	Yes	Yes
Indiana	Franklin	Yes	Yes	Yes
Indiana	Goshen	Yes	—	—
Indiana	Greencastle	Yes	Yes	Yes
Indiana	Greenfield	Yes	Yes	—
Indiana	Greensburg	Yes	Yes	—
Indiana	Greenwood	Yes	Yes	—
Indiana	Hancock County	Yes	Yes	Yes
Indiana	Henry County	Yes	Yes	—
Indiana	Indianapolis/Marion County	Yes	Yes	Yes
Indiana	Jeffersonville	Yes	Yes	—
Indiana	Kokomo	Yes	Yes	—
Indiana	Lawrence	Yes	Yes	Yes
Indiana	Madison	Yes	Yes	—
Indiana	Monroe County	Yes	Yes	Yes
Indiana	Plainfield	Yes	Yes	Yes
Indiana	Seymour	Yes	Yes	—
Indiana	Shelbyville	Yes	—	—
Indiana	Speedway	Yes	Yes	—
Indiana	Terre Haute	Yes	Yes	Yes
Indiana	Valparaiso	Yes	—	—
Indiana	Vanderburgh County	Yes	Yes	Yes
Indiana	Vigo County	Yes	Yes	Yes
Indiana	West Lafayette	Yes	Yes	Yes
Indiana	Westfield	Yes	—	—
Indiana	Whitestown	Yes	—	—
Indiana	Zionsville	Yes	Yes	Yes
Kansas	Abilene	—	Yes	—
Kansas	Bel Aire	—	Yes	Yes
Kansas	Derby	Yes	Yes	Yes
Kansas	Emporia	—	Yes	Yes
Kansas	Fairway	Yes	Yes	Yes
Kansas	Garden City	—	Yes	Yes
Kansas	Harvey County	Yes	Yes	Yes
Kansas	Hesston	Yes	Yes	Yes
Kansas	Johnson County	—	Yes	Yes
Kansas	Kansas City/ Wyandotte County	Yes	Yes	Yes
Kansas	Lawrence	—	Yes	Yes
Kansas	Leawood	Yes	Yes	Yes

Appended Data Table for Figure 14.6   Continued

State	City or county	100% workplaces	100% restaurants	100% bars
Kansas	Lenexa	Yes	Yes	Yes
Kansas	Maize	—	Yes	Yes
Kansas	Manhattan	Yes	Yes	Yes
Kansas	Merriam	Yes	Yes	Yes
Kansas	Mission	Yes	Yes	Yes
Kansas	Newton	Yes	Yes	Yes
Kansas	North Newton	Yes	Yes	Yes
Kansas	Olathe	Yes	Yes	Yes
Kansas	Ottawa	—	Yes	—
Kansas	Overland Park	Yes	Yes	Yes
Kansas	Prairie Village	Yes	Yes	Yes
Kansas	Pratt	Yes	—	—
Kansas	Pratt County	Yes	Yes	Yes
Kansas	Roeland Park	Yes	Yes	Yes
Kansas	Salina	Yes	Yes	Yes
Kansas	Shawnee	Yes	—	—
Kansas	Topeka	Yes	Yes	Yes
Kansas	Valley Center	Yes	Yes	Yes
Kansas	Walton	—	Yes	Yes
Kansas	Westwood	Yes	Yes	Yes
Kansas	Winfield	—	Yes	Yes
Kentucky	Ashland	Yes	Yes	Yes
Kentucky	Bardstown	Yes	Yes	Yes
Kentucky	Bowling Green	Yes	Yes	Yes
Kentucky	Campbellsville	Yes	Yes	Yes
Kentucky	Clark County	Yes	Yes	Yes
Kentucky	Corbin	Yes	Yes	Yes
Kentucky	Danville	Yes	Yes	Yes
Kentucky	Elizabethtown	Yes	Yes	Yes
Kentucky	Frankfort	—	Yes	Yes
Kentucky	Franklin County	—	Yes	Yes
Kentucky	Georgetown	Yes	Yes	Yes
Kentucky	Glasgow	—	Yes	Yes
Kentucky	Hardin County	Yes	Yes	Yes
Kentucky	Henderson	Yes	—	—
Kentucky	Kenton County	Yes	—	—
Kentucky	Letcher County	—	Yes	—
Kentucky	Lexington/Fayette County	Yes	Yes	Yes
Kentucky	London	Yes	Yes	Yes
Kentucky	Louisville/Jefferson County	Yes	Yes	Yes

Appended Data Table for Figure 14.6   Continued

State	City or county	100% workplaces	100% restaurants	100% bars
Kentucky	Madison County	Yes	Yes	Yes
Kentucky	Manchester	Yes	Yes	Yes
Kentucky	Morehead	Yes	Yes	Yes
Kentucky	Oldham County	—	Yes	—
Kentucky	Paducah	—	Yes	Yes
Kentucky	Paintsville	—	Yes	—
Kentucky	Pikeville	—	Yes	—
Kentucky	Prestonsburg	Yes	Yes	Yes
Kentucky	Radcliff	Yes	Yes	Yes
Kentucky	Somerset	Yes	Yes	Yes
Kentucky	Williamsburg	Yes	Yes	Yes
Kentucky	Woodford County	Yes	Yes	Yes
Louisiana	Alexandria	Yes	Yes	Yes
Louisiana	Gibsland	Yes	—	—
Louisiana	Grambling	Yes	—	—
Louisiana	Lafayette	Yes	—	—
Louisiana	Lafayette Parish	Yes	—	—
Louisiana	Mandeville	Yes	—	—
Louisiana	Sulphur	Yes	—	—
Massachusetts	Abington	Yes	Yes	Yes
Massachusetts	Acushnet	—	Yes	—
Massachusetts	Adams	Yes	—	—
Massachusetts	Amherst	Yes	Yes	Yes
Massachusetts	Andover		Yes	—
Massachusetts	Aquinnah	Yes	—	—
Massachusetts	Arlington	Yes	Yes	Yes
Massachusetts	Ashland	Yes	—	—
Massachusetts	Barnstable	—	Yes	Yes
Massachusetts	Barre	—	Yes	Yes
Massachusetts	Belchertown	—	Yes	Yes
Massachusetts	Bellingham	—	Yes	—
Massachusetts	Belmont	—	Yes	—
Massachusetts	Beverly	Yes	Yes	Yes
Massachusetts	Boston	Yes	Yes	Yes
Massachusetts	Bourne	Yes	Yes	Yes
Massachusetts	Braintree	Yes	Yes	Yes
Massachusetts	Brewster	Yes	Yes	Yes
Massachusetts	Bridgewater	Yes	Yes	Yes
Massachusetts	Brimfield	Yes	Yes	Yes
Massachusetts	Brookline	—	Yes	—

Appended Data Table for Figure 14.6 **Continued**

State	City or county	100% workplaces	100% restaurants	100% bars
Massachusetts	Buckland	Yes	Yes	Yes
Massachusetts	Cambridge	Yes	Yes	—
Massachusetts	Canton	Yes	Yes	Yes
Massachusetts	Carver	Yes	Yes	Yes
Massachusetts	Chatham	Yes	Yes	Yes
Massachusetts	Chelsea	Yes	Yes	Yes
Massachusetts	Chilmark	Yes	Yes	Yes
Massachusetts	Cohasset	—	Yes	Yes
Massachusetts	Concord	—	Yes	Yes
Massachusetts	Dedham	Yes	Yes	Yes
Massachusetts	Dover	—	Yes	Yes
Massachusetts	Dracut	Yes	—	—
Massachusetts	Duxbury	Yes	Yes	Yes
Massachusetts	Easthampton	Yes	Yes	Yes
Massachusetts	Easton	—	Yes	Yes
Massachusetts	Edgartown	Yes	Yes	Yes
Massachusetts	Egremont	Yes	Yes	Yes
Massachusetts	Essex	Yes	Yes	Yes
Massachusetts	Everett	Yes	Yes	Yes
Massachusetts	Framingham	Yes	Yes	Yes
Massachusetts	Freetown	Yes	Yes	Yes
Massachusetts	Great Barrington	Yes	Yes	Yes
Massachusetts	Hancock	Yes	Yes	Yes
Massachusetts	Hatfield	Yes	Yes	Yes
Massachusetts	Haverhill	Yes	—	Yes
Massachusetts	Hingham	—	Yes	Yes
Massachusetts	Holbrook	Yes	—	—
Massachusetts	Holliston	Yes	Yes	Yes
Massachusetts	Holyoke	Yes	—	—
Massachusetts	Hopkinton	—	Yes	Yes
Massachusetts	Hubbardston	—	Yes	Yes
Massachusetts	Lancaster	Yes	Yes	Yes
Massachusetts	Lee	Yes	Yes	Yes
Massachusetts	Leicester	Yes	—	—
Massachusetts	Lenox	Yes	Yes	Yes
Massachusetts	Lexington	Yes	Yes	Yes
Massachusetts	Lincoln	Yes	Yes	Yes
Massachusetts	Littleton	—	Yes	Yes
Massachusetts	Lynn	Yes	Yes	Yes
Massachusetts	Marblehead	—	Yes	—

Appended Data Table for Figure 14.6   Continued

State	City or county	100% workplaces	100% restaurants	100% bars
Massachusetts	Marion	Yes	Yes	Yes
Massachusetts	Marshfield	Yes	—	—
Massachusetts	Mashpee	Yes	Yes	Yes
Massachusetts	Maynard	—	Yes	Yes
Massachusetts	Medfield	Yes	Yes	Yes
Massachusetts	Melrose	—	Yes	Yes
Massachusetts	Middleton	Yes	Yes	Yes
Massachusetts	Millville	Yes	Yes	Yes
Massachusetts	Milton	Yes	Yes	Yes
Massachusetts	Monterey	Yes	Yes	Yes
Massachusetts	Nantucket	Yes	Yes	Yes
Massachusetts	Needham	Yes	Yes	Yes
Massachusetts	New Bedford	Yes	Yes	Yes
Massachusetts	New Braintree	—	Yes	Yes
Massachusetts	Newburyport	Yes	—	—
Massachusetts	Norfolk	—	Yes	Yes
Massachusetts	North Adams	Yes	—	—
Massachusetts	Northampton	Yes	Yes	Yes
Massachusetts	Norton	—	Yes	Yes
Massachusetts	Norwood	Yes	Yes	Yes
Massachusetts	Oak Bluffs	Yes	Yes	Yes
Massachusetts	Orleans	—	Yes	Yes
Massachusetts	Oxford	Yes	Yes	Yes
Massachusetts	Peabody	Yes	Yes	Yes
Massachusetts	Pittsfield	Yes	Yes	Yes
Massachusetts	Plymouth	—	Yes	Yes
Massachusetts	Provincetown	—	Yes	Yes
Massachusetts	Quincy	Yes	Yes	Yes
Massachusetts	Reading	—	Yes	Yes
Massachusetts	Revere	Yes	Yes	Yes
Massachusetts	Richmond	Yes	Yes	Yes
Massachusetts	Salem	Yes	Yes	Yes
Massachusetts	Sandwich	Yes	Yes	Yes
Massachusetts	Saugus	Yes	Yes	Yes
Massachusetts	Scituate	—	Yes	Yes
Massachusetts	Sharon	—	Yes	Yes
Massachusetts	Somerset	Yes	Yes	Yes
Massachusetts	Somerville	Yes	Yes	Yes
Massachusetts	Southborough	—	Yes	Yes
Massachusetts	Sterling	—	Yes	Yes

Appended Data Table for Figure 14.6   Continued

State	City or county	100% workplaces	100% restaurants	100% bars
Massachusetts	Stockbridge	Yes	Yes	Yes
Massachusetts	Stoneham	—	Yes	Yes
Massachusetts	Tisbury	Yes	Yes	Yes
Massachusetts	Truro	Yes	Yes	Yes
Massachusetts	Tyngsborough	Yes	Yes	Yes
Massachusetts	Tyringham	Yes	Yes	Yes
Massachusetts	Wakefield	Yes	Yes	Yes
Massachusetts	Walpole	Yes	Yes	Yes
Massachusetts	Wareham	—	Yes	Yes
Massachusetts	Watertown	Yes	Yes	Yes
Massachusetts	Wayland	Yes	Yes	—
Massachusetts	Wellesley	—	Yes	—
Massachusetts	Wellfleet	—	Yes	Yes
Massachusetts	West Tisbury	Yes	Yes	—
Massachusetts	Westford	Yes	Yes	Yes
Massachusetts	Westport	Yes	Yes	Yes
Massachusetts	Westwood	—	Yes	Yes
Massachusetts	Weymouth	Yes	Yes	Yes
Massachusetts	Whately	Yes	Yes	Yes
Massachusetts	Williamstown	—	Yes	Yes
Massachusetts	Winchendon	—	Yes	—
Massachusetts	Winchester	Yes	Yes	Yes
Massachusetts	Woburn	—	Yes	—
Massachusetts	Wrentham	Yes	Yes	Yes
Massachusetts	Yarmouth	—	Yes	Yes
Maryland	Baltimore	Yes	Yes	Yes
Maryland	Charles County	—	Yes	—
Maryland	Gaithersburg	—	Yes	—
Maryland	Howard County	Yes	Yes	Yes
Maryland	Kensington	—	Yes	Yes
Maryland	La Plata	—	Yes	Yes
Maryland	Montgomery County	—	Yes	Yes
Maryland	Prince George's County	—	Yes	Yes
Maryland	Rockville	—	Yes	Yes
Maryland	Takoma Park	—	Yes	Yes
Maryland	Talbot County	—	Yes	—
Michigan	Alger County	Yes	—	—
Michigan	Baraga County	Yes	—	—
Michigan	Benzie County	Yes	—	—
Michigan	Berrien County	Yes	—	—

Appended Data Table for Figure 14.6   Continued

State	City or county	100% workplaces	100% restaurants	100% bars
Michigan	Calhoun County	Yes	—	—
Michigan	Detroit	Yes	—	—
Michigan	Gogebic County	Yes	—	—
Michigan	Grand Rapids	Yes	—	—
Michigan	Houghton County	Yes	—	—
Michigan	Leelanau County	Yes	—	—
Michigan	Lenawee County	Yes	—	—
Michigan	Mackinac County	Yes	—	—
Michigan	Marquette	Yes	—	—
Michigan	Marquette County	Yes	—	—
Michigan	Midland County	Yes	—	—
Michigan	Muskegon County	Yes	—	—
Michigan	Ottawa County	Yes	—	—
Michigan	Schoolcraft County	Yes	—	—
Michigan	St. Clair County	Yes	—	—
Michigan	Traverse City	Yes	—	—
Michigan	Washtenaw County	Yes	—	—
Minnesota	Beltrami County	Yes	—	—
Minnesota	Bloomington	Yes	Yes	Yes
Minnesota	Carlton County	Yes	Yes	Yes
Minnesota	Cottage Grove	Yes	Yes	Yes
Minnesota	Duluth	Yes	Yes	Yes
Minnesota	Golden Valley	Yes	Yes	Yes
Minnesota	Hennepin County	—	Yes	Yes
Minnesota	Hutchinson	Yes	Yes	Yes
Minnesota	Mankato	Yes	Yes	Yes
Minnesota	McLeod County	Yes	—	—
Minnesota	Minneapolis	—	Yes	Yes
Minnesota	Moorhead	Yes	—	—
Minnesota	Olmsted County	Yes	Yes	Yes
Minnesota	St. Paul	—	Yes	Yes
Missouri	Ballwin	Yes	Yes	Yes
Missouri	Belton	Yes	—	Yes
Missouri	Blue Springs	Yes	—	—
Missouri	Brentwood	Yes	Yes	Yes
Missouri	Chillicothe	—	Yes	Yes
Missouri	Clayton	Yes	Yes	—
Missouri	Columbia	—	Yes	Yes
Missouri	Creve Coeur	Yes	Yes	Yes
Missouri	Fulton	Yes	Yes	Yes

Appended Data Table for Figure 14.6   Continued

State	City or county	100% workplaces	100% restaurants	100% bars
Missouri	Gladstone	Yes	—	—
Missouri	Grandview	Yes	Yes	—
Missouri	Hannibal	Yes	Yes	Yes
Missouri	Hazelwood	Yes	Yes	—
Missouri	Independence	Yes	Yes	Yes
Missouri	Jefferson City	Yes	Yes	Yes
Missouri	Kansas City	Yes	Yes	Yes
Missouri	Kirksville	—	Yes	Yes
Missouri	Kirkwood	Yes	Yes	Yes
Missouri	Lake Saint Louis	Yes	Yes	Yes
Missouri	Lee's Summit	Yes	Yes	Yes
Missouri	Liberty	Yes	Yes	Yes
Missouri	Maryville	Yes	Yes	Yes
Missouri	Nixa	—	Yes	—
Missouri	North Kansas City	Yes	Yes	Yes
Missouri	O'Fallon	Yes	Yes	Yes
Missouri	Parkville	Yes	—	—
Missouri	Raymore	Yes	—	—
Missouri	Rolla	Yes	Yes	Yes
Missouri	Springfield	Yes	Yes	Yes
Missouri	St. Louis	Yes	Yes	—
Missouri	St. Louis County	Yes	Yes	—
Missouri	Warrensburg	Yes	Yes	—
Mississippi	Aberdeen	—	Yes	Yes
Mississippi	Amory	Yes	Yes	Yes
Mississippi	Anguilla	Yes	Yes	Yes
Mississippi	Arcola	Yes	Yes	Yes
Mississippi	Bassfield	Yes	Yes	Yes
Mississippi	Batesville	—	Yes	Yes
Mississippi	Belzoni	Yes	Yes	Yes
Mississippi	Booneville	Yes	Yes	—
Mississippi	Brandon	—	Yes	—
Mississippi	Brookhaven	Yes	Yes	Yes
Mississippi	Byram	Yes	Yes	Yes
Mississippi	Calhoun City	Yes	Yes	Yes
Mississippi	Canton	Yes	Yes	Yes
Mississippi	Centreville	Yes	Yes	Yes
Mississippi	Clinton	—	Yes	Yes
Mississippi	Coahoma County	Yes	Yes	Yes
Mississippi	Coldwater	Yes	—	—

Appended Data Table for Figure 14.6   Continued

State	City or county	100% workplaces	100% restaurants	100% bars
Mississippi	Collins	Yes	Yes	Yes
Mississippi	Corinth	Yes	Yes	—
Mississippi	Crystal Springs	Yes	Yes	Yes
Mississippi	Duncan	Yes	Yes	Yes
Mississippi	Durant	Yes	Yes	Yes
Mississippi	Ecru	—	Yes	Yes
Mississippi	Flora	Yes	Yes	Yes
Mississippi	Flowood	Yes	Yes	—
Mississippi	Forest	Yes	Yes	Yes
Mississippi	Georgetown	Yes	Yes	Yes
Mississippi	Greenwood	Yes	Yes	Yes
Mississippi	Grenada	—	Yes	Yes
Mississippi	Gulfport	Yes	Yes	—
Mississippi	Hattiesburg	Yes	Yes	Yes
Mississippi	Hernando	Yes	Yes	Yes
Mississippi	Hollandale	Yes	Yes	Yes
Mississippi	Jackson	Yes	Yes	Yes
Mississippi	Jonestown	Yes	Yes	Yes
Mississippi	Kosciusko	Yes	Yes	Yes
Mississippi	Laurel	Yes	Yes	Yes
Mississippi	Lumberton	Yes	Yes	Yes
Mississippi	Madison	Yes	Yes	Yes
Mississippi	Mayersville	Yes	Yes	Yes
Mississippi	Meridian	Yes	Yes	Yes
Mississippi	Metcalfe	Yes	Yes	Yes
Mississippi	Monticello	—	Yes	Yes
Mississippi	Moss Point	Yes	Yes	Yes
Mississippi	New Albany	Yes	Yes	Yes
Mississippi	New Augusta	Yes	Yes	Yes
Mississippi	Oxford	—	Yes	Yes
Mississippi	Pearl	—	Yes	—
Mississippi	Petal	Yes	Yes	Yes
Mississippi	Picayune	—	Yes	—
Mississippi	Pontotoc	—	Yes	Yes
Mississippi	Prentiss	Yes	Yes	Yes
Mississippi	Ridgeland	Yes	Yes	Yes
Mississippi	Rienzi	—	Yes	—
Mississippi	Rolling Fork	Yes	Yes	Yes
Mississippi	Senatobia	—	Yes	Yes
Mississippi	Shuqualak	Yes	Yes	Yes

Appended Data Table for Figure 14.6   Continued

State	City or county	100% workplaces	100% restaurants	100% bars
Mississippi	Starkville	Yes	Yes	Yes
Mississippi	Sumner	Yes	Yes	Yes
Mississippi	Sumrall	Yes	Yes	Yes
Mississippi	Tupelo	Yes	Yes	Yes
Mississippi	Verona	Yes	Yes	Yes
Mississippi	Walls	Yes	Yes	—
Mississippi	Wesson	Yes	Yes	Yes
Mississippi	West	Yes	—	—
Montana	Bozeman	Yes	Yes	—
Montana	Helena	Yes	Yes	Yes
North Carolina	Boone	—	Yes	Yes
North Carolina	Garland	—	Yes	Yes
North Carolina	Montreat	Yes	—	—
North Carolina	Orange County	—	Yes	Yes
North Dakota	Bismarck	Yes	Yes	Yes
North Dakota	Cavalier	Yes	Yes	Yes
North Dakota	Devils Lake	Yes	Yes	Yes
North Dakota	Fargo	Yes	Yes	Yes
North Dakota	Grafton	Yes	—	—
North Dakota	Grand Forks	Yes	Yes	Yes
North Dakota	Linton	Yes	Yes	Yes
North Dakota	Lisbon	Yes	Yes	Yes
North Dakota	Munich	Yes	Yes	Yes
North Dakota	Napoleon	Yes	Yes	Yes
North Dakota	Pembina	Yes	Yes	Yes
North Dakota	West Fargo	Yes	Yes	Yes
Nebraska	Grand Island	Yes	Yes	Yes
Nebraska	Humboldt	Yes	Yes	Yes
Nebraska	Lincoln	Yes	Yes	Yes
New Jersey	Atlantic City	Yes	Yes	Yes
New Jersey	Highland Park Borough	Yes	—	—
New Jersey	Holmdel Township	Yes	—	—
New Jersey	Livingston Township	Yes	—	—
New Jersey	Manville Borough	Yes	—	—
New Mexico	Alamogordo	—	Yes	Yes
New Mexico	Albuquerque	Yes	—	—
New Mexico	Bayard	Yes	Yes	Yes
New Mexico	Carlsbad	Yes	—	—
New Mexico	Curry County	—	Yes	Yes
New Mexico	Dona Ana County	Yes	Yes	Yes

Appended Data Table for Figure 14.6   **Continued**

State	City or county	100% workplaces	100% restaurants	100% bars
New Mexico	Edgewood	Yes	Yes	Yes
New Mexico	Elephant Butte	—	Yes	Yes
New Mexico	Espanola	Yes	Yes	Yes
New Mexico	Farmington	—	Yes	Yes
New Mexico	Gallup	—	Yes	Yes
New Mexico	Las Cruces	—	Yes	Yes
New Mexico	Los Lunas	—	Yes	Yes
New Mexico	Magdalena	—	Yes	Yes
New Mexico	Mesilla	Yes	Yes	Yes
New Mexico	Portales	—	Yes	Yes
New Mexico	Rio Rancho	—	Yes	Yes
New Mexico	Roswell	—	Yes	Yes
New Mexico	Santa Clara	Yes	Yes	—
New Mexico	Santa Fe	Yes	Yes	Yes
New Mexico	Taos	—	Yes	Yes
New Mexico	Tucumcari	—	Yes	Yes
New York	Dutchess County	Yes	Yes	—
New York	Nassau County	Yes	Yes	Yes
New York	New York City	Yes	Yes	Yes
New York	Suffolk County	Yes	Yes	Yes
New York	Tompkins County	Yes	Yes	Yes
New York	Westchester County	Yes	Yes	Yes
Ohio	Bexley	Yes	Yes	Yes
Ohio	Centerville	Yes	—	—
Ohio	Columbus	Yes	Yes	Yes
Ohio	Dublin	Yes	Yes	Yes
Ohio	Findlay	Yes	—	—
Ohio	Gahanna	Yes	Yes	Yes
Ohio	Grandview Heights	Yes	Yes	Yes
Ohio	Granville	Yes	Yes	Yes
Ohio	Heath	Yes	Yes	Yes
Ohio	Hilliard	Yes	—	—
Ohio	Marble Cliff	Yes	Yes	Yes
Ohio	New Albany	Yes	Yes	Yes
Ohio	Newark	Yes	—	—
Ohio	Powell	Yes	Yes	Yes
Ohio	Summit County	Yes	Yes	Yes
Ohio	Upper Arlington	Yes	Yes	Yes
Ohio	Westerville	Yes	Yes	Yes
Ohio	Worthington	Yes	Yes	Yes

Appended Data Table for Figure 14.6   Continued

State	City or county	100% workplaces	100% restaurants	100% bars
Oregon	Baker City	Yes	—	—
Oregon	Benton County	Yes	—	—
Oregon	Central Point	Yes	—	—
Oregon	Corvallis	Yes	Yes	Yes
Oregon	Dallas	Yes	Yes	Yes
Oregon	Eugene	Yes	Yes	Yes
Oregon	Independence	Yes	Yes	Yes
Oregon	Manzanita	Yes	—	—
Oregon	Philomath	Yes	Yes	Yes
Oregon	Rockaway Beach	Yes	—	—
Oregon	St. Helens	Yes	—	—
Oregon	Tillamook	Yes	—	—
Oregon	Tillamook County	Yes	—	—
Oregon	Tualatin	Yes	—	—
Oregon	Wheeler	Yes	—	—
Pennsylvania	Philadelphia	—	Yes	—
South Carolina	Aiken	Yes	Yes	Yes
South Carolina	Aiken County	Yes	Yes	Yes
South Carolina	Atlantic Beach	—	Yes	Yes
South Carolina	Beaufort	Yes	Yes	Yes
South Carolina	Beaufort County	Yes	Yes	Yes
South Carolina	Bluffton	Yes	—	—
South Carolina	Camden	Yes	Yes	Yes
South Carolina	Cayce	Yes	Yes	Yes
South Carolina	Chapin	Yes	Yes	Yes
South Carolina	Charleston	—	Yes	Yes
South Carolina	Charleston County	—	Yes	Yes
South Carolina	Chesnee	Yes	Yes	Yes
South Carolina	Clemson	—	Yes	Yes
South Carolina	Columbia	Yes	Yes	Yes
South Carolina	Easley	Yes	Yes	Yes
South Carolina	Edisto Beach	Yes	Yes	Yes
South Carolina	Florence	—	Yes	Yes
South Carolina	Fort Mill	Yes	Yes	Yes
South Carolina	Greenville	Yes	Yes	Yes
South Carolina	Hampton	Yes	Yes	Yes
South Carolina	Hartsville	Yes	Yes	Yes
South Carolina	Hilton Head Island	—	Yes	Yes
South Carolina	Hollywood	Yes	Yes	Yes
South Carolina	Isle of Palms	—	Yes	Yes

Appended Data Table for Figure 14.6   **Continued**

State	City or county	100% workplaces	100% restaurants	100% bars
South Carolina	Kershaw	Yes	Yes	Yes
South Carolina	Lancaster County	Yes	Yes	Yes
South Carolina	Lexington	Yes	Yes	Yes
South Carolina	Lexington County	Yes	Yes	Yes
South Carolina	Liberty	—	Yes	—
South Carolina	Mount Pleasant	—	Yes	Yes
South Carolina	North Augusta	Yes	Yes	Yes
South Carolina	North Myrtle Beach	Yes	Yes	Yes
South Carolina	Pendleton	—	Yes	Yes
South Carolina	Pickens	—	Yes	Yes
South Carolina	Pine Ridge	Yes	Yes	Yes
South Carolina	Quinby	—	Yes	Yes
South Carolina	Ravenel	—	Yes	Yes
South Carolina	Richland County	Yes	Yes	Yes
South Carolina	Rock Hill	Yes	Yes	Yes
South Carolina	Simpsonville	Yes	Yes	Yes
South Carolina	South Congaree	Yes	Yes	Yes
South Carolina	Spartanburg	Yes	Yes	Yes
South Carolina	Springdale	Yes	Yes	Yes
South Carolina	Sullivan's Island	—	Yes	Yes
South Carolina	Summerville	—	Yes	Yes
South Carolina	Sumter	Yes	Yes	Yes
South Carolina	Surfside Beach	Yes	Yes	Yes
South Carolina	Timmonsville	—	Yes	Yes
South Carolina	Walterboro	Yes	Yes	Yes
South Carolina	West Columbia	Yes	Yes	Yes
South Carolina	York County	Yes	Yes	Yes
Texas	Abilene	Yes	Yes	Yes
Texas	Alpine	—	—	Yes
Texas	Alton	Yes	Yes	Yes
Texas	Angleton	—	Yes	—
Texas	Arlington	—	Yes	—
Texas	Athens	Yes	—	—
Texas	Austin	Yes	Yes	Yes
Texas	Baytown	Yes	Yes	Yes
Texas	Beaumont	Yes	Yes	Yes
Texas	Benbrook	Yes	Yes	Yes
Texas	Boerne	—	Yes	—
Texas	Brenham	—	Yes	—
Texas	Brownsville	Yes	Yes	Yes

Appended Data Table for Figure 14.6   Continued

State	City or county	100% workplaces	100% restaurants	100% bars
Texas	Caldwell	Yes	—	—
Texas	College Station	Yes	Yes	Yes
Texas	Conroe	Yes	Yes	—
Texas	Copperas Cove	Yes	Yes	Yes
Texas	Corpus Christi	Yes	Yes	Yes
Texas	Dallas	Yes	Yes	Yes
Texas	El Lago	—	Yes	Yes
Texas	El Paso	Yes	Yes	Yes
Texas	Ennis	Yes	Yes	Yes
Texas	Flower Mound	Yes	Yes	Yes
Texas	Forney	—	Yes	—
Texas	Fort Worth	Yes	Yes	—
Texas	Frisco	Yes	Yes	Yes
Texas	Galveston	Yes	—	—
Texas	Harlingen	Yes	Yes	Yes
Texas	Hewitt	Yes	—	—
Texas	Highland Village	Yes	—	—
Texas	Horseshoe Bay	Yes	Yes	Yes
Texas	Houston	Yes	Yes	Yes
Texas	Humble	Yes	Yes	—
Texas	Kaufman	Yes	—	—
Texas	Kerrville	—	—	Yes
Texas	Kilgore	Yes	—	—
Texas	Killeen	Yes	Yes	—
Texas	Laredo	Yes	Yes	Yes
Texas	Leander	Yes	—	—
Texas	Lewisville	—	Yes	Yes
Texas	Marshall	Yes	Yes	Yes
Texas	McKinney	Yes	Yes	Yes
Texas	Mesquite	—	Yes	Yes
Texas	Missouri City	Yes	Yes	Yes
Texas	Nacogdoches	Yes	Yes	Yes
Texas	New Braunfels	Yes	—	—
Texas	Palestine	Yes	—	—
Texas	Pasadena	Yes	Yes	—
Texas	Pearland	Yes	Yes	Yes
Texas	Plano	Yes	Yes	Yes
Texas	Portland	Yes	Yes	—
Texas	Prosper	—	Yes	—
Texas	Richardson	Yes	—	—

Appended Data Table for Figure 14.6 Continued

State	City or county	100% workplaces	100% restaurants	100% bars
Texas	Robinson	Yes	Yes	—
Texas	Rockwall	—	Yes	—
Texas	Rollingwood	—	Yes	Yes
Texas	Rosenberg	Yes	Yes	—
Texas	Round Rock	Yes	Yes	—
Texas	Rowlett	Yes	Yes	Yes
Texas	San Angelo	Yes	Yes	Yes
Texas	San Antonio	Yes	Yes	Yes
Texas	Socorro	Yes	Yes	Yes
Texas	Southlake	Yes	Yes	Yes
Texas	Sugar Land	Yes	Yes	—
Texas	Sweeny	—	Yes	—
Texas	Tyler	Yes	Yes	Yes
Texas	University Park	—	Yes	Yes
Texas	Vernon	Yes	Yes	Yes
Texas	Victoria	Yes	Yes	Yes
Texas	Woodway	Yes	Yes	Yes
Texas	Yoakum	Yes	—	—
Virginia	Norfolk	—	Yes	Yes
Vermont	Burlington	—	Yes	Yes
Vermont	South Burlington	—	Yes	Yes
Vermont	Williston	—	Yes	Yes
Vermont	Winooski	—	Yes	Yes
Washington	Clark County	Yes	Yes	Yes
Washington	King County	Yes	Yes	Yes
Washington	Mason County	Yes	Yes	Yes
Washington	Pierce County	Yes	Yes	Yes
Washington	Tacoma	Yes	Yes	Yes
Wisconsin	Appleton	Yes	Yes	Yes
Wisconsin	Beaver Dam	Yes	Yes	Yes
Wisconsin	Beloit	Yes	Yes	Yes
Wisconsin	Big Bend	Yes	Yes	Yes
Wisconsin	Chippewa County	Yes	Yes	Yes
Wisconsin	Dane County	Yes	Yes	Yes
Wisconsin	De Pere	Yes	Yes	Yes
Wisconsin	Eau Claire	Yes	Yes	Yes
Wisconsin	Fennimore	Yes	Yes	Yes
Wisconsin	Fitchburg	Yes	Yes	Yes
Wisconsin	Fond du Lac	Yes	Yes	Yes
Wisconsin	Glendale	Yes	Yes	Yes

Appended Data Table for Figure 14.6   Continued

State	City or county	100% workplaces	100% restaurants	100% bars
Wisconsin	Green Bay	Yes	Yes	Yes
Wisconsin	Hudson	Yes	Yes	Yes
Wisconsin	Kenosha	Yes	Yes	Yes
Wisconsin	Lake Delton Village	Yes	Yes	Yes
Wisconsin	Lincoln County	Yes	Yes	Yes
Wisconsin	Madison	Yes	Yes	Yes
Wisconsin	Marshfield	Yes	Yes	Yes
Wisconsin	Menomonie	Yes	—	—
Wisconsin	Merrill	Yes	Yes	Yes
Wisconsin	Middleton	Yes	Yes	Yes
Wisconsin	Milwaukee	Yes	Yes	Yes
Wisconsin	Monona	Yes	Yes	Yes
Wisconsin	Neenah	Yes	Yes	Yes
Wisconsin	North Hudson	Yes	Yes	Yes
Wisconsin	Oak Creek	Yes	Yes	Yes
Wisconsin	Oneida County	Yes	Yes	Yes
Wisconsin	Park Ridge	—	Yes	—
Wisconsin	Portage	Yes	Yes	Yes
Wisconsin	Prairie du Chien	Yes	Yes	Yes
Wisconsin	Reedsburg	Yes	Yes	Yes
Wisconsin	Rhinelander	Yes	Yes	Yes
Wisconsin	Shorewood	Yes	Yes	Yes
Wisconsin	Shorewood Hills	Yes	Yes	Yes
Wisconsin	Somerset	Yes	Yes	Yes
Wisconsin	South Milwaukee	Yes	Yes	Yes
Wisconsin	Stevens Point	Yes	—	—
Wisconsin	Suamico	Yes	Yes	Yes
Wisconsin	Verona	Yes	Yes	Yes
Wisconsin	Watertown	Yes	Yes	Yes
Wisconsin	West Allis	Yes	Yes	Yes
Wisconsin	Weston	Yes	Yes	Yes
Wisconsin	Winnebago County	Yes	Yes	Yes
Wisconsin	Wisconsin Dells	Yes	Yes	Yes
Wisconsin	Wisconsin Rapids	Yes	Yes	Yes
West Virginia	Barbour County	Yes	Yes	—
West Virginia	Berkeley County	Yes	Yes	—
West Virginia	Boone County	Yes	—	—
West Virginia	Braxton County	Yes	Yes	Yes
West Virginia	Brooke County	Yes	—	—
West Virginia	Cabell County	Yes	Yes	Yes

Appended Data Table for Figure 14.6   Continued

State	City or county	100% workplaces	100% restaurants	100% bars
West Virginia	Calhoun County	Yes	Yes	Yes
West Virginia	Clay County	Yes	Yes	—
West Virginia	Doddridge County	Yes	Yes	Yes
West Virginia	Fayette County	Yes	Yes	—
West Virginia	Grant County	Yes	Yes	Yes
West Virginia	Greenbrier County	Yes	Yes	Yes
West Virginia	Hardy County	Yes	—	—
West Virginia	Harrison County	Yes	Yes	Yes
West Virginia	Jackson County	Yes	Yes	Yes
West Virginia	Jefferson County	Yes	—	—
West Virginia	Kanawha County	Yes	Yes	Yes
West Virginia	Lewis County	Yes	Yes	—
West Virginia	Lincoln County	Yes	Yes	Yes
West Virginia	Marion County	Yes	Yes	—
West Virginia	Marlinton	Yes	Yes	Yes
West Virginia	Marshall County	Yes	—	—
West Virginia	McDowell County	—	Yes	—
West Virginia	Mercer County	Yes	Yes	—
West Virginia	Mineral County	Yes	—	—
West Virginia	Mingo County	Yes	—	—
West Virginia	Monongalia County	Yes	Yes	Yes
West Virginia	Monroe County	Yes	Yes	—
West Virginia	Morgan County	Yes	Yes	—
West Virginia	Morgantown	Yes	Yes	Yes
West Virginia	Nicholas County	Yes	—	—
West Virginia	Ohio County	Yes	Yes	Yes
West Virginia	Pendleton County	Yes	Yes	Yes
West Virginia	Pleasants County	Yes	Yes	Yes
West Virginia	Pocahontas County	Yes	Yes	Yes
West Virginia	Preston County	Yes	—	—
West Virginia	Raleigh County	Yes	—	—
West Virginia	Randolph County	Yes	Yes	Yes
West Virginia	Ritchie County	Yes	Yes	Yes
West Virginia	Roane County	Yes	Yes	Yes
West Virginia	Summers County	Yes	Yes	Yes
West Virginia	Taylor County	Yes	Yes	Yes
West Virginia	Tucker County	Yes	Yes	Yes
West Virginia	Upshur County	Yes	Yes	Yes
West Virginia	Wayne County	Yes	—	—
West Virginia	Webster County	Yes	Yes	—

Appended Data Table for Figure 14.6   Continued

State	City or county	100% workplaces	100% restaurants	100% bars
West Virginia	Wirt County	Yes	Yes	Yes
West Virginia	Wood County	Yes	Yes	Yes
West Virginia	Wyoming County	Yes	Yes	Yes
Wyoming	Burlington	Yes	Yes	Yes
Wyoming	Casper	—	Yes	Yes
Wyoming	Cheyenne	—	Yes	Yes
Wyoming	Evanston	—	Yes	Yes
Wyoming	Laramie	—	Yes	Yes
Wyoming	Mountain View	Yes	Yes	Yes
Wyoming	Rock Springs	—	Yes	—

Alaska Anchorage Yes Yes Yes Alaska Barrow — Yes — Ala

Appendix 14.3
Tobacco Litigation Case Summaries

Tobacco Litigation Case Summaries

Case Against Legacy Foundation

In 2001, the Lorillard Tobacco Company (Lorillard) launched a series of attacks claiming that the truth® campaign had violated the provisions of the Master Settlement Agreement (MSA), which prohibited the American Legacy Foundation (Legacy) from engaging in "vilification" or "personal attacks." After receiving notice of Lorillard's intent to sue under the MSA, Legacy moved first, seeking a declaratory judgment in the Delaware courts that it could not be sued under the MSA since it was not a party to the agreement and, in the alternative, that its ads violated no legal requirements. Lorillard quickly filed a second suit against Legacy and also filed suit against the National Association of Attorneys General and the attorney general of Delaware, contending that they were responsible for Legacy's actions. After 5 years of litigation activities, the Delaware Supreme Court unanimously rejected an effort by Lorillard to shut down Legacy or, at least, the truth® campaign, its edgy and effective youth public education campaign (*Lorillard Tobacco Co. v. American Legacy Foundation*, 903 A.2d 728 [Del. Supr. 2006]).

Light Cigarette Cases

"Light" or "low-tar" cigarettes have been successfully marketed as less risky than smoking conventional cigarette brands (Kozlowski and Pillitteri 2001). However, such cigarettes have not been found to be safer than higher-yield cigarettes and they are just as addictive (Thun and Burns 2001). Tragically, because of this all too common misconception, millions and millions of smokers switched to light cigarettes instead of quitting (Shiffman et al. 2001).

The National Cancer Institute (2001) published internal industry documents that suggest that the cigarette industry knew the truth about light cigarettes, but kept this information secret and continued to market light cigarettes. Believing that they were misled, light cigarette smokers filed class action lawsuits under their states' unfair and deceptive business practices statutes. The intent of these statutes is to give consumers broad-based protection against abusive business practices (Sweda et al. 2007). The principal allegation in the light cigarette lawsuits was that the cigarette manufacturers misled consumers by marketing light cigarettes as having less tar and nicotine than other cigarette brands, even though actual exposure levels are the same. Those who smoked (and continue to smoke) light cigarettes reasonably believed that they were being exposed to less tar and nicotine and are entitled to refunds. Furthermore, under state unfair and deceptive business statutes, consumers often are entitled to monetary relief in the amount of three times the amount they spent.

Courts across the country have split on whether these cases may proceed as class actions. In *Estate of Michelle Schwarz v. Philip Morris, Inc.,* 348 OR. 442, 235 P.3d 668 (2010), where a woman switched to light cigarettes rather than quitting and subsequently died of lung cancer, the jury returned a verdict of $168,000 in compensatory damages and $150 million in punitive damages. These damages were reduced to $25 million in a retrial necessitated for technical reasons, and was appealed and retried in 2010 by the Oregon Supreme Court.

Canadian Class Actions

Although class actions are not available in most countries, they are possible under provincial law in the Canadian civil justice system (Watson 2001). Two major class actions against tobacco manufacturers went to trial in 2012, where they are being tried together in a Montreal courtroom. Each involves class members from the province of Quebec. Together, the cases seek over $27 billion (Can.) from the three major cigarette manufacturers operating in Canada (Chung 2012).

In the "Letourneau" case, the plaintiffs are seeking a payment of $10,000 (Can.) for each of the estimated 1.8 million addicted smokers in the province (*Cécilia Létourneau v. JTI-Macdonald Corp, Imperial Tobacco Canada Ltd., and Rothmans, Benson & Hedges Inc.,* District of Montreal, PQ No. 500-06-000070-983 [2012]). In the other case, known as "Blais," the plaintiffs are seeking $105,000 (Can.) for each of the estimated 90,000 members of the class suffering from lung cancer, larynx cancer, throat cancer, or emphysema due to smoking (*Conseil québ*è*cois sur le tabac et la santé and Jean-Yves Blais v. JTI-Macdonald Corp, Imperial Tobacco Canada, and Rothmans, Benson & Hedges Inc.,* District of Montreal, PQ No. 500-06-000076-980 [2012]). Like the trials

in the United States, many of the internal documents from the manufacturers are being made publicly available (Chung 2012).

Individual Cases

Along with the state-brought suits and class actions, several individual plaintiffs have successfully brought claims against the tobacco industry in the third wave of tobacco litigation. Most of these plaintiffs raised claims similar to the product liability claims individual plaintiffs brought in the second wave. In addition to compensatory damages, juries have punished the tobacco industry's conduct by awarding punitive damages in many of these cases. Individuals injured from cigarettes and industry misconduct continue to bring claims against the tobacco industry.

In 1991, Grady Carter brought the first tobacco case to produce a verdict that the defendant actually paid. Carter, a lifetime smoker of Lucky Strike cigarettes, sued Brown & Williamson Tobacco Corporation under theories of negligence and strict liability after being diagnosed with lung cancer (*Tobacco Products Litigation Reporter* 1996, p. 1.114). In 1996, the jury found that the defendant's cigarettes were "unreasonably dangerous and defective" and awarded Carter $750,000. After exhausting all of its appeals, the defendant paid Carter in 2001 (Van Voris 2001).

In a more recent lawsuit, Mayola Williams sued Philip Morris on behalf of her deceased husband, who smoked about three packs of the defendant's cigarettes per day from the early 1950s until his death from lung cancer in 1997 (*Williams v. Philip Morris, Inc.*, 92 P.3d 126 [Or. Ct. App. 2004]; Guardino and Daynard 2005). After trial, an Oregon jury awarded Williams $821,485.80 in compensatory damages and $79.5 million in punitive damages. The trial judge reduced the damages to $500,000 and $32 million, respectively (Miura et al. 2006). The Oregon Court of Appeals reinstated the $79.5 million award for punitive damages. On the third appeal to the U.S. Supreme Court, the Court dismissed the writ of certiorari (the decision by the Supreme Court to hear an appeal from a lower court) as "improvidently granted," exhausting all of the defendant's appeals and finalizing the $79.5 million award (*Philip Morris Inc., v. Williams*, 556 U.S. 178, 129 S. Ct. 1436, 173 L. Ed. 2d 346, 2009 U.S. LEXIS 2493, 77 U.S.L.W. 3557, 21 Fla. L.Weekly Fed. S. 731 [2009]).

Four individuals have separately sued Philip Morris successfully in California for injuries they sustained from smoking cigarettes. The first California suit, *Henley v. Philip Morris Inc.*, 113 Cal.Rptr.2d 494, 93 Cal.

App.4th 824 (2001); 114 Cal. App. 4th 1429, 9 Cal.Rptr.3d 29 (2004), resulted in a jury verdict of $1.5 million in compensatory damages and $50 million (later reduced to $9 million) in punitive damages (Table 14.3.1) (Guardino and Daynard 2005). In *Whiteley v. R.J. Reynolds Tobacco Co.*, WL 3299595 (Cal. App. 1 Dist. Oct. 14, 2009), the jury initially awarded the plaintiff $1.7 million in compensatory damages and $20 million in punitive damages for her products liability claim. After a retrial, the jury awarded the plaintiff $2.4 million in compensatory damages, but no punitive damages.

The other two California cases involved extraordinarily large awards of punitive damages that the courts later reduced. In *Boeken v. Philip Morris USA, Inc.*, 48 Cal. 4th 788, 230 P.3d 342, 108 Cal. Rptr. 3d 806 (2010), the jury awarded the plaintiff, who was diagnosed with lung cancer after 10 years of smoking, $5.54 million in compensatory damages and $3 billion in punitive damages (Miura et al. 2006). A California appellate court reduced the punitive damages to $50 million, and the U.S. Supreme Court declined review, cutting off the defendant's final avenue of appeal (Miura et al. 2006). The jury in *Bullock v. Philip Morris, Inc.*, 159 Cal. App. 4th 655 (2008) also found in favor of the plaintiff and awarded compensatory damages of $850,000 and $28 billion in punitive damages. The trial court reduced the punitive damages amount to $28 million, and a California appellate court remanded the case for a new jury trial solely to recalculate punitive damages. On August 24, 2009, the second jury awarded the plaintiff $13.8 million in punitive damages, and on August 17, 2011, a California appellate court upheld the jury's award (*Bullock v. Philip Morris, Inc.*, 198 Cal. App. 4th 543 [2011]). California's highest court denied review of the $13.8 million punitive damages award.

In another individual plaintiff case, Willie Evans sued Lorillard in 2004 on behalf of his deceased mother, Marie Evans, alleging that the defendant negligently marketed Newport cigarettes (a menthol-flavored cigarette targeted at new, young, and African-American smokers) and negligently failed to warn consumers of the dangers associated with smoking Newports (*Evans v. Lorillard Tobacco Co.*, 465 Mass. 411 [2013]). Marie Evans began smoking when she was 13 years of age, several years after Lorillard began distributing free cigarettes to her and other residents of her housing project; she continued to smoke, despite many attempts to quit, until shortly before her death from lung cancer at 54 years of age. After trial, in December 2010, the jury found for the plaintiff and awarded a total of $71 million in compensatory damages (which the trial judge later reduced to $35 million) and $81 million in punitive damages (Valencia 2010). The $81 million punitive damages award, was reversed by the

Table 14.3.1 Punitive damages in tobacco litigation

Case Name	State	Verdict year	Initial punitive damages award	Final status of punitive damages award
Henley v. Philip Morris	CA	1999	$50 million	$9 million
Williams-Branch v. Philip Morris	OR	1999	$79.5 million	$79.5 million
Whiteley v R.J. Reynolds, Philip Morris	CA	2000	$20 million	$0
Engle v. R.J. Reynolds, et al.	FL	2000	$144.8 billion	$0
Boeken v. Philip Morris	CA	2001	$3 billion	$50 million
Burton v. Philip Morris	KS	2002	$15 million	$0
Schwarz v. Philip Morris	OR	2002	$150 million	$25 million (on appeal as of Dec. 2012)
Bullock v. Philip Morris	CA	2002	$28 billion	$13.8 million
Boerner v. Brown and Williamson Corp.	AR	2003	$15 million	$15 million
Price v. Philip Morris	IL	2003	$3 billion	$0
Frankson v. Brown and Williamson Corp.	NY	2004	$20 million	$5 million
Smith v. Brown and Williamson Corp.	MO	2005	$20 million	$1.5 million
Evans v. Lorillard	MA	2010	$81 million	$0

Supreme Judicial Court for technical reasons; the settlement of the case prevents this from being retried.

In addition to product liability suits, some individuals have brought consumer protection lawsuits against the tobacco industry, which also are referred to as private attorney general cases because the individual is acting in the interest of the public. In the early 1990s, a California individual sued R.J. Reynolds Tobacco Company (RJR) claiming that its Joe Camel advertising unfairly targeted minors (*Mangini v. R.J. Reynolds Tobacco Co.,* 7 Cal. 4th 1057 [1994]). Although the California Supreme Court later found that the *Federal Cigarette Labeling and Advertising Act* preempted this claim in *In re Tobacco Cases II*, 41 Cal. 4th 1257 (2007), Mangini and RJR settled this claim in 1997 (Mangini Settlement Agreement). RJR agreed to discontinue the Joe Camel advertising and paid $10 million, some of which was earmarked for educational programs to discourage minors from smoking, as part of the settlement agreement (Mangini Settlement Agreement 1997).

Secondhand Smoke Cases

It has been nearly four decades since the first reported case involving a nonsmoker's involuntary exposure to secondhand tobacco smoke (*Shimp v. New Jersey Bell Telephone Co.,* 368 A.2d 408, 145 N.J. Super. Dec. 20, 1976). Donna Shimp, an office worker for the New Jersey Bell Telephone Company was granted an injunction to ensure a smokefree area in her workplace. The company had already adopted a smokefree policy to protect its sensitive office equipment. The court held that the "evidence is clear and overwhelming. Cigarette smoke contaminates and pollutes the air, creating a health hazard not merely to the smoker but to all those around her who must rely upon the same air supply. The right of an individual to risk his or her own health does not include the right to jeopardize the health of those who must remain around him or her in order to perform properly the duties of their jobs."

The evidence of the hazards of exposure to secondhand smoke has only become stronger over the subsequent years (U.S. Department of Health and Human Services 2006). Whether in office settings, business establishments that are open to the public, prisons, multi-unit buildings, or in residences where child custody disputes are occurring, hundreds of lawsuits seeking to protect nonsmokers from the unnecessary hazards of exposure to secondhand smoke have proliferated throughout the United States.

In *Staron v. McDonald's Corp.*, 872 F. Supp. 1092 (D. Conn. 1993), 51 F.3d 353 (2nd Cir. 1995), the plaintiffs

brought an action under the *Americans with Disabilities Act* (1990); they argued that the presence of tobacco smoke in the defendant's restaurants prevents the plaintiffs from having the opportunity to benefit from the defendant's goods and services. Suffering from adverse physical reactions when in the presence of smoke, the plaintiffs also alleged that the defendant's restaurants are in fact places of public accommodation under 42 *U.S.C.* 12181. They were seeking an injunction against smoking in the defendant's restaurants, "thereby giving the plaintiffs equal access to said restaurants."

The U.S. Court of Appeals for the Second Circuit held "that plaintiffs' complaints do on their face state a cognizable claim against the defendants under the *Americans with Disabilities Act*," noting that "the determination of whether a particular modification is 'reasonable' involves a fact-specific, case-by-case inquiry that considers, among other factors, the effectiveness of the modification in light of the disability in question and the cost to the organization that would implement it . . . . We see no reason why, under the appropriate circumstances, a ban on smoking would not be a reasonable modification."

A child's exposure to secondhand smoke has been the core issue in a number of cases involving disputes about child custody when a couple is divorcing. In the case of *In Re Julie Anne, A Minor Child*, 121 Ohio Misc. 2d 20, 2002 Ohio 4489, 780 N.E.2d 635, 2002 Ohio Misc *LEXIS* 46 (2002), the court issued a restraining order against smokers to protect a child under the court's jurisdiction from the dangers of exposure to secondhand tobacco smoke. The Court took judicial notice of the harmful nature of secondhand smoke on the health of children, citing numerous studies that characterized secondhand smoke as a carcinogen and a hazard to those exposed to it. The Court concluded: "The overwhelming authoritative scientific evidence leads to the inescapable conclusion that a family court that fails to issue court orders restraining people from smoking in the presence of children under its jurisdiction is failing the children whom the law has entrusted to its care." The Court granted a restraining order with provisions that "the mother and father are hereby restrained under penalty of contempt from allowing any person, including themselves, to smoke tobacco in the presence of the minor child Julie Anne. If smoking is allowed in the house in which the child lives or visits on a regular basis, it shall be confined to a room well ventilated to the outside that is most distant from where the child spends most of her time when there."

In *Helling v. McKinney* 113 S. Ct. 2475, 509 U.S. 25 (1993), an inmate who was housed in a cell with a heavy smoker brought a civil rights action against prison officials alleging violation of the Eighth Amendment's cruel and unusual punishment provision due to his exposure to secondary cigarette smoke. In 1993 the U.S. Supreme Court affirmed a lower court "that McKinney states a cause of action under the Eighth Amendment by alleging that petitioners have, with deliberate indifference, exposed him to levels of exposure to secondary cigarette smoke that pose an unreasonable risk of serious damage to his future health."

In *Harwood Capital Corp. v. Carey*, No. 05-SP-00187 Boston Housing Court (2005), a landlord sought to evict two tenants after receiving complaints from abutting residents about the strong smell of smoke emanating from their apartment. The tenants' lease did not mention smoking. The tenants worked out of the unit; they combined to smoke about 40–60 cigarettes per day. After a 3-day trial, a jury returned a verdict that Carey had breached his lease under a clause in the standard Greater Boston Real Estate Board lease prohibiting tenants from creating a nuisance or engaging in activity that substantially interfered in the rights of other building occupants. The jury also ruled that, therefore, the landlord was entitled to possession of the unit.

Litigation over exposure to secondhand smoke is not limited to the United States. In the 1980s and 1990s, a substantial number of individuals brought legal claims against employers and hospitality venue operators in Australia after suffering harm from exposure to secondhand tobacco smoke (Scollo and Winstanley 2008). During the same period, many employers began to voluntarily impose smoking bans in workplaces. Across Australia, states and territories have enacted laws that ban smoking in most enclosed workplaces as well as some unenclosed public places.

Cigarette-Fire Cases

Several fire-related product liability suits against Philip Morris have been dismissed (Halbert 1999). However, in 2003 Philip Morris paid $2 million to settle a Texas lawsuit based on an incident in 1992 when a 21-month-old girl, Shannon Moore, was severely burned while asleep in a car seat when her mother's parked car burst into flames (Levin 2003). The lawsuit alleged that the girl's mother had inadvertently let her lit cigarette fall onto the car seat, where it smoldered before igniting the car seat. As the *Los Angeles Times* reported, "[o]ver the course of the litigation, lawyers took dozens of depositions and Philip Morris produced more than 100,000 pages of internal documents concerning its research and lobbying activities on fire-safe cigarettes" (Levin 2003).

Smokeless Tobacco Cases

In June 1986, an Oklahoma City, Oklahoma, jury returned a verdict for a defendant smokeless tobacco company (*Marsee v. U.S. Tobacco Co.*, 639 F.Supp. 466 [1986]; 866 F.2d 319 [10th Cir. 1989]). Sean Marsee had died at 19 years of age from tongue cancer after using Copenhagen snuff and chewing tobacco for at least 6 years. His family was unsuccessful in its attempt to have the defense verdict overturned on appeal.

However, in 2010, the family of a 42-year-old North Carolina man, Bobby Hill, who died of mouth cancer after three decades of using U.S. Smokeless Tobacco Company's Skoal and Copenhagen brands of smokeless tobacco, reached a $5 million settlement of a wrongful death lawsuit (Helliker 2010).

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Chapter 15
The Changing Landscape of Tobacco Control—Current Status and Future Directions

Introduction

This chapter addresses options for tobacco control in the United States moving forward after the 50 years of progress since the 1964 report. In this section, previous chapters have charted the course of the epidemic (see Chapter 13, "Patterns of Tobacco Use Among U.S. Youth, Young Adults, and Adults") and the state-of-knowledge related to tobacco control (see Chapter 14, "Current Status of Tobacco Control"). They have also documented the burden of tobacco-caused disease and premature death (see Chapter 12, "Smoking-Attributable Morbidity, Mortality, and Economic Costs"). This chapter summarizes the modeling that demonstrates this burden will persist well into the twenty-first century, absent the acceleration in the decline of cigarette smoking. Chapter 16, "A Vision for Ending the Tobacco Epidemic: Towards a Society Free of Tobacco-Caused Death and Disease," sets out a vision for the future, creating a society free of tobacco-related death and disease. This chapter addresses how that vision can be achieved, considers what we have learned and accomplished to date in tobacco control, and identifies challenges to accelerating the impact of tobacco control and to ending the tobacco epidemic. It considers what else we need to know through research and surveillance and what are the possible evidence-based paths toward the elimination of premature death, disease, and economic costs caused by tobacco use.

The target for future tobacco control initiatives is already well described in two key national reports: The Institute of Medicine's (IOM's) report, *Ending the Tobacco Problem: A Blueprint for the Nation* (Bonnie et al. 2007) and *Ending the Tobacco Epidemic: A Tobacco Control Strategic Action Plan for the U.S. Department of Health and Human Services* (*Strategic Action Plan*) (U.S. Department of Health and Human Services [USDHHS] 2010a). Potential future directions are examined in the context of today's rapidly changing tobacco control landscape, and plausible alternative strategies based on proven effective interventions and policies are discussed. Finally, proposed potential end game scenarios are reviewed. Some of these are potentially applicable in the United States, and others that are unlikely in the United States may be applicable elsewhere. They are presented to provide a starting point for exploring potential options that may profoundly reduce preventable disease and death as quickly as possible.

The Tobacco Control Landscape: Over a Hundred Years and Counting

This report's previous chapters have described the origins of the tobacco epidemic and its century-long course. As discussed in prior Surgeon General's reports (USDHHS 2000b, 2010b) and in Chapter 2, "Fifty Years of Change 1964–2014" of this report, tobacco has been grown and used in the Americas for many millennia, but widespread use of highly addictive cigarettes is relatively recent, beginning at the end of the nineteenth century. The massive cigarette-attributable disease epidemic we have faced since the middle of the twentieth century was precipitated by the emergence of the modern cigarette industry early in the twentieth century. The epidemic of morbidity and mortality in the United States has been largely driven by cigarette use, the most common form of tobacco use globally (with the exception of South Asia and parts of Africa) (USDHHS 2010b; Giovino et al. 2012).

Since tobacco consumption was first tracked in the 1880s, patterns of use of various combustible and noncombustible tobacco-derived nicotine products have varied over time, geographically, and among population groups in the United States (Figure 13.1); these various products also have potentially different levels of addiction and toxicity (see Chapter 13 and previous Surgeon General's reports for discussions of addiction and toxicity [USDHHS 1988, 2000b, 2010b, 2012b]). The rapidity of onset of the cigarette epidemic is notable; cigarette use increased tenfold in the United States between 1908–1925 (from 105 to 1,085 cigarettes per capita) (Figure 13.1) and by the 1940s cigarettes had almost replaced other forms of tobacco use in the United States (Centers for Disease Control and Prevention [CDC] 1999; Giovino 2002; Proctor 2011). This epidemic was fueled by the widespread marketing and dissemination of this product—a combustible, easily-inhaled mass-manufactured cigarette, instead of the less convenient pipes, cigars, and smokeless products widely used in earlier decades (USDHHS 2000b; Giovino 2002; World Health Organization [WHO] 2008; Proctor 2011).

Many factors are responsible for the rapid increase of cigarette smoking, but the tobacco industry was the central driver (see Chapter 2) through: (1) development of industrial technology enabling cigarette mass production, packaging, and distribution (USDHHS 2000b); (2) aggressive pricing and marketing combined with positive portrayals of cigarettes in movies—and endorsements by movie stars, sports idols, and even physicians (see Chapters 2 and 14) (USDHHS 2001, 2012b)—and including cigarettes in daily rations for soldiers in two World Wars (see Chapter 14, and Appendix 14.1 available online at www. surgeongeneral.gov); and (3) widespread industry actions throughout society to advance its interests, including lobbying and using tactics later found to constitute fraud and racketeering, such as misleading the public about the risks of smoking (see Chapter 14) (*United States v. Philip Morris 2006*).

The contemporary era of tobacco control, which originated in the 1950s and 1960s, was motivated by the recognition that tobacco smoking was having devastating and increasing consequences for public health. The rising numbers of cases of lung cancer reported by physicians in the 1920s became a well-documented epidemic of lung cancer deaths among men by the 1950s (see Chapter 4, "Advances in Knowledge of the Health Consequences of Smoking: From 1964–2014"; Figures 4.1 and 4.3). Early epidemiologic investigations readily found evidence that cigarette smoking had a primary role in this emerging lung cancer epidemic among men and also in the parallel epidemic of cardiovascular disease. Increasingly intense tobacco control over the last decades of the twentieth century brought success, considered one of the top public health achievements of the century (CDC 1999; Ward and Warren 2007). The prevalence of adult smoking was dramatically reduced from a high of 42.7% (1965) to 18.1% at present (2012) (see Chapter 13). Annual adult per capita cigarette consumption dropped by 72% from 4,345 cigarettes in 1963 to 1,196 in 2012 (see Figure 2.1). The many actions that drove this decline are described in Chapter 14 and in earlier Surgeon General's reports (see Chapter 14; online Appendices 14.1–14.5) (USDHHS 1989, 2000b).

Looking to the future, tobacco control needs to be shaped to address an increasingly heterogeneous pattern of use of tobacco products, including emerging noncombustible products (Chapter 13). Some of the highest prevalence rates are now among persons of lower socioeconomic status, some racial and ethnic minority groups, sexual minorities (including individuals who are gay, lesbian, bisexual and transgender, and individuals with same-sex relationships and/or attraction), high school dropouts (Fagan et al. 2007; Lee et al. 2009; Garrett et al. 2011; Substance Abuse and Mental Health Services Administration [SAMHSA] 2013b), persons with mental illness and alcohol and substance abuse disorders (Prochaska et al. 2008; Schroeder and Morris 2010; Villanti et al. 2012; CDC 2013), American Indians and Alaska Natives as well as recent immigrants from high-prevalence countries, and people with complex comorbid medical illnesses (e.g., HIV/AIDS and cardiovascular disease) (Crothers et al. 2009; Hoffman et al. 2009; Marshall et al. 2009; Vidrine 2009; Levine et al. 2010; Tesoriero et al. 2010; Pines et al. 2011; Rahmanian et al. 2011). There is also substantial geographic variation with the highest prevalence rate in Appalachia and the South (Pickle and Su 2002).

Smoking cessation needs increased attention. Although there has been significant progress during the last 50 years, there is a major gap between the current level of successful quit attempts and the level needed to achieve the *Healthy People 2020* goal (Levy et al. 2010c). While adolescents and adults want to quit (70% plan to, and more than 50% try each year), far too few have been successful in quitting (about 4–6% of the smoking population as a whole succeed annually) (Burns et al. 2000; CDC 2011b). Utilization of proven treatments remains low among those attempting to quit, and little has been done to improve the success rates of unassisted smoking cessation efforts (Chapman and MacKenzie 2010; Chapman and Wakefield 2013). Since these unaided quit attempts (e.g., called quitting "cold turkey," or described as quitting without seeking help from health care provider, program, or other cessation services) have historically accounted for up to 90% of those who quit each year, it has been suggested that price increases, smoke-free policies, media campaigns, and other factors that decrease the social acceptability of smoking could enhance the success of these unassisted smoking cessation efforts (Chapman and MacKenzie 2010; Chapman and Wakefield 2013).

More aggressive prevention is also needed. Even after decades of using multiple, comprehensive strategies, each day more than 3,200 youth younger than 18 years of age smoke their first cigarette and another 2,100 youth and young adults who are occasional smokers go on to become daily smokers (SAMHSA 2013a). Nearly 9 out of 10 smokers experiment before 18 years of age, and 98% start smoking by 26 years of age (see Chapter 13, Table 13.2). Adolescents are highly vulnerable to tobacco industry marketing, smoking imagery in movies, and peer influence, and are not fully able to appreciate the health risks they face in the future (USDHHS 2012b). While progress has been made in reducing the prevalence of smoking among high school students, the rate of decline in recent years has slowed (see Chapter 13, Figure 13.8), and the number of youth and young adults who annually initiate smoking was significantly higher in 2012 (2.3 million) than it was in 2002 (1.9 million) (see Figure 13.26).

Although the 50 years of progress should be celebrated, modeling shows a large gap between what has been achieved in reducing the tobacco epidemic and what could have been achieved if smoking had been eliminated after the 1964 Surgeon General's report (Moolgavkar et al. 2012). In a recent analysis by the National Cancer Institute's Cancer Intervention and Surveillance Modeling Network, a consortium of six research groups provided an estimate of the cumulative impact of the changes in smoking behavior that started in the mid-1950s on lung cancer mortality in the United States during 1975–2000 (Moolgavkar et al. 2012). Approximately 800,000 lung cancer deaths were estimated to have been averted in the United States during 1975–2000, but this figure comprises only about 32% of the lung cancer deaths that could have been avoided if tobacco smoking had been completely eliminated after the 1964 Surgeon General's report.

For the future, tobacco control needs to more forcefully impact the burden of avoidable disease and premature death. About one-half of the 42.1 million smokers in the United States in 2012 (CDC 2013) who continue smoking into later decades of life will die prematurely of a tobacco-related disease, primarily from cigarette smoking (Jha et al. 2013). By 2015, tobacco use is expected to be responsible for 10% of all deaths globally (Mathers and Loncar 2006). Should such trends continue without any change in interventions and policy, the tobacco epidemic will be prolonged well into the twenty-first century. In fact, the scope of the epidemic may even increase if any of the tobacco control measures that are in place today are eroded (see Appendix 15.1 available online at www.surgeongeneral.gov); (Mendez et al. 1998; Mendez and Warner 2000, 2004, 2007, 2008; Levy et al. 2001).

The various patterns of using more than one type of combustible product raises additional concerns about our progress toward ending the epidemic of tobacco-related disease. Although the prevalence of current smoking among adults has declined in recent years (see Chapter 13, Figure 13.4 and Table 13.19), a high percentage of adolescent and young adult cigarette smokers report using more than one tobacco product (see Chapter 13, Tables 13.16 and 13.17). The prevalence of adults 18 years of age and older who report smoking cigarettes, cigars, or roll-your-own cigarettes using pipe tobacco presents a much less optimistic picture than looking at the prevalence of cigarette smoking only (see Chapter 13, Table 13.19). While the prevalence of using any of these smoked products has declined since 2002 (from 28.8%), 25.2% of adults reported current use in 2012 (see Table 13.19).

Given the urgency of reducing smoking and the only partial success of tobacco control to date, this chapter considers potential additions to what we are already doing. Given the growing awareness of the highly lethal and addictive nature of cigarettes, more dramatic restrictions on the manufacture, distribution, marketing, and sale of tobacco products are being proposed (Daynard 2009; Proctor 2013). The public health community has begun discussion of end game strategies, described subsequently in this chapter, that can be used to augment existing strategies. A further and emerging consideration is the role of the new products being introduced rapidly into the marketplace that can deliver aerosolized nicotine without the harmful products of combustion in cigarette smoke. Their availability and marketing could result in a significant fraction of smokers switching completely to them (Sumner 2003). However, there is also the potential for such products to have effects on youth initiation, to lead to a renormalization of public use of nicotine, and to result in sustained dual use of both aerosolized nicotine and cigarettes.

Modeling Plausible Futures: What Is Possible Using our Current Policy Tools?

In considering how to accelerate the end of the tobacco epidemic, models are an essential tool for projecting the potential consequences of tobacco control strategies. Models are used to project future patterns of tobacco use, given various scenarios of tobacco control measures. Appendix 15.1 provides an overview of tobacco control simulation models and how they have been applied to such scenarios. The results of modeling document the need for more aggressive action than the current level of implementation. Projections indicate that the prevalence of adult smoking could likely still be above the *Healthy People 2020* objective of 12% even by mid-century, if there is little change to current strategies (Figure 15.1) (Warner and Mendez 2010; Mendez et al. 2013). Further modeling shows that the goal of 12% prevalence cannot be reached by 2020 unless national initiation and cessation rates become similar to those observed in California in 2005, when California led the nation in declining smoking prevalence (Figure 15.2) (Mendez and Warner 2008). The success of the California comprehensive statewide tobacco control program (see Chapter 14) demonstrates that existing tobacco control strategies are effective when implemented on a sustained basis and argue for more robust and sustained implementation of these existing strategies nationally (see Appendix 15.1, Figure 15.1.13).

Models have been used to examine the impact of strengthening existing tobacco control policies (taxation, smokefree indoor air, and mass media campaigns), and the components of cessation interventions and their delivery

Figure 15.1 Predicted rates of smoking initiation and cessation for U.S. adults, University of Michigan Tobacco Prevalence and Health Effects Model
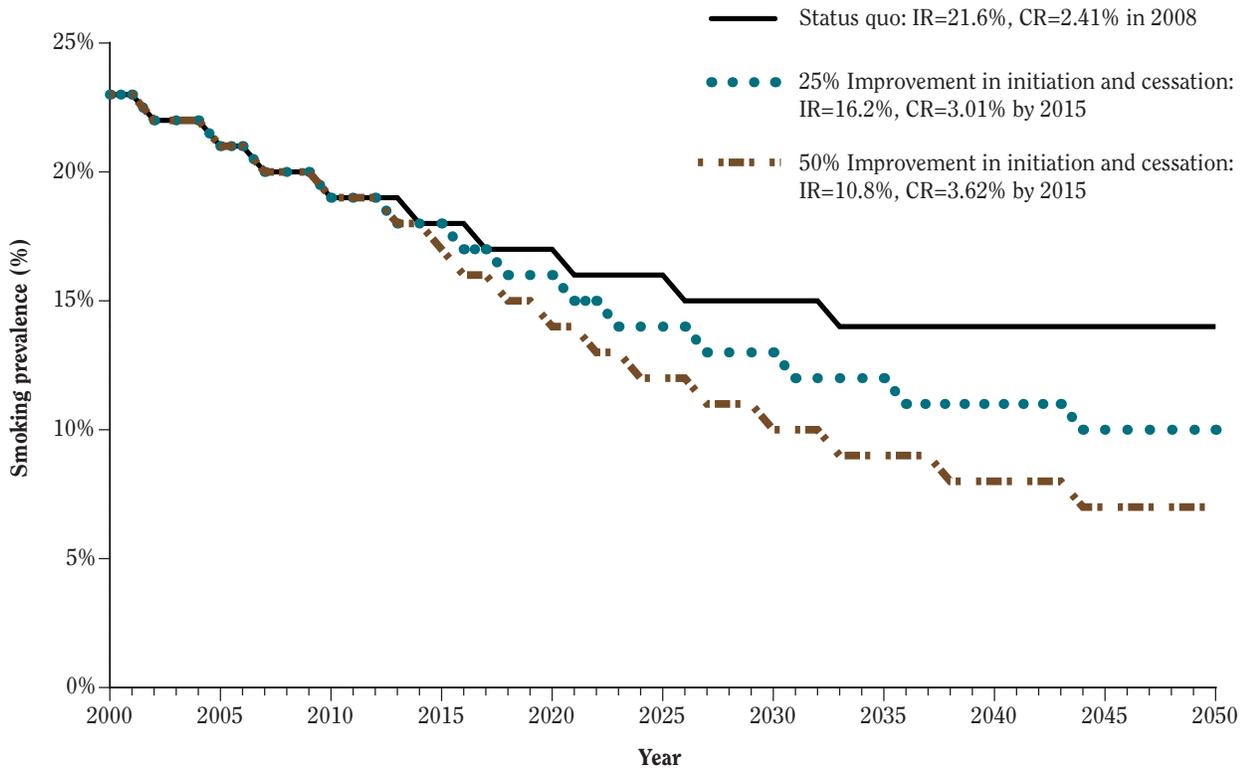
Source: University of Michigan, unpublished data.
Note: **CR** = cessation rate; **IR** = initiation rate.

(Figure 15.3) (Abrams et al. 2010; Levy et al. 2010a,b,c). Model results suggest that boosting quit attempts, treatment use, and treatment effectiveness by 100% would lead to moderate to dramatic reductions in the prevalence of adult smoking, by as early as 2020, to national levels ranging as low as 6.3–11.5% (Levy et al. 2010a). Building on the model of cessation treatments (Levy et al. 2010a), a broader simulation model explored the effects of implementing a comprehensive tobacco control strategy with four components directed at reducing the prevalence of smoking in the population: (1) price increases including those that result from cigarette tax increases, (2) smoke-free indoor air laws, (3) mass media/educational policies, and (4) evidence-based and promising new cessation treatment policies (Levy et al. 2010c). The goal of the models was to examine the relative effectiveness of the four policies and their potential combined contributions towards meeting the *Healthy People 2010* goal of 12% smoking prevalence. The modeling showed that implementing all four policies simultaneously at optimal levels in 2008,

without considering other potentially limiting factors, would increase the population quit rate by about 300% by 2013 (Levy et al. 2010c). Such aggressive efforts over a short period would have been needed to lower the prevalence from 20.1% in 2008 to the 12% *Healthy People 2010* goal by 2013. In actuality, in 2012, the prevalence was well above the *Healthy People 2010* goal (Figure 15.4).

Although a scenario with implementation of all four tobacco control policies at optimal levels at the same time was shown to produce a more optimistic projection, the projected increase of the population quit rate to about 300% would require significantly more effort than at present. Nevertheless, this simulation model illustrates the outcome of one scenario which produces higher impact estimates, involving the full suite of approaches currently known to be effective and implementing them with aggressive strategies, for example, improving the amount of reimbursement for the mandated insurance coverage of, and access to, evidence-based prevention and cessation services (Abrams 2007; Orleans et al. 2010).

The implications of the modeling carried out by Mendez and Warner (2007, 2010) are similar. Using a model that has forecast the prevalence of smoking in the United States quite accurately over a decade, Mendez and Warner (2007, 2010) demonstrated that if smoking initiation and cessation rates remain unchanged, the prevalence of adult smoking will stabilize at about 13.5% by the middle of the present century, a level of smoking that would exceed the *Healthy People 2020* goal of 12% and would still be higher than the percentage already achieved in California (Figure 15.2). Their analysis demonstrated that if the smoking initiation rate could be quickly brought down by 25% at the same time that cessation rates increased by 25%, the prevalence of smoking would fall to an estimated 10% by 2050. If initiation dropped by 50% and cessation rates increased by 50%, prevalence would drop to 6.7% by 2050. For 2020, the model predicts a smoking prevalence of 16.7% with status quo initiation and cessation rates, 15.5% with initiation and cessation improving by 25%, and 14.3% with initiation and cessation each improving by 50%. Even the most optimistic of these scenarios suggests that the *Healthy People 2020* target of 12% prevalence of adult smoking will not be achieved in 2020 (USDHHS 2012a). Even if this prevalence rate were achieved, one-eighth of adults would remain smokers, ensuring an annual mortality toll caused by smoking that would remain at hundreds of thousands of Americans for decades.

Simulation models are useful, but the projections are only as valid as their underlying assumptions and their input and transitional probability parameters, which are generally based on available data and sensitivity analysis (see Appendix 15.1). Nevertheless, there is utility in using simulation modeling to ask complex questions about future possibilities and then to suggest possible leverage points that could provide more efficient ways to reduce tobacco use. The results of simulation models also illustrate the potential population impact of systems integration of all intervention and policy elements, as recommended in IOM's report and the *Strategic Action Plan* (Bonnie et al. 2007; USDHHS 2010a). Systems-level modeling will remain a needed tool for continually revising tobacco control strategies, reflecting the dynamic nature of the tobacco epidemic and its drivers (see Figure 15.3).

Figure 15.2   Projection of U.S. adult smoking prevalence rates under status quo scenario and California rate scenarios, 2005–2020
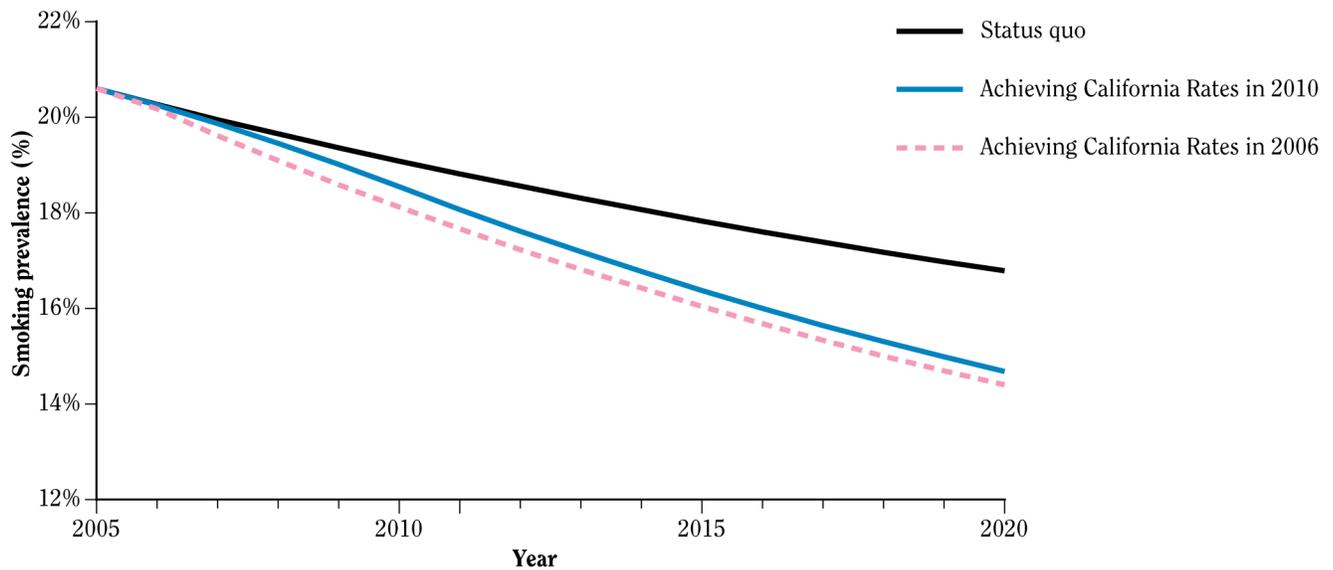
Source: Mendez and Warner 2008. Reprinted with permission from The Sheridan Press, © 2008.
Note: The bottom two lines depict corresponding scenarios assuming that the United States as a whole achieves California's 2005 rates (20% initiation rate and 3.33% cessation rate). The dotted line reflects the assumption that such rates are attained instantaneously (in 2006), whereas the solid line reflects the more plausible scenario that such rates will be achieved gradually (by 2010). The status quo initiation rate is 25%, and the cessation rate is 2.59%.

Figure 15.3   Simplified dynamic model of protobacco and antitobacco forces on patterns of tobacco use
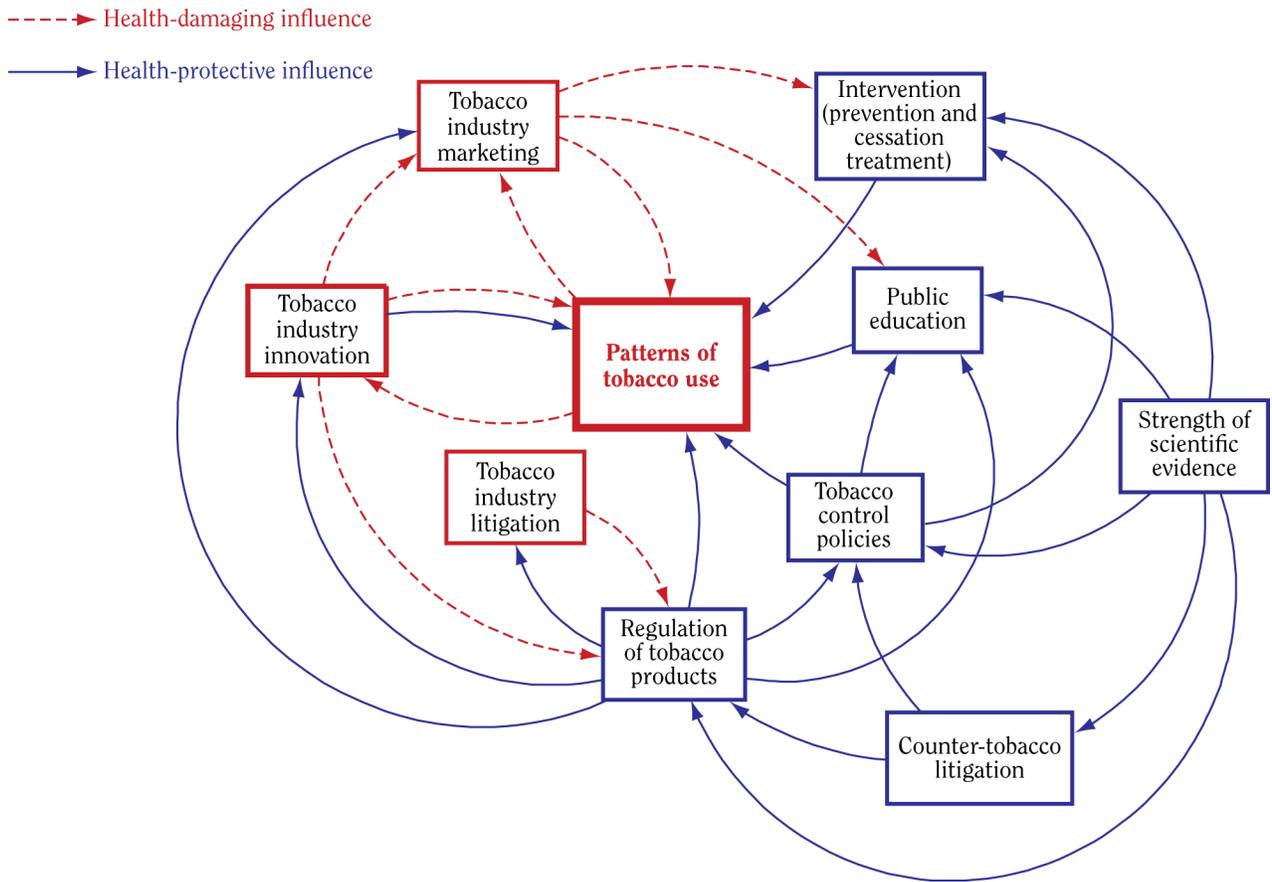
Source: Created by A. Villanti and D. Abrams for this Surgeon General's Report.

Figure 15.4   Effects of a 100% reduction in the quit attempt rate, treatment use, and treatment effectiveness on smoking prevalence, 2008–2020
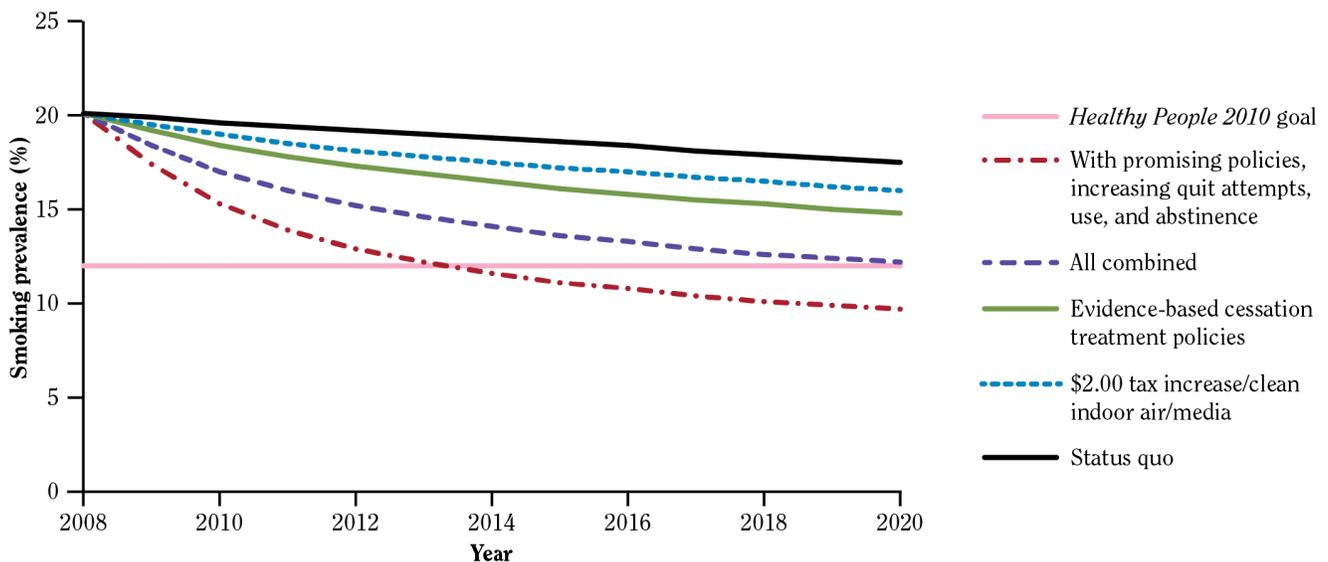
Source: Levy et al. 2010b.

Since the simulation models reviewed were completed, several additional years of survey data have been released, as reviewed in Chapter 13. As shown in Figure 13.4, the 2012 National Health Interview Survey estimate for the prevalence of current smoking among adults 18 years of age and older has declined to 18.1% and the trend downward from 2009 (20.6%) shows a more optimistic pattern than the data showing little change from 2005 (20.8%) to 2009, which were the basis for several of the simulation models reported above. However, other survey data from the National Survey on Drug Use and Health (see Table 13.19) show a small decline in the prevalence of current cigarette smoking among adults 18 years of age and older from 23% in 2009 to 22% in 2012, but almost no decline in the prevalence of adult current smoking between 2011 (21.7%) and 2012. Additional simulation models using these more recent data are needed to help provide further perspectives on progress toward meeting the *Healthy People 2020* objective of reducing the prevalence of adult smoking to 12% or less by 2020.

Looking to the Future

As noted above, the favorable impact of increasingly intense tobacco control efforts in the last decades of the twentieth century is considered one of the top public health achievements of the century (CDC 1999; Ward and Warren 2007). Nevertheless, the results from the models reviewed above exploring future scenarios of tobacco control indicate that the projected decline in tobacco use over coming decades will not be sufficiently rapid to meet the *Healthy People 2020* objective of 12% for adult smoking prevalence. A review of the effectiveness of evidence-based tobacco control interventions concluded that "further reductions in smoking in those developed countries that have achieved the most tobacco control success are likely to come frustratingly slowly; as well, smoking prevalence could level out at a rate far higher than anyone in tobacco control wants to contemplate" (Warner and Mendez 2010, p. 884). This observation by Warner and Mendez (2010) and the results of the models reviewed above suggest that without an acceleration in the rate of decline in the prevalence of smoking in the United States, the burden of tobacco-caused disease and premature deaths will persist well into the twenty-first century. Hence, the goal of ending the tragic burden of avoidable disease and premature death appears elusive for the near-term.

The 2007 IOM report (Bonnie et al. 2007) and the *Strategic Action Plan* (USDHHS 2010a) suggest that the rate of decline in youth and adult rates of smoking and tobacco use could be accelerated if the most effective tobacco control interventions were more fully imple-

mented simultaneously and the implementation was sustained. This report is also written at a time when legislation has brought new possibilities for strengthening tobacco control (see Chapter 14). Passage of the *Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act),* Public Law 111-13, *U.S. Statutes at Large* 123 (2009):1776, which provides the U.S. Food and Drug Administration (FDA) the authority to regulate tobacco products; the *Health Information Technology Economic and Clinical Health Act,* Public Laws 111-5, *U.S. Statutes at Large* 123 (2009):227, which will facilitate screening for tobacco use behaviors and implementation by health care providers of cessation services; and the 2010 *Patient Protection and Affordable Care Act,* Public Law 111-148, U.S. Statutes at Large 124 (2010):119, in combination with investment in tobacco control and prevention through the 2009 *American Recovery and Reinvestment Act,* Public Law 111-5, *U.S. Statutes at Large* 123 (2009):115, have resulted in substantial support for the implementation of evidence-based policies and programs to reduce tobacco use in recent years. Chapter 14 and Appendices 14.1–14.5 review the current status of tobacco control interventions that are known to be effective and could reach all the critical priority populations of at-risk youth and young adults, as well as those who are at greatest risk of dying in the short-term from a smoking-caused disease—adult smokers who have smoked for decades. Many have suggested that with full implementation of these strategies, far fewer youth and young adults would become smokers, and more smokers would successfully quit (USDHHS 2000b, 2012b; Abrams et al. 2010; Levy et al. 2010a,b; Orleans et al. 2010). The evidence reviewed in this and many previous reports document the benefits of smoking cessation. Additionally, the modeling results reviewed above show that increased access to evidence-based cessation treatments and aggressive promotion for all population groups would increase rates of successful cessation and thus reduce the consequences of smoking. With this imperative, and the opportunities provided by the *Affordable Care Act,* all groups of health care providers and systems should examine how they can establish a strong standard of care for smoking cessation for all (see Chapter 14). Additionally, the 2012 Surgeon General's report stated that "we have evidence-based strategies and tools that can rapidly drop youth initiation and prevalence rates down into the single digits" (USDHHS 2012b, p. 856). Although increased application of comprehensive tobacco control strategies recommended in that report could be highly effective, the current levels of implementation of these key strategies are far below the most effective levels.

Additional concerns about achieving more rapid progress have been raised. It has been suggested that some of these evidence-based policies and programs could be

less effective or less likely to be implemented in the future (Warner and Mendez 2010; Warner 2013). Evidence shows that large tax and, hence, price increases will decrease tobacco use each time they are implemented. But legislative willingness to substantially increase taxes would need to increase dramatically. Similarly, mass media campaigns can be very effective (McAfee et al. 2013); however, to produce large declines in the prevalence of adult smoking at the national level, these campaigns need to be implemented on a sustained basis with updated content (USDHHS 2012b). The impact of smokefree policies, and other factors affecting social norms, has increased dramatically during the last 50 years (see Chapters 2 and 14). However, since fewer states have implemented new comprehensive smokefree policies in the last few years, the pace of social norm change may have slowed. The pace of social norm change could be slowed by the recent increase in the level of tobacco depictions in top-grossing U.S. movies (see Chapter 14, Figures 14.3A and 14.3B) and the aggressive marketing and promotions for electronic cigarette brands (U.S. House of Representatives 2013).

Although the *Strategic Action Plan* provides a critical framework to guide and coordinate the implementation of comprehensive tobacco control policies and programs (USDHHS 2010a), we need to assure implementation of these evidence-based policies and programs on a sustained basis with strong intensity. For example, despite strong evidence of the efficacy of comprehensive state-wide tobacco control programs in reducing the initiation, prevalence, and intensity of smoking among youth and young adults (USDHHS 2012b), in 2010 the states were appropriating only 2.4% of their tobacco revenues for tobacco control (CDC 2012). Further, it has been noted that reaching CDC's recommended funding level would have required an additional 13% of tobacco revenues, or $3.1 billion of the $24 billion collected from the industry, yet the annual total state funding level has declined from the high in fiscal year 2003 and has declined even more sharply in several states where the efficacy of the programs was being demonstrated (CDC 2012) (see Chapter 14, Figure 14.7 and Table 14.5). Since the current levels of implementation of the evidence-based policies and programs need to be substantially increased and much more rapid declines in youth and adult rates of tobacco use are needed to end the tobacco epidemic, the academic and policy communities have proposed additional approaches that augment existing strategies to more quickly bring the tobacco epidemic to an end (Smith 2013; van der Eijk 2013). Some of these nascent strategies may eventually provide further possibilities for the United States, particularly as they are implemented and evaluated in international contexts. Others that may be impractical or inappropriate in the United States may have relevance in other countries.

Potential End Game Strategies

Faced with the challenge of achieving a vision of a society free of tobacco-related death and disease, a discussion has begun within the field of tobacco control about what has come to be called the tobacco "end game" in the published literature. This literature considers strategies that could be used, in addition to the expanded implementation of the proven tobacco control interventions, to accelerate declines in the use of cigarettes and other combusted tobacco products and end the epidemic of disease and premature death caused by tobacco. Scholars and the policy community have proposed interventions that could dramatically reduce the use of tobacco products, especially cigarettes (Benowitz and Henningfield 1994; Borland 2003; Callard et al. 2005a; Daynard 2009; Khoo et al. 2010; Proctor 2011; Thomson et al. 2010; Smith 2013). The editor of *Tobacco Control* has called for a robust discussion of the concept (Malone 2010); meetings of prominent tobacco control professionals have focused on individual proposals or on the concept more broadly (Smith 2013);

and sessions of both international and national tobacco control meetings have presented and debated the central ideas (2012 National Conference on Tobacco or Health, 2012 World Conference on Tobacco or Health, 2013 Annual Meeting of the Society for Research on Nicotine and Tobacco). This section briefly reviews what underlies the emergence of this discussion, considers the myriad ends toward which an end game might be oriented, and describes the principal end game proposals developed and discussed in the literature to date. Although some of these proposals are likely more potentially relevant to the U.S. situation than others, the consideration and potential implementation of less likely proposals elsewhere across the globe may eventually provide insights and evidence applicable for the United States as well. For example, decreases in morbidity and mortality resulting from rapid drops in cigarette use will be relevant regardless of the particular form of end game strategy applied. The principal approaches are summarized in Table 15.1.

Table 15.1. End game strategies discussed in the scientific literature

Proposal	Description	Source
Reducing nicotine yields	Gradual reduction of cigarette nicotine content to nonaddicting levels through government action	Benowitz and Henningfield 1994, 2013; Hatsukami et al. 2012, 2013
Reducing product toxicity	Implementation of product regulatory standards to require manufacture of tobacco products with very low toxicity	Hatsukami et al. 2010, 2013; Benowitz and Henningfield 2013
Gradual supply reduction	Phasing out tobacco use on a timetable by gradual reduction of supply to zero or some minimal level	Thomson et al. 2010; Wilson et al. 2013
Prohibiting sales to future generations	Implementing a ban on sales for people born after a particular date, so that smokefree cohorts are created that progressively increase in coverage and size	Khoo et al. 2010; Berrick 2013
Banning cigarettes and/or cigarettes plus additional tobacco products	Ban on the production and sale of cigarettes and/or cigarettes and additional tobacco products	Daynard 2009; Proctor 2011, 2013
Selling tobacco through a not-for-profit agency	To avoid the profit motive, transfer control of supply and sales to a not-for-profit agency that has the goal of reducing consumption	Borland 2003, 2013; Callard et al. 2005b; Callard and Collishaw 2013

One of the first such proposals was made in a 1994 article by Benowitz and Henningfield (1994), who described a policy approach of gradually reducing the nicotine in cigarettes to nonaddicting levels. Nearly a decade later, Borland (2003) advocated a "Regulated Market Model" for tobacco that would end direct-to-consumer marketing through the creation of a distribution agency with a harm reduction mandate. A subsequent paper by Callard and colleagues (2005b) also called for the removal of the profit incentive by transferring the tobacco market to a nonprofit entity. Only in the past 4 years, however, has the explicit notion of seeking an end game for cigarette smoking found its way into the scholarly literature (Malone 2010). Additional ideas range from a "sinking lid on supply" approach (Thomson et al. 2010; Wilson et al. 2013), to prohibiting the supply of cigarettes to people born in 2000 or later (Khoo et al. 2010; Berrick 2013), to outright abolition or banning of the sale and manufacture of cigarettes (Daynard 2009; Proctor 2011, 2013).

For this country, the feasibility and applicability of these various proposals range from possible (reducing the nicotine in cigarettes to nonaddicting levels) to almost certainly infeasible (transferring the tobacco product market to a nonprofit entity). Considering the weaknesses and limitations of several of these potential end game proposals, any application of them should come as an integrated national tobacco control strategy which is based on a foundation of enhanced implementation of the proven strategies: taxation, smokefree areas, increased cessation support, warning labels, public health campaigns, and restrictions on advertising, promotions, and sponsorship (van der Eijk 2013). Although more aggressive use of those evidence-based policies and programs (reviewed in Chapter 14) is an essential starting point, the simulation modeling results reviewed above suggest that new strategies may be needed to more rapidly reduce rates of smoking.

Ironically, the end game debate has arisen before there was any consensus on how the end related to tobacco should be defined, although there is recognition that the overriding objective is to maximize health (Smith 2013). There is no consensus to date, however, as to how that objective can best be achieved with regard to tobacco control. Some have focused on the complete elimination of all tobacco use as well as the use of any nicotine-containing product. Others counter that this target is unattainable and unnecessary to achieve dramatic reductions in morbidity and mortality, since eliminating (or nearly eliminating) the use of combusted tobacco products is more feasible and would come close to achieving the overall goal of maximizing health.

In perhaps the first end game proposal, Benowitz and Henningfield (1994) raised the possibility of greatly reducing cigarette smoking by requiring the reduction, over a number of years, of cigarette nicotine content to nonaddicting levels. This proposal has received greater attention in this country following passage of the *Tobacco Control Act* in 2009. The *Tobacco Control Act* gives FDA a number of powerful tools to regulate cigarettes and smokeless tobacco products, both extant and new. Among

its authorities is the ability to establish product standards. One such standard might include reducing maximal nicotine content to levels so low that they would be insufficient to cause or sustain nicotine addiction. The *Tobacco Control Act* specifically forbids FDA from requiring the complete (100%) removal of nicotine. The *Tobacco Control Act* also gives FDA the authority to address product toxicity, offering another avenue to reduce the harm from cigarettes.

Relevant research studies have been completed or are in progress, addressing questions such as whether and how much smokers might compensate (e.g., by smoking more cigarettes or inhaling more deeply) as nicotine content is reduced and how quickly smokers can transition from their regular higher nicotine cigarettes to extremely low nicotine cigarettes (Benowitz et al. 2012; Benowitz and Henningfield 2013). Of all the end game proposals, nicotine reduction is the one that appears to have created the most interest within the U.S. scientific and policy research communities, in part because the regulatory structure needed to implement it is already in place (Hatsukami et al. 2010, 2013). A parallel regulatory approach to reducing product toxicity can also be envisioned (Hatsukami 2013), although not considered in the original proposal from Benowitz and Henningfield (1994). This might include regulations that would further decrease the already lower toxicity of noncombustible products that may be substituted for nonaddictive cigarettes.

The Benowitz and Henningfield (1994) proposal was also made long before the current wave of noncombustible nicotine-containing products, such as those shown in Table 14.1. The rapid growth and development of emerging products, which may closely mimic the pharmacologic product characteristics of cigarettes while potentially minimizing harm, may make this approach even more appealing and potentially achievable. The availability of an acceptable substitute nicotine delivery system could mitigate some of the arguments that may be raised regarding reduction of nicotine content of cigarettes. A substitute delivery system may allow for a more rapid reduction, rather than the original plan of phasing in the reduction over a decade or more. Reduction of nicotine in cigarettes could thus provide smokers with the option of cessation, a switch to less harmful products such as nicotine replacement therapies or some noncombustible tobacco products, or continuing to smoke nonaddictive but deadly cigarettes.

The technical, social, medical, and regulatory feasibility of this concept continues to grow quickly (Hatsukami et al. 2010, 2013; Benowitz and Henningfield 2013). Reducing the addictiveness of cigarettes is increasingly viewed as a possible approach to prevent children from becoming smokers and to provide smokers with assistance to stop smoking. Additionally, the role of regulatory product standards by which tobacco companies could be required to manufacture and market noncombustible products with very low toxicity has been discussed (Hatsukami 2013). The *Tobacco Control Act* empowers FDA to issue product standards to control the allowable levels of chemicals or chemical compounds, or ingredients in tobacco products or smoke for the protection of public health. In addition to a product standard reducing the nicotine in tobacco products, strict standards for levels of toxicants in tobacco products could be established, as well as standards to make some or all tobacco products less appealing.

Several of the other end game proposals relate to reducing the supply of tobacco products. However the *Tobacco Control Act* specifically forbids FDA from banning cigarette sales. Nevertheless, as discussed in the section above, the *Tobacco Control Act* does authorize FDA to set standards for tobacco products which could significantly impact regulated tobacco products marketed (Hatsukami 2013). Additionally, the prohibition of FDA banning categories of products in the *Tobacco Control Act* does not apply to states or localities. It has been noted that every state (and municipality) in the United States has the power to ban the sale of cigarettes, a power upheld by the U.S. Supreme Court in Austin vs. The State of Tennessee (Proctor 2011). However, while states generally may have the capability, other factors including states' constitutions or other state laws, could preempt some municipalities from enacting such measures.

The following proposals, while certainly not feasible for implementation in the United States are reviewed to provide a description of options under discussion internationally. Borland (2003, 2013), Callard and colleagues (2005a,b), and Callard and Collishaw (2013) have observed that the tobacco industry's objective—maximizing profits (or maximizing shareholder value)—is fundamentally antithetical to reducing tobacco use. As such, the researchers argued, moving toward the end of tobacco-produced harms requires that control over the supply of tobacco products be transferred from the for-profit sector to a not-for-profit agency (either governmental or governmentally supervised) with a public health mandate to reduce tobacco use. Tobacco farmers would continue to produce tobacco, and product manufacturers would continue to produce cigarettes and other tobacco products. However, the agency (Borland calls it the "Tobacco Products Agency") would determine how many products would be acquired for sale to the public, and how it would control the conditions of sale (when, where, to whom, at what price, and with what packaging). Driven by its directive to

reduce the population harm caused by tobacco, the goal of the agency would be to reduce tobacco consumption, especially consumption of cigarettes. Some have argued that the development of noncombustible aerosolized forms of nicotine delivery could enable tobacco companies, with firm regulatory oversight and pressure on combustibles, to mobilize the profit motive to speed up the conversion of the population to much lower-risk products, while still retaining shareholder value.

Diverse challenges can be anticipated in the implementation of an integrated strategy that includes any of the proposed end game policies (Isett 2013; Rabe 2013; Thomas and Gostin 2013). The challenges will likely come from two constituencies: those with a financial stake in the survival and continuing economic success of cigarette (and other tobacco products) sales; and some smokers and others who would be opposed to any policy that significantly threatened the availability of cigarettes in their current form, and the ability of adults to choose to consume them. Another challenge will be the tobacco industry's attempts to influence decision makers to oppose effective strategies (Rabe 2013). Legal issues would be raised as well (Thomas and Gostin 2013).

Additional Concepts that Complement National Tobacco Control Efforts

There are additional approaches that embody the evidence-based interventions that have defined the success of the first 50 years of tobacco control. They represent extensions of measures that have been used, but with changing the application of empirical and theory-based measures.

Beginning with Canada in 2000, the new generation of larger graphic warning labels has been implemented in nearly 50 countries. Research has demonstrated that the new labels attract the attention of smokers and lead them to report that the labels have motivated them to consider quitting (Hammond 2011). To date, direct effects of such warnings on quitting are still being evaluated (Borland et al. 2009a,b; Partos et al. 2013). For example, a recent analysis of the Canadian pack warnings that disentangled the effects of concomitant price increases found the graphic warning labels resulted in a decline in smoking prevalence of 2.9–4.7%, a relative reduction of 12.1–19.6% (Huang et al. 2013). Many of the laws initially implemented require labels to occupy 50% of the front and back of cigarette packs, but even larger warnings are now emerging. At least 2 countries have far more substantial requirements:

Uruguay has required that 80% of the front and back of packs bear graphic warning labels; Australia implemented a law requiring that 75% of the front of the pack and 100% of the back be devoted to warning labels (WHO 2013). As the fraction of pack coverage changes, researchers will face a moving target in their evaluation of the effectiveness of graphic warning labels.

Another new approach is plain packaging, adopted by Australia in early 2013. The health ministries of several other countries are now considering implementing this strategy (Freeman et al. 2008; Quit, Cancer Council Victoria 2011; Moodie et al. n.d.). Plain packaging requires the use of a uniform, standard pack color (for that portion of the pack not bearing the warning label) with the brand name printed in a uniform, standard, same-sized font. Increasing evidence indicates that plain packaging has the potential to decrease smoking (Hammond and Parkinson 2009; Hoek et al. 2011; Gallopel-Morvan et al. 2012; Hammond et al. 2013; Wakefield et al. 2013). In Australia, the process by which the pack color was chosen involved a great deal of scientific investigation, including extensive use of focus groups (Wakefield 2012).

Other unlikely but potentially complementary policies exist only in concept at present. Glantz (2012) recently reintroduced the concept that the government impose large fines on tobacco companies based on the quantity of their products consumed by minors with the fines needing to be substantially larger than the revenues gained from sales. This approach would create an economic incentive for the industry to work hard to avoid illegal sale or distribution to children. Another example is Chapman's (2012) notion of licensing smokers. The ability to buy cigarettes, in a specific daily quantity, would require possession of an annual license purchased from the state by the smoker. If the smoker decided to quit, he or she could get the license expenses refunded, but with the provision that this would be a one-time only incentive. Given the novelty of these concepts, there is every reason to expect the development of other new ideas that could be useful in the search for ways to end the disease toll caused by tobacco.

End game strategies might be aided by future approaches and devices for nicotine delivery that better substitute for the cigarette. As discussed in Chapter 14, various new products are increasingly being introduced into the market. In 2012 Lorillard acquired Blu Electronic Cigarettes, in 2013 R.J. Reynolds Tobacco Company introduced Vuse electronic cigarettes in limited markets, and Altria announced that it will introduce an electronic cigarette in 2014 (Esterl 2013; Lorillard 2013; Reynolds American 2013; Wells Fargo Securities Research 2013). Additionally, other electronic nicotine delivery systems have been developed and marketed by companies

with little or no experience in developing and marketing traditional tobacco products (WHO 2009; Henningfield and Zaatari 2010; Cobb and Abrams 2011). Warner (2013) suggests that the introduction and marketing of new products like these could complement an end game strategy. However, the potential risks of continuing the use of addictive levels of nicotine on the population would need careful consideration (see Chapter 5, "Nicotine") if users completely switch from traditional (or conventional) combusted cigarettes to noncombusted products which continue to deliver high levels of nicotine. Also, as noted in Chapter 13, given the rapid increase in electronic cigarette use among both adults and adolescents, rigorous surveillance of these products is particularly important, including their impact on the initiation and cessation of conventional tobacco use and concurrent use with other conventional tobacco products.

Ending the Tobacco Epidemic in the United States

The *Strategic Action Plan* provides a framework for achieving a society free of tobacco-related death and disease by emphasizing the implementation of proven tobacco control strategies (USDHHS 2010a). This chapter makes the case for dramatically increasing and sustaining the level of this implementation. This chapter also discusses various new "end game" strategies; the feasibility and applicability are reviewed above. It has been suggested that an integrated national tobacco control strategy should be considered—based on a foundation of enhanced implementation of the proven strategies (taxation, smoke-free areas, increased barrier-free cessation support, warning labels, public health campaigns, and restrictions on advertising, promotions, and sponsorship) into which the most feasible end game strategies are included (van der Eijk 2013). Thus, a more aggressive use of those evidence-based policies and programs reviewed in Chapter 14 would strengthen current tobacco control measures and create a climate that enhances the feasibility of the implementation of end game strategies (van der Eijk 2013). Examples of end game options which could complement the proven interventions in accomplishing our overall goal of a society free of tobacco-related death and disease include but are not limited to:

(1) reducing the nicotine content to make cigarettes less addictive (Benowitz and Henningfield 2013), and

(2) greater restrictions on sales, particularly at the local level, including bans on entire categories of tobacco products (Berrick 2013; Malone 2013).

In November 2010, HHS released its *Strategic Action Plan*—the first enunciation of a national plan in the United States to curb the tobacco-produced disease epidemic. The plan focuses on a number of interventions that, collectively, could significantly diminish the toll of tobacco (USDHHS 2010a). The plan, which came 3 years after IOM's report *Ending the Tobacco Problem: A Blueprint for the Nation* was issued (Bonnie et al. 2007), announced that ending the epidemic is in fact a national goal. The IOM report also developed a strategy that, if fully implemented, would significantly decrease tobacco use and its burden. To successfully implement both the IOM blueprint and the *Strategic Action Plan* will require vigorous action at the federal, state, and local levels, as well as by the private sector.

Frustration with the slowness of recent progress in tobacco control that motivates the end game discussion reflects, in part, heightened expectations due to how much success has been achieved in the last 50 years. To date, tobacco control strategies have cut the prevalence of cigarette smoking by nearly 60%, per capita consumption is one-fourth of what it was at the dawn of the anti-smoking era, and relative to the size of the population, the disease toll of tobacco in the United States has declined substantially. It has been estimated that this decline in smoking since 1964 was associated with the avoidance of 8 million premature smoking-attributable deaths, with 157 million life years saved (Holford et al. in press). The analysis also demonstrated that tobacco control since 1964 had an important impact on the life expectancy of U.S. adults, contributing an increase of 2.3 years for males and 1.6 years for females, or about 30% of the overall national increase in life expectancy over the period 1964–2012 (Holford et al in press). More background on this analysis and findings in this paper are provided in Appendix 15.1

Despite this success, the authors note that over the half century since 1964, for each of the 8 million premature smoking-attributable deaths averted, two deaths were

caused by smoking (Holford et al. in press). They further correctly observe that "no other behavior comes close to contributing so heavily to the nation's mortality burden" (Holford et al. in press). The evidence reviewed in this chapter emphasize that making more rapid progress toward eliminating the remaining burden of tobacco will be more challenging, but history teaches that the obstacles to success are not invariably insurmountable.

Chapter Summary

Since the first Surgeon General's report in 1964, significant progress has been made in mitigating the tobacco-caused epidemic of disease and premature death. This progress has been accomplished through the implementation of effective tobacco control programs and policies focused on prevention and cessation. This chapter discussed the current status of tobacco control efforts in relation to two key national reports: IOM's *Ending the Tobacco Problem: A Blueprint for the Nation* (Bonnie et al. 2007) and *Ending the Tobacco Epidemic: A Tobacco Control Strategic Action Plan for the U.S. Department of Health and Human Services* (USDHHS 2010a). Potential future directions are examined in the context of today's rapidly changing tobacco control landscape, and plausible alternatives based on proven effective interventions and policies are discussed. Finally, proposed potential end game scenarios are reviewed.

The evidence is clear—we know what works. Chapter 14 and Appendices 14.1–14.5 review the current status of tobacco control interventions that are known to be effective and could reach all the critical priority populations of at-risk youth and young adults, as well as those who are at greatest risk of dying in the short-term from a smoking-caused disease—older adult smokers who have smoked for decades. Many have suggested that with full implementation of these strategies, far fewer youth and young adults would become smokers, and more smokers would successfully quit (Abrams et al. 2010; Levy et al. 2010a,b; Orleans et al. 2010; USDHHS 2000b, 2012b). Health care policies following from the *Health Information Technology Economic and Clinical Health Act* and the *Affordable Care Act* should increase screening for tobacco use and offering cessation counseling in health care settings. The 2007 IOM report (Bonnie et al. 2007) and *the Strategic Action Plan* (USDHHS 2010a) suggest that the rate of decline in youth and adult levels of smoking and tobacco use could be accelerated if the most effective tobacco control interventions were more fully implemented simultaneously and this implementation was sustained. However, the current levels of implementation of these key strategies are far below the most effective levels. In 2000, Surgeon General Dr. David Satcher stated the challenge we face, namely, "Our lack of greater progress in tobacco control is more the result of failure to implement proven strategies than it is the lack of knowledge about what to do" (USDHHS 2000a).

Looking to the future, tobacco control needs to be shaped to address an increasingly heterogeneous pattern of use of tobacco products, including emerging noncombustible products, and changing demographics of users of these tobacco products (Chapter 13). Some of the highest prevalence rates of smoking are now among persons of lower socioeconomic status, some racial and ethnic minority groups, sexual minorities (including individuals who are gay, lesbian, bisexual and transgender, and individuals with same-sex relationships and/or attraction), high school dropouts (Fagan et al. 2007; Lee et al. 2009; Garrett et al. 2011; SAMHSA 2013b), persons with mental illness and alcohol and substance abuse disorders (Prochaska et al. 2008; Schroeder and Morris 2010; Villanti et al. 2012; CDC 2013), American Indians and Alaska Natives as well as recent immigrants from high-prevalence countries, and people with complex comorbid medical illness (e.g., HIV/AIDS and cardiovascular disease) (Crothers et al. 2009; Hoffman et al. 2009; Marshall et al. 2009; Vidrine 2009; Levine et al. 2010; Tesoriero et al. 2010; Pines et al. 2011; Rahmanian et al. 2011). There is also substantial geographic variation with the highest prevalence rates in Appalachia and the South (Pickle and Su 2002). The patterns of using more than one type of smoked tobacco product raises additional concerns about our progress toward ending the epidemic of tobacco-related disease. Chapter 14 discusses several of the strategies that are in current use to address these disparities. Comprehensive statewide tobacco control programs have been leading innovators in implementing culturally appropriate interventions which effectively reach and impact diverse populations with the highest prevalence of tobacco use. Also, nationwide campaigns and health communication interventions can successfully reach diverse populations with high impact messages. CDC's Tips from Former Smokers campaign and the proposed FDA prevention campaigns are examples

of such interventions. As reviewed in Appendix 14.4, integrating tobacco use cessation treatment with treatment for substance use disorders increases the efficacy of both efforts. More forceful implementation of these and other current initiatives presented in the *Strategic Action Plan* (USDHHS 2010a) can help to eliminate these disparities in tobacco use.

This report is also written at a time when legislation has brought new possibilities for strengthening tobacco control. Passage of the 2009 *Tobacco Control Act,* which provides FDA the authority to regulate tobacco products, and the 2010 *Affordable Care Act*, in combination with investment in tobacco control and prevention through the 2009 *American Recovery and Reinvestment Act*, have resulted in substantial support for the implementation of evidence-based policies and programs to reduce tobacco use in recent years. The global and U.S. tobacco industries have indicated in various ways that they plan to undergo a major paradigm shift toward making and marketing a wider range of tobacco-derived nicotine delivery products with a purported reduced harm goal (Calantzopoulous 2012; Delen 2012). The *Tobacco Control Act* gives FDA a number of powerful tools to regulate cigarettes and smokeless tobacco products, both extant and new. Among its authorities is the ability to establish product standards.

Much more rapid declines in youth and adult rates of tobacco use are needed to end the epidemic of tobacco-caused disease and death, but the current levels of implementation of the evidence-based policies and programs are below the most effective levels. Academic and policy communities have proposed untested approaches that could be combined with more robust implementation of

existing strategies to more quickly bring the tobacco epidemic to an end (Smith 2013; van der Eijk 2013). Some of these still untested strategies may eventually provide further possibilities for the United States, particularly as they are implemented and evaluated in international contexts. Others that may be impractical or inappropriate in the United States may have relevance in other countries. Examples of end game options which could complement the proven interventions in accomplishing this nation's overall goal of a society free of tobacco-related death and disease include but are not limited to:

(1) reducing the nicotine content to make cigarettes less addictive (Benowitz and Henningfield 2013), and

(2) greater restrictions on sales, particularly at the local level, including bans on entire categories of tobacco products (Berrick 2013; Malone 2013).

It is important to remember that many policy innovations in tobacco control, once thought inconceivable, have now become the law of the land. Just a decade ago, few if any, public health experts would have envisioned that 26 U.S. states and more than 30 entire countries would have legally mandated smokefree workplaces (including all restaurants and bars) in 2014. The history of tobacco control suggests that it would be unwise not to contemplate the end game. New developments will continue to occur, and the public health community will be far better positioned to address them if the community has thought seriously about them.

Conclusions

1. Together, experience since 1964 and results from models exploring future scenarios of tobacco control indicate that the decline in tobacco use over coming decades will not be sufficiently rapid to meet targets. The goal of ending the tragic burden of avoidable disease and premature death will not be met quickly enough without additional action.

2. Evidence-based tobacco control interventions that are effective continue to be underutilized and implemented at far below funding levels recommended by the Centers for Disease Control and Prevention. Implementing tobacco control policies and programs as recommended by *Ending the Tobacco Epidemic: A Tobacco Control Strategic Plan* by the U.S. Depart-

ment of Health and Human Services and the *Ending the Tobacco Problem: A Blueprint for the Nation* by the Institute of Medicine on a sustained basis at high intensity would accelerate the decline of tobacco use in youth and adults, and also accelerate progress toward the goal of ending the tobacco epidemic.

3. New "end game" strategies have been proposed with the goal of eliminating tobacco smoking. Some of these strategies may prove useful for the United States, particularly reduction of the nicotine content of tobacco products and greater restrictions on sales (including bans on entire categories of tobacco products).

Implications for Ending the Tobacco Epidemic

Ending the Tobacco Epidemic: A Tobacco Control Strategic Plan (USDHHS 2010a) and the E*nding the Tobacco Problem: A Blueprint for the Nation* (Bonnie et al. 2007) set out a vision for the future, calling for ending the epidemic of tobacco smoking as rapidly as possible. This chapter addresses how that vision can be achieved, considers what we have learned and accomplished to date in tobacco control, and identifies challenges to accelerating the impact of tobacco control and to ending the tobacco epidemic. The evidence makes clear that we need to fully implement and sustain the most effective tobacco control interventions as well as fully realizing the potential of FDA's tobacco product regulation. The evidence also emphasizes the need for more rapid progress in reducing tobacco use among youth and adults. If smoking persists at the current rate among young adults in this country, 5.6 million of today's Americans younger than 18 years of age are projected to die prematurely from a smoking-related illness (see Chapters 12 and 13).

In today's changing landscape, there are multiple factors influencing the state of the tobacco epidemic and how it changes. First, the clear mandate of the new FDA authority is to employ science-based rulemaking to reduce the impact of tobacco products at the population level, taking into account both users and nonusers who may become users. FDA has broad new authority to regulate existing and new tobacco products and can educate the public in order to reduce the death, disease, and other costs associated with use of tobacco products. Second, although rates of use of cigarettes have declined modestly in the past decade, alternative, noncigarette forms of tobacco and the dual use of combustible and noncombustible tobacco products are being aggressively promoted. A variety of unregulated noncombustible products with potential modified risk or reduced harm are being developed and aggressively marketed. This shift in patterns of tobacco use could have a number of potential impacts, ranging from the positive effect of accelerating the rate at which smokers quit smoking cigarettes completely to a negative effect of slowing down the decrease in the use of all tobacco products, especially cigarettes. Availability of these products may reduce or increase harm to the population.

New regulatory actions described as end game strategies may offer tremendous opportunities to address these challenges and transform approaches to ending the tobacco epidemic. In addition to a product standard reducing the nicotine content to make cigarettes less addictive, FDA has the authority to establish strict standards for levels of toxicants in tobacco products, as well as standards to make some or all tobacco products less appealing (see "The influence of the design of tobacco products on the use of tobacco by young people," Chapter 5, pages 535-541, USDHHS 2012). The impact of the noncombustible aerosolized forms of nicotine delivery on population health is much more likely to be beneficial in an environment where the appeal, accessibility, promotion, and use of cigarettes and other combusted tobacco products are being rapidly reduced, especially among youth and young adults. For example, other end game strategies which could involve greater restrictions on sales, particularly at the local level, including bans on entire categories of tobacco products, could significantly alter the strategic environment for tobacco control.

These conclusions show that we have still underutilized approaches for reducing use of tobacco products. Together, they indicate a need for coordination within the federal government and across the local, state, and national levels. A strategic framework is available, and recent legislation has brought new approaches for tobacco control. As potential future directions are examined in the context of today's rapidly changing tobacco control landscape, sustained implementation of evidence-based tobacco control interventions at high intensity would accelerate the decline of tobacco use in youth and adults, and also accelerate progress toward the goal of ending the tobacco epidemic.

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Chapter 16
A Vision for Ending the Tobacco Epidemic: Toward a Society Free of Tobacco-caused Death and Disease

A Vision for Ending the Tobacco Epidemic

This nation must create a society free of tobacco-related death and disease. The leadership of U.S. Department of Health and Human Services (USDHHS) committed to this vision when it published the first ever tobacco control strategic action plan for the United States in 2010—*Ending the Tobacco Epidemic: A Tobacco Control Strategic Action Plan for the U.S. Department of Health and Human Services* (hereafter referred to as the *Strategic Action Plan*) (USDHHS 2010a). This 50th anniversary Surgeon General's report provides the scientific basis for accelerating the implementation of this national action plan. Our work to protect our children's health and improve the public's health is not close to completion; this report finds that if more is not done to combat tobacco use, then 5.6 million of today's youth will die prematurely from a smoking-related illness.

This report provides an historical perspective that reviews and updates evidence on the health consequences of smoking and exposure to tobacco smoke as well as the extensive evidence base on effective tobacco control interventions. The report also presents findings of models of future tobacco use that show the challenge ahead: at the current trajectory of decline of tobacco use, it is not possible to meet the goal of ending the tobacco epidemic quickly enough. Finally, the report discusses different ways to achieve a society free of premature death and disease caused by tobacco.

Historical Perspective

The *Strategic Action Plan* stated "The United States has made historic progress in combating the epidemic of tobacco-caused illness and death since the landmark 1964 Surgeon General's Report on the health effects of cigarette smoking" (USDHHS 2010a, p. 9). The evidence in this Surgeon General's report provides a wealth of findings supporting that statement.

- Per capita cigarette consumption has declined by 72% from 4,345 cigarettes in 1963 to 1,196 in 2012 (see Figure 2.1);

- The prevalence of high school students who currently smoke[1] declined from 36.4% in 1997 to 18.1%

in 2011, the lowest level since the start of national surveys (see Chapter 13);

- The prevalence of current smoking[2] among adults has declined from 42.7% in 1965 to 18.1% in 2012 (see Chapter 13).

This progress is considered one of the top public health achievements of the twentieth century (Centers for Disease Control and Prevention [CDC] 1999; Ward and Warren 2007). However, smoking continues to cause unacceptable harm to public health. Several key findings of this report highlight the continuation of the still massive tobacco epidemic in the United States:

- Despite the dramatic decline in per capita cigarette consumption (see Figure 2.1), almost 25 trillion cigarettes have been consumed since 1965 (Figure 16.1).

- More than twenty million Americans have died from smoking-attributable illnesses since 1964 (see Chapter 12).

- Nearly one-half million adults still die prematurely from tobacco use each year (see Chapter 12).

- Approximately 800,000 lung cancer deaths were estimated to have been avoided in the United States during 1975–2000. However, these averted lung cancer deaths are only about 32% of the lung cancer deaths that could have been avoided if tobacco smoking had been completely eliminated after the 1964 Surgeon General's report (Chapter 15).

- The tobacco industry continues to position itself to sustain its sales by recruiting youth and young adults and by maintaining current smokers as consumers of all their nicotine-containing products including cigarettes (see Chapters 13, 14, 15).

- For each smoker who dies from tobacco-related disease, there are two new, younger replacement smokers (USDHHS 2012).

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[1]Based on respondents who reported that they smoked cigarettes on at least 1 day during the 30 days before the survey.
[2]Based on adult respondents who reported smoking ≥100 cigarettes in their lifetime and smoking every day or on some days.

Figure 16.1 Total cigarette consumption, United States, 1900–2012

24.7 trillion cigarettes smoked between 1964–2012
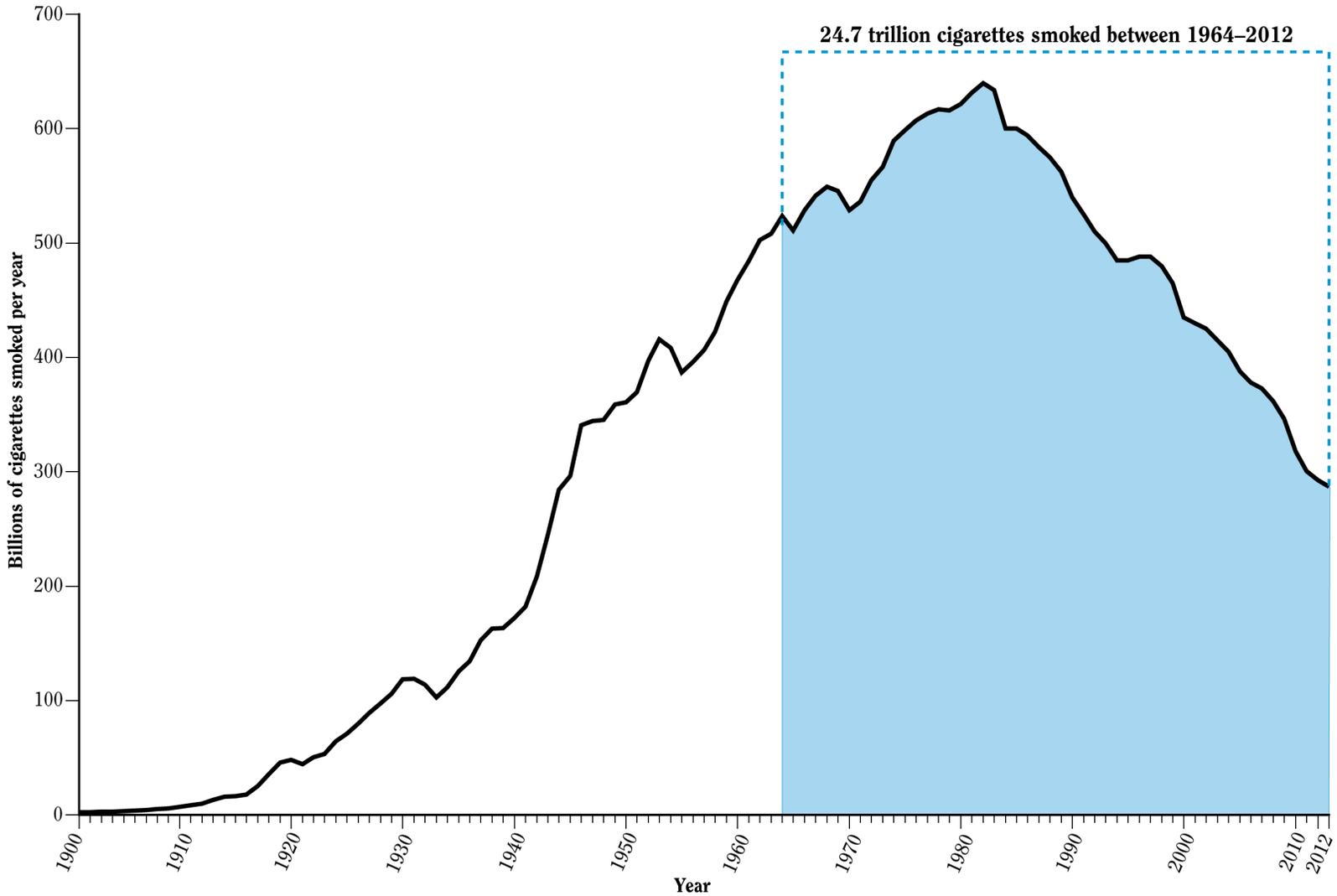
Sources: Miller 1981; U.S. Department of Agriculture, 1987, 1996, 2005, 2007a,b; Centers for Disease Control and Prevention 2012.
Note: Data shown are annual total consumption of cigarettes. This differs from Figure 2.1, which reports the annual adult (18 years of age and older) per capita consumption.

- Disparities in smoking rates persist. Some of the highest prevalence rates are among persons of lower socioeconomic status, some racial/ethnic minority groups, sexual minorities, high school dropouts, and other vulnerable populations including those living with mental illness and substance use disorders.

- Due to the persisting prevalence of smoking among young adults in this country, 5.6 million Americans younger than 18 years of age are projected to die prematurely from a smoking-related illness (see Chapters 12 and 13).

Previous Surgeon General's reports have tracked the evolution of cigarettes into the current highly engineered, addictive, and deadly products containing thousands of chemicals that are themselves harmful. The burning of tobacco produces the complex chemical mixture of over 7,000 compounds that cause a wide range of diseases and premature deaths as a result (USDHHS 2010b). Although the prevalence of smoking has declined significantly over the past half century, risks for smoking-related disease and mortality have not. In fact, today's cigarette smokers—both men and women—have a much higher risk for lung cancer and chronic obstructive pulmonary disease than smokers in 1964, despite smoking fewer cigarettes (see Chapters 6, 7, and 11, and Figures 12.2 and 13.16).

Since 2000, each Surgeon General's report has ended with a call for action. In 2000, Surgeon General Dr. David Satcher clearly stated the challenge that is still applicable today, namely, "Our lack of greater progress in tobacco control is more the result of failure to implement proven strategies than it is the lack of knowledge about what to do" (USDHHS 2000). Knowledge garnered over the subsequent 14 years makes this statement even more cogent today.

In 2007, the Institute of Medicine's report, *Ending the Tobacco Problem: A Blueprint for the Nation*, provided 42 recommendations with the ultimate goal stated as: "… to end the tobacco problem; in other words, to reduce smoking so substantially that it is no longer a significant public health problem for our nation" (Bonnie et al. 2007, p. 1). The 2010 Surgeon General's report (2010b) listed these recommendations along with the detailed recommendations of the President's Cancer Panel for addressing tobacco use prevention and treatment and exposure to secondhand tobacco smoke (Reuben 2007). The 2012 Surgeon General's report built upon recommendations in previous reports in its final chapter: "A Vision for Ending the Tobacco Epidemic" by noting that "we have evidence-based strategies and tools that can rapidly drop youth initiation and prevalence rates down into the single digits" (USDHHS 2012, p. 856).

There is extensive knowledge about what needs to be done—not achieving greater progress results in part from not fully implementing existing knowledge about what works, and in part from the continued efforts of the tobacco industry to promote and market cigarettes and other products. The vision set forth in the *Strategic Action Plan* (USDHHS 2010a) recognizes that dramatic action is needed to change social norms further and to continue to decrease the acceptability of tobacco use (USDHHS 2012), especially smoking.

In recent years, a number of critical legislative steps have been taken to reduce tobacco use, including measures that can reduce the ability of the tobacco industry to promote tobacco use. These legislative measures bring new possibilities for tobacco control.

In February 2009, the *Children's Health Insurance Program Reauthorization Act,* Public Law 111-3, *U.S. Statutes at Large* 8 was signed, which included an unprecedented $0.62 increase in the federal excise tax on cigarettes to $1.01 per pack. This single legislative act—increasing the price of cigarettes—is projected to have reduced the number of middle and high school students who smoke by over 220,000 and the number using smokeless tobacco products by over 135,000 (Huang and Chaloupka 2012).

Raising prices on cigarettes is one of the most effective tobacco control interventions (USDHHS 2012; International Agency for Research on Cancer [IARC] 2011). Even with this tax increase in 2009, the average retail price of cigarettes in this country is still too low in comparison with other countries (World Health Organization [WHO] 2013). Additional price increases would accelerate progress in reducing youth and young adult rates of tobacco use (IARC 2011; USDHHS 2012; WHO 2013). The understanding of price elasticity suggests that the average retail price of cigarettes in the United States across the country would need to be raised to at least $10 a pack, similar to prices in many other countries, in order to have a large and rapid impact (IARC 2011; USDHHS 2012; WHO 2013; Jha and Peto, in press).

In June 2009, the *Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act),* Public Law 111-31, *U.S. Statutes at Large* 123, was signed, thereby granting the U.S. Food and Drug Administration (FDA) the authority to comprehensively regulate thousands of tobacco products for the first time in history. This law gives FDA a number of powerful tools to regulate tobacco products, both existing and new (see Chapter 14). Effective implementation of FDA's tobacco product regulation mandate is needed to reduce the harm caused by tobacco products.

In March 2010, the *Patient Protection and Affordable Care Act (Affordable Care Act),* Public Law 111-148,

U.S. Statutes at Large 124 (2010):119, was signed into law. As part of its emphasis on prevention and health promotion, the law (a) requires private insurance plans and Medicaid expansion plans to cover tobacco cessation treatments, including medications that help people quit smoking; (b) requires state Medicaid programs to cover tobacco cessation medications; (c) expands smoking cessation coverage for pregnant women who receive Medicaid; and (d) provides Medicare beneficiaries with an annual wellness visit that includes personalized prevention plan services with referrals for tobacco cessation services. The *Affordable Care Act* also established the Prevention and Public Health Fund, which represents the most significant investment in U.S. history to scale up and promote effective public health and preventive measures, including programs to prevent and reduce tobacco use. The *Affordable Care Act* strengthens a key element of tobacco use cessation services by making them more available and barrier-free to almost all smokers.

The extensive evidence base supports the conclusion in Chapter 14 that mass media campaigns, comprehensive community programs, and comprehensive statewide tobacco control programs prevent initiation of tobacco use and reduce the prevalence of tobacco use among youth and adults. Although increased application of these and other proven tobacco control strategies would be highly effective, the current levels of implementation of these key strategies are far below the most effective levels according to the evidence base. State funding of tobacco control programs has been declining for years. For example, in 2010 states were only appropriating 2.4% of their tobacco revenues from both tobacco excise taxes and Master Settlement Agreement payments for tobacco control. Reaching CDC's recommended funding level would have required an additional 13% of tobacco revenues, or 3.1 billion of the $24 billion collected (see Chapter 14) (CDC 2012).

Health Consequences

The 2004 Surgeon General's report showed that smoking impacts nearly every organ of the body (USDHHS 2004). The 2006 report concluded that the scientific evidence indicates that there is no risk-free level of exposure to secondhand smoke (USDHHS 2006). The new evidence in this report provides still more support for these conclusions. Fifty years after the first report in 1964, it is striking that the scientific evidence in this report expands the list of diseases and other adverse health effects caused by smoking and exposure to tobacco smoke. Figures 1.1A and 1.1B highlight these new findings and show that the risks for disease are even greater than presented in previous reports. These new findings include:

- Liver cancer and colorectal cancer are now added to the long list of cancers caused by smoking;

- Exposure to secondhand smoke is a cause of stroke;

- Smoking increases the risk of dying from cancer and other diseases in cancer patients and survivors;

- Smoking is a cause of diabetes mellitus; and

- Smoking causes general adverse effects on the body including inflammation and it impairs immune function. Smoking is a cause of rheumatoid arthritis.

This report also updates the estimates of disease, death, and economic costs attributable to smoking and exposure to tobacco smoke. The morbidity burden caused by smoking-attributable diseases is large, and new evidence suggests that over 16 million people alive today live with disease caused by smoking (see Chapter 12). In addition, the risks of death from diseases already on the causal list have increased in recent decades. This is particularly true for lung cancer risk among female smokers and chronic obstructive pulmonary disease risk for both male and female smokers (see Chapters 6 and 7). As the list of diseases caused by smoking has continued to grow, the updated estimate of the annual number of deaths attributable to smoking and exposure to secondhand smoke is now approaching 500,000 (see Chapter 12). This increase has occurred despite decreases in per capita cigarette consumption and prevalence, emphasizing our enhanced understanding of the lethality of cigarettes.

The estimated economic costs attributable to smoking and exposure to tobacco smoke have also increased. The annual indirect costs due to productivity losses are now estimated to be over $150 billion (see Chapter 12). The estimates of direct medical expenditures have also increased as well, now ranging from at least $130 billion annually up to $176 billion or more (see Chapter 12).

Ending the Tobacco Epidemic

The burden of smoking-attributable disease and premature death and its high costs to the nation will continue for decades unless smoking prevalence is reduced more rapidly than the current trajectory. The evidence in this report shows that the nation will fail to achieve the *Healthy People 2020* objective of reducing the prevalence of smoking among adults to 12%. Model estimates sug-

gest that if the status quo in tobacco control in 2008 were maintained, the projected prevalence of smoking among adults in 2050 could still be as high as 15% (see Chapter 15). Trends in smoking rates among youth and adults show progress, but the prevalence of current smoking among youth and adults is only slowly declining and the actual number of youth and young adults starting to smoke has increased since 2002 (see Chapter 13). Additionally, the use of multiple tobacco products is increasingly common, especially among young smokers. Concerns remain that use of these new products may increase initiation rates among youth and young adults, delay quitting, and prolong the smoking epidemic.

As reviewed in this report, the root cause of the smoking epidemic is also evident: the tobacco industry aggressively markets and promotes lethal and addictive products, and continues to recruit youth and young adults as new consumers of these products (see Chapter 14) (USDHHS 2012). As reviewed in Chapter 14, U.S. District Judge Gladys Kessler entered her final opinion and order on August 17, 2006, and found that the tobacco industry defendants violated the *Racketeer Influenced and Corrupt Organizations Act,* Public Law 91-452, *U.S. Statutes at Large* 84 (1970):992, codified at *U.S. Code* 18§§ 1961–68 (1994), by lying, misrepresenting, and deceiving the public "including smokers and the young people they avidly sought as 'replacement smokers,' about the devastating health effects of smoking and environmental tobacco smoke" (*United States v. Philip Morris,* 449 *F. Suppl. 2d1(D.D.C. 2006)*:852). The *Tobacco Control Act* incorporates as congressional findings of fact Judge Kessler's determinations that "the major United States cigarette companies continue to target and market to youth," that the companies sought to "encourage youth to start smoking subsequent to the signing of the Master Settlement Agreement in 1998," and that they "have designed their cigarettes to precisely control nicotine delivery levels and provide doses of nicotine sufficient to create and sustain addiction while also concealing much of their nicotine-related research" (*Tobacco Control Act* 2009, §2(47) – (49)).

Therefore, this report addresses the question: what steps are needed to end the tobacco epidemic? There are different ways to achieve this vision. Should the emphasis be on ending cigarette use; ending the use of the most harmful tobacco products while reducing the harm of remaining products; or ending the use of all tobacco products?

The scientific findings of the 2012 Surgeon General's report (USDHHS 2012) show that there are evidence-based strategies that can rapidly drop initiation and prevalence rates of smoking among youth to single digits. To reach this target, these strategies need to be fully implemented and sustained with sufficient intensity and duration. Without such increased and sustained action, 5.6 million youth younger than 18 years of age in this country today are projected to die prematurely from a smoking-related illness. But millions of these projected deaths could be averted, making tobacco control a highest priority in our overall public health commitment and strategy.

Achieving this goal of rapidly reducing rates of smoking among youth still leaves 42 million current adult smokers who are at risk of dying from a smoking-related disease. The evidence in this and previous reports highlights how deadly inhaling tobacco smoke is, especially from burning cigarettes (USDHHS 2004, 2006, 2010, 2012). Approximately 85% of the tobacco products used since 1964 have been cigarettes (U.S. Department of Agriculture 2008).

The scientific findings of the 2010 Surgeon General's report were definitive on the causation of disease by smoking:

- Major Conclusion #2: "Inhaling the complex chemical mixture of combustion compounds in tobacco smoke causes adverse health outcomes, particularly cancer and cardiovascular and pulmonary diseases, through mechanisms that include DNA damage, inflammation, and oxidative stress."

- Major Conclusion #4: "Sustained use and long-term exposures to tobacco smoke are due to the powerfully addicting effects of tobacco products, which are mediated by diverse actions of nicotine and perhaps other compounds, at multiple types of nicotinic receptors in the brain" (USDHHS 2010b, p. 9).

The scientific evidence is incontrovertible: inhaling the combustion compounds from tobacco smoke, particularly from cigarettes, is deadly. It has been stated that "The cigarette is also a defective product, meaning not just dangerous but *unreasonably* dangerous, killing half its long-term users. And addictive by design" (Proctor 2013, p. i27). The high risks of cigarette smoking and the historic and current patterns of tobacco use in the United States lead to a primary conclusion of this report:

- The burden of death and disease from tobacco use in the United States is overwhelmingly caused by cigarettes and other combusted tobacco products; rapid elimination of their use will dramatically reduce this burden.

Could the use of cigarettes and other combusted tobacco products be rapidly reduced in this country? As noted above, evidence-based strategies that can rapidly drop youth initiation and prevalence rates down to single digits have already been identified and used (USDHHS 2012). Chapter 14 reviews a broad range of well-defined and effective interventions proven to reduce adult smoking rates if implemented and sustained at funding levels consistent with CDC's recommended levels (see Chapter 14). This and previous reports outline effective programs and policies:

- Fully funded comprehensive statewide tobacco control programs funded at levels recommended by CDC;

- A higher average retail price of cigarettes in the United States. Experience from across the globe suggests at least $10 a pack in the United States;

- Complete protection of the entire U.S. population from exposure to tobacco smoke through comprehensive smokefree indoor air policies;

- High-impact media campaigns, such as CDC's Tips from Former Smokers campaign and the proposed U.S. Food and Drug Administration prevention campaigns at a high-frequency level and exposure for 12 months a year for a decade or more; and

- Full access to cessation treatment for nicotine addiction including counseling and medication for all smokers, especially those with mental and physical comorbidities.

However, these five actions are not all that needs to be done. Although more aggressive use of those evidence-based policies and programs reviewed in Chapter 14 is a starting point, the simulation modeling results reviewed (see Chapter 15) suggest that new strategies may be needed to more rapidly reduce rates of smoking. Recently, such tobacco control strategies are beginning to be formulated that might dramatically reduce the use of tobacco products, especially cigarettes. These proposed strategies have been labeled tobacco end game scenarios (see Chapter 15). For the United States, the feasibility and applicability of these various proposals range from possible (reducing the nicotine in cigarettes to nonaddicting levels) to almost certainly infeasible (transferring the tobacco product market to a nonprofit entity). Any application of these end game interventions should come as an integrated national tobacco control strategy that is based on a foundation of enhanced implementation of the proven strategies. Examples of end game options (see Chapter 15), which could complement the proven interventions in accomplishing our overall goal of a society free of tobacco-related death and disease, include but are not limited to: (1) reduce the nicotine content to make cigarettes less addictive (Benowitz and Henningfield 2013), and (2) greater restrictions on sales, particularly at the local level, including bans on entire categories of tobacco products (Berrick 2013; Malone 2013).

In considering options for reducing the health burden caused by smoking, many additional recommended actions have been defined in evidence reviews and guidance documents discussed in this report. For example, selected state experience suggests that all levels of government can enhance revenue collection and minimize tax avoidance and evasion through several policy approaches, such as implementing a high-tech cigarette tax stamp, improving tobacco licensure management, and making the stamps harder to counterfeit (see Chapter 14). These state practices could also be expanded to the national level with a national track and trace system. A track and trace system, in the tobacco control context, is a system that can track goods from manufacture to distribution to sale, identifying points in the supply chain where taxes should be paid and confirm payment. Enforcement enhancements would also be beneficial. Implementing such systems would also simultaneously retain the positive public health effects of taxation and protect product regulation in the market.

In addition to actions taken by the federal government, actions by national and local nongovernmental organizations can have significant impacts on social norms. As reviewed in Chapter 14, the portrayals of tobacco use in U.S. films appear to have rebounded upward in the last 2 years (see Chapter 14, Figures 14.3A and 14.3B). Based on box office attendance data, it has been estimated that youth were exposed to 14.9 billion in-theater tobacco-use impressions[3] in youth-rated films in 2012. Youth who are exposed to images of smoking in movies are more likely to smoke; those who experience the most exposure to onscreen smoking are approximately twice as likely to begin smoking as those who receive the least exposure (USDHHS 2012). Actions that would eliminate depiction of tobacco use in movies that are produced and rated as appropriate for children and adolescents could have a sig-

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[3]One impression equals one tobacco use incident on screen viewed by one audience member.

nificant benefit in reducing the numbers of youth who become tobacco users. It has been suggested that the movie industry modernize the Motion Picture Association of America voluntary rating system to eliminate smoking from youth-rated films by awarding any film with smoking or other protobacco imagery an R rating (with exceptions for real historical figures who actually smoked or films that actually depict the dangers of smoking or exposure to secondhand smoke) (Glantz and Polansky 2012; Sargent et al. 2012). Further, if such a change in the Motion Picture Association of America rating system would reduce in-theater exposures from a current median of about 275 annual exposures per adolescent from PG-13 movies down to approximately 10 or less, adolescent smoking would be reduced by an estimated 18% (95% confidence interval, 14–21%) (Sargent et al. 2012).

The increasing availability of noncombustible products raises the question of using them to help eliminate the harm caused by tobacco. The *Tobacco Control Act* is governed by a requirement to protect public health, an acknowledgement that the goal of tobacco control is to improve public health overall. A public health standard is critical because strategies that reduce potential harm from toxicant exposure to individual users of tobacco products could adversely affect other individuals and public health by increasing the number of new users of cigarettes and by reducing the number of quitters (Figure 16.2).

This issue of reducing direct *individual* harm in those substituting noncombustibles for cigarettes while minimizing impact on other individuals, who may start or not stop using cigarettes (Figure 16.2), arises in facing the regulatory challenge posed by electronic cigarettes (e-cigarettes or electronic nicotine delivery systems). Although these new products are entering the marketplace rapidly, and will soon be marketed by all three major tobacco manufacturers in the United States, significant questions remain about (1) how to assess the potential toxicity and health effects of the more than 250 electronic cigarette brands; (2) the magnitude of the potential reduced risk from electronic versus continuing use of conventional cigarettes for individual smokers; (3) the need to weigh the potential individual benefits and risks versus population benefits and risks; (4) how the advertising and marketing of these new products should be regulated; and (5) even assuming that electronic cigarettes could be sufficiently safe to users and offer net public health benefits, there are significant questions about the manner in which they should be regulated (Benowitz 2013).

The issue of weighing the relative benefits and risks to individuals and populations is critical when considering the potential role of any noncombustible tobacco products

in reducing the occurrence of smoking-caused diseases and morbidity. Currently, there are varying scenarios being discussed. In one scenario, noncombustible tobacco products would be substituted for cigarette smoking among a subset of smokers (people who otherwise would not quit smoking and thus are at high risk for smoking-caused diseases). Proponents claim that such a switch would significantly reduce the burden of death and disease attributable to smoking if smokers completely substituted combustible products with noncombustible products. The perspective rests on the assumption that (a) noncombustible tobacco products, used alone, are far less dangerous to individual users than continued smoking, a conclusion that appears correct based on current understanding (Levy et al. 2004; USDHHS 2010b); (b) with proper marketing, differential taxation, and other carefully calibrated policies, noncombustible products would be adopted as a complete substitute for smoking by significant numbers of current smokers, a thus far unproven assumption; (c) smokers who switched to noncombustible products otherwise would continue to smoke (as opposed to quitting), another area with significant uncertainty; and (d) the net impact on health of all the various outcomes, intended and unintended, would contribute meaningfully to tobacco harm reduction, a proposition that has been explored only once in the literature (Mejia et al. 2010). In that analysis which related only to snus, it was concluded that it would be unlikely that the promotion of the snus form of smokeless tobacco would be associated with substantial health benefits. The probability that the use of snus could delay complete cessation of cigarette smoking among health-concerned smokers would decrease the potential health benefit at the population level.

An alternative scenario regarding noncombustible products as a harm reduction strategy holds that the availability and promotion of noncombustible tobacco products would increase the aggregate damage to health produced by tobacco. Proponents of this position vary on how much they emphasize the inherent dangers of noncombustible tobacco products. Even those who concur that the use of noncombustible tobacco products may not constitute a large direct risk to individual health propose that a strategy based on their use would increase total tobacco-related harm to health. Proponents of this position argue that the availability of noncombustible products can have adverse consequences, especially under current conditions with the widespread marketing and use of cigarettes. These consequences include (a) encouraging children to experiment with tobacco products (with the expectation that a percentage of those who become regular users of noncombustible products will graduate

Figure 16.2   Potential patterns of use of combustible products (CP) and non-combustible products (NCP)
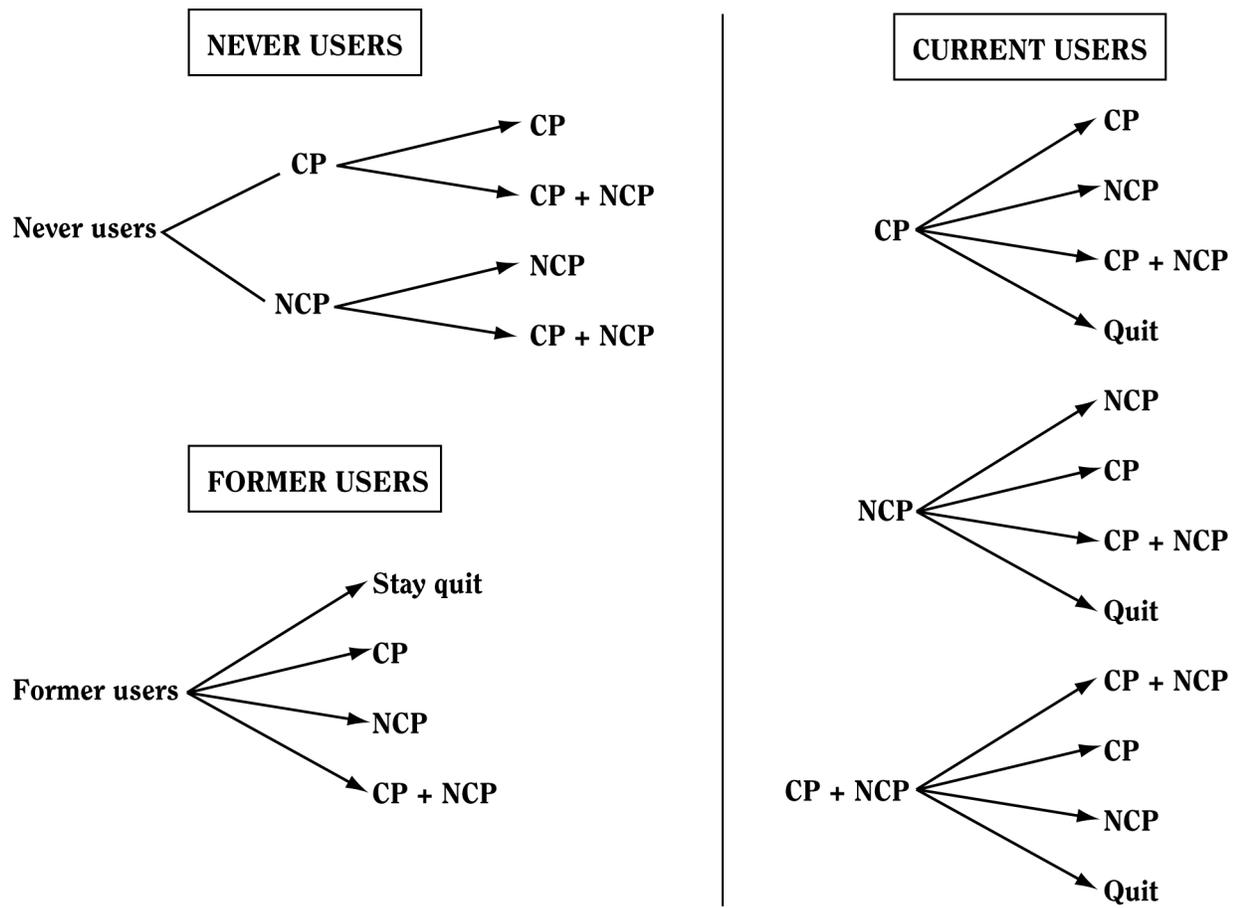
Source: Created by J. Samet for this Surgeon General's Report.

to smoking); (b) helping smokers maintain their addiction by using noncombustible products in environments where they cannot smoke; (c) acting as a non-risk-free substitute for cigarettes for smokers who otherwise would have quit; and (d) giving smokers an alternative means of satisfying their addiction that may lead to higher levels of recidivism to smoking. The evidence indicates that current industry practices raise concerns about all of these potential adverse consequences (USDHHS 2012). One study found that transnational tobacco companies promote less harmful tobacco products in order to maintain and extend the sales of cigarettes and to create alternative forms of tobacco use among young people who are no longer smoking (Peeters and Gilmore 2013). Uncertainties as to the role of noncombustible tobacco products as part of a harm reduction strategy raises issues of promotion of noncombustible tobacco. Further research with attention to their individual and population-level consequences will be helpful to fully address these questions. However, the promotion of noncombustible products is much more likely to provide public health benefits only in an environment where the appeal, accessibility, promotion, and use of cigarettes and other combusted tobacco products are being rapidly reduced.

Accelerating the National Movement to Reduce Tobacco Use

These key conclusions of this report provide evidence that calls for dramatic action:

- The current rate of progress in tobacco control is not fast enough. More needs to be done.

- High levels of smoking-attributable disease and death costs will persist for decades into this twenty-first century unless more rapid progress is made in tobacco control. The current burden is unacceptable.

- The almost 500,000 annual premature deaths due to smoking and exposure to tobacco smoke are far too many. Even 100,000 or 200,000 annual attributable deaths are far too many; yet this is a realistic projection of the burden well into the middle of this twenty-first century if more rapid progress is not made in tobacco control.

- The burden of death and disease from tobacco use in the United States is overwhelmingly caused by cigarettes and other combusted tobacco products; rapid elimination of their use will dramatically reduce this burden.

There are important lessons to be learned from other successes in public health. In confronting worldwide epidemics caused by smallpox and polio, the eradication of the diseases was the clear objective. From this single-minded focus, the best strategies and actions based on public health science and practice were applied, evaluated, refined, and sustained for decades. The results are now evident: smallpox was eradicated decades ago and polio is on the verge of elimination. The nation should firmly commit to this goal of creating a society free of tobacco-related death and disease by engaging all sectors of society to an equally single-minded focus.

In the last 50 years, the smoking rate in the United States has been cut by more than one-half (from 42.7% in 1965 to 18% in 2012). The *Strategic Action Plan* provides a critical framework to guide and coordinate efforts to reduce the smoking rate to less than 10% for both youth and adults in 10 years, averting millions of smoking-related deaths. This national commitment will require increased and sustained action to rapidly eliminate the use of cigarettes and other forms of combustible tobacco products. As end game strategies are being developed, the following actions should be implemented:

- Counteracting industry marketing by sustaining high impact national media campaigns like the CDC's Tips from Former Smokers campaign and FDA's youth prevention campaigns at a high frequency level and exposure for 12 months a year for a decade or more;

- Raising the average excise cigarette taxes to prevent youth from starting smoking and encouraging smokers to quit;

- Fulfilling the opportunity of the *Affordable Care Act* to provide access to barrier-free proven tobacco use cessation treatment including counseling and medication to all smokers, especially those with significant mental and physical comorbidities;

- Expanding smoking cessation for all smokers in primary and specialty care settings by having health care providers and systems examine how they can establish a strong standard of care for these effective treatments;

- Effective implementation of FDA's authority for tobacco product regulation in order to reduce tobacco product addictiveness and harmfulness;

- Expanding tobacco control and prevention research efforts to increase understanding of the ever changing tobacco control landscape;

- Fully funding comprehensive statewide tobacco control programs at CDC recommended levels; and

- Extending comprehensive smokefree indoor protections to 100% of the U.S. population.

Former WHO Director General Gro Brundtland was correct in 1999 in stating the need to evaluate current action from the perspective of our grandchildren and their children (Asma et al. 2002). As future generations look back on our current actions and knowledge of the tobacco epidemic, will current efforts show the commitment to public health and social justice set forth in our national plans and objectives?

This nation's decades-long battle against the tobacco epidemic has successfully prevented millions of premature deaths that would otherwise have occurred—an historic achievement by any measure. On the fiftieth anniversary of the landmark 1964 Surgeon General's report, this nation must rededicate itself not only to carrying forward the successful tobacco control efforts that have long been under way but also to expanding and accelerating those efforts in full recognition of the challenge that remains.

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List of Abbreviations

4-ABP	4-aminobiphenyl
AAP	American Academy of Pediatrics
AAT	α-1 antitrypsin
ACE	acute coronary events
ACOG	American Congress of Obstetricians and Gynecologists
ACS	American Cancer Society
ADHD	attention deficit hyperactivity disorder
AMA	American Medical Association
AMD	age-related macular degeneration
AMI	acute myocardial infarction
anti-CCP	anti-cyclic citrullinated peptide
anti-HCV	antibodies to hepatitis C virus
ANR	Americans for Nonsmokers' Rights
ANRF	American Nonsmokers' Rights Foundation
AOR	adjusted odds ratio
ARIC	Atherosclerosis Risk in Communities
ASSIST	American Stop Smoking Intervention Study
ATS	American Thoracic Society
B[a]P	benzo[a]pyrene
BACH	Boston Area Community Health survey
BALT	bronchus-associated lymphoid tissue
BAT	British American Tobacco
BCFR	Breast Cancer Family Registry
BMI	body mass index
Breg	B regulatory cells
BRFSS	Behavioral Risk Factor Surveillance System
B&W	Brown & Williamson Tobacco Co.
Cal/EPA	California Environmental Protection Agency
CBCL	child behavior checklist
CBO	Congressional Budget Office
CC16	Clara cell secretory protein 16
CDC	Centers for Disease Control and Prevention
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
CHARGE	Cohorts for Heart and Aging Research in Genomic Epidemiology
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
CISNET	Cancer Intervention and Surveillance Modeling Network
CL/P	cleft lip with or without cleft palate
CLUE II	Campaign Against Cancer and Heart Disease
cm	centimeter
CMS	Centers for Medicare & Medicaid Services
CNS	central nervous system
CNV	choroidal neovascularization
CO	carbon monoxide
COLD	chronic obstructive lung disease
COMMIT	Community Intervention Trial for Smoking Cessation
COPD	chronic obstructive pulmonary disease
COSMIC	Catalogue of Somatic Mutations in Cancer
CP	cleft palate
CPP	Collaborative Perinatal Project
CPS	Cancer Prevention Study
CRP	C-reactive protein
CSE	cigarette smoke extract
CT	computed tomography
CTR	The Council for Tobacco Research—U.S.A., Inc.
CVD	cardiovascular disease
CYP	cytochrome P-450
DALYs	disability-adjusted life years
DAMPs	damage-associated molecular patterns
DFS	decayed/filled tooth surface
DFT	decayed/filled permanent teeth
dL	deciliter
DMF	decayed/missing due to caries/filled
DMFS	decayed/missing due to caries/filled tooth surface
DMFT	decayed/missing due to caries/filled permanent teeth
DOD	U.S. Department of Defense
DOJ	U.S. Department of Justice
DTPs	dissolvable tobacco products
E1	estrone
E2	estradiol
E3	estriol
ECLIPSE	Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints

ED	erectile dysfunction
EGRCIBD-Japan	Epidemiology Group of the Research Committee of Inflammatory Bowel Disease in Japan
EHR	electronic health record
ENDS	electronic nicotine delivery system
EP	ectopic pregnancy
EPA	U.S. Environmental Protection Agency
EPIC	European Prospective Investigation into Cancer and Nutrition
ER	estrogen receptor
ETS	environmental tobacco smoke
FCA	Framework Convention Alliance
FCC	Federal Communications Commission
FCTC	Framework Convention on Tobacco Control
FDA	U.S. Food and Drug Administration
FEV$_1$	forced expiratory volume in 1 second
FMD	flow-mediated dilation
FOXP3	forkhead box PC
FTC	U.S. Federal Trade Commission
FVC	forced vital capacity
g	gram
GA	geographic atrophy
GABA	gamma-aminobutyric acid
GAO	U.S. Government Accounting Office
GATS	Global Adult Tobacco Survey
GENICA	Gene Environment Interaction and Breast Cancer
GenKOLS	Genetics of Chronic Obstructive Lung Disease
GINA	Global Initiative for Asthma
GM-CSF	granulocyte macrophage colony-stimulating factor
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSP	Global Smokefree Partnership
GST	glutathione S-transferase
GWAS	genome-wide association studies
HBV	hepatitis B virus
HBsAg	HBV surface antigen
HCC	hepatocellularcarcinoma
HCV	hepatitis C virus
Hg	mercury
HIP	Health Insurance Plan
HITECH	*Health Information Technology Economic and Clinical Health Act*
HIV/AIDS	human immunodeficiency virus infection/ acquired immunodeficiency syndrome
HMGB1	high mobility group box 1
HMOX	heme oxygenase
HPHCs	harmful and potentially harmful constituents [in tobacco products]
HPV	human papillomavirus
HR	hazard ratio
HRS	Health and Retirement Study
HRT	hormone replacement therapy
HSPs	heat shock proteins
IARC	International Agency for Research on Cancer
IBD	inflammatory bowel disease
ICD	*International Classification of Diseases*
IFN	interferon
IFNγ	interferon gamma
Ig	immunoglobulin
IgG	immunoglobulin G
IHD	ischemic heart disease
IIEF	International Index of Erectile Function
IL	interleukin
IMPACT	Initiatives to Mobilize for the Prevention and Control of Tobacco Use Program
IOM	Institute of Medicine
IPF	idiopathic pulmonary fibrosis
IQ	intelligence quotient
IUD	intrauterine device
IUGR	intrauterine growth retardation
JNK	c-Jun N-terminal kinase
LD50	dose causing 50% lethality
LMIC	low- and middle-income countries
LPS	lipopolysaccharide
M. tuberculosis	*Mycobacterium tuberculosis*
mcg	micrograms
MEPS	Medical Expenditure Panel Survey
MeSH	Medical Subject Headings
mg	milligram
MHC	major histocompatibility complex
MI	myocardial infarction
mL	milliliter
mm	millimeter
mmol	millimole
mmol/L	millimoles per liter
MMP	matrix metalloproteinase
MRFIT	Multiple Risk Factor Intervention Trial
mRNA	messenger RNA
MSA	Master Settlement Agreement
MyD88	myeloid differentiation factor 88

nAChR	nicotinic acetylcholine receptor		**PAI-1**	plasminogen activator inhibitor-1
NAQC	North American Quitline Consortium		**PAMPs**	pathogen-associated molecular patterns
NAT	*N*-acetyltransferase		**Pap**	Papanicolaou
NBDPS	National Birth Defects Prevention Study		**PARC**	pulmonary-and activation-regulated chemokine
NCHS	National Center for Health Statistics		**PBI**	penile-brachial index
NCI	National Cancer Institute		**PCR**	polymerase chain reaction
NE	neutrophil elastase		**PDAY**	Pathobiological Determinants of Atherosclerosis in Youth study
NETT	National Emphysema Treatment Trial		**PHS**	U.S. Public Health Service
NF-κB	nuclear factor-kappa B		**PID**	pelvic inflammatory disease
NFPA	National Fire Protection Association		$PM_{2.5}$	particulate matter
ng	nanogram		**PR**	progesterone receptors
NHANES	National Health and Nutrition Examination Survey		**PRAMS**	Pregnancy Risk Assessment Monitoring System
NHDS	National Hospital Discharge Survey		**PRRs**	pattern recognition receptors
NHIS	National Health Interview Survey		**PSA**	prostate-specific antigen
NHLBI	National Heart, Lung, and Blood Institute		**PSAM**	probability of smoking-attributable mortality
NHS	Nurses' Health Study		**PVFE**	present value of future earnings
NIDA	National Institute on Drug Abuse		**QALYs**	quality-adjusted life years
NIH	National Institutes of Health		**RA**	rheumatoid arthritis
NK	natural killer		**RAI**	Reynolds American, Inc.
NKG2D	NK group 2D		**RCP**	Royal College of Physicians
NKT	natural killer T		**RCT**	randomized clinical trial
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol		**RDFS**	root-surface caries decayed/filled tooth surface
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone		**RDS**	root-surface caries decayed tooth surface
NNN	*N´*-nitrosonornicotine		**RF**	rheumatoid factor
NO	nitric oxide		*RICO*	*Racketeer Influenced and Corrupt Organizations Act*
NP	nicotine polacrilex gum		**RJR**	R.J. Reynolds Tobacco Company
NPCR	National Program of Cancer Registries		**ROS**	reactive-oxygen species
NPT	nocturnal penile tumescence		**RPE**	retinal pigment epithelium
NPTR	nocturnal penile tumescence and rigidity		**RR**	relative risk
NRT	nicotine replacement therapy		**RSV**	respiratory syncytial virus
NSAIDs	nonsteroidal anti-inflammatory drugs		**RT**	response time
NSCLC	non-small-cell lung cancer		*S. pneumonia*	*Streptococcus pneumoniae*
NSDUH	National Survey on Drug Use and Health		**SAB**	spontaneous abortion
NTHi	nontypeable *Haemophilus influenza*		**SAF**	smoking-attributable fraction
NV	neovascular		**SAM**	smoking-attributable mortality
NYTS	National Youth Tobacco Survey		**SAMHSA**	Substance Abuse and Mental Health Services Administration
ODD	oppositional defiant disorder		**SAMMEC**	Smoking-Attributable Mortality, Morbidity, and Economic Costs
OR	odds ratio			
P. aeruginosa	*Pseudomonas aeruginosa*		**SCD**	sudden coronary death
PACT	*Prevent All Cigarette Trafficking Act*		**SCE**	sister chromatid exchange
PAD	peripheral arterial disease		**SEER**	Surveillance, Epidemiology, and End Results
PAF	population-attributable fraction			
PAH	polycyclic aromatic hydrocarbon			

SES	socioeconomic status
SF-12	Short Form 12
SF-36	Short Form 36
sFlt-1	soluble fms-like tyrosine kinase-1
S/G$_2$/M	synthesis/gap$_2$/mitosis
SIDS	sudden infant death syndrome
SLE	systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SNP	single nucleotide polymorphism
SOD2	superoxide dismutase 2
STI	sexually transmitted infection
SULT	sulfotransferase
TB	tuberculosis
TCDD	tetrachlorodibenzo-p-dioxin
TCR	T cell receptor
Th cell	T helper cell
TI	The Tobacco Institute, Inc.
TIA	transient ischemic attack
TIPS	Tips from Former Smokers
TIRC	Tobacco Industry Research Committee
TLR4	toll-like receptor 4
tPA	tissue plasminogen activator
TPSAC	Tobacco Products Scientific Advisory Committee
TRIPS	Trade-Related Aspects of Intellectual Property Rights

TRPA1	transient receptor patential cation channel, subfamily A, member 1
TST	tuberculin skin test
UGT	uridine-5′-disphosphate-glucuronosyltransferase
UICC	Union for International Cancer Control
UN	United Nations
UPRs	unfolded protein responses
USDHEW	U.S. Department of Health, Education, and Welfare
USDHHS	U.S. Department of Health and Human Services
USEPA	U.S. Environmental Protection Agency
USGAO	U.S. General Accounting Office
USPSTF	U.S. Preventive Services Task Force
USRTC	U.S. Radiologic Technologist Cohort
VA	U.S. Department of Veterans Affairs
VDJ	variable, diversity, and joining gene segments recombination
WHI	Women's Health Initiative
WHO	World Health Organization
WTO	World Trade Organization
YPLL	years of potential life lost
YRBS	Youth Risk Behavior Survey
YRBSS	Youth Risk Behavior Surveillance System

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Definitions and Alternative Nomenclature of Genetic Symbols Used in This Report

Throughout this report, genes are represented by their abbreviations in italics. In many cases, proteins and enzymes related to these genes have the same abbreviation, presented in roman type. Definitions, alternative genetic symbols, related proteins and enzymes, and polymorphisms and variant genotypes are listed alphabetically by gene abbreviation.

Gene symbol used in this report	Definition	Alternative gene symbol	Related protein/ enzyme	Polymorphism/ variant genotype
AAT	α1-antitrypsin	*SERPINA1*	AAT	*PI*S, PI*Z, PI MZ, PI 22, GLN6VAL (S), GLN6LYS (Z)*
ADD	adducin 1 (alpha)	*ADD1*	ADD1	GLY460TRP
AGT	O^6-alkylguanine–DNA alkyltransferase		AGT	*ILE143VAL, GLY160ARG*
AHR	aryl hydrocarbon receptor		AHR	
AHRR	aryl-hydrocarbon receptor repressor		AHRR	
AIB1	amplified in breast 1	*NCOA3*	AIB1	
AKT	v-akt murine thymoma viral oncogene homolog 1		AKT	
ATM	ataxia telangiectasia mutated		ATM	
APC	adenomatous polyposis coli		APC	
APO2	tumor necrosis factor receptor superfamily, member 10a		APO2	
APOE	apolipoprotein E	*TNFRSF10A*	APOE	**2*
ARMS2	age-related maculopathy susceptibility 2	*LOC387715 A69S*	ARMS2	*rs10490942, rs10490912, rs10490924*
BAD	BCL2-associated agonist of cell death	*BBC2, BCL2L8*	BAD	
BAX	BCL2-associated X protein	*BCL2L4*	BAX	
BCL3	B-cell CLL/lymphoma 3		BCL3	
BCL2L8	BCL2-associated agonist of cell death	*BAD*	BCL2L8	
BCL2L4	BCL2-associated X protein	*BAX*	BCL2L4	
BHLHB5	basic helix-loop-helix family, member e22	*BHLHE22*	BHE22	
BHLHE22	basic helix-loop-helix family, member e22	*BHLHB5*	BHLHB5	
BICD1	bicaudal D homolog 1 (*Drosophila*)		BICD1	
BMP4 T538C	bone morphogenetic protein 4		BMP4	
BOLL	bol, boule-like		BOLL	
BRCA1	breast cancer 1, early onset		BRCA1	
BRCA2	breast cancer 2, early onset	*BRCC2*	BRCA2	*HIS372ASN (T27113G), ILE3412VAL (G93268A*

Gene symbol used in this report	Definition	Alternative gene symbol	Related protein/ enzyme	Polymorphism/ variant genotype
BRCC2	breast cancer 2, early onset	*BRCA2*	BRCC2	
BRMS1	breast cancer metastasis suppressor 1		BRMS1	
C3	complement component 3 (C3)		C3	*R102G, rs1047286, rs11569536, rs3745565, P314L*
C7	complement component 7	*CXCL10*	C7	
CARD15	nucleotide-binding oligomerization domain containing 2	*NOD2*	CARD15	
CC2	complement component 2		CC2	
CDKN2A	cyclin-dependent kinase inhibitor 2A	*P16*	CDKN2A	
CFB	complement factor B		CFB	
CFH	complement factor H		CFH	*rs3753394, rs800292, rs1061147, rs1061170, rs380390, rs1329428, Y402H, rs1410996, rs2274700, T1277C, CAATTTAG (P1), CGGCTTAG (P2), rs1410996-AG, rs1410996-GG, (GG)rs10490924/ (TT), (TT)rs10490924/(CC), Y402H, YY, AA, CC, TT, CT, HH*
CHRNA3	cholinergic receptor, nicotinic, α3		CHRNA3	
CHRNA5	cholinergic receptor, nicotinic, α5		CHRNA5	
CHRNB4	cholinergic receptor, nicotinic, β4		CHRNB4	
COX2	mitochondrially encoded cytochrome c oxidase II		COX2	
CRP	C-reactive protein		CRP	
CXCL10	chemokine (C-X-C motif) ligand 10	*C7*	CXCL10	
CYP17	cytochrome P450, family 17, subfamily A, polypeptide 1	*CYP17A1*	CYP17	
CYP1A1	cytochrome P-450, family 1, subfamily A, polypeptide 1 (CYP1A1)		CYP1A1	*2A, *2C, m1/m2, *1, *2, MSPI*
CYP1A2	cytochrome P-450, family 1, subfamily A, polypeptide 1		CYP1A1	
CYP1B1	cytochrome P450, family 1, subfamily B, polypeptide 1		CYP1B1	*LEU/LEU, VAL/VAL, 119S*
CYP2A6	cytochrome P-450, family 2, subfamily A, polypeptide 6		CYP2A6	
CYP2E1	cytochrome P450, family 2, subfamily E, polypeptide 1		CYP2E1	*RSAI*
DAT1	dopamine active transporter 1	*SLC6A3*	DAT1	+/+

Gene symbol used in this report	Definition	Alternative gene symbol	Related protein/ enzyme	Polymorphism/ variant genotype
DCC	deleted in colorectal carcinoma		DCC	
EGFR	epidermal growth factor receptor (erythroblastic leukemia viral (v-erb-b) onco homolog, avian)		EGFR	
ELN	Elastin		ELN	
ELOVL4	ELOVL fatty acid elongase 4		ELOVL4	
ENOS	endothelial nitric oxide synthase	*NOS3*	ENOS, NOS3	
EPHB2	EPH receptor B2	*ERK*	EPHB2	
EPHX	epoxide hydrolase		EPHX	
EPHX1	epoxide hydrolase 1, microsomal (xenobiotic)		EPHX1	
ERBB2	v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2	*HER2*	ERBB2	
ERCC2	excision repair cross-complementing rodent repair deficiency, complementation group 2	*XPD*	ERCC2	
ERCC4	excision repair cross-complementing rodent repair deficiency, complementation group 4	*XPF*	ERCC4	
ERCC5	excision repair cross-complementing rodent repair deficiency, complementation group 5	*XPG*	ERCC5	
ERCC6	excision repair cross-complementing rodent repair deficiency, complementation group 6		ERCC6	
ERK	extracellular signal-regulated kinase	*EPHB2*	ERK	
ESR1	estrogen receptor 1		ESR1	
FAM13A	family with sequence similarity 13, member A		FAM13A	
FBLN5	fibulin 5		FBLN5	
FBXW7	F-box and WD repeat domain containing 7, E3 ubiquitin protein ligase		FBXW7	
FUT2	fucosyltransferase 2 (secretor status included)	*SE*	FUT2	
GADD45	growth arrest and DNA-damage-inducible, alpha		GADD45	

Gene symbol used in this report	Definition	Alternative gene symbol	Related protein/ enzyme	Polymorphism/ variant genotype
GFI1	growth factor independent 1 transcription repressor		GFI1	
GST	glutathione-*S*-transferase		GST	
GSTA1	glutathione *S*-transferase alpha 1		GSTA1	
GSTA4	glutathione-*S*-transferase α4		GSTA4	
GSTM1	glutathione-*S*-transferase μ1 (GSTM1)	*GSTM1-1*	GSTM1	*A/B*
GSTM3	glutathione *S*-transferase μ3 (brain)		GSTM3	
GSTP1	glutathione *S*-transferase π1		GSTP1	
GSTT1	glutathione-*S*-transferase θ1 (GSTT1)	*GSTT1-1*	GSTT1	*DEL*
HER2	human epidermal growth factor receptor 2	*ERBB2*	HER2	
HHIP	hedgehog interacting protein		HHIP	
HIF1A	hypoxia inducible factor 1, alpha subunit (basic helix-loop-helix transcription factor)		HIF1A	
HLA	major histocompatibility complex	*HLA-A*	HLA	*SE*
HLA-DPB1	major histocompatibility complex, class II, DP beta 1		HLA-DPB1	
HLA-DPB2	major histocompatibility complex, class II, DP beta 2 (pseudogene)		HLA-DPB2	
HO-1	heme oxygenase (decycling) 1	*HMOX1*	HMOX1	
HRAS	ν-Ha-ras Harvey rat sarcoma viral oncogene homolog	C-HRAS	C-HRAS, HRAS1 proto-oncoprotein	
HTRA1	HtrA (high temperature requirement factor A) serine peptidase 1		HTRA1	*GG, rs11200638, AA*
IBD1	nucleotide-binding oligomerization domain containing 2		IBD1	
ICAM-1	intercellular adhesion molecule 1		ICAM-1	*GLY241ARG*
IGHMP2	immunoglobulin mu binding protein 2		IGHMP2	
*IKK*β	inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta		IKK	
*IL-1*β	interleukin-1β (IL-1β)		IL-1β	
IL-12			IL-12	
IL-13	interleukin-13		IL-13	

Gene symbol used in this report	Definition	Alternative gene symbol	Related protein/ enzyme	Polymorphism/ variant genotype
IL-4	interleukin-4		IL-4	
IL-5	interleukin-5		IL-5	
IL-6	interleukin-6		IL-6	
IL-8	interleukin-8		IL-8	
IL-10	interleukin-10		IL-10	
IL-17A	interleukin -17A		IL-17A	
IL-18	interleukin -18		IL-18	
IL-23	interleukin -23		IL-23	
IL-33	interleukin -33		IL-33	
IP-10	chemokine (C-X-C motif) ligand 10	*C-7, CXCL10*	CXL 10	
IREB2	iron-responsive element binding protein 2		IREB2	
IRF6	interferon regulatory factor 6		IRF6	
JNK-1	c-Jun N-terminal kinase 1	*MAPK8*	JNK-1	
KRAS	K-ras (v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog)		KRAS	
LacZ	beta-galactosidase		LACZ	
LC3B	microtubule-associated protein 1 light chain 3 beta		LCB3	
LGALS4	lectin, galactoside-binding, soluble, 4		LGALS4	
LIG4	ligase IV, DNA, ATP-dependent		LIG4	
LOC387715 A69S	age-related maculopathy susceptibility 2	*ARMS2*	LOC387715	*GG, GT+TT, rs10490924, rs10490942*
MAOA	monoamine oxidase A		MAOA	*5'uVNTR*
MAPK8	mitogen-activated protein kinase 8	*JNK-1*	MK08	
mEH3	microsomal epoxide hydrolase (mEH) polymorphism in exon 3		mEH3	
MEK	mitogen-activated protein kinase		MEK	
MGMT	O^6-methylguanine-DNA methyltransferase		MGMT	*LEU84PHE, ILE143VAL*
MnSOD2	manganese superoxide dismutase 2		MnSOD2	*VAL* (wild type), *ALA*
MMP	matrix metallopeptidase		MMP	

Gene symbol used in this report	Definition	Alternative gene symbol	Related protein/ enzyme	Polymorphism/ variant genotype
MMP 9	matrix metallopeptidase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase)		MMP 9	
MMP 12	matrix metallopeptidase 12 (macrophage elastase)		MMP 12	
MPO	myeloperoxidase		MPO	
MYH9	myosin, heavy chain 9, non-muscle		MYH9	
MSX1	muscle segment homeobox 1		MSX1	*CA, X1.1, X1.3, X2.1, X2.4, T2090G*
MTHFR	methylenetetrahydrofolate reductase		MTHFR	*677C→T, CC*
NAT1	*N*-acetyltransferase 1		NAT1, ARY1	*1088, 1095, AA* vs. *TT, AA* vs. *CC, T1095A, 1088A, 1088T→A, 1095C→A*
NAT2	*N*-acetyltransferase 2		NAT2, ARY2	*_SNP2, 282C→T, 341T→C, 481T→C, 590G→A, 857G→A, *4, *5, *6, *7, *12, *13, *14, rs9987109, rs1208*
NCOA3	nuclear receptor coactivator 3	*AIB1*	NCOA3	
NOD2	nucleotide-binding oligomerization domain containing 2	*CARD15*	NOD2	
NOS3	nitric oxide synthase 3 (endothelial cell)	*ENOS*	ENOS, NOS3	*A(-922)G, SNP2, GLU298ASP, G894T*
NOTCH1	notch1		NOTCH1	
NPPA	natriuretic peptide A		NPAA	*2238T→C*
P16	cyclin-dependent kinase inhibitor 2A	*CDKN2A*	P16	
P53	tumor suppressor		P53	
PI	glutathione S-transferase pi 1	*SERPINA1*		S, Z, ZZ
PI7	polymerase (DNA directed), epsilon 3, accessory subunit	*POLE3*	P17	
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha		PIK3CA	
polA	polymerase (DNA directed), alpha 1, catalytic subunit	*POLA1*	POLA	
PTPN22	protein tyrosine phosphatase, non-receptor type 22		PTPN22	
RAD23B	RAD23 homolog B (*S. cerevisiae*)		RAD23B	
RAF	rapidly accelerated fibrosarcoma		RAF	

Gene symbol used in this report	Definition	Alternative gene symbol	Related protein/ enzyme	Polymorphism/ variant genotype
Rag1	recombination activating gene 1		Rag1	
RAS	rat sarcoma		RAS	
RASSF1A	Ras association (RalGDS/AF-6) domain family member 1 (A isoform)		RASSF1A	
RUNX1	runt-related transcription factor 1		RUNX1	
SE	fucosyltransferase 2	*FUT2*	SE	*Rs4646903*
SERPINA1	serpin peptidase inhibitor, clade A (α-1 antiproteinase, antitrypsin), member 1	*AAT*	SERPINA1	*PI*Z, SZ*
SERPINE2	serpin peptidase hihibotir, clade E (nexin, plasminogen activator inhibitor type 2), member 2	*PI7*	SERPINE2	
SERPINA3	serpin peptidase inhibitor, clade A (α-1 antiproteinase, antitrypsin), member 3		SERPINA3	
SOD2	superoxide dismutase 2		SOD2	
SOX5	SRY (sex determining region Y)-box 5		SOX5	
STK11	serine/threonine protein kinase 11		STK11	
SULT	sulfotransferase		SULT	
SULT1A1	sulfotransferase family, cytosolic, 1A, phenol-preferring, member 1		SULT1L1	*ARG/HIS, *HIS*
TGF-α	transforming growth factor-α		TGF-	*TAQ1*
TNFα	tumor necrosis factor (TNF superfamily, member 2) α		TNFα	
TGF-β	transforming growth factor-β		TGF-β	
TGF-β3	transforming growth factor-β3		TGF-β3	*CA, x5.1, 5'UTR.1, T-24in4C, C641A, G15572*
TNFRSF10A	tumor necrosis factor receptor superfamily, member 10a		TNFRSF10A	
TNFRSF10C	tumor necrosis factor receptor superfamily, member 10c, decoy without an intracellular domain		TNFRSF10C	
TP53	tumor protein 53		TP53	
TP63	tumor protein 63		TP63	
TRPA1	transient receptor potential cation channel, subfamily A, member 1		TRPA1	
UGT1A7	UDP glucuronosyltransferase 1 family, polypeptide A7		UGT1A7	*SNP1*
VEGF	vascular endothelian growth factor	*VEGFA*	VEGF	

Gene symbol used in this report	Definition	Alternative gene symbol	Related protein/ enzyme	Polymorphism/ variant genotype
XPC	xeroderma pigmentosum, complementation group C		XPC	
XPD	xeroderma pigmentosum. Complementation group D	*ERCC2*	XPD	*LYS751GLN, GLN/GLN*
XPF	xeroderma pigmentosum, complementation group F	*ERCC4*	XPF	
XPG	xeroderma pigmentosum, complementation group G	*ERCC5*	XPG	
XRCC1	x-ray repair complementing defective repair in Chinese hamster cells 1		XRCC1	*ARG399GLN, ARG213HIS, ARG194TRP, ARG280HIS, C26602T, GLN632GLN, 194 ARG/ ARG*
XRCC2	x-ray repair complementing defective repair in Chinese hamster cells 2		XRCC2	
XRCC3	x-ray repair complementing defective repair in Chinese hamster cells 3		XRCC3	
XRCC5	x-ray repair complementing defective repair in Chinese hamster cells 5		XRCC5	

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Note: *t* following a number refers to a table; *f* following a number refers to a figure; *S* preceding number indicates supplement.

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Errata

The Health Consequences of Smoking—50 Years of Progress. A Report of the Surgeon General. Atlanta, Georgia: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.

Please note that these errors are reflected in the copies that were distributed at the release on January 17, 2014. The online version has been corrected, and any subsequent copies will be printed with these corrections.

Page iii, Preface

The Preface should read as follows:

On January 11, 1964, Luther L. Terry, M.D., the 9th Surgeon General of the United States, released the first report on the health consequences of smoking: Smoking and Health: Report of the Advisory Committee of the Surgeon General of the Public Health Service. That report marked a major step to reduce the adverse impact of tobacco use on health worldwide.

Over the past 50 years, 31 Surgeon General's reports have utilized the best available evidence to expand our understanding of the health consequences of smoking and involuntary exposure to tobacco smoke. The conclusions from these reports have evolved from a few causal associations in 1964 to a robust body of evidence documenting the health consequences from both active smoking and exposure to secondhand smoke across a range of diseases and organ systems.

The 2004 report concluded that smoking affects nearly every organ of the body, and the evidence in this report provides even more support for that finding. A half century after the release of the first report, we continue to add to the long list of diseases caused by tobacco use and exposure to tobacco smoke. This report finds that active smoking is now causally associated with age-related macular degeneration, diabetes, colorectal cancer, liver cancer, adverse health outcomes in cancer patients and survivors, tuberculosis, erectile dysfunction, orofacial clefts in infants, ectopic pregnancy, rheumatoid arthritis, inflammation, and impaired immune function. In addition, exposure to secondhand smoke has now been causally associated with an increased risk for stroke.

Smoking remains the leading preventable cause of premature disease and death in the United States. The science contained in this and prior Surgeon General's reports provide all the information we need to save future generations from the burden of premature disease caused by tobacco use. However, evidence-based interventions that encourage quitting and prevent youth smoking continue to be underutilized. This report strengthens our resolve to work together to accelerate and sustain what works— such as hard-hitting media campaigns, smokefree air policies, optimal tobacco excise taxes, barrier-free cessation treatment, and comprehensive statewide tobacco control programs funded at CDC- recommended levels. At the same time, we will explore "end game" strategies that support the goal of eliminating tobacco smoking, including greater restrictions on sales. It is my sincere hope that 50 years from now we won't need another Surgeon General's report on smoking and health, because tobacco- related disease and death will be a thing of the past. Working together, we can make that vision a reality.

Boris D. Lushniak, M.D., M.P.H.
Rear Admiral, U.S. Public Health Service
Acting Surgeon General
U.S. Department of Health and Human Services

Page 65, Figure 4.3

Figure 4.3 has been revised as follows:
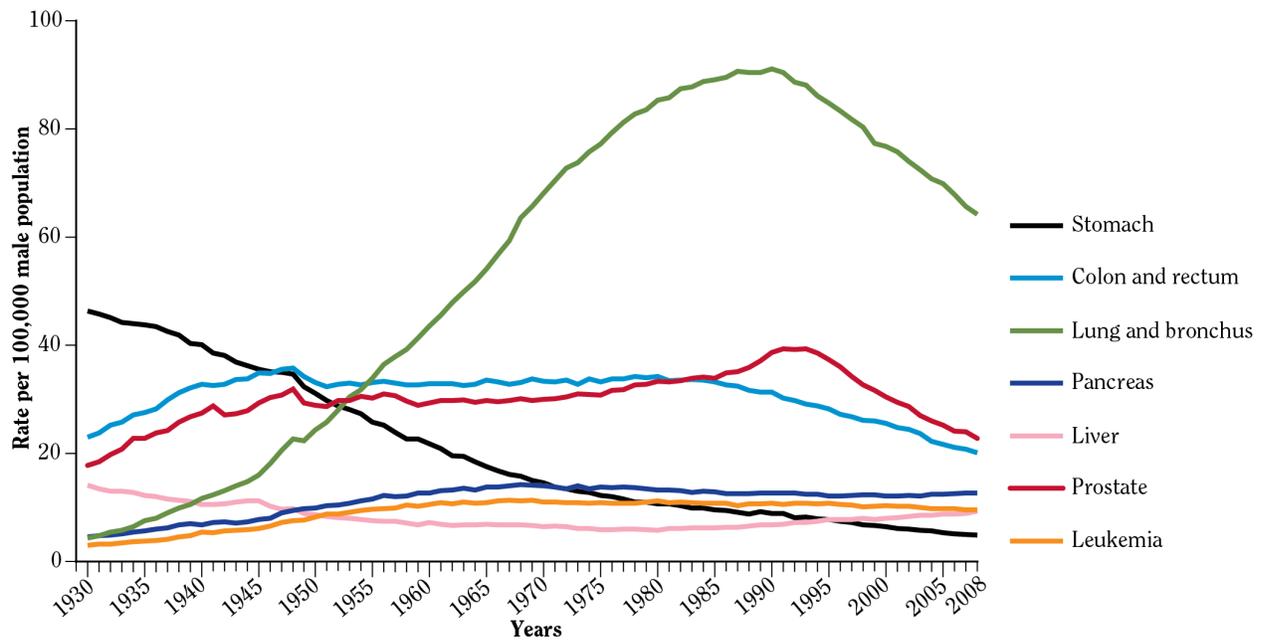
Page 872

In the last paragraph of the right column, the third sentence should read as follows: "Based on box office attendance data, it has been estimated that youth were exposed to 14.9 billion in-theater tobacco-use impressions[3] in youth-rated films in 2012."