NATIONAL CANCER INSTITUTE
Women's Health Report, Fiscal Years 2003-2004
March 2005

EXECUTIVE SUMMARY

Cancer continues to take a devastating toll on American women. In 2005, an estimated 662,870 women will have been diagnosed with cancer, and approximately 275,000 women will have died of the disease.[1] Despite these grim statistics, our nation is making important progress in the fight against cancer overall and in women. Cancer incidence rates for all cancers in women have recently declined slightly. Mortality rates have decreased for all cancers combined in the general population, and for 8 of the top 15 cancers in women. Lung cancer death rates among women leveled off for the first time between 1995 and 2001, after increasing for many decades. Five-year cancer survival rates have improved since the late 1970s, although less significantly for women than for men.

NCI is committed to continuing efforts to reduce the toll of cancer through scientific discovery and its application to people. Through its strategic planning process, NCI identifies many of the questions that need to be answered, areas of research and care that need to be supported, and infrastructure that needs to be strengthened, to ultimately eliminate the suffering and death due to cancer (see http://plan2006.cancer.gov). NCI's Office of Women's Health, organizationally located within the Office of Science Planning and Assessment, assists in planning, evaluating, and coordinating activities related to cancers in women. In addition to the extensive research supported at the NCI and through research grants, a number of specific programs and activities in NCI focus on women's cancers, including the Breast and Gynecologic Cancer Research Group in the Division of Cancer Prevention, the Breast Cancer Surveillance Consortium in the Division of Cancer Control and Population Sciences, the Gynecologic Oncology Group clinical trials cooperative group in the Division of Cancer Treatment and Diagnosis, and the Breast and Gynecologic Malignancies Faculty and the HPV (Human Papillomavirus) Working Group in the Center for Cancer Research. By working with partners from public, private, and academic settings and focusing investment in strategic areas with high potential, we have the opportunity to accelerate the pace of discovery and facilitate the translation of research knowledge to clinical application.

This report describes many of the activities and accomplishments of the National Cancer Institute's (NCI's) research programs in fiscal years 2003 and 2004, addressing cancers specific to or primarily affecting women, as well as those cancers with high incidence or mortality among women. Included are breast, cervical, ovarian, endometrial, colorectal, lung and other tobacco-related cancers, as well as AIDS (acquired immunodeficiency syndrome)-associated malignancies.

Biology, Genetics, and Cancer Risk. To develop more effective approaches to cancer prevention, early detection, and treatment, a better understanding of the molecular mechanisms that lead to cancer development and progression is required. In addition, the identification and interactions between inherited genetic and environmental factors that increase cancer risk is critical. For example, NCI supports research to develop and apply animal models of human cancers, identify genetic and proteomic factors associated with cancer development and progression, and elucidate molecular interactions among cancer cells and their microenviroment. NCI supports consortia and networks to pool the resources of multidisciplinary researchers for large population studies that explore genetic and environmental risk factors. For example, the NCI Consortium of Cohorts conducts large-scale collaborations for study of gene-gene and gene-environment interactions in the cancer etiology. NCI is supporting large cohort studies in Costa Rica and the United States to better define risk factors for progression of precancerous lesions among HPV infected women. The Cancer Genetics Network Colon Sibling Pair study seeks to identify genetic and environmental factors involved in the development of colorectal cancer.

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1 Incidence and mortality statistics reported for 2003 and after are age-adjusted to the 2000 U.S. population standard. Previous statistics based on the 1970 population standard should not be compared to new data generated from the 2000 age-adjusted population standard. Additionally, some of the rates, particularly for different racial/ethnic groups, were changed as the new statistics were calculated. A complete summary can be found at: http://www.cancer.gov/newscenter/pressreleases/Census2000

Cancer Prevention Research. Researchers are applying their knowledge about cancer risk to develop cancer prevention strategies. For example, NCI and partners are designing vaccines to prevent cervical cancer by protecting women against persistent HPV infection. Researchers are investigating selective estrogen receptor modulators and aromatase inhibitors for use in breast cancer prevention and cholesterol-lowering statins for colorectal cancer prevention. Other researchers are also identifying dietary and behavioral factors that can help prevent different types of cancer.

Early Detection. NCI and partners are developing and applying techniques to detect cancer in its earliest, most treatable stages. Investigators are conducting large, multi-site studies of digital mammography for breast cancer screening and low-dose spiral computed tomography for lung cancer screening. A proteomics-based test for early detection of ovarian cancer is now in clinical trials. NCI is helping to test a gene expression profiling technique to predict risk of breast cancer recurrence. Finally, NCI scientists have demonstrated that HPV DNA testing predicts increased risk for future cervical precancers and cancers.

Cancer Treatment. Research has led recently to improved regimens of traditional chemotherapeutic agents for breast, cervical, ovarian, endometrial, lung, and colorectal cancers, and AIDS-associated malignancies. New treatment modalities, such as aromatase inhibitors for breast cancer, are improving survival and quality of life for patients. Increasing knowledge of the molecular changes that cause cancer, as well as the reaction of the immune system to cancer, is enabling researchers to identify potential targets for the discovery of new targeted therapies and preventives. Molecularly targeted therapies, including monoclonal antibodies, are being developed to treat breast, endometrial, lung, and colorectal cancers. NCI researchers are also helping to develop a treatment vaccine for non-small cell lung cancer.

Cancer Health Disparities, Quality of Care, Outcomes, and Survivorship. NCI's Center to Reduce Cancer Health Disparities provides the organizational locus for the critical tasks needed to advance understanding of the causes of cancer health disparities and to develop and integrate effective interventions to eliminate them. For example, the Center has an ongoing program to understand the origins of and address the entrenched pattern of high cervical cancer mortality found in distinct U.S. populations and geographic areas. The NCI-funded Center for Psycho-Oncology Research conducts behavioral, psychological, social, and biomedical research on the interrelationships among cognition, emotion, biological processes, and physical health in patients with cancer. NCI and partners develop and disseminate educational materials targeting minority and underserved women, addressing topics such as smoking cessation, use of mammography, and surgery choices for early-stage breast cancer. NCI-funded researchers also are assessing the effects of energy balance-related behaviors on the health and quality of life of cancer survivors.

Tobacco and Cancer. The devastating impact of tobacco use and exposure to tobacco is being addressed by studies to understand the genetic, social, behavioral, and environmental factors involved in tobacco addiction and control; assess cancer risk factors that differentially affect smokers and nonsmokers; identify behavioral and pharmaceutical interventions for smoking prevention and smoking cessation; and improve detection of and treatments for tobacco-associated cancers. A working group meeting, held in February 2003, *Women, Tobacco, and Cancer: An Agenda for the 21st Century*, assembled researchers, clinicians, and members of the advocacy community to identify gaps and research priorities, and to identify and prioritize needs in dissemination and application. The working group released their report in July 2004, recommending strategies to meet five overall goals in the areas of discovery, development, delivery, partnerships, and evaluation and surveillance that will contribute to reducing and ultimately eliminating the harmful health effects of smoking in women.

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INTRODUCTION

This report describes many of the activities and accomplishments of the National Cancer Institute's (NCI's) research programs in fiscal years 2003 and 2004, addressing cancers specific to or primarily affecting women, as well as those cancers with high incidence or mortality among women. Included are breast, cervical, ovarian, endometrial, colorectal, and lung and other tobacco-related cancers, as well as AIDS (acquired immunodeficiency syndrome)-associated malignancies.

Cancer continues to take a devastating toll on American women. In 2005, an estimated 662,870 women will have been diagnosed with cancer, and approximately 275,000 women will have died of the disease.[1] Despite these grim statistics, our nation is making important progress in the fight against cancer overall and in women. In the 1990s, cancer incidence rates for all cancers combined decreased for men and remained relatively stable for women. Cancer incidence rates for women have since declined slightly, from 1999 to 2001. Mortality rates have decreased for all cancers combined in the general population and for 8 of the top 15 cancers in women. Lung cancer death rates among women leveled off for the first time between 1995 and 2001, after increasing for many decades. Comparison of five-year survival rates for cancer patients diagnosed in the years 1975 to 1979 to those diagnosed from 1995 to 2000 show improvement overall, although less significantly for women than for men.

NCI is committed to continuing efforts to reduce the toll of cancer through scientific discovery and its application to people. NCI's Office of Women's Health, organizationally located within the Office of Science Planning and Assessment, assists in planning, evaluating, and coordinating activities related to cancers in women. In addition to the extensive research supported at the NCI and through research grants, a number of specific programs and activities in NCI focus on women's cancers, including the Breast and Gynecologic Cancer Research Group in the Division of Cancer Prevention, the Breast Cancer Surveillance Consortium in the Division of Cancer Control and Population Sciences, the Gynecologic Oncology Group clinical trials cooperative group in the Division of Cancer Treatment and Diagnosis, and the Breast and Gynecologic Malignancies Faculty and the HPV Working Group in the Center for Cancer Research.

NCI supports a number of broad-based research programs that apply to all types of cancer in both women and men. Through its strategic planning process, NCI has identified many of the questions that need to be answered, areas of research and care that need to be supported, and infrastructure that needs to be strengthened to ultimately eliminate the suffering and death due to cancer. Seven strategic priority areas for investment are outlined in *The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2006* (http://plan2006.cancer.gov/). As part of the planning process, we periodically examine our progress in meeting strategic goals. NCI has recently released a report that assesses progress in addressing research priorities identified in the 1998 report of the Breast Cancer Progress Review Group (PRG). This report, as well as other PRG reports, implementation plans, and additional information is accessible from http://planning.cancer.gov/disease/index.shtml.

NCI staff participate in multiple, diverse scientific partnerships and collaborative activities with other federal and nonfederal scientists. By working with partners from public, private, and academic settings and focusing investment in strategic areas with high potential, we take advantage of opportunities to accelerate the pace of discovery and facilitate the translation of research knowledge to clinical application.

1Incidence and mortality statistics reported for 2003 and after are age-adjusted to the 2000 U.S. population standard. Previous statistics based on the 1970 population standard should not be compared to new data generated from the 2000 age-adjusted population standard. Additionally, some of the rates, particularly for different racial/ethnic groups, were changed as the new statistics were calculated. A complete summary can be found at: http://www.cancer.gov/newscenter/pressreleases/Census2000

CROSSCUTTING INITIATIVES

(Links to related crosscutting initiatives can be found at the end of the narrative of this report.)

TRENDS IN CANCER

Accurate information on the incidence and impact of disease is critical to decision making in science and public health. For this reason, NCI has established a number of programs and initiatives to provide surveillance infrastructure, track trends, and report cancer statistics. NCI continues to expand its surveillance efforts to cover a broader spectrum of the racial, ethnic, socioeconomic, and cultural diversity of our country.[2]

CANCER BIOLOGY AND GENETICS

Basic studies exploring the science of how cancer develops and progresses form the foundation of cancer research. Identifying, at the molecular and cellular level, the fundamental processes that underlie a cell's normal development and transformation from normal to premalignant to malignant can lead to new prevention, detection, diagnosis, and treatment approaches. NCI supports initiatives and programs that stimulate interdisciplinary research on cancer biology and genetics.[3]

PRECLINICAL RESEARCH

NCI supports a broad range of pre-clinical research initiatives and resources to develop new agents and novel approaches for the prevention, early detection, and treatment of cancer.[4]

CLINICAL RESEARCH

NCI's clinical trials system includes researchers from NCI's intramural program, Cancer Centers, Cooperative Groups, Specialized Programs of Research Excellence (SPOREs), Community Clinical Oncology Program (CCOP), and minority-based CCOPs, and investigator-initiated grants. These scientists conduct over 1,500 clinical trials annually to evaluate improved and novel cancer prevention, early detection, diagnosis, treatment, and quality of life strategies.[5]

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2 **TRENDS IN CANCER**

- Surveillance, Epidemiology, and End Results (SEER) Program, http://seer.cancer.gov
- Cancer Mortality Maps & Graph, http://www3.cancer.gov/atlasplus/
- Cancer Intervention and Surveillance Modeling Network (CISNET), http://cisnet.cancer.gov
- Cancer Progress Report, http://progressreport.cancer.gov/
- Cancer Control Supplements to National Health Interview Survey http://appliedresearch.cancer.gov/surveys/nhis/
- Cancer Control Supplements to California Health Interview Survey http://appliedresearch.cancer.gov/surveys/chis/module.html

3 **CANCER BIOLOGY AND GENETICS**

- Integrative Cancer Biology Program, http://dcb.nci.nih.gov/branchdetail.cfm?branch=1
- Specialized Programs of Research Excellence (SPOREs) (including 10 breast cancer, 2 gynecologic, and 5 ovarian cancer SPORES), http://spores.nci.nih.gov
- The Cancer Genetics Network (CGN), http://epi.grants.cancer.gov/CGN/
- The Breast/Ovarian and Colon Cancer Family Registries (CFRs), http://epi.grants.cancer.gov/CFR/
- Cancer Genome Anatomy Project (CGAP), http://cgap.nci.nih.gov
- Mammalian Gene Collection (MGC), http://mgc.nci.nih.gov/
- Cancer Molecular Analysis Project (CMAP), http://cmap.nci.nih.gov/
- Early Detection Research Network (EDRN), http://edrn.nci.nih.gov
- Tissue Array Resource Program (TARP), http://ccr.cancer.gov/tech_initiatives/tarp/
- Specimen Resource Locator, http://pluto3.nci.nih.gov/tissue/

4 **PRECLINICAL RESEARCH**

- Strategic Partnering to Evaluate Cancer Signatures (SPECS), http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-04-015.html
- Director's Challenge: Toward a Molecular Classification of Tumors, http://dc.nci.nih.gov
- Mouse Models of Human Cancer Consortium (MMHCC), http://emice.nci.nih.gov/
- Comparative Oncology Program, http://ccr.nci.nih.gov/resources/cop/announcement.asp
- Rapid Access to Intervention Development (RAID), http://dtp.nci.nih.gov/docs/raid/raid_index.html
- Rapid Access to NCI Discovery Resources (RAND), http://dtp.nci.nih.gov/docs/rand/rand_index.html
- Rapid Access to Prevention Intervention Development (RAPID), http://www3.cancer.gov/prevention/rapid/
- Developmental Therapeutics Program (DTP), http://dtp.nci.nih.gov/about.html

5 **CLINICAL RESEARCH**

- Cancer Therapy Evaluation Program (CTEP), http://ctep.cancer.gov/index.html
- Cancer Prevention Clinical Trials Consortium, http://www.cancer.gov/newscenter/pressreleases/preventtrials
- Community Clinical Oncology Program, http://cancer.gov/prevention/ccop

CANCER CONTROL AND OUTCOMES

NCI supports patient-oriented research that includes intervention, nutrition, chemoprevention, biobehavioral influences on disease, cancer screening, pain and symptom management, quality of life, ethics, confidentiality, and understanding health disparities. For example, NCI plans to establish Centers for Transdisciplinary Research on Energetics and Cancer (TREC: http://cancercontrol.cancer.gov/TREC/), modeled after the successful Transdisciplinary Tobacco Use Research Centers (TTURCs), to foster transdisciplinary collaborations that aim to reduce the cancer incidence, morbidity, and mortality associated with obesity, low levels of physical activity, and poor diet.[6]

ADVANCED TECHNOLOGIES

NCI supports the development of highly effective advanced technologies and their use to streamline research, enhance the options for patient care, and connect investigators with one another and with the heath care provider and patient communities. [7]

ADDRESSING HEALTH DISPARITIES

NCI supports a number of programs to understand the causes and extent of cancer health disparities and to develop and implement culturally appropriate and sensitive interventions for the elimination of such disparities. Research studies have provided definitive evidence that equal treatment at the same stage of disease yields equal outcomes across all populations. A dramatic reduction in cancer incidence as well as mortality could be achieved by equitably applying evidence-based interventions for tobacco control and energy balance; providing equal access to clinical trials; and providing universal access and encouraging utilization of available, state of the science interventions for cancer prevention, early detection, and treatment with follow-up care.

NCI's Center to Reduce Cancer Health Disparities (http://crchd.nci.nih.gov/) provides the organizational locus for the critical tasks needed to translate discovery research into delivery of health disparity interventions. The Trans-HHS (Health and Human Services) Cancer Health Disparities Progress Review Group met in 2003 to identify new opportunities for HHS agencies to address cancer health disparities, implement new initiatives to eliminate them, and evaluate progress toward that end. Their report, released in March 2004, can be viewed at http://www.hhs.gov/chdprg/pdf/chdprg.pdf .[8]

- Cancer Imaging Program's clinical trials program, http://imaging.cancer.gov/clinicaltrials/
- Cancer Trials Support Unit (CTSU), http://www.ctsu.org/
- Program for the Assessment of Clinical Cancer Test (PACCT), http://www.cancerdiagnosis.nci.nih.gov/assessment.
- Physician Data Query database (PDQ®), http://www.cancer.gov/cancertopics/pdq/cancerdatabase
- Clinical Trials Database: http://www.cancer.gov/clinicaltrials/
- NCI Clinical Trials at NIH, http://www.bethesdatrials.cancer.gov/

6 **CANCER CONTROL AND OUTCOMES**

- The Cancer Care Outcomes Research and Surveillance Consortium (CanCORS), (lung and colorectal cancer), http://healthservices.cancer.gov/cancors/
- Cancer Control PLANET (Plan, Link, Act, Network with Evidence-based Tools), http://cancercontrolplanet.cancer.gov/
- The HMO Cancer Research Network, http://crn.cancer.gov/
- The Patterns of Care/Quality of Care initiative, http://healthservices.cancer.gov/surveys/poc/
- SEER-Medicare Linked Database, http://healthservices.cancer.gov/seermedicare/

7 **ADVANCED TECHNOLOGIES**

- NCI Center for Bioinformatics (NCICB), http://ncicb.nci.nih.gov/
- Cancer Biomedical Informatics Grid (caBig), http://cabig.nci.nih.gov/
- NCI Alliance for Nanotechnology in Cancer, http://nano.cancer.gov/
- Clinical Proteomics Program, http://home.ccr.cancer.gov/ncifdaproteomics/
- Biomedical Proteomics Program http://ccr.nci.nih.gov/tech_initiatives/bpp/
- The Cancer Imaging Programs, http://imaging.cancer.gov/ and http://ccr.cancer.gov/tci/imaging.asp
- *In vivo* Cancer Molecular Imaging Centers (ICMICs), http://imaging.cancer.gov/programsandresources/specializedinitiatives/icmics
- Small Animal Imaging Resource Program (SAIRP), http://imaging.cancer.gov/programsandresources/specializedinitiatives/SAIRP

8 **ADDRESSING HEALTH DISPARITIES**

- The Patient Navigator Research Program, http://crchd.nci.nih.gov/Navigator/index.htm
- The Special Populations Network, http://crchd.nci.nih.gov/spn/
- Community Networks Program to Reduce Cancer Health Disparities, to be launched in 2005, http://crchd.nci.nih.gov/RFA/
- Centers for Population Health and Health Disparities, http://cancercontrol.cancer.gov/populationhealthcenters/

CANCER INFORMATION AND EDUCATION

NCI educates cancer patients, health and research professionals, and the public about women's health in a variety of formats. The NCI Cancer Information Service (CIS) shares information about cancer prevention, risk factors, symptoms, diagnosis, treatment, research, and quitting smoking. CIS information specialists provide the latest, most accurate information about cancer by telephone (1-800-4-CANCER), TTY (1-800-332-8612) and on the Internet through *LiveHelp* instant messaging service on NCI's Web site (http://cancer.gov). CIS also provides printed and electronic NCI publications through the NCI Pubs Locator https://cissecure.nci.nih.gov/ncipubs/ or by calling 1-800-4-CANCER. Through its Partnership Program, the CIS works with established national, regional, and state partner organizations to reach and educate minority and medically underserved women with limited access to health and cancer information.

NCI also provides information to the public, the cancer community, and journalists through its Web site, http://www.cancer.gov. Included are press releases and fact sheets (http://www.cancer.gov/newscenter), supplemented with in-depth background information through NCI BenchMarks (http://www.cancer.gov/newscenter/benchmarks), NCI Clinical Trial Results (http://cancer.gov/clinicaltrials/results/), the NCI Cancer Bulletin (http://cancer.gov/ncicancerbulletin/cancerbulletin), the biannual Cancer Progress Report (http://progressreport.cancer.gov) and the annual publication of *The Nation's Progress in Cancer Research* (http://planning.cancer.gov/planning/budget.shtml). The NCI's Women's Health Page provides information about initiatives, reports, and meetings pertaining to women's health issues. (http://planning.cancer.gov/whealth/). Cancer information is also provided through staffed NCI exhibits at key conferences, meetings, and events.

NCI's Office of Education and Special Initiatives (OESI; http://www.cancer.gov/aboutnci/oesi) has developed the Clinical Trials Education Series, a group of print and audiovisual materials, and a Web-based course about participating in cancer clinical trials. OESI also sponsors breast and cervical cancer screening education programs that target health professionals. The OESI Facing Forward Survivor Series, which includes Spanish language adaptations, addresses the issues that survivors face after treatment.

BREAST CANCER

Although advances in prevention, detection, diagnosis, and treatment, are having a beneficial impact on breast cancer incidence, mortality, and survival, this disease continues to have a devastating impact on American women. By the end of 2005, an estimated 211,240 women are expected to be diagnosed with breast cancer and nearly 40,410 women will have died of the disease. An estimated 2 million women in the United States have either survived breast cancer or are living with breast cancer today. Breast cancer is responsible for the highest number of new, invasive cancer cases among women each year and is the second leading cause of cancer deaths in women, after lung cancer. The increase in breast cancer incidence that began in the early 1980s continues today, although this increase has slowed dramatically since 1987. Overall, breast cancer mortality rates have shown an encouraging downward trend, dropping 2.3 percent per year from 1990 to 2001 following a slow rate of rise from 1975 to 1990. Breast cancer survival rates have improved by 13 percent since the mid 1970s. Unfortunately, this progress is not impacting all populations equally. Even when controlled for age and stage at diagnosis, black, Hispanic white, and American Indian/Alaska Native women have higher breast cancer mortality rates compared with white and Asian/Pacific Islander women.

- The Cancer Information Service Partnership Program, http://cis.nci.nih.gov/community/community.html
- Cancer Disparities Research Partnership Program, http://www3.cancer.gov/rrp/fund_cdrp.html
- The California Health Interview Survey (CHIS), http://appliedresearch.cancer.gov/surveys/chis/
- Health Information National Trends Survey, http://cancercontrol.cancer.gov/hints/
- Network for Cancer Control Research among American Indian/Alaska Native (AI/AN) Populations, http://surveillance.cancer.gov/disparities/network.html
- Cancer Surveillance, Epidemiology and End Results (SEER) Program, http://seer.cancer.gov
- Minority-based Community Clinical Oncology Program, http://www3.cancer.gov/prevention/ccop/
- Cancer Care Outcomes Research and Surveillance Consortium, http://healthservices.cancer.gov/cancors/
- Cancer Survivorship Research, http://dccps.nci.nih.gov/ocs/
- Cancer Continuing Umbrella of Research Experience (CURE), http://minorityopportunities.nci.nih.gov/mTraining/index.html
- Minority Institution-Cancer Center Partnerships, http://minorityopportunities.nci.nih.gov/institutions/miccp.html

In 2004, an internal working group reviewed NCI's progress in addressing the research priorities identified in the 1998 report of the Breast Cancer Progress Review Group, *Charting the Course: Priorities for Breast Cancer Research.* The 2004 Breast Cancer Progress Report (http://planning.cancer.gov/disease/breast.shtml) documents trends in the NCI breast cancer research portfolio from 1998 to 2003, with progress measures as broad as overall NCI funding levels and as specific as numbers of projects relevant to particular research priorities and examples of research advances. The report is designed to assist the NCI in accelerating progress against breast cancer by assessing past research and identifying future research needs.

Avon-NCI Progress for Patients Awards Program. A unique public-private partnership between NCI and the Avon Foundation helps fund innovative translational science at multiple research institutions, supporting early clinical research focused on breast cancer prevention, detection, diagnosis, prediction, prognosis, and treatment. Awards made in 2004 support 11 new projects, including research to evaluate aromatase inhibitors for cancer prevention, estradiol therapy for women with advanced stage disease, and molecular therapies that target the HER2 receptor in metastatic breast cancers.

Breast Cancer SPOREs. Nine breast cancer SPORES (http://spores.nci.nih.gov/current/breast/breast.html) conduct collaborative, multidisciplinary research to develop novel agents and technologies for breast cancer treatment and prevention and to identify biomarkers for diagnosis, prognosis, screening, prevention, and treatment. For example, breast cancer SPORE researchers have recently developed an experimental nanotechnology-based system for delivery of molecularly targeted treatment agents directly to cancer cells and demonstrated the safety and modest efficacy of treatment vaccines using peptides from HER-2/neu proteins.

BIOLOGY AND GENETICS

Mouse Models. Researchers from the Mouse Models of Human Cancers Consortium (MMHCC; http://emice.nci.nih.gov/) have recently developed models for use in the elucidation of the roles of *c-Myc* overexpression, transforming growth factor beta (TGF-β), estrogen receptor status, pregnancy-associated changes, and dietary factors in human breast cancers. These models provide important tools for studying key molecular pathways that might provide targets for therapies through better understanding of tumor growth and metastasis. Modeling breast cancer in mice has also led to the isolation and characterization of functional mouse mammary gland stem cells. This advance may aid in the identification of progenitor cells of different types of mammary cancer.

HER2 and AIB1. Breast tumors exhibiting HER2 overexpression tend to have a poorer prognosis and a lesser response to tamoxifen. The protein, AIB1, is activated via the HER2 signaling pathway and is a co-activator of the estrogen receptor. Evidence suggests that in the presence of AIB1, the therapeutic estrogen receptor inhibition properties of tamoxifen may be attenuated or reversed. Treatment strategies in preclinical testing that target AIB1 and/or HER2 include anti-HER2 vaccines, HER2 inhibitory agents, and drugs to reverse tamoxifen resistance.

Twist. NCI researchers have discovered that Twist, a protein important in early embryonic development, is reactivated in malignancy and plays a crucial role in breast cancer metastasis. Suppression of Twist expression in highly metastatic breast cancer cells inhibits their ability to metastasize and, hence, may be an important therapeutic target.

Biology of Normal Breast Tissue. NCI supports studies using laser capture microdissection and gene expression profiling of tissue samples obtained from the breasts of women who have various levels of risk for developing breast cancer, but no history of the disease. A better understanding of the biology of normal breast tissue will help researchers to identify early molecular changes that lead to cancer and to develop more effective prevention, early detection, and treatment strategies.

Genetic Epidemiology. NCI formed the Consortium of Cohorts, which now includes more than 20 cohorts, to address the need for large-scale collaborations for study of gene-gene and gene-environment interactions in the etiology of cancer. In 2003, the Consortium launched its first initiative to pool data and biospecimens from 10 large cohorts, which include nearly 800,000 research participants, for studies of hormone-related gene variants and environmental factors involved in development of breast and prostate cancer.

Specimen Resources. The Cooperative Breast Cancer Tissue Resource Database (http://www-cbctr.ims.nci.nih.gov/) is a Web-based "virtual tissue bank" with a central database to track each tissue in the system. Researchers can search this database online and obtain tissues with associated clinical information. The resource has recently also begun to provide tissue microarrays to researchers studying molecular signatures of breast cancer.

RISK FACTORS

Genetic Factors. Collaborative research teams from NCI, Memorial Sloan-Kettering Cancer Center, and Celera Diagnostics recently found a number of single nucleotide polymorphisms (SNPs) related to breast cancer risk in two estrogen receptor genes (ESR1 and ESR2), especially in Ashkenazi Jews, and other SNPs that were protective against breast cancer. Other NCI researchers discovered SNP variants within DNA repair pathways and BRCA1-interacting proteins that may play a low penetrance role in breast cancer risk.

The *HER2* polymorphism, I655V may elevate breast cancer risk in some ethnic groups. NCI researchers estimated age-specific breast cancer risk from *HER2* I655V based on genetic analysis and family history of 5,318 Ashkenazi Jews from the Washington, DC area. They found an overall 30 percent increase in estimated cumulative risk of breast cancer to age 70 among *HER2* I655V carriers compared with noncarriers. The increased risk was most marked for women younger than 50 years with a family history of breast cancer.

Age-related Factors. NCI researchers who analyzed data from a population case control study conducted in Atlanta, GA between 1990 and 1992, identified a number of risk predictors more strongly or uniquely associated with breast cancer in women less than age 35 years compared with women age 45-54 years. These predictors include African-American race, recent use of oral contraceptives, early childbearing (reflecting a short term increase in risk immediately following birth), and family history of early-onset breast cancer. These findings suggest that breast cancers that develop in very young women may be etiologically as well as clinically distinct.

Reproductive Factors. The Early Reproductive Events and Breast Cancer Workshop, held in February 2003, was attended by epidemiologists, clinicians, basic scientists, and breast cancer advocates. Workshop participants reviewed evidence from epidemiologic, clinical, and animal studies to provide an integrated scientific assessment of the association between early reproductive events and the risk of breast cancer. Findings in these areas were rated by strength of evidence. They identified gaps in research knowledge and provided recommendations for future research. The following findings were rated with the highest strength of evidence: well established evidence for an association between decreased breast cancer risk and early age at first term birth, increasing parity, and long duration of lactation; no association between increased breast cancer risk and either recognized spontaneous or induced abortions; in animal models pregnancy, estrogen and progesterone combinations, and short-term estrogen exposure are protective against carcinogen-induced breast cancer. In March 2003, the NCI Board of Scientific Advisors and Board of Scientific Counselors reviewed and unanimously approved the Workshop findings. The summary report can be viewed at http://cancer.gov/cancerinfo/ere-workshop-report.

Diet. Phase II clinical studies of soy isoflavones and green tea compounds for prevention of breast and other cancers are in progress or planned. Soy and tea consumption are both associated with lower incidences of cancers in humans and have demonstrated cancer prevention properties in laboratory and animal studies.

Physical Activity. Data from the Women's Health Initiative (WHI) Observational Study (http://www.nhlbi.nih.gov/whi/os.htm), a large prospective cohort study of postmenopausal U.S. women age 50 to 79, demonstrate a protective role of even moderate levels of physical activity on breast cancer risk.

Aspirin. Researchers from the NCI-funded Long Island Breast Cancer Study Project (http://epi.grants.cancer.gov/LIBCSP) reported findings in 2004 that reinforce previous suggestions that regular aspirin use may reduce breast cancer risk. Women with either estrogen or progesterone sensitive tumors as well as women who took aspirin at least seven times a week for at least six months benefited the most. The NCI-supported Women's Health Study (http://www.brighamandwomens.org/preventivemedicine/research/whs.aspx) is now assessing the impact of low-dose aspirin and/or vitamin E on women's risk of cardiovascular disease and cancer.

Antibiotics. In 2004, NCI researchers reported finding an association between antibiotic use and increased risk of breast cancer. The magnitude of risk was dependent on the level of antibiotic use. Further research is needed to identify possible cause/effect relationships.

Radiation. NCI researchers examined breast cancer mortality among 69,525 female radiologic technologists certified in the United States from 1926 to 1982. Breast cancer mortality risks were highest among women first employed as radiologic technologists prior to 1940, and declined over time consistent with the dramatic reduction in recommended radiation exposure limits. Risk increased with number of years employed as a technologist prior to 1950, but not with total years worked as a technologist.

Electromagnetic Fields. Researchers from the Long Island Breast Cancer Study Project (LIBCSP) (http://www.epi.grants.cancer.gov/LIBCSP) reported in June 2003 that they found no association between residential electromagnetic fields and increased risk for breast cancer.

Breast Implants. NCI researchers who analyzed data from one of the largest studies on the long-term health effects of breast implants found no convincing evidence that breast implants have an effect on the development of connective tissue disorders.

Hormones. Researchers from the WHI (http://www.nhlbi.nih.gov/whi) reported in 2002 that the overall risks of estrogen plus progestin hormone replacement therapy for post-menopausal women outweigh the benefits. After 5.6 years of follow up, findings included increased risks of breast cancer, heart disease, stroke and blood clots. In March 2004, NIH stopped the estrogen-alone arm of the trial, concluding that estrogen alone appears neither to increase nor decrease heart disease, while increasing the risk of stroke, and decreasing the risk of hip fracture. Estrogen did not increase participant's risk of breast cancer during the study period.

Results from a population-based case control study of 1,640 breast cancer patients showed an increase in breast cancer risk associated with oral contraceptive use, especially in women less than age 35 and in women taking preparations containing the highest levels of ethinyl estradiol and/or progestin. These findings suggest that newer, low-potency/low estrogen oral contraceptives may confer a lower risk of breast cancer than earlier high-potency/high estrogen versions.

Researchers examined the association of *in utero* exposure to diethylstilbestrol (DES), a synthetic estrogen, and risk of adult breast cancer among a cohort of exposed and unexposed women, followed for an average of 19 years. DES exposure was associated with an increased breast cancer risk among women aged 40 and older and was modestly associated with estrogen receptor-positive tumors. Researchers will continue surveillance of this cohort.

In recent study, NCI investigators found that postmenopausal women with high levels of C-peptide, a protein marker of insulin secretion, and C-peptide:fructosamine ratio, a marker of insulin resistance, were more likely to have epithelial hyperplasia or localized breast cancer than women with the lowest levels of these biomarkers. These findings suggest a role for insulin and insulin resistance in breast pathology in postmenopausal women.

Breast Cancer Risk after Hodgkin's Disease. An international team of scientists recently reported that higher radiation doses to the breast during Hodgkin's disease treatment increased risk for future breast cancers. Higher dosages of alkylating agents and higher radiation doses to the ovaries were associated with decreased risk, possibly due to treatment-related premature menopause. Risk levels assessed in the study may not apply to Hodgkin's disease survivors who were treated with more recent therapeutic regimens.

Other Studies of Environmental and Lifestyle Risks. Current research aimed at defining breast cancer risk associated with environmental and lifestyle factors include studies of regional differences in breast cancer rates in the United States; prenatal-to-adult environmental exposures potentially leading to breast cancer; possible relationships between DDT exposure and breast cancer risk, benign breast cancer conditions, and other outcomes among women; the effects of lifetime radiation on breast cancer risk; the role of residential distance from steel mills, chemical factories, toxic waste sites, and other industries as risk factors for breast cancer.

Registries. The Breast and Ovarian Cancer Family Registries is an international registry system available to researchers who are planning to conduct population- and clinic-based interdisciplinary research with a main focus on

the genetic and molecular epidemiology of breast and/or ovarian cancers.
http://epi.grants.cancer.gov/CFR/

PREVENTION

Chemoprevention. Several ongoing breast cancer prevention studies are assessing selective estrogen receptor modulators (SERMs) such as tamoxifen and raloxifene (Evista®). A recent risk-benefit analysis demonstrated that two million U.S. women have a sufficiently high breast cancer risk that they might benefit from tamoxifen use without undue risk for side effects. Researchers with the Breast Cancer Prevention Trial (BCPT; http://www.cancer.gov/clinicaltrials/digestpage/BCPT) reported findings that tamoxifen helps prevent development of benign breast abnormalities, decreasing risk for precancerous growth and reducing the need for breast biopsy.

The Study of Tamoxifen and Raloxifene (STAR; http://www.cancer.gov/star), underway at more than 500 centers across the United States, Puerto Rico, and Canada, has completed accrual of over 19,000 postmenopausal women at increased risk for breast cancer. Data may be available as early as mid-2006. Prior observational evidence has suggested that raloxifene, a SERM used to treat osteoporosis, may help prevent breast cancer.

Aromatase inhibitors (AIs) are compounds that suppress estrogen levels by inhibiting an enzyme necessary for estrogen production. An NCI-sponsored phase II clinical trial will determine the preventive effects of the AI, exemestane, alone or in combination with celecoxib, on mammographic density in postmenopausal women at high risk for invasive breast cancer.

NCI is also supporting investigator-initiated research to identify potential molecular targets for prevention of human estrogen receptor negative breast cancer.

EARLY DETECTION, DIAGNOSIS, AND PROGNOSIS

Imaging Technologies. NCI is funding research on a variety of technologies for breast imaging, including digital mammography, computer-aided diagnosis, elastography, magnetic resonance imaging (MRI), magnetic resonance spectroscopy, ultrasound techniques, positron emission tomography (PET), single photon emission computed tomography (SPECT), and thermography. Selected studies seek to improve screening techniques for women with dense breast tissue and for women with *BRCA* mutations.

The Breast Cancer Surveillance Consortium (BCSC), http://breastscreening.cancer.gov/index.html, studies breast cancer screening practices and fosters collaborative research to improve the practice of community-based mammography screening. Recent BCSC research found that increasing age, breast density, and the presence of rapidly growing tumors decreased screening accuracy. Hormone replacement therapy, because it increases breast density, also reduced screening accuracy. Related research has found that a large portion of late-stage breast cancers are detected in women who have not received recommended screening, although a substantial number of diagnoses were made in women who had been screened. This research suggests the need for better early detection methods, as well as for increasing women's use of mammography.

The NCI-supported American College of Radiology Imaging Network (ACRIN) has completed enrollment to its Digital Mammography Imaging Screening Trial (DMIST; http://cancer.gov/dmist). This multi-center clinical trial is comparing the diagnostic power of digital mammography to film-based mammography. Researchers will also assess the accuracy of different techniques and instrument types for digital mammography, and factors that affect diagnostic accuracy.

Gene Expression Profiles. Recent NCI-supported testing of a commercially-developed 21-gene panel test, demonstrated that this method could successfully predict the risk of breast cancer recurrence in a sizable group of patients, as well as which patients would benefit most from chemotherapy. The Oncotype DX was used to analyze the gene expression patterns of fixed, paraffin embedded biopsy tissue from women with estrogen-dependent, lymph-node negative breast cancer. About one-quarter of patients were assessed to be at high risk for recurrence and likely to benefit from chemotherapy in addition to tamoxifen, while about half of patients were at low risk and not expected to benefit. A subsequent trial will test whether the Oncotype DX can predict which intermediate risk patients would benefit from chemotherapy.

NCI researchers and partners are performing genetic testing of women in the BCPT to determine whether variations in genes related to estrogen and tamoxifen metabolism might help predict which women are more likely to benefit from tamoxifen therapy.

Protein Biomarkers. Researchers at MD Anderson Cancer Center are exploring whether measurements of the protein Cyclin E, which helps regulate normal cell growth, can be used to predict breast cancer outcomes. Other NCI researchers are studying whether measurement of tumor levels of the proteins, HER2 and AIB1, involved in estrogen regulation, may be useful in predicting the outcome of tamoxifen therapy. Additionally, one member group of NCI's Early Detection Research Network (EDRN) is focusing on developing biomarkers of breast and gynecologic cancers.

Epidemiological Factors. To identify factors that increase a women's risk of dying from breast cancer, NCI researchers analyzed SEER (http://seer.cancer.gov/) data for more than 400,000 breast cancer patients diagnosed between 1973 and 2000. Factors associated with increased breast cancer mortality included diagnosis at a younger age, a later stage of disease, or with larger tumors; estrogen receptor negative tumors status; and black race.

TREATMENT

Anti-hormone Adjuvant Therapy.

Tamoxifen. Researchers are exploring ways to improve the effectiveness of tamoxifen therapy, combat tamoxifen resistance, and identify alternative therapies. Current regimens of tamoxifen treatments are effective for five years, after which tumors develop resistance to the drug. Scientists are attempting to prolong this window of effectiveness by using a second adjuvant in conjunction with, or instead of, tamoxifen.

In two recent clinical trails, a disproportionate number of strokes occurred among women who received tamoxifen, raising concerns that this anti-hormonal agent may be to blame. A recent NCI-funded study, in partnership with Kaiser Permanente Southern California, showed that chemotherapy, but not tamoxifen therapy, was responsible for the observed increase in the risk for stroke.

Aromatase inhibitors Recent updates from an international trial show that post-menopausal survivors of early-stage, node-negative and node-positive breast cancer who took the AI, letrozole after five years of tamoxifen, had a reduced risk of cancer recurrence. The rate of distant cancer spread was reduced by 40 percent compared to placebo and overall survival rates of women who were diagnosed with node positive cancers were improved by 39 percent. Survival rates for women with node negative tumors are still under study.

A phase II SPORE trial will compare the safety, acceptability, and side effects of letrozole (Femara ®), versus placebo in postmenopausal women at increased risk for breast cancer recurrence. Recent non-NCI-funded studies suggest that the AI, anastrozole (Arimidex ®) may be superior to tamoxifen as a first line, adjuvant treatment and the AI, exemestane, given after two years of tamoxifen, may improve disease-free survival.

Radiation Therapy Scientists from the National Surgical Adjuvant Breast and Bowel Project (http://www.nsabp.pitt.edu/) reported in late 2002 that women with very small breast tumors who received both radiation therapy and tamoxifen after surgery had fewer recurrences of cancer in the same breast than women who received either radiation or tamoxifen, but not both.

Conventional Chemotherapies.

Paclitaxel Adding the drug paclitaxel to standard adjuvant chemotherapy of adriamycin and cytoxan improved disease-free survival by 17 percent in women with node positive breast cancer, according to clinical trial results. Women receiving a dose-dense chemotherapy regimen benefited the most. As a result of this discovery, 4,000 more women could be alive and disease-free 4 years after diagnosis.

Age effects NCI-sponsored NSABP researchers reported, in 2003, that post-operative chemotherapy can improve outcomes in women diagnosed with estrogen receptor-negative, node negative breast cancer. More recently, NSABP investigators reported that benefits from post-operative chemotherapy with either cyclophosphamide plus methotrexate and 5-fluorouracil or doxorubicin with cyclophosphamide were greater, the younger the age of the patient. Also, premenopausal women experienced a greater recurrence-free survival benefit than post-menopausal women.

Effectiveness of Differing Treatment Regimens NCI is sponsoring clinical trials for breast cancer treatment to compare the effectiveness of four different treatment schedules using the drugs doxorubicin, cyclophosphamide, and paclitaxel in treating patients who have undergone surgery for breast cancer.

Immune Therapy. NCI researchers have found promising evidence that immune cell transplant therapy can help shrink tumors of metastatic breast cancer. Partial or minor responses lasting an average of three months were seen in six of the sixteen treated breast cancer patients. However, more research is needed to lower toxic graft-versus-host effects and improve treatment response.

Radiation Therapy. NCI is conducting a clinical trial of partial-breast irradiation to test whether this technique is equivalent to irradiation treatment of the whole breast.

Monoclonal Antibodies. Herceptin, a monoclonal antibody that binds to HER2, has been approved by the FDA for treatment of metastatic breast cancer. However, less than 35 percent of patients with HER2-overexpressing metastatic breast cancer respond to herceptin. Researchers have now shown that PTEN deficiency is a powerful predictor for herceptin resistance. This finding may help guide treatment choices for patients with PTEN-deficient tumors. In other work, NCI researchers are developing potential breast cancer treatment strategies that use monoclonal antibodies to target apoptosis-inducing death receptors located on cancer cells.

Novel Compounds. Researchers supported by NCI preclinical research programs are helping to develop novel compounds that may be effective for breast cancer treatment. These include parthenolide, an anti-angiogenic compound produced by medicinal plants; a synthetic improvement of a naturally-occurring anti-tumor antibiotic; and a synthetic compound derived from a marine sponge.

CANCER CONTROL, SURVIVORSHIP, AND OUTCOMES RESEARCH

Education Outreach. In partnership with the Centers for Medicare and Medicaid Services (CMS) and the National Asian Women's Health Organization, NCI adapted, tested, and disseminated nationally an Asian American/Pacific Islander mammography education resource. This brochure targets Chinese, Vietnamese, and Pacific Islander women in their 40s and older. http://www.cancer.gov/cancertopics/breasthealth

Researchers funded by the NCI and the Agency for Health Care Research and Quality (AHRQ) are studying how to communicate benefits and limitations of breast cancer screening tests; developing tools to help women ask themselves important questions and make informed decisions about screening; and exploring new communication technologies, including online and other interactive health communications tools to address women's concerns.

NCI's Office of Education and Special Initiatives has produced the booklet, *Surgery Choices for Women with Early-Stage Breast Cancer* in partnership with several federal agencies and offices and the National Research Center for Women and Families. This booklet (http://www.cancer.gov/cancertopics/breast-cancer-surgery-choices) helps women weigh surgical options for early-stage breast cancer and take a more active role in their treatment.

NCI is participating in the DHHS Initiative on Breast Cancer Prevention and Education to consolidate Department-wide information on breast cancer in one Web location. Designers anticipate launching the Web site in 2005.

Survivorship Research. NCI-funded and other researchers have shown exercise programs or training to positively impact cardiopulmonary function, quality of life, levels of fatigue, and functional ability in breast cancer survivors. Exercise in combination with group psychotherapy appears to improve women's quality of life beyond the benefits received from group participation alone, particularly in relation to physical and functional outcomes. Behavioral interventions also appear to have enormous appeal to survivors eager to reduce the perceived stress in their lives and to 'take control' of their bodies after cancer.

HEALTH DISPARITIES

While white women have the highest rate of breast cancer, African American women have the highest death rate of all races from the disease. Researchers funded by NCI and the U.S. Department of Defense have found that African American women are much more likely than white women to be diagnosed with aggressive breast cancer and to carry alterations in the tumor suppressor gene, *p53*. More research is needed to identify potential implications of racial/ethnic differences in *p53* alterations on breast cancer mortality rates.

A study linking data from NCI's SEER databases and Medicare data have revealed that disabled women with breast cancer are diagnosed at a later stage of disease than non-disabled women, with the disparity greater for women with fee-for-service coverage compared with HMO coverage.

CERVICAL CANCER

An estimated 10,370 cases of invasive cervical cancer are expected to be diagnosed in the United States in 2005 and 3,710 women are expected to die from the disease. Incidence and mortality rates have decreased steadily over the past five decades, largely due to the widespread use of the Papanicolaou test (Pap smear) which detects cervical cancer and pre-cancerous lesions. The Pap smear has made cervical cancer one of the most preventable cancers, but older, poorer, and less educated women are less likely to be screened and screening is not available in many low-resource regions of the world. Worldwide, cervical cancer has a significant impact, with nearly 500,000 new cases and nearly 250,000 deaths reported annually.

Cervical Cancer SPORE. The SPORE for cervical cancer research, located at the Johns Hopkins University School of Medicine, includes integrated projects for identification of biomarkers for cervical cancer progression; development of vaccines for cervical cancer prevention and treatment; and development of antigen-specific cancer immunotherapies and anti-angiogenesis agents for treatment of advanced cervical cancer The SPORE also facilitates career development of individuals with an interest in translational cervical cancer research.

RISK FACTORS

Human Papillomavirus (HPV). Although oncogenic HPV infections are common and usually clear within 1 to 2 years, infection with certain HPV subtypes is now recognized as the major cause of cervical cancer. Virtually all cases of cervical cancer worldwide are caused by a group of approximately 15 HPVs, with HPV types 16 and 18 accounting for approximately 70 percent of all cases.

In prior research to identify cofactors for cervical cancer risk among HPV-infected women, HPV infection was identified by DNA testing. Because this technique detects only current infection, NCI researchers conducted a study using seropositivity to five oncogenic HPV types as a marker of past exposure. Independent, significant predictors of seropositivity among uninfected controls included numbers of sexual partners, black race, and oral contraceptive use. Condom use was protective. Among HPV-exposed women, Papanicolaou screening, black race, and yeast infection were significantly associated with reduced cancer risk. Significant predictors of increased risk included smoking, low education and income, and history of nonspecific genital infection. In contrast to previous findings, oral contraceptive use was unrelated to cervical cancer risk and multiparity was only weakly related to risk.

NCI is supporting large, population-based cohort studies, including the Guanacaste Study of HPV Natural History study in Costa Rica and the Portland Kaiser Permanente cohort study in the United States, to better define risk factors for progression of precancerous lesions among HPV infected women. The Costa Rican study will assess the various roles of mucosal immune response, HLA alleles, chromosomal alterations, contraceptive and reproductive practices, diet, cigarette smoking, and infection with sexually transmitted agents other than HPV. The U.S. study is investigating specific immune responses to viral infection and risk of persistence and/or progression of lesions. Researchers will test *in vitro* biological specimens for immunological markers that may correlate with disease status over time.

NCI researchers recently published *Future Directions in Epidemiologic and Preventive Research on HPV and Cancer*, a monograph of forward-thinking commentaries written by senior epidemiologists and their interdisciplinary colleagues. This Monograph was published in the Journal of the National Cancer Institute in follow up to a 2002 meeting held at NCI, where the authors discussed topics including the natural history of HPV, immunosuppression, vaccines, cofactors that promote cancer, and descriptive epidemiology.

Human Immunodeficiency Virus (HIV). Women with HIV are often co-infected with HPV, and HPV infection is more likely to be persistent and less likely to regress in HIV positive than HIV negative women. Women positive for both HIV and HPV also have a 6.8 fold greater risk of invasive anal cancer than HIV negative/HPV positive women.

Human Leukocyte Antigen (HLA). NCI investigators are exploring the relationship between HLA class I alleles and cervical neoplasia in a subset of participants in three large U.S. and Costa Rican studies. Findings are consistent with previous hypotheses that a single HLA allele may be sufficient to protect women from progression of early precancerous lesions and suggest that natural killer cell function may play a role in HPV infection and cervical neoplasia.

Tobacco. According to the 2004 Surgeon General's report on the health consequences of smoking, there is sufficient evidence to support a causal relationship between smoking and cervical cancer. In a recent, large cohort study of HPV-infected women, smoking increased the risk of cervical precancer and cancer by about two-fold. Smoking after a cervical cancer diagnosis shortens survival time, increases risk of recurrence and the development of another primary tumor, reduces treatment efficacy, and increases treatment complications. Even so, about one third of patients who smoked prior to their diagnosis continue to smoke after their diagnosis.

DES. NCI continues to follow cohorts of women and their offspring exposed to DES during pregnancy. Recent analysis of data from the DES Follow-up study has shown no excess risk of cancer overall in DES-exposed offspring, compared with levels of risk for the general population, as calculated from SEER data. Preliminary data from the Third Generation Study, which will assess DES-related cancer risk in women whose mothers were exposed to DES *in utero*, shows no effects of DES on age at menarche or menstrual irregularity. NCI maintains a Web-based DES reference for clinicians at http://www.cancer.gov/cancerinfo/persons-exposed-to-des .

PREVENTION

HPV Vaccine. NCI and partners are designing vaccines to prevent cervical cancer by protecting women against persistent HPV infection. NCI researchers have designed a promising recombinant vaccine composed of HPV virus-like particles. Merck and GlaxoSmithKline (GSK) have licensed this vaccine technology from NIH and are developing vaccines that target HPV types 16 and/or 18. In early phase I and II clinical trials, these vaccines have conferred almost complete protection (94-100 percent), in fully vaccinated women, against persistent infection by the HPV type(s) targeted. Phase III clinical trials are in progress. NCI and public health research partners are conducting a parallel efficacy trial of the GSK vaccine in Costa Rica, where cervical cancer is the most common malignancy in women.

Obesity. NCI scientists evaluated whether obesity, which can influence hormone levels, plays a role in adenocarcinoma and/or squamous cell carcinoma of the cervix. Researchers found a positive association between height, weight, body mass index, and waist-to-hip ratio and adenocarcinoma. Higher BMI and WHR were associated with more advanced disease stage at adenocarcinoma diagnosis, even among recently and frequently screened patients. Associations between BMI and WHR with squamous cell carcinoma were weaker and no association was found for height or weight.

EARLY DETECTION, DIAGNOSIS, AND PROGNOSIS

Pap Smear Screening. In 1987, approximately 73 percent of women aged 18 and older had a Pap smear within the past three years, and by 2000, 81 percent of women ages 18 and older had a Pap smear within the past 3 years. This includes 77 percent of Hispanics, 84 percent of blacks, and 82 percent of whites.

Imaging. NCI-supported researchers are developing fluorescence and reflectance spectroscopic imaging technologies to detect cervical neoplasia. Early clinical testing has shown that the imaging techniques are feasible in large populations and can be used at any time during the menstrual cycle except during menstruation. Trial participants reported significantly less pain and anxiety and were more satisfied with spectroscopy than with the usual care procedures. Research is ongoing to test the accuracy and reproducibility of this detection technique.

HPV Testing. Researchers have demonstrated that HPV DNA detection predicts increased risk of cervical precancers and cancers that may develop up to several years following testing. It can be used to detect high-grade cervical neoplasia, and is more sensitive than cytologic methods for detecting HPV infection in its earliest, as well as latter stages. Findings from a large study suggest that HPV testing in combination with Pap smear testing may safely permit longer screening intervals among patients with negative results for both measures. These results were incorporated into recent FDA licensure of HPV DNA testing as an adjunct for Pap smear screening. Findings from a related study suggest that about 15 percent of women in annual cervical screening programs who have a negative

Pap smear and a positive oncogenic HPV test will have a subsequent abnormal Pap smear within five years. These findings support the use of HPV DNA testing as a highly sensitive screening test.

The NCI-funded ASCUS-LSIL Triage Study (ALTS), http://www3.cancer.gov/prevention/alts/index.html, demonstrated that HPV DNA testing can be used to triage equivocal Pap test interpretations. There are more than 2 million such results per year in the United States. HPV DNA negativity implies very low risk of cervical precancer or cancer.

Another study is using computer-based modeling of the health benefits and cost-effectiveness of preventive HPV vaccination and screening strategies. Findings suggest that vaccination initiated at age 12, followed by cytology screening for HPV every 3 years beginning at age 25 may be the most cost-effective strategy. This approach was estimated to reduce cervical cancer mortality by 94 percent compared with no intervention.

TREATMENT

Chemoradiation. Five randomized phase III trials all have shown a significant overall survival advantage for cisplatin-based therapy given concurrently with radiation therapy for treatment of cervical cancer patients. In these trials, which varied somewhat in terms of stage of disease, dose of radiation, and schedule of cisplatin and radiation, the risk of death from cervical cancer was decreased by 30 percent to 50 percent by concurrent chemoradiation.

Treatment-Related Side Effects. Researchers are examining the efficacy of drugs to alleviate or prevent side effects of cervical cancer treatment, including treatment-induced anemia and quality of life changes.

CANCER CONTROL, SURVIVORSHIP, AND OUTCOMES RESEARCH

Psychosocial Issues. The NCI-funded Center for Psycho-Oncology Research conducts behavioral, psychological, social, and biomedical research on the interrelationships between cognition, emotion, biological processes, and physical health in patients affected by cancer, including women at high risk for cervical cancer due to co-infection with HIV and HPV. An NCI-supported study is looking at behavioral and immunologic components that correlate with psychological distress and coping in women diagnosed with mild dysplasia of the cervix caused by HPV infection.

Sexuality Issues. Several studies are under way to assess sexual function and general quality of life for women receiving treatment for different stages of cervical cancer.

HEALTH DISPARITIES

Access to Health Care and Screening. The NCI Center to Reduce Cancer Health Disparities (CRCHD) has an ongoing program to address the entrenched pattern of high cervical cancer mortality found in distinct U.S. populations and geographic areas (http://crchd.nci.nih.gov/initiatives/#Reducing). Women most affected include African American women in the South, Latino women along the Texas-Mexico border, white women in Appalachia, American Indians of the Northern Plains, Vietnamese-American women, and Alaska Natives. A report, *Excess Cervical Cancer Mortality: A Marker for Low Access to Health Care in Poor Communities* will be released in the spring of 2005. The report offers recommendations for improving elements of the health system, particularly publicly funded health services.

NCI's Cancer Information Service is collaborating on a project focused on reducing cancer health disparities among women rarely or never screened for cervical or breast cancer, in partnership with CDC and the American Cancer Society. This public-private partnership is working with regional and local public health practitioners and stakeholders from eight Appalachian states with the highest cervical and breast cancer mortality and the lowest screening rates for these cancers.

In cooperation with CRCHD and the Deep South Network for Cancer Control, NCI researchers are conducting a study of cervical cancer screening in the Mississippi Delta using self-collected cervical specimens tested by sensitive HPV DNA assays. The study will determine whether self-testing for HPV can be used to screen women reluctant or unable to obtain Pap tests.

NCI is also piloting the Patient Navigator Program (http://www3.cancer.gov/rrp/CDRP/navigator.html) to provide patients with social service case management to help them navigate the healthcare system to receive prompt

follow-up care after an abnormal cervical cancer screen or diagnosis. This program directly addresses an NCI Gynecologic PRG recommendation for a navigator program.

Surveillance. A recent study suggests that census-based socioeconomic measures such as geographic area, income, and education levels could serve as important surveillance tools for monitoring temporal trends in cancer-related health inequalities and targeting interventions.

OVARIAN CANCER

In 2005, approximately 22,220 women in the United States are expected to be diagnosed with ovarian cancer, and approximately 16,210 are expected to die of the disease. Incidence rates decreased by 0.8 percent per year between 1985 and 2001. Ovarian cancer is responsible for the highest mortality rates of all gynecologic cancers. Incidence and mortality rates are highest in white women compared to other racial and ethnic groups. When detected early, ovarian cancer is highly treatable, with a 5-year survival rate of 95 percent. Ovarian cancer is often asymptomatic in its early stages, and symptoms that do occur are often not of the type that would alert most women or their health care providers. Thus, most diagnoses occur at advanced stages of disease, when survival rates are 69 percent for regionally advanced stages and 29 percent for stages with distant metastases.

Ovarian Cancer SPOREs. NCI's five Ovarian Cancer SPOREs (http://spores.nci.nih.gov/current/ovarian/ovarian.html) frequently collaborate to develop prognostic, screening, prevention, and therapeutic tools for ovarian cancer. Biomarkers under study for the early detection of ovarian cancer include CA-125, mesothelin, HE4, apolipoprotein A1, transthyretin, and inter-alpha-trypsin inhibitor heavy chain H4. Examples of other ovarian cancer SPORE research include clinical trials of the monoclonal antibody, TRA-8, for treatment of breast and ovarian cancer and development of therapies that target the phosphatidylinositol 3 kinase (PI3K) pathway, which is frequently mutated in ovarian cancer.

BIOLOGY

Mouse Models. Development of genetically engineered mouse models of ovarian epithelial cancer is challenging due to the unusual properties of ovarian surface epithelium, the proposed cell of origin for these malignancies, and the need for a cell-type-specific promoter to drive gene expression. NCI-supported researchers recently developed a model with deficiencies in expression of the tumor suppressor genes, *p53* and *Rb*, which are frequently lost or mutated in ovarian cancer. These mice, quickly succumbed to aggressive ovarian cancer and many of the cancers were associated with notable characteristics of the human disease. In another model, the powerful T-antigen oncogene was incorporated in the ovarian epithelium by use of a special promoter, resulting a poorly differentiated form of ovarian cancer typical of late-stage human ovarian cancer.

Other NCI-supported researchers developed a mouse model that mimics estrogen receptor positive, invasive, metastatic endometrioid ovarian adenocarcinoma by activating an oncogenic *K-ras* and conditionally deleting the tumor suppressor, *PTEN*. This model will be valuable for preclinical studies of selective estrogen receptor modulators as well as other conventional chemotherapeutic agents.

Researchers recently improved a rat model of human ovarian cancer by using a much lower dose of the initiating carcinogen. This improved model exhibits characteristics of the human disease, including preneoplastic and early neoplastic lesions, point mutations in *p53* and *K-ras* genes, and over-expression of the estrogen and progesterone receptors. This model should permit study of the role of hormone receptors and genetic alterations in tumor etiology and progression and provide a platform to test novel interventions.

VEGF. NCI Researchers have discovered that women with ovarian cancer who had a greater sense of well being had markedly lower blood levels of vascular endothelial growth factor (VEGF), a stress-related cytokine that stimulates angiogenesis. This research suggests that effects on VEGF may be one way that biobehavioral factors affect ovarian cancer progression.

RISK FACTORS

In the United States approximately 1 woman in 70, or 1.4 percent, will develop ovarian cancer during her lifetime. Although reproductive, demographic, and lifestyle factors affect risk of ovarian cancer, the single greatest risk factor

is a family history of the disease. Three inherited ovarian cancer susceptibility syndromes have been described: (1) familial site-specific ovarian cancer, (2) familial breast/ovarian cancer, and (3) Lynch II syndrome (combination of breast, ovarian, endometrial, gastrointestinal, and genitourinary cancers). It is believed that 5–10 percent of ovarian cancers are caused by inherited mutations in the *BRCA1* or *BRCA2* genes.

Infertility/Fertility Drugs. NCI researchers identified a higher rate of ovarian cancer incidence in a cohort of 12,193 women evaluated for infertility between 1965 and 1988, compared to incidence rates for the general female population. Among this group, risk was higher for patients with primary than those with secondary infertility, particularly for those who never subsequently conceived, and was highest in patients with endometriosis. No evidence that either of the two commonly used fertility drugs, clomiphene and gonadotrophins, increased risk for ovarian cancer. Researchers will continue monitoring the cohort for possible long-term risks.

Inherited Risk Factors. In a recent NCI study, researchers found that the levels of ovarian cancer risk reduction associated with gynecologic surgery are similar for women carrying *BRCA1* and *BRCA2* mutations and non-carriers of these mutations.

Registries. The Breast and Ovarian Cancer Family Registries (http://epi.grants.cancer.gov/CFR/) is an international registry system available to researchers who are planning to conduct population- and clinic-based interdisciplinary research with a main focus on the genetic and molecular epidemiology of breast and/or ovarian cancers.

PREVENTION

Oral contraceptive use, having had at least one full term pregnancy, and having breast fed are associated with a reduced risk of ovarian cancer. Tubal ligation and hysterectomy may be associated with a decreased incidence of ovarian malignancy. HRT in postmenopausal women may be associated with an increased risk of developing ovarian cancer.

NCI is sponsoring a multi-center clinical trial that will quantify the extent of cancer risk reduction after preventive removal of the ovaries and fallopian tubes and will assess quality of life and incidence of non-cancer diseases related to premature menopause. Researchers will also evaluate a novel approach to ovarian cancer screening based on quantitative assessment of changes in the tumor marker, CA-125, over time.

EARLY DETECTION, DIAGNOSIS, AND PROGNOSIS

Proteomics. Researchers from the FDA/NCI Clinical Proteomics Program, (http://home.ccr.cancer.gov/ncifdaproteomics/ppatterns.asp) Correlogic Systems Inc., and the Frederick Cancer Research Center Biomedical Proteomics Program (http://web.ncifcrf.gov/rtp/prot/site/default_flash.asp) are refining a proteomic profiling technique for early detection of ovarian cancer. In a preliminary trial, this test identified, with 100 percent sensitivity and 100 percent specificity, 68 women previously diagnosed with ovarian cancer and 43 women who were cancer free. Researchers will conduct a multi-institutional clinical trial to investigate the method's ability, when used in large numbers of patients and by multiple operators, to distinguish between blood samples from women with recurrent ovarian cancer and those who are cancer free. This research addresses a Gynecologic Cancers PRG recommendation to develop proteomic technologies for early detection of ovarian cancer.

NCI intramural researchers, in collaboration with selected SPORE and EDRN member institutions, will develop a repository of serum samples collected from women in first clinical remission of advanced ovarian cancer. These samples will be used to develop and test proteomic and biomarker panels for detecting minimal residual disease.

National Ovarian Cancer Early Detection Program: Screening and Genetic Study. This multi-site clinical trial seeks to identify effective screening and genetic testing methods to identify women at increased risk for developing ovarian cancer; identify and develop highly sensitive and specific early detection tumor markers; develop therapies based on molecular, genetic, and biochemical insights; and determine the utility of minimally invasive office diagnostic laparoscopy and the "Ovarian Pap Test." http://www.clinicaltrials.gov/ct/gui/show/NCT00005095

Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO) Trial. Screening for ovarian cancers, one component of the PLCO trial, includes a physical examination of the ovaries, a blood test for the tumor marker

CA-125, and transvaginal ultrasound in healthy women, ages 55–74 (http://dcp.nci.nih.gov/plco). Analysis of the results of screening tests done in the first year of the PLCO will be published in 2005.

TREATMENT

New Drug Strategies. Standard post-surgery chemotherapy for newly diagnosed ovarian cancer usually consists of treatment with paclitaxel and/or a platinum-based drug (e.g. carboplatin or cisplatin). Patients whose disease recurs more than six months after completion of chemotherapy are usually re-treated with a platinum-based drug. In 2003, NCI clinical trial researchers reported that patients treated with a combination of paclitaxel plus platinum-based drugs lived a median of five months longer than those who received a platinum-based drug alone. Both groups of women experienced about the same quality of life.

NCI-supported investigators are exploring the effectiveness of various drug combinations and treatment regimens for treating advanced stage and recurrent ovarian cancer. Drugs currently in clinical testing include bortezomib, docetaxel, erlotinib, gemcitabine, ixabepilone, liposomal doxorubicin, nitrocamptothecin, oxaliplatin, sorafenib, TLK286, and topotecan. Innovative approaches to the treatment of advanced ovarian cancer in development or in early trials include therapeutic vaccines, monoclonal antibody therapies, donor lymphocyte infusion, nonmyeloablative allogeneic transplantation, gene therapy, and antiangiogenic agents.

ENDOMETRIAL CANCER

Cancer of the corpus uteri, or endometrium, is the fourth most common invasive cancer among women in the United States. An estimated 40,880 American women will be diagnosed with uterine cancer in 2005, and approximately 7,310 will die from the disease. The incidence of endometrial cancer declined from 1975 to 1988, increased slightly over the next decade, and has begun again to decline. Average incidence rates for white women were 26.1 per 100,000 from 1992 to 2001, while incidence rates for African American women were significantly less at 18.0 per 100,000. Average mortality rates show an opposite trend, with the mortality rate for white women at 3.9 per 100,000 and mortality rates for African Americans nearly double that at 7.0 per 100,000.

Gynecologic Cancer SPORE: The Gynecological Cancer SPORE at The University of Texas M. D. Anderson Cancer Center, first funded in 2003, conducts innovative translational research for the prevention and treatment of uterine tumors. Major projects of the SPORE aim to:

- Decipher the fundamental molecular differences between Type 1 and Type 2 endometrial cancers.
- Provide a panel of molecular markers that will be useful in endometrial cancer prognosis and in identifying patients at risk for developing the malignancy.
- Dissect the molecular pathways involved in estrogen and progesterone mediated growth regulation of the uterine endometrium and smooth muscle.
- Promote novel strategies in the chemoprevention of endometrial cancer.
- Understand, at the molecular level, the complex mechanism of action of selective estrogen receptor modulators (SERMs) such as tamoxifen, raloxifene, and a new third generation SERM, Arzoxifene, in the epithelial and smooth muscle compartments of the uterus.

BIOLOGY

Microsatellite Instability (MSI). Approximately 20 percent of endometrial cancers demonstrate MSI, which is the abnormal expansion or contraction of small repetitive DNA sequences due to defects in the DNA mismatch repair pathway. NCI supports research to determine the cause of MSI in endometrial tumors. Emerging insights into the initiation of endometrial cancer may help in the development of targeted therapies that will benefit patients with this disease.

Gene Expression Profiling. NCI Researchers have discovered differences in gene expression among histologic types of endometrial cancers and normal endometrium and between serous and endometrial cancer tissues. Other NCI-supported researchers discovered two highly distinct molecular subtypes that help define estrogen-dependent and estrogen-independent endometrial carcinoma. This research provides the basis for investigation of previously unrecognized novel pathways involved in the development of endometrial cancers and addresses a recommendation of the NCI Gynecologic PRG to identify genetic and molecular signatures of endometrial cancer.

Specimen Resources. The Gynecologic Oncology Group tissue bank provides specimens for researchers studying endometrial cancer. Requests for tissues are assessed by peer review. The Tissue Expediter and the Specimen Resource Locater Web site (http://pluto3.nci.nih.gov/tissue/default.cfm) can assist researchers to identify sources of tissue.

Mouse Models. NCI researchers generated a mouse model of endometrial carcinoma by regulating the expression of the tumor suppressor gene *PTEN* and one of the mismatch repair genes, *MLH1*. These mice develop invasive carcinoma closely resembling the human disease.

RISK FACTORS

An increased risk for endometrial cancer has been associated with estrogen-only hormone therapy, personal history of breast cancer, tamoxifen use, obesity, age, lack of physical activity, HNPCC, and diabetes and other medical conditions, but possible mechanisms remain obscure. Cigarette smoking and high intake of complex carbohydrates appear to reduce risk. Recent research suggests that family history of breast cancer may not be associated with increased for endometrial cancer.

Diet. Researchers with an NCI-supported case-control study in Shanghai, China found that regular consumption of soy protein or soy isoflavones was inversely associated with the risk of endometrial cancer, especially among women with high body mass index and high waist:hip ratio. An NCI-funded case-control study based in the greater San Francisco Bay Area found an association between consumption of some phytoestrogenic compounds (isoflavones, coumestans, and lignans) at levels typical of an American-style diet, and reduced risk of endometrial cancer.

Menstrual and Reproductive Factors. NCI-supported researchers evaluated the association of menstrual and reproductive factors with the risk of endometrial cancer in a population-based case-control study conducted in urban Shanghai. Findings suggest that prolonged menstruation was related to an increased risk of endometrial cancer while pregnancy, full-term and interrupted, reduced the risk of endometrial cancer.

Tamoxifen. Tamoxifen, used in the prevention and treatment of ER-positive breast cancer, has been linked with an increased risk of endometrial cancer. Studies indicate that tamoxifen may have delayed effects, such as the increased risk of rare but aggressive uterine tumors of unclear pathogenesis. New drugs, such as aromatase inhibitors, that can be used alone or in combination with tamoxifen for treatment of hormone-dependent tumors are being investigated.

Insulin-like Growth Factor. NCI researchers found an inverse association between development of endometrial cancer and certain serum insulin-like growth factors (IGF-1, 2) and an insulin-like binding protein (IGFBP-3) in a case-control study of postmenopausal women with endometrial cancer and matched population-based controls. Further research is needed to explore the potential role of the IGF system in endometrial carcinogenesis and proliferation.

PREVENTION

NCI prevention studies are focusing on developing breast cancer prevention and treatment agents that do not increase endometrial cancer risk; developing chemoprevention methods for endometrial cancer; and determining the effects of obesity and nutrition on endometrial cancer. A Phase 2 randomized study comparing medroxyprogesterone and ethinyl estradiol and norgestrel for the prevention of endometrial cancer in HNPCC patients is ongoing.

EARLY DETECTION, DIAGNOSIS, AND PROGNOSIS

NCI-supported researchers have discovered a strong correlation between methylation of ribosomal DNA (rDNA) in endometrial tumors and risk of recurrence. NCI is funding a new study to confirm this observation and to develop a high-throughput assay for rDNA methylation that may help identify women with high risk of recurrence who would benefit from adjuvant therapy in addition to surgery.

TREATMENT
Surgery, including hysterectomy and bilateral salpingo-oophorectomy, is the most common treatment for endometrial cancer. Researchers are identifying adjuvant chemotherapy regimens that can improve survival in women with endometrial cancer. In women who have not completed childbearing, alternative treatments that address fertility issues are being investigated.

Chemotherapy. The NCI-funded Gynecologic Oncology Group (GOG; http://www.gog.org/) conducts research focused on women with pelvic malignancies, including endometrial cancer. In a recent phase III GOG clinical trial, post-surgical adjuvant chemotherapy with cisplatin and doxorubicin improved survival by 33 percent in women with advanced endometrial cancer, compared to women who were treated with standard radiation treatment. The GOG is also examining the potential role of paclitaxel (Taxol®) as a treatment agent, either singly or in combination with other agents, such as megestrol acetate and medroxyprogesterone acetate.

Radiation Therapy. In a recent GOG clinical trial, researchers concluded that adjunctive radiation therapy in early stage intermediate risk endometrial carcinoma decreases the risk of recurrence, but should be limited to patients whose risk factors fit a high intermediate risk definition.

Hormonal Therapies. NCI is conducting a phase II pilot study to compare the efficacy of medroxyprogesterone in patients with progesterone receptor-positive versus progesterone-receptor negative endometrial adenocarcinoma of the uterine corpus.

Combined Modality and Targeted Therapies. NCI supports studies comparing different chemotherapies, alone or in combination, and with or without radiotherapy. Most trials are in Phase I or II. Studies are also in progress to test the effectiveness of the molecularly targeted agents, trastuzumab (Herceptin®), bevacizumab (Avastin™), lapatinib (GW572016), and sorafenib (BAY 43-9006) for treating endometrial cancer. Side effects of therapy and quality-control issues in radiation equipment are also being investigated.

LUNG AND OTHER TOBACCO-RELATED CANCERS

The 2004 Surgeon General's Report, *The Health Consequences of Smoking* (http://www.cdc.gov/tobacco/sgr/sgr_2004/), estimates that smoking tobacco causes 159,600 cancer deaths each year. Research shows that tobacco use causes an increasing number of cancers of particular concern to women, including lung, cervical, and ovarian. Scientific evidence is also suggestive of a causal relationship between smoking and colorectal adenomatous polyps and colorectal cancer. Epidemiological studies exploring a possible link between smoking and breast cancer have yielded inconclusive results, although animal, human biomarker, and *in vitro* cellular studies strongly suggest that tobacco carcinogens may be involved in breast cancer development. Tobacco use also causes leukemia and cancers of the bladder, esophagus, kidney, larynx, oral cavity, pancreas, and stomach.

Since 1987, more women have died each year of lung cancer than of breast cancer, which had been the major cause of cancer death in women for more than 40 years. It is estimated that 79,560 women will be diagnosed with lung cancer in 2005 and 73,020 women will die from this disease in the United States. Although incidence and mortality rates in men have been declining since the early 1980s and 1990s, respectively, these rates for women have continued to increase until recently. The latest analysis of SEER data shows a decline in incidence rates, from 1998 to 2001, and stabilization of mortality rates since 1995. Declining incidence rates appear to be a result of reductions in cigarette consumption. High mortality rates reflect our limited ability to detect lung cancer at an early and potentially more curable stage. Over half of new cases are diagnosed in advanced stages of the disease, for which the 5-year relative survival is only 3.3 percent. With the exception of Asian/Pacific Islander (API) patients, the chance of dying from lung cancer was 4–23 percent higher from 1998 to 2001 in minority populations compared with non-Hispanic white patients. Survival rates for API women diagnosed with lung cancer were comparable to those for non-Hispanic whites.

Women, Tobacco, and Cancer. NCI has taken the lead in a public/private partnership to address the high rate of tobacco-related cancers in women. A working group meeting, held in February 2003, *Women, Tobacco, and Cancer: An Agenda for the 21st Century*, assembled researchers, clinicians, and members of the advocacy

community to identify gaps and research priorities, and to identify and prioritize needs in dissemination and application. The working group released their report (http://searchosp1.nci.nih.gov/whealth/reports/wtobacco.pdf) in July 2004, recommending strategies to meet five overall goals in the areas of discovery, development, delivery, partnerships, and evaluation and surveillance that will contribute to reducing and ultimately eliminating the harmful health effects of smoking in women.

Lung Cancer Integration and Implementation Team. NCI has created the lung cancer Integration and Implementation (I2) team to address the recommendations of the NCI's Lung Cancer Progress Review Group (PRG), http://prg.nci.nih.gov/pdfprgreports/2001lung.pdf . The I2 team, an internal working group, will inventory NCI's current lung cancer research portfolio and analyze strategies for implementing PRG recommendations. Team members will use this analysis to identify three to five high impact, focused initiatives to reduce lung cancer mortality rates and identify potential collaborations to advance lung cancer research.

Transdisciplinary Tobacco Use Research Centers (TTURCs). TTURCs (http://dccps.nci.nih.gov/tcrb/tturc) help provide the needed infrastructure for tobacco research across many disciplines and address an NCI Lung Cancer PRG recommendation to continue research on the genetic, social, and biobehavioral aspects of tobacco control. NIH has announced nearly $12 million in new TTURC funding to be awarded over the next 5 years by NCI, National Institute on Drug Abuse, and the National Institute on Alcohol Abuse and Alcoholism. A group of seven TTURCs will study a range of topics, including genetic and psychological factors that influence tobacco use and addiction; effective smoking cessation treatments; molecules or genes that could affect tobacco exposure and disease risk; and public health impact of regional and national tobacco control policies.

Lung Cancer SPOREs. NCI currently funds seven lung cancer SPOREs (http://spores.nci.nih.gov/current/lung/lung.html). The Lung SPORE at the University of Pittsburgh Cancer Institute has a focus on improving detection and treatment of lung cancer and understanding the mechanisms of women's susceptibility to lung cancer. Researchers at this SPORE are investigating the role of estrogen receptors in lung cancer in women. A clinical trial is planned to explore possible protective effects of administering estrogen receptor antagonists to lung cancer patients.

RISK FACTORS

Tobacco. Results from two cohort studies, the Nurses' Health Study (http://www.channing.harvard.edu/nhs/) and the Health Professionals Follow-Up Study of men, indicate that men and women with comparable smoking histories have similar risks of developing lung cancer. Previous case-controlled studies have suggested that women are at greater risk.

A multicenter case-control study of lung cancer and tobacco use is ongoing in Milan, Italy. This trial includes collection of extensive questionnaire and biospecimen data, and is unique in collecting information on many other factors, including tumor tissue obtained in surgery, demographics, tobacco use, alcohol use, occupational exposures, diet, and medical illness.

The PLCO (http://www3.cancer.gov/prevention/plco/) and the Shanghai Women's Health Study (http://epi.grants.cancer.gov/ResPort/ShanghaiWomen.html) are large, ongoing cohort studies that include biospecimens and questionnaire data with a focus on tobacco-related cancers.

NCI supports transdisciplinary research on the interplay of behavior, chemistry, toxicology, biology, and epidemiology to determine the cancer risk potential of reduced-exposure tobacco products (http://grants.nih.gov/grants/guide/pa-files/PA-04-103.html). Current scientific evidence is insufficient to evaluate whether these new products actually reduce the user's exposure or risk for tobacco-related diseases.

Radon. NCI researchers pooled data from two large case-control studies of residential radon conducted in China to show that long-term radon exposure at concentrations found in many homes appears to increase lung cancer risk.

Diet. In follow-up study to the Beta-Carotene and Retinol Efficacy Trial (CARET), researchers at the Fred Hutchinson Cancer Research Center confirmed that beta-carotene supplements are harmful to those at risk for lung cancer. People who took beta-carotene dietary supplements while enrolled in the trial continued to have increased

rates of lung cancer six years after the trial was stopped early and the supplements discontinued. These results reinforce earlier findings from this study and the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study.

Genetics. An international consortium of researchers has found a major lung cancer susceptibility region on a segment of chromosome 6 that likely contains a gene(s) that increases lung cancer risk. Non-carriers of the gene(s) experienced increased risk for lung cancer in proportion to the amount they smoked. In carriers, any amount of smoking increased risk. Researchers next seek to specifically identify the potential susceptibility gene(s), which may one day enable screening for increased lung cancer risk.

Investigators from the University of Pittsburgh Cancer Center used high throughput SNP analysis to demonstrate an increased risk of lung cancer in people with polymorphisms in genes for DNA repair and metabolite elimination. In 2003, these investigators reported that SNP-related variability in estrogen metabolism was associated with an increased risk for lung cancer.

NCI scientists recently found cigarette smoking to increase the prevalence and spectrum of tumor suppressor gene *p53* mutations in breast tumors, suggesting a genotoxic effect of smoking in breast tissue. This study also has important implications because breast tumors having *p53* mutations exhibit more aggressive growth and are associated with poor prognosis, and smokers are more than twice as likely to have *p53* mutation positive breast cancer.

PREVENTION AND CONTROL

Tobacco Use and Addiction. Recent analysis of prospective data from the National Collaborative Perinatal Project shows that both male and female offspring of mothers who reported smoking a pack or more of cigarettes during their pregnancy were significantly more likely to be susceptible to tobacco-dependence than offspring of mothers who reported never smoking during pregnancy.

Results from a longitudinal study surveying nearly 5,000 rural middle school children about a variety of behaviors suggest that viewing smoking in movies strongly predicts whether or not adolescents initiate smoking, and the effect increases significantly with greater movie smoking exposure. Fully 52 percent of smoking initiation among adolescents in the study could be attributed to this risk factor.

TTURC researchers developed the 68 question Wisconsin Inventory of Smoking Dependence Motives (WSDM-68) questionnaire to identify motivations for smoking. Researchers found that individuals who smoked automatically, to enhance mental activity, to alleviate distress, or because they were in a smoking environment were most likely to relapse while quitting.

Tobacco Cessation.
Tobacco Control Interventions The NCI and American Cancer Society-supported American Stop Smoking Intervention Study (ASSIST) (http://cancer.gov/newscenter/pressreleases/ASSISTQandA) provided the first evidence that investing in state tobacco control programs can reduce smoking rates. Interventions were developed and implemented in 17 states by networks of state and local tobacco control coalitions. Researchers estimate that if all 50 states and the District of Columbia had implemented ASSIST policies, approximately 1,213,000 fewer people would smoke.

NCI and the Centers for Disease Control and Prevention (CDC) have launched a National Network of Tobacco Cessation Quitlines to connect callers with local programs that deliver information, advice, support, and referrals to tobacco users who want to quit. An easy-to-remember, toll-free telephone number, 1-800-QUIT-NOW, serves as a single access point to state-based cessation services. In addition, the NCI-supported Web site – www.smokefree.gov – offers smoking cessation advice and downloadable information.

A recent survey of state employers shows that only 29 of 45 states surveyed require smoking cessation treatment to be included in health insurance plans of state employees. Only 17 states provided the complete range of coverage for smoking cessation recommended by the U.S. Public Health Service. This research shows that states are lagging in adopting this promising avenue for reducing smoking rates among their employees.

According to a recent TTURC audit of the Wisconsin Medicaid medical records, physicians asked only 55 percent of adolescent patients about their smoking status during a 2-year period. The older the patient, the more likely the physicians were to record smoking status. Pregnant teenagers were also more likely to be questioned about smoking. Previous studies based on physician self report may have overestimated smoking interventions with adolescents.

NCI's Smoking and Tobacco Control Monographs (http://cancercontrol.cancer.gov/tcrb/monographs/) have provided timely information about emerging public health issues in smoking and tobacco control and accelerated its dissemination to the scientific and public policy communities. In 2003, NCI released the final monograph in the original series, *Those Who Continue to Smoke: Is Achieving Abstinence Harder and Do We Need to Change Our Interventions?*

In May 2002, the NCI-supported National Partnership to Help Pregnant Smokers Quit (http://www.helppregnantsmokersquit.org/) published an action plan to achieve the Healthy People 2010 goal of decreasing the percentage of pregnant women who smoke to less than two percent. In September 2002, a collaboration of 10 public and private organizations released *A National Blueprint for Disseminating and Implementing Evidenced-Based Clinical and Community Strategies to Promote Tobacco-Use Cessation*. *Preparing for Action: Implementing the Youth and Adult Tobacco-Use Cessation National Blueprints* was released in July 2003 (http://ctcinfo.org/resources/blueprints.asp).

Smoking-related NCI publications available to the public include *Clearing the Air*, a manual designed to help smokers quit; *Clear Horizons*, a quitting guide for those older than 50; and the Spanish-language guide on smoking cessation, *Guia para Dejar de Fumar* (http://www.smokefree.gov/info.html).

Cessation Treatments Early results from a TTURC-sponsored a study of selegiline (an MAO-B inhibitor that inhibits dopamine metabolism) as a treatment for tobacco addiction suggests that selegiline was safe and superior to placebo for smoking cessation. Further research will show whether this drug can improve smokers' ability to quit.

Genetics TTURC investigators discovered that the *CYP2B6* gene, which causes reduced nicotine metabolism in the brain, may influence the effectiveness of buproprion treatment for smoking cessation. In the study, smokers received placebo or bupropion, plus behavioral group counseling. Smokers who had variants of *CYP2B6* were less successful in quitting smoking. Buprobrion seemed to help overcome this genetic effect in women smokers by decreasing withdrawal symptoms.

A smoking cessation study revealed that smokers with a specific combination of genetic variants of the *SLC6A3* dopamine transport gene and the *DRD2* dopamine receptor gene had significantly higher abstinence rates and a longer time before relapse than smokers who did not carrying these variants. This study provides the first evidence that genes altering dopamine function may influence smoking cessation and relapse during treatment. Other researchers reported that smokers with a particular variant of the dopamine receptor gene are more likely to experience a greater sense of food reward, leading to weight gain after quitting smoking. Bupropion helped to prevent post-smoking cessation weight gain in these individuals.

Chemoprevention. NCI supports preclinical studies focused on identifying and prioritizing agents that prevent cancers in tobacco-susceptible organ systems. Clinical researchers are evaluating the efficacy of chemopreventive agents in specific cohorts of former smokers.

EARLY DETECTION, DIAGNOSIS, AND PROGNOSIS

Imaging. Researchers have completed enrollment of 50,000 current smokers and former smokers into the ACRIN and NCI-supported National Lung Screening Trial (NLST; http://www.nci.nih.gov/nlst). Approximately half of the participants are women and about 4 percent are racial/ethnic minorities. This 8-year, multi-site study will determine whether lung cancer screening using low-dose spiral computed tomography in high-risk populations reduces mortality from this disease compared with standard x-ray screening. NLST scientists will also assess the stage of tumors when first detected, quality-of-life and psychological issues for people who test positive for lung cancer, economic consequences, and other potential differences between the two screening methods.

In other NCI-supported work, researchers are investigating spiral computer tomography (CT) with computer-aided diagnosis for detection of small lung nodules, and PET for prognostic measurement of treatment-related tumor volume changes in non-small cell lung cancer (NSCLC) patients. A recent NCI-supported meta-analysis has shown PET scans to be superior to CT scans for detecting NSCLC mediastinal lymph node metastasis.

Molecular Signatures. Researchers supported by the NCI Director's Challenge program have identified a molecular signature that distinguishes early lung cancers that are likely to recur quickly, from those with a more favorable prognosis. A large multi-site confirmatory study is now underway.

TREATMENT

Chemotherapy. Findings of two large clinical trials, one NCI funded, show conclusively that post-surgical chemotherapy for early-stage NSCLC significantly improves overall survival. In the NCI-supported trial, the risk of death from lung cancer was reduced by 49 percent in patients who received chemotherapy with carboplatin and paclitaxel (Taxol). The second study showed improved survival in patients receiving cisplatin and vinorelbine. Choice of chemotherapy, length of administration, and role of post-surgical radiation therapy need to be further defined in clinical trials.

In the largest Phase III trial of second line therapy for NSCLC patients, pemetrexed (Alimta®) was found to be equivalent to docetaxel (Taxotere®), the standard agent for second line therapy, in terms of response. However, pemetrexed was much better tolerated by patients and has since been approved by the FDA for NSCLC therapy.

Molecularly Targeted Therapy. The FDA has approved two epidermal growth factor receptor (EGFR) inhibitors, gefitinib (Iriessa®) and erlotinib (Tarceva®), for use in NSCLC patients. About 10 percent of advanced-stage NSCLC patients respond dramatically to these targeted agents, while the other 90 percent do not respond as well. NCI-supported researchers recently discovered that a subgroup of NSCLC patients have *EGFR* mutations, shown in parallel *in vitro* studies to correlate with clinical responsiveness to erlotinib and gefitinib. This research suggests that mutational analysis of EGFR in tumors should help identify patients who are likely to respond to these agents and paves the way for genetic identification of patients who may respond to other molecularly targeted drugs.

Immunotherapy. In partnership with Cell Genesys, NCI is sponsoring one of two Phase II trials of the patient-specific vaccine, GVAX® against NSCLC. This vaccine, which uses genetically modified, irradiated cells from individual patient's tumors, caused only low level toxicities in phase I studies, and the majority of patients showed at least some immune response, with some patients stabilized for up to 3 years after treatment. The role of immunotherapy in lung cancer remains to be determined.

HEALTH DISPARITIES

The National Conference on Tobacco and Health Disparities, held in December 2002, was the first scientific gathering to convene researchers and practitioners with the purpose of developing a research agenda to eliminate tobacco-related disparities. The summary report (http://dccps.nci.nih.gov/TCRB/eliminating_tobacco_hd.pdf) presents key recommendations to provide direction for research action, processes, and communication needed to build the evidence base for reducing tobacco use and the disproportionate burden of tobacco use and its consequences.

The Tobacco and Health Disparities Research Network, supported by NCI, Pennsylvania State University, and the American Legacy Foundation conducts interdisciplinary research to understand tobacco-related health disparities, translate scientific knowledge into practice, and inform public policy. This is the only national research network on tobacco and health disparities and offers a unique forum for stimulating scientific inquiry, promoting scientific collaborations, and evaluating the scientific evidence of research. One of the first major questions to be addressed is focused on the effects of tobacco control policy and women of low socio-economic status.

COLORECTAL CANCER

It is estimated that 73,470 women in the United States will be diagnosed with cancer of the colon or rectum in 2005 and an estimated 27,750 women will die of the disease by the end of the year, making colorectal cancer the third leading cause of cancer death among women. African American women have the highest incidence and mortality rates, followed by white women. Modest decreases in colorectal cancer incidence and mortality over the past

decade have been largely attributed to the detection and removal of precancerous polyps, the early detection of tumors through screening, and improved treatments. However, the rate of colorectal screening remains low nationally and the potential benefit with broader utilization has yet to be achieved. Five-year survival rates are highest among Asian Pacific Islander women and lowest among black women. Lower rates of treatment with adjuvant therapy among black patients may contribute to differences in cancer survival.

Gastrointestinal (GI) SPOREs. NCI supports five GI SPOREs, which focus research on cancers of the colon, rectum, and other digestive organs. For example, SPORE researchers are evaluating the role of COX-2 and other proteins in the development and progression of colorectal cancer; identifying molecular markers for risk prediction and treatment prognosis; developing chemoprevention regimens; and developing chemoradiation, immune, and molecularly targeted therapies.

RISK FACTORS

Diet. Researchers from the Arizona Cancer Center analyzed data from 1,763 participants of three randomized colorectal cancer prevention trials. They concluded that higher blood selenium concentrations were associated with lower risk for developing recurrent colorectal adenomas. Earlier, smaller epidemiological studies have variously shown either a protective effect for selenium against colorectal cancer or no association. Other NCI-supported investigators found serum levels of a vitamin D metabolite, 25-hydroxyvitamin D [25(OH)D] to be associated with lower risk for advanced colorectal adenoma in women. Analysis of data from the PCLO (http://www3.cancer.gov/prevention/plco/) trial showed an inverse association between dietary fiber intake, especially from grains, cereals, and fruits, and risk for distal large bowel adenomas, both advanced and non-advanced.

Exogenous Hormones. Investigators from the Women's Health Initiative (http://www.nhlbi.nih.gov/whi/) reported a decreased incidence of invasive colorectal cancers in postmenopausal women taking estrogen plus progestin compared to women taking a placebo, even after data were adjusted for other risk factors. However, cancers diagnosed in women in the hormone group were more advanced and showed more lymph node involvement than those diagnosed in the placebo group.

Genetics. Five hundred pairs of siblings who have had colon or rectal cancer and precancerous polyps are being recruited for the Cancer Genetics Network-sponsored Sibling Pair Colon Cancer Study (http://biostatistics.mgh.harvard.edu/siblingpair) for identification of genetic and environmental factors involved in colorectal cancer development. The investigations will be conducted in individuals where there is no known HNPCC or familial adenomatous polyposis (FAP) in the hope of identifying cancer genetic susceptibility regions.

Colon Cancer Family Registries (CFRs). The Colon Cancer Family Registries (http://epi.grants.cancer.gov/CFR/) is an international registry system available to researchers who are planning to conduct population- and clinic-based interdisciplinary research with a main focus on the genetic and molecular epidemiology of colon cancer.

PREVENTION

Celecoxib. NCI suspended use of celecoxib, in late 2004, for all participants in the Adenoma Prevention with Celecoxib (APC) trial after analysis of an independent Data Safety and Monitoring Board showed a 2.5-fold increased risk of major fatal and non-fatal cardiovascular events for participants taking the drug compared to those taking a placebo. Although the drug was stopped in ongoing trials, the data on the efficacy of Celecoxib in reducing polyps will not be known until the clinical follow-up is completed in mid-2005. In earlier studies, Celecoxib, a selective COX-2 inhibitor, has been shown to significantly reduce polyp formation in patients with FAP, without affecting blood clotting and with fewer gastric side effects than those caused by traditional non-steroidal anti-inflammatory drugs (NSAIDS). Safety monitoring of a study similar to the FAP trial, sponsored by Pfizer, did not find an increased risk of cardiovascular events. Investigators will continue to analyze the efficacy data from the APC trial.

NSAIDS. Through two NCI-funded, randomized clinical trials, investigators confirmed earlier observational studies that daily aspirin can reduce the development of colorectal polyps. Patients at increased risk for colorectal cancer who took daily aspirin for 3 years reduced colorectal polyp development by up to 35 percent. A randomized phase II

clinical trial will compare the effectiveness of three drugs in preventing colorectal cancer: two NSAIDS – aspirin and (Clinoril®) – and the naturally occurring bile salt, ursodiol (Actigal®). The latter drug is used to dissolve gall stones or to treat a rare inflammatory disease of the bile ducts and has been shown to reduce levels of deoxycholic acid, a bile acid with tumor promoting properties.

Statins. NCI will conduct a randomized clinical trial to test early findings that cholesterol-lowering statins may help prevent colorectal cancer in individuals who are at high risk for the disease. Statins, the most frequently prescribed medications in the United States, work by blocking HMG-CoA, an enzyme which the body needs to make cholesterol.

Vaccines. NCI researchers recently demonstrated that immunosuppressive, anti-inflammatory chemoprevention agents could be used effectively in combination with immune-stimulating prevention vaccines. These scientists tested the combined effects of celecoxib and the experimental CEA prevention vaccine in a mouse model for human FAP. Mice receiving celecoxib plus the vaccine developed fewer tumors than mice receiving either intervention alone. The combination therapy resulted in 95 percent less tumor development and significantly improved overall long-term survival compared to the untreated group.

Proteomics. In 2003, NCI scientists reported on the use of proteomic analysis to predict patient response to a cancer chemoprevention drug. Researchers, who analyzed serum samples from 55 participants in a clinical prevention trial of the drug celecoxib, identified a protein pattern that differed between patients who benefited from celecoxib from those who did not. Further research is needed before patients' responses to specific chemopreventive drugs can be reliably predicted. NCI's Colorectal Cancer PRG emphasized the need for new technologies such as this to improve colorectal cancer prevention, detection, and treatment.

EARLY DETECTION, DIAGNOSIS, AND PROGNOSIS

Colorectal Cancer Screening. NCI's Colorectal Cancer Screening initiative supports exploratory and developmental research aimed at improving the delivery, use, and short-term outcomes of colorectal cancer screening in primary care practice. This initiative also supports efforts by primary care practices to improve their capacity to collect patient, provider, practice, and clinical data and to conduct interventions that focus on increasing colorectal cancer screening.

Recent analysis of results from the National Survey of Colorectal Cancer Screening Practices (http://healthservices.cancer.gov/surveys/colorectal/) identified underutilized screening techniques and procedures and showed that, although colorectal screening awareness is high among primary care physicians, there are knowledge gaps about the appropriate timing and frequency of screening. Results from another NCI-sponsored survey suggest that physicians may be performing surveillance colonoscopies at frequencies higher than those recommended by evidence-based medical guidelines. For patients considered to be at low risk for colon cancer, the cumulative chance of complications from colonoscopy along with access issues, could offset the benefits of the test.

NCI researchers found that physician-oriented reminder-feedback and educational intervention significantly increased performance rates of complete diagnostic evaluation or CDE (i.e., colonoscopy, or combined flexible sigmoidoscopy plus barium enema X-ray) after an abnormal screening fecal occult blood test (FOBT).

PLCO Trial Results. Researchers from the PLCO Cancer Screening Trial have reported that three years following a negative sigmoidoscopy, 13.9 percent of 9,317 trial participants had a polyp growth, 2.3 percent had nonadvanced adenomas, and 0.8 percent had advanced adenomas or cancer. These results provide new insight into the appropriate screening intervals for colorectal cancer after a negative exam.

DNA Screening. NCI scientists are developing the multitarget assay panel (MTAP), a new, noninvasive method for colorectal cancer screening. The MTAP detects the presence of 21 specific DNA mutations known to be present in colorectal cancer, as well as changes in DNA structure. In early testing, researchers found the sensitivity and specificity of the MTAP to compare favorably with the FOBT. The MTAP correctly identified over 60 percent of patients known to have colorectal cancer versus 40 percent detected correctly using the FOBT. The MTAP improperly diagnosed about 4 percent of control group patients as having cancer versus a 6 percent false positive rate for the FOBT.

TREATMENT

Surgery. Most patients diagnosed with colorectal cancer are treated surgically, with adjuvant chemo- and/or radiation therapy. In a large, NCI-sponsored, randomized clinical trial, patients with colon cancer experienced similar rates of recurrence whether they were treated with laparoscopically assisted surgery or open colectomy. The trial's investigators concluded that laparoscopically assisted surgery is an acceptable, less invasive alternative for many patients with colon cancer. Another NCI study of over 7,000 rectal cancer patients has revealed that rates for permanent colostomy and postoperative mortality were lower, and overall survival higher, for patients undergoing surgery at high- compared to low-volume hospitals. Researchers recommend further study to identify processes of care that contribute to these differences in outcomes.

Chemotherapy. NCI researchers recently updated findings on the effectiveness of the FOLFOX regimen (oxaliplatin, 5-fluorouracil, and leucovorin) in patients with metastatic colorectal cancer, reporting a median survival of 19.5 months compared to 14-15 months for patients treated with ILF (irinotecan, folinic acid, and infusional 5-fluorouracil). A group of non-NCI-funded researchers showed that oxaliplatin administered with 5-fluorouracil and leucovorin was also superior to ILF as post-surgery adjuvant for patients with stage II and stage III colorectal cancer.

Immune Therapy. NCI is sponsoring a phase III clinical trial testing therapy with the angiogenesis-targeting, anti-VEGF monoclonal antibody bevacizumab (Avastin™), in patients who have received prior chemotherapy. Partially NCI-funded Genentech trials have shown that, in patients who had not yet been treated with chemotherapy, addition of bevacizumab to standard chemotherapy (fluorouracil, leucovorin, and irinotecan) improved survival (14 versus 19 months), response rate, and time to progression.

Research supported by NCI and others has led to the FDA approval in February 2004 of the monoclonal antibody, cetuximab (Erbitux®) for treatment of advanced colorectal cancer in combination with irinotecan chemotherapy. Cetuximab, the first monoclonal antibody approved for colorectal cancer treatment, has not been shown to improve overall survival, but was shown to shrink tumors and slow tumor growth in some patients.

AIDS-ASSOCIATED MALIGNANCIES

AIDS and HIV infection continue to be major public health concerns. From 1981 to 2001, 929,985 cases of AIDS were reported to the CDC. In 2003, 43,171 new cases of AIDS were reported to the CDC; more than one third were in women. There were also 33,301 new cases of HIV infection reported; however, this is likely an underestimate since not all states report new cases. In 2003, 28 percent of HIV/AIDS cases were in women and 69 percent of those were in black women. Heterosexual transmission of HIV increased from 3 percent in 1985 to almost 31 percent in 2003. About 70 percent of HIV-positive women were infected by this route in 2003. While the numbers of deaths per year in the United States due to AIDS has decreased in the era of highly active antiretroviral therapy (HAART), the numbers of persons living with the disease has increased. Approximately 580,500 persons are currently living with HIV infection or AIDS in the United States. Of those, 141,048 adult and adolescent women are living with AIDS, mostly minority women, and 49,226 are living with HIV infection.

The longer life expectancy of HIV positive people with access to HAART, who are living with partially restored immune function, may increase the cumulative risk of developing both AIDS-defining and non-defining cancers. The ultimate risk of such patients developing cancers more commonly associated with aging or those with longer latency, such as hepatocellular carcinoma, is not yet known. The AIDS-defining malignancies are non-Hodgkin's lymphoma (NHL), cervical cancer, anal cancer, and Kaposi's sarcoma (KS). Although KS is extremely rare among women, NHL currently ranks sixth in overall female cancer incidence and mortality. In addition, there is an increased incidence of NHL in women from the pre-HAART to HAART period. The risk of cervical neoplasia is five times higher in women with HIV infection than in HIV negative women, due to a higher prevalence and persistence of oncogenic HPV infection. The prognosis for cervical cancer is also poorer for HIV positive than for HIV negative women. Women infected with HIV and HPV also have a 6.8 fold greater risk of invasive anal cancer than HIV negative, HPV positive women.

Lymphoma SPORE. The NCI lymphoma SPORE located at John Hopkins University (http://spores.nci.nih.gov/current/lymphoma/lymphoma_docs/lym-ambinder.html) is investigating the molecular

epidemiology of AIDS-related NHL (AIDS-NHL). These researchers seek to identify immune-related molecular changes that precede AIDS-NHL development and molecular markers for AIDS-NHL risk assessment, as well as treatment strategies for high-risk individuals.

Women's Interagency HIV Study (WIHS). Since 1995, NCI has co-funded the WIHS to support malignancy studies in this NIAID/NICHD/NIDA initiative (https://statepiaps.jhsph.edu/wihs), the largest U.S. study of HIV infection in women. HIV-infected women have increased incidence rates for KS (more than 200-fold), NHL (23-fold), and lung cancer (10-fold) when compared to SEER rates. No significant increases have been detected among HIV-infected and high-risk uninfected WIHS women for lung cancer after adjusting for cigarette smoking. Only one confirmed case of invasive cervical cancer has occurred to date in an HIV-infected woman participating in WHIS, most likely detected due to the intensive cytologic surveillance conducted in this study. Other studies have reported excess of invasive cervical cancer in HIV positive women. Despite concerns to the contrary, no increased risk of breast cancer or unusual types of breast tumors have been detected in over 5,000 woman-years of follow-up. HIV-infected women who initiated HART experienced significant reductions in overall cancer risks. However, NHL incidence remains significantly higher in this population compared to the HIV uninfected U.S. population. WIHS women have high rates of infection with oncogenic tumor viruses, including hepatitis C and human herpes virus 8.

RISK

Immune suppression. NCI researchers linked records from AIDS and cancer registries in eleven U.S. regions to evaluate the relationship between cancer risk and AIDS-related immunosuppression as measured by CD4 count at AIDS onset. Based on the records of 82,217 adults, risks for KS and NHL were inversely related to CD4 count. Risks for other cancers, including cervical cancer, were unrelated to CD4 counts.

TREATMENT

DA-EPOCH. In 2003, NCI researchers reported development of the dose-adjusted EPOCH (DA-EPOCH) treatment regimen for patients with AIDS-related lymphoma (ARL). DA-EPOCH substantially improved survival for ARL patients in comparison with then standard CHOP therapy. Patients treated with DA-EPOCH were given low, individualized drug dosages, thereby reducing drug resistance and toxicity. Importantly, antiretroviral therapy was safely suspended during DA-EPOCH therapy, boosting treatment effectiveness.

Developing Novel Therapies. NCI researchers are searching for more effective AIDS therapies that will reduce the incidence of AIDS-related malignancies. Investigators recently discovered characteristic differences in gene expression patterns among cells harboring latent HIV, those infected with replicating virus, and uninfected cells. They identified several genes that may provide targets for new treatment strategies that force latent virus to replicate, making the virus more vulnerable to antiretroviral therapy. NCI researchers are also investigating novel treatments for AIDS malignancies, including potential anti-angiogenesis therapies for treating KS.

AIDS Malignancy Program (AMP). NCI developed the multi-component AMP, http://cancer.gov/dctd/aids, to assist the research community in studying the interplay of viruses, immune dysfunction, aberrant growth factor expression, and the development of cancer in AIDS patients, with the goal of developing more effective treatment regimens. The AMP includes the AIDS-Associated Malignancies Clinical (AMC) Trials Consortium (http://www.amc.uab.edu) and the AIDS and Cancer Specimen Resource (ACSR) (http://acsr.ucsf.edu). The ACSR contains or provides access to over 100,000 specimens and associated clinical data collected from cohort studies, clinical trials, and other research. The AMC unites 15 main member sites that conduct innovative treatment trials for AIDS-associated malignancies. A recent phase III AMC clinical trial found that improvements in tumor response associated with addition of rituximab to CHOP chemotherapy in patients with AIDS lymphoma may be offset by an increase in deaths from infections, particularly in individuals with low CD4 lymphocyte counts.

Centers for AIDS Research (CFAR). The CFAR (http://www.niaid.nih.gov/research/cfar), a program co-funded by seven NIH institutes including NCI, provides administrative and shared research support to synergistically enhance and coordinate high quality AIDS research projects, both nationally and internationally. There are 20 CFARs located at academic and research institutions throughout the U.S. Core facilities provide expertise, resources, and services not readily obtained through more traditional funding mechanisms. CFAR funding in 2005 will include awards to elucidate the natural history and pathobiology of HIV-related malignancies in diverse

populations in men, women, and children, and to explain the role of sex and gender in AIDS therapy and prevention through collaborative studies in women and girls.

HIV and AIDS Malignancy Branch. NCI's intramural HIV and AIDS Malignancy Branch (http://bethesdatrials.cancer.gov/patients/search_result.asp?Disease=10&Stage=&ProtocolID=&Owner=&TextSearch=&Search=) conducts translational research on HIV infection and AIDS-related malignancies in children and adults. Investigators engage in basic laboratory research, preclinical studies, and clinical trials aimed at developing novel therapies for AIDS and AIDS-related malignancies and at understanding the effects of these therapies on disease pathogenesis.

TRAINING

AIDS International Training and Research Program (AITRP). NCI is a co-sponsor of the AITRP (http://www.fic.nih.gov/programs/aitrp/aitrp.html), which supports HIV/AIDS-related research training to strengthen the capacity of institutions in low- and middle-income countries.

Requests for Applications (RFAs) and Program Announcements (PA/PARs)
Relevant to Women's Health, FY 2003-2004

PA-03-003
Exploratory Studies in Cancer Detection, Diagnosis and Prediction
This initiative promotes the initial evaluation of molecular or cellular characteristics in human specimens and/or the development of assays that may result in important advances in the detection, diagnosis, and treatment of cancers.

PA-04-012 (NCI, AHRQ)
Studies of the Economics of Cancer Prevention, Screening, and Care
The goal of this PA, in partnership with AHRQ, is to generate new economic knowledge that will promote the optimal design of cancer prevention and control trial studies and interventions and will facilitate the formulation of effective health care policy related to cancer prevention and control.

PA-04-034
Exploratory Grants for Behavioral Research in Cancer Control
This PA invites research grant applications from interested investigators to conduct developmental and formative behavioral research in cancer prevention and control through a program of exploratory investigator-initiated R21 grants.

PA-04-046
Clinical Cancer Therapy and Prevention Research
The overall aims of this renewed PA are two-fold: (1) To stimulate development of innovative therapeutic/preventive clinical trials with or without laboratory correlative studies (2) to support innovative correlative laboratory studies linked to therapeutic/preventive clinical trials.

PA-04-053 (NCI, NINR, NIDCR, NCCAM)
Developmental Projects in Complementary Approaches to Cancer Care
The purpose of this Project Announcement (PA) is to encourage and support the development of basic and clinical complementary cancer research and to provide the basis for more extended research projects by establishing the methodological feasibility, strengthening the scientific rationale for these projects, and collecting preliminary data.

PA-04-094, PA-04-095 (NCI, NIEHS, NIDDK, NINDS)
Novel Technologies for *In Vivo* Imaging
This PA supports applications for the development and delivery of novel image acquisition or enhancement technology and methods for biomedical imaging and image-guided interventions and therapy. Applicants may incorporate limited pilot or clinical feasibility evaluations using preclinical models or clinical studies.

PA-04-099
Diet, Epigenetic Factors, and Cancer Prevention
The objective of this PA is to encourage collaboration between nutrition and epigenetic experts to study bioactive food components with cancer preventative properties and to examine key epigenetic events in cancer processes (i.e., carcinogen metabolism, cell division, differentiation, apoptosis) so that investigators can begin to establish linkages between epigenetics, methylation pattern, and tumor incidence/behavior.

PA-04-102
Phased Application Awards in Cancer Prognosis and Prediction
This PA invites applications for research projects to evaluate the utility and pilot the application of new strategies for determining prognosis or predicting response to therapy. This research will provide tools to improve clinical decision-making in the care of cancer patients. This PA provides support for a first phase (R21) for technical development and a second phase (R33) for application and evaluation of clinical utility.

PA-04-103 (NCI, NIDA)
Testing Tobacco Products Promoted To Reduce Harm
The purpose of this PA is to stimulate multidisciplinary research on potential reduced-exposure tobacco products, both smoked and smokeless, through the interplay of basic, biological, and behavioral research, surveillance, and epidemiology.

PA-04-157 (NCI, NIDCR)
Research on Malignancies in AIDS and Acquired Immune Suppression
The purpose of this initiative is to stimulate research that will improve our understanding of the biological basis of development and progression of cancer in the context of HIV infection and AIDS or acquired immune suppression not associated with HIV infection such as organ transplantation.

PA-05-006 (NCI, NIDDK, OBSSR, NHLBI, NIBIB, NIDA)
The Effect of Racial and Ethnic Discrimination/Bias on Healthcare Delivery
The purposes of this PA are: (1) To improve the measurement of racial/ethnic discrimination in healthcare delivery systems through improved instrumentation, data collection, and statistical/analytical techniques; (2) to enhance understanding of the influence of racial/ethnic discrimination in healthcare delivery and its association with disparities in disease incidence, treatment, and outcomes among disadvantaged racial/ethnic minority groups; and (3) to reduce the prevalence of racial/ethnic health disparities through the development of interventions to reduce the influence of racial/ethnic discrimination on healthcare delivery systems in the United States.

PA-05-009 (NCI, NIDDK, NIBIB, NIA, OBSSR)
Research on the Economics of Diet, Activity, and Energy Balance
The major focus of this PA is to solicit projects that enhance the state-of-the-science on the causes of obesity and to inform federal decision making on effective public health interventions for reducing the rate of obesity in the United States. Research strategies that nest economic analysis within a broader interdisciplinary context of other social and behavioral sciences as well as the epidemiological, biostatistical, medical, and biological disciplines relevant to public health policy are especially encouraged.

PA-05-016 (NCI, NIDA, NIAAA)
Decision Making in Health: Behavior Maintenance
The purpose of this initiative is to invite applications for research projects that will expand our knowledge of basic decision-making processes underlying initiation and long-term maintenance of healthy lifestyle behaviors that may reduce one's risk of cancer and other chronic diseases, such as cardiovascular disease, diabetes, and addiction.

PA-05-017
Decision Making in Cancer: Single-Event Decisions
The purpose of this PA is to invite applications for research projects that will enhance understanding of human decision-making processes so that individuals can make more informed and satisfying choices regarding their health, related to cancer prevention, detection, treatment, survivorship, or end-of-life care.

PA-05-029 (OBSSR, NCI, NCCAM, NHLBI, NICHD, NIDCR, NIDDK, NIEHS, NIMH, NINR, NIA, NIAAA, NIAMS, NIDA, NIDCD)
Social and Cultural Dimensions of Health
The ultimate goal of this PA is to encourage the development of health research that integrates knowledge from the biomedical and social sciences by (1) elucidating basic social and cultural constructs and processes used in health research, (2) clarifying social and cultural factors in the etiology and consequences of health and illness, (3) linking basic research to practice for improving prevention, treatment, health services, and dissemination, and (4) exploring ethical issues in social and cultural research related to health.

PAR-03-158
Specialized Programs of Research Excellence (SPOREs) in Human Cancer for the Year 2004
A SPORE should support a mix of basic and clinical researchers whose formal interactive and collaborative research efforts will result in new approaches for early detection, diagnosis, therapy, prevention, and control of human cancer. SPOREs are expected not only to conduct a wide spectrum of research activities but also to contribute

significantly to the development of specialized research resources (or cores), improved research model systems, and collaborative research projects with other institutions.

PAR-04-147
Cancer Prevention Research Small Grant Program
The Small Grants Program is designed to aid and facilitate the growth of a nationwide cohort of scientists with a high level of research expertise in cancer prevention research.

PAR-04-020
Small Grants for Behavioral Research in Cancer Control
Studies funded by this initiative may contribute to the design, implementation, or evaluation of intervention programs, descriptive baseline surveys, testing, modification and validation of surveys or program materials for use in the proposed population groups, testing of recruitment, intervention, or compliance procedures for participants, etc.

PAR-04-036 (NCI, AHRQ)
Colorectal Cancer Screening in Primary Care Practice
The objective of this PA, in partnership with AHRQ, is to encourage health services, social and behavioral, and outcomes researchers to develop innovative research projects to increase the knowledge base for enhanced translation of effective colorectal cancer screening techniques into community practice.

PAR-04-069
***In Vivo* Cellular and Molecular Imaging Centers (ICMICs)**
This initiative, for new or competing P50 Research Center Grants, is designed to capitalize on the extraordinary opportunity for molecular imaging to have an impact on the diagnosis and treatment of cancer patients non-invasively and quantitatively.

PAR-04-155
Quick-Trials for Novel Cancer Therapies: Exploratory Grants
This PA is intended to provide investigators with rapid access to support for pilot, Phase I, and Phase II cancer clinical trials as well as support for patient monitoring and laboratory studies linked to a cancer clinical trial.

RFA-ES-03-001 (NIEHS, NCI)
Breast Cancer and the Environment Research Centers
The NCI joins the NIEHS in an initiative to create a network of research centers in which multidisciplinary teams of scientists, clinicians, and breast cancer advocates collaboratively focus on how chemical, physical, biological, and social factors in the environment work together with genetic factors to cause breast cancer. The centers will work collaboratively on two projects; "Defining the Effects of Environmental Exposures on the Molecular Architecture of the Mammary Gland over the Lifespan," and "Environmental and Genetic Determinants of Puberty."

RFA-CA-04-002
Mouse Models of Human Cancers Consortium (MMHCC)
The activities of the MMHCC include fresh approaches to mouse genetic engineering and phenotyping, significantly advancing the field and stimulating interest in derivation and application of mouse cancer models to cancer research. The intent is to foster research investigations, technological innovation, and extensive collaboration that cannot be pursued with traditional grant support

RFA-CA-04-003
Long Term Cancer Survivors: Research Initiatives
The goal of this RFA is to promote and support research that will lead to the decrease in physiologic and psychosocial morbidity and mortality associated with long term (more than 5 years) survival from cancer.

RFAs -CA-04-006 , CA-05-005, CA-05-009, CA-05-023
Early Detection Research Network
The national Early Detection Research Network (EDRN) is responsible for the development, evaluation, and validation of new or existing biomarkers for earlier cancer detection and risk assessment. The intent of these RFAs

is to continue to foster research investigations, technological innovation, and collaboration to accelerate the development of biomarkers and tools that have the potential of moving rapidly to Phase II and Phase III.

RFA-CA-04-008, CA-05-014
Community Clinical Oncology Program (CCOP)
The reissuance of this RFA seeks to build on the strength and success of the network over the past 20 years by continuing to support community participation in cancer treatment, prevention, and control clinical trials through research bases (NCI-supported clinical cooperative groups and Cancer Centers); expanding and strengthening the cancer prevention and control research effort; utilizing the CCOP network for conducting NCI-assisted cancer prevention and control research; and evaluating CCOP performance and impact in the community.

RFA-CA-04-009 (NCI, NIDDK, OBSSR, ODP, ORWH)
Understanding Mechanisms of Physical Activity and Behavior Change
The purpose of this RFA is to increase the knowledge base necessary to develop effective physical activity interventions in children, adolescents, adults, and older adults. Studies that consider the psychosocial, environmental, and physiological factors that influence the mechanisms of physical activity behavior change are of interest, and the physiological and psychosocial influences affected by disease status are of particular interest.

RFA-CA-04-011
Small Animal Imaging Resource Programs
These programs will support (1) shared imaging research resources to be used by cancer investigators, (2) research related to small animal imaging technology, and (3) training of both professional and technical support personnel interested in the science and techniques of small animal imaging.

RFA-CA-04-012 (NCI, NIDA, NIAAA)
Transdisciplinary Tobacco Use Research Centers
This reissued RFA reflects recognition of the public health impact of tobacco use and the scientific need for integrative transdisciplinary research across the full spectrum of basic and applied research on tobacco use and control. Collaborative research across disciplinary boundaries permits scientific exploration of the complex and interactive determinants of tobacco use.

RFA-CA-04-013
Integrative Cancer Biology Program
This initiative is designed to foster the emergence of the new field of systems biology focused on the analysis of cancer as a complex biological disease. The initiative will support the development of reliably predictive in silico or computational models of cancer initiation and progression that can ultimately lead to the development of improved cancer interventions. It will enable the formation of teams of researchers from a spectrum of fields, including biology, imaging, engineering, technology, bioinformatics, and computational modeling, who can focus on understanding and modeling some aspect of the complexity of cancer.

RFA-CA-04-015
Strategic Partnering to Evaluate Cancer Signatures
The purpose of this initiative is to build on recent demonstrations that molecular signatures correlate with important clinical parameters in cancer. NCI invites investigators to form strategic partnerships that will bring together the multi-disciplinary expertise and resources needed to determine how the information derived from comprehensive molecular analyses can be used to improve patient care and ultimately, patient outcomes.

RFA-CA-05-010
Transdisciplinary Research on Energetics and Cancer
These Centers will involve scientists from multiple disciplines and will encompass projects spanning the biology and genetics of behavioral, socio-cultural, and environmental influences on nutrition, physical activity, weight, energy balance, and energetics.

RFA-CA-05-012
Community Networks to Reduce Cancer Health Disparities (CNP)
The purpose of the CNP is to reduce cancer health disparities by conducting community-based participatory

education, training, and research among racial/ethnic minorities and underserved populations. The overall goals of this program are to significantly improve access to and utilization of beneficial cancer interventions in communities with cancer health disparities, thereby reducing these disparities.

RFA-CA-05-013 (NCI, NINR, ORWH)
Reducing Barriers in Symptom Management and Palliative Care
This RFA will support research directed at developing and testing interventions to reduce or overcome barriers to the delivery of appropriate symptom management and palliative care, thereby decreasing the suffering and improving the health and quality of life of persons living with cancer.

RFA-CA-05-015
Minority-Based Clinical Oncology Program
The reissuance this RFA is intended to provide support to expand clinical research in minority community settings; bring state-of-the-art treatment and cancer prevention and control research to minority individuals in their communities; increase involvement of primary healthcare providers and specialists in prevention and control studies; establish an operational base for extending prevention and control and reducing cancer incidence, morbidity, and mortality in minority populations; and examine issues in Minority-Based CCOP performance.

RFA-CA-05-019
Patient Navigation Research Program
The purpose of the Patient Navigation Research Program (PNRP) is to develop interventions to reduce the time to delivery of standard cancer care services – non-cancer resolution or cancer diagnosis and treatment after identifying an abnormal finding from a cancer detection procedure.

RFA-CA-05-020
Planning Grant for Minority Institution/Cancer Center Collaboration (P20)
The objective of this initiative is to help researchers and faculty in Minority Serving Institutions (MSIs) in collaboration with the researchers and faculty of NCI-designated Cancer Centers (or other institutions with highly organized, integrated research efforts focused on cancer) plan and initiate focused cancer research, cancer research training, and career development or cancer research education and outreach collaborations that will lead to the submission of specific grant applications traditionally supported by the NCI or other equivalent funding agencies.

RFA-CA-05-021
Comprehensive Minority/Institution/Cancer Center Partnership (U54)
This initiative supports cooperative agreements for the implementation of Comprehensive Minority Institution/Cancer Center Partnerships between MSIs and NCI-designated Cancer Centers (or groups of Centers). The purpose of this grant is to provide opportunities for intensive collaborations among MSIs and the Cancer Centers in order to develop stronger national cancer programs aimed at understanding the reasons behind the significant cancer disparities and impact on minority populations.

RFA-CA-05-022
Cooperative Planning Grant for Comprehensive Minority Institution/Cancer Center (MSIs) Partnership
Partners in these U54 programs are expected to: (1) Build and stabilize the independent competitive cancer research capacity at the MSIs; (2) Improve the effectiveness of the NCI-designated Cancer Centers in conducting activities specifically designed to address the cancer disparities in underserved racial and ethnic minority populations and among the socio-economically disadvantaged; (3) Create stable, long-term collaborative relationships between MSIs and Cancer Centers in all areas of cancer research, training, and education; and (4) Export successful approaches and new models to other MSIs and NCI-designated Cancer Centers, as well as other key networks supported by the NCI.

SELECTED MEETINGS OF INTEREST
(Sponsored or co-sponsored by NCI, FY2003-2004)

Emerging Topics in Breast Cancer and the Environment Research
(Princeton, NJ; November 04, 2004 - November 06, 2004)

Mini-Symposium on Work and Women's Health at the International Symposium on Epidemiology in Occupational Health
(Melbourne, Australia; October 13-15, 2004)

Exploring Genomics in Ovarian Cancer - Division of Cancer Epidemiology and Genetics (DCEG) Seminar Series
(Rockville, MD; September 16, 2004)

Cancer Health Disparities Summit 2004 - Special Populations Networks for Cancer Awareness Research & Training
(Washington, DC; July 18, 2004 - July 20, 2004)

Workshop on Cancer Risk Prediction Models: Development, Utility, Evaluation and Applications
(Washington, DC; May 20-21, 2004)

Working Together to Address the Unequal Burden of Cancer - Reaching Special Populations in the Mid South to Lessen Cancer Disparities: Sharing Innovative Ideas and Sustaining Outcomes
(Lexington, KY; May 18, 2004 - May 20, 2004)

8th International Conference on Malignancies in AIDS and Other Immunodeficiencies (ICMAOI)): Basic, Epidemiologic and Clinical Research
(Bethesda, MD; April 29, 2004 - April 30, 2004)

State of the Science Conference on Workplace Strategies and Interventions for Improving Health and Well-Being
(Bethesda, MD; April 13 - 14, 2004)

9th Biennial Symposium on Minorities, the Medically Underserved & Cancer
(Washington, DC; March 24-28, 2004)

Parenthood after Cancer: Today's Options and Tomorrow's Hopes
(Houston, TX; March 5-7, 2004)

Cervix Carcinogenesis in Terms of HPV Infection
(Bethesda, MD; March 03, 2004)

24th Congress of the International Association for Breast Cancer Research: Advances in Human Breast Cancer Research & Preclinical Models of Breast Cancer Research
(Sacramento, CA; November 2003)

DNA Repair, Smoking, and the Risk of Lung Cancer
(Rockville, MD; November 13, 2003)

Borderline Ovarian Tumors Consensus Workshop
(Bethesda, MD; August 27-28, 2003)

Breast Cancer Faculty Annual Retreat
(Warrenton, VA; July 9-10, 2003)

International Meeting on Angiogenesis in Cancer
(Reykjavik, Iceland; June 26-28,2003)

Mammary Gland Biology Seminar Series
(Bethesda, MD; Spring 2003)

7th International Conference on Malignancies in AIDS and Other Immunodeficiencies: Basic, Epidemiologic and Clinical Research
(Bethesda, MD; April 28, 2003 - April 29, 2003)

NCI Rosalind E. Franklin Award for Women in Cancer Research: An Approach to Studying Genetic Susceptibility of Lung Cancer - Division of Cancer Epidemiology and Genetics (DCEG) Seminar Series
(Rockville, MD; March 06, 2003)

Future Vaccines for Papilloma and AIDS Viruses
(Bethesda, MD; February 28, 2003)

Early Reproductive Events and Breast Cancer
(Bethesda, MD; February 24 – 26, 2003

4th National Forum on Biomedical Imaging in Oncology
(Bethesda, MD; February 06, 2003 - February 07, 2003)

Women, Tobacco and Cancer: An Agenda for the 21st Century
(Houston, TX; February 03, 2003 - February 05, 2003)

Ovarian Cancer: Insights from Gene Expression Profiling
(Bethesda, MD; January 23, 2003)

KEY WORDS

Breast Cancer
Breast Cancer Progress Report, aramotase inhibitor(s) (AI), SPORE(s), biomarker(s), mouse models, HER2, AIB1, vaccine(s), gene expression profile(-ing), Consortium of Cohorts, specimen resources, genetic factors, oral contraceptives, diet, soy, isoflavones, physical activity, exercise, Women's Health Initiative (WHI), aspirin, Long Island Breast Cancer Study Project (LIBCSP), estrogen, progesterone, progestin, estrogen receptor, antibiotics, radiation, hormones, hormone replacement therapy (HRT), DES, insulin, environment(-al), lifestyle, DDT, registry(-ies), SERMS, raloxifene (Evista®), Breast Cancer Prevention Trial (BCPT), Study of Tamoxifen and Raloxifene (STAR), exemestane, celecoxib, mammography, digital mammography, MRI, ultrasound, PET, SPECT, BRCA, BRCA1, BRCA2, Breast Cancer Surveillance Consortium (BCSC), Digital Mammography Screening Trial (DMIST), gene expression, chemotherapy, estrogen-dependent, adjuvant therapy, node negative, node positive, letrozole (Femara ®), anastrozole (Arimidex ®), paclitaxel (Taxol®), dose-dense chemotherapy, age, immune therapy, monoclonal antibodies, herceptin PTEN, education, screening, survivorship, quality of life, cancer survivors, health disparities.

Cervical Cancer
SPORE, Pap smear, HPV, cofactors, Gaunacaste Study of HPV Natural History study, Portland Kaiser Permanente cohort study, HLA, diet, smoking, immunological markers, immunosupression, HIV, tobacco, DES, HPV vaccine, obesity, imaging, HPV testing, ASCUS-LSIL Triage Study (ALTS), chemoradiation, cisplatin, treatment-related side effects, psychosocial issues, sexuality issues, health disparities, screening, Patient Navigator Program, surveillance.

Ovarian Cancer
SPOREs, screening, biomarkers, CA-125, mouse models, tumor suppressor gene(s), estrogen receptor, PTEN, estrogen, progesterone, hormone receptor(s), VEGF, biobehavioral, BRCA1, BRCA2, infertility, fertility drugs, inherited risk factors, registries, oral contraceptives, breast fed, pregnancy, tubal ligation, hysterectomy, HRT,

preventive removal of the ovaries, quality of life, premature menopause, proteomics, screening, genetic testing, tumor markers, ovarian pap test, Prostate, Lung, and Ovarian Cancer Screening (PLCO) trial, chemotherapy, monoclonal antibody(-ies), donor lymphocyte infusion, nonmyeloblative allogeneic transplantation, gene therapy, antiangiogenic agents.

Endometrial Cancer
SPORE, molecular markers, estrogen, progesterone, SERM(s), tamoxifene, raloxifene, Arzoxifene, microsatellite instability (MSI), gene expression profiling, specimen resources, Gyneccologic Oncology Group, mouse models, PTEN, hormone/hormonal therapy(-ies), HNPCC, smoking, complex carbohydrates, diet, menstrual and reproductive factors, insulin-like growth factor, insulin-like binding protein, chemoprevention, obesity, nutrition, medroxyprogesterone, ethinyl estradiol, norgestrel, ribosomal DNA (rDNA), surgery, chemotherapy, cisplatin, doxorubicin, radiation therapy, targeted therapies, trastuzumab (Herceptin ®), bevacizumab (Avastin™), lapatinib (GW572016), sorafenib (BAY 43-9006).

Lung and Other Tobacco-Related Cancers
Smoking, tobacco, lung cancer, cervical cancer, ovarian cancer, colorectal cancer, breast cancer, leukemia, bladder, esophagus, kidney, larynx, oral cavity, pancreas, stomach, Lung Cancer Integration and Implementation (I2) team, Transdisciplinary Tobacco Use Research Centers (TTURCs), tobacco use and addiction, smoking/tobacco cessation, SPOREs, Nurse's Health Study, biospecimen(s), PLCO, Shanghai Women's Study, reduced-exposure tobacco products, radon, diet, beta-carotene, genetics, p53, pregnancy/pregnant, tobacco control, American Stop Smoking Intervention Study (ASSIST), National Network of Tobacco Cessation Quitlines, Smoking and Tobacco Control Monographs, buproprion, dopamine, chemoprevention, National Lung Screening Trial (NLST), commuted tomography, quality of life, psychosocial issues, PET, molecular signatures, carboplatin, paclitaxel (Taxol), pemetrexed (Alimta®), docetaxel (Taxotere®), molecularly targeted therapy, EGFR, gefitinib (Iriessa®), erlotinib (Tarceva®), immunotherapy, Health Disparities.

Colorectal Cancer
Screening, diet, selenium, vitamin D, fiber intake, exogenous hormones, estrogen, progestin, genetics, Sibling Pair Colon Cancer Study, HNPCC, familial adenomatous polyposis (FAP), registries, celecoxib (Celebrex), COX-2, NSAIDs, sulindac (Clinoril®), ursodiol (Actigal®), statins, vaccines, proteomics, chemoprevention, DNA screening, surgery, radiation therapy, laparoscopically-assisted surgery, colostomy, chemotherapy, FOLFOX, oxaliplatin, immune therapy, VEGF, monoclonal antibody(-ies), bevacizumab (Avastin™), cetuximab (Erbitux®).

AIDS-Associated Malignancies
AIDS, HIV, highly active antiretroviral therapy (HAART), non-Hodgkin's lymphoma (NHL), cervical cancer, anal cancer, Kaposi's sarcoma (KS), SPORE, AIDS-related NHL (AIDS-NHL), Women's Interagency HIV Study, immune suppression, DA-EPOCH, AIDS Malignancy Program, Centers for AIDS Research, HIV and AIDS Malignancy Branch, AIDS International Training and Research Program.