Chapter 7
Cancer Among Adults from Exposure to Secondhand Smoke

Introduction

Active cigarette smoking causes cancer in multiple organs (U.S. Department of Health and Human Services [USDHHS] 2004). Secondhand tobacco smoke contains the same carcinogens that are inhaled by smokers and consequently, there been a concern for a long time that involuntary smoking also causes cancer. Secondhand smoke was first determined to be causally associated with lung cancer (USDHHS 1986), and research on secondhand smoke exposure and cancer risk has been extended to other sites for which there are multiple studies, including the breast, nasal sinuses, and the cervix. This chapter returns to the topic of lung cancer and updates the 1986 evaluation; reviews of the evidence on secondhand smoke exposure and risk for cancer of other sites are also included.

Lung Cancer

The first Surgeon General's report in 1964 identified active smoking as a cause of lung cancer (U.S. Department of Health, Education, and Welfare 1964). Researchers have identified more than 50 carcinogenic compounds and many other toxic substances in tobacco smoke (USDHHS 1986; Hoffmann and Hecht 1990; Hecht 1999) (see "Carcinogens in Sidestream Smoke and Secondhand Smoke" in Chapter 2). Smoking tobacco is acknowledged as the leading cause of lung cancer. Because the compounds that are inhaled by the active smoker are also present in the mixture of sidestream and exhaled mainstream smoke inhaled by involuntary smokers, it is biologically plausible that secondhand smoke is also a cause of lung cancer among nonsmokers, a conclusion reached 20 years ago in the 1986 report (USDHHS 1986).

In 1981, the first major epidemiologic studies of secondhand smoke and lung cancer showed that nonsmoking women married to smokers had a higher risk of lung cancer than did nonsmoking women married to nonsmokers (Garfinkel 1981; Hirayama 1981; Trichopoulos et al. 1981). These three initial studies were followed by numerous investigations that were specifically conducted to evaluate secondhand smoke exposure and the risk of lung cancer among nonsmokers. The combined evidence from more than 50 additional epidemiologic studies on this topic has confirmed and expanded the 1981 findings of an association between secondhand smoke exposure and lung cancer. These more recent studies were conducted within and outside of the United States, and several authoritative scientific panels in the United States and elsewhere have reviewed the findings (Table 7.1). These reviews have carefully considered the possibility of whether the association of secondhand smoke with lung cancer risk could reflect solely uncontrolled bias or confounding. This possibility has been set aside by each group. The number of studies has increased since 1986, but the conclusions of each major review and each of the pooled relative risk (RR) estimates have remained consistent—exposure to secondhand smoke causally increases the risk for lung cancer.

This chapter considers the full body of evidence on secondhand smoke exposure and lung cancer published through 2002, the ending date for the systematic review of the epidemiologic studies. The chapter includes details of more recent studies and provides results of an updated meta-analysis of published studies.

Methods

This chapter includes an updated literature review for lung cancer that focused on studies published since the release of prior major reports. Medline was used to identify the studies included in this review by searching for the following terms: environmental tobacco smoke, secondhand smoke, passive smoking, and lung cancer. Reference lists from each study were also reviewed. These later studies include 3 cohort studies (Table 7.2) (de Waard et al. 1995; Jee et

Table 7.1 Conclusions of selected authoritative scientific bodies on the role of secondhand smoke and the risk of lung cancer among lifetime nonsmokers

Year of publication/agency	Studies reviewed	Conclusions and summary comments
1982 Office of the Surgeon General, U.S. Department of Health and Human Services (USDHHS) *The Health Consequences of Smoking: Cancer*	The first 3 epidemiologic studies on secondhand smoke and lung cancer (Garfinkel 1981; Hirayama 1981; Trichopoulos et al. 1981)	"Although the currently available evidence is not sufficient to conclude that passive or involuntary smoking causes lung cancer in nonsmokers, the evidence does raise concern about a possible serious public health problem." (p. 9)
1986 International Agency for Research on Cancer *Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Tobacco Smoking*	7 epidemiologic studies on secondhand smoke and lung cancer published between 1981 and 1984 (Garfinkel 1981; Hirayama 1981 [Japan]; Trichopoulos et al. 1981 [Greece]; Chan and Fung 1982 [Hong Kong]; Correa et al. 1983; Kabat and Wynder 1984; Koo et al. 1984)	"Knowledge of the nature of sidestream and mainstream smoke, of the materials absorbed during 'passive' smoking, and of the quantitative relationships between dose and effect that are commonly observed from exposure to carcinogens, however, leads to the conclusion that passive smoking gives rise to some risk of cancer." (p. 314)
1986 National Research Council *Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects*	12 studies on secondhand smoke and lung cancer published since 1981 (Chan and Fung 1982; Correa et al. 1983; Tricholoupos et al. 1983; Buffler et al. 1984; Gillis et al. 1984; Hirayama 1984; Kabat and Wynder 1984; Garfinkel et al. 1985; Akiba et al. 1986; Lee et al. 1986; Koo et al. 1987; Pershagen et al. 1987)	"The weight of evidence derived from epidemiologic studies shows an association between ETS [environmental tobacco smoke] exposure of nonsmokers and lung cancer that, taken as a whole, is unlikely to be due to chance or systematic bias. The observed estimate of increased risk is 34%, largely for spouses of smokers compared with spouses of nonsmokers." (p. 245)
1986 Office of the Surgeon General, USDHHS *The Health Consequences of Involuntary Smoking*	12 studies on spousal secondhand smoke and lung cancer published since 1981 (Chan and Fung 1982; Correa et al. 1983; Trichopoulos et al. 1983; Gillis et al. 1984; Hirayama 1984; Kabat and Wynder 1984; Koo et al. 1984; Garfinkel et al. 1985; Wu et al. 1985; Akiba et al. 1986; Lee et al. 1986; Pershagen et al. 1987)	"Involuntary smoking can cause lung cancer in nonsmokers." (p. 13)

Table 7.1 Continued

Year of publication/agency	Studies reviewed	Conclusions and summary comments
1992 U.S. Environmental Protection Agency (USEPA) *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders*	32 epidemiologic studies on secondhand smoke and lung cancer; 24 of 32 showed a positive association (Garfinkel 1981; Trichopoulos et al. 1981, 1983; Chan and Fung 1982; Correa et al. 1983; Buffler et al. 1984; Hirayama 1984; Kabat and Wynder 1984; Garfinkel et al. 1985; Lam 1985; Wu et al. 1985; Akiba et al. 1986; Lee et al. 1986; Brownson et al. 1987; Gao et al. 1987; Humble et al. 1987; Koo et al. 1987; Lam et al. 1987; Pershagen et al. 1987; Butler 1988; Geng et al. 1988; Inoue and Hirayama 1988; Katada et al. 1988; Shimizu et al. 1988; Hole et al. 1989; Svensson et al. 1989; Janerich et al. 1990; Kalandidi et al. 1990; Sobue 1990; Wu-Williams and Samet 1990; Fontham et al. 1991; Liu et al. 1991); the association between exposure levels (amount smoked by spouses) and the risk of lung cancer was also examined	"ETS constituents include essentially all of the same carcinogens found in [mainstream tobacco smoke], and many of these appear in greater amounts in [sidestream tobacco smoke]. . . . This quantitative comparison is consistent with the observation noted above that [sidestream] condensates apparently have even greater carcinogenic potential than [mainstream] condensates." (p. 4-28) "The unequivocal causal association between tobacco smoking and lung cancer in humans with dose-response relationships extending down to the lowest exposure categories, as well as the corroborative evidence of the carcinogenicity of both [mainstream] and ETS provided by animal bioassays and in vitro studies and the chemical similarity between [mainstream] and ETS, clearly establish the plausibility that ETS is also a human lung carcinogen. In addition, biomarker studies verify that passive smoking results in detectable uptake of tobacco smoke constituents by nonsmokers, affirming that ETS exposure is a public health concern. In fact, these observations are sufficient in their own right to establish the carcinogenicity of ETS to humans." (p. 4-28) "ETS is a human lung carcinogen, responsible for approximately 3,000 lung cancer deaths annually in U.S. nonsmokers." (p. 1-1)
1999 National Cancer Institute *Health Effects of Exposure to Environmental Tobacco Smoke: The Report of the California EPA*. Smoking and Tobacco Control Monograph No. 10	• 8 epidemiologic studies published since the 1992 U.S. EPA report that have information on secondhand smoke exposure and lung cancer (Brownson et al. 1992; Stockwell et al. 1992; Liu et al. 1993; Fontham et al. 1994; Kabat et al. 1995; Schwartz et al. 1996; Cardenas et al. 1997; Ko et al. 1997) • 13 epidemiologic studies with data on secondhand smoke workplace exposures and 14 studies with data on other household members	"The 1986 Report of the Surgeon General, the 1986 National Research Council report. . . and the 1992 U.S. EPA report. . . have established that ETS exposure causes lung cancer. Results from recent epidemiological studies are compatible with the causal association already established." (p. ES-12)
2001 Office of the Surgeon General, USDHHS *Women and Smoking*	• 9 studies on spousal secondhand smoke and lung cancer (Brownson et al. 1992; Stockwell et al. 1992; Liu et al. 1993; Fontham et al. 1994; Wang et al. 1994; Kabat et al. 1995; Cardenas et al. 1997; Boffetta et al. 1998; Jöckel et al. 1998) • 16 epidemiologic studies with data on secondhand smoke workplace exposures	"Exposure to ETS is a cause of lung cancer among women who have never smoked." (p. 16)

Table 7.2 Cohort studies of the associations between adult exposure to secondhand smoke and the relative risks for lung cancer incidence and mortality among women who had never smoked

Study	Population/follow-up	Number of lung cancer events	Data collection
de Waard et al. 1995	2 population-based breast screening cohorts, 12,000–13,000 women in each cohort Netherlands 15 years	23 incident cases and deaths	Active smoking histories were collected at the time of urine collection; no information was collected on secondhand smoke exposure
Jee et al. 1999	157,436 married women aged >40 years Health insurance subscribers Korea 3.5 years	79 incident and prevalent cases	Questionnaires and medical exams of the husbands in 1992 and 1994; women completed questionnaires in 1993
Nishino et al. 2001	9,675 women aged >40 years Miyagi Prefecture, Japan 9 years	24 incident cases	Self-completed questionnaire by 31,345 (13,992 men and 17,353 women)

al. 1999; Nishino et al. 2001) and 13 case-control studies from around the world (Table 7.3) (Lei et al. 1996; Shen et al. 1996, 1998; Wang et al. 1996, 2000; Jöckel et al. 1998; Nyberg et al. 1998a; Zaridze et al. 1998; Rapiti et al. 1999; Zhong et al. 1999; Kreuzer et al. 2000; Lee et al. 2000; Zhou et al. 2000; Johnson et al. 2001; Seow et al. 2002). The case-control studies are organized by geographic areas because the relative importance of different sources of secondhand smoke exposure and the prevalence of other risk factors of lung cancer (such as occupational exposures, other sources of indoor air pollutants, and previous lung diseases) may differ from one country to another. Study design issues such as the reliance on pathologic confirmation and the proportion of surrogate respondents also differ by study area.

Researchers have conducted several meta-analyses on secondhand smoke exposure and the risk of lung cancer (National Research Council [NRC] 1986; Dockery and Trichopoulos 1997; Hackshaw et al. 1997; Zhong et al. 2000). This chapter also contains a meta-analysis that includes the more recent studies through 2002 in the pooled estimates, and in the estimates from the stratification of the studies by parameters such as gender and geographic area. Pooled estimates associated with secondhand smoke exposure from spouses, at the workplace, and during childhood are specifically presented (see "Pooled Analyses" later in this chapter).

Cohort Studies

A total of eight cohort studies have evaluated secondhand smoke and the risk of lung cancer: three in the United States (Garfinkel 1981; Butler 1988; Cardenas et al. 1997), two in Japan (Hirayama 1981; Nishino et al. 2001), one in Scotland (Hole et al. 1989), one in Korea (Jee et al. 1999), and one in the Netherlands (de Waard et al. 1995). These cohort studies used questionnaires that asked about spousal smoking behaviors and used spousal smoking as the

Findings	Measure of secondhand smoke	Relative risk (95% confidence interval)	Comments
• Urinary nicotine and cotinine levels were significantly associated with lung cancer risk • Risk increased with increasing urinary cotinine levels	Cotinine levels (nanograms/milligram): <9.2 9.2–23.4 23.4–100	 1.0 2.7 (0.8–9.1) 2.4 (0.7–8.3)	Crude risk estimates; the only published study with an objective measure of secondhand smoke exposure
• Risk increased with increasing duration and amount smoked by the husband	Husband's smoking status: Lifetime nonsmokers Former smokers Current smokers	 1.0 1.30 (0.6–2.7) 1.90 (1.0–3.5)	Controlled for age of husbands and wives, social class, residency, and husbands' occupation and vegetable intake; husbands' smoking was associated with an increased risk of breast cancer but not with cancers at other sites (cervix, stomach, liver)
• No increased risk was associated with secondhand smoke exposure from other household members	Husband smoked: No Yes	 1.0 1.8 (0.7–4.6)	Controlled for age; study area; intake of alcohol, green and yellow vegetables, fruit, and meat; and history of lung disease; husbands' smoking was associated with an increased risk of rectum and smoking-related cancers combined; there was no increased risk of breast cancer

exposure variable to examine the relationship between secondhand smoke and either incidence (Hole et al. 1989; Jee et al. 1999; Nishino et al. 2001) or mortality from lung cancer (Garfinkel 1981; Hirayama 1981; Butler 1988; Cardenas et al. 1997) among nonsmokers. All of the studies reported a higher risk among women whose husbands smoked than among women whose husbands did not smoke. The RR ranged from 1.18 to 2.02 among women whose husbands smoked. Two studies included data for men (Hirayama 1981; Cardenas et al. 1997), and one study found a higher risk of lung cancer among men married to women who smoked (Hirayama 1981). One nested case-control study using urinary cotinine as a marker of secondhand smoke exposure found that cotinine levels were associated with the risk of lung cancer among nonsmoking women (de Waard et al. 1995). Appendix 7.1 (at the end of this chapter) provides detailed information on the more recent cohort studies reviewed in this chapter on the association between exposure to secondhand smoke and lung cancer.

Case-Control Studies

More than 40 case-control studies have examined the relationship of exposure to secondhand smoke and lung cancer. The studies are almost equally divided between hospital-based and population-based. Methodologic differences across the studies include sources of the cases, types of controls, the use of surrogate respondents, the degree of pathologic confirmation of lung cancer diagnoses, and data collection, such as the assessment of secondhand smoke exposure and other relevant covariates. The first studies tended to be small and classified secondhand smoke exposures largely or solely on the basis of spousal smoking habits (Correa et al. 1983; Kabat and Wynder 1984; Wu et al. 1985; Brownson et al. 1987; Humble et al. 1987). Many larger studies have since been conducted in the United States (Brownson et al. 1992; Stockwell et al. 1992; Fontham et al. 1994) and elsewhere (Wu-Williams et al. 1990; Boffetta et al. 1998; Nyberg et al.

Table 7.3 Case-control studies by geographic area of exposure to secondhand smoke and the relative risks for lung cancer among lifetime nonsmokers

Study	Population/date of study	Cases/histologic confirmation and cell type (%)*	Controls	Data collection
		Canada		
Johnson et al. 2001	Women aged 20–74 years from 8 Canadian Tumor Registries Frequency was matched for age and province of residence Canada 1994–1997	161 100% histologic confirmation No cell type information	1,271 selected from insurance/ property assessment databases or by random-digit telephone dialing (RDD)	Mailed questionnaire Response rate Cases: 70% Controls: 70% Approximately all self-respondents
		Europe		
Jöckel et al. 1998	Men and women well enough to be interviewed from all hospitals in the study area Germany (Bremen, Frankfurt) 1988–1993	55 lifetime nonsmokers 100% histologic or cytologic confirmation	160 lifetime nonsmokers selected from population registries (general population)	In-person interview 100% self-respondents
Nyberg et al. 1998a	Men and women aged >30 years from 3 main local hospitals 2 controls per case Frequency matched for gender, age, and area of residence Sweden (Stockholm county) 1989–1995	124 (35 men, 89 women) 96% histologic confirmation Squamous cell carcinoma: 10% Small cell carcinoma: 2% Adenocarcinoma: 67%	235 (72 men, 163 women) selected from population register	In-person interview or by telephone Response rate Cases: 86% Controls: 83% 100% self-respondents
Zaridze et al. 1998	2 main cancer treatment hospitals Controls were from the same hospital as cases Russia (Local Moscow residents only)	189 women 100% histologic confirmation Squamous cell carcinoma: 22% Small cell carcinoma: 5% Adenocarcinoma: 56%	358 other cancer patients	In-person interview within 3 days of hospital admission Response rate was not reported 100% self-respondents

Findings	Measure of secondhand smoke	Relative risk (95% confidence interval)	Comments (covariates considered, definition of lifetime nonsmokers)
	Canada		
• Significant trend with smoker-years[†] of workplace and residential/workplace (i.e., total) secondhand smoke exposures	Any secondhand smoke exposure (childhood and adulthood): No Yes Total (smoker-years): None 1–36 37–77 ≥78	 1.0 1.63 (0.8–3.5) 1.0 0.83 (0.3–2.1) 1.54 (0.7–3.5) 1.82 (0.8–4.2)	Controlled for age (10-year age group), education, province, fruit and vegetable intake; these results were based on 71 cases and 761 controls who had a more complete secondhand smoke exposure history; lifetime nonsmokers had smoked <100 cigarettes per lifetime
	Europe		
• Risk increased with high secondhand smoke exposure during childhood and adulthood from spouse and other sources (all sources combined = total)	Secondhand smoke exposure from spouse: No Yes Total secondhand smoke exposure by intensity: None Medium High	 1.0 1.12 (0.54–2.32) 1.0 0.87 (0.36–2.07) 3.24 (1.44–7.32)	Controlled for gender, age, fruit and vegetable intake, and region; lifetime nonsmokers smoked regularly for <6 months (regular = 1 cigarette/day); intensity of the secondhand smoke exposure was based on hours and years of exposure and the degree of smokiness[‡]
• Significant trends of increasing risk with increasing years of workplace secondhand smoke exposure • Strongest association with recent secondhand smoke exposure	Men Spousal secondhand smoke: No Yes Workplace secondhand smoke: No Yes Women Spousal secondhand smoke: No Yes Workplace secondhand smoke: No Yes	 1.0 1.96 (0.72–5.36) 1.0 1.89 (0.53–6.67) 1.0 1.05 (0.60–1.86) 1.0 1.57 (0.80–3.06)	Controlled for age, gender, catchment area, occasional smoking, vegetable intake, degree of urban residence, and occupation; lifetime nonsmokers smoked <1 cigarette/day or <10 cigarettes/week and other equivalences for cigars, pipes, and cigarillos
• Increased risk with husband's smoking was stronger when restricted to controls with nonsmoking-related cancers • Stronger association with squamous cell cancers	Husband smoked: No Yes Workplace secondhand smoke: No Yes	 1.0 1.53 (1.06–2.21) 1.0 0.88 (0.55–1.41)	Controlled for age and education; lifetime nonsmokers were not defined; age of participants and the study period were not reported

Table 7.3 Continued

Study	Population/date of study	Cases/histologic confirmation and cell type (%)	Controls	Data collection
		Europe		
Kreuzer et al. 2000	Men and women aged <76 years from 15 clinics/ hospitals Area residents for at least 25 years Frequency matched for gender, age, region, and length of residence East/West Germany 1990–1996	292 (234 women, 58 men) 100% histologic confirmation Squamous cell carcinoma: 20% Adenocarcinoma: 59% (n = 173)	1,338 (535 women, 803 men) RDD and local residential registries	In-person interview within 3 months of diagnosis Response rate: Cases: 76% Controls: 41% 100% self-respondents
		Asia		
Du et al. 1996; Lei et al. 1996	Reviewed death certificates of local residents Matched for gender, age, year of death, and block of residence Guangzhou, China 1986	75 women No histologic confirmation or cell type information	128 women Excluded those with history of respiratory disease/tumors	In-person interview with next of kin Response rate was not reported No self-respondents
Shen et al. 1996, 1998	Hospital-based Local residents ≥20 years Matched for age, gender, neighborhood, and occupation Nanjing, China 1986–1993	70 women 100% histologic confirmation Included only adenocarcinoma	70 women General population	In-person interview Response rate was not reported 100% self-respondents
Wang et al. 1996; Zhou et al. 2000	18 hospitals Aged 35–69 years Matched for age and lifetime nonsmoking status Shenyang, China 1991–1995	135 women, 72 with adenocarcinoma Approximately 50% histologic confirmation Squamous cell carcinoma: 16% Small cell carcinoma: 20% Adenocarcinoma: 55%	135 women, 72 designated specifically for adenocarcinoma patients General population	In-person interview within 2 weeks of case diagnosis Response rate was not reported 100% self-respondents
Rapiti et al. 1999	1 hospital Men and women Excluded some diseases among hospital controls No matching Chandigarh, India 1991–1992	58 (17 men, 41 women) 100% histologic confirmation Squamous cell carcinoma: 28% Small cell carcinoma: 19% Adenocarcinoma: 51%	123 (56 men, 67 women) 2 sources: other hospital patients and visitors	In-person interview Response rate was not reported 100% self-respondents

Findings	Measure of secondhand smoke	Relative risk (95% confidence interval)	Comments (covariates considered, definition of lifetime nonsmokers)
	Europe		
• No significant association with any secondhand smoke exposure from spouse, work, or childhood • Increased risk with weighted duration of secondhand smoke exposures from all sources	Men and women Spouse smoked: No Yes Secondhand smoke from all sources with weighted duration: None Low Medium	 1.0 0.99 (0.73–1.34) 1.0 1.29 (0.79–2.09) 1.78 (1.05–3.04)	Controlled for gender, age, region, occupation, education, radon, family history, previous lung diseases, length of residence, and selected vegetable intake; lifetime nonsmokers had smoked <400 cigarettes/lifetime; secondhand smoke from all sources combined included exposures inside and outside the home (weighted duration = hours times smokiness)
	Asia		
• No significant increased risk was associated with husband's smoking by amount or duration	Husband smoked: No Yes	 1.0 1.19 (0.66–2.16)	Crude risk estimate; definition of lifetime nonsmokers was not reported; there were many limitations in the study methods
• No significant trend with amount and duration of secondhand smoke exposure at home	Daily household secondhand smoke exposure: No Yes	 1.0 1.63 (0.68–3.89)	Controlled for neighborhood, gender, age, and occupation; possible overmatching
• No significant trend with years/amount smoked by husband • Results in analyses restricted to adenocarcinoma were similar	Husband smoked: No Yes Workplace exposure: No Yes	 1.0 1.11 (0.65–1.88) 1.0 0.89 (0.45–1.77)	Crude risk estimates; histologic cell type classification is questionable
• No significant association with years of spousal smoking • Increased risk with secondhand smoke exposure during childhood	Husband smoked: No Yes	 1.0 1.1 (0.5–2.6)	Controlled for gender, age, religion, and residence; lifetime nonsmokers had smoked <400 cigarettes/lifetime

Table 7.3 Continued

Study	Population/date of study	Cases/histologic confirmation and cell type (%)*	Controls	Data collection
		Asia		
Zhong et al. 1999	Women aged 35–69 years Permanent residents of the area Frequency matched for age Shanghai, China Cancer Registry 1992–1994	504 Approximately 77% histologic confirmation Squamous cell carcinoma: 12.4% Small cell carcinoma: 2% Adenocarcinoma: 76.5%	601 General population	In-person interview at home, hospital, or work Response rate: Cases: 92% Controls: 84% Self-respondents: Cases: 80% Controls: 98%
Lee et al. 2000	1 hospital Women only Matched for age, lifetime nonsmoking status, date of admission Kaohsiung (Taiwan) 1992–1998	268 100% histologic confirmation Squamous cell carcinoma: 18% Small cell carcinoma: 11% Adenocarcinoma: 68%	445 hospital controls Eye or orthopedic patients, or in for check-ups	In-person interview Response rate: Cases: 91% Controls: 90% 100% self-respondents
Wang et al. 2000	Local hospitals and clinics Aged 30–75 years Frequency matched for age, gender, and prefecture of residence Gansu Province (China) 1994–1998	233 (33 men, 200 women) 30% histologic confirmation Cell type distribution was not reported	521 (114 men, 407 women) General population	In-person interview at home/hospital Response rate: Cases: 95% Controls: 90% Self-respondents: Cases: 46% Controls: 96%
Seow et al. 2002	3 major hospitals Aged <90 years (alert enough for interview) Frequency matched for age, hospital, and date of admission Singapore 1996–1998	176 women 100% histologic confirmation Squamous cell carcinoma: 10% Small cell carcinoma: 1.1% Adenocarcinoma: 72%	663 No history of cancer, heart or chronic respiratory disease, or renal failure	In-person interview within 3 months of diagnosis Response rate: Cases: 95% Controls: 97% 100% self-respondents

*Percentages do not add up to 100%.
†Smoker-years = The number of years of exposure weighted by the number of smokers.
‡Smokiness = Subjective index: (1) not visible but smellable, (2) visible, and (3) very smoky.

Findings	Measure of secondhand smoke	Relative risk (95% confidence interval)	Comments (covariates considered, definition of lifetime nonsmokers)
	Asia		
• Significant association between secondhand smoke exposure at work and risk when stratified by various intensity measures	Secondhand smoke at home: No Yes Workplace exposure: No Yes	 1.0 1.2 (0.8–1.7) 1.0 1.9 (0.9–3.7)	Controlled for age, income, vitamin C intake, respondent status, smokiness of kitchen, family history of lung cancer, and high-risk occupations; lifetime nonsmokers had smoked <1 cigarette/day for 6 months
• Significant associations between various sources of secondhand smoke exposure and risk (husband, work, and paternal smoking)	Husband smoked: No In wife's absence In wife's presence Lifetime exposure: None 1–20 smoker-years 21–40 smoker-years 41–60 smoker-years >60 smoker-years	 1.0 1.2 (0.7–2.0) 2.2 (1.5–3.3) 1.0 1.3 (0.6–2.6) 1.6 (0.9–2.6) 2.0 (1.2–3.5) 2.8 (1.6–4.8)	Controlled for area of residence, education, occupation, tuberculosis, cooking fuels, and fume extractor; lifetime nonsmokers had smoked <1 cigarette/day for 1 year or <365 cigarettes/lifetime
• No significant association with secondhand smoke exposure in adulthood • Significant association with secondhand smoke exposure in childhood	Secondhand smoke in adulthood: No Yes Secondhand smoke in childhood: No Yes Lifetime secondhand smoke: No Yes	 1.0 0.90 (0.6–1.4) 1.0 1.52 (1.1–2.2) 1.0 1.19 (0.7–2.0)	Controlled for age, social class, prefecture, and other potential confounders; lifetime nonsmokers smoked cigarettes or pipes regularly for ≤6 months
• Increased risk with any household secondhand smoke exposure	Any secondhand smoke: No Yes	 1.0 1.3 (0.9–1.8)	Controlled for age, birthplace, family history of cancer, soy intake, length of menstrual cycle; lifetime nonsmokers had smoked <1 cigarette/day for 1 year; there was a single question on secondhand smoke exposure

1998a; Zaridze et al. 1998; Zhong et al. 1999; Kreuzer et al. 2000; Lee et al. 2000; Wang et al. 2000; Seow et al. 2002) that expanded the assessment of the exposure to include smoking habits of other household members during childhood and adulthood, and exposure at work and in other social settings. Recent studies based largely on interviews with the index participants also attempted to determine intensity measures of exposure by assessing hours of exposure, the number of smokers, and whether the exposure occurred in the presence of the participants (Jöckel et al. 1998; Nyberg et al. 1998a; Kreuzer et al. 2000; Lee et al. 2000). These newer studies have demonstrated that under certain circumstances, investigators may be able to classify exposure at least semiquantitatively. Appendix 7.1 provides detailed information on the more recent case-control studies reviewed in this chapter on the association between exposure to secondhand smoke and lung cancer.

Summary of New Epidemiologic Studies on Lung Cancer and Secondhand Smoke Exposure

Between 1996 and 2001, 15 epidemiologic studies were published that further expand the evidence supporting a causal association between secondhand smoke exposure and the risk of lung cancer among lifetime nonsmokers. Recent cohort studies from Korea (Jee et al. 1999) and Japan (Nishino et al. 2001) have improved the assessment of secondhand smoke exposure by obtaining information on the husband's smoking on two occasions during medical examinations approximately two years apart (Jee et al. 1999), or by asking about smoking by other household members (Nishino et al. 2001). Potential confounders were considered in both studies and their results were very similar to those reported by Hirayama (1981). By design, five hospital-based European studies (Jöckel et al. 1998; Nyberg et al. 1998a; Zaridze et al. 1998; Kreuzer et al. 2000, 2001) and one study from Taiwan (Lee et al. 2000) restricted the study population to patients diagnosed with lung cancer who were well enough to participate in an in-person interview shortly after diagnosis. Thus, these investigators were able to obtain more information regarding the intensity of secondhand smoke exposure than was previously available in most population-based, case-control studies. The higher RR estimates in these studies are likely due to the incorporation of intensity measures of exposure that separated those who were highly exposed to secondhand smoke from those who were less highly exposed.

Six additional studies were conducted among Chinese persons who resided in China or other countries in Asia. Although some of these studies were small and the quality of the methods uncertain, three studies are large and well-designed. Conducted in Shanghai, China; Kaohsiung, Taiwan; and Gansu Province, China (Zhong et al. 1999; Lee et al. 2000; Wang et al. 2000), these larger studies showed that secondhand smoke exposures at home and at work during adulthood were associated with an increased risk of lung cancer among lifetime nonsmokers. This association remained consistent even in populations where other sources of indoor and outdoor air pollution were also prevalent. In addition to the questionnaire-based studies, de Waard and colleagues (1995) conducted a small nested case-control study that provided supportive evidence based on urinary cotinine for an association between secondhand smoke exposure and an increased risk of lung cancer among lifetime nonsmokers.

Pooled Analyses

Secondhand Smoke Exposure from Spouses: An Update of the Literature

Of the published meta-analyses on secondhand smoke and lung cancer, only two recent comprehensive meta-analyses are mentioned here, as their findings subsume those of earlier reports. Hackshaw and colleagues (1997) pooled 37 published studies and obtained an estimated RR of 1.24 (95 percent confidence interval [CI], 1.13–1.36) for nonsmokers who lived with a smoker. The results were remarkably consistent with analyses stratified by gender, geographic region, year of publication, and study design. Zhong and colleagues (2000) reached similar conclusions when they updated that same pooled analysis to include 40 published studies. They obtained a RR of 1.20 (95 percent CI, 1.12–1.29) for lung cancer risk among nonsmoking women with exposure to secondhand smoke from their husbands' smoking. The increased RR was observed for case-control and cohort studies and separately by gender, study location, year of publication, and other parameters.

The update of the pooled analyses that follows was prepared by reviewing published studies already included in the meta-analyses conducted by Hackshaw and colleagues (1997) and Zhong and

colleagues (2000), as well as the new studies discussed in the Appendix at the end of this chapter. Results of the meta-analyses were calculated with the method of DerSimonian and Laird (1986). Random-effects analyses were used to account for heterogeneity between studies. The statistical program Stata was used for the calculations. For studies that reported both crude (or minimally adjusted) and more adjusted RR estimates, the more adjusted risk estimate was selected for the meta-analysis. Table 7.4 provides the findings.

There are 52 studies in this analysis on spousal secondhand smoke exposure (8 cohort, 44 case-control studies). Those studies that lacked specific information on spousal smoking were not included (Svensson et al. 1989; Wang et al. 1994; de Waard et al. 1995; Seow et al. 2002). Three studies (Jöckel et al. 1998; Nyberg et al. 1998b; Kreuzer et al. 2000) that were part of the International Agency for Research on Cancer (IARC) European multicenter study (Boffetta et al. 1998) were also published as separate reports. The study by Jöckel and colleagues (1998) was not included because almost all of the lifetime nonsmokers in this report (71 of the 76 cases and 229 of the 236 controls) were already included in the IARC European multicenter study (Boffetta et al. 1998). However, because the study by Nyberg and colleagues (1998b) included an additional 54 cases and 123 controls and the study by Kreuzer and colleagues (2000) included an additional 119 cases and 1,123 controls who were not included in the European multicenter study, these two studies were included in the meta-analysis presented here.

When RR estimates from prospective cohort and case-control studies were combined, the RR of lung cancer among male and female nonsmokers who were ever exposed to secondhand smoke from their spouses was 1.21 (95 percent CI, 1.13–1.30). The RR estimates were 1.20 (95 percent CI, 1.11–1.29) from case-control studies and 1.29 (95 percent CI, 1.125–1.49) from cohort studies. The magnitude of the effect associated with spousal secondhand smoke exposure was comparable for men (odds ratio [OR] = 1.37 [95 percent CI, 1.05–1.79]) and women (OR = 1.22 [95 percent CI, 1.13–1.31]). There were no significant differences in the RR estimates by geographic area; the point estimate was 1.15 (95 percent CI, 1.04–1.26) for studies conducted in the United States and Canada, 1.16 (95 percent CI, 1.03–1.30) for studies conducted in Europe, and 1.43 (95 percent CI, 1.24–1.66) for studies conducted in Asia. The pooled RR estimates were 1.30 (95 percent CI, 1.13–1.50) for studies published between 1981 and 1986, 1.20 (95 percent CI, 1.05–1.38) for studies published between 1987 and 1994, and 1.20 (95 percent CI, 1.09–1.31) for studies published since 1994. Significantly increased risks were observed regardless of the sample size: the pooled RR estimate was 1.44 (95 percent CI, 1.16–1.78) for studies with 55 or fewer lung cancer cases, 1.25 (95 percent CI, 1.08–1.46) for studies with 56 to 99 cases, and 1.18 (95 percent CI, 1.08–1.29) for studies with 100 or more lung cancer cases.

Secondhand Smoke Exposure in the Workplace

In addition to the home, the workplace has been a location where significant exposure takes place (see Chapter 4, Prevalence of Exposure to Secondhand Smoke) (Jaakkola and Samet 1999). Large cross-sectional studies have consistently demonstrated the prevalence of secondhand smoke exposure in the workplace and in other settings outside the home (National Cancer Institute [NCI] 1999). In the Third National Health and Nutrition Examination Survey, which included a large representative sample of the U.S. population, nearly 40 percent of working people who were nontobacco users reported secondhand smoke exposure in the workplace (Pirkle et al. 1996). Reviews of indoor air nicotine and/or respirable suspended particulate concentrations in different microenvironments show that the levels were essentially comparable between work and residential environments in the United States and other countries. Secondhand smoke exposures in homes and workplaces were not only qualitatively similar in chemical composition but also in concentrations (Guerin et al. 1992; U.S. Environmental Protection Agency [USEPA] 1992; Hammond 1999).

A total of 25 epidemiologic studies (7 from the United States, 1 from Canada, 7 from Europe, and 10 from Asia) have provided information on workplace secondhand smoke exposure and the risk of lung cancer among lifetime nonsmokers (Table 7.5). The questions on workplace secondhand smoke exposure are heterogeneous among the studies (Wu 1999), and nine of the studies have assessed individual lifetime workplace secondhand smoke exposure. Almost all of the controls in these studies were self-respondents, so differences in exposure prevalences may reflect the heterogeneous questions that were asked, different workplace smoking policies, and/or different demographic characteristics of the controls, such as social class. Of the studies conducted in the United States and Canada, an estimated 38 to 66 percent of the controls reported any exposure at the workplace; the prevalence of exposure was similar for men and women (Kabat and Wynder 1984; Kabat et al. 1995). The prevalence of workplace secondhand

Table 7.4 Quantitative estimate of lung cancer risk with differing sources of exposure to secondhand smoke

Study	Data source	Exposure vs. referent	Relative risk	95% confidence interval
		Previous meta-analyses		
Hackshaw et al. 1997	37 studies	Smoking vs. nonsmoking spouse	1.24	1.13–1.36
Zhong et al. 2000	40 studies (including 37 from Hackshaw et al. 1997)	Smoking vs. nonsmoking husband	1.20	1.12–1.29
		Spousal smoking (52 studies)		
Meta-analysis conducted for this 2006 Surgeon General's report	Case-control (44 studies)	Smoking vs. nonsmoking spouse	1.21	1.13–1.30
	Cohort (8 studies)	Smoking vs. nonsmoking spouse	1.29	1.125–1.49
	Men	Smoking vs. nonsmoking wife	1.37	1.05–1.79
	Women	Smoking vs. nonsmoking husband	1.22	1.13–1.31
	United States and Canada	Smoking vs. nonsmoking spouse	1.15	1.04–1.26
	Europe	Smoking vs. nonsmoking spouse	1.16	1.03–1.30
	Asia	Smoking vs. nonsmoking spouse	1.43	1.24–1.66
		Workplace exposure (25 studies)		
Meta-analysis conducted for this 2006 Surgeon General's report	Nonsmokers (25 studies)	Workplace secondhand smoke vs. none	1.22	1.13–1.33
	Nonsmoking men (11 studies)	Workplace secondhand smoke vs. none	1.12	0.86–1.50
	Nonsmoking women (25 studies)	Workplace secondhand smoke vs. none	1.22	1.10–1.35
	Nonsmokers in the United States and Canada (8 studies)	Workplace secondhand smoke vs. none	1.24	1.03–1.49
	Nonsmokers in Europe (7 studies)	Workplace secondhand smoke vs. none	1.13	0.96–1.34
	Nonsmokers in Asia (10 studies)	Workplace secondhand smoke vs. none	1.32	1.13–1.55
		Childhood exposure (24 studies)		
Meta-analysis conducted for this 2006 Surgeon General's report	Men and women	Maternal smoking	1.15	0.86–1.52
	Men and women	Paternal smoking	1.10	0.89–1.36
	Men and women	Smoking by either parent	1.11	0.94–1.31
	Women	Maternal smoking	1.28	0.93–1.78
	Women	Paternal smoking	1.17	0.91–1.50
	United States and Canada (8 studies)	Smoking by either parent	0.93	0.81–1.07
	Europe (6 studies)	Smoking by either parent	0.81	0.71–0.92
	Asia (10 studies)	Smoking by either parent	1.59	1.18–2.15

Table 7.5 Relative risks for lung cancer associated with any workplace exposure to secondhand smoke among lifetime nonsmokers

Study	Population	Types of questions asked regarding workplace secondhand smoke exposure	Percentage with workplace secondhand smoke exposure		Relative risk (95% confidence interval)
			Cases	Controls	
		United States			
Kabat and Wynder 1984	Men Women U.S. cities	Exposure at current or last job	72 49	44 58	3.3 (1.0–10.4) 0.7 (0.3–1.5)
Garfinkel et al. 1985	Women New Jersey and Ohio	Exposure—past 5 years past 25 years	45	47	0.88 (0.7–1.2) 0.93 (0.7–1.2)
Wu et al. 1985	Women Los Angeles	Exposure at all jobs	55	50	1.3 (0.5–3.3)
Butler 1988	Men Women	Years worked with smokers	29 33	38 43	0.98 (0.2–5.4) 1.0 (0.2–5.4)
Brownson et al. 1992	Women Missouri	Exposure at current/last job	NR*	NR	0.98 (0.74–1.32)†
Kabat et al. 1995	Men Women 4 U.S. cities	Exposure at 4 jobs lasting >1 year	56 60	56 57	1.02 (0.50–2.09) 1.15 (0.62–2.13)
Reynolds et al. 1996	Women 5 U.S. cities	Exposure at all jobs	73	66	1.6 (1.2–2.0)
Schwartz et al. 1996	Men and women Detroit	Not specified	53	46	1.5 (1.0–2.2)
		Canada			
Johnson et al. 2001	Women	Exposure at all jobs	54	49	1.20 (0.74–1.95)‡
		Europe			
Lee et al. 1986	Men Women United Kingdom	Not specified	70 20	59 29	1.61 (0.39–6.6) 0.63 (0.17–2.33)
Kalandidi et al. 1990	Women Greece	Exposure at current/last job	73	66	1.39 (0.76–2.54)
Boffetta et al. 1998	Men Women 7 European countries	Exposure at all jobs	74 53	71 47	1.13 (0.68–1.86) 1.19 (0.94–1.51)
Nyberg et al. 1998a	Men Women Sweden	Exposure at all jobs	86 75	81 66	1.89 (0.53–6.67) 1.57 (0.80–3.06)
Zaridze et al. 1998	Women Russia	Exposure—past 20 years	19	19	0.88 (0.55–1.41)

Table 7.5 Continued

Study	Population	Types of questions asked regarding workplace secondhand smoke exposure	Percentage with workplace secondhand smoke exposure		Relative risk (95% confidence interval)
			Cases	Controls	
		Europe			
Boffetta et al. 1999	Men and women 7 European countries	Exposure at all jobs	55	54	1.0 (0.5–1.8)
Kreuzer et al. 2000, 2001	Men Women Germany	Exposure at all jobs	66 53	71 52	0.78 (0.44–1.38) 1.14 (0.83–1.57)
		Asia			
Koo et al. 1984	Women Hong Kong	Exposure at all jobs	NR	NR	1.19 (0.48–2.95)
Shimizu et al. 1988	Women Japan	Most recent/current job, any smokers at work	NR	NR	1.2 (0.7–2.04)
Wu-Williams et al. 1990	Women Northern China	Exposure at all jobs	55	50	1.2 (1.0–1.6)
Sun et al. 1996	Women Northern China	Not specified	NR	NR	1.38 (0.94–2.04)
Wang et al. 1996	Women Shenyang, China	Not specified	84	85	0.89 (0.45–1.77)
Rapiti et al. 1999	Men and women India	Not specified	NR	NR	1.1 (0.3–4.1)
Zhong et al. 1999	Women Shanghai, China	Exposure at each job held for ≥2 years	27	21	1.7 (1.3–2.3)
Lee et al. 2000	Women Taiwan	Exposure at each job held for ≥5 years	10	7	1.2 (0.5–2.4)
Wang et al. 2000	Men and women Gansu Province	Any workplace exposure	NR	NR	1.56 (0.7–3.3)
Zhou et al. 2000	Women Shenyang, China	Not specified	85	82	0.89 (0.25–3.16)

*NR = Data were not reported.
†Relative risk from calculations presented by Wells 1998 (Table 2).
‡Calculations based on the numbers presented in Table 2 of Johnson et al. 2001.

smoke exposure was more varied among controls in European countries: women in Moscow had the lowest prevalence (Zaridze et al. 1998) and Swedish men in Stockholm had the highest (Nyberg et al. 1998a). Similarly, there was a wide range of prevalences in workplace secondhand smoke exposure in Asia.

Despite these geographic differences in exposure prevalences, the effect of secondhand smoke exposure in the workplace on the risk of lung cancer among lifetime nonsmokers is remarkably consistent. On the basis of these 25 studies, the pooled RR estimate associated with reported workplace secondhand

smoke exposure was 1.22 (95 percent CI, 1.13–1.33) for all studies combined, 1.12 (95 percent CI, 0.86–1.50) for men, and 1.22 (95 percent CI, 1.10–1.35) for women. When the pooled analysis was conducted separately by geographic area, the pooled RR estimate was 1.24 (95 percent CI, 1.03–1.49) for the United States and Canada, 1.13 (95 percent CI, 0.96–1.34) for European countries, and 1.32 (95 percent CI, 1.13–1.55) for Asia.

Studies have also assessed dose-response relationships between secondhand smoke exposure in the workplace and lung cancer risk among lifetime nonsmokers (Table 7.6). At least six studies have reported RR estimates stratified by years of exposure (Fontham et al. 1994; Boffetta et al. 1998; Nyberg et al. 1998a; Zhong et al. 1999; Wang et al. 2000; Johnson et al. 2001), and these studies concur that there is a trend of an increase in risk with an increased duration of exposure. In addition, studies that used a combined index incorporating years and intensity of exposure, such as the number of hours of exposure and the number of smokers in the work environment (Boffetta et al. 1998; Nyberg et al. 1998a; Zhong et al. 1999; Kreuzer et al. 2000; Johnson et al. 2001), found up to a threefold increase in risk associated with the highest intensity levels of workplace exposure (Table 7.6).

Secondhand Smoke Exposure During Childhood

At least 24 epidemiologic studies have investigated secondhand smoke exposure during childhood (Table 7.7). The prevalence of secondhand smoke exposure during childhood varied and depended on whether the source of the exposure was from mothers, fathers, both parents, other household members, or a combined index that incorporated all sources of exposure. Although some studies found suggestions of a significantly increased risk of lung cancer in association with childhood exposures (Janerich et al. 1990; Sun et al. 1996; Rapiti et al. 1999; Wang et al. 2000), most studies did not find significant associations. When a pooled RR estimate in association with maternal and paternal smoking was calculated, in addition to a calculated combined index that represented childhood exposure from either parent, there was some increase in risk in association with secondhand smoke exposure to maternal smoking (OR = 1.15 [95 percent CI, 0.86–1.52]), paternal smoking (OR = 1.10 [95 percent CI, 0.89–1.36]), or smoking by either parent (OR = 1.11 [95 percent CI, 0.94–1.31]). The risk pattern was slightly stronger in analyses restricted to women (maternal smoking OR = 1.28 [95 percent CI, 0.93–1.78]; paternal smoking OR = 1.17 [95 percent CI, 0.91–1.50]). The pooled RR estimate associated with childhood secondhand smoke exposure was 0.93 (95 percent CI, 0.81–1.07) for studies conducted in the United States, 0.81 (95 percent CI, 0.71–0.92) for studies conducted in European countries, and 1.59 (95 percent CI, 1.18–2.15) for studies conducted in Asian countries.

There are several alternative explanations for the generally weaker association between childhood exposures and lung cancer risk compared with exposure during adulthood. Nyberg and colleagues (1998a) found that recent secondhand smoke exposures had the greatest impact on overall lung cancer risk among lifetime nonsmoking adults. If more recent exposures convey a greater risk, then remote childhood exposures would be anticipated to have little effect. In addition, assessments of childhood exposure may also have higher rates of misclassification than assessments of exposure during adulthood. In some studies, interviews with next of kin were conducted when the case patient was ill or deceased (Janerich et al. 1990; Brownson et al. 1992; Stockwell et al. 1992; Fontham et al. 1994; Wang et al. 2000). Next of kin, particularly spouses, who may not be knowledgeable about childhood events and exposures could provide incomplete and/or misclassified exposure histories. But most of these studies included few or no interviews with next of kin among the controls. Thus, differential misclassification of secondhand smoke exposures during childhood may have occurred in some studies.

Evidence Synthesis

Twenty years after secondhand smoke was first classified as a cause of lung cancer in lifetime nonsmokers, the evidence supporting causation continues to mount (USDHHS 1986). More than 50 epidemiologic studies have addressed the association between secondhand smoke exposure and the risk of lung cancer among lifetime nonsmokers. These studies included men and women of diverse racial and ethnic backgrounds and were conducted using heterogeneous study designs in some 20 countries of North America, Europe, and Asia. An increased risk of lung cancer associated with secondhand smoke exposure was found in most of the studies, with few exceptions (Chan et al. 1982; Buffler et al. 1984; Kabat and Wynder 1984; Lee et al. 1986; Wu-Williams et al. 1990; Liu et al. 1991; Brownson et al. 1992; Wang et al. 1996). A consistent association obtained in different populations under diverse circumstances strengthens a causal interpretation because different patterns of potential bias and confounding would be expected across different populations. Not surprisingly,

Table 7.6 Dose-response relationships between workplace secondhand smoke exposure and lung cancer risk among lifetime nonsmokers

	Exposure level		Weighted exposure level	
Study/gender	**Duration**	**Relative risk (95% confidence interval)**	**Intensity**	**Relative risk (95% confidence interval)**
Fontham et al. 1994	In years:		NR*	NR
Women	None	1.0		
	1–15	1.30 (1.01–1.67)		
	16–30	1.40 (1.04–1.88)		
	≥31	1.86 (1.24–2.78)		
	p for trend	0.001		
Boffetta et al. 1998	In years:		Level × hours/day	
Men and women	None	1.0	× years:	
	1–29	1.15 (0.91–1.44)	None	1.0
	30–38	1.26 (0.85–1.85)	0.1–46.1	0.97 (0.76–1.25)
	≥39	1.19 (0.77–1.86)	46.2–88.9	1.41 (0.93–2.12)
	p for trend	0.21	≥89	2.07 (1.33–3.21)
			p for trend	<0.01
Nyberg et al. 1998a	In years:		Hour-years‡:	
Men and women	None	1.0	None	1.0
	<30	1.40 (0.76–2.56)	<30	1.27 (0.69–2.34)
	≥30	2.21 (1.08–4.52)	≥30	2.51 (1.28–4.93)
	p for trend†	0.03	p for trend†	0.01
Zhong et al. 1999	In years:		Number of hours per	
Women	None	1.0	day:	
	1–12	2.0 (1.2–3.3)	None	1.0
	13–24	1.4 (0.9–2.3)	1–2	1.0 (0.6–1.7)
	>24	1.8 (1.1–2.8)	3–4	1.6 (1.0–2.5)
	p for trend	0.50	>4	2.9 (1.8–4.7)
			p for trend	<0.001
Kreuzer et al. 2000	In hours:		Hours times smokiness§	
Men and women	0–29,000	1.0	level:	
	>29,000–61,000	1.57 (0.97–2.54)	0–56,200	1.0
	>61,000	1.36 (0.71–2.61)	>56,200–100,600	1.09 (0.55–2.19)
	p for trend	0.10	>100,600	1.93 (1.04–3.58)
			p for trend	0.06
Wang et al. 2000	In years:		NR	NR
Men and women	None	1.0		
	<20	1.29 (0.5–3.3)		
	≥20	1.76 (0.5–5.6)		
	p for trend	0.19		
Johnson et al. 2001	In years:		Smoker-years¶:	
Women	None	1.0	None	1.0
	Residential only:	1.21 (0.5–2.8)	Residential only:	1.21 (0.5–2.8)
	1–7	1.24 (0.5–3.3)	1–25	1.16 (0.4–3.1)
	8–19	1.71 (0.7–4.3)	26–64	1.98 (0.8–4.9)
	≥20	1.71 (0.7–4.3)	≥65	1.58 (0.6–4.0)
	p for trend	NSΔ	p for trend	NS

*NR = Data were not reported.
†Calculations are based on the data presented.
‡Hour-years = 365 hours or the equivalent of 1 hour per day per year.
§Smokiness = Subjective index: (1) not visible but smellable, (2) visible, and (3) very smoky.
ΔNS = Not statistically significant.
¶Smoker-years = The number of years of exposure weighted by the number of smokers.

Table 7.7 Relative risks for lung cancer associated with exposure to secondhand smoke during childhood among lifetime nonsmokers

Study	Population	Childhood secondhand smoke exposure	Percentage with childhood secondhand smoke exposure		Relative risk (95% confidence interval) with any exposure from a family member
			Cases	Controls	
		United States			
Garfinkel et al. 1985	Women 4 U.S. hospitals	Any childhood exposure	NR*	NR	0.91 (0.74–1.12)
Wu et al. 1985	Women Los Angeles	Parents	40	53	0.6 (0.2–1.7)
Janerich et al. 1990	Men and women New York	Any childhood exposure†	70	54	1.3 (0.85–1.99)
Brownson et al. 1992	Women Missouri	Parents Other household members	17 25	25 31	0.7 (0.5–0.9) 0.8 (0.6–1.1)
Stockwell et al. 1992	Women Central Florida	Mother‡ Father Siblings	NR NR NR	NR NR NR	1.6 (0.6–4.3) 1.2 (0.6–2.3) 1.7 (0.8–3.9)
Fontham et al. 1994	Women 5 U.S. cities	Father Mother Other household members Any household member during childhood	50 12 21 62	55 13 21 65	0.83 (0.67–1.02) 0.86 (0.62–1.18) 1.03 (0.80–1.32) 0.89 (0.72–1.10)
Kabat et al. 1995	Men Women 4 U.S. cities	Any childhood exposure	62 68	65 57	0.90 (0.43–1.89) 1.55 (0.95–2.79)
		Canada			
Johnson et al. 2001	Women National cancer registry	Any childhood exposure	83	78	1.39 (0.8–2.2)
		Europe			
Pershagen et al. 1987	Women Sweden	1 or both parents smoked	19	NR	1.0 (0.4–2.3)
Svensson et al. 1989	Women Sweden	Father Mother	12 3	71 5	0.9 (0.4–2.3) 3.3 (0.5–18.8)
Boffetta et al. 1998	Men and women 7 European countries	Father Mother Any childhood exposure	NR NR 60	NR NR 66	0.76 (0.61–0.94) 0.92 (0.57–1.49) 0.78 (0.64–0.96)
Nyberg et al. 1998a	Men	Father Mother	69 40	52 21	1.90 (0.69–5.23) 0.90 (0.14–6.00)
	Women Sweden	Father Mother	46 8	49 15	0.76 (0.42–1.37) 0.29 (0.07–1.14)

Table 7.7 Continued

Study	Population	Childhood secondhand smoke exposure	Percentage with childhood secondhand smoke exposure		Relative risk (95% confidence interval) with any exposure from a family member
			Cases	Controls	
		Europe			
Zaridze et al. 1998	Women Russia	Father (assumed during childhood)	49	50	0.92 (0.64–1.32)
Kreuzer et al. 2000	Men and women Germany	Any exposure	62	64	0.84 (0.63–1.11)
		Asia			
Koo et al. 1987	Women Hong Kong	During childhood	NR	NR	2.07 (0.51–95.17)
Shimizu et al. 1988	Women Japan	Father Mother Brothers or sisters	NR NR NR	41 3 32	1.1 ($p > 0.05$) 4.0 ($p < 0.05$) 0.8 ($p > 0.05$)
Sobue 1990	Women Japan	Father Mother Other household member	76 12 22	80 9 16	0.79 (0.52–1.21) 1.33 (0.74–2.37) 1.18 (0.76–1.84)
Wu-Williams et al. 1990	Women Northern China	Father Mother	44 29	42 32	1.1 (0.8–1.4) 0.9 (0.6–1.1)
Sun et al. 1996	Women Northern China	Father Mother	NR NR	NR NR	2.4 (1.6–3.5) 2.1 (1.3–3.3)
Wang et al. 1996	Women Shenyang (China)	During childhood	59	61	0.91 (0.55–1.49)
Rapiti et al. 1999	Women India	Father Mother	73 31	18 6	12.6 (4.9–32.7) 7.7 (1.6–37.2)
Zhong et al. 1999	Women Shanghai (China)	During childhood	34	36	0.9 (0.5–1.6)
Lee et al. 2000	Women Taiwan	Father Mother	49 3	45 2	1.2 (0.9–1.6) 1.5 (0.6–3.9)
Wang et al. 2000	Men Women Gansu (China) (nonindustrial)	During childhood	63 67	49 61	1.46 (0.6–3.7) 1.51 (1.0–2.2)

*NR = Data were not reported.
†The respective relative risks were 1.0, 1.1, and 2.1 associated with 0, 1–24, and ≥25 smoker-years, in childhood and adolescence. (Smoker-years = The number of years of exposure weighted by the number of smokers.)
‡The respective relative risks were 1.0, 1.6, 1.1, and 2.4 associated with 0, <18, 18–21, and >21 years, in childhood and adolescence.

associations did not reach statistical significance in all studies because of variations in the sample sizes; some had modest sample sizes with low statistical power. The pooled analyses of earlier reports (Hackshaw et al. 1997; Zhong et al. 2000) and of this report document a 20 to 30 percent increase in RR of lung cancer in association with secondhand smoke exposures during adulthood; the effects are comparable in cohort and case-control studies, among men and women, in different geographic areas, by year of publication, and by study population size (Table 7.4). In addition, the pooled analyses showed comparable increases in risk in association with secondhand smoke exposures from spousal smoking and from smoking in the workplace, thus emphasizing that all sources of exposure increase the risk for lung cancer. Most of the studies published during the 1990s were designed to address weaknesses that previous studies on secondhand smoke and lung cancer were criticized for, including small sample size, possible selection bias, possible misclassification biases, and inadequate adjustments for potential confounders. With the improved designs, therefore, bias becomes an unlikely explanation for the observed increase in risk.

There is strong biologic support for a role of secondhand smoke in the etiology of lung cancer in nonsmokers, and the association is coherent based on the total weight of the evidence (see "Human Carcinogen Uptake from Secondhand Smoke" in Chapter 2). Exposure to secondhand smoke has been repetitively linked to elevation of biomarker levels in nonsmokers, including the tobacco-specific biomarkers nicotine, cotinine, and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), and nonspecific biomarkers such as white blood cell adducts. As reviewed in Chapter 2, mechanistic understanding related to tobacco smoke and lung cancer has advanced greatly since the 1986 report of the Surgeon General. The development of a cancer is considered to result from multiple genetic changes, and exposure to secondhand smoke involves exposure to the same carcinogens that are linked to genetic changes in active smokers. The genetic basis of susceptibility to these carcinogens is an active area of investigation.

The risk associated with involuntary smoking is consistent with the dose-response relationship observed with active smoking and lung cancer. Hackshaw and colleagues (1997) demonstrated that the risk estimate obtained directly from a meta-analysis of epidemiologic studies was compatible with the risk estimate calculated indirectly from a linear extrapolation of risk among active current smokers. This concept is considered to have limitations (USDHHS 1986). Lubin's (1999) calculations led to a similar conclusion. Thus, the strength of the secondhand smoke and lung cancer association is consistent with current knowledge of dosimetry and exposure-response relationships among active smokers. Studies of active smoking and lung cancer risk have consistently demonstrated compelling exposure-response relationships (Blot and Fraumeni 1986). As already discussed (see "Secondhand Smoke Exposure in the Workplace" earlier in this chapter), investigators have demonstrated exposure-response relationships with various aspects of secondhand smoke exposure, including duration (e.g., years of spousal smoking and years of exposure at work) and intensity (e.g., number of cigarettes smoked by spouse, number of coworkers who smoked, or hours of exposure per day) (Hackshaw et al. 1997; Zhong et al. 2000). Most of the studies that reported results separately on secondhand smoke and different lung cancer histologic types show a stronger increase in the risk of squamous cell and small cell carcinomas than in the risk of adenocarcinoma. These findings are compatible with the pattern of association found in active smoking and lung cancer by histologic type (Boffetta et al. 1999; Zhong et al. 2000).

The criterion of temporality requires that secondhand smoke exposure antedate the onset of cancer. Support for this criterion is provided by prospective studies in which men and women initially free of lung cancer were followed over varying time intervals, and their risk differed in accordance with a secondhand smoke exposure that was either self-reported (e.g., spousal smoking history) or determined by a biologic marker of exposure (e.g., urinary cotinine levels) (de Waard et al. 1995).

Despite the extent of the evidence and its consistency, coherence, and temporality, the causal association between secondhand smoke exposure and lung cancer risk has been continuously questioned because of concerns related to various biases (see "Use of Meta-Analysis" in Chapter 1). Much of the criticism has come from the tobacco industry around the association of secondhand smoke with lung cancer (Drope and Chapman 2001; Muggli et al. 2001). Public health researchers recognize the difficulties inherent in studying exposures such as secondhand smoke, where the RR associated with the exposure is anticipated to be small and the exposure is common. Two comprehensive commentaries on this topic reviewed four primary concerns related to studies of secondhand smoke and lung cancer: confounding, measurement error, misclassification, and publication bias (Kawachi and Colditz 1996; Smith and Phillips 1996), and several reports have addressed publication

bias specifically (Bero et al. 1994; Misakian and Bero 1998). These investigators independently concluded that the observed increase in risk of lung cancer associated with secondhand smoke exposure cannot be "explained" by these inherent methodologic limitations.

One concern raised has been that secondhand smoke itself may not be causally related to lung cancer, but that the association reflects confounding by factors that are causally linked to lung cancer. In cross-sectional studies of nonsmoking women, some investigators observed a higher risk profile for potential confounding factors such as a higher alcohol intake, a lower intake of vitamin supplements and dietary sources of various antioxidants, and a higher body mass index among women exposed to secondhand smoke compared with unexposed women (Koo et al. 1987; Matanoski et al. 1995; Kawachi and Colditz 1996). Other investigators, however, have not found these differences (Cardenas et al. 1997; Steenland et al. 1998; Curtin et al. 1999; Forastiere et al. 2000), and the relevance of these studies that investigated current patterns of association of possible confounders with secondhand smoke exposure to patterns from previous decades is uncertain. More important, unlike studies of heart disease where numerous risk factors have been identified, there are few true potential confounders for studies of secondhand smoke and lung cancer (Kawachi and Colditz 1996). Although many of the earlier studies of secondhand smoke and lung cancer did not consider lifestyle variables such as diet in the statistical analysis, most of the larger studies published since the 1990s have accounted for these factors and have found that the effect of secondhand smoke remained after adjusting for them (Stockwell et al. 1992; Fontham et al. 1994; Cardenas et al. 1997; Boffetta et al. 1998; Jöckel et al. 1998; Nyberg et al. 1998a; Zhong et al. 1999; Kreuzer et al. 2000; Lee et al. 2000; Wang et al. 2000; Seow et al. 2002). Finally, in a comprehensive investigation of the possible confounding effect of dietary factors (intake of fruits, vegetables, and dietary fat) that included data from nearly 20 studies on this topic, Fry and Lee (2001) concluded that the pooled RR for secondhand smoke exposure and lung cancer was negligibly altered after allowing for these potential dietary confounders.

In analyses of workplace secondhand smoke exposures, occupational exposures to other carcinogens may also confound this association. However, Zhong and colleagues (1999) documented that the strong association between workplace secondhand smoke exposure and lung cancer risk remained even after making additional adjustments for other occupational exposures. The comparable effects of secondhand smoke exposure from spouses and from the workplace on risk also argue against uncontrolled potential confounding as an explanation for the observed association, because the same set of confounders is unlikely to be operative for both exposure settings.

Because secondhand smoke exposure is ubiquitous, some investigators have expressed concern that exposure measurement error (or misclassification) affects estimates, particularly in studies that do not ascertain exposures outside the home. In fact, ideally, the exposure assessment would cover all environments where exposures occur so the total exposure could be estimated. Although a questionnaire remains the only feasible method for assessing these long-term exposures, some investigators have made concerted international efforts to validate and test the reliability of other instruments (Riboli et al. 1990). For example, many of the questions and approaches used in the IARC collaborative study have been adopted, modified, and used in subsequent case-control studies on secondhand smoke and lung cancer (Riboli et al. 1990). Almost all of the studies reviewed (see "Cohort Studies" earlier in this chapter), and other studies published since the 1990s, have included a comprehensive assessment of all sources of secondhand smoke exposure during childhood and adulthood. Of the more than 20 studies investigating secondhand smoke and lung cancer that included assessments of exposures at work and in social settings, most found an increased risk of lung cancer comparable to the risk associated with spousal smoking (NCI 1999; USDHHS 2001). Thus, the total risk of exposure was likely underestimated in studies that investigated only spousal smoking or single sources of exposures. The increased risk of lung cancer in relation to increased urinary cotinine levels among nonsmokers was documented in a Dutch cohort study (de Waard et al. 1995). Using a biomarker to classify past exposure, the investigators confirmed that secondhand smoke exposure is causally related to lung cancer risk among nonsmokers. Interestingly, results from this single study suggest a twofold increased risk of lung cancer among nonsmokers associated with an objective marker of exposure. The lower risk estimate associated with secondhand smoke exposure in questionnaire-based, case-control studies may be attributable to a misclassification of exposures from self-reports, although a single cotinine measurement is an imprecise measure of exposure. Overall, random misclassification of

exposure in a particular environment or of an overall estimate would tend to bias estimates of risk from the true value toward the null.

A second type of misclassification error, frequently cited by tobacco industry-funded experts (Lee 1992), is potential misclassification from the claim by some current or former smokers that they are lifetime nonsmokers and that the observed increase in risk from involuntary smoking is really attributable to their former (or current) smoking. This potential bias has been repeatedly considered and found not to explain the association of lung cancer with secondhand smoke (Wu 1999). Recent studies have confirmed that the proportion of former smokers who classify themselves as lifetime nonsmokers is low (Nyberg et al. 1997). Several investigators have also demonstrated that the proportion of nonsmokers misclassified as those who had ever smoked (based on cotinine measurements) is low (Riboli et al. 1990; Wu 1999). In the only case-control study of secondhand smoke and lung cancer among reported lifetime nonsmokers that also determined urinary cotinine levels as a marker of recent exposure to tobacco smoke, 0.6 percent of cases and 2.3 percent of controls were considered to be misclassified as lifetime nonsmokers because their urinary cotinine levels exceeded the designated limit for involuntary smoking only (Fontham et al. 1994). Nyberg and colleagues (1998a) also showed that the risk of lung cancer among misclassified smokers was low. These findings are consistent with the conclusion of the NRC that smoker misclassification cannot explain the secondhand smoke effect on lung cancer risk among lifetime nonsmokers (NRC 1986). The EPA reached a similar conclusion in its risk assessment analysis (USEPA 1992).

Publication bias, or the failure to publish findings construed as "negative" or that are not statistically significant, has also been raised as a concern. For example, if the apparent association between secondhand smoke and lung cancer reflects the failure of investigators to publish negative findings from studies that do not find an increased risk associated with secondhand smoke, the omission of such unpublished findings can skew the conclusions of meta-analyses (Copas and Shi 2000). Vandenbroucke (1988) conducted a formal statistical analysis and found no evidence of a selective publication bias. Woodward and McMichael (1991) searched for unpublished data on secondhand smoke by contacting the tobacco industry and investigators listed in the *Directory of Ongoing Research in Cancer Epidemiology* and found few unpublished studies on secondhand smoke. Other investigators who reached similar conclusions reported a publication delay for studies with nonsignificant results, but with no evidence of a publication bias in the peer-reviewed literature (Bero et al. 1994; Misakian and Bero 1998). Copas and Shi (2000) again raised the question of publication bias in their analysis. They estimated that allowing for a publication bias could reduce a pooled RR of 1.25 associated with exposure to secondhand smoke and lung cancer to 1.15. However, this calculation assumes that 40 percent of all studies on lung cancer have not been published. As already mentioned, because unpublished studies have yet to be identified, this assumption is inappropriate.

This report, published 20 years after the 1986 report, again concludes that involuntary smoking causes lung cancer in lifetime nonsmokers. The evidence was judged sufficient in 1986, and there is even greater certainty now, reflecting the substantial new research published since 1986 that has reduced uncertainties related to mechanistic considerations and to methodologic issues in the epidemiologic studies. The body of epidemiologic research now includes a number of large studies that were designed specifically to limit misclassification and confounding. The estimated risk for lung cancer associated with involuntary smoking has changed little as new evidence has become available.

Conclusions

1. The evidence is sufficient to infer a causal relationship between secondhand smoke exposure and lung cancer among lifetime nonsmokers. This conclusion extends to all secondhand smoke exposure, regardless of location.

2. The pooled evidence indicates a 20 to 30 percent increase in the risk of lung cancer from secondhand smoke exposure associated with living with a smoker.

Implications

Eliminating or reducing secondhand smoke exposure at home, in the workplace, and in other public settings will reduce the risk of lung cancer among lifetime nonsmokers.

Other Cancer Sites

Active smoking is firmly established as a causal factor of cancer for a large number of sites including lung, urinary tract, upper aerodigestive tract, liver, stomach, pancreas, and many others (USDHHS 2004; Vineis et al. 2004). The absence of a threshold for carcinogenesis in active smoking (i.e., a level of smoking that does not increase the risk of cancer), the presence of the same carcinogens in mainstream and sidestream smoke, and the demonstrated uptake of tobacco smoke constituents by involuntary smokers are compelling arguments for the hypothesis that secondhand smoke would increase the risk of cancer in other smoking-related sites in nonsmokers. The role of secondhand smoke in the risk of cancers among nonsmokers has been investigated mainly for lung cancer, with considerably less data on other cancer sites. However, for some sites the evidence is now sufficient to warrant review and evaluation. The discussion that follows reviews studies on involuntary smoking and three adult cancers for which the evidence are most abundant: breast cancer, cervical cancer, and nasal sinus/nasopharyngeal cancer. The chapter covers all investigations of secondhand smoke in relation to breast cancer, a site that was also addressed in the 2001 report (USDHHS 2001).

Breast Cancer

The role of tobacco smoke in the etiology of breast cancer has been investigated in numerous epidemiologic studies since the 1960s (USDHHS 2001). Studies have addressed the risk of active smoking in current and former smokers and the risk of involuntary smoking in lifetime nonsmokers. Several recent reports have considered the evidence on active and involuntary smoking and breast cancer risk (USDHHS 2001, 2004; Cal/EPA 2005).

There is substantial evidence that active smoking is not associated with an increased risk of breast cancer in studies that compare active smokers with persons who have never smoked (Hamajima et al. 2002). In a pooled analysis of data from 53 studies, the RR for women who were current smokers versus lifetime nonsmokers was 0.99 (95 percent CI, 0.92–1.05) for 22,255 cases and 40,832 controls who reported not drinking alcohol. The effect of smoking did not vary by menopausal status.

In spite of this overall null finding, active smoking could be involved in breast cancer risk. Active smoking may have effects on breast cancer development that tend to increase and decrease risk; tissues of smokers are exposed to carcinogens but smoking has antiestrogenic effects (USDHHS 2004). Carcinogens in tobacco smoke, such as 3-4 benzo[*a*]pyrene, and their metabolites are distributed systemically, and many known tobacco carcinogens, including heterocyclic aromatic amines, polycyclic aromatic hydrocarbons, and arylamines, are also mammary mutagens and carcinogens (Nagao et al. 1994; Dunnick et al. 1995; El-Bayoumy et al. 1995). Convincing data document that constituents of cigarette smoke reach tissues outside of the respiratory system, including the breast. For example, mutagens from cigarette smoke have been found in nipple aspirates of nonlactating female smokers, and nicotine levels in breast fluid tend to increase with the daily amount smoked (Petrakis et al. 1978, 1988). Aromatic DNA adducts that are characteristic of tobacco smoke exposure have been found in normal breast tissues of breast cancer patients but not in healthy women without cancer (Li et al. 1996).

However, tobacco smoking also has antiestrogenic consequences; it is consistently associated with an earlier age at menopause and a lower risk of endometrial cancer (USDHHS 2001, 2004). Smokers have lower urinary estrogen levels (MacMahon et al. 1982) and increased estradiol 2-hydroxylation, resulting in less urinary excretion of estriol relative to estrone in smokers compared with nonsmokers (Michnovicz et al. 1986). However, uncertainty remains concerning the influence of tobacco smoke on blood estrogen levels, and the evidence is not consistent (Key et al. 1991, 1996; Terry and Rohan 2002). Nonetheless, the information on smoking and hormones has led to the hypothesis that the antiestrogenic effects of active smoking, but not of involuntary smoking, may obscure an increase in breast cancer risk that would otherwise result from the carcinognens in tobacco smoke. Thus, researchers have hypothesized that the dual carcinogenic and antiestrogenic effects of tobacco smoking may counteract and potentially balance influences on breast cancer risk (Palmer and Rosenberg 1993).

When considering the biologic plausibility of a causal association of secondhand smoke exposure with breast cancer, the evidence on active smoking is

critical. The absence of an established and consistent relationship between active smoking and breast cancer in epidemiologic studies weakens the biologic plausibility of a possible causal association of involuntary smoking with breast cancer. Other conditions caused by secondhand smoke exposure, such as lung cancer and coronary heart disease (CHD), are strongly and causally related to active smoking. Evidence on the association between active smoking and breast cancer risk was reviewed thoroughly in the Surgeon General's reports of 2001 and 2004 (USDHHS 2001, 2004). The reports addressed both the biologic basis for a possible association and the findings of epidemiologic studies. These reviews considered large, well-designed studies published in the 1990s that investigated risk patterns among various meaningful subgroups and carefully considered the role of potential confounders. These reports concluded that the weight of epidemiologic evidence strongly suggests that active smoking is not causally related to breast cancer risk. A similar conclusion was reached by IARC in its 2004 monograph on smoking (IARC 2004). Possibly, the dose-response relationship for tobacco smoke and breast cancer might be complex and nonlinear, such that the doses associated with secondhand smoke cause breast cancer and the far greater doses from active smoking do not. There is neither mechanistic nor empiric evidence supporting this possibility.

The absence of a net increase in breast cancer risk among active, female smokers does not exclude the possibility that certain subgroups of women may be at an increased risk because of genetic or other factors. However, such groups have yet to be consistently identified (USDHHS 2004). Studies continue on active smoking and breast cancer risk. There are recent reports of elevated RRs in smokers in some recent studies, notably in two large prospective cohort studies. In the Nurses Health Study II (NHS-II) cohort of young women (aged 25 through 42 years at the time of enrollment), there was an association between 20 or more years of active smoking and a significant 21 percent increase in risk (Al-Delaimy et al. 2004). In the California Teachers Study, current smokers showed a statistically significant increase in risk of 30 percent compared with lifetime nonsmokers (Reynolds et al. 2004). Nonetheless, sufficient evidence has not accumulated since 2004 to suggest that the conclusions of the Surgeon General's report and the IARC monograph should be revised, and the possibility of selective reporting of positive associations for active smoking needs to be considered when interpreting these recent reports.

Since the 1980s, studies have also examined the relationship between secondhand smoke exposure and breast cancer risk. One of the first reports was based on Hirayama's (1984) cohort study in Japan—the same cohort that provided evidence on involuntary smoking and lung cancer. Horton (1988) hypothesized a role for secondhand smoke in the etiology of breast cancer on the basis that countries with high male mortality rates of lung cancer generally had high rates of breast cancer, and countries with low rates of lung cancer had low rates of breast cancer. Another ecologic study that investigated the relationship between female breast cancer and male lung cancer in five countries found little support for this hypothesis (Williams and Lloyd 1989). Substantial data from cohort and case-control studies that directly address the hypothesis have now been published. Seven prospective cohort studies (Hirayama 1984; Jee et al. 1999; Wartenberg et al. 2000; Nishino et al. 2001; Egan et al. 2002; Reynolds et al. 2004; Hanaoka et al. 2005) and 14 case-control studies (Sandler et al. 1985a,b; Smith et al. 1994; Morabia et al. 1996, 2000; Millikan et al. 1998; Lash and Aschengrau 1999, 2002; Zhao et al. 1999; Delfino et al. 2000; Johnson et al. 2000; Liu et al. 2000; Kropp and Chang-Claude 2002; Gammon et al. 2004; Shrubsole et al. 2004; Bonner 2005) offer information on secondhand smoke and breast cancer. Several reports described findings using different measures of secondhand smoke exposure and breast cancer risk (Hirayama 1984; Wells 1991; Sandler et al. 1985a,b; Morabia et al. 1996, 2000; Millikan et al. 1998; Marcus et al. 2000). As for secondhand smoke and lung cancer, studies of breast cancer should include a comprehensive assessment of lifetime secondhand smoke exposure and adequate controls for potential confounders. However, the approaches to exposure assessment vary among the studies, and consideration of confounding has also been variable.

Several reports have evaluated the evidence on secondhand smoke exposure and breast cancer risk. The 1986 IARC monograph commented on the general issue of causation of cancer by secondhand smoke: "It is unlikely that any effects will be produced in passive smokers that are not produced to a greater extent in smokers and that types of effects that are not seen in smokers will not be seen in passive smokers" (IARC 1986, p. 314). The IARC monograph on involuntary smoking, published in 2004, concluded that the evidence did not support a causal association between breast cancer and secondhand smoke (IARC 2004). The 2001 Surgeon General's report also addressed the topic. The report considered cohort and case-control studies on involuntary smoking and breast cancer

and found that the issue had not been "resolved" (USDHHS 2001, p. 217). Most recently, the 2005 report of the California EPA (Cal/EPA) found the evidence to be conclusive for secondhand smoke as a cause of premenopausal breast cancer (Cal/EPA 2005).

The following section describes the prospective cohort and case-control studies on involuntary smoking and breast cancer. Whenever available, results on active smoking and breast cancer in the same study population are shown so the findings on involuntary and active smoking can be compared.

Prospective Cohort Studies

There are seven published prospective cohort studies on secondhand smoke exposure and the risk of breast cancer among lifetime nonsmoking women (Table 7.8) (Hirayama 1984; Wells 1991; Jee et al. 1999; Wartenberg et al. 2000; Nishino et al. 2001; Egan et al. 2002; Reynolds et al. 2004; Hanaoka et al. 2005). In these studies, exposure was classified based on information collected at the start of follow-up. Because this information was not updated in most of the studies, exposure misclassification may have increased as duration of the follow-up lengthened and the exposure status of the participants changed. Some studies only assessed spousal smoking; other studies covered additional sources of exposure, including during childhood. Secondhand smoke exposure was not significantly associated with breast cancer risk in these studies, although two studies did find increased point estimates of RR (Hirayama 1984; Jee et al. 1999), and a third study found an increased risk in premenopausal women (Hanaoka et al. 2005).

Hirayama (1984) published the first report based on a population-based, prospective cohort in Japan. Active and involuntary smoking statuses were based on information supplied on enrollment and were not updated. After 15 years of follow-up, this study identified 115 breast cancer deaths among women who had never smoked. Lifetime nonsmoking women whose husbands smoked had an increase in the RR compared with women married to nonsmokers (RR = 1.26 [95 percent CI, 0.8–2.0]) (Table 7.8). In a further analysis of this data set, Wells (1991) reported that the increased risk associated with the husband's smoking was more marked among women who were younger than 60 years of age. The effect of active smoking on breast cancer risk was similar to that of involuntary smoking (RR = 1.28 [95 percent CI, 0.93–1.73]).

A similar increase in risk of breast cancer associated with the husband's smoking was reported in a Korean cohort study (Jee et al. 1999) (see "Lung Cancer" earlier in this chapter). During three and one-half years of follow-up, 138 women with breast cancer were identified. The exposure status was fixed based on baseline information. The risks of breast cancer were 1.2 (95 percent CI, 0.8–1.8) for nonsmoking women married to former smokers and 1.3 (95 percent CI, 0.9–1.8) for nonsmoking women married to current smokers compared with nonsmoking women married to nonsmokers. These investigators reported that the RR increased significantly with the duration of the husband's smoking (>30 years), but details were not provided. Information on active smoking and breast cancer risk was also not reported in this study, but smoking by women in Korea is still uncommon (Jee et al. 1999, 2004).

The relationship between secondhand smoke and breast cancer was investigated in the Japan Public Health Center (JPHC)-based prospective cohort study of 21,805 middle-aged women of whom 20,169 were lifetime nonsmokers (Hanaoka et al. 2005). Participants completed a self-administered questionnaire and provided information about exposure to secondhand smoke at home before and after 20 years of age. For exposure outside the home, such as at work and other settings, participants were asked about exposures of at least one hour per day, including the frequency of exposure (e.g., almost never, one to three days per month, one to four days per week, almost every day). During the nine years of follow-up, this information was not updated. After the nine years, the investigators identified 180 breast cancers; 162 occurred in lifetime nonsmokers (Table 7.8). Compared with lifetime nonsmokers who were not exposed to secondhand smoke, women who were exposed did not show a significant increase in the RR (adjusted RR = 1.1 [95 percent CI, 0.8–1.6]). The RR was 1.0 (95 percent CI, 0.7–1.4) for exposure at home and 1.3 (95 percent CI, 0.9–1.9) for exposure outside of the home (i.e., occupational and/or public exposure). However, risk patterns differed by menopausal status. Secondhand smoke exposure (residential or occupational) was not associated with breast cancer risk in postmenopausal women (n = 83) (adjusted RR = 0.7 [95 percent CI, 0.4–1.0]) but it was associated with an increased RR in premenopausal women (n = 77) (adjusted RR = 2.6 [95 percent CI, 1.3–5.2]). Exposures at home (adjusted RR = 1.6 [95 percent CI, 0.9–2.7]) and outside of the home (adjusted RR = 2.3 [95 percent CI, 1.4–3.8]) were both associated with risk in premenopausal women. Active smoking was associated with an increased

risk in this study population. The RR of breast cancer among current smokers was 1.9 (95 percent CI, 1.0–3.6) compared with lifetime nonsmokers without secondhand smoke exposure. Researchers found an association between active smoking and breast cancer only in premenopausal women (adjusted RR = 3.9 [95 percent CI, 1.5–9.9]) and not in postmenopausal women (adjusted RR = 1.1 [95 percent CI, 0.5–2.5]).

This study included a comprehensive assessment of secondhand smoke exposure. Childhood exposures were not explored, but both residential and workplace exposures were considered. There were differences in the profiles of breast cancer risk factors across the smoking exposure groups, but these profiles were not explored by menopausal status. However, the estimates of breast cancer risk associated with active and involuntary smoking were adjusted for these factors.

In contrast, secondhand smoke exposure was not associated with breast cancer risk in four other cohort studies, including another study conducted in Japan (Nishino et al. 2001) and three in the United States (Wartenberg et al. 2000; Egan et al. 2002; Reynolds et al. 2004). The third Japanese cohort study was conducted in Miyagi Prefecture (see "Lung Cancer" earlier in this chapter). During nine years of follow-up, Nishino and colleagues (2001) identified 67 women with breast cancer. The age-adjusted RR for breast cancer was 0.58 (95 percent CI, 0.34–0.99) for women whose husbands were smokers at baseline compared with women married to nonsmokers. The reduced risk in association with the husbands' smoking was unchanged but no longer statistically significant after further adjustment for reproductive history and lifestyle factors (multivariate-adjusted RR = 0.58 [95 percent CI, 0.32–1.11]) (Table 7.8) (Nishino et al. 2001). Smoking by other household members was also not associated with breast cancer risk in this same population (multivariate-adjusted RR = 0.81 [95 percent CI, 0.44–1.5]); an association between active smoking and breast cancer risk was not reported.

Studies also investigated the relationship between secondhand smoke and breast cancer risk in a group of women in the American Cancer Society's (ACS's) Cancer Prevention Study II (CPS-II) cohort; this study included 146,488 lifetime nonsmoking women who were married only once and who were free of cancer when they entered the study in 1982 (Wartenberg et al. 2000). Exposures classified at baseline were based on index participant and spousal reports and were considered to be fixed. Breast cancer mortality, not incidence, was the outcome measure in this study. Mortality from breast cancer reflects not only incidence, but factors determining survival. A total of 669 women who had died of breast cancer were identified after 12 years of follow-up. All of the RRs associated with different categories of secondhand smoke exposure, including husbands' current and former smoking patterns, tobacco products used, number of years and pack-years[1], and timing of the exposure, were close to unity with or without adjustment for numerous dietary and nondietary covariates. Compared with lifetime nonsmokers married to nonsmokers, lifetime nonsmokers whose husbands were current smokers (adjusted RR =1.0 [95 percent CI, 0.8–1.2]) or former smokers (adjusted RR = 1.0 [95 percent CI, 0.8–1.2]) did not have increased risks (Table 7.8). The RR for breast cancer was not significantly associated with secondhand smoke exposures at home (RR = 1.1 [95 percent CI, 0.9–1.3]), at work (RR = 0.8 [95 percent CI, 0.6–1.0]), or in other places (RR = 0.9 [95 percent CI, 0.7–1.2]). Exposures from all sources combined were also not associated with breast cancer mortality (RR = 1.0 [95 percent CI, 0.8–1.2]). The only observed elevated risk was among women who were younger than 20 years of age when they married smokers (RR = 1.2 [95 percent CI, 0.8–1.8]). Using the results from six years of follow-up of CPS-II participants, Calle and colleagues (1994) observed that current active smoking was associated with an increased risk for breast cancer mortality. Women who were current smokers at baseline showed an increased risk (RR = 1.26 [95 percent CI, 1.05–1.50]) compared with lifetime nonsmokers, but the RR did not increase among former smokers (RR = 0.85 [95 percent CI, 0.70–1.03]).

Using data from the NHS, Egan and colleagues (2002) investigated the relationship between secondhand smoke exposure and breast cancer risk. Persons who were eligible (n = 78,206) for participation in the study included women who responded to the baseline and subsequent questionnaires that assessed dietary habits and secondhand smoke exposures, including childhood and current adult exposures at home, at work, and in other settings, as well as other factors. Involuntary smoking was assessed at only one time point (1982), while other information on other risk factors was updated every two years. After 14 years of follow-up, the investigators identified 3,140 women with invasive breast cancer, of whom 1,359 were lifetime nonsmokers (Table 7.8) (Egan et

[1]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Table 7.8 Cohort studies of associations between exposures to secondhand smoke and the relative risks for breast cancer incidence and mortality among women who had never smoked

Study	Population/follow-up	Number of breast cancer events	Data collection
Hirayama 1984 Wells 1991	91,540 wives who had never smoked 6 prefectures in Japan 16 years	115 breast cancer deaths	Brief in-person interview at the time of study enrollment
Jee et al. 1999	157,436 married women who had never smoked Health insurance subscribers Korea 3.5 years	138 (incident and prevalent cases)	Husbands of women who had never smoked completed medical exams and questionnaires on active smoking in 1992 and 1994 Women who had never smoked completed questionnaires in 1993
Wartenberg et al. 2000	146,488 single-marriage women who had never smoked American Cancer Society 12 years	669 breast cancer deaths	Secondhand smoke questions were based on active smoking histories reported by spouses Women reported the number of hours per day they were exposed to the smoke of others at home, at work, and in other settings
Nishino et al. 2001	9,675 women who had never smoked Aged ≥40 years Miyagi Prefecture (Japan) 9 years	67 incident cases	Self-completed questionnaires on lifestyle habits Secondhand smoke questions asked about smokers in the household and, if so, whether husband, father, mother, children, or other household members smoked
Egan et al. 2002	78,206 women (35,193 who had never smoked, 22,258 former smokers, 20,755 current smokers) Nurses Health Study United States 14 years	3,140 invasive breast cancer (1,359 lifetime nonsmokers)	Completed a 1976 baseline questionnaire on reproductive factors and active smoking, and follow-up questionnaires every 2 years The 1980 and 1982 questionnaires asked about diet and secondhand smoke exposure

Findings	Measure of secondhand smoke	Relative risk (95% confidence interval)	Comments
• Effect of secondhand smoke was similar to the effect of active smoking	Husband's smoking: Lifetime nonsmoker Ever smoked	 1.0 1.26 (0.8–2.0)	Controlled for age
• Risk increased significantly with duration of husband's smoking (>30 years)	Husband's smoking: Lifetime nonsmoker Former smoker Current smoker	 1.0 1.2 (0.8–1.8) 1.3 (0.9–1.8)	Controlled for age of husbands and wives, social class, residence, and husband's vegetable intake and occupation; data on duration of smoking were not reported; analyses included incident and prevalent cases
• No increased risk with any source of secondhand smoke exposure • No dose-response relationships • Current active smokers showed an increase in risk but former smokers did not	Husband's smoking: Lifetime nonsmoker Former smoker Current smoker Duration of smoking (years): None 1–10 11–20 21–30 ≥31	 1.0 1.0 (0.8–1.2) 1.0 (0.8–1.2) 1.0 0.8 (0.6–1.2) 0.7 (0.5–1.0) 1.0 (0.7–1.3) 1.1 (0.9–1.4)	Controlled for age, race, education, family history, age at first live birth, age at menarche, menopause, number of spontaneous abortions, use of oral contraceptives and hormone replacement therapy, body size, history of breast cysts, alcohol use, intake of dietary fat and vegetables, and the occupation of the wife and her spouse; there were no changes in results with or without adjustments
• Inverse association between risk and secondhand smoke exposure based on the smoking habits of the husband and other household members • No active smoking data	Husband's: Nonsmoker Smoker Other household members: Nonsmoker Smoker	 1.0 0.58 (0.32–1.1) 1.0 0.81 (0.44–1.5)	Controlled for age; study area; alcohol, fruit, and green/yellow vegetable intake; age at first birth; number of live births; age at menarche; and body mass index (BMI)
• No association with any sources of secondhand smoke exposure—results were similar in premenopausal and postmenopausal women • Very weak association with active smoking	Parental smoking: Neither Mother only Father only Both parents Current home/work secondhand smoke exposure: None Occasional Regular (home or work) Regular (home and work)	 1.0 0.98 (0.70–1.38) 1.12 (0.99–1.27) 0.92 (0.76–1.13) 1.0 1.16 (0.98–1.36) 1.0 (0.83–1.20) 0.90 (0.67–1.22)	Controlled for age, age at menarche, age at first birth and parity, history of benign breast disease, family history of breast cancer, menopausal status, age at menopause, weight at 18 years of age, adult weight change, adult height, alcohol use, total carotenoid intake, and use of menopausal hormones

Table 7.8 Continued

Study	Population/follow-up	Number of breast cancer events	Data collection
Reynolds et al. 2004	76,189 lifetime nonsmokers from the California Teachers Study Cohort 5 years	1,150 incident breast cancer	Self-administered questionnaire at the time of study enrollment to determine household secondhand smoke exposure during childhood and adulthood
Hanaoka et al. 2005*	20,169 women who had never smoked* Recruited from 4 public health centers in Japan Japan Public Health Center Cohort Aged 40–59 years 9 years	162 incident breast cancer	Self-administered questionnaire at the time of study enrollment to determine household secondhand smoke exposure before and after 20 years of age; exposure at the workplace and in other settings (≥1 hour/day) and frequency of exposure

*The number 20,169 was listed in Table 1 of this paper. However, the number of lifetime nonsmokers in Table 2 added up to 20,193. (It is unclear why the numbers in the two tables differ.)

al. 2002). Almost all estimated RRs associated with childhood and adulthood secondhand smoke exposures were close to 1.0. The estimates were unchanged with and without adjustment for a large number of covariates. There was a small increase in the RR associated with paternal smoking (adjusted RR = 1.12 [95 percent CI, 0.99–1.27]) but not with maternal smoking (adjusted RR = 0.98 [95 percent CI, 0.70–1.38]) (Table 7.8). Current secondhand smoke exposures were also unrelated to risk; the RR was 1.0 (95 percent CI, 0.83–1.20) in association with regular secondhand smoke exposure at home or at work and 0.90 (95 percent CI, 0.67–1.22) for regular exposures in both settings (Table 7.8). Similarly, the investigators found no evidence that long-term adult exposures to household smoke increased breast cancer risk (p for trend = 0.87); the RR for living with a smoker as an adult for 30 or more years was 1.03 (95 percent CI, 0.86–1.24). The RR of breast cancer among women with the highest levels of secondhand smoke exposure as adults was similar to that of women who reported no current exposure to secondhand smoke (RR = 1.01 [95 percent CI, 0.80–1.29]). The results were similar in premenopausal and postmenopausal women. Active smoking was weakly associated with a risk of breast cancer in this study. Compared with lifetime nonsmokers, Egan and colleagues (2002) reported that the RR of breast cancer was 1.04 (95 percent CI, 0.94–1.15) among current smokers and 1.09 (95 percent CI, 1.00–1.18) among former smokers. A modest increase in the RR was confined to women who initiated active smoking before 17 years of age (RR = 1.19 [95 percent CI, 1.03–1.37]). This large prospective study assessed childhood and adulthood household and workplace secondhand

Findings	Measure of secondhand smoke	Relative risk (95% confidence interval)	Comments
• No significant positive association between breast cancer risk and secondhand smoke exposure during childhood and/or adulthood • Results were similar in premenopausal, perimenopausal, and postmenopausal women	Household: Never exposed Childhood only Adulthood only Childhood and adulthood	 1.0 0.92 (0.78–1.07) 0.94 (0.79–1.12) 0.93 (0.79–1.09)	Controlled for age, race, family history of breast cancer, age at menarche, parity, age at first full-term pregnancy, physical activity, alcohol use, BMI, menopausal status, and use of hormone therapy
• No significant positive association between household and/or workplace exposure and breast cancer risk in all participants combined • Household and workplace exposures were associated with a significantly increased risk in premenopausal women; a reduced risk in postmenopausal women was nonsignificant	All participants Household/work: No Household Workplace Premenopausal: No Household Workplace Postmenopausal: No Household Workplace	 1.0 1.0 (0.7–1.4) 1.3 (0.9–1.9) 1.0 1.6 (0.9–2.7) 2.3 (1.4–3.8) 1.0 0.7 (0.4–1.1) 0.4 (0.2–1.0)	Controlled for study area, age, employment status, education, BMI, family history of breast cancer, parity, age at menarche, alcohol intake, menopausal status (in a combined analysis), history of benign breast disease, and hormone use

smoke exposures. Almost all of the risk estimates associated with adulthood exposure were near unity, regardless of the duration of exposure.

The relationship between secondhand smoke and breast cancer risk was investigated in the California Teachers Study, which included 116,544 women who had no personal history of breast cancer and who completed a baseline questionnaire in 1995 to determine their active and involuntary smoking status (Reynolds et al. 2004). That analysis was limited to the 77,708 members who were lifetime nonsmokers (i.e., smoked fewer than 100 cigarettes during their lifetime) and who responded to questions on household secondhand smoke that covered both childhood and adulthood. A total of 1,150 breast cancers were identified in lifetime nonsmokers after five years of follow-up. Lifetime nonsmokers were categorized as unexposed, only exposed during childhood, only exposed during adulthood, or exposed during both childhood and adulthood. All of the RRs associated with secondhand smoke exposure were close to unity after adjustment for various reproductive factors and nondietary covariates. The RR of breast cancer was 0.92 (95 percent CI, 0.78–1.07) among women with only childhood household secondhand smoke exposure, 0.94 (95 percent CI, 0.79–1.12) among women with only adulthood household secondhand smoke exposure, and 0.93 (95 percent CI, 0.79–1.09) among women with both exposures compared with unexposed lifetime nonsmokers. Results were very similar for premenopausal/perimenopausal (n = 254) and postmenopausal (n = 778) women (Table 7.8). In contrast, active smoking was associated with breast cancer risk. Compared with lifetime nonsmokers with

no secondhand smoke exposure, the RR of breast cancer was 1.03 (95 percent CI, 0.89–1.18) among former smokers and 1.25 (95 percent CI, 1.02–1.53) among current smokers. However, the increased risk among current smokers was restricted to women who were postmenopausal at baseline (adjusted RR = 1.21 [95 percent CI, 0.95–1.54]) and was not observed among women who were premenopausal or perimenopausal at baseline (adjusted RR = 0.96 [95 percent CI, 0.55–1.68]). One limitation of this large, prospective cohort study is that information on work place secondhand smoke exposure was not assessed. In addition, this analysis was limited to relatively crude measures of childhood and adulthood household secondhand smoke exposures.

Case-Control Studies

Fourteen case-control studies have investigated the association between secondhand smoke exposure and a risk of breast cancer among lifetime nonsmokers. These studies were conducted in the United Kingdom (Smith et al. 1994), Switzerland (Morabia et al. 1996, 2000), Germany (Kropp and Chang-Claude 2002), the United States (Sandler et al. 1985a; Millikan et al. 1998; Lash and Aschengrau 1999, 2002; Delfino et al. 2000; Marcus et al. 2000; Gammon et al. 2004; Bonner et al. 2005), Canada (Johnson et al. 2000), and China (Zhao 1999; Liu et al. 2000; Shrubsole et al. 2004) (Table 7.9).

The first study that included data on secondhand smoke exposures during childhood and adulthood and the risk of breast cancer among lifetime nonsmokers was a hospital-based, multicancer site study conducted in North Carolina (Sandler et al. 1985a). The analysis on adult secondhand smoke exposures was based on 59 breast cancer cases and 330 controls; 32 cases and 178 controls were nonsmokers. Secondhand smoke exposure based on the husbands' smoking was associated with an increased RR of breast cancer among nonsmokers (OR = 2.0 [95 percent CI, 0.9–4.3]) (Sandler et al. 1985a). The risk of breast cancer in relation to secondhand smoke exposure during childhood was investigated using a slightly smaller set of participants (52 breast cancer cases, 312 controls) (Sandler et al. 1985b). The risk of breast cancer among nonsmokers was not associated with maternal (OR = 0.9) or paternal (OR = 0.9) smoking. On the basis that 27 out of 59 breast cancer patients and 152 out of 330 controls were active smokers, the crude OR for active smoking calculated in one report was 1.0 (Sandler et al. 1985b). Methodologic limitations of the study included the use of a control group of friends and acquaintances with no adjustment for reproductive factors (only age, race, and education were considered), and the small number of nonsmokers among the breast cancer cases.

A second study on this topic was conducted as part of the United Kingdom National Case-Control Study Group, which was originally designed to investigate the relationship between oral contraceptive use and breast cancer risk in young women (Smith et al. 1994). Although the original study (755 case-control pairs) was not designed to evaluate the role of secondhand smoke, Smith and colleagues (1994) were able to successfully recontact approximately one-third of the participants (208 cases with breast cancer and 201 healthy controls) who completed a questionnaire on exposures to secondhand smoke during childhood and adulthood (partner/spouse, cohabitant, workplace). Complete data for 204 cases and 199 controls from the original 755 pairs were available for the exposure analysis. The association between secondhand smoke exposure and breast cancer risk was investigated among nonsmokers (94 cases, 99 controls) after controlling for various potential confounders. The investigators estimated an associated OR of 1.32 (95 percent CI, 0.16–10.8) for childhood exposure only, 3.13 (95 percent CI, 0.73–13.31) for adulthood exposure only, and 2.63 (95 percent CI, 0.73–9.44) for both time periods combined compared with unexposed nonsmokers (Table 7.9) (Smith et al. 1994). There was no evidence of an exposure-response relationship with cigarette-years[2] of exposure during childhood, from partners in adulthood, or at work. In the parent case-control study, active smoking was not associated with a risk of breast cancer (adjusted OR = 1.01 [95 percent CI, 0.81–1.26]) (Smith et al. 1994).

Morabia and colleagues conducted a study of secondhand smoke and breast cancer risk in Switzerland (Morabia et al. 1996; USDHHS 2001). The study included 244 women with breast cancer (cases) and 1,032 healthy controls from the general population, of whom 126 cases and 620 controls were lifetime nonsmokers (Table 7.9). The data collection attempted a complete assessment of active smoking and secondhand smoke exposure. Specifically, active smoking and secondhand smoke exposure histories were recorded year by year from 10 years of age to the date of the interview. Those who were classified as active smokers were women who had smoked at least

[2]Cigarette-years = The number of years of smoking multiplied by the number of cigarettes smoked per day.

100 cigarettes in their lifetime; those who had smoked regularly during the two years before the study interview were categorized as current smokers. Secondhand smoke exposure was defined as an exposure lasting at least one hour per day during one year or more either at home, at work, or during leisure time (Morabia et al. 1996).

This study showed that several measures of secondhand smoke exposure were associated with at least a doubling of breast cancer risk after adjusting for relevant covariates. Morabia and colleagues (1996) found that compared with lifetime nonsmokers who had never been exposed to secondhand smoke in this classification approach (28 cases, 241 controls), nonsmokers with exposure from spousal smoking (adjusted OR = 2.6 [95 percent CI, 1.6–4.3]) or from all sources combined including at home, at work, or during leisure time (adjusted OR = 2.3 [95 percent CI, 1.5–3.7]) had an increased risk of breast cancer. However, there was little difference in risk between those with high exposures (>50 hours per day-years[3] adjusted OR = 2.5 [95 percent CI, 1.5–4.2]) and those with lower exposures (1 to 50 hours per day-years adjusted OR = 2.2 [95 percent CI, 1.3–3.7]). The RRs associated with active smoking were stronger than those associated with secondhand smoke when lifetime nonsmokers with no secondhand smoke exposure served as the baseline comparison group: for active smokers, the ORs were 2.4 (1 to 9 cigarettes per day), 3.6 (10 to 19 cigarettes per day), and 3.7 (≥20 cigarettes per day, p trend = 0.09).

Using this parental case-control study, Morabia and colleagues (2000) conducted a substudy to investigate whether the *N-acetyltransferase 2* (*NAT2*) genotype influenced the effects of smoking on breast cancer risk. The investigators hypothesized that the association between secondhand smoke and breast cancer would be modified by the *NAT2* genotype, which some studies of active smoking have found to be associated with cancer risk. Researchers contacted cases and a subset of controls who were still alive in 1996–1997 (n = 205) and asked them to provide a buccal cell swab for DNA analysis. Data were available on active smoking, secondhand smoke exposure, and the *NAT2* genotyping for 160 cases and 162 controls (Morabia et al. 2000).

Morabia and colleagues (2000) showed that, compared with lifetime nonsmokers with no exposure to secondhand smoke, lifetime nonsmokers exposed to secondhand smoke had an increased risk of breast cancer regardless of the *NAT2* genotype. The OR was 1.9 (95 percent CI, 0.7–4.6) for persons with the *NAT2* slow acetylation genotype and 5.9 (95 percent CI, 2.0–17.4) for those with the *NAT2* fast acetylation genotype. Compared with unexposured lifetime nonsmokers, current active smokers with the *NAT2* slow acetylator genotype had an OR of 2.7 (95 percent CI, 1.1–6.6), and those with the fast genotype had an OR of 4.2 (95 percent CI, 1.5–12.0). The researchers interpreted these findings as supportive of a role for secondhand smoke in causing breast cancer because the increased risks associated with both active smoking and secondhand smoke exposure were more apparent among *NAT2* fast acetylators. However, the evidence that the *NAT2* genotype influences breast cancer risk among active smokers is weak. Although one small study suggested an increased risk of breast cancer among women who were both active smokers and slow *NAT2* acetylators (Ambrosone et al. 1996), this finding has not been confirmed in subsequent, larger studies (Hunter et al. 1997, 1998; Millikan et al. 1998).

Lash and Aschengrau (1999) investigated the role of secondhand smoke and breast cancer using a population-based case-control study that was originally designed to evaluate the role of various environmental contaminants on the risk of multiple cancers, including breast cancer (Aschengrau et al. 1996). A total of 265 women with breast cancer and 765 controls were included in the study that investigated an association between active and involuntary smoking and breast cancer risk (Lash and Aschengrau 1999). Of the parental study participants, 120 cases and 406 controls were lifetime nonsmokers.

Cases and controls were categorized by their active cigarette smoking history and, among lifetime nonsmokers, by residential secondhand smoke exposure with consideration of age at first exposure (secondhand smoke exposures outside of the home were not assessed). Compared with lifetime nonsmokers who reported no secondhand smoke exposure (40 cases, 139 controls), those with any secondhand smoke exposure had a significantly increased risk of breast cancer (adjusted OR = 2.0 [95 percent CI, 1.1–3.7]) (Table 7.9) (Lash and Aschengrau 1999). Risk did not increase with an increase in the duration of exposure (adjusted OR = 3.2 [95 percent CI, 1.5–7.1] for 1 to 20 years and 2.1 [95 percent CI, 1.0–4.1] for

[3]Day-years = The sum of hours per day exposed to secondhand smoke multiplied by the number of years of all episodes of secondhand smoke exposure, whether at home, at work, or during leisure time.

Table 7.9 Case-control studies of the association between exposures to secondhand smoke and relative risks for breast cancer incidence and mortality among women who had never smoked

Study	Population	Cases	Controls	Data collection
Sandler et al. 1985a	Hospital based Aged 15 and 59 years United States (North Carolina) 1979–1981	59 32 lifetime nonsmokers	330 friends or from telephone lists 178 lifetime nonsmokers	Mailed questionnaire
Smith et al. 1994	Aged ≥36 years Only 3 out of 11 health regions were included in the study United Kingdom 1982–1985	204 94 lifetime nonsmokers	199 99 lifetime nonsmokers	In-person interview for all lifestyle factors; mailed questionnaire on secondhand smoke exposure
Morabia et al. 1996	Population-based Aged 30–74 years Resident of Geneva in Switzerland 1992–1993	244 126 lifetime nonsmokers	1,032 620 lifetime nonsmokers	In-person interview, detailed lifetime history on active smoking and secondhand smoke exposure
Millikan et al. 1998	Population-based registry Aged 20–74 years United States (North Carolina) Included only persons enrolled between 1993 and 1996 who granted home interviews and gave blood samples	498 248 lifetime nonsmokers	473 253 lifetime nonsmokers (sources were drivers' licenses or HCFA‡)	In-person interviews Classified as exposed if the participant was >18 years of age when living with a smoker
Lash and Aschengrau 1999	State cancer registry 5 Massachusetts towns United States 1983–1986	265 120 lifetime nonsmokers	765 406 lifetime nonsmokers 3 sources: RDD$^{\Delta}$, HCFA, and deceased	Mix of in-person and telephone interviews 33% of cases and 45% of controls were interviews with next of kin

Findings	Measure of secondhand smoke	Relative risk (95% confidence interval)	Comments
• Husband's smoking increased the risk; stronger among premenopausal women • No association with parental smoking • No association with active smoking	Husband smoked: No Yes	 1.0 2.0 (0.9–4.3)	Controlled for age, race, and education
• Partner's and workplace smoking were associated with increased risk • No exposure-response relationship • No association with active smoking	Partner (cigarette-years*): None ≥1 Workplace exposure (duration): None 1–5 years ≥6 years Exposure by period: None Childhood only Adulthood only Childhood plus adulthood	 1.0 1.58 (0.81–3.10) 1.0 1.66 (0.72–3.83) 1.35 (0.59–3.07) 1.0 1.32 (0.16–10.8) 3.13 (0.73–13.3) 2.63 (0.73–9.4)	Controlled for age (<32 years and ≥32 years), region, menstrual and reproductive factors, family history, biopsy for breast disease, and alcohol intake; role of secondhand smoke was studied in a subset of the total number of cases (n = 755) and controls (n = 755)
• Increased risk associated with husband's smoking • Risk estimates were very similar to those for all sources of secondhand smoke • Little difference in risk from intensity of exposure	None All sources Hours/day/years† (all sources): 1–50 >50	1.0 2.3 (1.5–3.7) 2.2 (1.3–3.7) 2.5 (1.5–4.2)	Controlled for age, education, body mass index (BMI), age at menarche, age at first live birth, oral contraceptive use, family history of breast cancer, and history of a breast biopsy
• This analysis was based on secondhand smoke exposures occurring after 18 years of age • No association with active smoking • No association with *N-acetyltransferase (NAT) 1* or *NAT2* genotype and risk	All lifetime nonsmokers: No exposure Exposed By menopausal status: Premenopausal No Yes Postmenopausal No Yes	 1.0 1.3 (0.9–1.9) 1.0 1.5 (0.8–2.8) 1.0 1.2 (0.7–2.2)	Controlled for age, race, age at menarche, AFTP§, parity, family history, benign breast biopsy, and alcohol intake; 889 cases and 841 controls were interviewed, but this analysis included only those who also gave blood samples
• Risk associated with any secondhand smoke exposure was as strong or stronger than the association with active smoking	Residential exposure: Never Any By duration (years): ≤20 >20	 1.0 2.0 (1.1–3.7) 3.2 (1.5–7.1) 2.1 (1.0–4.1)	Controlled for age, BMI, family history of breast cancer, history of breast cancer other than the index diagnosis and history of radiation therapy, parity, and history of benign breast disease; the number of cases with previous breast cancer and the number of cases/controls with previous cancer and radiation therapy were not specified

Table 7.9 Continued

Study	Population	Cases	Controls	Data collection
Zhao et al. 1999	Hospital-based Aged 26–82 years Clinical diagnosis of breast cancer China (Chengdu) 1994–1997	265 265 nonsmokers	265 265 nonsmokers (included family members, visitors, friends, neighbors, other outpatients), matched for age, residence, occupation, and education	No information was presented except questions about a history of cigarette smoking and exposure to secondhand smoke
		Active smoking status was given for 272 cases (259 did not smoke); the discrepancy was not explained	Active smoking status was given for 258 controls (252 did not smoke); the discrepancy was not explained	
Delfino et al. 2000	3 breast cancer centers Recruitment was based on moderate/high clinical suspicion of breast cancer United States (Orange county, California)	113 64 lifetime nonsmokers	278 147 lifetime nonsmokers who had benign masses histopathologically	All participants completed a self-administered risk factor questionnaire before the biopsy test
Johnson et al. 2000	Aged 25–74 years 8 Canadian provincial tumor registries Canada 1994–1997	Premenopausal women: 520 222 lifetime nonsmokers Postmenopausal women: 895 386 lifetime nonsmokers	Premenopausal women: 512 229 lifetime nonsmokers Postmenopausal women: 1,012 498 lifetime nonsmokers	Mailed questionnaire Role of secondhand smoke was investigated among those with information on residential secondhand smoke exposure for at least 90% of their lifetimes and for whom menopausal status and active smoking status were provided

Findings	Measure of secondhand smoke	Relative risk (95% confidence interval)	Comments
• Significant positive association with any secondhand smoke exposure	Any exposure: No Yes	 1.0 2.49 (1.65–3.77)	Controlled for history of benign breast disease, breastfeeding, and intake of soybean products
• No association with active smoking • No association between *NAT2* genotype and breast cancer risk overall or by smoking	All participants: No exposure Any exposure Premenopausal: No exposure Exposed Postmenopausal: No exposure Exposed	 1.0 1.32 (0.69–2.52) 1.0 2.69 (0.91–8.0) 1.0 1.01 (0.45–2.27)	Controlled for age, age at menarche, menopausal status, AFTP, parity, total months of pregnancy, lactation history, education, race, ethnicity, family history of breast cancer among first- and second-degree relatives, and BMI
• Active smoking/breast cancer association was weaker than the secondhand smoke effect in premenopausal women	Premenopausal: None Secondhand smoke only Former smokers only Current smokers Postmenopausal: None Secondhand smoke only Former smokers Current smokers	 1.0 2.3 (1.2–4.6) 2.6 (1.3–5.3) 1.9 (0.9–3.8) 1.0 1.2 (0.8–1.8) 1.4 (0.9–2.1) 1.6 (1.0–2.5)	Controlled for 10-year age groups, province, education, BMI, alcohol use, age at menarche, age at end of first pregnancy of 5 months or later, number of live births, months of breastfeeding, and height

Table 7.9 Continued

Study	Population	Cases	Controls	Data collection
Liu et al. 2000	Hospital-based Aged 24–55 years Chongqing, China	186 lifetime nonsmokers	186 lifetime nonsmokers free of cancer Matched for age (±2 years) and date of admission (Women's Health Care and Breast Surgery Department)	In-person interview Household secondhand smoke exposure during childhood (aged <10 years), adolescence (aged 10–16 years), and adulthood; asked about the number of smokers and amount smoked during each time period; workplace exposure: if worked around smokers, number of smokers, and amount smoked
Marcus et al. 2000	Population-based registry (same study population as Millikan et al. 1998) United States (North Carolina) Included all participants enrolled between 1993 and 1996	864 445 lifetime nonsmokers	790 423 lifetime nonsmokers	Exposures to secondhand smoke before and after 18 years of age were investigated in all participants and in lifetime nonsmokers
Kropp and Chang-Claude 2002	Population-based Aged <51 years Two regions in Southern Germany Original study 1992–1996 Participants were recontacted in 1999–2000	468 197 lifetime nonsmokers 76.9% premenopausal	1,093 459 lifetime nonsmokers (resident listing) 2 controls matched to each case by age and study region in original study 81.1% premenopausal	Telephone interviews (blinded to case/control status) Household exposure during childhood and adulthood, and workplace exposure; many details collected included number of smokers, duration of exposure (amount/day), and years of exposure Definition of "exposed" was 1 hour a day for at least 1 year

Findings	Measure of secondhand smoke	Relative risk (95% confidence interval)	Comments
• Significant positive association with household exposure during childhood and adulthood; similar results during youth but not significant • Significant positive association with workplace exposure	Household exposure Childhood: None Light Medium Heavy Very heavy p trend Adulthood: None Light Medium Heavy Very heavy p trend Workplace exposure: None 1–4 smokers 5–9 smokers ≥10 smokers p trend	 1.0 0.69 (0.36–1.31) 1.31 (0.73–2.33) 1.64 (0.83–3.23) 1.74 (0.70–4.36) p <0.05 1.0 0.47 (0.18–1.20) 1.64 (0.96–2.79) 2.14 (0.88–5.25) 3.09 (0.98–10.3) p <0.01 1.0 1.56 (0.95–2.56) 0.77 (0.33–1.78) 2.94 (1.26–6.99) p <0.05	Results remained statistically significant in multivariate analyses (see text); analyses controlled for secondhand smoke variables simultaneously and other variables that included age at menarche, body weight in childhood and adulthood, family income during youth, history of hospitalization, benign breast disease, and stress
• No active smoking association • Little change in findings when secondhand smoke exposures occurring after 18 years of age were considered	Lifetime nonsmokers <18 years of age: No Yes	 1.0 0.8 (0.6–1.1)	Controlled for race, age, age at diagnosis and selection, and sampling design
• Significant positive association with lifetime exposure • No significant association with childhood exposure • No significant effects from the timing of exposure (before or after first pregnancy)	Any: No Yes Former smoker Current smoker Timing in life: None Childhood only Adulthood only Childhood and adulthood Lifetime (hours/day; years): 1–50 ≥51 p trend	 1.0 1.59 (1.06–2.39) 1.61 (1.08–2.39) 1.55 (1.00–2.40) 1.0 1.11 (0.55–2.27) 1.86 (1.16–2.98) 1.63 (1.03–2.57) 1.42 (0.90–2.26) 1.83 (1.16–2.87) p = 0.009	Stratified by age (5 years); controlled for education, alcohol intake, breastfeeding, family history of breast cancer, menopausal status, and BMI

Table 7.9 Continued

Study	Population	Cases	Controls	Data collection
Lash and Aschengrau 2002	Population-based Aged ≥65 years 8 Cape Cod towns that reported to the Massachusetts Cancer Registry 1987–1993	666 305 lifetime nonsmokers	615 249 lifetime nonsmokers from (RDD and HCFA)	Interviews were conducted with self-respondents and proxies; no description except that the methods were similar to those used in Lash and Aschengrau 1999
Gammon et al. 2004	Population-based Aged 24–98 years Nassau and Suffolk counties of Long Island (New York) (Long Island Breast Cancer Study) United States 1996–1997	1,356 598 lifetime nonsmokers 211 premenopausal and 387 postmenopausal women	1,383 627 lifetime nonsmokers 231 premenopausal and 396 postmenopausal women RDD and Medicare records	In-person interview; residential history; history of active smoking and exposure to secondhand smoke, including living with smokers, age at exposure, and duration of exposure
Shrubsole et al. 2004	Population-based Aged 25–64 years China (Shanghai) 1996–1998	1,119 1,013 married lifetime nonsmokers 684 premenopausal and 329 postmenopausal	1,231 1,117 lifetime married nonsmokers 763 premenopausal and 354 postmenopausal women (selected from Shanghai Resident Registry listing)	In-person interview Sources: (1) Husband's smoking (amount and years smoked) (2) Exposure at work for the 5 years before interview/diagnosis (minutes of exposure per day)

Findings	Measure of secondhand smoke	Relative risk (95% confidence interval)	Comments
• No association between lifetime exposure and risk • No association when duration or timing of exposure (before or after first birth) was considered	Lifetime exposure: No Yes Duration (years): Never 0 to <20 20 to <40 ≥40	 1.0 0.85 (0.63–1.1) 1.0 0.87 (0.59–1.3) 0.94 (0.66–1.3) 0.75 (0.47–1.2)	Controlled for parity, age at first birth, alcohol use, family history and personal history of breast cancer, history of benign breast disease, use of medical radiation, and BMI
• No significant association between any exposure or duration of household exposure before 18 years of age or adulthood (all or from spouses) • Some suggestion of an increased risk with ≥27 years of exposure to spousal smoking was not significant • No significant association in subgroup analyses considering menopausal status, weight, family history, and other factors	Household exposure: No Yes Total duration (months): None 1–192 193–360 ≥361 Total duration (months) of spousal exposure: None 1–181 182–325 ≥326 p trend	 1.0 1.04 (0.81–1.35) 1.0 1.07 (0.73–1.57) 0.84 (0.62–1.14) 1.22 (0.90–1.66) 1.0 1.50 (1.05–2.14) 1.01 (0.70–1.47) 2.10 (1.47–3.02) p >0.05	Controlled for age, number of pregnancies, menopausal status, history of benign breast disease, BMI at 20 years of age and at reference date, family history of breast cancer, history of fertility problems, use of oral conraceptives, and alcohol use
• No association with husbands' smoking among premenopausal and postmenopausal women • No association with any workplace exposure but a suggestion of an increased risk with ≥5 hours of daily exposure; results were stronger in premenopausal women	Husband: No Yes Workplace: No Yes Adult life: None Workplace only Husband only Work and husband Workplace (minutes/day): None 1–59 60–179 180–299 ≥300 p trend	 1.0 1.0 (0.8–1.2) 1.0 1.1 (0.9–1.4) 1.0 1.1 (0.8–1.5) 0.9 (0.7–1.2) 1.1 (0.8–1.4) 1.0 0.9 (0.6–1.3) 1.1 (0.8–1.6) 1.1 (0.8–1.7) 1.6 (1.0–2.4) p = 0.02	Controlled for age, education, household income, age at menarche, age at first live birth, age at menopause, body size, physical activity, breast cancer in first-degree relatives, history of fibroadenoma; no information on household exposure during childhood; workplace exposure was limited to previous 5 years

Table 7.9 Continued

Study	Population	Cases	Controls	Data collection
Bonner et al. 2005	Population-based Aged 35–79 years Erie and Niagara counties in western New York United States 1996–2001	1,122 525 lifetime nonsmokers 149 premenopausal and 376 postmenopausal	2,036 1,012 lifetime 326 nonsmokers were premenopausal and 686 postmenopausal Frequency was matched to cases by age, race, and county of residence; Department of Motor Vehicles and HCFA	In-person interview Household exposure for 7 age periods (<21 years of age, 21–30, 31–40, 41–50, 51–60, 61–70, >70); number of smokers, years of exposure; workplace exposure: number of hours and years of exposure to coworkers who smoked Lifetime residential history of number of smokers at each residence for 334 cases and 609 controls

*Cigarette years = The number of years of smoking multiplied by the number of cigarettes smoked per day.
†Hours/day/year = The sum of hours per day of exposure to secondhand smoke multiplied by the number of years of all episodes of secondhand smoke exposure whether at home, at work, or during leisure time.
‡HCFA = Health Care Financing Administration.
§AFTP = Age at first full-term pregnancy.
ΔRDD = Random-digit telephone dialing.

>20 years) (Table 7.9). In this study, the effect of active smoking (adjusted OR = 2.0 [95 percent CI, 1.1–3.6]) was quantitatively similar to that of secondhand smoke exposure when compared with lifetime nonsmokers with no secondhand smoke exposure. However, when active smokers were compared with all nonsmokers, regardless of secondhand smoke exposure, the effect of active smoking was weaker (the calculated crude OR was 1.34) than the effect of secondhand smoke exposure. Age, history of radiation therapy, a history of breast cancer other than the index diagnoses, parity, and several other covariates were included in the analyses (Lash and Aschengrau 1999).

The study has several limitations. First, multiple cancer sites (the largest three sites were lung, breast, and colorectal) were included in the parental case-control study, and it was unclear whether controls in the breast cancer analysis were appropriate and "matched" to the breast cancer cases. Information bias cannot be dismissed because a substantial proportion of control (45 percent) and case (33 percent) interviews were conducted with surrogate respondents, and the accuracy and completeness of the information on secondhand smoke exposure may differ by respondent type. Presumably, some proportion of the breast cancer controls had a history of breast cancer and other cancers because a history of breast cancer, other than the index diagnosis, and a history of radiation therapy were included as covariates in the secondhand smoke analysis. The inclusion of persons with previous breast or other cancers further limits this study because it is unclear whether information on secondhand smoke exposure and other factors was assessed up to the first cancer diagnosis or to the index cancer diagnosis.

Lash and Aschengrau (2002) conducted a second case-control study using similar study methods in the same study area (Table 7.9). They included cases of invasive breast cancers diagnosed between 1987 and 1993 among residents of eight Cape Cod towns,

Findings	Measure of secondhand smoke	Relative risk (95% confidence interval)	Comments
• No significant associations between risk and household (lifetime or before 21 years of age) or workplace exposure • Using data from lifetime residential histories, there were no significant associations between risk and exposure at other times (birth, menarche, and first birth) • Results were similar in premenopausal and postmenopausal women	Premenopausal Household (person-years): 0 >0 to ≤20 >20 to ≤33 >33 to ≤49 >49 p trend Postmenopausal Household (person-years): 0 >0 to ≤20 >20 to ≤33 >33 to ≤49 >49 p trend	 1.0 1.31 (0.70–2.44) 1.56 (0.77–3.14) 1.35 (0.69–2.63) 1.16 (0.51–2.62) p = 0.60 1.0 1.24 (0.79–1.95) 0.82 (0.50–1.36) 1.03 (0.64–1.66) 1.25 (0.79–1.96) p = 0.38	Controlled for age, education, race, history of benign breast disease, age at menarche, age at first birth, BMI, family history of breast cancer, alcohol intake, and age at menopause in analyses for postmenopausal women

which were reported to the Massachusetts Cancer Registry. Controls were women who were matched to cases on age and vital status and were selected by random-digit dialing or from rosters of Medicare beneficiaries. Interviews were conducted with the study participants or their proxies (the number of proxy interviews was not specified). This analysis included 305 cases and 249 controls who were lifetime nonsmokers. Compared with lifetime nonsmokers who reported no secondhand smoke exposure (80 cases, 53 controls), those with any exposure showed no increased risk of breast cancer (adjusted OR = 0.85 [95 percent CI, 0.63–1.1]). The null finding persisted with consideration of the duration of secondhand smoke exposure, age at exposure, and timing of exposure relative to age at pregnancy (Table 7.9). Active smokers also showed no increased risk of breast cancer relative to unexposed lifetime nonsmokers (adjusted OR = 0.81 [95 percent CI, 0.64–1.0]).

The differences in results in these two case-control studies, both conducted in the Cape Cod area, cannot be readily explained. Comparison of demographic and other relevant characteristics of lifetime nonsmoking cases and controls from the first study (Lash and Aschengrau 1999) with this series of cases and controls may provide some clues regarding the differences in results. Selection bias and the use of proxies for deceased participants in the two studies may have contributed to the differences in results. Duration of secondhand smoke exposure and timing of exposure were missing for 20 to 30 percent of the participants in the two studies, raising additional concerns regarding the quality of the information.

A role of secondhand smoke and breast cancer risk was investigated in a large, population-based study of cancer that included 19,453 Canadians who were diagnosed with 1 of 18 types of cancer and 4,523 population controls (Johnson et al. 2000). The influence of secondhand smoke on the risk of lung cancer

in this population (Johnson et al. 2001) was described above (see "Lung Cancer" earlier in this chapter for study methods). In brief, 8 of the 10 provinces in the National Enhanced Cancer Surveillance System participated in this study and identified 3,310 women aged 25 through 74 years with histologically confirmed invasive primary breast cancer. Controls were selected from provincial health insurance plans, property assessment databases, or random-digit telephone dialing. A total of 2,340 women with breast cancer (77.4 percent of 3,023 women contacted) and 2,531 controls (71.3 percent of 3,550 women contacted) responded to a mailed questionnaire that asked about lifestyle factors, including a lifetime history of residential and occupational secondhand smoke exposure.

The association of secondhand smoke with breast cancer risk was investigated among 1,415 cases (520 premenopausal and 895 postmenopausal) and 1,524 controls (512 premenopausal and 1,012 postmenopausal) who provided information on residential secondhand smoke exposure for at least 90 percent of their lifetimes, in addition to menopausal and active smoking information. After adjusting for various covariates, Johnson and colleagues (2000) found that premenopausal lifetime nonsmokers exposed to secondhand smoke showed an increased risk of breast cancer (OR = 2.3 [95 percent CI, 1.2–4.6]) compared with those who had not been exposed to secondhand smoke. This increased risk was comparable to the risk of former smokers (OR = 2.6 [95 percent CI, 1.3–5.3]) and was higher than that of current smokers (OR = 1.9 [95 percent CI, 0.9–3.8]) compared with unexposed nonsmokers. Associations between secondhand smoke exposure and breast cancer risk were weaker among postmenopausal women. The investigators found that the RR of breast cancer was 1.2 (95 percent CI, 0.8–1.8) among lifetime nonsmokers exposed to secondhand smoke, 1.4 (95 percent CI, 0.9–2.1) for former smokers, and 1.6 (95 percent CI, 1.0–2.5) for current smokers compared with unexposed nonsmoking postmenopausal women (Johnson et al. 2000). There was also a significant trend of an increase in RR with increasing years and increasing smoker-years[4] of exposure (residential plus occupational years) for premenopausal women; these trends were weaker among postmenopausal women (Johnson et al. 2000). For perimenopausal breast cancer, ORs were 1.5 (95 percent CI, 0.5–4.4), 2.0 (95 percent CI, 0.9–4.5), 2.9 (95 percent CI, 1.3–6.6), and 3.0 (95 percent CI, 1.3–6.6) for increasing levels of total secondhand smoke exposure (p for trend = 0.03). The postmenopausal dose-response results with increasing exposures were ORs of 1.1, 1.3, and 1.4 (95 percent CI, 0.9–2.3).

When interpreting these findings, researchers need to consider the substantial amount of missing information. Complete information on secondhand smoke exposure was not available for 919 women with breast cancer (cases) and 1,006 controls, and they were subsequently excluded from the analysis, leaving those women who provided information for at least 90 percent of their lifetimes. For the premenopausal women with breast cancer, complete information about secondhand smoke exposure and potential confounders was available for 59 percent of the lifetime nonsmokers, 73 percent of the former smokers, and 67 percent of the current smokers. Corresponding figures for the premenopausal controls were 62 percent, 71 percent, and 67 percent, respectively. Among postmenopausal women with breast cancer, information about secondhand smoke was available for 55 percent of the lifetime nonsmokers, 62 percent of the former smokers, and 65 percent of the current smokers. Corresponding figures for the postmenopausal controls were 59 percent, 62 percent, and 66 percent, respectively. The high proportion of incomplete data on residential secondhand smoke exposure is a concern. The authors noted that 314 cases and 347 controls were missing exposure data. The consequences of these exclusions are uncertain without additional information about those persons with missing exposure histories. It should be noted that the role of secondhand smoke in the risk of lung cancer was analyzed using the same large population-based study that did find an association with secondhand smoke exposure (Johnson et al. 2001). It is unclear whether the controls in the breast cancer analysis were also in the lung cancer analysis.

Another case-control study on secondhand smoke exposure and breast cancer identified participants from one of three breast cancer centers in Orange County, California (Delfino et al. 2000). Persons (n = 535) diagnosed with a suspicious breast mass that was detected clinically or by mammography were considered eligible. A total of 391 women were recruited, and 374 completed a self-administered risk factor questionnaire before having a breast biopsy. Participants were asked about active smoking (current or former smokers, smoking duration, and average number of cigarettes smoked per day) and secondhand smoke exposure. Of the 374 women, 113 were

[4]Smoker-years = The number of years of exposure weighted by the number of smokers.

diagnosed with histopathologically confirmed malignant tumors (cases), and 278 women were diagnosed with benign masses (controls). The controls were further categorized as "high-risk" (n = 148) if they had breast lesions that displayed hyperplasia with no atypia, atypical hyperplasia, or complex fibroadenomas; they were classified as "low-risk" (n = 107) if they had no proliferative changes in the breast. There were 23 controls with insufficient tissue surrounding the fibroadenocarcinoma who were not classified by their proliferative state. A total of 64 cases and 147 controls had never smoked.

Compared with lifetime nonsmokers classified as having "low" exposure (33 cases, 96 controls), lifetime nonsmokers with "high" secondhand smoke exposure had an increased risk (adjusted OR = 1.32 [95 percent CI, 0.69–2.52]) of breast cancer after adjusting for age, menopausal status, and family history of breast cancer (Table 7.9) (Delfino et al. 2000). In contrast to lifetime nonsmokers with low secondhand smoke exposure, former smokers (adjusted OR = 0.94 [95 percent CI, 0.53–1.68]) and current smokers (OR = 0.55 [95 percent CI, 0.18–1.67]) showed no increase in risk. In subgroup analyses stratified by risk for breast cancer based on the biopsy findings, the increased RR associated with secondhand smoke exposure was observed among women in the "low-risk" controls (OR = 1.78 [95 percent CI, 0.77–4.11]) but not among those in the "high-risk" controls (OR = 1.03 [95 percent CI, 0.50–2.12]). The RR of secondhand smoke exposure was greater among premenopausal women (OR = 2.69 [95 percent CI, 0.91–8.01]) than among postmenopausal women (OR = 1.01 [95 percent CI, 0.45–2.27]) (Table 7.9) (Delfino et al. 2000). This study was small and the exposure assessment was limited. With regard to the potential for information bias, the risk factor questionnaires on secondhand smoke and other lifestyle factors were obtained before the biopsy test or before the diagnosis of breast cancer, thus minimizing concerns regarding selective recall.

Secondhand smoke exposure and breast cancer risk was investigated in a population-based case-control study in North Carolina that included women aged 20 through 74 years who had been diagnosed with invasive primary breast cancer between 1993 and 1996 (Millikan et al. 1998; Marcus et al. 2000). All cases in African Americans younger than 50 years of age and about an equal number of cases in African Americans and Whites 50 years of age and older were included in the study. Controls were identified from listings of drivers' licenses or Medicare beneficiaries (if participants were aged ≥65 years). During the in-person interview, participants were asked about age at initiation of cigarette smoking, alcohol use, and exposure to secondhand smoke at home.

The first report on active smoking and secondhand smoke exposure from this case-control study was based on 498 cases and 473 controls who participated in the interview and who also donated blood specimens (Table 7.9) (Millikan et al. 1998). Compared with lifetime nonsmokers (248 cases, 253 controls), the RR of breast cancer was 1.3 (95 percent CI, 0.9–1.8) for former smokers and 1.0 (95 percent CI, 0.7–1.4) for current smokers. Compared with lifetime nonsmokers who were not exposed to secondhand smoke, women who reported secondhand smoke exposure after 18 years of age (based on living with a smoker at age 18 years or older) had a RR of 1.3 (95 percent CI, 0.9–1.9); this association was stronger among premenopausal women (OR = 1.5 [95 percent CI, 0.8–2.8]) than among postmenopausal women (OR = 1.2 [95 percent CI, 0.7–2.2]).

A second report on active smoking and secondhand smoke exposure from this population was based on all participants (864 cases, 790 controls) who were interviewed between 1993 and 1996, including 445 cases and 423 controls who had never smoked (Table 7.9) (Marcus et al. 2000). Lifetime nonsmokers who reported secondhand smoke exposures before 18 years of age did not show an elevated risk of breast cancer (OR = 0.8 [95 percent CI, 0.6–1.1]) compared with women who reported no exposures. The association with secondhand smoke exposures before 18 years of age did not change after adjusting for exposures after 18 years of age. In both reports, Millikan and colleagues (1998) and Marcus and colleagues (2000) adjusted the results on secondhand smoke exposure for race, age at diagnosis/selection, and sampling design, but not for other covariates. Questions on secondhand smoke exposure were not comprehensive, but focused primarily on exposures in the home before and after the women were 18 years of age.

Kropp and Chang-Claude (2002) conducted a case-control study of breast cancer in women 51 years of age or less in two study areas in Germany (Table 7.9). Active smoking, but not involuntary smoking, was assessed in the original study, which was conducted between 1992 and 1995. In 1999, the 706 women with in situ or invasive breast cancer and the 1,381 controls who were interviewed in the original study were recontacted. A total of 468 cases (66.3 percent) and 1,093 (79.2 percent) controls participated in the second interview; 115 cases and 3 controls were deceased by the time of the attempted recontact. Participants were asked extensive questions regarding active smoking

and involuntary smoking that included household exposure during childhood and adulthood, as well as workplace exposure. Information on age at exposure, duration of exposure, and intensity of exposure (i.e., number of smokers, hours of daily exposure) was obtained. Compared with lifetime nonsmokers with no secondhand smoke exposure, lifetime nonsmokers who were exposed showed a significantly increased risk (adjusted OR = 1.61 [95 percent CI, 1.08–2.39]). The increased risk was associated with exposure during adulthood (adjusted OR = 1.80 [95 percent CI, 1.12–2.89]) but not with exposure only during childhood (adjusted OR = 1.07 [95 percent CI, 0.52–2.19]). There was little difference in risk by duration of exposure; the adjusted OR was 1.85 (95 percent CI, 1.15–2.98) for a shorter duration (1 to 10 years) and 1.51 (95 percent CI, 0.89–2.56) for a longer duration of exposure (≥21 years). Risk patterns were also similar for current versus former secondhand smoke exposure. There was a trend of increasing risk with lifetime exposure (childhood and adulthood combined) when an index of lifetime hours per day-years of exposure was used: the ORs were 1.83 (95 percent CI, 1.16–2.87) for high exposures (≥51 hours per day-years) and 1.42 (95 percent CI, 0.90–2.26) for lower exposures (1 to 50 hours per day-years). However, in this study, the estimated OR for secondhand smoke exposure (OR = 1.61) was higher than for former (OR = 1.15) or current active smokers (OR = 1.47).

This study has several limitations. First, the women were recontacted specifically regarding a secondhand smoke exposure history, raising the possibility of information bias. Second, a substantial proportion of both cases and controls did not participate, indicating a potential for the introduction of selection bias.

Gammon and colleagues (2004) investigated the role of secondhand smoke and breast cancer using the Long Island Breast Cancer Study, which was conducted among residents of Nassau and Suffolk counties. The study included 1,356 women with breast cancer and 1,383 controls from the general population; 598 cases and 627 controls were lifetime nonsmokers (Table 7.9). Lifetime exposure to residential secondhand smoke was assessed, including exposure to smoking by parents, spouses, and other household members. Compared with lifetime nonsmokers who were not exposed to secondhand smoke (155 cases, 170 controls), lifetime nonsmokers who were exposed showed no increased risk (adjusted OR = 1.04 [95 percent CI, 0.81–1.35]). The risk of breast cancer was not increased in association with exposure to parental smoking before 18 years of age or exposure before a first full-term pregnancy. When the total duration of exposure was considered, there was little indication that long-term exposure to household tobacco smoke increased breast cancer risk; the OR for living with a smoker for 361 or more months was 1.22 (95 percent CI, 0.90–1.66). When the analysis was restricted to household exposure from spouses, the OR for living with a spouse who smoked for 361 or more months was 2.10 (95 percent CI, 1.47–3.02), but there was not a significant trend of increasing risk with increasing duration. Analysis by menopausal status showed a small increased risk associated with secondhand smoke exposure in premenopausal women (adjusted OR = 1.21 [95 percent CI, 0.78–1.90]), but not in postmenopausal women (adjusted OR = 0.93 [95 percent CI, 0.68–1.29]). Exposure to secondhand smoke was not significantly associated with risk in analyses that were stratified by other parameters of interest including age, body mass index, use of alcohol, use of hormone replacement therapy, use of oral contraceptives, and family history of breast cancer.

A risk of breast cancer was not related to active smoking in this study. Compared with lifetime nonsmokers who were not exposed to secondhand smoke, the adjusted OR was 1.06 (95 percent CI, 0.76–1.48) for active smokers and 1.15 (95 percent CI, 0.90–1.48) for active smokers who were also exposed to secondhand smoke. The study did not assess exposure in the workplace.

Bonner and colleagues (2005) investigated the role of secondhand smoke and breast cancer among residents in Erie and Niagara counties as part of the Western New York Exposures and Breast Cancer Study. This population-based, case-control study included women aged 35 to 79 years who were diagnosed with histologically confirmed, primary incident breast cancer. Population controls from the study areas were selected from Department of Motor Vehicles driver's license list or from the Centers for Medicare and Medicaid Services lists. There were questions about exposure to secondhand smoke from other household residents and coworkers for seven time periods (<21 years of age and for each subsequent decade of life). The questions asked for the number of smokers in the household and how long they lived in the same residence. Workplace exposure was estimated by the number of hours per week study participants were exposed to coworkers' smoking. The main analysis on lifetime household and workplace exposure included 525 cases (149 premenopausal, 376 postmenopausal) and 1,012 controls (326 premenopausal, 686 postmenopausal) who were lifetime nonsmokers. In addition, secondhand smoke exposure was

determined as part of the residential history assessment. Participants listed every residence for their entire life with corresponding information on the number of smokers at each residence. On the basis of this information, exposures at birth, at menarche, and at the time of first birth were evaluated. Residential history assessment was obtained from a subset of lifetime nonsmoking cases (106 premenopausal, 228 postmenopausal) and controls (238 premenopausal, 371 postmenopausal).

Breast cancer risk increased, but not significantly, in association with lifetime household exposure to secondhand smoke; there were no significant trends of increasing risks with increasing duration of exposure in premenopausal (p trend = 0.60) and postmenopausal (p trend = 0.38) women (Table 7.9). In an analysis restricted to household smoking before 21 years of age, risk did not increase significantly in premenopauasal (p trend = 0.99) and postmenopausal (p trend = 0.09) women. Breast cancer risk was unrelated to workplace secondhand smoke exposure in premenopausal (p trend = 0.38) and postmenopausal (p trend = 0.41) women; almost all of the RR estimates were below unity. In premenopausal women, exposures to smoking at birth, at menarche, and at the time of first birth were associated with an 11 to 49 percent increase in risk, but none of the associations was statistically significant. In postmenopausal women, all the RR estimates were close to or below unity.

This case-control study obtained extensive information on lifetime household and workplace exposure. In addition, exposure to household smoking was collected using a second method as part of a residential history assessment. Risk of breast cancer was not significantly associated with any of the measures of secondhand smoke exposure in premenopausal and postmenopausal women. This is one of the few studies that presented data on lifetime nonsmoking cases and controls by menopausal status, so comparability of the case and control groups can be assessed.

Three Chinese studies have addressed the role of secondhand smoke exposure and breast cancer risk in lifetime nonsmokers (Zhao et al. 1999; Liu et al. 2000; Shrubsole 2004). As discussed below, there is concern regarding the design of two of the studies (Zhao et al. 1999; Liu et al. 2000). Zhao and colleagues (1999) conducted a hospital-based study of breast cancer in Chengdu, China, between 1994 and 1997. The study included 265 women who were clinically determined to have breast cancer and an equal number of female controls who were individually matched to cases for age, area of residence, similar occupation, and similar education (the nature of this matching was not specified). The sources of controls were heterogeneous and included family members, visitors, neighbors, friends, or outpatients with benign conditions. Although 259 breast cancer patients and 252 controls were identified as nonsmokers of cigarettes, information on secondhand smoke was presented on 265 cases and 265 controls who were presumably nonsmokers, although this difference was not specifically mentioned in the text. The authors reported a significantly increased risk associated with secondhand smoke exposure (adjusted OR = 2.49 [95 percent CI, 1.65–3.77]) after adjustment for various covariates including breastfeeding, history of benign breast disease, and intake of soybean products. On the basis of 13 cases and 6 controls who were cigarette smokers (it is not known whether these were current smokers or former smokers), breast cancer risk increased more than twofold among smokers (OR = 2.75 [95 percent CI, 0.87–8.65]) compared with nonsmokers (Table 7.9). Methodologic limitations of this study include the uncertain selection criteria of the cases (i.e., incident versus prevalent cases, clinical diagnosis of breast cancer), the suitability of the control groups, and a lack of information regarding the questions on secondhand smoke exposure (e.g., sources and timing of exposure).

Liu and colleagues (2000) conducted a hospital-based, case-control study of breast cancer in Chongqing, China, that included 186 women with incident breast cancer and 186 controls who were outpatients in the same hospital and were individually matched to cases for age (±2 years), date of hospitalization/admission, and marital status, and were lifetime nonsmokers. Cases and controls were 24 to 55 years of age. Questions related to secondhand smoke exposure for three time periods: childhood (aged <10 years), youth (aged 10 through 16 years), and adulthood (including exposures at home and at work). Two variables were used to describe exposures at home: number of smokers and a combined exposure index that included the number of smokers and the amount they smoked (light, medium, heavy, and very heavy). The risk of breast cancer increased significantly in association with the number of smokers in the household during childhood (p trend <0.05) but not during youth (p trend >0.05) or adulthood (p trend >0.05). When the amount smoked was also considered (i.e., using the combined exposure index), there was a significant trend of increasing risk with increasing levels of exposure during childhood (p trend <0.05) and adulthood (p trend <0.01) but not during youth. When household exposures during childhood, youth, and adulthood and workplace exposure were considered

simultaneously, the researchers found a significantly increased risk associated with childhood household exposure (adjusted OR = 1.24 [95 percent CI, 1.07–1.43]), adulthood household exposure (adjusted OR = 4.07 [95 percent CI, 2.21–7.50]), and workplace exposure (adjusted OR = 1.27 [95 percent CI, 1.04–1.55]).

Cases and controls differed considerably in terms of education, occupation, and social class. Cases had less education than controls (26 percent of cases versus 9 percent of controls had less than high school). A significant excess of cases also reported below average family socioeconomic status (SES) during each of the three time periods (childhood, youth, adulthood) than controls. However, cases were more likely to be professionals (46 percent) than controls (25 percent) and were less likely to be workers (29 percent) than controls (66 percent). Exposure to secondhand smoke at home and in the workplace may vary by education, occupation, and family SES. In the multivariate analysis, only socioeconomic class during youth was considered. Thus, potential confounding by these social class and occupational variables cannot be ruled out in this study.

Shrubsole and colleagues (2004) investigated the role of secondhand smoke exposure in the Shanghai Breast Cancer Study, a large population-based study of 1,459 breast cancer cases and 1,556 population controls aged 25 to 64 years. Questions about secondhand smoke exposure were added to the study seven months after data collection began, and 1,119 cases and 1,231 controls responded. Analyses on secondhand smoke exposure and risk were restricted to lifetime nonsmokers who were currently married (1,103 cases and 1,117 controls). Two sources of secondhand smoke exposure were assessed: husband's smoking and exposure at work the during the five years before diagnosis/interview. A risk of breast cancer was unrelated to the husband's smoking (adjusted OR = 1.0 [95 percent CI, 0.8–1.2]); all of the ORs associated with different categories of the husband's smoking, including the number of cigarettes smoked and the number of years and pack-years of smoking, were close to unity. Breast cancer risk was also unrelated to secondhand smoke exposure in the workplace (adjusted OR = 1.1 [95 percent CI, 0.9–1.4]). The RRs were also close to unity when both sources of exposure were considered together (i.e., none, workplace only, husband's smoking only, and both exposures); these results were similar in premenopausal and postmenopausal women (Table 7.9). However, breast cancer risk tended to increase with an intense exposure at work. When women with workplace secondhand smoke exposure (457 cases, 463 controls) were compared with those with no exposure at work or from their husbands (176 cases, 184 controls), there was a significant trend of an increase in risk with an increase in duration of daily workplace secondhand smoke exposure (p trend = 0.02). In premenopausal women, the ORs were 1.0, 0.9, 1.1, 1.1, and 1.6, respectively, in association with none, 1 to 59, 60 to 179, 180 to 299, and 300 or more minutes of exposure per day (p trend = 0.03). The corresponding ORs were 1.0, 1.1, 1.3, 1.4, and 1.4, respectively (p trend = 0.37), in postmenopausal women. To date, this is the largest case-control study of breast cancer in lifetime nonsmokers that assessed information on household and workplace exposures. One limitation is that information on workplace exposures was limited to the five years before the interview. In addition, there was no information on childhood exposures.

Quantitative Meta-Analysis

To synthesize the observational evidence, the technique of quantitative meta-analysis was used. The RR estimates for the various exposure measures from reports on cohort and case-control studies were abstracted and then combined using the statistical software package Stata. The studies used a variety of exposure measures to assess childhood or adulthood exposures, sources of exposure, and location of exposure. A documented set of decisions was made as to the selection of estimates from the studies. Additionally, some of the studies provided results by menopausal status.

Pooled estimates were calculated for three population samples: all women in a study (regardless of menopausal status), premenopausal women, and postmenopausal women. Eight exposure categories were considered: (1) any source during adulthood (adult all sources), (2) adult spousal/partner (adult spousal), (3) adult at home (includes smoking from any cohabitant), (4) adult at work, (5) child at home (usually parental), (6) both childhood and adulthood exposure (either at home or work or both), (7) ever exposure in studies that measured child and adult exposures (either at home or at work or both), and (8) the most comprehensive exposure for each study. For all categories, estimates of independent effects were selected over estimates of "ever" effects. In other words, if a study presented results for "ever exposed as a child" (regardless of adulthood exposure) as well as "exposed during childhood only" (no adulthood exposure), the latter was used in the analysis of childhood exposure because it represents a more unbiased estimate of the effect of childhood exposure independent of exposure during adulthood.

Whenever possible, the studies used adjusted estimates. The researchers performed subanalyses to investigate the influence of adjustment on the results. Studies were categorized according to whether they adjusted for reproductive factors (age at menarche, age at first birth, and parity) and for alcohol consumption. These factors were the focus of attention because they were the most important potential confounders.

Table 7.10 provides the main findings of the meta-analysis, including the pooled estimates and 95 percent CIs. Overall, breast cancer risk in lifetime nonsmokers was significantly associated with secondhand smoke exposure, but with stratification by menopausal status, the association was limited to premenopausal women, and estimates for postmenopausal women for adult exposure were below unity, although not statistically significant (Table 7.10, Figures 7.1–7.4). The pattern was similar when spousal smoking alone was considered (Table 7.10) and the estimate for workplace exposure was also higher for women with premenopausal breast cancer than for those with postmenopausal breast cancer. Exposure in childhood was not associated with increased risk.

Sensitivity analyses were carried out that explored variations in the pooled estimates by the type of study, the extent of the exposure information available, and consideration of confounding (Table 7.10). Findings from the cohort studies showed no association overall of breast cancer risk with secondhand smoke exposure, although the pooled estimate from the case-control studies was positive and statistically significant. The estimate was particularly high for hospital-based case-control studies. Comparing estimates for studies with and without consideration of confounding, the estimate was lower for those studies that included adjustment for potential confounding.

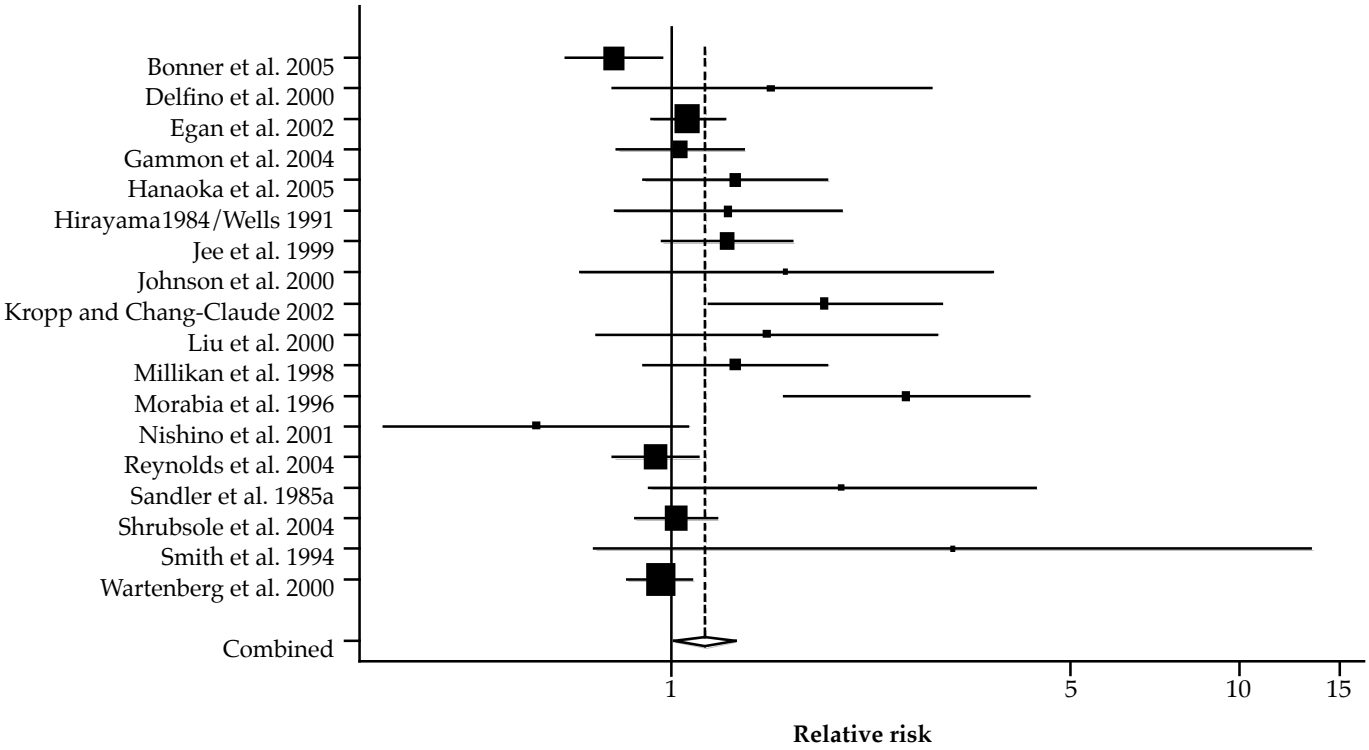
In Figure 7.5, the 21 studies are evaluated for potential publication bias using a funnel plot and a test developed by Begg and Mazumdar (1994). The funnel plot shows that less precise studies tended to have more strongly positive results, a pattern indicative of possible publication bias. The formal test for such bias was statistically significant ($p < 0.05$).

Table 7.10 Pooled risk estimates and 95% confidence intervals (CI) for breast cancer meta-analysis

	All women		Premenopausal		Postmenopausal	
Exposure	**n***	**Relative risk (95% CI)**	**n**	**Relative risk (95% CI)**	**n**	**Relative risk (95% CI)**
Adulthood						
All sources	18	1.15 (1.02–1.29) [0.000]†	10	1.45 (1.04–2.01) [0.000]	9	0.90 (0.81–1.01) [0.691]
Spouse	9	1.17 (0.96–1.44) [0.002]	4	1.40 (0.92–2.12) [0.1]	3	0.86 (0.67–1.12) [0.645]
Home	8	1.01 (0.85–1.19) [0.006]	4	1.28 (0.94–1.74) [0.355]	3	0.92 (0.76–1.11) [0.591]
Work	6	1.06 (0.84–1.35) [0.008]	4	1.21 (0.70–2.09) [0.000]	3	0.83 (0.53–1.29) [0.086]
Childhood (parent)	9	1.01 (0.90–1.12) [0.101]	4	1.14 (0.90–1.45) [0.342]	3	1.04 (0.86–1.26) [0.242]
Both childhood and adulthood	4	1.39 (0.88–2.18) [0.021]	3	1.63 (0.68–3.91) [0.016]	2	1.02 (0.74–1.42) [0.160]
Ever exposed (in studies measuring lifetime exposure)	10	1.40 (1.12–1.76) [0.000]	6	1.85 (1.19–2.87) [0.001]	5	1.04 (0.84–1.30) [0.048]
"Best" of each study‡	21	1.20 (1.08–1.35) [0.000]	11	1.64 (1.25–2.14) [0.001]	10	1.00 (0.88–1.12) [0.321]
Cohort studies	7	1.02 (0.92–1.13) [0.162]				
Case-control studies	14	1.40 (1.17–1.67) [0.000]				

*n = Number of studies included in each analysis.
†[in brackets] = p value for test of heterogeneity (null hypothesis is no heterogeneity).
‡"Best" of each study includes the most comprehensive measure of association from each study: ever being exposed in any setting was preferred over all sources during adulthood, which was preferred over spousal exposure.

Figure 7.1 Relative risks (with 95% confidence intervals) of breast cancer associated with all sources of adult exposure to secondhand smoke



Note: Different sized squares represent the weights of each study's relative risks in the combined estimates.

Evidence Synthesis

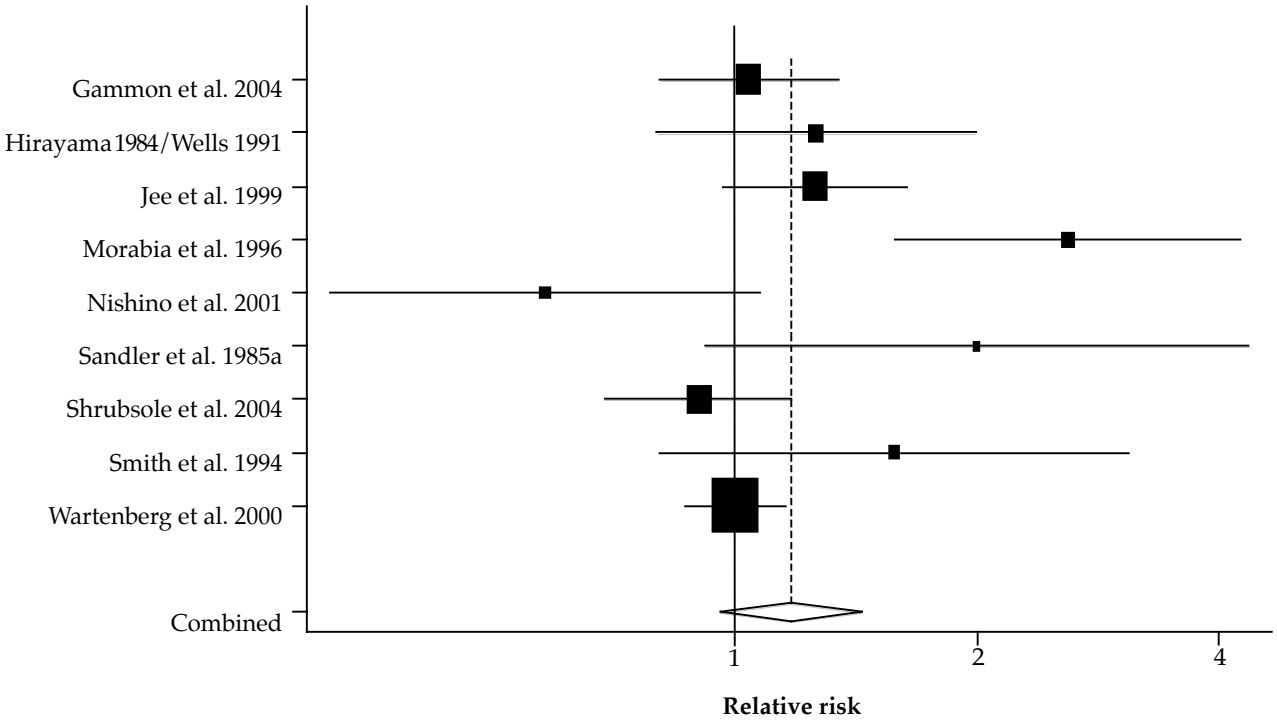
The full body of evidence on secondhand smoke and breast cancer was evaluated with the criteria for causality, which have been used in this series of reports for a long time (Chapter 1, Introduction, Summary, and Conclusions). Consideration was also given to the extensive information on active smoking and breast cancer. Issues related to sources of secondhand smoke exposure, dose-response relationships, and differences in findings by menopausal status were also considered.

Consistency

Consistency refers to the replication of findings across studies with different designs, in different populations, and conducted by different investigators (USDHHS 2004). To the extent that findings are comparable across a range of study characteristics, alternative explanations to causation in explaining associations become less tenable, particularly bias arising from methodologic limitations of particular designs.

There are currently 21 epidemiologic studies (7 cohort, 14 case-control) that have directly investigated the association between secondhand smoke exposure and the risk of breast cancer among lifetime nonsmokers. The overall evidence does not consistently show an increased risk of breast cancer in association with secondhand smoke, although the pooled estimate of all the evidence is above unity, the level of no effect (Table 7.10); the evidence is not consistent by study design. Three well-established U.S. cohort studies each include a large number of breast cancer events: 669 breast cancer deaths in the ACS cohort; 1,359 incident invasive breast cancers in the NHS cohort; and 1,174 incident invasive breast cancers in the California Teachers Study cohort. These studies did not find an association between exposure to secondhand smoke and breast cancer risk; all RR estimates were around unity (Wartenberg et al. 2000; Egan et al. 2002; Reynolds et al. 2004).

Figure 7.2 Relative risks (with 95% confidence intervals) of breast cancer associated with adult exposure to secondhand smoke from spouses' smoking

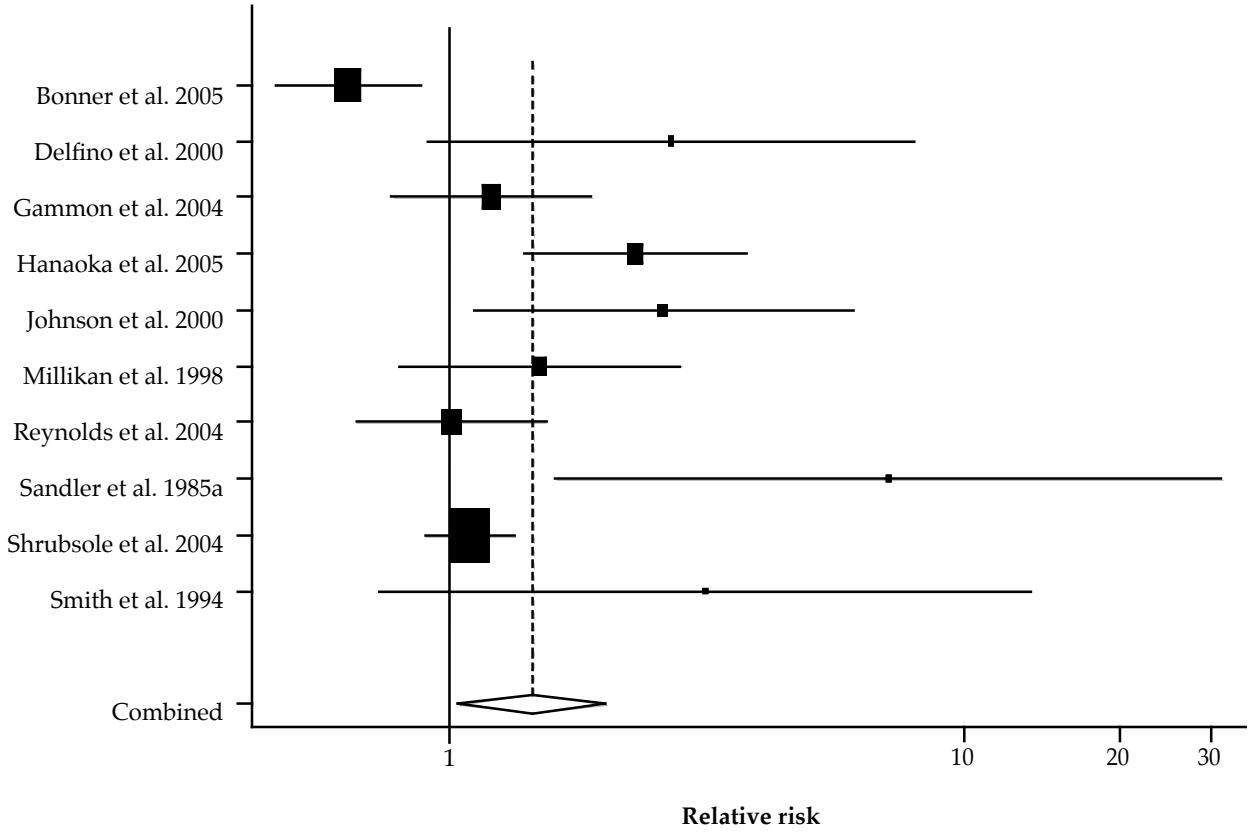


Note: Different sized squares represent the weights of each study's relative risks in the combined estimates.

Results from the four cohort studies from Asia are based on fewer breast cancer events (<200 breast cancer incident cases/deaths) and are more varied, but also do not provide consistent evidence for an association. Small RR increases of 10 to 30 percent were reported in three of the studies (Hirayama 1984; Jee et al. 1999; Hanaoka et al. 2005), whereas a RR less than unity was reported in the fourth study, which is from Japan (Nishino et al. 2001). The only significant finding came from a subgroup analysis in a cohort study in Japan with stratification by menopausal status (Hanaoka et al. 2005). This finding was based on 77 breast cancers in premenopausal women. The pooled estimate for the cohort studies is 1.02 overall. This null finding from the cohort studies cannot be set aside as a result of methodologic limitations, because some of these studies have shown an increased risk for lung cancer and CHD associated with secondhand smoke.

Results from the 14 case-control studies are more supportive of an increased risk associated with secondhand smoke exposure, but there is considerable heterogeneity in the study results. Five studies found at least a twofold increase in RRs associated with secondhand smoke exposure (Smith et al. 1994; Morabia et al. 1996; Lash and Aschengrau 1999; Johnson et al. 2000; Kropp and Chang-Claude 2002); results were statistically significant in four of these studies. As described above, the study conducted by Lash and Aschengrau (1999) had design limitations, and a subsequent study in the same area conducted by the same investigators using a comparable design did not confirm the earlier results (all RR estimates were <1.0) (Lash and Aschengrau 2002). The other four studies (Smith et al. 1994; Morabia et al. 1996; Johnson et al. 2000; Kropp and Chang-Claude 2002) considered by Johnson (2005) to be more complete in assessing lifetime secondhand smoke exposures had other study limitations, including the potential for differential recall bias, misclassification due to missing data, and selection bias. In the study by Kropp and Chang-Claude (2002), participants were

Figure 7.3 Relative risks (with 95% confidence intervals) of breast cancer associated with all sources of adult exposure to secondhand smoke among premenopausal women

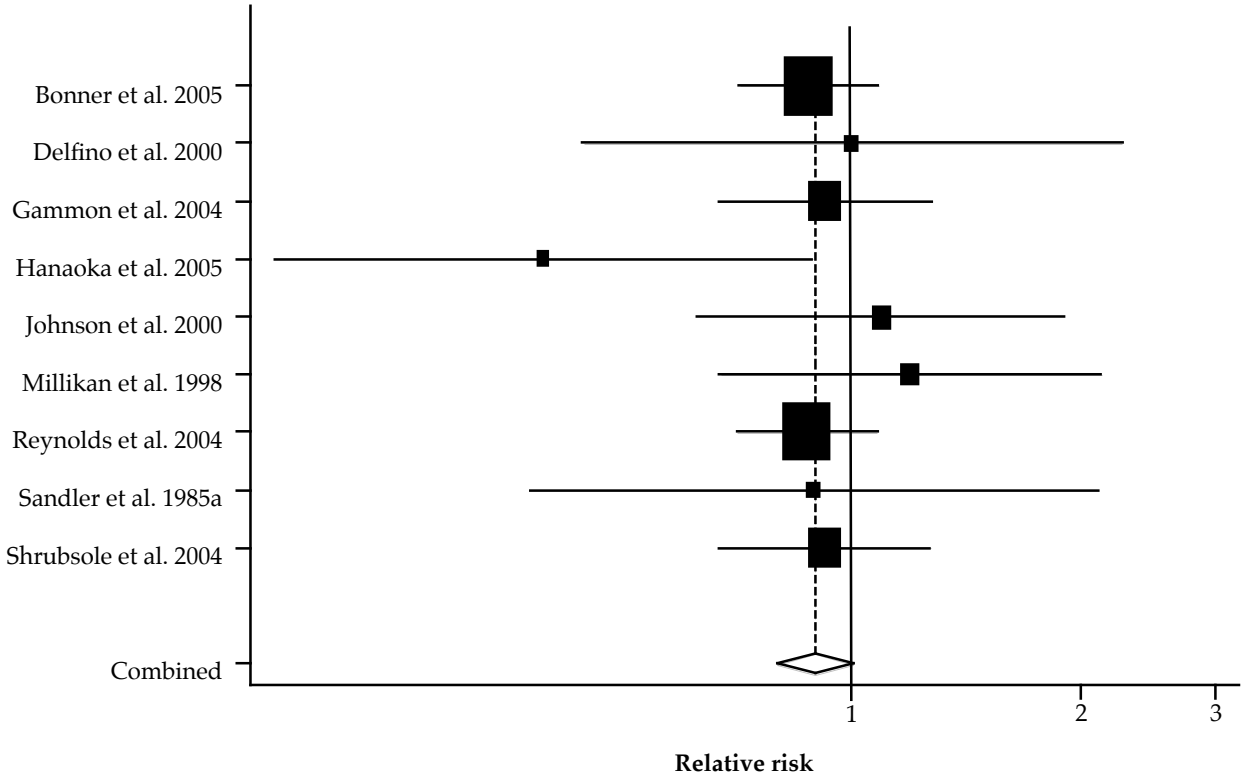


Note: Different sized squares represent the weights of each study's relative risks in the combined estimates.

recontacted four to seven years after the initial interview, and the reinterview response rate was lower in cases (66 percent) than in controls (79 percent). Given that the focus of the reinterview was to determine the history of active smoking and exposure to secondhand smoke, it would have been difficult to "blind" participants as to the study hypothesis, and the possibility of differential recall bias by case/control status exists and may have led to an overestimate of the risk. Smith and colleagues (1994) also recontacted study participants to determine histories of secondhand smoke exposure, and thus the findings of this study are subject to the limitations discussed in regard to the study by Kropp and Chang-Claude (2002). In the study by Johnson and colleagues (2000), information on secondhand smoke exposure was obtained via a mailed questionnaire and was incomplete for 37 percent of the lifetime nonsmoking cases and 40 percent of the controls. Consequently, 470 (1,078 minus 608) lifetime nonsmoking cases and 487 (1,214 minus 727) lifetime nonsmoking controls were not included in the analysis. In the study by Morabia and colleagues (1996), controls were younger (21 percent were younger than 45 years of age) than cases (11 percent were younger than 45 years of age), and variables related to menopause status were not considered in the analysis. There were also methodologic limitations of the studies carried out in China.

In contrast, no significant increase in risk was found in four large population-based, case-control studies (Millikan et al. 1998; Gammon et al. 2004; Shrubsole et al. 2004; Bonner et al. 2005). According to Johnson (2005), results from three of these studies are less credible because exposure assessment was

Figure 7.4 Relative risks (with 95% confidence intervals) of breast cancer associated with all sources of adult exposure to secondhand smoke among postmenopausal women



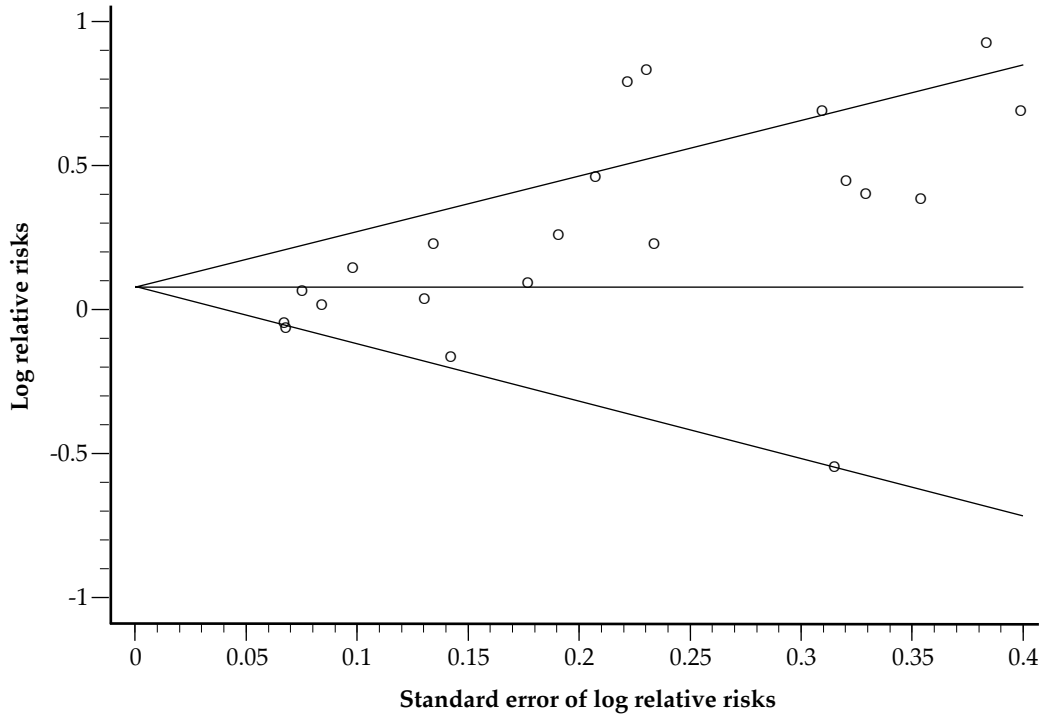
Note: Different sized squares represent the weights of each study's relative risks in the combined estimates.

incomplete (Millikan et al. 1998; Gammon et al. 2004; Shrubsole et al. 2004) (the study by Bonner et al. [2005] was published after Johnson's 2005 review). In fact, major lifetime sources of secondhand smoke exposure (childhood exposure from parents, adult residential exposure, and adult occupational exposure) were assessed in the western New York study, and there was no association between risk and each source of exposure nor with lifetime exposure across these different sources (Bonner et al. 2005). Two of the studies did not assess workplace exposure (Millikan et al. 1998; Gammon et al. 2004), and one study limited workplace secondhand smoke exposure assessment to the most recent job, and did not obtain information on childhood exposure (Shrubsole et al. 2004).

A strength of the epidemiologic evidence on secondhand smoke and lung cancer has been the consistency across prospective cohort and case-control studies. Cohort and case-control studies are generally subject to somewhat differing sources of bias, and a comparability of findings in the two designs weighs against bias as the source of association. The findings of the two designs differ for secondhand smoke exposure and breast cancer, raising a concern that bias affected the findings of the case-control studies. The hospital-based, case-control studies show the strongest association and are particularly prone to bias from the noncomparability of cases and controls, and from the differential reporting of exposures by cases and controls.

To further assess the consistency of the association between secondhand smoke exposure and risk of breast cancer, risk patterns were examined by the sources of exposure. There are three major classes of exposure (childhood exposure from parental smoking, adult residential exposures, and occupational exposures). To date, all studies have characterized adulthood household exposure. Information on

Figure 7.5 Begg's funnel plot with pseudo 95% confidence limits for 21 studies of breast cancer and secondhand smoke exposure



Note: Asymmetry on the right side of the graph (where studies with high standard errors are plotted) provides evidence of publication bias.

childhood secondhand smoke exposure is available in three cohort (Egan et al. 2002; Reynolds et al. 2004; Hanaoka et al. 2005) and seven case-control studies (Smith et al. 1994; Morabia et al. 1996; Johnson et al. 2000; Marcus et al. 2000; Kropp and Chang-Claude 2002; Gammon et al. 2004; Bonner et al. 2005). Workplace exposure was captured in three cohort (Wartenberg et al. 2000; Egan et al. 2002; Hanaoka et al. 2005) and six case-control studies (Smith et al. 1994; Morabia et al. 1996; Johnson et al. 2000; Kropp and Chang-Claude 2002; Gammon et al. 2004; Bonner et al. 2005).

Those studies that have obtained lifetime secondhand smoke exposure histories are also informative because risk patterns by source of exposure may provide information regarding the timing and intensity of exposure. There are different exposure assessment approaches in the studies, however, and results have not been consistently reported for all epochs of exposure, thus complicating comparisons across studies. Researchers have considered exposure to secondhand smoke early in life to be particularly important for premenopausal breast cancer. In two U.S. cohort studies, breast cancer risk did not increase in association with childhood exposure from parents (Egan et al. 2002; Reynolds et al. 2004). Similarly, a risk of breast cancer was not significantly associated with childhood secondhand smoke exposure in case-control studies (Smith et al. 1994; Johnson et al. 2000; Kropp and Chang-Claude 2002; Gammon et al. 2004; Bonner et al. 2005) (risk patterns were presented for childhood and adulthood exposures combined in two studies [Marcus et al. 2000; Hanaoka et al. 2005]). There is also little support for the hypothesis that secondhand smoke exposure before a first pregnancy is associated with breast cancer risk (Kropp and Chang-Claude 2002; Lash and Aschengrau 2002; Gammon et al. 2004; Bonner et al. 2005). Thus, the collective evidence does not consistently show an association

of secondhand smoke exposure during childhood/adolescence or before a first pregnancy—a period of time when the breast may be particularly susceptible to carcinogen exposure, as in the case of ionizing radiation (NRC 2005).

The risk of breast cancer was not significantly related to workplace secondhand smoke exposure in two U.S. cohort studies (Wartenberg et al. 2000; Egan et al. 2002) and in two case-control studies (Smith et al. 1994; Bonner et al. 2005); lifetime workplace exposure was assessed in the case-control studies. In a cohort study conducted in Japan, the risk of breast cancer in premenopausal women was increased in association with workplace secondhand smoke exposure, but no increased risk was observed in postmenopausal women (Hanaoka et al. 2005). In Shanghai, China, an intense (>300 minutes per day), daily, and recent workplace exposure was associated with an increased risk of breast cancer in both premenopausal and postmenopausal women, although the estimate was statistically significant only in premenopausal women (Shrubsole et al. 2004). In the three studies that found a significantly increased risk associated with adulthood exposure (Morabia et al. 1996; Johnson et al. 2000; Kropp and Chang-Claude 2002), RR estimates were not shown separately for occupational versus household exposures. However, in the study by Morabia and colleagues (1996), the risk estimates for spousal smoking were slightly stronger than for all sources of exposure during adulthood combined. Thus, some (but not all) studies offer evidence that breast cancer risk may be increased in association with workplace secondhand smoke exposure.

Temporality

The criterion of temporality requires that exposure to secondhand smoke antedate the onset of cancer, so information from prospective cohort studies is particularly relevant. In prospective cohort studies, women initially free of breast cancer are followed over varying time intervals, and their risk is estimated in relation to secondhand smoke exposure. As described above, there is currently little evidence indicating an increased breast cancer risk from prospective cohort studies, including the three large, well-established cohorts in the United States (Wartenberg et al. 2000; Egan et al. 2002; Reynolds et al. 2004). The risk of breast cancer was unrelated to adulthood secondhand smoke exposure in the ACS study (Wartenberg et al. 2000), the NHS (Egan et al. 2002), and the California Teachers Study (Reynolds et al. 2004) (information on workplace secondhand smoke was available in the NHS and ACS studies). Similarly, a risk of breast cancer was not related to exposure during childhood in the NHS and the California Teachers Study (Egan et al. 2002; Reynolds et al. 2004). One of the Japanese cohort studies (JPHC study) collected information on household secondhand smoke exposure during childhood and adulthood and on workplace exposure; this study also showed no overall association between secondhand smoke exposure and risk in all subjects combined (Hanaoka et al. 2005). In general, secondhand smoke exposure extends across the life span and typically would have begun long before the onset of breast cancer.

Strength of Association

Increasing the strength of association weighs more heavily against alternatives to causal association (USDHHS 2004). For involuntary smoking and breast cancer risk, the overall association in the pooled estimates for premenopausal breast cancer indicate elevations of 40 to 60 percent (Table 7.10). However, the highlighted limitations of the case-control studies of passive smoking and breast cancer, particularly selection bias and information bias, may be responsible, at least in part, for the increased risk. The inconsistent findings of the case-control and cohort studies for the association of passive smoking with premenopausal breast cancer also raise concerns about potential bias or unmeasured confounding, since consistency of risk estimates across varying study designs would weigh against such bias.

Assessment of dose-response relationships is another aspect of this criterion. Duration of exposure to spousal and household smoking was used in most studies for assessing exposure-response relationships (Smith et al. 1994; Jee et al. 1999; Lash and Aschengrau 1999, 2002; Wartenberg et al. 2000; Egan et al. 2002; Gammon et al. 2004; Shrubsole et al. 2004; Bonner et al. 2005). A few studies also collected information on intensity of exposure (i.e., hours and days of secondhand smoke exposure), and on estimated risk patterns by hours per day-years (Morabia et al. 1996; Kropp and Chang-Claude 2002) or minutes of secondhand smoke exposure per day (Shrubsole et al. 2004). Of the four studies showing a strong positive association between exposure and breast cancer risk (Smith et al. 1994; Morabia et al. 1996; Johnson et al. 2000; Kropp and Chang-Claude 2002), only one showed a trend of increasing risk with increasing duration of exposure and only among premenopausal women (Johnson et al. 2000). Among premenopausal women, the ORs were 1.2, 1.8, 2.0, 3.3, and 2.9, respectively, in

association with 1 to 6, 7 to 16, 17 to 21, 22 to 35, and 36 or more years of residential and occupational exposures. The pattern of association is much weaker in postmenopausal women (ORs were 1.1, 1.3, and 1.3, respectively, in association with 1 to 30, 31 to 56, and more than 56 years) (Johnson et al. 2000). However, in three other studies, RR estimates were similar for varying durations of exposure and for current versus former exposures. In the study by Morabia and colleagues (1996), the ORs were 2.2 and 2.5 in association with 1 to 50 and more than 50 hours per day-year of exposure, respectively. In the study by Kropp and Chang-Claude (2002), the ORs were 1.85, 1.59, and 1.51 with 1 to 10, 11 to 20, and 21 or more years of exposure, respectively. In the same study, the risks were 1.55 for former and 1.67 for current exposures to secondhand smoke. In the study by Smith and colleagues (1994), the ORs were 2.82 and 2.24 in association with 1 to 200 and more than 200 cigarette-years, respectively.

Of the studies not showing any overall association between secondhand smoke and breast cancer risk, one showed a twofold increase among women exposed to 326 or more months of spousal smoking, but there was no evidence of an exposure-response gradient (Gammon et al. 2004). Another study showed a 70 percent increase in risk among women married to current smokers of 30 or more years (Jee et al. 1999). However, in several larger cohort (Wartenberg et al. 2000; Egan et al. 2002) and case-control studies (Shrubsole et al. 2004; Bonner et al. 2005), there is little evidence of elevated risks even with the highest duration of household exposure.

Biologic Plausibility

There is substantial literature on carcinogenesis in relation to breast cancer, but with more limited information directly relevant to tobacco smoke. One key aspect of biologic plausibility of secondhand smoke as a cause of breast cancer is the finding on active smoking and breast cancer. Additionally, the potential heterogeneity of breast cancer in relation to etiologic risk factors merits consideration. Epidemiologic research has only recently been directed at subgroups of breast cancer cases, defined by phenotype, such as estrogen and progesterone receptor status and genotype (e.g., susceptibility [*BRCA1* or *BRCA2*] or carcinogen metabolism [*NAT2*]). To date, the evidence has not consistently shown active smoking to be associated with an increased risk in a particular subgroup (Althuis et al. 2004; Ghadirian et al. 2004; USDHHS 2004).

The weight of epidemiologic evidence suggests that active smoking is not causally related to breast cancer risk overall (USDHHS 2001, 2004; IARC 2004). In 2002, an international pooled analysis of 53 studies examining alcohol and active smoking and breast cancer risk found that the association between smoking and breast cancer was substantially confounded by alcohol intake. When the analysis was limited to nondrinkers, to exclude potential confounding by alcohol consumption, no relationship was found between active (former or current) smoking and breast cancer risk (Hamajima et al. 2002). However, this combined analysis did not examine relationships by dose/duration of smoking or timing of tobacco use—parameters of tobacco use that are potentially relevant (Terry et al. 2002). Results from several recent cohort studies show a 20 to 60 percent increase in the RR with 20 or more years of active smoking (Terry et al. 2002; Al-Delaminy et al. 2004; Reynolds et al. 2004; Gram et al. 2005), suggesting that the risk of breast cancer from long-term active smoking cannot be definitively excluded. However, the participants in the pooled analysis had an average age of approximately 52 years, implying more than 30 years of smoking on average, and the overall findings were null. There may now be selective publications of reports with positive findings. Possible consequences of smoking at an early age (i.e., during teenage years) for breast cancer risk continue to be investigated (Gram et al. 2005), although a meta-analysis of 11 studies showed that smoking before the birth of a first child was not associated with an increased risk (Lawlor et al. 2004). Because most of the published studies on active smoking and breast cancer risk examined the association using lifetime nonsmokers as the baseline group, thus including those involuntarily exposed, there has been concern that the effect of active smoking is underestimated (Morabia et al. 1996). Several recent studies have examined the association between active smoking and breast cancer risk after the removal of involuntary smokers from the referent category, and the effect of active smoking continues to be weak (Gammon et al. 2004; Reynolds et al. 2004; Gram et al. 2005).

Some case-control studies report a twofold increase in the RR of breast cancer in association with secondhand smoke exposure (Morabia et al. 1996; Johnson et al. 2000; Kropp and Chang-Claude 2002). This high point estimate, higher than for some well-established risk factors for breast cancer, appears biologically implausible because the weight of the evidence does not support a causal association between active smoking and breast cancer. A recent

study reported that nonsmoking women exposed to secondhand smoke displayed significantly decreased levels of urinary estrone conjugates (the major metabolite of estrogen) throughout their menstrual cycles, suggesting that secondhand smoke exposure may have antiestrogenic effects (Chen et al. 2005). These results, which need to be confirmed, suggest that both involuntary smoking and active smoking have some antiestrogenic consequences (Baron et al. 1990; USDHHS 2004). There is presently no evidence to support the hypothesis that secondhand smoke exposure may have direct harmful effects on the breast that are not balanced by opposing antiestrogenic effects of involuntary smoking (Johnson 2005).

The findings were heterogeneous by menopausal status. In four case-control studies (Millikan et al. 1998; Gammon et al. 2004; Shrubsole et al. 2004; Bonner et al. 2005) and one cohort study (Reynolds et al. 2004), breast cancer risk was not significantly associated with secondhand smoke exposure in both premenopausal and postmenopausal women (Figure 7.1). All five studies examined adult household exposures; workplace (Shrubsole et al. 2004; Bonner et al. 2005) and childhood (Reynolds et al. 2004; Bonner et al. 2005) secondhand smoke exposures were investigated in fewer studies. In contrast, in a case-control study conducted in Canada (Johnson et al. 2000) and in a cohort study conducted in Japan (Hanaoka et al. 2005), exposure to secondhand smoke was associated with a significant twofold to threefold increased risk in premenopausal women, whereas the RR in postmenopausal women was around unity (Johnson et al. 2000; Hanaoka et al. 2005). The stronger association in premenopausal women in these two studies cannot readily be explained. Although both studies assessed secondhand smoke exposure during childhood, risk patterns associated with childhood versus adulthood exposure were not presented. Thus, it is not known whether secondhand smoke exposure during different time periods contributed to differing risks in premenopausal and postmenopausal women in these studies. However, in two other studies of primarily premenopausal women (Smith et al. 1994; Kropp and Chang-Claude 2002), breast cancer risk was not significantly influenced by secondhand smoke exposure during childhood. Three other studies reported higher (approximately threefold to sevenfold) RR estimates in premenopausal women than in all women combined (Sandler et al. 1985a; Morabia et al. 1996; Delfino et al. 2000), but the CIs were wide, and the actual number of premenopausal lifetime nonsmoking cases and controls that were involved were not presented in these studies. Thus, the overall evidence on secondhand smoke exposure and breast cancer risk is consistent in postmenopausal women, showing no association (Table 7.10). However, findings are not consistent in premenopausal women.

To an extent, characteristics of premenopausal and postmenopausal breast cancer differ. Although the reproductive risk factors have similar effects in premenopausal and postmenopausal cases, the effects of obesity and physical activity vary by menopausal status (van den Brandt et al. 2000; Friedenreich 2004). Integrated models for breast cancer risk have been proposed that acknowledge the potential interplay of environmental and genetic factors across the life course (Hankinson et al. 2004; Colditz 2005). Such varying effects of risk factors with age would seem most plausible for those related to endogenous estrogens, as well as for exogenous estrogen (Hankinson et al. 2004). There is not yet an established biologic rationale for similarly considering that the effect of involuntary smoking would vary by menopausal status. Consequently, the differing findings by menopausal status cannot yet be interpreted within an established biologic framework, and the findings by menopausal status need to be interpreted with consideration of this constraint.

For one environmental carcinogen, ionizing radiation, there is greater susceptibility with exposure in adolescence (Preston et al. 2002; NRC 2005). By analogy, a greater RR might be anticipated for secondhand smoke exposure during childhood, on the assumption that exposure persists across adolescence. There was no increased risk in association with childhood exposure.

Summary

The overall evidence is mixed and does not strongly or consistently support a causal relationship between secondhand smoke and breast cancer. Findings from prospective cohort studies and case-control studies differ to an extent that cannot plausibly be explained by differences in the quality of exposure measurements. The positive association is largely observed in case-control studies among women with premenopausal breast cancer. While greater susceptibility to tobacco smoke carcinogens during adolescence or at an early age has been hypothesized, there is still considerable uncertainty as to why secondhand smoke would only affect risk for premenopausal breast cancer. The overall pooled estimate is elevated, but the elevation largely comes

from the increased risks estimated for premenopausal women in selected case-control studies. With regard to biologic plausibility, involuntary smoking would be expected to expose breast tissue to the carcinogens in secondhand smoke, as would active smoking. However, the evidence that active smoking causes no overall increase in breast cancer risks weighs against a causal role for involuntary smoking.

Conclusion

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

Implications

Because breast cancer remains one of the most frequent cancers, research should be continued on its potential causes, including secondhand smoke exposure. While awaiting further evidence, women should be encouraged to avoid involuntary exposures to secondhand smoke because of the many documented adverse effects of inhaling secondhand smoke.

Nasal Sinus Cavity and Nasopharyngeal Carcinoma

Nasal Sinus Cavity

Cancers of the nasal cavity and paranasal sinuses are extremely rare; they account for less than 1 percent of all invasive incident cancers and for less than 2 percent of all newly diagnosed respiratory cancers in the United States (Rousch 1996). Occupational exposures such as wood dust, use of tobacco products, history of nasal polyps, and certain dietary factors, including a low intake of plant foods and a high intake of salted preserved foods, have been implicated as risk factors for these tumors (Elwood 1981; Brinton et al. 1984; Hayes et al. 1987; Zheng et al. 1993; Demers et al. 1995; Rousch 1996; Mannetje et al. 1999). In different studies, investigators have observed a 1.5- to 5-fold greater risk in association with heavy smoking. Because the association between active smoking and nasal sinus cancers is strongest for squamous cell carcinomas, the strength of the association between active smoking (and secondhand smoke exposure) and all nasal sinus cancers combined is likely to depend on the proportion of squamous cell carcinomas that is included in different studies.

A few studies have investigated the relationship between secondhand smoke exposure and the risk of cancers in the upper respiratory tract, including nasal sinus cavity and nasopharyngeal carcinoma (NPC), among lifetime nonsmokers. These sites are potentially at risk because both gases and particles in secondhand smoke are removed to some extent in the upper airway. In one cohort study (Hirayama 1984) and two case-control studies (Fukuda and Shibata 1990; Zheng et al. 1993) conducted among Caucasian men in the United States (Zheng et al. 1993) and among women in Japan (Fukuda and Shibata 1990; Zheng et al. 1993), secondhand smoke exposure was associated with up to a threefold increase in risk of nasal sinus cancer after adjusting for potential confounders. These studies were reviewed in detail in the Cal/EPA report (NCI 1999), which concluded that the positive association between risk and secondhand smoke exposure was consistent and suggestive of a causal association. The positive association with secondhand smoke exposure is consistent with the relationship between active smoking and the risk of nasal sinus cancers. However, because the published studies were based on very modest sample sizes, further studies are needed to confirm the magnitude of risk associated with secondhand smoke exposure, to establish dose-response relationships, and to characterize the risk by the source (e.g., spouse, other household members, or coworkers) and by the timing of the exposure (current versus past exposure). The role of potential confounders, particularly occupational exposures, should be considered. Future studies should examine the association between secondhand smoke and nasal sinus cancer by histology type and subsite because the effects of tobacco smoke on nasal sinus cancers vary by both of those characteristics (Rousch 1996).

Nasopharyngeal Carcinoma

In addition to studies on the nasal sinus cavity, three case-control studies investigated the role of secondhand smoke in the etiology of NPC among lifetime nonsmokers (Yu et al. 1990; Cheng et al. 1999; Yuan et al. 2000). NPC is rare in most populations (rates below 1 per 100,000); an exception is the high rate among Chinese, particularly southern Chinese (Yu et al. 1990). Ingestion of Chinese salted fish is an important risk factor for NPC among both high-risk and low-risk Chinese populations. Among nondietary environmental exposures, tobacco smoking has been associated with a modest increase in risk (OR = 1.3 [95 percent CI, 0.9–1.9]) (Yu et al. 1990). An association between active smoking and secondhand smoke exposure and NPC is biologically plausible

because the inhalation of cigarette smoke directly exposes the nasopharynx to carcinogens present in tobacco smoke.

Secondhand smoke exposure was not associated with a risk of NPC among nonsmokers in two case-control studies (Yu et al. 1990; Cheng et al. 1999). Yu and colleagues (1990) conducted a case-control study of NPC in Guangzhou (Canton city), China, a high-risk NPC area. In the local primary treatment facility for NPC, 329 histologically confirmed incident cases diagnosed in persons under 50 years of age were identified between 1983 and 1985. A total of 306 NPC cases (209 men, 97 women) were interviewed along with an equal number of age-, gender-, and neighborhood-matched controls. In 1989, Yu and colleagues investigated dietary factors, and in 1990 they investigated nondietary environmental exposures that included active and involuntary smoking, the lifetime use of cigarettes and water pipes by study participants and their spouses, and the smoking patterns of parents and other household members at the time of birth and at 10 years of age (Yu et al. 1989, 1990).

These studies found that active smoking was a risk factor for NPC: persons who had ever smoked cigarettes had a risk of 1.3 (95 percent CI, 0.9–1.9) after adjusting for relevant dietary factors such as salted fish. There was also a significant trend of an increase in risk with increasing amounts of tobacco smoked (adjusted OR = 1.0 [0 pack-years], 1.2 [1 to 14 pack-years], 1.6 [15 to 29 pack-years], and 2.9 [≥30 pack-years], $p < 0.05$). Among the lifetime nonsmokers (142 cases, 154 controls), however, secondhand smoke exposure was not associated with any increased risk of NPC. After adjusting for age and gender, there was no increase in risk associated with secondhand smoke exposure from spousal (OR = 0.8 [95 percent CI, 0.3–1.2]), paternal (OR = 0.6 [95 percent CI, 0.3–1.2]), or maternal smoking (OR = 0.7 [95 percent CI, 0.3–1.5]) (Yu et al. 1989, 1990).

A second study on active smoking, secondhand smoke exposure, and the risk of NPC was conducted in Taiwan, where the risk for NPC falls between that of low- and high-risk countries (Cheng et al. 1999). Incident cases of histologically confirmed NPC (n = 378) among individuals who were younger than 75 years of age at diagnosis were prospectively ascertained from two teaching hospitals in Taipei between 1991 and 1994. Efforts were made to individually match controls for age, gender, and residence. A total of 375 NPC patients (260 men, 115 women) and 327 community controls (223 men, 104 women) were interviewed using a structured interview that asked about secondhand smoke exposures during childhood and adulthood, including the number of smokers in the household, duration of the exposures (person-years), and cumulative exposures (pack-years and person-years). The last two variables, duration and cumulative exposures, were derived from information obtained on smoking intensity and duration for each member reported to have smoked in the household.

Participants who had ever smoked cigarettes showed a small increase in risk (OR = 1.4 [95 percent CI, 0.9–2.0]) after adjusting for age, gender, race, education, family history of NPC, and drinking status. The risk of NPC tended to increase with an increase in the duration of cigarette smoking (OR = 1.0 [0 years of smoking], 1.1 [1 to 24 years of smoking], and 1.7 [≥25 years of smoking], p for trend = 0.03). Among lifetime nonsmokers (178 cases, 173 controls), Cheng and colleagues (1999) observed no increased risks in association with secondhand smoke exposure during childhood (adjusted OR = 0.6 [95 percent CI, 0.4–1.0]) or adulthood (adjusted OR = 0.7 [95 percent CI, 0.5–1.2]). These results did not change when the duration and amount of secondhand smoke exposures during childhood and adulthood were considered.

A third case-control study on secondhand smoke and NPC was conducted in Shanghai, China (Yuan et al. 2000). Similar to Taiwan, this area is also at an intermediate risk of NPC. Between January 1987 and September 1991, the Shanghai Cancer Registry identified 1,110 patients aged 15 through 74 years with histologically confirmed NPC. A total of 935 eligible patients (668 men, 267 women) were interviewed in person and compared with 1,032 age- and gender-matched controls randomly selected from the urban Shanghai population. Yuan and colleagues (2000) collected information on demographic characteristics, usual dietary habits during adulthood, use of tobacco and alcohol, lifetime exposure to secondhand smoke, type of oils and fuels used for cooking, lifetime occupational history, history of chronic ear and nose conditions, and family history of NPC. They also assessed secondhand smoke exposures during childhood (up to 18 years of age) and adulthood (home and workplace). If the person interviewed reported secondhand smoke exposure from a specific household member, then the participants were asked additional questions about the average daily amount smoked and the number of years of smoking. Similarly, if the response was positive to a workplace exposure, then the participants were asked questions about the number of hours of exposure (per day, week, or month) and duration (in years). For each exposed participant, a summary exposure index was constructed by computing a weighted average of job-specific exposures

(number of hours exposed to secondhand smoke per working day). The weighting factor was the number of years at a given job divided by the total number of years holding jobs where secondhand smoke exposure occurred.

The investigators found that active smoking was a significant risk factor for NPC among men and women combined (OR = 1.28 [95 percent CI, 1.02–1.61]). Although the increased risk was statistically significant only for men (OR = 1.28 [95 percent CI, 1.01–1.63]), the magnitude of the effect was comparable for women (OR = 1.28 [95 percent CI, 0.67–2.45]). The association between exposure to secondhand smoke and the risk of NPC was investigated in 429 cases (187 men, 242 women) and 546 controls (240 men, 306 women) who were lifetime nonsmokers only. Yuan and colleagues (2000) observed a significantly increased risk among nonsmoking women associated with the husbands' smoking (adjusted OR = 3.09 [95 percent CI, 1.48–6.46]), any household smoking (OR = 2.88 [95 percent CI, 1.39–5.96]), and coworkers' smoking (OR = 2.47 [95 percent CI, 1.12–5.44] for <3 hours and 3.28 [95 percent CI, 1.48–7.27] for ≥3 hours). However, the association between secondhand smoke exposure and a risk of NPC among men was substantially weaker. There was some increase in risk among men whose wives smoked (OR = 1.53 [95 percent CI, 0.26–8.93]) but no increase associated with other smokers in the household (OR = 0.92 [95 percent CI, 0.41–2.04]). A small, nonsignificant increase in risk was associated with workplace secondhand smoke exposure (OR = 1.32 [95 percent CI, 0.63–2.76]). These results were found in men and women and were adjusted for several potential confounders including dietary factors, exposure to cooking fuels, occupational exposures, and family history.

The gender differences in secondhand smoke associations with NPC among lifetime nonsmokers were of borderline statistical significance. Because there were comparable risk estimates between men and women for active smoking and NPC, the investigators expected to find similar associations with secondhand smoke exposure. However, this was not the case. In addition, the researchers expected the magnitude of risks associated with secondhand smoke exposure to be no higher than the risks associated with active smoking, and this also was not the case.

Conclusions

1. The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and a risk of nasal sinus cancer among nonsmokers.

2. The evidence is inadequate to infer the presence or absence of a causal relationship between secondhand smoke exposure and a risk of nasopharyngeal carcinoma among nonsmokers.

Implications

Larger studies with more complete information on secondhand smoke exposure are needed, with data on exposures at home and outside the home, timing of the exposure, other potential confounders (occupational factors), and tumor characteristics (histology, subsite) to definitively establish the relationship between secondhand smoke exposure and nasal sinus cancer. Studies that are designed to investigate the mechanism(s) of action of active smoking and secondhand smoke exposure will help to elucidate their respective roles in the development of nasal sinus cancer.

Further studies that include adequate numbers of men and women are needed to clarify whether the significant positive association between secondhand smoke exposure and a risk of NPC among women might reflect a chance finding.

Cervical Cancer

Several reviews have addressed effects of exposures from secondhand smoke on the risk for cervical cancer (NCI 1999; USDHHS 2001). Since these reviews, two studies with data on cervical cancer or abnormalities of the cervix have been published (Jee et al. 1999; Scholes et al. 1999).

Some supportive evidence from epidemiologic and biochemical studies does exist that implicates a role for secondhand smoke exposure in the etiology of cervical cancer among nonsmokers. In a Japanese cohort study, the investigators observed a nonsignificant 15 percent increase in risk of cervical cancer among nonsmoking wives associated with the husbands' smoking (Hirayama 1981). However, no association was found between the husbands' smoking and a risk of cervical cancer among participants in a Korean cohort study (adjusted OR = 0.9 [95 percent CI, 0.6–1.2]) (Jee et al. 1999). Among the case-control studies, a significant positive association was observed in two studies (Sandler et al. 1985b; Slattery et al. 1989). In the third case-control study, Coker and

colleagues (1992) found that spousal secondhand smoke was associated with an increased risk of cervical cancer and intraepithelial neoplasia among nonsmokers that was of borderline statistical significance.

In the United States, Scholes and colleagues (1999) investigated the role of active smoking and secondhand smoke exposure in the etiology of lower grade cervical abnormalities at the Group Health Cooperative of Puget Sound in western Washington state. Between 1995 and 1996, a population-based automated cervical cytology database was used to identify women 18 years of age or older who had had cervical cytologic testing. Women with severe dysplastic changes (cervical intraepithelial neoplasia [CIN] 3) or invasive cervical cancer (Class 5 and 6 Pap smear results) were excluded from the study. Women with mild or moderate dysplastic cytologic changes (Class 3 or 4 Pap smear results, also known as CIN 1 or 2) or Class 2 changes with epithelial cell abnormalities were classified as cases, and women with normal or Class 1 cytology results served as the control group.

Women aged 18 through 44 years who were not pregnant and did not have a history of hysterectomy were contacted and interviewed by telephone using a behavioral survey that included questions on active smoking and secondhand smoke exposure. Participants were specifically asked whether they had ever smoked as many as 100 cigarettes in their lifetime. Smokers who averaged one cigarette or more per day during the past 12 months were classified as current smokers. Women who had smoked at least 100 cigarettes in their lifetime but did not smoke daily now were classified as former smokers. Exposure to secondhand smoke was based on the smoking patterns of husbands or partners or other household members (Scholes et al. 1999).

A total of 2,448 women—582 cases (i.e., 465 had Class 2 and 117 had Class 3 to 4 Pap smear results) and 1,866 controls (i.e., normal cytology)—were included in this analysis. Fifty-four percent (n = 315) of cases and 62 percent (n = 1,158) of controls were lifetime nonsmokers. Compared with lifetime nonsmokers, current smokers had an increased risk of an abnormal Pap smear (adjusted OR = 1.4 [95 percent CI, 1.1–1.8]) but former smokers did not (adjusted OR = 1.0 [95 percent CI, 0.8–1.3]). Compared with unexposed lifetime nonsmokers, nonsmokers who were exposed to secondhand smoke also showed an increased risk of abnormal Pap smear results of Class 2 to 4 (adjusted OR = 1.4 [95 percent CI, 1.0–2.0]). These results were adjusted for the lifetime number of sexual partners, age, and age at first sexual intercourse.

Conclusion

1. The evidence is inadequate to infer the presence or absence of a causal relationship between secondhand smoke exposure and the risk of cervical cancer among lifetime nonsmokers.

Implications

There is a need for additional studies with adequate sample sizes and more complete information on secondhand smoke exposures, including exposures at home and outside the home and the timing of the exposure, and other potential confounders to definitively establish an association between secondhand smoke exposure and the risk for cervical cancer and cervical abnormalities.

Conclusions

Lung Cancer

1. The evidence is sufficient to infer a causal relationship between secondhand smoke exposure and lung cancer among lifetime nonsmokers. This conclusion extends to all secondhand smoke exposure, regardless of location.

2. The pooled evidence indicates a 20 to 30 percent increase in the risk of lung cancer from secondhand smoke exposure associated with living with a smoker.

Breast Cancer

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

Nasal Sinus Cavity and Nasopharyngeal Carcinoma

4. The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke exposure and a risk of nasal sinus cancer among nonsmokers.

5. The evidence is inadequate to infer the presence or absence of a causal relationship between secondhand smoke exposure and a risk of nasopharyngeal carcinoma among nonsmokers.

Cervical Cancer

6. The evidence is inadequate to infer the presence or absence of a causal relationship between secondhand smoke exposure and the risk of cervical cancer among lifetime nonsmokers.

Overall Implications

The California Environmental Protection Agency (Cal/EPA) has estimated that more than 3,000 (a range of 3,423 to 8,866) lung cancer deaths in the United States each year are attributable to secondhand smoke exposure (Cal/EPA 2005). The estimated number of lung cancer deaths for men (a range of 863 to 3,498) was lower than the estimated number of deaths for women (a range of 2,560 to 5,368), because a lower proportion of nonsmoking men are exposed to spousal smoking. However, the estimate for men did not consider the potential risk from secondhand smoke exposure at work or in other venues where exposures may be higher for men than for women (Cal/EPA 2005).

There is a need for additional research on the risks of other cancers related to secondhand smoke exposure, particularly nasal sinus cancer, breast cancer in both premenopausal and postmenopausal women, nasopharyngeal carcinoma, and cervical cancer.

Appendix 7.1
Details of Recent Lung Cancer Studies

Cohort Studies on the Relationship of Exposure to Secondhand Smoke and Lung Cancer

Nishino and colleagues (2001) investigated the relationship between secondhand smoke exposure at home and the incidence of lung and other cancers in a population-based, prospective study of lifetime nonsmoking women who lived in Miyagi Prefecture, Japan. At the time of enrollment in 1984, 31,345 persons (13,992 men and 17,353 women) completed a baseline questionnaire on smoking, drinking and dietary habits, and reproductive history. To assess residential secondhand smoke exposure, the participants were asked to identify any smokers in their households (husband, wife, father, mother, children, or other household members).

Of the 10,334 lifetime nonsmoking women, 9,675 had no history of cancer and had a complete history of secondhand smoke exposure that included the smoking status of the husband and other household members. Nishino and colleagues (2001) used the population-based cancer registry of Miyagi Prefecture to identify 24 nonsmoking women who had developed lung cancer during the nine-year follow-up period. These investigators also found that the relative risk (RR) for lung cancer was higher among women whose husbands were smokers (1.9 [95 percent confidence interval (CI), 0.8–4.4]) than among women married to nonsmokers. This risk estimate was slightly weakened (RR = 1.8 [95 percent CI, 0.7–4.6]) after further adjustment for demographic characteristics and fruit and vegetable intake. When the smoking status of the husbands and other household members were considered jointly, the risk of lung cancer was 1.2 (95 percent CI, 0.3–4.0) among women who were exposed to secondhand smoke. The very small number of persons with lung cancer in each category of secondhand smoke exposure limits the interpretation of this study.

Jee and colleagues (1999) evaluated the relationship between smoking by the husbands and lung cancer incidence among 157,436 nonsmoking women in Korea whose husbands were enrolled in a health insurance plan. At the time of enrollment in 1992, information on the smoking patterns of the husbands (never, former, current smoker) was obtained during routine medical examinations, and was reassessed two years later. The classification of exposure to secondhand smoke was based on smoking intensity (the number of cigarettes currently smoked) and duration (the number of years of continuous smoking to date). During the three and one-half years of follow-up, Jee and colleagues (1999) identified 79 persons with lung cancer both existing and newly incident during follow-up.

The adjusted lung cancer incidence rates were 30 percent higher (RR = 1.3 [95 percent CI, 0.6–2.7]) among women whose husbands were former smokers and 90 percent higher (RR = 1.9 [95 percent CI, 1.0–3.5]) among women whose husbands were current smokers compared with women married to nonsmokers. Jee and colleagues (1999) also noted a significant trend in risk with an increase in the duration of exposure. For example, the RR for women who were exposed to secondhand smoke for 1 to 29 years was 1.6, and the RR for those who were exposed for 30 or more years was 3.1 (p trend <0.01). There was not a similar trend with an increase in the amount smoked: the RR for women whose husbands smoked 1 to 19 cigarettes per day was 2.0, and the RR for women whose husbands smoked 20 or more cigarettes per day was 1.5 (p trend <0.1). Other characteristics of husbands who smoked, such as occupation, alcohol intake, and vegetable consumption, did not significantly influence the risk of lung cancer in their wives (Jee et al. 1999). Although a risk of breast cancer was also significantly associated with the husbands' smoking patterns (see "Breast Cancer" earlier in this chapter), there was no significant influence on the wives' risk of developing other cancers, including cancers of the cervix, stomach, and liver.

de Waard and colleagues (1995) conducted a nested case-control study of lung cancer that used the urinary cotinine level as a marker of secondhand smoke exposure. In 1975, the investigators established a cohort of 14,697 women from Utrecht, Netherlands, to study breast cancer risk factors. There was a second screening one year later and baseline urine samples were collected from 12,865 women. In 1982 and 1983, the same investigators enrolled another breast screening cohort and collected urine specimens from more than 12,000 women aged 40 through 49 years. In 1989, 1991, and 1992, these cohorts were linked to the Netherlands Cancer Registry, and the

researchers identified 92 women who had died of lung cancer (69 smokers, 23 nonsmokers). From the same cohorts, two to four comparably age-matched controls donated urine specimens on the same day that the cases were selected. Smoking status was assessed from self-reports at the time of urine collection. A total of 448 participants (257 smokers, 191 nonsmokers) participated in an evaluation of the risk of lung cancer in relation to urinary cotinine levels and self-reported smoking status (de Waard et al. 1995).

All self-reported nonsmokers had urinary cotinine levels of less than 100 nanograms per milligram (ng/mg) of creatinine; all active smokers had levels above that amount. The RR of lung cancer was 1.0 for the reference group (persons whose urinary cotinine levels were less than 100 ng/mg of creatinine), 1.3 for persons with levels of 100 to 900 ng/mg, 10.3 for those with levels of 901 to 2,251 ng/mg, and 9.8 for those with levels greater than 2,251 ng/mg. For nonsmokers (23 persons with lung cancer and 191 persons without lung cancer), the RR of lung cancer was 1.0 for persons with urinary cotinine levels of less than 9.2 ng/mg of creatinine, 2.7 for those with levels of 9.2 to 23.4 ng/mg, and 2.4 for those with levels greater than 23.4 ng/mg. Using a biomarker as an exposure classification, de Waard and colleagues (1995) confirmed that secondhand smoke exposure is a risk factor for lung cancer among nonsmokers. These results established a relationship between exposure to secondhand smoke and cotinine levels measured in urine samples from a cohort of women followed for up to 15 years. Because information on self-reported secondhand smoke exposure was not available, the investigators could not compare risk estimates in relation to both urinary cotinine and self-reported secondhand smoke exposure in this study population.

Speizer and colleagues (1999) investigated the relationship between secondhand smoke exposure and lung cancer risk using data from the Nurses Health Study (NHS). Women who were eligible (n = 118,251) for inclusion in this analysis were free from cancer (except nonmelanoma skin cancer) at baseline and had responded to the 1982 questionnaire that assessed childhood and current adult tobacco smoke exposures at home, at work, and in other settings. After 16 years of follow-up, 593 confirmed cases of lung cancer were identified; 58 cases occurred among lifetime nonsmokers. Thirty-five of the 58 lung cancers were diagnosed after 1982 and provided information on secondhand smoke exposure. All but two of the 35 women reported adult secondhand smoke exposure at home and/or work; the age-adjusted RR for secondhand smoke exposure in adulthood was 1.5 (95 percent CI, 0.3–6.3).

This report on secondhand smoke exposure and lung cancer in the NHS is limited by the small number of lung cancers among lifetime nonsmokers—only a subset could be included in the analysis. Although information on exposure during childhood was obtained, these results were not presented. In addition, only age was considered in the analysis.

Case-Control Studies on the Relationship of Exposure to Secondhand Smoke and Lung Cancer

Canada and the United States

Of the 1 Canadian and 12 U.S. published case-control studies with data on secondhand smoke exposure and lung cancer risk in lifetime nonsmokers, 5 larger studies conducted in the 1990s were designed to address potential methodologic concerns such as misclassification of lifetime nonsmoking status, assessment of secondhand smoke exposure, and inclusion of potential confounders (Table 7.1) (Brownson et al. 1992; Stockwell et al. 1992; Fontham et al. 1994; Kabat et al. 1995; Schwartz et al. 1996; National Cancer Institute [NCI] 1999). One population-based, case-control study included female lung cancer patients who were identified through 8 of the 10 Canadian provincial cancer registries (Table 7.3) (Johnson et al. 2001). A total of 4,089 women responded to the mailed questionnaire. Of these respondents, 1,558 had histologically confirmed primary lung cancer and 2,531 did not have lung cancer. Of those who were eligible and who agreed to participate, 161 cases and 1,271 controls were identified; all were lifetime nonsmokers (i.e., they had smoked fewer than 100 cigarettes in a lifetime). Each respondent answered questions about the number of regular smokers in the household, the duration of residence, and a lifetime occupational history (for each job of at least one year) that included the number of regular smokers in the participant's immediate work area and the number of years at that job. This study investigated (1) the duration and smoker-years (the number of years of exposure weighted by the number of smokers) of residential secondhand smoke, which was defined as residential years multiplied by the number of regular smokers in the residence; and (2) occupational secondhand smoke exposure, which was defined as years worked multiplied by the number of regular smokers in the workplace.

For 71 women with lung cancer and 761 healthy controls, all lifetime nonsmokers, Johnson and colleagues (2001) obtained a complete residential history of secondhand smoke exposure that covered at least 90 percent of their lifetime. There was less information on residential exposure to secondhand smoke for the rest of the women. Using data from these 71 lifetime nonsmokers and 761 controls, Johnson and colleagues (2001) found that any secondhand smoke exposure during childhood and adulthood was associated with an increased risk of lung cancer (odds ratio [OR] =1.63 [95 percent CI, 0.8–3.5]) after adjusting for age, province, education, and total fruit and vegetable consumption. The total number of years of combined residential and occupational secondhand smoke exposure was not associated with a significant trend of increased risks for lung cancer. The ORs were 1.00, 1.46, 1.40, and 1.35 in association with 0, 1 to 24, 25 to 45, and 46 or more years, respectively, of combined exposure (p for trend = 0.36). The association between secondhand smoke exposure and risk for lung cancer was strengthened when the total number of smoker-years was considered. For lifetime nonsmokers, the ORs were 1.00, 0.83, 1.54, and 1.82 in association with 0, 1 to 36, 37 to 77, and 78 or more smoker-years, respectively, of residential and workplace secondhand smoke exposure (p for trend = 0.05) (Table 7.3) (Johnson et al. 2001).

This study was limited because assessments of secondhand smoke exposures were available only for 44 percent (71 out of 161) of the lifetime nonsmoking cases and 60 percent (761 of 1,271) of the lifetime nonsmoking controls. The positive associations between lung cancer risk and residential and occupational secondhand smoke exposures weakened substantially when the analyses included participants with less complete information on their exposures (137 cases and 1,178 controls), or when the participants were all lifetime nonsmokers (161 cases and 1,271 controls). Although the diluted secondhand smoke effect in all lifetime nonsmokers may be due to random (nondifferential) misclassification, the investigators acknowledged the modest overall response rate (70 percent) from the persons who had received the mailed questionnaire, and the relatively high proportion of respondents with incomplete exposure information. It is unclear whether all of the missing data for lifetime nonsmoking cases (56 percent) and controls (40 percent) was attributable to living outside of Canada. Comparisons of demographic characteristics (such as social class, age, and birthplace) and characteristics of persons with complete and incomplete secondhand smoke exposure histories may provide some clues regarding the nature of bias (if any) as a result of the missing information.

European Countries

Case-control studies from Greece (Trichopoulos et al. 1981; Kalandidi et al. 1990), the United Kingdom (Lee et al. 1986), Sweden (Pershagen et al. 1987; Svensson et al. 1989; Nyberg et al. 1998a), Germany (Jöckel et al. 1998; Kreuzer et al. 2000, 2001), Russia (Zaridze et al. 1998), and a multicenter European study (Boffetta et al. 1998) have investigated the relationship between secondhand smoke and lung cancer risk among nonsmokers. As with the U.S. studies, those studies published before 1992 were generally small (Trichopoulos et al. 1981; Lee et al. 1986; Pershagen et al. 1987; Svensson et al. 1989), and the exposure assessments were based largely on the husband's smoking habits (Trichopoulos et al. 1981; Pershagen et al. 1987). Three studies (Jöckel et al. 1998; Nyberg et al. 1998a; Kreuzer et al. 2000, 2001) that were part of the European multicenter study (Boffetta et al. 1998) were also published as separate reports. These investigators not only examined the usual measures of secondhand smoke exposure, such as ever exposed, years of exposure, and amount of exposure, but they also evaluated risk patterns in association with measures of the intensity of the exposure, including the number of hours, the number of smokers, how recently the exposure occurred, and a subjective index of smokiness defined as (1) not visible but smellable, (2) visible, and (3) very smoky (Jöckel et al. 1998; Nyberg et al. 1998a; Kreuzer et al. 2000). Updated results from Sweden (Nyberg et al. 1998a) and Germany (Kreuzer et al. 2000) showed significant increases in the numbers of cases and controls than were in the multicenter European study (Boffetta et al. 1998). The discussion that follows describes studies from Russia (Zaridze et al. 1998), Sweden (Nyberg et al. 1998a), and Germany (Jöckel et al. 1998; Kreuzer et al. 2000).

The results of the first large, multicenter study of secondhand smoke and lung cancer that was conducted at 12 centers in seven European countries by the International Agency for Research on Cancer were published in 1998 (Boffetta et al. 1998). Five centers were hospital-based, one was hospital- and community-based, and six were community-based. Instead of a single protocol, this study incorporated a core of common questions used by all 12 centers. The selection of controls varied by center: controls were individually matched to cases by gender and age in some centers and by frequency matching in others. Nonsmoking status was defined as smoking no more

than 400 cigarettes in a lifetime. For men and women combined, the overall RR for lung cancer associated with ever having had a childhood exposure to secondhand smoke was 0.78 (95 percent CI, 0.64–0.96). The RR was 1.16 (95 percent CI, 0.93–1.44) among those with spousal secondhand smoke exposure and 1.17 (95 percent CI, 0.94–1.45) among those with workplace secondhand smoke exposure. The investigators found no significant trends of an increase in risk with increasing years of exposure to spousal or workplace secondhand smoke. However, they did observe significant trends of an increase in risk with increasing intensity-years (hours per day times years) of exposure to spousal ($p = 0.02$) and workplace ($p < 0.01$) secondhand smoke.

Russia

This section focuses on a hospital-based, case-control study conducted in Moscow that compared female lifetime nonsmokers with histologically confirmed lung cancer (n = 189) and other oncology patients (n = 358) admitted to the same hospital (Table 7.3) (Zaridze et al. 1998). Cases and controls were interviewed within days of their hospital admission or before starting treatment. The investigators based secondhand smoke exposure on the smoking habits of parents during childhood, and of husbands, other household members, and coworkers during adulthood.

Smoking by the husbands was associated with a significantly increased risk of lung cancer (OR = 1.53 [95 percent CI, 1.06–2.21]) (Table 7.3). Having a husband who smoked papirosy, a special high-tar (>30 mg/cigarette) and high-nicotine (>1.8 mg/cigarette) Russian cigarette, was strongly associated with risk (OR = 2.12 [95 percent CI, 1.32–3.40]). For lifetime nonsmoking women with lung cancer, the risk of lung cancer increased with the number of years a woman had lived with a husband who smoked (duration), although there was not a clear dose-response trend. For example, the OR was 1.86 for women who were exposed to secondhand smoke for 1 to 15 years and 1.42 for those who were exposed for more than 15 years (p trend = 0.07). In relation to the number of cigarettes smoked by the husbands, the OR was 1.66 for women married to men who smoked 1 to 10 cigarettes per day and 1.35 for those married to men who smoked more than 10 cigarettes per day (p trend = 0.10). However, Zaridze and colleagues (1998) found no associated risk of secondhand smoke and lung cancer with exposure during adulthood from household members (OR = 0.91 [95 percent CI, 0.58–1.42]) or from exposure at work (OR = 0.88 [95 percent CI, 0.55–1.41]) (Table 7.3). There was also no associated risk among women who were exposed to secondhand smoke from fathers during childhood (OR = 0.92 [95 percent CI, 0.64–1.32]).

For women with husbands who smoked, Zaridze and colleagues (1998) found that the risks for both squamous cell carcinoma (OR = 1.94 [95 percent CI, 0.99–3.81]) and adenocarcinoma of the lung (OR = 1.52 [95 percent CI, 0.96–2.39]) were associated with exposure to secondhand smoke. An association between husbands who smoked and lung cancer risk was more pronounced when the controls in the analyses were restricted to women who had cancer diagnosed in sites where cancer is not associated with active smoking, including breast and endometrial cancer (OR = 1.82 [95 percent CI, 1.18–2.80]). This association was weaker when the analyses included only women who had cancer diagnosed in sites where cancer is associated with smoking, such as cervical and gastric cancers (OR = 1.22 [95 percent CI, 0.79–1.88]).

Although a strength of this study was that all of the interviews were conducted with self-respondents, limitations in the methods included selection of controls and the failure to biochemically validate secondhand smoke exposure. The definition of a lifetime nonsmoker and the process used to determine and verify this status were not described, and the investigators only adjusted for age and education (Zaridze et al. 1998).

Sweden

This section discusses a hospital-based, case-control study of secondhand smoke exposure and lung cancer conducted among male and female lifetime nonsmokers in Stockholm county, Sweden, between 1989 and 1995 (Nyberg et al. 1998a,b). The researchers interviewed 124 lifetime nonsmokers (35 men, 89 women) with histologically confirmed lung cancer, and 235 frequency-matched population controls of lifetime nonsmokers without lung cancer (72 men, 163 women).

Nyberg and colleagues (1998a) conducted a thorough review process to determine the lifetime nonsmoking status of study participants. Specifically, they contacted the next of kin of all cases (n = 124) and of every second control (n = 118 of 235) to confirm the lifetime nonsmoking status for 99.1 percent of the lifetime nonsmokers with lung cancer and 97.2 percent of the lifetime nonsmokers without lung cancer (Nyberg et al. 1998a). The authors assessed exposure to secondhand smoke using questions developed in a study

on urinary cotinine and secondhand smoke exposure (Riboli et al. 1990) that covered childhood exposure, domestic exposure from the spouse and other cohabitants, exposure at all workplaces and other places, and exposure in vehicles.

The investigators used gender, age, catchment area, and other covariates to adjust the results on secondhand smoke (Nyberg et al. 1998a). The researchers found that secondhand smoke exposure from spouses was associated with a small increase in risk. This association was stronger among men (OR = 1.96 [95 percent CI, 0.72–5.36]) than among women (OR = 1.05 [95 percent CI, 0.60–1.86]) (Table 7.3). Any secondhand smoke exposure in the workplace was associated with increased risks among both men (OR = 1.89 [95 percent CI, 0.53–6.67]) and women (OR = 1.57 [95 percent CI, 0.80–3.06]) (Table 7.3). In men and women combined, a significant trend of an increase in risk of lung cancer was evident with more years of secondhand smoke exposure at work. For example, adults who were exposed to less than 30 years of secondhand smoke at work had an OR of 1.40, and those who had been exposed for 30 or more years had an OR of 2.21 (p for trend = 0.03). When they considered hours of exposure per day in the workplace, the investigators found that the trends in risks associated with secondhand smoke exposure were strengthened slightly: the OR was 1.27 for persons who were exposed for less than 30 hour-years[1], and the OR was 2.51 for those who were exposed for 30 or more hour-years (p for trend = 0.01). Lung cancer risk in women was not associated with secondhand smoke exposure in other indoor locations or in vehicles (OR = 0.41 [95 percent CI, 0.09–1.75]), but the risks increased nonsignificantly among men (OR = 1.71 [95 percent CI, 0.49–5.98]) (Nyberg et al. 1998a). When secondhand smoke exposures from spouses and coworkers were considered together, those who were currently exposed (within the past two years) had more than a twofold increase in risk (OR = 2.12 [95 percent CI, 0.91–4.92]). The risk was highest (OR = 2.52 [95 percent CI, 1.08–5.85]) among individuals with the highest levels of exposure or in the top 90th percentile of hour-years of exposure. Paternal smoking was associated with an increased risk among men (OR = 1.90 [95 percent CI, 0.69–5.23]) but not among women (OR = 0.76 [95 percent CI, 0.42–1.37]), whereas maternal smoking was not associated with risk in either group (Nyberg et al. 1998a).

One weakness of this study is that 36 participants (12 cases and 24 controls) were occasional smokers (lifetime total of 20 to 408 packs); 11 had smoked during the 10 years before the study. Although the investigators reported no evidence that these occasional smokers confounded the secondhand smoke association, results excluding this group of participants were not presented. An important strength of this study is that a next of kin validation substudy was conducted using all cases and a subset of controls (Nyberg et al. 1998a). There was high concordance exhibited between next of kin and lung cancer cases and controls with the reported lifetime nonsmoking status of cases and controls and their exposures to spousal secondhand smoke. Because interviews were conducted with self-respondents, measures of intensity such as hours of exposure at work and at home (from spouses) were also documented and appeared to be more sensitive markers of exposure than duration of exposure or amount smoked. The stronger effects associated with current secondhand smoke exposure in this study may partially explain the more heterogeneous results associated with childhood secondhand smoke exposure (Nyberg et al. 1998a).

Germany

One hospital-based, case-control study investigated the role of occupational exposure by including 1,004 persons with incident lung cancer (839 men, 165 women) and an equal number of individually matched population controls from Frankfurt, Bremen, and surrounding areas in Germany (Jöckel et al. 1998). An analysis of secondhand smoke exposure was based on 55 cases and 160 controls who reported that they had never smoked regularly, which was defined as smoking for less than six months (Jöckel et al. 1998). Almost all were also included in the European multicenter study (Boffetta et al. 1998), but the results are described separately because of additional data on the intensity of the exposures.

For each source of secondhand smoke exposure (childhood, spouse, workplace, transportation, and other public places), variables of exposure were defined based on hours of exposure, years of exposure, and the degree of smokiness (defined as [1] not visible but smellable, [2] visible, and [3] very smoky). Participants were classified into three exposure categories: no or low exposures from a specific source

[1]One hour-year equals 365 hours per year, or 1 hour per day for one year.

if all exposure variables were below the respective 75th percentile, intermediate or medium if at least one variable was above the respective 75th percentile but below the 90th percentile, and high if at least one variable was above the respective 90th percentile. Because secondhand smoke exposure is ubiquitous, this approach focused on those who were highly exposed. The results from an earlier validation study that used urinary cotinine among healthy women in the Bremen area showed that the misclassification of questionnaire-based secondhand smoke exposure tends to be greater in the lower three quartiles of exposure than in the top quartile (Becher et al. 1992).

After adjusting for gender, age, and region, there was a small increased risk associated with ever having lived with a smoking spouse (OR = 1.12 [95 percent CI, 0.54–2.32]) (Table 7.3) (Jöckel et al. 1998). When persons were reclassified to no or low spousal secondhand smoke exposure, or to medium and high exposure (low = all exposure variables below the 75th percentile, medium = at least one variable above the 75th percentile but below the 90th percentile, and high = at least one variable above the 90th percentile), the investigators found that those with a medium exposure showed a risk of 0.22 (95 percent CI, 0.05–1.07) and those with a high exposure showed a risk of 1.87 (95 percent CI, 0.45–7.74). Persons with a high secondhand smoke exposure during childhood, with exposures from other sources during adulthood including workplace, public transportation, and other public places, and persons with a high total of associated secondhand smoke exposures in childhood and in adulthood had a twofold to threefold increase in risk. The investigators also noted that individuals with high combined exposures during childhood and adulthood had a significantly increased risk (OR = 3.24 [95 percent CI, 1.44–7.32]) of lung cancer than did those with no or low secondhand smoke exposure (Table 7.3) (Jöckel et al. 1998). In this and another study from Germany (Kreuzer et al. 2000, 2001), any effect of secondhand smoke exposure on lung cancer risk was stronger among those who were highly exposed.

One clinic-based, case-control study was designed to investigate the role of radon in the etiology of lung cancer in East and West Germany (Kreuzer et al. 2000). Persons with histologically confirmed lung cancer and frequency-matched population controls were interviewed. The analysis included 292 adults (234 women, 58 men) and 1,338 controls (535 women, 803 men) who had smoked fewer than 400 cigarettes during their life (lifetime nonsmokers) (Table 7.3). A subset of these lifetime nonsmokers (173 cases and 215 controls) was previously included in the European multicenter study (Boffetta et al. 1998) as part of the data collected in Germany (referred to as Germany 2 and Germany 3 in the report by Boffetta et al. 1998). The interviews with the participants included questions on secondhand smoke exposure during childhood, from spouses and other cohabitants, at all workplaces and other public places, and in vehicles. Besides classifying persons by ever or never having an exposure to various sources of secondhand smoke, the study determined several measures of intensity that included the duration of exposure (in hours) during childhood; spousal and workplace exposures; pack-years[2] of exposure from spouses; and a weighted duration of exposure (based on hours of exposure and the level of smokiness) at work, in other indoor settings, and in vehicles (Kreuzer et al. 2000).

After the investigators adjusted for age and region, they found that the risk of lung cancer among female lifetime nonsmokers was not significantly associated with secondhand smoke exposure during childhood (OR = 0.78 [95 percent CI, 0.56–1.08]) or adulthood, including exposure from husbands (OR = 0.96 [95 percent CI, 0.70–1.33]), in the workplace (OR = 1.14 [95 percent CI, 0.83–1.57]), in vehicles (OR = 0.96 [95 percent CI, 0.57–1.60]), and in other indoor settings (OR = 0.95 [95 percent CI, 0.66–1.38]). Similar results were obtained when they considered cumulative pack-years of exposure from husbands, or duration of exposure (in hours) during childhood and from spouses (Kreuzer et al. 2000). However, the risk was substantially higher when they considered weighted duration of secondhand smoke exposure (hours times the level of smokiness) at the workplace. There were statistically significant risks (twofold greater) in association with the highest levels of duration (i.e., hours) and with weighted duration of workplace exposures. The risk of lung cancer among women also increased in relation to the weighted duration of secondhand smoke from all sources (hours times the level of smokiness): the ORs were 0.87 (95 percent CI, 0.57–1.34) for those with no or low exposure and

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

1.51 (95 percent CI, 0.97–2.33) for those with medium or high secondhand smoke exposures (p trend = 0.21). When the investigators considered the weighted duration of the exposure outside the home, the ORs were 1.38 (95 percent CI, 0.74–2.57) for those with low or no exposure and 1.99 (95 percent CI, 0.95–4.15) for those with medium or high exposures (p trend = 0.11) (Kreuzer et al. 2000). Because of the smaller numbers of male lifetime nonsmokers in the study, the investigators noted that a risk of lung cancer among men was not significantly associated with secondhand smoke exposures from their wives' smoking (OR = 0.8 [95 percent CI, 0.11–6.38] for a high exposure) or in the workplace (OR = 1.1 [95 percent CI, 0.47–2.70] for a high exposure) (Kreuzer et al. 2001). In this study, effects were not confounded by social class; a family history of lung cancer; occupational exposure to carcinogens; radon in their residence; previous lung disease; and consumption of carrots, salad, or fresh fruits. The risk estimate associated with a high exposure from all sources combined remained essentially unchanged when each covariate was included in the regression model.

Adenocarcinoma of the lung accounted for 59 percent (n = 173) of the lung cancers among lifetime nonsmokers in this study population (Table 7.3) (Kreuzer et al. 2000). Results were generally similar in cell-type specific analyses (adenocarcinoma versus nonadenocarcinoma) among women and with both genders combined. Spousal smoking was not associated with a risk for adenocarcinoma or for other types of lung cancer. Secondhand smoke exposure at work was associated with increased risks for both adenocarcinoma and nonadenocarcinoma that were qualitatively similar, but the result was statistically significant only for the latter group.

Using a combined index of exposures during childhood and adulthood, Jöckel and colleagues (1998) found increased risks of lung cancer in association with high secondhand smoke exposures. Kreuzer and colleagues (2000, 2001) found that high levels of secondhand smoke exposure at the workplace in terms of hours or weighted duration (hours times smokiness) were associated with an increased risk of lung cancer. Although this exposure measure cannot be validated because it is self-reported, it appears to identify a highly exposed group that is at an increased risk. Undoubtedly, questions such as hours of exposure, number of smokers, and level of smokiness can be asked directly only when conducting interviews with both cases and controls. Because these two studies included only self-respondents who were well enough to participate in an interview lasting at least an hour, the information may be valid and useful for identifying an at-risk subgroup: those in the highest category of exposure.

A hospital-based study of lung cancer was conducted among Czech women in Prague to investigate the role of active smoking and secondhand smoke (Kubik et al. 2001). The researchers interviewed females diagnosed with a histologically confirmed lung cancer (n = 140) and control participants who were spouses, relatives, or friends of other patients in the hospital (n = 462). The investigators based secondhand smoke exposure on the smoking behaviors of parents, husbands, cohabitants, and coworkers. Specifically, participants were asked to assess the number of hours per day spent in smoky rooms (at home, at work, and elsewhere) as adults and exposure during childhood before 16 years of age. Using data from 24 cases and 176 controls who were lifetime nonsmokers (i.e., they had smoked fewer than 100 cigarettes in a lifetime), these investigators found that any secondhand smoke exposure during childhood was associated with an increased risk of lung cancer (OR = 2.02 [95 percent CI, 0.8–4.9]) after adjusting for age, residence, and education. The OR was 1.17 (95 percent CI, 0.2–5.6) among women exposed to secondhand smoke as adults (defined as >3 hours per day). For women with both childhood and adulthood exposures, the OR was 3.68 (95 percent CI, 0.6–21.9).

Although this study attempted to obtain information on secondhand smoke exposure at home and outside of the home during childhood and adulthood, the sample size of lifetime nonsmoking lung cancer patients was limited, and the appropriateness of the control groups was uncertain. Information on potential confounders was also lacking.

Chinese in Taiwan, Singapore, Hong Kong, and the People's Republic of China

Chinese women have a high incidence of lung cancer despite a low prevalence of active smoking (Wu-Williams et al. 1990). This elevated incidence, particularly of adenocarcinoma of the lung, has been noted for Chinese women residing in Singapore (Law et al. 1976), Hong Kong (Kung et al. 1984), Shanghai (Gao et al. 1988), and northern China (Xu et al. 1989). A number of case-control studies have investigated secondhand smoke and other sources of indoor air pollution as possible explanations for the high lung cancer rates among Chinese women. Some of the study locations were selected specifically because of local cooking or heating practices considered to be possible sources of carcinogenic indoor pollutants

(Wu-Williams et al. 1990; Liu et al. 1991; Wang et al. 2000). These locations were Hong Kong (Chan and Fung 1982; Koo et al. 1987; Lam et al. 1987), Taiwan (Ko et al. 1997; Lee et al. 2000), Singapore (Seow et al. 2000), and the People's Republic of China: Guangdong Province in the south (Liu et al. 1993; Du et al. 1996; Lei et al. 1996), Xuanwei County in Yunnan Province (Liu et al. 1991), urban regions including Shanghai (Gao et al. 1987; Zhong et al. 1999), Nanjing (Shen et al. 1998), Tianjin (Geng et al. 1988), Harbin and Shenyang in northeastern China (Wu-Williams et al. 1990; Wang et al. 1994, 1996), and Gansu Province in northwestern China (Wang et al. 2000). Study methods and data quality were quite varied. Six of these studies had large sample sizes (Gao et al. 1987; Wu-Williams et al. 1990; Zhong et al. 1999; Lee et al. 2000; Seow et al. 2000; Wang et al. 2000), four were population-based (Gao et al. 1987; Wu-Williams et al. 1990; Zhong et al. 1999; Wang et al. 2000), and two were hospital-based (Lee et al. 2000; Seow et al. 2000). In the four largest studies, exposure to secondhand smoke was assessed from smoking by spouses, by other household members during childhood and adulthood, and by others in the workplace (Wu-Williams et al. 1990; Zhong et al. 1999; Lee et al. 2000; Wang et al. 2000). Although these four studies provided detailed information on secondhand smoke exposures and potential confounders, other studies included no information on key features such as age range of participants (Lei et al. 1996; Shen et al. 1996), the definition of lifetime nonsmokers (Wang et al. 1994, 1996; Lei et al. 1996; Shen et al. 1996, 1998), and response rates (Wang et al. 1994, 1996; Shen et al. 1996, 1998). In an early study conducted in Shanghai (Gao et al. 1987), secondhand smoke exposure was based only on smoking habits of the husbands. The study conducted in Singapore asked a single question about secondhand smoke exposure at home (Seow et al. 2000). Four studies presented crude risk estimates associated with secondhand smoke exposure (Wang et al. 1994; Lei et al. 1996; Shen et al. 1996, 1998). Studies also varied in the degree of pathologic confirmation, particularly those conducted in the People's Republic of China, and the proportion of histologically confirmed participants was generally considerably lower than in studies conducted in western countries or elsewhere in Asia (Table 7.3).

Taiwan

A hospital-based study of lung cancer conducted in Kaohsiung, an industrialized city in southern Taiwan, investigated the role of secondhand smoke, previous lung diseases, cooking practices, and the indoor environment (Ko et al. 1997; Lee et al. 2000). The investigators compared secondhand smoke exposure and other lifestyle factors of female lifetime nonsmokers who had a histologically confirmed lung cancer (n = 268), and of hospital controls who were ophthalmic or orthopedic patients or who were admitted to the same hospital for physical check-ups (n = 445) (Table 7.3) (Lee et al. 2000). Information on secondhand smoke exposure during childhood (aged <19 years) and adulthood (aged ≥19 years) at home and at work was obtained from a structured interview with the study participants. Secondhand smoke exposures were classified as no exposure, absence (secondhand smoke exposure but not in the presence of the participant), and presence of secondhand smoke exposure in the presence of the study participant.

In their analysis, Lee and colleagues (2000) adjusted for demographic characteristics and other potential confounders. These investigators found that husbands who smoked in the presence of participants significantly increased participants' risk of lung cancer (OR = 2.2 [95 percent CI, 1.5–3.3]). The study also noted a significant trend of an increase in risk among wives with increasing pack-years smoked by the husbands: the OR was 1.5 for 1 to 20 pack-years, 2.5 for 21 to 40 pack-years, and 3.3 for more than 40 pack-years.

There were nonsignificant increases in risks of 1.2 to 1.5 in association with other sources of secondhand smoke exposure during adulthood, including exposures from other family members at home and from coworkers at work (Lee et al. 2000). The risk of lung cancer increased significantly in association with a combined index of all sources of exposure during adulthood. For those with no reported exposure in the reference category, the OR was 1; for those with cumulative exposures of 1 to 20 smoker-years, the OR was 1.2; for 21 to 40 smoker-years, the OR was 1.4; and for 41 or more smoker-years, the OR was 2.2 (p trend = 0.002). The risk of lung cancer increased in association with smoking in the presence of the study participant during childhood by fathers (OR = 1.7 [95 percent CI, 1.1–2.6]) and other family members (OR = 1.4 [95 percent CI, 0.8–2.2]) but not by mothers (OR = 0.9 [95 percent CI, 0.3–3.1]). The investigators also observed a significant trend of an increase in risk among women with increasing secondhand smoke exposures during childhood: the ORs were 1.5 for exposures of 1 to 20 smoker-years and 1.8 for exposures of more than 20 smoker-years (p for trend = 0.01). When exposures during childhood and adulthood were considered together, individuals with childhood exposures and with the highest levels of

exposure during adulthood, defined as 40 or more smoker-years, showed more than a fourfold increase in risk (OR = 4.7 [95 percent CI, 2.4–9.4]) compared with individuals with no exposures.

One strength of this study is the assessment of smoking by family members and coworkers in the presence of the study participants. In fact, the risks associated with secondhand smoke exposure during childhood, from husbands, and from coworkers were invariably higher when the exposure was in the presence of the study participants. The risk estimates were reduced when the comparison was between women with no exposure and those with any exposure (combining absence and presence). The ORs associated with smoking by fathers (1.19), by other family members during childhood (1.11), by husbands (1.72), by other family members during adulthood (1.27), and by coworkers (1.24) showed weaker effects. These effects were similar to the risk estimates reported in other studies when secondhand smoke exposure in the presence of the study participants was not specifically distinguished.

Singapore

A hospital-based, case-control study in Singapore included women who had pathologically confirmed primary lung cancer (n = 303), and controls who were admitted to the same hospital (n = 756) but did not have a history of malignant or chronic respiratory disease, heart disease, or renal failure (Seow et al. 2000, 2002). All participants were interviewed in person using a standardized questionnaire that asked extensively about diet, reproductive history, and cooking practices, but the question on secondhand smoke exposure was crude. Persons were asked a single question regarding secondhand smoke exposure: whether any household members (spouse, parents, children, or any other relative or friend) had smoked in their presence more often than once a week.

Of the total cases and controls interviewed, 176 cases and 663 controls were lifetime nonsmokers, defined as fewer than one cigarette a day for a year (Table 7.3). Based on the single question on secondhand smoke exposure during childhood and adulthood, an estimated 52 percent of cases and 45 percent of controls had been exposed to secondhand smoke at home at least weekly. The OR was 1.3 (95 percent CI, 0.9–1.8) after adjusting for dietary and nondietary factors (Table 7.3) (Seow et al. 2002). Although this study is well-designed, information on secondhand smoke exposure was extremely limited.

Hong Kong and Southern China

Three studies from Hong Kong (Chan and Fung 1982; Koo et al. 1987; Lam et al. 1987) and three from southern China (Liu et al. 1991, 1993; Lei et al. 1996) have investigated the role of spousal smoking and lung cancer risk among women who had never smoked. Only one study (Lei et al. 1996) had not been previously reviewed (U.S. Environmental Protection Agency [USEPA] 1992; NCI 1999). Two studies found that exposure to smoking by the husbands was associated with a statistically significant increase in the risk of lung cancer among lifetime nonsmokers (Lam et al. 1987; Liu et al. 1993).

The role of secondhand smoke exposure in the risk of lung cancer mortality was investigated in a case-control study in Guangzhou, China (Table 7.3) (Du et al. 1996; Lei et al. 1996). The investigators reviewed death records maintained by the local police stations in the study area. All registered deaths from primary lung cancer (n = 831) of persons who had resided in Guangzhou for at least 10 years were considered eligible for the study. After excluding persons with a history of respiratory diseases or tumors, the investigators successfully identified controls for 792 of the 831 lung cancer deaths that were then matched by gender, age, same year of death, and block of residence. A standardized interview asked spouses or cohabiting relatives of the decedents about active smoking, exposure to secondhand smoke, living conditions, cooking facilities, exposure to coal dust, and dietary habits.

A total of 126 adults with a registered death of lung cancer (85 women, 41 men) and 270 matched adults who had died of causes other than lung cancer (147 women, 123 men) were classified as nonsmokers, but the analysis was based on 75 women who had died of lung cancer and 128 women who had died of other causes. Nonsmoking women married to smokers had a small increase in risk of lung cancer (OR = 1.19 [95 percent CI, 0.66–2.16]) (Table 7.3) (Du et al. 1996; Lei et al. 1996). Compared with nonsmoking women married to nonsmokers, women exposed to 1 to 19 cigarettes per day had an OR of 0.72 and women exposed to 20 or more cigarettes per day an OR of 1.62 (p for trend = 0.20). Risk did not significantly increase in association with duration of the husbands' smoking. For example, the OR for an exposure of 1 to 29 years was 1.39 compared with an OR of 1.17 for an exposure of 30 or more years (Du et al. 1996; Lei et al. 1996).

There are noted limitations in the study methods (see "Chinese in Taiwan, Singapore, Hong Kong, and the People's Republic of China" earlier in this chapter). Some of the adults who died of causes other than lung cancer may have had smoking-related diseases, because only those with respiratory diseases or other tumors were excluded from the analyses. In addition, the accuracy of a diagnosis of lung cancer based on reviewed death records is not known for China, and the quality and completeness of information on secondhand smoke exposures obtained from next of kin were not described.

Urban Areas in Central and Northern China

Six studies were conducted in central and northern China (Gao et al. 1987; Geng et al. 1988; USEPA 1992; Shen et al. 1996, 1998; Zhong et al. 1999). Secondhand smoke exposure from the husbands' smoking was implicated as a risk factor in the studies conducted in Shanghai (Gao et al. 1987) and in Tianjin (Geng et al. 1988; USEPA 1992). Shen and colleagues (1996) examined lung cancer among long-term (at least 20 years) female residents of Nanjing in a hospital-based, case-control study. Shen and colleagues (1998) then investigated the role of secondhand smoke exposure among nonsmoking women diagnosed with adenocarcinoma of the lung (n = 70) and among "healthy" women individually matched for age, neighborhood of residence, and occupation to the women with lung cancer. A standardized questionnaire administered to study participants included questions on secondhand smoke exposures and other lifestyle factors.

Exposure to secondhand smoke was associated with a nonsignificant increase in the risk of adenocarcinoma of the lung (OR = 1.63 [95 percent CI, 0.68–3.89]) (Table 7.3) (Shen et al. 1998). No significant trends were observed in risk with increased numbers of cigarettes per day or increased duration (in years) of the exposure. The investigators noted that the risk associated with any secondhand smoke exposure was weakened after adjusting for other factors that included chronic lung diseases, conditions of living quarters, type of fuel used for cooking and heating, and cooking practices. It was unclear whether the study participants were specifically asked about secondhand smoke exposure from spouses and other household members. The investigators also matched the study participants for occupation, which may have led to overmatching on certain exposures including secondhand smoke (Shen et al. 1996, 1998).

A population-based study of female lung cancer patients was designed to investigate the role of secondhand smoke exposure and other lung cancer risk factors in Shanghai (Zhong et al. 1999). Interviews that asked about active smoking, exposures to secondhand smoke, lifetime occupational history, residential history, family history of lung cancer, cooking activities, and dietary habits were conducted with 649 women diagnosed with lung cancer (cases) and 675 women from the general population (controls). Exposures to secondhand smoke in the home during childhood and adulthood were assessed by asking about all household members who smoked: the type of tobacco product used, the average number of cigarettes smoked per day, and the number of years of smoking while the participant lived in the household. Workplace exposure to secondhand smoke for jobs that lasted at least two years were also assessed. For each job, questions included the number of coworkers who smoked, and the total number of years and average number of hours per day spent with smoking coworkers (Zhong et al. 1999).

The analysis on secondhand smoke and lung cancer among lifetime nonsmokers was based on 504 women diagnosed with lung cancer (cases) and 601 women from the general population (controls); 145 cases and 74 controls reported smoking at least one cigarette per day for at least six months. The investigators adjusted demographic variables and other relevant covariates in the analyses on secondhand smoke exposure and found that compared with nonsmoking women married to nonsmoking husbands, nonsmoking women married to smokers showed a small increased risk (OR = 1.1 [95 percent CI, 0.8–1.5]). The study documented little variation in risk when the amount or duration of the husbands' smoking was considered: increased risks were 1.2 (95 percent CI, 0.8–1.7) and 1.9 (95 percent CI, 0.9–3.7) in association with secondhand smoke exposures during adulthood at home and at work, respectively (Table 7.3) (Zhong et al. 1999). Persons with secondhand smoke exposures both at home and at work as adults showed a significant increase in risk (OR = 1.9 [95 percent CI, 1.1–3.5]). Further investigation of workplace secondhand smoke exposures revealed statistically significant trends of an increase in risk with an increase in the number of hours of daily exposure. (For example, the OR for women exposed to secondhand smoke 1 to 2 hours per day was 1.0; 1.6 for those exposed 3 to 4 hours per day; and 2.9 for those exposed >4 hours per day [p trend <0.001].) A similar trend was noted with an increase in the number of coworkers who smoked (OR = 1.0 [1 to 2 coworkers who smoked], 1.7 [3 to 4 coworkers who smoked],

and 3.0 [>4 coworkers] [p trend <0.001]). However, the trend for risk with an increasing number of years of secondhand smoke exposure at work was not significant (OR = 1.0 [0 years], 2.0 [1 to 12 years], 1.4 [13 to 24 years], and 1.8 [>24 years] [p trend = 0.50]). Women with only a childhood exposure to secondhand smoke did not show any increased risk (OR = 0.9 [95 percent CI, 0.5–1.6]); the results remained similar when the investigators considered the duration (number of years) of exposure (Zhong et al. 1999).

Although some of the numbers became quite sparse, Zhong and colleagues (1999) conducted separate analyses among the 387 pathologically or cytologically confirmed lung cancer cases for adenocarcinoma (n = 297), for nonadenocarcinoma (n = 55), and for unknown cell types such as those diagnosed radiologically or clinically. Results associated with any workplace secondhand smoke exposure and the husbands' smoking were generally similar in these cell-type specific analyses. For example, the ORs associated with workplace secondhand smoke exposure were 1.8 (95 percent CI, 1.3–2.6) for adenocarcinoma, 1.7 (95 percent CI, 1.0–2.9) for nonadenocarcinoma, and 1.3 (95 percent CI, 0.7–2.3) for an unknown cell type. All three risk estimates associated with the husbands' smoking were between 1.1 and 1.2. However, the risks associated with secondhand smoke exposure during childhood were only substantially (but not significantly) higher for nonadenocarcinoma (OR = 2.4 [95 percent CI, 0.9–6.4]) than for adenocarcinoma (OR = 0.8 [95 percent CI, 0.3–1.9]), or for those with unknown cell types (OR = 0.8). Because of this risk difference by cell type, a cumulative index of secondhand smoke exposure during childhood and adulthood was more strongly associated with a risk of nonadenocarcinoma (OR = 2.1 [95 percent CI, 0.9–4.8]) than with adenocarcinoma (OR = 1.2 [95 percent CI, 0.7–1.8]), or with those of unknown cell types (OR = 1.0 [95 percent CI, 0.5–1.8]).

Strengths of this study include the population-based design, high response rates, high percentage of completed interviews with self-respondents, a comprehensive assessment of lifetime exposure to secondhand smoke that included various measures of intensity of exposure, and other potential confounding factors. Although only approximately three-fourths of the women diagnosed with lung cancer (i.e., cases) were histologically or cytologically confirmed, the investigators were able to conduct cell-type specific analyses because of the large sample size (Zhong et al. 1999).

Four case-control studies conducted in northern China investigated the role of secondhand smoke in the etiology of lung cancer among women. The locations included a large population-based study in Heilongjiang Province (Wu-Williams et al. 1990) and Gansu Province (Wang et al. 2000), and smaller hospital-based studies in Harbin (Wang et al. 1994) and Shenyang (Wang et al. 1996; Zhou et al. 2000). The RR of lung cancer was below 1.0 in association with secondhand smoke exposure in a large case-control study conducted in northern China (Wu-Williams et al. 1990). This observation should be considered anomalous as this result differs from the collective evidence of studies conducted in other Chinese populations as well as from the overall evidence (see "Pooled Analyses" earlier in this chapter). The effects of secondhand smoke may have been obscured in this study because other sources of indoor air pollution, such as coal-burning stoves and *kang* (brick beds that are typically heated either directly by a stove underneath them or by pipes connected to the cooking stove), were associated with an increased risk.

The role of secondhand smoke and the risk of lung cancer among lifetime nonsmoking women was investigated in a hospital-based, case-control study conducted in Shenyang, China (Table 7.3) (Wang et al. 1996; Zhou et al. 2000). The investigators compared female lifetime nonsmokers diagnosed with primary lung cancer (a total of 135) and an equal number of age-matched lifetime nonsmoking women (controls) selected from the general population of Shenyang. A structured questionnaire was administered to obtain information on demographic characteristics, exposure to tobacco, dietary and cooking practices, the type of fuel used, general medical conditions, history of previous lung diseases, history of cancer, menstrual and pregnancy history, and job history.

Lung cancer risk was not associated with any secondhand smoke exposure during childhood (OR = 0.91 [95 percent CI, 0.55–1.49]) or in the workplace during adulthood (OR = 0.89 [95 percent CI, 0.45–1.77]). Adult exposures to husbands' smoking were associated with a small increase in risk (OR = 1.11 [95 percent CI, 0.65–1.88]), but there were no significant trends of an increase in risk with an increase in duration of exposure (OR = 1.41 [<20 years], 1.08 [20 to 29 years], 1.08 [30 to 39 years], and 1.08 [≥40 years]) or in the amount smoked by the husbands (OR = 1.0 [0 cigarettes per day], 0.35 [1 to 9 cigarettes per day], 1.35 [10 to 19 cigarettes per day], and 1.40 [≥20 cigarettes per day]) (Wang et al. 1996).

A second report investigated the role of secondhand smoke exposure among persons diagnosed with adenocarcinoma of the lung (n = 72) and an equal number of persons from the general

population (controls) (Wang et al. 1996; Zhou et al. 2000). A risk of adenocarcinoma of the lung was not associated with secondhand smoke exposures from parents during childhood (OR = 0.89 [95 percent CI, 0.43–1.84]), from husbands (OR = 0.94 [95 percent CI, 0.45–1.97]), or from the workplace (OR = 0.89 [95 percent CI, 0.25–3.16]). There was little variation in risk with years of exposure during childhood or from husbands who smoked (Zhou et al. 2000).

The validity of a diagnosis of adenocarcinoma can be questioned because Wang and colleagues (1996) stated that determining the histologic cell type was "based on review of relevant medical records, chest X-ray and CT films, and cytologic and histologic slides" (p. S94). The cases presented in these two reports overlap. All of the adenocarcinoma cases and their corresponding controls from the general population included in the study by Wang and colleagues (1996) were also included in the study by Zhou and colleagues (2000).

A population-based, case-control study investigated the role of secondhand smoke exposure and other risk factors for lung cancer in Gansu Province, a nonindustrial area in northwestern China (Wang et al. 2000). A total of 886 lung cancer cases (656 men and 230 women) and 1,765 general population controls (1,310 men and 455 women) were interviewed. Cases (or next of kin, n = 481) and controls all completed a structured questionnaire on demographic characteristics; smoking habits of the participant, spouse, and other cohabitants; diet and cooking practices; and occupational, residential, and medical histories. The analysis was based on 233 lung cancer cases (33 men, 200 women) and 521 controls (114 men, 407 women) who had never smoked (Table 7.3) (Wang et al. 2000).

Wang and colleagues (2000) found that secondhand smoke exposure in adulthood, defined as ever having an exposure (OR = 0.90), or the number of pack-years of exposure (OR = 0.81 [1 to 9 pack-years], 0.90 [10 to 19 pack-years], and 0.86 [≥20 pack-years]) was not associated with risk. For men and women combined, there was a statistically significant increase in risk (OR = 1.52 [95 percent CI, 1.1– 2.2]) associated with any childhood exposure to secondhand smoke; the ORs increased with increasing pack-years of exposure (OR = 1.43 [1 to 9 pack-years], 1.81 [10 to 19 pack-years], and 2.95 [≥20 pack-years]; p for trend = 0.02). Overall, there was a nonsignificant increase in risk (OR = 1.19 [95 percent CI, 0.7–2.0]) from a lifetime exposure to secondhand smoke with some suggestion of increased risks with more pack-years of exposure (OR = 1.04 [1 to 9 pack-years], 1.13 [10 to 19 pack-years], and 1.51 [≥20 pack-years]). The patterns of association were generally similar among men and women and in the analyses restricted to self-respondents or those with histologically confirmed tumors. For example, among the 115 adults with lung cancer (cases) compared with the 501 adult controls from the general population who were self-respondents and who had never smoked, the ORs for ever having an exposure to secondhand smoke were 1.75 (95 percent CI, 1.1–2.8) in childhood and 0.76 (95 percent CI, 0.4–1.3) in adulthood. Among the histologically confirmed lung cancer cases, the risks associated with secondhand smoke were 1.55 (95 percent CI, 0.9–2.8) in childhood and 0.99 (95 percent CI, 0.5–2.0) in adulthood.

Other Asian Populations

Japan

In addition to the case-control studies conducted in various Chinese populations, case-control studies conducted in Japan (Akiba et al. 1986; Inoue and Hirayama 1988; Shimizu et al. 1988; Sobue 1990) generally support the finding that exposure to secondhand smoke is associated with an increased risk of lung cancer in nonsmokers. These studies have been included and discussed in previous reviews.

India

A small hospital-based, case-control study of lifetime nonsmokers in Chandigarh, India, compared 58 nonsmoking adults (17 men and 41 women) diagnosed with lung cancer (histologically confirmed cases) and 123 nonsmoking controls (56 men and 67 women). Controls were either other adult patients admitted to the hospital or visitors in the hospital. Although the conditions of the patients who were admitted to the hospital were not described, the investigators excluded patients with diseases related to smoking, alcohol, or diet. No attempt was made to match cases and controls by gender, age, or other variables (Table 7.3) (Rapiti et al. 1999).

Participants were interviewed in the hospital and responded to a questionnaire designed to assess demographic factors, active smoking, and lifetime secondhand smoke exposure. Questions on secondhand smoke were modeled after those used in a European multicenter case-control study (Boffetta et al. 1998). Among all participants combined, Rapiti and colleagues (1999) found a significantly increased risk associated with secondhand smoke exposure during childhood (OR = 3.9 [95 percent CI, 1.9–8.2]) after adjusting for gender, age, residence, and

religion. A significantly increased risk was not observed in association with secondhand smoke from spouses (OR = 1.1 [95 percent CI, 0.5–2.6]) when all sources of tobacco products were considered. Indian smokers use not only cigarettes but bidis, tobacco wrapped in a leaf, and chilum, similar to a pipe. However, the risk of lung cancer increased significantly in association with cigarette smoking by spouses (OR = 5.1 [95 percent CI, 1.5–17]) but was reduced in association with bidi smoking (OR = 0.1 [95 percent CI, 0.01–1.2]). These results among men and women combined were also observed in the analyses that were restricted to women only (Rapiti et al. 1999).

The study was small and the appropriateness of the control groups is uncertain. Information on potential confounders was also lacking. The very high estimate of risk associated with secondhand smoke exposure in childhood may be a chance finding because results from most published studies show either no risk or a much weaker effect on risk. The results observed in association with cigarettes versus bidis smoked by the spouses were also divergent. Although the investigators explained that a bidi is smaller in size and may emit less smoke than a cigarette, they found no basis for anticipating a protective effect from bidis.

References

Akiba S, Kato H, Blot WJ. Passive smoking and lung cancer among Japanese women. *Cancer Research* 1986;46(9):4804–7.

Al-Delaimy WK, Cho E, Chen WY, Colditz G, Willet WC. A prospective study of smoking and risk of breast cancer in young adult women. *Cancer Epidemiology, Biomarkers & Prevention* 2004;13(3): 398–404.

Althuis MD, Fergenbaum JH, Garcia-Closas M, Brinton LA, Madigan MP, Sherman ME. Etiology of hormone receptor–defined breast cancer: a systematic review of the literature. *Cancer Epidemiology, Biomarkers & Prevention* 2004;13(10):1558–68.

Ambrosone CB, Freudenheim JL, Graham S, Marshall JR, Vena JE, Brasure JR, Michalek AM, Laughlin R, Nemoto T, Gillenwater KA, et al. Cigarette smoking, *N*-acetyltransferase 2 genetic polymorphisms, and breast cancer risk. *Journal of the American Medical Association* 1996;276(18):1494–501.

Aschengrau A, Ozonoff D, Coogan P, Vezina R, Heeren T, Zhang Y. Cancer risk and residential proximity to cranberry cultivation in Massachusetts. *American Journal of Public Health* 1996;86(9):1289–96.

Baron JA, La Vecchia C, Levi F. The antiestrogenic effect of cigarette smoking in women. *American Journal of Obstetrics and Gynecology* 1990;162(2): 502–14.

Becher H, Zatonski W, Jöckel K-H. Passive smoking in Germany and Poland: comparison of exposure levels, sources of exposure, validity, and perception. *Epidemiology* 1992;3(6):509–14.

Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50(4):1088–101.

Bero LA, Glantz SA, Rennie D. Publication bias and public health policy on environmental tobacco smoke. *Journal of the American Medical Association* 1994;272(2):133–6.

Blot WJ, Fraumeni JF Jr. Passive smoking and lung cancer [editorial]. *Journal of the National Cancer Institute* 1986;77(5):993–1000.

Boffetta P, Agudo A, Ahrens W, Benhamou E, Benhamou S, Darby SC, Ferro G, Fortes C, Gonzalez CA, Jöckel K-H, et al. Multicenter case-control study of exposure to environmental tobacco smoke and lung cancer in Europe. *Journal of the National Cancer Institute* 1998;90(19):1440–50.

Boffetta P, Ahrens W, Nyberg F, Mukeria A, Brüske-Hohlfeld I, Fortes C, Constantinescu V, Simonato L, Batura-Gabryel H, Lea S, et al. Exposure to environmental tobacco smoke and risk of adenocarcinoma of the lung. *International Journal of Cancer* 1999;83(5):635–9.

Bonner MR, Nie J, Han D, Vena JE, Rogerson P, Muti P, Trevisan M, Edge SB, Freudenheim JL. Secondhand smoke exposure in early life and the risk of breast cancer among never smokers (United States). *Cancer Causes and Control* 2005;16(6):683–9.

Brinton LA, Blot WJ, Becker JA, Winn DM, Browder JP, Farmer JC Jr, Fraumeni JF Jr. A case-control study of cancers of the nasal cavity and paranasal sinuses. *American Journal of Epidemiology* 1984;119(6): 896–906.

Brownson RC, Alavanja MCR, Hock ET, Loy TS. Passive smoking and lung cancer in nonsmoking women. *American Journal of Public Health* 1992; 82(11):1525–30.

Brownson RC, Reif JS, Keefe TJ, Ferguson SW, Pritzl JA. Risk factors for adenocarcinoma of the lung. *American Journal of Epidemiology* 1987;125(1):25–34.

Buffler PA, Pickle LW, Mason TJ, Contant C. The causes of lung cancer in Texas. In: Mizell M, Correa P, editors. *Lung Cancer: Causes and Prevention*. Deerfield Beach (FL): Verlag Chemie International, 1984:83–99.

Butler TL. The relationship of passive smoking to various health outcomes among Seventh-day Adventists in California [dissertation]. Los Angeles: University of California, 1988.

California Environmental Protection Agency. *Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant. Part B: Health Effects*. Sacramento (CA): California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, 2005.

Calle EE, Miracle-McMahill HL, Thun MJ, Heath CW Jr. Cigarette smoking and risk of fatal breast cancer. *American Journal of Epidemiology* 1994;139(10): 1001–17.

Cardenas VM, Thun MJ, Austin H, Lally CA, Clark WS, Greenberg RS, Heath CW Jr. Environmental tobacco smoke and lung cancer mortality in the American Cancer Society's Cancer Prevention Study II. *Cancer Causes and Control* 1997;8(1):57–64.

Chan WC, Fung SC. Lung cancer in non-smokers in Hong Kong. In: Grundmann E, Clemmesen J, Muir CS, editors. *Geographical Pathology in Cancer Epidemiology*. Cancer Campaign. Vol. 6. New York: Gustav Fischer Verlag, 1982:199–202.

Chen C, Wang X, Wang L, Yang F, Tang G, Xing H, Ryan L, Lasley B, Overstreet JW, Stanford JB, Xu X. Effect of environmental tobacco smoke on levels of urinary hormone markers. *Environmental Health Perspectives* 2005;113(4):412–7.

Cheng Y-J, Hildesheim A, Hsu M-M, Chen I-H, Brinton LA, Levine PH, Chen C-J, Yang C-S. Cigarette smoking, alcohol consumption and risk of nasopharyngeal carcinoma in Taiwan. *Cancer Causes and Control* 1999;10(3):201–7.

Coker AL, Rosenberg AJ, McCann MF, Hulka BS. Active and passive cigarette smoke exposure and cervical intraepithelial neoplasia. *Cancer Epidemiology, Biomarkers & Prevention* 1992;1(5):349–56.

Colditz GA. Epidemiology and prevention of breast cancer. *Cancer Epidemiology, Biomarkers & Prevention* 2005;14(4):768–72.

Copas JB, Shi JQ. Reanalysis of epidemiological evidence on lung cancer and passive smoking. *British Medical Journal* 2000;320(7232):417–8.

Correa P, Pickle LW, Fontham E, Lin Y, Haenszel W. Passive smoking and lung cancer. *Lancet* 1983;2(8350):595–7.

Curtin F, Morabia A, Bernstein MS. Relation of environmental tobacco smoke to diet and health habits: variations according to the site of exposure. *Journal of Clinical Epidemiology* 1999;52(11):1055–62.

de Waard F, Kemmeren JM, van Ginkel LA, Stolker AAM. Urinary cotinine and lung cancer risk in a female cohort. *British Journal of Cancer* 1995; 72(3):784–7.

Delfino RJ, Smith C, West JG, Lin HJ, White E, Liao S-Y, Gim JSY, Ma HL, Butler J, Anton-Culver H. Breast cancer, passive and active cigarette smoking and *N*-acetyltransferase 2 genotype. *Pharmacogenetics* 2000;10(5):461–9.

Demers PA, Kogevinas M, Boffetta P, Leclerc A, Luce D, Gérin M, Battista G, Belli S, Bolm-Audorf U, Brinton LA, et al. Wood dust and sino-nasal cancer: pooled reanalysis of twelve case-control studies. *American Journal of Industrial Medicine* 1995;28(2):151–66.

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;7(3):177–88.

Dockery DW, Trichopoulos D. Risk of lung cancer from environmental exposures to tobacco smoke. *Cancer Causes and Control* 1997;8(3):333–45.

Drope J, Chapman S. Tobacco industry efforts at discrediting scientific knowledge of environmental tobacco smoke: a review of internal industry documents. *Journal of Epidemiology and Community Health* 2001;55(8):588–94.

Du Y-X, Cha Q, Chen X-W, Chen Y-Z, Huang L-F, Feng Z-Z, Wu X-F, Wu JM. An epidemiological study of risk factors for lung cancer in Guangzhou, China. *Lung Cancer* 1996;14(Suppl 1):S9–S37.

Dunnick JK, Elwell MR, Huff J, Barrett JC. Chemically induced mammary gland cancer in the National Toxicology Program's carcinogenesis bioassay. *Carcinogenesis* 1995;16(2):173–9.

Egan KM, Stampfer MJ, Hunter D, Hankinson S, Rosner BA, Holmes M, Willett WC, Colditz GA. Active and passive smoking in breast cancer: prospective results from the Nurses' Health Study. *Epidemiology* 2002;13(2):138–45.

El-Bayoumy K, Chae Y-H, Upadhyaya P, Rivenson A, Kurtzke C, Reddy B, Hecht SS. Comparative tumorigenicity of benzo[*a*]pyrene, 1-nitropyrene and 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine administered by gavage to female CD rats. *Carcinogenesis* 1995;16(2):431–4.

Elwood JM. Wood exposure and smoking: association with cancer of the nasal cavity and paranasal sinuses in British Columbia. *Canadian Medical Association Journal* 1981;124(12):1573–7.

Fontham ETH, Correa P, Reynolds P, Wu-Williams A, Buffler PA, Greenberg RS, Chen VW, Alterman T, Boyd P, Austin DF, et al. Environmental tobacco smoke and lung cancer in nonsmoking women: a multicenter study. *Journal of the American Medical Association* 1994;271(22):1752–9.

Fontham ETH, Correa P, Wu-Williams A, Reynolds P, Greenberg RS, Buffler PA, Chen VW, Boyd P, Alterman T, Austin DF, et al. Lung cancer in nonsmoking women: a multicenter case-control study. *Cancer Epidemiology, Biomarkers & Prevention* 1991;1(1):35–43.

Forastiere F, Mallone S, Lo Presti E, Baldacci S, Pistelli F, Simoni M, Scalera A, Pedreschi M, Pistelli R, Corbo G, et al. Characteristics of nonsmoking women exposed to spouses who smoke: epidemiologic study on environment and health in women from four Italian areas. *Environmental Health Perspectives* 2000;108(12):1171–7.

Friedenreich CM. Physical activity and breast cancer risk: the effect of menopausal status. *Exercise and Sport Science Reviews* 2004;32(4):180–4.

Fry JS, Lee PN. Revisiting the association between environmental tobacco smoke exposure and lung cancer risk. IV. Adjustments for the potential confounding effects of fruit, vegetables, and dietary fat. *Indoor Built Environment* 2001;10(1):20–39.

Fukuda K, Shibata A. Exposure-response relationships between woodworking, smoking or passive smoking, and squamous cell neoplasms of the maxillary sinus. *Cancer Causes and Control* 1990;1(2):165–8.

Gammon MD, Eng SM, Teitelbaum SL, Britton JA, Kabat GC, Hatch M, Paykin AB, Neugut AI, Santella RM. Environmental tobacco smoke and breast cancer incidence. *Environmental Research* 2004;96(2):176–85.

Gao Y-T, Blot WJ, Zheng W, Ershow AG, Hsu CW, Levin LI, Zhang R, Fraumeni JF Jr. Lung cancer among Chinese women. *International Journal of Cancer* 1987;40(5):604–9.

Gao YT, Blot WJ, Zheng W, Fraumeni JF, Hsu CW. Lung cancer and smoking in Shanghai. *International Journal of Epidemiology* 1988;17(2):277–80.

Garfinkel L. Time trends in lung cancer among nonsmokers and a note on passive smoking. *Journal of the National Cancer Institute* 1981;66(6):1061–6.

Garfinkel L, Auerbach O, Joubert L. Involuntary smoking and lung cancer: a case-control study. *Journal of the National Cancer Institute* 1985;75(3):463–9.

Geng G-Y, Liang ZH, Zhang A-Y, Wu GL. On the relationship between smoking and female lung cancer. In: Aoki M, Hisamichi S, Tominaga S, editors. *Smoking and Health 1987*. Proceedings of the 6th World Conference on Smoking and Health, Nov 9–12, 1987; Tokyo. Amsterdam: Elsevier Science, 1988:483–6.

Ghadirian P, Lubinski J, Lynch H, Neuhausen SL, Weber B, Isaacs C, Baruch R-G, Randall S, Ainsworth P, Freidman E, et al. Smoking and the risk of breast cancer among carriers of BRCA mutations. *International Journal of Cancer* 2004;110(3):413–6.

Gillis CR, Hole DJ, Hawthorne VM, Boyle P. The effect of environmental tobacco smoke in two urban communities in the west of Scotland. *European Journal of Respiratory Diseases* 1984;65(Suppl 133):121–6.

Gram IT, Braaten T, Terry PD, Sasco AJ, Adami HO, Lund E, Weiderpass E. Breast cancer risk among women who start smoking as teenagers. *Cancer Epidemiology, Biomarkers & Prevention* 2005;14(1):61–6.

Guerin MR, Jenkins RA, Tomkins BA. *The Chemistry of Environmental Tobacco Smoke: Composition and Measurement*. Chelsea (MI): Lewis Publishers, 1992.

Hackshaw AK, Law MR, Wald NJ. The accumulated evidence on lung cancer and environmental tobacco smoke. *British Medical Journal* 1997;315(7114): 980–8.

Hamajima N, Hirose K, Tajima K, Rohan T, Calle EE, Heath CW Jr, Coates RJ, Liff JM, Talamini R, Chantarakul N, et al. Alcohol, tobacco and breast cancer—collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. *British Journal of Cancer* 2002;87(11):1234–45.

Hammond SK. Exposure of U.S. workers to environmental tobacco smoke. *Environmental Health Perspectives* 1999;107(Suppl 2):329–40.

Hanaoka T, Yamamoto S, Sobue T, Sasaki S, Tsugane S, the Japan Public Health Center-Based Prospective Study on Cancer and Cardiovascular Disease Study Group. Active and passive smoking and breast cancer risk in middle-aged Japanese women. *International Journal of Cancer* 2005;114:317–22.

Hankinson SE, Colditz GA, Willett WC. Towards an integrated model for breast cancer etiology: the lifelong interplay of genes, lifestyle, and hormones. *Breast Cancer Research* 2004;6(5):213–8.

Hayes RB, Kardaun JWPF, de Bruyn A. Tobacco use and sinonasal cancer: a case-control study. *British Journal of Cancer* 1987;56(6):843–6.

Hecht SS. Tobacco smoke carcinogens and lung cancer. *Journal of the National Cancer Institute* 1999; 91(14):1194–210.

Hirayama T. Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan. *British Medical Journal* 1981;282(6259):183–5.

Hirayama T. Cancer mortality in nonsmoking women with smoking husbands based on a large scale cohort study in Japan. *Preventive Medicine* 1984;13(6):680–90.

Hoffmann D, Hecht SS. Advances in tobacco carcinogenesis. In: Cooper CS, Grover PL, editors. *Handbook of Experimental Pharmacology*. 94/I ed. Heidelberg: Springer-Verlag, 1990:63–102.

Hole DJ, Gillis CR, Chopra C, Hawthorne VM. Passive smoking and cardiorespiratory health in a general population in the west of Scotland. *British Medical Journal* 1989;299(6696):423–7.

Horton AW. Indoor tobacco smoke pollution: a major risk factor for both breast and lung cancer. *Cancer* 1988;62(1):6–14.

Humble CG, Samet JM, Pathak DR. Marriage to a smoker and lung cancer risk. *American Journal of Public Health* 1987;77(5):598–602.

Hunter D, Gertig D, Speigelman D. Response [letter]. *Carcinogenesis* 1998;19(9):1705.

Hunter DJ, Hankinson SE, Hough H, Gertig DM, Garcia-Closas M, Spiegelman D, Manson JE, Colditz GA, Willett WC, Speizer FE, Kelsey K. A prospective study of NAT2 acetylation genotype, cigarette smoking, and risk of breast cancer. *Carcinogenesis* 1997;18(11):2127–32.

Inoue R, Hirayama T. Passive smoking and lung cancer in women. In: Aoki M, Hisamichi S, Tominaga S, editors. *Smoking and Health 1987*. Proceedings of the 6th World Conference on Smoking and Health, Nov 9–12, 1987; Tokyo. Amsterdam: Elsevier Science, 1988:283–5.

International Agency for Research on Cancer. *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Tobacco Smoking*. Vol. 38. Lyon (France): World Health Organization, International Agency for Research on Cancer, 1986.

International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Tobacco Smoke and Involuntary Smoking*. Vol. 83. Lyon (France): International Agency for Research on Cancer, 2004.

Jaakkola MS, Samet JM. Summary: workshop on health risks attributable to ETS exposure in the workplace. *Environmental Health Perspectives* 1999;107(Suppl 6): 823–8.

Janerich DT, Thompson WD, Varela LR, Greenwald P, Chorost S, Tucci C, Zaman MB, Melamed MR, Kiely M, McKneally MF. Lung cancer and exposure to tobacco smoke in the household. *New England Journal of Medicine* 1990;323(10):632–6.

Jee SH, Ohrr H, Kim IS. Effects of husbands' smoking on the incidence of lung cancer in Korean women. *International Journal of Epidemiology* 1999;28(5): 824–8.

Jee SH, Samet JM, Ohrr H, Kim JH, Kim IS. Smoking and cancer risk in Korean men and women. *Cancer Causes and Control* 2004;15(4):341–8.

Jöckel K-H, Pohlabeln H, Ahrens W, Krauss M. Environmental tobacco smoke and lung cancer. *Epidemiology* 1998;9(6):672–5.

Johnson KC. Accumulating evidence on passive and active smoking and breast cancer risk. *International Journal of Cancer* 2005;117(4):619–28.

Johnson KC, Hu J, Mao Y, the Canadian Cancer Registries Epidemiology Research Group. Passive and active smoking and breast cancer risk in Canada, 1994–97. *Cancer Causes and Control* 2000;11(3): 211–21.

Johnson KC, Hu J, Mao Y, the Canadian Cancer Registries Epidemiology Research Group. Lifetime residential and workplace exposure to environmental tobacco smoke and lung cancer in never-smoking women, Canada 1994–97. *International Journal of Cancer* 2001;93(6):902–6.

Kabat GC, Stellman SD, Wynder EL. Relation between exposure to environmental tobacco smoke and lung cancer in lifetime nonsmokers. *American Journal of Epidemiology* 1995;142(2):141–8.

Kabat GC, Wynder EL. Lung cancer in nonsmokers. *Cancer* 1984;53(5):1214–21.

Kalandidi A, Katsouyanni K, Voropoulou N, Bastas G, Saracci R, Trichopoulos D. Passive smoking and diet in the etiology of lung cancer among nonsmokers. *Cancer Causes and Control* 1990;1(1):15–21.

Katada H, Mikami R, Konishi M, Koyama Y, Narita N. The effects of passive smoking in the development of female lung cancer in the Nara district [Japanese]. *Gan No Rinsho* 1988;34(1):21–7.

Kawachi I, Colditz GA. Invited commentary: confounding, measurement error, and publication bias in studies of passive smoking. *American Journal of Epidemiology* 1996;144(10):909–15.

Key TJA, Pike MC, Baron JA, Moore JW, Wang DY, Thomas BS, Bulbrook RD. Cigarette smoking and steroid hormones in women. *Journal of Steroid Biochemistry and Molecular Biology* 1991;39(4A):529–34.

Key TJA, Pike MC, Brown JB, Hermon C, Allen DS, Wang DY. Cigarette smoking and urinary oestrogen excretion in premenopausal and post-menopausal women. *British Journal of Cancer* 1996;74(8):1313–6.

Ko Y-C, Lee CH, Chen MJ, Huang CC, Chang WY, Lin HJ, Wang HZ, Chang PY. Risk factors for primary lung cancer among non-smoking women in Taiwan. *International Journal of Epidemiology* 1997; 26(1):24–31.

Koo LC, Ho JH-C, Saw D. Is passive smoking and [sic] added risk factor for lung cancer in Chinese women? *Journal of Experimental and Clinical Cancer Research* 1984;3(3):277–83.

Koo LC, Ho JH-C, Saw D, Ho C-Y. Measurements of passive smoking and estimates of lung cancer risk among non-smoking Chinese females. *International Journal of Cancer* 1987;39(2):162–9.

Kreuzer M, Gerken M, Kreienbrock L, Wellmann J, Wichmann HE. Lung cancer in lifetime nonsmoking men—results of a case-control study in Germany. *British Journal of Cancer* 2001;84(1):134–40.

Kreuzer M, Krauss M, Kreienbrock L, Jöckel K-H, Wichmann H-E. Environmental tobacco smoke and lung cancer: a case-control study in Germany. *American Journal of Epidemiology* 2000;151(3):241–50.

Kropp S, Chang-Claude J. Active and passive smoking and risk of breast cancer by age 50 years among German women. *American Journal of Epidemiology* 2002;156(7):616–26.

Kubik A, Zatloukal P, Boyle P, Robertson C, Gandini S, Tomasek L, Gray N, Havel L. A case-control study of lung cancer among Czech women. *Lung Cancer* 2001;31(2–3):111–22.

Kung IT, So KF, Lam TH. Lung cancer in Hong Kong Chinese: mortality and histological types, 1973–1982. *British Journal of Cancer* 1984;50(3):381–8.

Lam WK. A clinical and epidemiological study of carcinoma of lung in Hong Kong [dissertation]. Hong Kong: University of Hong Kong, 1985.

Lam TH, Kung ITM, Wong CM, Lam WK, Kleevens JWL, Saw D, Hsu C, Seneviratne S, Lam SY, Lo KK, et al. Smoking, passive smoking and histological types in lung cancer in Hong Kong Chinese women. *British Journal of Cancer* 1987;56(5):673–8.

Lash TL, Aschengrau A. Active and passive cigarette smoking and the occurrence of breast cancer. *American Journal of Epidemiology* 1999;149(1):5–12.

Lash TL, Aschengrau A. A null association between active or passive cigarette smoking and breast cancer risk. *Breast Cancer Research and Treatment* 2002;75(2):181–4.

Law CH, Day NE, Shanmugaratnam K. Incidence rates of specific histological types of lung cancer in Singapore Chinese dialect groups, and their aetiological significance. *International Journal of Cancer* 1976;17(3):304–9.

Lawlor DA, Ebrahim S, Smith GD. Smoking before the birth of a first child is not associated with increased risk of breast cancer: findings from the British Women's Heart and Health Cohort Study and a meta-analysis. *British Journal of Cancer* 2004;91(3):512–8.

Lee PN. *Environmental Tobacco Smoke and Mortality: A Detailed Review of Epidemiological Evidence Relating Environmental Tobacco Smoke to the Risk of Cancer, Heart Disease, and Other Causes of Death in Adults Who Have Never Smoked.* New York: Karger, 1992.

Lee C-H, Ko Y-C, Goggins W, Huang J-J, Huang M-S, Kao E-L, Wang H-Z. Lifetime environmental exposure to tobacco smoke and primary lung cancer of non-smoking Taiwanese women. *International Journal of Epidemiology* 2000;29(2):224–31.

Lee PN, Chamberlain J, Alderson MR. Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases. *British Journal of Cancer* 1986;54(1):97–105.

Lei Y-X, Cai W-C, Chen Y-Z, Du Y-X. Some lifestyle factors in human lung cancer: a case-control study of 792 lung cancer cases. *Lung Cancer* 1996;14(Suppl 1): S121–S136.

Li D, Wang M, Dhingra K, Hittelman WN. Aromatic DNA adducts in adjacent tissues of breast cancer patients: clues to breast cancer etiology. *Cancer Research* 1996;56(2):287–93.

Liu L, Wu K, Lin X, Yin W, Zheng X, Tang X, Mu L, Hu Z, Wang J. Passive smoking and other factors at different periods of life and breast cancer risk in Chinese women who have never smoked—a case-control study in Chongqing, People's Republic of China. *Asian Pacific Journal of Cancer Prevention* 2000;1(2):131–7.

Liu Q, Sasco AJ, Riboli E, Hu MX. Indoor air pollution and lung cancer in Guangzhou, People's Republic of China. *American Journal of Epidemiology* 1993;137(2):145–54.

Liu Z, He X, Chapman RS. Smoking and other risk factors for lung cancer in Xuanwei, China. *International Journal of Epidemiology* 1991;20(1):26–31.

Lubin JH. Estimating lung cancer risk with exposure to environmental tobacco smoke. *Environmental Health Perspectives* 1999;107(Suppl 6):879–83.

MacMahon B, Trichopoulos D, Cole P, Brown J. Cigarette smoking and urinary estrogens. *New England Journal of Medicine* 1982;307(17):1062–5.

Mannetje A, Kogevinas M, Luce D, Demers PA, Bégin D, Bolm-Audorff U, Comba P, Gérin M, Hardell L, Hayes RB, et al. Sinonasal cancer, occupation, and tobacco smoking in European women and men. *American Journal of Industrial Medicine* 1999; 36(1):101–7.

Marcus PM, Newman B, Millikan RC, Moorman PG, Baird DD, Qaqish B. The associations of adolescent cigarette smoking, alcoholic beverage consumption, environmental tobacco smoke, and ionizing radiation with subsequent breast cancer risk (United States). *Cancer Causes and Control* 2000;11(3): 271–87.

Matanoski G, Kanchanaraksa S, Lantry D, Chang Y. Characteristics of nonsmoking women in NHANES I and NHANES I Epidemiological Follow-up Study with exposure to spouses who smoke. *American Journal of Epidemiology* 1995;142(2):149–57.

Michnovicz JJ, Hershcopf RJ, Naganuma H, Bradlow HL, Fishman J. Increased 2-hydroxylation of estradiol as a possible mechanism for the anti-estrogenic effect of cigarette smoking. *New England Journal of Medicine* 1986;315(21):1305–9.

Millikan RC, Pittman GS, Newman B, Tse C-KJ, Selmin O, Rockhill B, Savitz D, Moorman PG, Bell DA. Cigarette smoking, *N*-acetyltransferases 1 and

2, and breast cancer risk. *Cancer Epidemiology, Biomarkers & Prevention* 1998;7(5):371–8.

Misakian AL, Bero LA. Publication bias and research on passive smoking: comparison of published and unpublished studies. *Journal of the American Medical Association* 1998;280(3):250–3.

Morabia A, Bernstein M, Héritier S, Khatchatrian N. Relation of breast cancer with passive and active exposure to tobacco smoke. *American Journal of Epidemiology* 1996;143(9);918–28.

Morabia A, Bernstein MS, Bouchardy I, Kurtz J, Morris MA. Breast cancer and active and passive smoking: the role of the *N*-acetyltransferase 2 genotype. *American Journal of Epidemiology* 2000;152(3): 226–32.

Muggli ME, Forster JL, Hurt RD, Repace JL. The smoke you don't see: uncovering tobacco industry scientific strategies aimed against environmental tobacco smoke policies. *American Journal of Public Health* 2001;91(9):1419–23.

Nagao M, Ushijima T, Wakabayashi K, Ochiai M, Kushida H, Sugimura T, Hasegawa R, Shirai T, Ito N. Dietary carcinogens and mammary carcinogens: induction of rat mammary carcinomas by administration of heterocyclicamines in cooked foods. *Cancer* 1994;74(Suppl):1063–9.

National Cancer Institute. *Health Effects of Exposure to Environmental Tobacco Smoke: The Report of the California Environmental Protection Agency*. Smoking and Tobacco Control Monograph No. 10. Bethesda (MD): U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, 1999. NIH Publication No. 99-4645.

National Research Council. *Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects*. Washington: National Academy Press, 1986.

National Research Council. *Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII–Phase 2*. Washington: National Academy Press, 2005.

Nishino Y, Tsubono Y, Tsuji I, Komatsu S, Kanemura S, Nakatsuka H, Fukao A, Satoh H, Hisamichi S. Passive smoking at home and cancer risk: a population-based prospective study in Japanese nonsmoking women. *Cancer Causes and Control* 2001;12(9):797–802.

Nyberg F, Agrenius V, Svartengren K, Svensson C, Pershagen G. Environmental tobacco smoke and lung cancer in nonsmokers: does time since exposure play a role? *Epidemiology* 1998a;9(3):301–8.

Nyberg F, Agudo A, Boffetta P, Fortes C, González CA, Pershagen G. A European validation study of smoking and environmental tobacco smoke exposure in nonsmoking lung cancer cases and controls. *Cancer Causes and Control* 1998b;9(2):173–82.

Nyberg F, Isaksson I, Harris JR, Pershagen G. Misclassification of smoking status and lung cancer risk from environmental tobacco smoke in never-smokers. *Epidemiology* 1997;8(3):304–9.

Palmer JR, Rosenberg L. Cigarette smoking and the risk of breast cancer. *Epidemiologic Reviews* 1993:15(1):145–56.

Pershagen G, Hrubec Z, Svensson C. Passive smoking and lung cancer in Swedish women. *American Journal of Epidemiology* 1987;125(1):17–24.

Petrakis NL, Gruenke LD, Beelen TC, Castagnoli N Jr, Craig JC. Nicotine in breast fluid of nonlactating women. *Science* 1978;199(4326):303–5.

Petrakis NL, Miike R, King EB, Lee L, Mason L, Chang-Lee B. Association of breast fluid coloration with age, ethnicity, and cigarette smoking. *Breast Cancer Research and Treatment* 1988;11(3):255–62.

Pirkle JL, Flegal KM, Bernert JT, Brody DJ, Etzel RA, Maurer KR. Exposure of the US population to environmental tobacco smoke: the Third National Health and Nutrition Examination Survey, 1988 to 1991. *Journal of the American Medical Association* 1996;275(16):1233–40.

Preston DL, Mattsson A, Holmberg E, Shore R, Hildreth NG, Boice JD Jr. Radiation effects on breast cancer risk: a pooled analysis of eight cohorts. *Radiation Research* 2002;158(2):220–35.

Rapiti E, Jindal SK, Gupta D, Boffetta P. Passive smoking and lung cancer in Chandigarh, India. *Lung Cancer* 1999;23(3):183–9.

Reynolds P, Hurley S, Goldberg DE, Anton-Culver H, Bernstein L, Deapen D, Horn-Ross PL, Peel D, Pinder R, Ross RK, et al. Active smoking, household passive smoking, and breast cancer: evidence from the California Teachers Study. *Journal of the National Cancer Institute* 2004;96(1):29–37.

Reynolds P, Von Behren J, Fontham ETH, Correra P, Wu A, Buffler PA, Greenberg RS. Occupational exposure to environmental tobacco smoke [letter]. *Journal of the American Medical Association* 1996;275(6):441–2.

Riboli E, Preston-Martin S, Saracci R, Haley NJ, Trichopoulos D, Becher H, Burch D, Fontham ET, Gao Y-T, Jindal SK, et al. Exposure of nonsmoking women to environmental tobacco smoke: a 10-country collaborative study. *Cancer Causes and Control* 1990;1(3):243–52.

Rousch GC. Cancers of the nasal cavity and paranasal sinuses. In: Schottenfeld D, Fraumeni J Jr, editors.

Cancer Epidemiology and Prevention. 2nd edition. New York: Oxford University Press, 1996:587–602.

Sandler DP, Everson RB, Wilcox AJ. Passive smoking in adulthood and cancer risk. *American Journal of Epidemiology* 1985a;121(1):37–48.

Sandler DP, Wilcox AJ, Everson RB. Cumulative effects of lifetime passive smoking on cancer risk. *Lancet* 1985b;1(8424):312–4.

Scholes D, McBride C, Grothaus L, Curry S, Albright J, Ludman E. The association between cigarette smoking and low-grade cervical abnormalities in reproductive-age women. *Cancer Causes and Control* 1999;10(5):339–44.

Schwartz AG, Yang P, Swanson GM. Familial risk of lung cancer among nonsmokers and their relatives. *American Journal of Epidemiology* 1996;144(6): 554–62.

Seow A, Poh WT, Teh M, Eng P, Wang YT, Tan WC, Chia KS, Yu MC, Lee HP. Diet, reproductive factors and lung cancer risk among Chinese women in Singapore: evidence for a protective effect of soy in nonsmokers. *International Journal of Cancer* 2002;97(3):365–71.

Seow A, Poh W-T, Teh M, Eng P, Wang Y-T, Tan W-C, Yu MC, Lee H-P. Fumes from meat cooking and lung cancer risk in Chinese women. *Cancer Epidemiology, Biomarkers & Prevention* 2000;9(11): 1215–21.

Shen X-B, Wang G-X, Huang Y-Z, Xiang L-S, Wang X-H. Analysis and estimates of attributable risk factors for lung cancer in Nanjing, China. *Lung Cancer* 1996;14(Suppl 1):S107–S112.

Shen X-B, Wang G-X, Zhou B-S. Relation of exposure to environmental tobacco smoke and pulmonary adenocarcinoma in non-smoking women: a case control study in Nanjing. *Oncology Reports* 1998;5(5):1221–3.

Shimizu H, Morishita M, Mizuno K, Masuda T, Ogura Y, Santo M, Nishimura M, Kunishima K, Karasawa K, Nishiwaki K, et al. A case-control study of lung cancer in nonsmoking women. *Tohoku Journal of Experimental Medicine* 1988;154(4):389–97.

Shrubsole MJ, Gao YT, Dai Q, Shu XO, Ruan ZX, Jin F, Zheng W. Passive smoking and breast cancer risk among non-smoking Chinese women. *International Journal of Cancer* 2004;110(4):605–9.

Slattery ML, Robison LM, Schuman KL, French TK, Abbott TM, Overall JC Jr, Gardner JW. Cigarette smoking and exposure to passive smoke are risk factors for cervical cancer. *Journal of the American Medical Association* 1989;261(11):1593–8.

Smith GD, Phillips AN. Passive smoking and health: should we believe Philip Morris's "experts"? *British Medical Journal* 1996;313(7062):929–33.

Smith SJ, Deacon JM, Chilvers CED, members of the UK National Case–Control Study Group. Alcohol, smoking, passive smoking and caffeine in relation to breast cancer risk in young women. *British Journal of Cancer* 1994;70(1):112–9.

Sobue T. Association of indoor pollution and passive smoking with lung cancer in Osaka, Japan. *International Journal of Epidemiology* 1990;19(Suppl 1): S62–S66.

Speizer FE, Colditz GA, Hunter DJ, Rosner B, Hennekens C. Prospective study of smoking, antioxidant intake, and lung cancer in middle-aged women (USA). *Cancer Causes and Control* 1999;10(5):475–82.

Steenland K, Sieber K, Etzel RA, Pechacek T, Maurer K. Exposure to environmental tobacco smoke and risk factors for heart disease among never smokers in the Third National Health and Nutritional Examination Survey. *American Journal of Epidemiology* 1998;147(10):932–9.

Stockwell HG, Goldman AL, Lyman GH, Noss CI, Armstrong AW, Pinkham PA, Candelora EC, Brusa MR. Environmental tobacco smoke and lung cancer risk in nonsmoking women. *Journal of the National Cancer Institute* 1992;84(18):1417–22.

Sun X-W, Dai X-D, Lin C-Y, Shi Y-B, Ma Y-Y, Li W. Lung cancer among nonsmoking women in Harbin, China [abstract]. *Lung Cancer* 1996;14(Suppl 1): S237.

Svensson C, Pershagen G, Klominek J. Smoking and passive smoking in relation to lung cancer in women. *Acta Oncologica* 1989;28(5):623–9.

Terry PD, Rohan TE. Cigarette smoking and the risk of breast cancer in women: a review of the literature. *Cancer Epidemiology, Biomarkers & Prevention* 2002;11(10 Pt 1):953–71.

Trichopoulos D, Kalandidi A, Sparros L. Lung cancer and passive smoking: conclusion of Greek study [letter]. *Lancet* 1983;2(8351):677–8.

Trichopoulos D, Kalandidi A, Sparros L, MacMahon B. Lung cancer and passive smoking. *International Journal of Cancer* 1981;27(1):1–4.

U.S. Department of Health and Human Services. *The Health Consequences of Smoking: Cancer. A Report of the Surgeon General.* Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, 1982. DHHS Publication No. (PHS) 82-50179.

U.S. Department of Health and Human Services. *The Health Consequences of Involuntary Smoking. A Report of the Surgeon General*. Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Health Promotion and Education, Office on Smoking and Health, 1986. DHHS Publication No. (CDC) 87-8398.

U.S. Department of Health and Human Services. *Women and Smoking. A Report of the Surgeon General*. Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Office of the Surgeon General, 2001.

U.S. Department of Health and Human Services. *The Health Consequences of Smoking: A Report of the Surgeon General*. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2004.

U.S. Department of Health, Education, and Welfare. *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service*. Washington: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, 1964. PHS Publication No. 1103.

U.S. Environmental Protection Agency. *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders*. Washington: U.S. Environmental Protection Agency, Office of Research and Development, Office of Air and Radiation, 1992. EPA/600/6-90/006F.

van den Brandt PA, Spiegelman D, Yaun SS, Adami HO, Beeson L, Folsom AR, Fraser G, Goldbohm RA, Graham S, Kushi L, et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. *American Journal of Epidemiology* 2000;152(6):514–27.

Vandenbroucke JP. Passive smoking and lung cancer: a publication bias? *British Medical Journal Clinical Research Edition* 1988;296(6619):391–2.

Vineis P, Alavanja M, Buffler P, Fontham E, Franceschi S, Gao YT, Gupta PC, Hackshaw A, Matos E, Samet J, et al. Tobacco and cancer: recent epidemiological evidence. *Journal of the National Cancer Institute* 2004;96(2):99–106.

Wang F-L, Love EJ, Liu N, Dai X-D. Childhood and adolescent passive smoking and the risk of female lung cancer. *International Journal of Epidemiology* 1994:23(2):223–30.

Wang L, Lubin JH, Zhang SR, Metayer C, Xia Y, Brenner A, Shang B, Wang Z, Kleinerman RA. Lung cancer and environmental tobacco smoke in a non-industrial area of China. *International Journal of Cancer* 2000;88(1):139–45.

Wang T-J, Zhou B-S, Shi J-P. Lung cancer in nonsmoking Chinese women: a case-control study. *Lung Cancer* 1996;14(Suppl 1):S93–S98.

Wartenberg D, Calle EE, Thun MJ, Heath CW Jr, Lally C, Woodruff T. Passive smoking exposure and female breast cancer mortality. *Journal of the National Cancer Institute* 2000;92(20):1666–73.

Wells AJ. Breast cancer, cigarette smoking, and passive smoking [letter]. *American Journal of Epidemiology* 1991;133(2):208–10.

Wells AJ. Lung cancer from passive smoking at work. *American Journal of Public Health* 1998;88(7):1025–9.

Williams FLR, Lloyd OL. Associations between data for male lung cancer and female breast cancer within five countries. *Cancer* 1989;64(8):1764–8.

Woodward A, McMichael AJ. Passive smoking and cancer risk: the nature and uses of epidemiological evidence. *European Journal of Cancer* 1991;27(11):1472–9.

Wu AH. Exposure misclassification bias in studies of environmental tobacco smoke and lung cancer. *Environmental Health Perspectives* 1999;107(Suppl 6):873–77.

Wu AH, Henderson BE, Pike MC, Yu MC. Smoking and other risk factors for lung cancer in women. *Journal of the National Cancer Institute* 1985;74(4):747–51.

Wu-Williams AH, Dai XD, Blot W, Xu ZY, Sun XW, Xiao HP, Stone BJ, Yu SF, Feng YP, Ershow AG, et al. Lung cancer among women in north-east China. *British Journal of Cancer* 1990;62(6):982–7.

Wu-Williams AH, Samet JH. Environmental tobacco smoke: exposure-response relationships in epidemiolgic studies. *Risk Analysis* 1990;10(1):39–48.

Xu ZY, Blot WJ, Xiao HP, Wu A, Feng YP, Stone BJ, Sun J, Ershow AG, Henderson BE, Fraumeni JF Jr. Smoking, air pollution, and the high rates of lung cancer in Shenyang, China. *Journal of the National Cancer Institute* 1989;81(23):1800–6.

Yu MC, Garabrant DH, Huang T-B, Henderson BE. Occupational and other non-dietary risk factors for nasopharyngeal carcinoma in Guangzhou, China. *International Journal of Cancer* 1990;45(6):1033–9.

Yu MC, Huang TB, Henderson BE. Diet and nasopharyngeal carcinoma: a case-control study in Guangzhou, China. *International Journal of Cancer* 1989;43(6):1077–82.

Yuan J-M, Wang X-L, Xiang Y-B, Gao Y-T, Ross RK, Yu MC. Non-dietary risk factors for nasopharyngeal carcinoma in Shanghai, China. *International Journal of Cancer* 2000;85(3):364–9.

Zaridze D, Maximovitch D, Zemlyanaya G, Aitakov ZN, Boffetta P. Exposure to environmental tobacco smoke and risk of lung cancer in non-smoking women from Moscow, Russia. *International Journal of Cancer* 1998;75(3):335–8.

Zhao Y, Shi Z, Liu L. Matched case-control study for detecting risk factors of breast cancer in women living in Chengdu [Chinese]. *Zhonghua Liu Xing Bing Xue Za Zhi* 1999;20(2):91–4.

Zheng W, McLaughlin JK, Chow W-H, Chien HTC, Blot WJ. Risk factors for cancers of the nasal cavity and paranasal sinuses among white men in the United States. *American Journal of Epidemiology* 1993;138(11):965–72.

Zhong L, Goldberg MS, Gao Y-T, Jin F. A case-control study of lung cancer and environmental tobacco smoke among nonsmoking women living in Shanghai, China. *Cancer Causes and Control* 1999;10(6):607–16.

Zhong L, Goldberg MS, Parent M-E, Hanley JA. Exposure to environmental tobacco smoke and the risk of lung cancer: a meta-analysis. *Lung Cancer* 2000;27(1):3–18.

Zhou B-S, Wang T-J, Guan P, Wu JM. Indoor air pollution and pulmonary adenocarcinoma among females: a case-control study in Shenyang, China. *Oncology Reports* 2000;7(6):1253–9.