Lung Cancer in Never Smokers: Clinical Epidemiology and Environmental Risk Factors

Jonathan M. Samet,[1] Erika Avila-Tang,[1] Paolo Boffetta,[2] Lindsay M. Hannan,[3] Susan Olivo-Marston,[4] Michael J. Thun,[3] and Charles M. Rudin[1]

Abstract More than 161,000 lung cancer deaths are projected to occur in the United States in 2008. Of these, an estimated 10 to 15% will be caused by factors other than active smoking, corresponding to 16,000 to 24,000 deaths annually. Thus lung cancer in never smokers would rank among the most common causes of cancer mortality in the United States if considered as a separate category. Slightly more than half of the lung cancers caused by factors other than active smoking occur in never smokers. As summarized in the accompanying article, lung cancers that occur in never smokers differ from those that occur in smokers in their molecular profile and response to targeted therapy. These recent laboratory and clinical observations highlight the importance of defining the genetic and environmental factors responsible for the development of lung cancer in never smokers. This article summarizes available data on the clinical epidemiology of lung cancer in never smokers, and several environmental risk factors that population-based research has implicated in the etiology of these cancers. Primary factors closely tied to lung cancer in never smokers include exposure to known and suspected carcinogens including radon, second-hand tobacco smoke, and other indoor air pollutants. Several other exposures have been implicated. However, a large fraction of lung cancers occurring in never smokers cannot be definitively associated with established environmental risk factors, highlighting the need for additional epidemiologic research in this area. (Clin Cancer Res 2009;15(18):5626–45)

Lung Cancer Occurrence in Never Smokers

Approximately 10 to 15% of all lung cancers arise in never smokers, making lung cancer in never smokers one of the leading causes of cancer-related mortality (1–3). Given the impact of this disease, there is surprisingly little information available on the descriptive epidemiology of lung cancer in never smokers. General population statistics are largely uninformative because neither cancer registries nor routinely collected death certificates provide reliable information on lifetime smoking histories. In addition, reports on smoking from next-of-kin or in medical records are incomplete and often unreliable (4, 5). Only large-scale cohort studies can measure age- and sex-specific lung cancer rates in never smokers with reasonable precision, and these have generally studied mortality rather than incidence. Consequently, limited data have been available to resolve controversies such as whether women are more susceptible than men to develop lung cancer in the absence of smoking, whether the risk is higher in African Americans and Asians than in Caucasians, and whether the background risk has changed over time.

The other articles within this issue of *CCR Focus* present an overview and a description of the implications of recent molecular insights (6, 7). This article reviews current information on the clinical epidemiology of and environmental risk factors for lung cancer in never smokers. It describes the sources of data, including historical records that preceded the widespread introduction of manufactured cigarettes; examines incidence and mortality rates in relation to age, gender, race and/or ethnicity, geographic location, and temporal trends; and identifies research needs.

Historical records indicate that lung cancer was rarely diagnosed in North America and Europe before the introduction and promotion of manufactured cigarettes. In 1912, it was described as "one of the rarest forms of cancer" (8). In 1914, the U.S. Census Office systematically surveyed death certificate information on 52,420 cancer deaths and identified only 371 attributed to cancer of the lung and pleura, representing 0.7% of the total (9). In Britain, the increase in lung cancer was seen

Authors' Affiliations: [1]Johns Hopkins University, Baltimore, Maryland; [2]International Agency for Research on Cancer, Lyon, France; [3]American Cancer Society, Atlanta, Georgia; and [4]National Cancer Institute, Bethesda, Maryland

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Requests for reprints: Charles M. Rudin, Johns Hopkins University School of Medicine, David H. Koch Cancer Research Building, Room 544, 1550 Orleans Street, Baltimore, MD 21231. Phone: 410-502-0678; Fax: 410-502-0677; E-mail: rudin@jhmi.edu.

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earlier than in the United States because officers learned to smoke hand-rolled cigarettes in the Crimean war (1854-1856; ref. 10). Whereas lung cancer comprised only two tenths of 1% of all hospitalizations for cancer at the Manchester Royal Infirmary during the period from 1868 to 1885, this percentage had increased tenfold in men by 1901 to 1905 (11).

Population-based data on lung cancer incidence or death rates among people who never smoked are available for women in the United States during the 1930s and for women in other countries during time periods when few women smoked. In contrast, the lung cancer rates among men in Western countries were dominated by the effects of active cigarette smoking during most of the 20th century. In the United States for example, the lung cancer mortality rate among men was already increasing exponentially by the early 1930s when national mortality statistics first became available (12). In contrast, regular smoking was uncommon among women in the United States before World War II. National data on mortality and regional statistics on lung cancer incidence compiled during the 1930s largely reflect the background rates among women who never smoked actively. Similarly, smoking remains uncommon even today among women in many countries of Africa and Asia in which strong cultural norms discourage women from smoking.

Also informative are large cohort studies that measure incidence or death rates prospectively in people who report their smoking history and various other risk factors at enrollment. Only the largest cohort studies provide stable age- and sex-specific rates. Detailed mortality data have been published on lung cancer death rates among never smokers enrolled in two large American Cancer Society cohorts, the Cancer Prevention Studies I (CPS-I) and II (CPS-II), which were initiated in the late 1950s and early 1980s, respectively, to characterize the risks of smoking. Approximately 1 million men and women in 25 states were enrolled in CPS-I in 1959 (3) and nearly 1.2 million men and women were enrolled nationwide in CPS-II in 1982. Researchers have followed their vital status through the present and have published detailed information on age-, sex-, and race-specific lung cancer death rates in never smokers for the entire 12-year follow-up of CPS-I (1959-1972) and 18-year follow-up of CPS-II (1982-2000; ref. 3).

Descriptive Epidemiology

Population characteristics

Age. Lung cancer risk increases with age in both smokers and never smokers. Figure 1 shows the age-related increase in lung cancer death rates among white men and women, aged 40 to 84 years, who reported no history of regular smoking in either of the large ACS cohorts, CPS-I and CPS-II (Fig. 1; ref. 3). Similar age patterns among never smokers have been reported previously for whites (13–16), Japanese (17), and African Americans (women only; ref. 3). However, even the largest cohort studies cannot measure lung cancer rates reliably at younger ages. Lung cancer is sufficiently rare in people under the age of 40, especially among never smokers, that cohort studies would need to be prohibitively large and hence costly to accurately estimate the incidence or death rates in young adults. The diagnosis of lung cancer across all age cohorts depends strongly on access to minimally invasive diagnostic technologies that have become increasingly available over time, particularly in economically developed countries. These include the introduction of chest X-rays beginning in the 1930s (12), flexible bronchoscopy since the late 1960s (18), thin needle aspiration and computerized scans during the 1980s (19–21), and helical computed tomography (CT) scans since the late 1990s (22, 23).

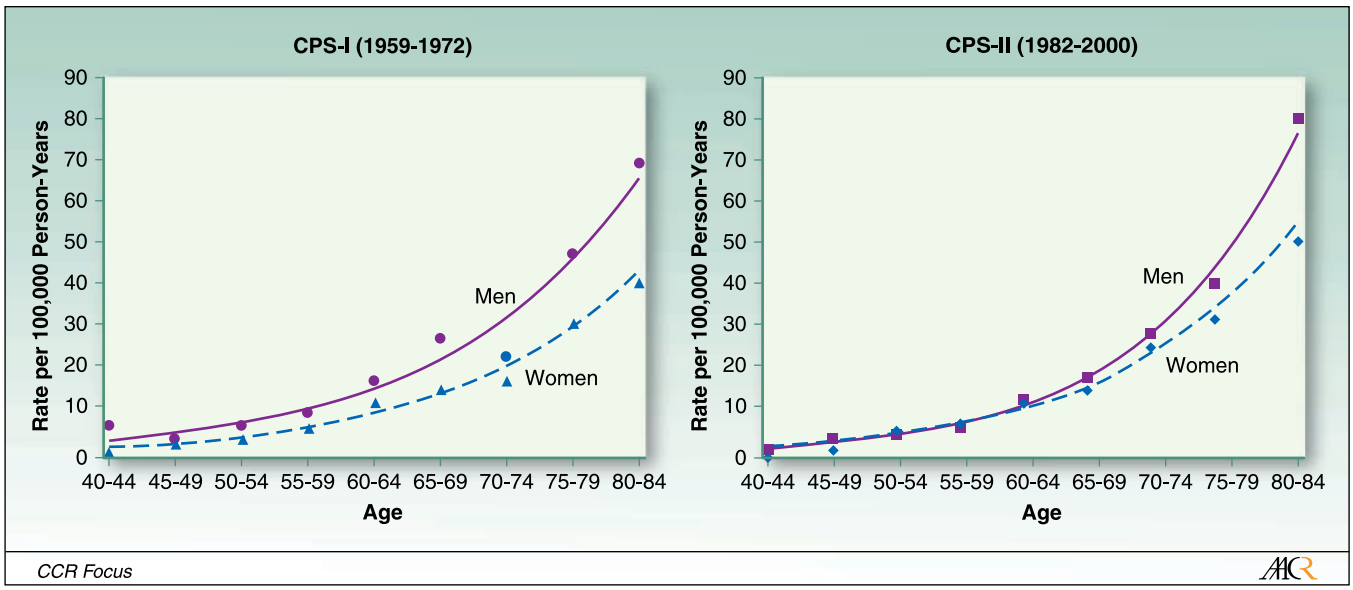

Fig. 1. Age- and sex-specific lung cancer death rates among white never smokers in the American Cancer Society Cancer Prevention Study cohorts, stratified by study.

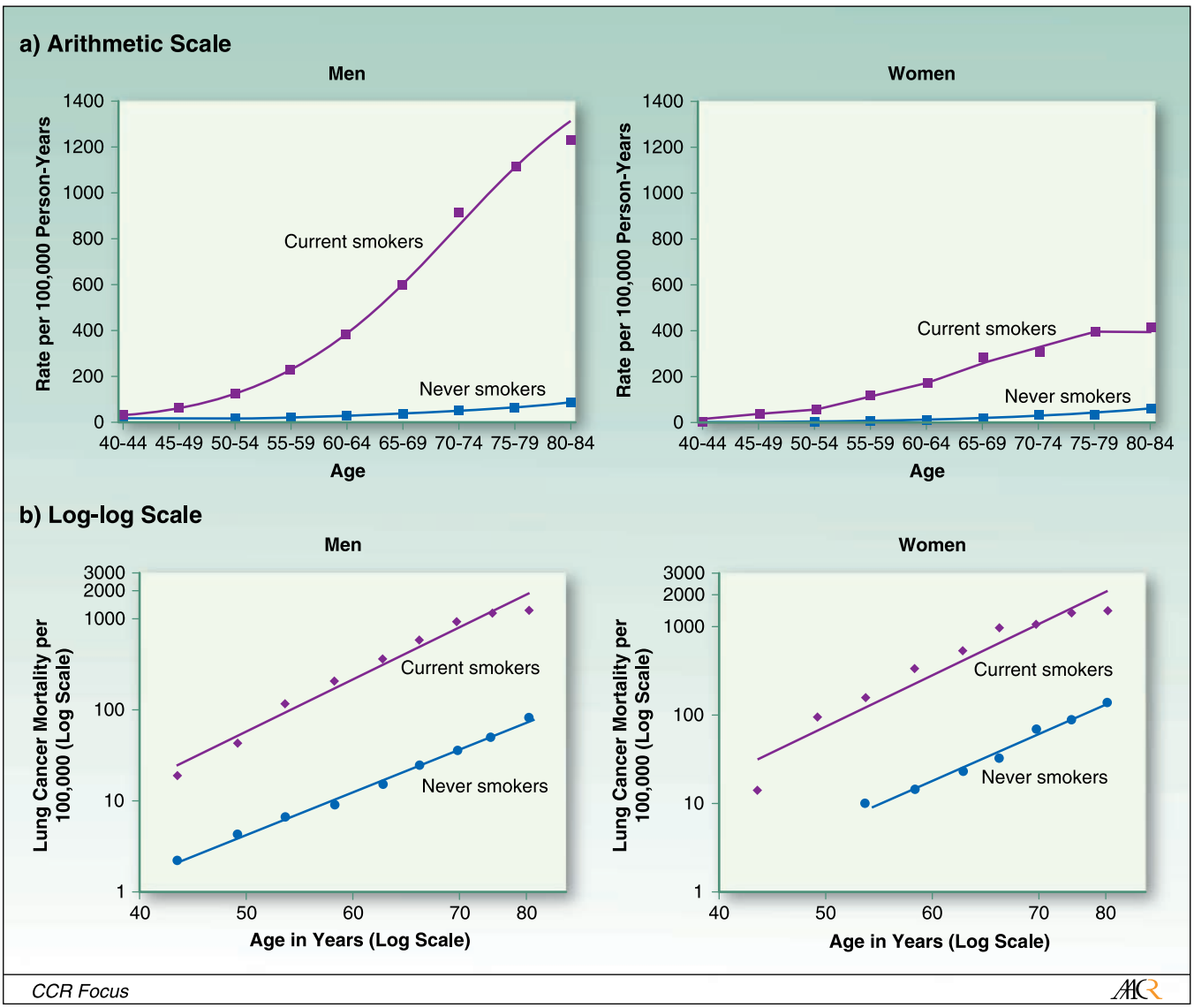

Fig. 2. Age-specific lung cancer death rates among white current smokers and never smokers in CPS-II, 1982 to 1988, stratified by sex (*A*, arithmetic scale and *B*, log-log scale).

Gender. Clinicians have observed that women outnumber men among lung cancer patients who report never having smoked regularly. This has been misinterpreted as evidence that "women who have never smoked are more likely to develop lung cancer than men who have never smoked" (24). However, risk represents the probability that an individual will develop the disease, not the number of affected people. There are more than twice as many women as men age 60 years and older who have never smoked, and this female predominance increases with age (3).

Prospective cohort studies have consistently found that the death rate from lung cancer is higher in men than women, both in the absence (Fig. 1; ref. 3) and presence (Fig. 2; refs. 25–27) of active smoking. However, the relationship with sex is less clear for incidence than for mortality (28). Wakelee and colleagues have noted that lung cancer incidence rates were slightly, although not significantly, higher in women than men among never smokers, age 40 to 79 years in six cohort studies (29). Henschke and colleagues have observed that women are more likely to be diagnosed with lung cancer than men when screened using spiral CT (30, 31). On the basis of this observation, Henschke has hypothesized that lung cancer incidence may be higher in women than in men who smoke, even though the opposite is true for mortality. However, screening tests such as helical CT detect prevalent rather than incident cases, and therefore may be detecting undiagnosed lung cancers that progress more slowly in women than in men rather than representing higher occurrence (incidence) rates in women.

Race and/or ethnicity. Lung cancer risk among never smokers has also been hypothesized to be higher in African

Americans (3) and Asians (32) than in whites. The age-standardized death rate from lung cancer was approximately 40% higher among African American than white women who reported never smoking in CPS-II (3), but a statistically significant racial difference was not seen for never-smoking women in CPS-I; there were insufficient data to measure the risk in black men. A case-control study found no evidence that lung cancer incidence was higher in African American than white never smokers in men or women, except among men aged 40 to 54 years (33).

Geographic variability. The incidence of lung cancer in women varies by as much as 30-fold, even among countries reported to have low prevalence of female smoking (34), and even in the age range 40 to 69 years in which ascertainment is most comparable. The lowest female lung cancer incidence rates are reported in Africa (Algeria and Mali) and India (Ahmedabad, Bangalore, Madras, and Mumbai), whereas the highest rates are in Pacific Rim countries (Philippines, Hong Kong, Japan, and the Chinese population of Singapore) and in China. Even within China, lung cancer risk in women varies widely (35). Li and colleagues reported a 20 fold difference in the lung cancer death rate between Chinese women living in counties at the 10th versus 90th percentiles of lung cancer death rates, as estimated from a retrospective mortality survey conducted from 1973 to 1975 (36). Some of this variation reflects historical patterns of high active smoking by older women in northeastern China (Tianjin and Harbin) and northern Thailand (Chiang Mai and Lampang). Other factors thought to contribute to the increased risk among some groups of Chinese women include indoor air pollution from coal smoke generated by unventilated coal-fueled fire pits and stoves (37, 38), volatilization of oils from cooking at high temperatures in open woks (39–42), and secondhand smoke (SHS; refs. 39, 43–45).

Temporal trends

Several researchers have suggested that lung cancer risk is increasing in the general population because of factors other than tobacco smoking (46–50). However, there is little evidence to support this claim and considerable evidence against it. Vital statistics data for women aged 40 to 69 years in the United States in 1935 to 1940 show that female lung cancer death rates before the advent of female smoking were similar to those of women of the same age who have reported no history of active smoking in cohort studies carried out since 1960. In addition, changes have not been observed in the lung cancer death rates among men and women who reported never-smoking status in comparisons of CPS-I (1959-1972) and CPS-II (1982-2004) (Fig. 3; ref. 3). The death rate was slightly lower in CPS-II than in CPS-I for white men ages 40 years and above [hazard ratio (HR) = 0.83; 95% confidence interval (CI) 0.66-1.05], but slightly higher for white [risk ratio (RR) = 1.11; CI 0.98-1.25] and African American women (RR = 1.15; 95% CI 0.62-2.13). The lung cancer death rates among never smokers in the two studies seem to be converging with longer follow-up of CPS-II, even at ages 80 years and above.

The analyses supporting a possible increase in lung cancer among never smokers have been based either on statistical modeling (47–50), or on a comparison of rates up to 1968 with the 1914 U.S. census survey (46). The modeling studies used epidemiological principles related to rates in populations to estimate the rate in never smokers; they did not have direct estimates as with the CPS-I and CPS-II data. Additionally, these modeling studies did not take into account the large and progressive increase in lung cancer risk associated with cigarette smoking that took place as the average duration of smoking has increased over time in the population. The 1914 survey is limited as a basis of comparison as it was conducted before pathologists began to look systematically for lung cancer.

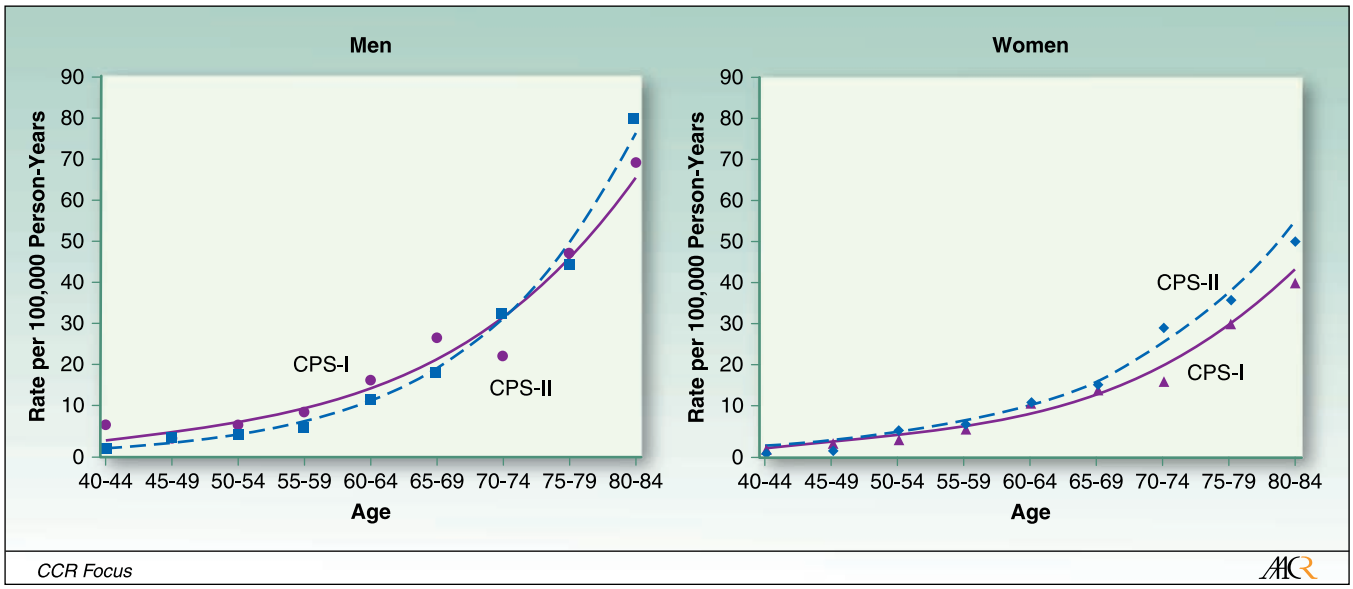

Fig. 3. Age- and sex-specific lung cancer death rates among white never smokers in CPS-I (1959-1972) and CPS-II (1982-2000), stratified by sex.

Neither respiratory cancer nor cancers of the lung and pleura were included in the International Classification of Diseases (ICD) until 1929 and 1938, respectively (51). It is plausible that some of the deaths attributed to tuberculosis in the early 20th century may have involved misdiagnosis of lung cancer. The death rate from tuberculosis decreased by two thirds between 1915 and 1935 (52), a period when lung cancer mortality was rising, especially in men (9, 53).

To summarize, the best evidence on time trends of lung cancer in never smokers comes from CPS-I and CPS-II. At least for the time period covered by these two studies, lung cancer mortality does not seem to be increasing in never smokers.

Putting risks into perspective

It is not surprising that lung cancer risk is substantially lower among lifelong nonsmokers than cigarette smokers. Figure 2 illustrates the magnitude of the difference in lung cancer death rates between the CPS-II participants who reported either current or never smoking at the time of enrollment in the study. The data are presented graphically on both an arithmetic (above) and log-log scale (below) to illustrate that the age-related increase is almost linear in both groups when the data are transformed logarithmically, indicating approximately exponential relationships (25). The absolute rates are 20 to 25 times higher for the male current than never smokers, and 10 to 12 times higher for female current smokers than never smokers. Figure 2 is based on a 6-year follow-up of CPS-II (1982-1988) to minimize misclassification of current smokers who quit during follow-up (25).

The lung cancer death rate among never smokers, although "rare" by conventional definitions (<40,000 U.S. deaths per year), is similar to the death rates from leukemia and endometrial cancer in women and cancers of the esophagus, kidney, and liver in men in the United States, and may be even more important in other populations, including Chinese women (25, 54).

Research needs

Better data are needed to answer several basic questions about the descriptive epidemiology of lung cancer in lifelong nonsmokers. Additional information on lung cancer incidence and death rates in relation to age, sex, and race and/or ethnicity will soon become available from a collaborative effort to pool data from large cohort studies. This will be a valuable resource, but will not resolve limitations in the data for African Americans (particularly men), and Asians (particularly for incidence), and will provide no data on lung cancer risk in never-smoking Hispanics. It is unlikely that cohort studies alone can provide reliable estimates of lung cancer risk in never smokers under age 40 years, and so different approaches will be needed if this is to be resolved. Finally, further studies are needed to understand variations in lung cancer incidence and etiology among never-smoking women in populations outside Europe and North America, in particular in East Asia.

Histopathology

Beginning in the late 1960s, changes have been observed in many countries in the frequency of different histological subtypes of lung cancer, with a declining proportion of squamous cell carcinomas and an increasing proportion of adenocarcinomas (55). These changes have been observed to vary by both gender and smoking status. At the start of the epidemic, the most frequently observed histological type of lung cancer among smokers was squamous cell carcinoma, especially in males. However, adenocarcinomas were more frequently observed in females regardless of smoking status. Among never smokers included in the past studies, largely women, adenocarcinomas were more frequent than squamous cell carcinomas and comprised the majority of tumors (56).

Many studies that have examined changes in the trends of histological subtypes, primarily using cancer registry data, have shown that adenocarcinomas have been rising among both men and women whereas rates of squamous cell carcinoma have been decreasing among men (56). Although most studies have not separated histological subtypes by smoking status, a few studies have examined the trends among never smokers (Supplementary Table S1). One study in Poland of 20,567 lung cancer cases found that squamous cell carcinoma was most common among male never smokers and current smokers (57). However, female never and current smokers were more likely to be diagnosed with adenocarcinomas. Data from the Cancer Surveillance Program of Orange County in the United States showed that, although squamous cell carcinoma was the most common histological subtype observed among male never and current smokers, among women, adenocarcinoma was the most frequent type (58). This study was based on 1984 data.

Time trend studies have shown that regardless of smoking status, the rate of adenocarcinoma is increasing, whereas that of squamous cell carcinoma is decreasing among men. In several studies, the frequency of adenocarcinoma has surpassed that of squamous cell carcinoma. For example, a study of 437,976 Korean men in whom 1,357 new lung cancer cases were identified found that adenocarcinoma was the most frequent histological type among never smokers, former smokers, and current smokers (59). A study in Malaysia similarly showed that squamous cell carcinoma was the most frequent histological subtype among both male and female smokers from 1967 to 1976, but by 1991 to 1999 adenocarcinoma became the most frequent histological subtype for both sexes (60). However, among never smokers adenocarcinoma was the most frequent histological subtype in the periods 1967 to 1976 and 1991 to 1999.

The available evidence shows a bias toward adenocarcinoma among never smokers relative to smokers. There seem to be gender differences as well, with female never smokers and smokers tending to have adenocarcinomas more commonly than parallel male cohorts. Although adenocarcinoma is the most common histologic type among male never smokers, male smokers tend to have more squamous cell carcinomas.

Hypotheses about the shift in histopathology among smokers have focused on the potential role of the substantial changes in the characteristics of cigarettes and the associated changes in the dosages of carcinogens inhaled and the pattern of deposition in the lung (61). Puff volume has likely increased in the past few decades with the possibility that patterns of deposition in the lung have changed, tending toward enhanced deposition of tobacco smoke in the peripheral airways and alveoli (61). Nitrate levels in tobacco smoke have also increased, which enhances the combustion of tobacco smoke. Although more

complete combustion decreases the concentrations of polycyclic aromatic hydrocarbons, the increased production of nitrogen oxides contributes to increased formation of tobacco specific nitrosamines (TSNA). An increase in dosage of the potent TSNA 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNAL) has been postulated as one factor leading to the increase in adenocarcinomas (61, 62). NNAL induces lung carcinomas, predominantly adenomas and adenocarcinomas, in mice, regardless of route of administration (62, 63). These hypotheses about the shift in histopathology among smokers are also relevant for never smokers. Nonsmokers inhale a mixture of sidestream smoke and exhaled mainstream smoke that is generally referred to as SHS. Never smokers exposed to SHS have experienced changes in the SHS mixture in the past few decades because increases in puff volume and enhancement of the combustion of tobacco smoke have increased the formation of TSNAs (49). These diverse changes in the inhaled doses of carcinogens delivered to smokers and nonsmokers are likely to have contributed to the time trend of changing histopathology. To date there has been limited research on differences in lung cancer histology subtypes among never smokers, pointing to a need to develop evidence in this area.

Risk Factors

Secondhand smoke

In 1981 published reports from Japan (64) and Greece (65) indicated increased lung cancer risk in never-smoking women married to cigarette smokers. Subsequently this association has been examined in more than 50 investigations conducted in the United States and other countries. Over the past 20 years, review groups have repeatedly and consistently concluded that exposure to SHS causes lung cancer in never smokers.

A causal association of involuntary smoking with lung cancer derives biological plausibility from the presence of carcinogens in sidestream smoke and the lack of a documented threshold dose for respiratory carcinogens in active smokers (66–69). Genotoxic activity had been shown for many components of SHS (70–73). Experimental and real-world exposures of nonsmokers to SHS lead to excretion of NNAL, a tobacco-specific carcinogen, in the urine (74, 75). Nonsmokers exposed to SHS also have increased concentrations of adducts of tobacco-related carcinogens (76, 77). Additionally, Mauderly and colleagues, using an animal model, found that whole-body exposure in rats to cigarette smoke increases the risk of neoplastic proliferative lung lesions and induces lung cancer (78). In an autopsy study in Greece, Trichopoulos and colleagues (79) examined lung specimens from 400 persons 35 years of age and older and found that airway epithelial lesions were more common in nonsmokers married to smokers than in nonsmokers married to nonsmokers.

Epidemiologists who have tested the association between lung cancer and involuntary smoking using case-control and cohort designs have consistently found that SHS exposure is associated with lung cancer risk in never smokers. For decades, the tobacco industry and its consultants attributed the association to bias (80). The potential for bias and the related methodologic issues are addressed at length in the 2006 Report of the U.S. Surgeon General (81) and elsewhere. Specific methodologic concerns have been misclassification of ever smokers as never smokers and inaccuracy in the classification of SHS exposure status in the different places where exposure occurs, particularly the home and workplaces. Quantitative and qualitative assessments of these sources of misclassification have led to the conclusion that bias from misclassification does not account for the observed association (81–85).

Use of spouse smoking alone to represent exposure to SHS does not cover exposures outside of the home (86), or necessarily all exposure inside the home, particularly during the time period relevant to the epidemiological studies. Klepeis and colleagues used data from the National Human Activity Pattern Survey to assess the contribution of the home and other indoor environments to SHS exposures (87). Overall, the data show that 43% of the time spent with a smoker is in a residence, whereas 7% is in the workplace, 9% in a vehicle, and 15% in a bar or restaurant. This survey may help to explain the results of a European study that found that the number of cigarettes smoked per day by the husband is only moderately correlated with "actual" exposure of women married to smokers (88). A pooled analysis of large-scale studies to assess the risk of lung cancer of never smokers exposed to spouse and workplace sources of SHS found an excess risk of 23% from exposure to spousal smoking and 27% from exposure to workplace sources of SHS (89).

In considering alternatives to a causal association, confounding has also been proposed as contributing to the association of SHS with lung cancer. Critics of these findings on SHS and lung cancer have argued that uncontrolled confounding by lifestyle, occupation, or other factors may explain the association (90, 91). In some countries, including the United States, smoking prevalence varies markedly with indicators of income and education, more recently tending to increase sharply with decreasing educational level and income (66, 92). In general, exposure to SHS follows a similar trend, and critics of the findings on SHS and lung cancer have argued that uncontrolled confounding by lifestyle, occupation, or other factors may explain the association. In fact, current data for the United States do indicate a generally less healthy lifestyle in those with greater SHS exposure (93). However, other than a few occupational exposures at high levels, as well as indoor radon, risk factors for lung cancer in never smokers that might confound the SHS association cannot be proffered and the relevance to past studies of these current associations of potential confounders with SHS exposure is uncertain.

The first major studies on SHS and lung cancer were reported in 1981, including Hirayama's prospective cohort study of 91,540 never-smoking women in Japan (64), and the case-control study in Athens, Greece, carried out by Trichopoulos and colleagues (65). By 1986, the evidence had mounted and three reports published in that year concluded that SHS was a cause of lung cancer. The International Agency for Research on Cancer (IARC; ref. 69) concluded that exposure to SHS "gives rise to some risk of cancer." In its monograph on tobacco smoking, the agency supported this conclusion on the basis of the characteristics of sidestream and mainstream smoke, the absorption of tobacco smoke materials during involuntary smoking, and the nature of dose response relationships for carcinogenesis. The National Research Council (94) and the U.S. Surgeon

General (68) also concluded that involuntary smoking increases the incidence of lung cancer in never smokers. In reaching this conclusion, the National Research Council (94) cited the biological plausibility of the association between exposure to SHS and lung cancer and the supporting epidemiological evidence. On the basis of a pooled analysis of the epidemiological data adjusted for bias, the report concluded that the best estimate for the excess risk of lung cancer in never smokers married to smokers was 25%. The 1986 report of the Surgeon General (68) characterized involuntary smoking as a cause of lung cancer in never smokers. This conclusion was based on the extensive information already available on the carcinogenicity of active smoking, on the qualitative similarities between SHS and mainstream smoke, and on the epidemiological data on involuntary smoking.

In 1992 the U.S. Environmental Protection Agency (EPA; ref. 84) published its risk assessment of SHS as a group A carcinogen. The agency's evaluation drew on the toxicologic evidence on SHS and the extensive literature on active smoking. A meta-analysis of the 31 studies published to that time was central in the decision to classify SHS as a group A carcinogen-namely a known human carcinogen. The meta-analysis considered the data from the epidemiologic studies by tiers of study quality and location and used an adjustment method for misclassification of smokers as never smokers. Overall, the analysis found a significantly increased risk of lung cancer in never-smoking women married to smoking men; for the studies conducted in the United States, the estimated relative risk was 1.19 (90% CI 1.04-1.35).

Subsequent to the 1992 risk assessment, more than 20 additional studies and several major reports have been published that further contribute to the evidence supporting a causal association between SHS and the risk of lung cancer (81, 95, 96). Among the additional studies, the multicenter study of Fontham and colleagues is the largest published to date (97), with 651 cases and 1,253 controls. It shows a significant increase in overall relative risk (OR = 1.26; 95% CI 1.04-1.54).

Hackshaw and colleagues (98) carried out a comprehensive meta-analysis in 1997, which included 39 published studies, and estimated an excess risk of lung cancer for never smokers married to smokers as 23% (95% CI 13-34%). Adjustment for potential bias and confounding by diet did not alter the estimate. A subsequent IARC meta-analysis (96) including 46 studies and 6,257 cases yielded similar results: 24% (95% CI 14-34%); incorporating the results from a cohort study with null results overall, but only 177 cases (99), did not change the findings (100). The most recent summaries from the 2006 Surgeon General's Report are provided in Table 1.

The extent of the lung cancer hazard associated with involuntary smoking in the United States and in other countries remains subject to some uncertainty, however, although estimates have been made that are useful indications of the magnitude of the disease risk (68, 101). In 1990 Repace and Lowrey (102) reviewed the risk assessments of lung cancer and exposure to SHS and estimated the numbers of lung cancer cases in U.S. nonsmokers attributable to exposure to SHS based on a mean of nine different risk estimates, suggesting an overall incidence of 4,500 to 5,000 cases. Similarly the 1992 estimate of the EPA, based on the epidemiologic data, was about 3,000 cases annually (84). The California EPA estimates that at least 3,423, and perhaps as many as 8,866, lung cancer deaths were caused by SHS in the United States in 2003. Of those 3,423 deaths, 967 were attributed to nonspousal exposures to SHS and 2,456 to spousal exposure (95). In summary, most comprehensive analyses suggest that in the United States, SHS exposure is responsible for approximately 3,000 to 5,000 lung cancer deaths annually.

These calculations illustrate that exposure to SHS must be considered an important cause of lung cancer death from a public health perspective; exposure is involuntary and not subject to control. The Biological Effects of Ionizing Radiation (BEIR) VI Committee estimated that from 5 to 10% of lung cancer deaths in the United States in 1995 were in never smokers. The corresponding range of 8,000 to 16,000 deaths, as the total from lung cancer in never smokers, implies that from about 20 to 50% of the deaths are attributable to SHS (103). The specific risk assessments require assumptions about the extent and degree of exposure to SHS, exposure-response relationships, and the lifetime expression of the excess risk associated with exposure to SHS at different ages. Moreover the calculations do not consider the potential contributions of other exposures, such as occupational agents and indoor radon. The current decline in the prevalence of active smoking and the implementation of strong clean indoor air policies will reduce the relevance of estimates based on past patterns of smoking behavior.

Radon

Radon, long established as a respiratory carcinogen, is not only of concern for underground miners but for the population generally, as a ubiquitous contaminant of indoor air. Radon is an inert gas, produced naturally from radium in the decay series of uranium. Radon decays with a half-life of 3.82 days into a series of solid, short-lived radioisotopes that collectively are referred to as radon daughters, progeny, or decay products. As the biologic basis of respiratory carcinogenesis was analyzed and the lung dosimetry of radon and its short-lived progeny were described, it was recognized that alpha-particle emissions from inhaled radon progeny, not from radon itself, cause lung cancer (103). Two of those decay products, polonium-218 and polonium-214, emit alpha particles, which are high-energy and high-mass particles consisting of two protons and two neutrons that cause DNA base mutations and chromosomal strand breaks. The energy of these particles is invariant with concentration of radon progeny so that the potential for passage of alpha particles to damage target cells is the same at high and low concentrations. When the alpha emissions take place within the lung as inhaled and deposited radon progeny decay, the DNA of cells lining the airways is damaged and lung cancer may ultimately result. Animal studies have shown that radon alone through its progeny can induce cancer in the respiratory tract (103).

Elegant experimental studies have documented the occurrence of permanent damage to a cell from just one hit by an alpha particle (103). This experimental finding suggests that assuming a linear nonthreshold relationship between exposure

Table 1. Results of studies on exposure to secondhand smoke and risk of lung cancer among never smokers

Study	Design/population	Exposure group		Reference group	Risk estimate (95% CI)	Adjustment variables
Hackshaw et al. (98)	Meta-analysis: 39 studies (5 cohort, 34 case-control) of "lifelong nonsmokers"; 5005 total lung cancer cases; Study locations: United States, Europe, Asia; Publication dates: 1981-1997	***Spousal exposure:***				Age only, when possible
		Women (37 studies, 4,626 cases):				
		Husband currently smoked	vs.	Husband never smoked	1.24 (1.13–1.36)	
		Men (9 studies, 274 cases):				
		Wife currently smoked	vs.	Wife never smoked	1.34 (0.97–1.84)	
		Men and women (39 studies, 5,005 cases):				
		Spouse currently smoked	vs.	Spouse never smoked	1.23 (1.13–1.34)	
Zhong et al. (41)	Meta-analysis: 40 studies (5 cohort, 35 case-control) of "lifetime nonsmoking" subjects; 5,140 total lung cancer cases; Study locations: United States, Europe, Asia; Publication dates: 1981-1999	***Spousal exposure:***				Age and demographic characteristics, when possible
		Women (40 studies, no. cases not stated):				
		Husband ever smoked	vs.	Husband never smoked	1.20 (1.12–1.29)	
		Men (11 studies, 443 cases):				
		Wife ever smoked	vs.	Wife never smoked	1.48 (1.13–1.92)	
		Workplace exposure:				
		Women (14 studies, 2,594 cases):				
		Workplace SHS exposure	vs.	No workplace SHS exposure	1.15 (1.04–1.28)	
		Men (5 studies, 254 cases):				
		Workplace SHS exposure	vs.	No workplace SHS exposure	1.29 (0.93–1.78)	
		Men and women (19 studies, 2,848 cases):				
		Workplace SHS exposure	vs.	No workplace SHS exposure	1.16 (1.05–1.28)	
		Childhood exposure:				
		Women (18 studies, 3,584 cases):				
		Ever exposed to SHS during childhood	vs.	Never exposed to SHS during childhood	0.91 (0.83–1.00)	
Surgeon General Report (81)	Meta-analysis: 52 studies (8 cohort, 44 case-control) of "lifetime nonsmokers"; Total number of cases not stated; Study locations: North America, Europe, Asia; Publication dates: 1981–2002	***Spousal exposure:***				Not stated
		Women (no. studies and cases not stated):				
		Smoking husband	vs.	Nonsmoking husband	1.22 (1.10–1.35)	
		Men (no. studies and cases not stated):				
		Smoking wife	vs.	Nonsmoking wife	1.37 (1.05–1.79)	
		Workplace exposure:				
		Women (25 studies, no. cases not stated):				
		Workplace SHS exposure	vs.	No workplace SHS exposure	1.22 (1.10–1.35)	
		Men (11 studies, no. cases not stated):				
		Workplace SHS exposure	vs.	No workplace SHS exposure	1.12 (0.86–1.50)	
		Men and Women (25 studies, no. cases not stated):				
		Workplace SHS exposure	vs.	No workplace SHS exposure	1.22 (1.13–1.33)	
		Childhood Exposure:				
		Women (no. studies and cases not stated):				
		Mother smoked during childhood	vs.	Mother did not smoke during childhood	1.28 (0.93–1.78)	
		Father smoked during childhood	vs.	Father did not smoke during childhood	1.17 (0.91–1.50)	
		Men and women (no. studies and cases not stated):				
		Mother smoked during childhood	vs.	Mother did not smoke during childhood	1.15 (0.86–1.52)	
		Father smoked during childhood	vs.	Father did not smoke during childhood	1.10 (0.89–1.36)	
		Either parent smoked during childhood	vs.	Neither parent smoked during childhood	1.11 (0.94–1.31)	

Table 2. Results of pooled analyses of case-control studies evaluating risks of radon for lung cancer among never smokers

Study	Design/population	Exposure group	Reference group	Risk estimate (95% CI)	Adjustment variables
Krewski et al. (177)	Meta-analysis: 7 case-control studies with 659 lung cancer cases and 2,185 population controls who "never smoked"; Study location: North America; Publication dates: 1992-2000	Per 100 Bq/m^3 increase in radon exposure during the 5–30 years before index (diagnosis or death) date vs.	<25 Bq/m^3 radon exposure during the 5–30 years before index (diagnosis or death) date	10% increased risk (0.91–42%)	Study, gender, age, number of residences, years with a-track measurements
Darby et al. (178)	Meta-analysis: 13 case-control studies with 884 lung cancer cases and 5,418 controls that were "lifelong nonsmokers";Study location: Europe; Publication dates: 1992–2005	Per 100 Bq/m^3 increase in radon exposure during the 5–30 years before index (diagnosis or death) date vs.	<25 Bq/m^3 radon exposure during the 5–30 years before index (diagnosis or death) date	10.6% increased risk (0.3–28.0%)	Not stated
Darby et al. (179)	Meta-analysis: 13 case-control studies with 884 lung cancer cases and 5,418 controls that were "lifelong nonsmokers";Study location: Europe; Publication dates: 1992–2005	<25 Bq/m^3 cumulative radon exposure during 5–30 years before index (diagnosis or death) date vs.	0 Bq/m^3 cumulative radon exposure during the 5–30 years before index (diagnosis or death) date	1.06 (0.78–1.45)	Study, age, gender, residence location
		25–49 Bq/m^3 cumulative radon exposure during 5–30 years before index (diagnosis or death) date vs.	0 Bq/m^3 cumulative radon exposure during the 5–30 years before index (diagnosis or death) date	1.07 (0.90–1.26)	Study, age, gender, residence location
		50–99 Bq/m^3 cumulative radon exposure during 5–30 years before index (diagnosis or death) date vs.	0 Bq/m^3 cumulative radon exposure during the 5–30 years before index (diagnosis or death) date	1.02 (0.90–1.16)	Study, age, gender, residence location
		100–199 Bq/m^3 cumulative radon exposure during 5–30 years before index (diagnosis or death) date vs.	0 Bq/m^3 cumulative radon exposure during the 5–30 years before index (diagnosis or death) date	1.23 (1.02–1.48)	Study, age, gender, residence location
		200–399 Bq/m^3 cumulative radon exposure during 5–30 years before index (diagnosis or death) date vs.	0 Bq/m^3 cumulative radon exposure during the 5–30 years before index (diagnosis or death) date	1.37 (1.00–1.90)	Study, age, gender, residence location
		≥400 Bq/m^3 cumulative radon exposure during 5–30 years before index (diagnosis or death) date vs.	0 Bq/m^3 cumulative radon exposure during the 5–30 years before index (diagnosis or death) date	1.72 (1.04–2.88)	Study, age, gender, residence location

Abbreviation: Bq/m^3, becquerels per cubic meter.

and risk at the levels found not only in mines but indoors is biologically appropriate, supporting concern that indoor radon represents a significant public health problem. In this same type of experimental system, a bystander mutagenic effect has been shown; a hit to a cell affects cells adjacent to the cell damaged by a single alpha particle (104). This effect may amplify the risks of radon exposure beyond those anticipated on the basis of the construct that passage of an alpha particle through a cell affects only that cell.

Radon was the first identified environmental cause of lung cancer. As early as the 1920s, the elevated risk of lung cancer in miners in Eastern Europe working in mines with high levels of radon had led to the hypothesis that radon was the causal agent (105). Numerous subsequent epidemiological studies

of miners showed a strong association of radon exposure with lung cancer risk (106). These worker groups included several comprised largely of never smokers. In fact, the original case report of respiratory malignancy in underground miners in Schneeberg was published in 1879, long before manufactured cigarettes were available (107). In the United States, Navajo uranium miners, almost all never smokers, experienced a clear excess of lung cancer (108–110). In a cohort study of 757 members of this group, 34 deaths from lung cancer were identified when only 10.2 were expected [standardized mortality ratio (SMR) 3.3, 95% CI 2.3-4.6; ref. 111]. In a population-based case-control study of lung cancer in Navajo males from 1969 to 1982, the majority of the cases were attributable to radon exposure in uranium mines. A cohort study of 516 white miners who have never smoked cigarettes, pipes, or cigars from the Colorado Plateau cohort showed 14 lung cancer deaths with only 1.1 expected, on the basis of comparison to the never smokers in a cohort study of U.S. veterans (112).

The risk of lung cancer in never-smoking uranium miners has been quantified in a pooled analysis of data from 11 cohort studies, all having estimates of the exposures of individual miners to radon progeny. A pooled analysis of the 2,798 never-smoking miners in the cohorts quantified the risk per working-level month (WLM) as almost three times as high in never smokers as in smokers, consistent with the submultiplicative interaction between smoking and radon found with analysis of the full data set (113).

Beginning in the 1970s, there was widespread recognition that radon is present in indoor environments, including homes where people spend the majority of their time (106). At the time, given the already recognized carcinogenicity of radon, concern was raised about the risk of indoor radon, and consideration was given to the most appropriate risk management strategies. Case-control studies of radon and lung cancer risk in the general population were carried out to quantify the risk as a basis for risk management; numerous studies, most involving measurement of radon in the current and previous residences, were initiated. These studies have now been completed, the findings of individual studies reported, and two pooled analyses completed, one of studies in North America and the other of studies in Europe. The results show a significantly increased risk that is comparable in the two analyses (Table 2). The estimated number of lung cancer cases in the United States in never smokers attributable to radon alone is approximately 2,100 to 2,900 annually (103).

In summary, radon is a well-established cause of lung cancer in never smokers. Radon progeny act through a mechanism that predicts risk at any level of exposure, regardless of smoking. Epidemiological studies of miners and of the general population provide strong evidence for a causal association, and the risk has been quantified for both groups. Estimates of the burden of lung cancer attributable to radon place indoor radon among the leading causes of lung cancer in never smokers.

Indoor air pollution

Combustion of coal and biomass, and cooking fumes in the household. About half of the world's population, mostly in low- and medium-resource countries, use solid fuels for cooking or heating, often in poorly ventilated spaces (114). Products of incomplete combustion contain respirable particles and many organic compounds, including carcinogens such as benzo[a]-pyrene, formaldehyde, and benzene. Occupational exposure to the combustion products of coal by inhalation is known to cause lung cancer (115), and many studies, mostly from China, now show similar effects from household use of coal. These studies have been recently reviewed by an IARC Working Group that concluded that there is sufficient evidence in humans for the carcinogenicity of indoor emissions from household combustion of coal (116). This evaluation is supported by the results of studies in experimental animals and by mechanistic evidence from humans and animals.

Coal. Although the IARC evaluation was not specific to never smokers, one important feature of the studies of indoor air pollution from coal burning in China (and to a less extent other countries) is that they included a large number of (and often were restricted to) never-smoking women. Results of epidemiological studies of indoor combustion of coal and lung cancer risk in never smokers are summarized in Supplementary Table S2. Use of coal for cooking and heating was associated with increased lung cancer risk among never smokers in two of the earliest studies (117, 118). A population-based case-control study found that the risk of lung cancer among women in China is strongly dependent on the type of coal used for home heating and cooking (119). A retrospective cohort study noted a striking correlation between improved ventilation and decreased lung cancer rates in the same population ($P < 0.001$; ref. 120). Using coal for cooking throughout life compared with using modern cooking fuels (gas, electricity, or kerosene) increased the risk of lung cancer (OR = 7.5; 95% CI 2.2-25.9) among never-smoking males and females in India, after adjustment for age, gender, center, socioeconomic status, and use of noncigarette tobacco products (121).

Biomass. Worldwide, biomass is much more widely used as fuel than coal but the adverse health effects have been studied less (Supplementary Table S2). In five studies, researchers investigated indoor exposure to smoke from wood, straw, and other solid fuel and lung cancer risk among never-smoking women. Three studies, conducted in Japan, China, and Mexico, found an increased risk in lung cancer among never-smoking women exposed to smoke produced while cooking with various biomass fuels. However, in two studies conducted in India, ever use of biomass fuels was not associated with an increased risk of lung cancer among never-smoking women, nor was long-term use of solid cooking fuel in comparison to modern cooking fuel (gas, electricity, or kerosene). These studies suggest that exposure to smoke from wood combustion is associated with an increased risk of lung cancer, but the results on exposure duration and intensity are difficult to interpret. Furthermore, a study from Central and Eastern Europe provided no supporting evidence that use of solid fuels, including coal and wood, increases the risk of lung cancer among nonsmokers (122). The epidemiological evidence of an increased risk of lung cancer for exposure to biomass (mainly wood) combustion emissions was classified by the IARC working group as limited (116): this evaluation, however, was not specific to nonsmokers.

Cooking fumes. Stir-frying, deep-frying, and pan-frying, which involve heating oil to high temperatures, are practiced worldwide, especially in China. The epidemiological evidence

on cancer from exposure to emissions from high-temperature frying was classified as limited by the IARC Working Group (116). Results from 10 case-control studies have investigated the relationship between exposure to cooking fumes and the risk for lung cancer among never smokers (Supplementary Table S3). The majority of the studies found a positive association between lung cancer in never-smoking women and various methods of cooking with oil at high temperatures. A study of Chinese women from Singapore, however, did not detect an increased risk for stir-frying (123).

In summary, an increased risk of lung cancer has been consistently shown among never-smoking women exposed to indoor biomass smoke and cooking fumes. Less consistent results were found for different types of oils used for cooking and exposure to smoke from coal and risk of lung cancer among never smokers.

Occupational agents

Asbestos. The effect of asbestos exposure on risk of lung cancer among never smokers has been investigated in several cohort and case-control studies (Supplementary Table S4). With a few exceptions, these studies found an increased risk of lung cancer among never smokers who were occupationally exposed to asbestos relative to comparison groups of unexposed never smokers. The relative risks for exposure to asbestos varied between the studies, likely reflecting both the heterogeneity of exposure circumstances (level of exposure, type of fibers) and differences in the definition of asbestos exposure and never smokers. The relative risks of lung cancer for asbestos exposure tended to be higher in never smokers than in smokers [relative asbestos effect (RAE) ranging from 1.5 to 5.4 in most studies]. Although the precise nature of the interaction between asbestos and tobacco smoking in lung carcinogenesis remains subject to debate (96), the evidence of a carcinogenic effect of asbestos independent from smoking is very strong.

Arsenic. In a case-control study nested in a cohort of copper smelter workers from Sweden, Pershagen and colleagues (124) reported an OR of 2.6 [95% CI 0.29-23 (calculated on the basis of raw data)] for exposure to arsenic among nonsmokers (defined as subjects who had not smoked daily during more than 2 years at any time). An expanded analysis of this population confirmed the increased risk of lung cancer (OR 1.4, 5.6 < 15, and ≥15 $\mu g/m^3$/year arsenic exposure; Supplementary Table S5; refs. 125, 126). Similar results were reported in a study of Chinese tin mines (127). Additional cohort studies from United States and Japan also reported an increased risk of lung cancer among never (128) and nonsmoking (129, 130) miners or smelters, with risk estimates ranging from 2.6 to 5.1, as compared with unexposed workers. Occupational exposure to arsenic was self-reported in a community-based case-control study from Missouri (OR 1.1; 95% CI 0.2-5.8; ref. 131). In a study from Sweden, residence near a nonferrous smelter emitting arsenic together with other metals was not associated with increased risk of lung cancer (117).

Silica. Several industry-based studies of workers exposed to silica and of silicotic patients reported an increased risk of lung cancer among never smokers (Supplementary Table S6). In a multicenter case-control study from seven European countries, in which exposure to 70 agents was assessed by industrial hygienists on the basis of detailed occupational questionnaires, the RR for ever exposure to silica was 1.76 (95% CI 0.97-3.21), and a positive relationship was suggested with duration of exposure and cumulative exposure (118). Two additional studies reported an increased risk of lung cancer among never and nonsmoking workers exposed to silica (132, 133).

At least 10 studies analyzed lung cancer risk among never-smoking silicosis patients, defined either on the basis of compensation or medical (including necropsy) records. All but three showed an increased RR, in the range 1.6 to 2.2 (with the exception of a RR of 5.3 with broad CI). In the three studies with point estimates of the RR below unity, the CIs were compatible with an excess risk on the order of 80%. Although a formal meta-analysis is made difficult by the lack of CI of several of the risk estimates, the overall evidence points toward an increased risk of cancer among persons with silicosis in the absence of tobacco smoking.

Exposure to other agents. In the case-control study of lifetime nonsmoking women from Missouri, an increased risk of lung cancer was detected for exposure to pesticides (OR 3.1; 95% CI 1.3-7.5; ref. 131). In the multicentric European study (118), results were reported for 11 agents, in addition to silica: the OR for ever exposure to nonferrous metal dust and fumes was 1.73 (95% CI 1.02-2.92), and OR for ever exposure to organic solvents was 1.46 (95% CI 0.94-2.24). For these two agents, a duration-response relationship was suggested.

Exposure to any known or suspected occupational lung carcinogens. Three European case-control studies reported results according to employment in job and industries entailing exposure to known (list A) or suspected (list B) occupational lung carcinogens, on the basis of a simplified job exposure matrix developed by Ahrens and Merletti (Supplementary Table S7; ref. 134). In a pooled analysis of 12 European case-control studies of never-smoking women, the OR for employment and jobs entailing exposure to suspected carcinogens was 1.69 (95% CI 1.09-2.63), whereas the risk estimate for employment in jobs entailing exposure to known carcinogens was imprecise (OR 1.50; 95% CI 0.49-4.53; ref. 135).

Employment in specific occupations and industries. In a few studies, risk estimates of lung cancer among never smokers were reported according to employment in specific occupational or industry categories (Supplementary Table S8). A systematic analysis of jobs and industries of employment and lung cancer risk among nonsmoking U.S. veterans revealed an increased risk for employment as a baker, agent, farm and home management advisor, therapist or healer, building manager, bookbinder, decorator or window dresser, and painter. The large number of job and industries included in this analysis, however, has likely generated false positive results.

In summary, an increased risk of lung cancer has been consistently shown among workers exposed to asbestos, arsenic, and silica. Results on exposure to other known or suspected occupational lung carcinogens among never smokers are sparse. In general, the findings on occupational risk factors in never smokers parallel those in smokers, although the measure of the magnitude of the smoking interaction is complicated by

Table 3. Risk of lung cancer associated with previous lung disease among never smokers

Study	Design/population	Exposure group	Reference group	Risk estimate (95% CI)	Adjustment variables
Hinds et al. (166)	Case-control: 211 female lung cancer cases (never smokers); 419 female population controls (never smokers); Study location: HI;Study years: 1968–1978	History of pulmonary tuberculosis infection vs.	No history of pulmonary tuberculosis infection	8.2 (1.3–54.4)	Age, birthplace, race
Zheng et al. (165)	Case-control: 415 male and female lung cancer cases (never smokers); 714 male and female population controls (never smokers);Study location: Shanghai, China;Study years: 1984–1986	Diagnosed with tuberculosis <20 years ago vs.	Never diagnosed with tuberculosis	3.5 (1.5–8.0)	Age, education, gender
		Diagnosed with tuberculosis ≥20 years ago vs.	Never diagnosed with tuberculosis	1.0 (0.7–1.5)	Age, education, gender
Alavanja et al. (180)	Case-control: 186 female lung cancer cases (never smokers); 234 female population controls (never smokers); Study location: MO;Study years: 1986–1991	History of lung disease (asthma, chronic bronchitis, emphysema, pleurisy, pneumonia, tuberculosis) vs.	No history of lung disease	1.4	None stated
		History of asthma vs.	No history of asthma	2.7	None stated
		History of pneumonia vs.	No history of pneumonia	1.5	None stated
		History of tuberculosis vs.	No history of tuberculosis	"No association" (estimate not stated)	None stated
		History of pleurisy vs.	No history of pleurisy	"No association" (estimate not stated)	None stated
		History of chronic bronchitis vs.	No history of chronic bronchitis	"No association" (estimate not stated)	None stated
Lan et al. (181)	Case-control: 139 female lung cancer cases (nonsmokers);139 female population controls (nonsmokers);Study location: Xuanwei, China; Study years: 1988–1990	History of chronic bronchitis vs.	No history of chronic bronchitis	7.04 (1.79–27.77)	Age, menstrual cycle length, age of menopause, smoky coal exposure
Ko et al. (182)	Case-control: 105 female lung cancer cases (never smokers); 105 female hospital controls (never smokers);Study location: Taiwan;Study years: 1992–1993	History of pulmonary tuberculosis infection vs.	No history of pulmonary tuberculosis infection	5.9 (1.3–25.9)	Age, living near industrial district, cooking fuels, fume extractor use, vegetable consumption, SES, residential area, education
Shen et al. (183)	Case-control: 70 female adenocarcinoma cases (never smokers);70 female population controls (never smokers);Study location: Nanjing, China;Study year: 1993	History of pulmonary tuberculosis or chronic bronchitis vs.	No history of pulmonary tuberculosis or chronic bronchitis	3.90 (1.00–20.94)	Age, occupation, neighborhood, cooking fumes, family history of cancer
Santillan et al. (167)	Meta-analysis:5 case-control studies;1,370 total male and female lung cancer cases;Study locations: United States, China; Publication dates: 1985–2001	History of asthma vs.	No history of asthma	1.8 (1.3–2.3)	Not stated

(*Continued on the following page*)

Table 3. Risk of lung cancer associated with previous lung disease among never smokers (Cont'd)

Study	Design/population	Exposure group	Reference group	Risk estimate (95% CI)	Adjustment variables
Neuberger et al. (184)	Case-control: 56 female lung cancer cases (never smokers); 414 female population controls (never smokers); Study location: IA; Study years: 1993–1996	Previous lung disease (bronchitis, emphysema, asthma, tuberculosis, silicosis, asbestosis, COPD) vs.	No previous lung disease	2.28 (1.24–4.18)	Age, education, radon
Seow et al. (185)	Case-control: 126 female lung cancer cases (never smokers); 162 female hospital controls (never smokers); Study location: Singapore;Study years: 1996–1998	History of asthma, allergic rhinitis, or atopic dermatitis (all histological types) vs.	No history of asthma, allergic rhinitis, or atopic dermatitis (all histological types)	1.5 (0.8–2.6)	Age, fruit and vegetable intake, birthplace, SHS exposure
		History of asthma, allergic rhinitis, or atopic dermatitis (adenocarcinomas) vs.	No history of asthma, allergic rhinitis, or atopic dermatitis (adenocarcinomas)	1.6 (0.9–3.1)	Age, fruit and vegetable intake, birthplace, SHS exposure

Abbreviation: SES, socioeconomic status.

the small number of cases of lung cancer among never smokers included in most studies.

Outdoor air pollution

An increased risk of lung cancer has been reported in populations exposed to high levels of outdoor air pollution. This association, however, might result from confounding by other factors, notably tobacco smoking, rather than from air pollution. Cohort and case-control studies are limited by difficulties in assessing past exposure to the relevant air pollutants. In several studies, exposure to air pollution has been assessed either on the basis of proxy indicators, such as the number of inhabitants in the community, or residence near a major pollution source: which limits the interpretation of the results. In a small number of studies, exposure to outdoor air pollution has been assessed on the basis of data on pollutant level matched to the residence of the study subjects. Two of these studies have reported results for never smokers (Supplementary Table S9): an increased risk of lung cancer for increasing level of exposure to air pollution (measured either as fine particles of nitrogen oxide) has been reported in these studies, although none reached the conventional level of statistical significance. In a third study, which included an equal number of never smokers and long-term quitters, no association was found between exposure to particulate matter of 10 μm or less (PM_{10}) and lung cancer risk (136).

On the one hand, results on lung cancer risk from outdoor air pollution exposure among never smokers can be biased by residual confounding from occupational exposure to lung carcinogens and other social class-related factors. On the other hand, retrospective exposure to outdoor air pollution may be particularly vulnerable to misclassification, which in prospective studies would likely result in underestimation of the effect. Although an increased risk of lung cancer among never smokers exposed to high levels of outdoor air pollution is plausible, the available evidence does not allow an accurate estimate of risk.

Diet

Dietary factors have been noted to be leading preventable causes of cancer (137). The second expert report from the World Cancer Research Fund and the American Institute for Cancer Research comprehensively reviewed the evidence for the association between diet and cancer for both smokers and nonsmokers. For lung cancer, the expert panel concluded that fruits and foods containing carotenoids likely protect against lung cancer (138). The expert panel also concluded "[t]here is limited evidence suggesting that nonstarchy vegetables protect against lung cancer." Similarly, for consumption of foods containing selenium, selenium supplements, and foods containing quercetin, they also concluded that the limited evidence was suggestive of protection against lung cancer. The potential protective effect of selenium is the basis of an ongoing randomized clinical study of selenium supplementation versus placebo in patients with a history of resected stage I lung cancer.

The panel concluded that there is convincing evidence that arsenic in drinking water is a cause of lung cancer, and that there is limited, inconsistent evidence suggesting that high-dose retinol supplements (in smokers), consumption of red meat, processed meats, total fat, and butter are causes of lung cancer (138).

Fruit. In 14 studies, researchers investigated fruit consumption and lung cancer among never smokers. Among these studies, three were cohort studies (139–141), including one multicenter study involving follow-up of 16 cohorts from seven countries over 25 years (141), and one multicenter case-control study with participants from six European countries (142). None of the cohort studies found a significant association between total fruit consumption and lung cancer risk. Of 11 case-control studies (142–152), three found that never smokers who consumed the highest amount of fruit were less likely to have lung cancer when compared with those who consumed the lowest amount (147, 152, 153). The risk reductions observed ranged from 40 to 70% (Supplementary Table S10).

Dose-response relationships were identified in two case-control studies. A multicenter case-control study, the study with the largest number of cases found in this literature review, did not find a relationship between total fruit consumption and lung cancer risk (142).

Vegetables. Two cohort studies (139, 140) and eight case-control studies (142, 144, 147, 148, 150–152) investigated consumption of total vegetables and lung cancer among never smokers. The Seven Countries study found a 10% reduction (95% CI 0.67-1.08) in the risk of lung cancer development

Table 4. Results of studies on exposure to radiation and risk of lung cancer among never smokers

Study	Design/population	Exposure group	Reference group	Risk estimate (95% CI)	Adjustment variables
Neugut et al. (173)	Case-control:16 female lung cancer cases among breast cancer survivors (nonsmokers); 348 female breast cancer survivor controls (nonsmokers); Study location: CT;Study years: 1986–1989	Received radiation therapy for breast cancer vs.	Did not receive radiation therapy for breast cancer	3.2 (0.6–17.4)	Age
van Leeuwen et al. (175)	Case-control:From a cohort of 1,939 Hodgkin's disease patients:8 male and female lung cancer cases (nonsmokers);33 male and female controls (nonsmokers);Study location: The Netherlands; Study years: 1966–1986	Received 1–5 Gy radiation therapy for Hodgkin's disease vs.	Received <1 Gy radiation therapy for Hodgkin's disease	0.99 (0.07–14.7)	Age, gender, treatment center, date of Hodgkin's diagnosis
		Received ≥5 Gy radiation therapy for Hodgkin's disease vs.	Received <1 Gy radiation therapy for Hodgkin's disease	2.5 (0.21–29.4) P_{trend} = 0.43	Age, gender, treatment center, date of Hodgkin's diagnosis
Hu et al. (144)	Case-control:161 female lung cancer cases (never smokers);483 female population controls;Study location: Canada;Study years: 1994–1997	Occupational radiation sources vs.	No occupational exposure to radiation sources	2.1 (0.7–6.8)	Age, province, education, social class
Ford et al. (186)	Case–control:41 female lung cancer cases among breast cancer survivors (never smokers);159 female breast cancer survivor controls (never smokers);Study location: TX;Study years: 1960–1997	Received radiation therapy for breast cancer vs.	Did not receive radiation therapy for breast cancer	0.60	Age, ethnicity, breast cancer histology, type of breast cancer surgery, date of breast cancer diagnosis
Boffetta et al. (187)	Case–control:209 male and female lung cancer cases (never smokers);976 male and female hospital and population controls (never smokers);Study location: Czech Republic, Hungary, Poland, Romania, Russia, Slovakia;Study years: 1998–2002	1–30 occupational X–ray examinations vs.	No occupational X-ray examinations	1.22 (0.73–2.03)	None stated
		>30 occupational X-ray examinations vs.	No occupational X-ray examinations	2.30 (1.15–4.57)	None stated
Prochazka et al. (174)	Case series:82 women diagnosed with breast cancer and then subsequent lung cancer (nonsmokers); Study location: Sweden; Study years: 1958–2000	Received ipsilateral radiation therapy for breast cancer (breast and lung cancer on same side) vs.	Contralateral radiation dose to lung ≤15% of the ipsilateral dose (lung on opposite side of breast cancer served as control)	0.9 (0.37–2.22)	None stated

Abbreviation: Gy, gray.

among never smokers per 18 g increase in total vegetable consumption (139). The Japan Public Health cohort study followed 56,049 participants for 7 to 10 years; a total of 106 cases of lung cancer developed among never smokers. The authors reported a 40% increased risk (95% CI 0.79-2.30) of developing lung cancer for those with a high consumption of total vegetables when compared with those with low consumption (140). Of the eight case-control studies that examined total consumption of vegetables, most found a decreased risk for lung cancer among those in the highest category of consumption (Supplementary Table S10).

Most of the studies that considered total vegetable consumption also investigated specific vegetables. Additionally, four studies (one cohort and three case-control studies) were found on the association between specific grouping of vegetables and lung cancer. Results of the few studies in each category are presented in Supplementary Table S10.

Meat and fish. One cohort study and five case-control studies investigated meat consumption and risk of lung cancer among never smokers, mostly women. The cohort study of more than 50,000 Japanese women found those consuming ham and sausages three to four times or more a week had a twofold increased risk (95% CI 1.15-3.53; *P*-trend < 0.05) of lung cancer compared with those that ate ham and sausages fewer than one to two times a month, after adjustment of age, and family history of lung cancer. SHS exposure was not a confounder in this study (141).

High fish consumption was found to decrease the risk of lung cancer among never smokers in China. A case-control study of Chinese women found a 60% (95% CI 25%-84%; *P*-trend < 0.05) decreased risk of developing lung cancer among women in the highest tertile of fish consumption compared with women in the lowest tertile, after adjustment for age, number of live births, and education (153).

Miscellaneous. The majority of studies looking at other aspects of diet, including fat consumption, food preparation, and dairy, egg, and soy product consumption (Supplementary Table S10), found no significant association with lung cancer in never smokers.

Micronutrients. One nested case-control study and eight case-control studies investigated dietary carotenoid consumption. A case-control study conducted in Stockholm reported a protective effect and a dose-response with increasing intake of total carotenoids, with adjustment for SHS exposure (146). Candelora and colleagues conducted a study in Florida, among never-smoking women and found a decreased risk in lung cancer with increasing consumption of total carotenoids, alpha- and beta-carotene, vitamin A, and vitamin C (152). A few studies also investigated other micronutrients (Supplementary Table S10).

Arsenic in drinking water. In a case-control study from Chile, the risk ratios of lung cancer were 5.9 (95% CI 1.2-40) and 8.0 (95% CI 1.7-52) for 50 to 199 and ≥200 μg arsenic per liter of drinking water, as compared with less than 50 μg/L, after adjustment for age and gender (154). In a similar study from Taiwan, risk ratios were 1.24 (95% CI 0.53-2.91) and 2.21 (95% CI 0.71-6.86) for exposure to 10 to 699 and 700 or more μg/L as compared with less than 10 μg/L, adjustment for age, gender, education, and alcohol consumption (155). The relevance of these data to never smokers specifically has not been addressed.

Other risk factors

Hormone replacement therapy. There is relatively little research in the area of hormone replacement therapy (HRT) and lung cancer risk, although some studies indicate a reduction of lung cancer risk associated with HRT use (Supplementary Table S11). Although this inverse association has been present in case-control studies that have adjusted for smoking, stratification by smoking status reveals this inverse association exists for current smokers only (156, 157). For example, one study that examined risk among smokers and never smokers who had taken HRT showed that only the current smokers had a significant decrease in lung cancer risk (157). When examining lung cancer risk and hormone replacement therapy among never smokers, there does not appear to be a statistically significant association (158), although very few studies have been conducted that stratified by smoking status. Furthermore, the studies that have examined never smokers include a very small number of patients, so that their results are imprecise. In conclusion, although several studies have shown an inverse association between HRT use and lung cancer risk, it is unclear whether such an association is present among never smokers.

Infections

Human papillomavirus. Several studies have examined whether chronic infections can increase lung cancer risk. Human papillomavirus (HPV) infection has been observed in association with lung cancer cases in many studies, particularly in China (Supplementary Table S12). These studies suggest that HPV 6, HPV 16, and HPV 18 are all more prevalent among lung cancer cases than controls. HPV 6, which was examined in only one of these studies, seemed to be associated with smoking status, with male smokers having higher odds of having HPV 6 than male never smokers (OR 7.35; 95% CI 2.11-25.58; ref. 159). Although these studies suggest an association of HPV infection with lung cancer risk, it is still unclear if HPV infection is associated with lung cancer risk among never smokers. These studies were limited to China, and it is unknown if similar associations are present in other countries.

Human immunodeficiency virus. Human immunodeficiency virus (HIV) has been studied in association with lung cancer risk, although this has not been a large area of study. Results from a retrospective cohort study conducted at an HIV specialty clinic showed that people infected with HIV had approximately a twofold significant increase in lung cancer risk, after adjustment for smoking status (160). Kirk and colleagues conducted a cohort study among injection drug users and reported that people infected with HIV have a significant increase in lung cancer risk (HR 3.6, 95% CI 1.6-7.9), independent of smoking status (161). Although it has been shown that people infected with HIV have an increased lung cancer risk, this has not been stratified by smoking status, so it is unclear of whether the risk is the same or different among never smokers.

Chlamydia pneumoniae. *Chlamydia pneumoniae* has also been investigated in relation to lung cancer risk, under the

hypothesis that chronic infections may increase risk (162, 163). It has been reported that former smokers that are infected have a larger risk of lung cancer than current smokers, but there were no never smokers included in this study (163). A recent report examining chlamydial immunoglobulin titers in 90 never smokers (defined here as <400 lifetime cigarettes smoked) with lung cancer and 68 never-smoking controls found no evident association between infection and cancer, but the power of this study was clearly suboptimal (164).

History of lung disease prior to lung cancer diagnosis. History of lung disease has been examined in association with lung cancer risk, including tuberculosis, asthma, emphysema, and chronic obstructive pulmonary disease (COPD). Studies have shown that persons with tuberculosis have as much as a 50% increase in lung cancer risk (165), although differences by smoking status has been examined in only a few studies (Table 3). Interestingly, one study that examined lung cancer risk among smokers and never smokers with tuberculosis found that female never smokers with tuberculosis had approximately an eightfold increase in lung cancer risk, whereas there was no association among female smokers (166). This study is limited by the small number of never-smoking lung cancer patients.

Asthma has also been frequently studied in terms of lung cancer risk. Several studies have examined this potential risk factor, including a meta-analysis consisting of 8 case-control and 10 cohort studies (167). Most of these studies showed an increased risk of lung cancer in never smokers with asthma (Table 3).

Several studies have suggested that patients with idiopathic pulmonary fibrosis or other fibrotic disorders are at increased risk for lung cancer (168–171), but these risk factors have not been clearly defined in never smokers. There has been little research on COPD and lung cancer risk specific to never smokers, as never smokers rarely develop this disease. In a Chinese province in which exposure indoor smoky coal combustion is common, COPD (chronic bronchitis) in never-smoking women has been associated with increased lung cancer risk (172).

Ionizing radiation. Many studies have examined the risk of lung cancer due to ionizing radiation among never smokers. Most of the studies have examined risk following radiation therapy for Hodgkin's disease or for breast cancer, although some have examined occupational X-ray exposure as well (Table 4). Most studies show an increased risk of lung cancer due to radiation for treatment of Hodgkin's disease or breast cancer. However, most of these studies show that this increased risk is higher among smokers, possibly because of the multiplicative effects of cigarette smoking and radiotherapy (173–175). For atomic bomb survivors, the effect of radiation exposure and smoking on lung cancer has been found to be additive (176).

Summary

The large numbers of current and former smokers dying of lung cancer have obscured the important problem of lung cancer in never smokers. Lung cancer in never smokers accounts for 16,000 to 24,000 deaths annually in the United States, among the top 10 causes of cancer mortality as a separate entity from smoking-related cancer. Incidence of lung cancer in never smokers increases with age. Current epidemiologic data do not indicate a significant change in risk over time, or a clear gender bias in the risk of lung cancer in never smokers. However, among female never smokers, large differences in lung cancer risk exist between populations, with strikingly higher risk in several East Asian countries, and in particular China. Factors contributing to these population differences may include both underlying genetic susceptibility as well as exposure to carcinogens including coal smoke, aerosolized cooking oils, and SHS. Studies evaluating gene-environment interactions may provide important insights into carcinogenesis pathways of lung cancer in never smokers. Such studies require not only adequate sample sizes, but also detailed exposure assessments in relevant populations.

Strong evidence from multiple sources supports the causal association of SHS exposure in lung cancer in never smokers. Similarly, exposure to radon, common in indoor environments, is a well-established cause of lung cancer in never smokers. In the United States, these two factors may account for the majority of cases of lung cancer in never smokers. Indoor air pollution, including combustion of coal or solid fuels for cooking or heating in poorly ventilated spaces, has been clearly associated with increased risk of lung cancer in never smokers, and may be a particularly important factor contributing to the high incidence of lung cancer in never smokers in the East Asia. In addition to radon, other exogenous ionizing radiation exposures have been clearly linked to lung cancer risk. Additional exposures associated with lung cancer in never smokers in multiple studies include asbestos, which has known carcinogenic synergy with tobacco smoke, arsenic, and silica.

Studies of dietary factors contributing to lung cancer have been less consistent, and data specific to never smokers have not been extensively explored. Diets containing relatively high levels of carotenoids, selenium, or quercetin seem to be associated with decreased risk of lung cancer; conversely consumption of meat, fat, and butter may be associated with increased risk of lung cancer.

Viral infections including HPV and HIV have been implicated in lung cancer risk in studies that included both never smokers and ever smokers. It is unclear whether these viruses act synergistically with tobacco, or constitute independent risk factors for lung cancer in never smokers. Finally, chronic lung diseases including tuberculosis, COPD, and asthma have been associated with increased lung cancer risk. Of these, asthma seems to be significantly associated with lung cancer risk in never smokers.

The death rate due to lung cancer in never smokers over several decades has remained relatively constant in the United States, and represents a significant ongoing public health problem. Common limitations found in many of the epidemiologic studies reviewed included a failure to clearly stratify analyses by smoking status (never versus ever; never versus former versus active), failure to quantify exposure to SHS and other risk factors, and variable definitions of the terms nonsmoker and never smoker. Given the significant impact of lung cancer in never smokers, focused research on genetic

and environmental factors associated with this disease, in carefully defined and extensively characterized populations, is warranted.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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