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Epidemiology and Prevention of Lung Cancer in Nonsmokers

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INTRODUCTION

Lung cancer is the leading cause of cancer mortality in the United States accounting for an estimated 28 percent of all cancer deaths in 1998, or a total of 160,100 deaths (1). Lung cancer is also the most common cause of cancer mortality worldwide (2). Although the majority of lung cancers can be attributed to cigarette smoking, particularly in Asian and middle eastern countries, a substantial percentage of lung cancer cases occurs among never smokers (3). For example, the proportion of female lung cancer cases who have never smoked is as high as 65 percent in China (4), 70 percent in Japan (5), and 94 percent in northern India (6). In the United States, typically 9–13 percent of female lung cancer cases are never smokers (7–11). In males, the patterns differ considerably. Among male lung cancer patients, the proportion of never smokers is about 2 percent in the United States (11–13), 3 percent in China (14), 9 percent in Japan (5), and 19 percent in northern India (6).

Compared with the relation between smoking and lung cancer, very few studies have examined risk factors for lung cancer among nonsmokers. It is important to understand the patterns and etiology of lung cancer among nonsmokers for several reasons. First, Schneiderman et al. (15) have estimated US nonsmoking lung cancer death rates; if their estimates are valid, only colon and prostate cancer in men and colon and breast cancer in women exceed nonsmoking lung in annual cancer mortality. Second, while US lung cancer mortality has begun to decline in recent years (16, 17), primarily due to declining smoking prevalence, few studies are available to determine whether trends in lung cancer among nonsmokers show similar declining trends. Third, the effect of cigarette smoking on lung cancer is large—on the order of a 10- to 20-fold relative risk. Many of the risk factors for lung cancer among nonsmokers are much smaller in magnitude, often showing relative risk values less than 2. Therefore, it is extremely difficult to control for cigarette smoking while accurately quantifying weak risk factors. And fourth, several of the potential risk factors for lung cancer in nonsmokers (e.g., residential radon, environmental tobacco smoke) are amenable to primary prevention efforts.

This review focuses on the epidemiology of lung cancer in nonsmokers. As noted in the preceding and following sections, lung cancer among nonsmokers occurs relatively more frequently among women than among men. Therefore, many of the studies discussed were conducted exclusively among women.

DESCRIPTIVE EPIDEMIOLOGY

Examination of lung cancer trends, histologic types, and survival patterns can provide clues that can be investigated more fully in etiologic studies. There appear to be substantially different patterns in Western societies, compared with Asian countries, that are worthy of investigation.

Time trends

Limited data are available to examine temporal trends in nonsmoking lung cancer incidence and/or mortality in the United States. In the data presented below on time trends, the denominator includes both nonsmokers and smokers, and all rates have been age-adjusted.

Using prospective data of the American Cancer Society, Burns et al. (18) calculated age-adjusted mortality rates among nonsmokers for three periods, 1960–1964, 1964–1968, and 1968–1972. Among men, the rates per 100,000 for the three periods were 12.5, 18.5, and 15.8, respectively. The corre-

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Abbreviations: CI, confidence interval; CPS-I, Cancer Prevention Study I; CPS-II, Cancer Prevention Study II; OR, odds ratio; PAR, population attributable risk; RR, relative risk; SEER, Surveillance, Epidemiology, and End Results.

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sponding rates in women were 13.8, 12.9, and 13.1 (18). The National Cancer Institute recently published data on lung cancer among nonsmokers from the American Cancer Society's Cancer Prevention Study I (CPS-I) and Cancer Prevention Study II (CPS-II) (19). The age-adjusted death rate for lung cancer among nonsmoking men was 15.7 per 100,000 in CPS-I (1959–1965) and 14.7 per 100,000 in CPS-II (1982–1988). Rates for women were 9.6 in CPS-I and 12.0 in CPS-II.

We present time trend data on lung cancer incidence from the Surveillance, Epidemiology, and End Results (SEER) Program and the Missouri Cancer Registry. The SEER Program of the National Cancer Institute provides data from seven regions of the United States. Reporting registries are population-based and the SEER Program data are presently the closest to representative of the entire US population. Data are also presented from the Missouri Cancer Registry, a population-based registry established in 1972. These data are presented as a comparison because the Missouri Cancer Registry is one of the few cancer registries that routinely collects smoking information on cancer patients; it may be the only registry for which these risk factor data have been validated (20). Information on ever versus never smoking among registry-reported cases has shown reasonably high accuracy (overall exact agreement of 83 percent (20)). For smoking-related cancers (i.e., cancers of the oral cavity, esophagus, larynx, and lung), exact agreement on dichotomous smoking history was 96 percent.

Figure 1 describes trends in age-adjusted lung cancer incidence (and least-squares regression lines) in the United States and Missouri for the period 1986–1992 (21). Although rates among men are slightly higher in Missouri than in the United States as a whole, the trends are similar. Among women, incidence rates are increasing in both the United States and Missouri. Due to the availability of smoking information, trends in nonsmoking (i.e., lifetime nonsmokers) lung cancer in Missouri are shown (figure 2). In Missouri, it appears that nonsmoking lung cancer incidence is decreasing in both genders, albeit more rapidly among men than among women.

In Japan, age-adjusted mortality from lung cancer in nonsmoking women was estimated at 0.8 per 100,000 in 1950 and 6.1 in 1985 (22).

Histologic patterns

Although all lung cancers arise from epithelial tissue, the histologic distribution of lung cancer differs markedly between smoking and nonsmoking populations. Kreyberg (23) suggested the categorization of lung cancers as Kreyberg I (i.e., squamous cell, large cell, and small cell carcinomas) and Kreyberg II (i.e., adenocarcinomas and bronchioloalveolar carcinomas). A strong relation between cigarette smoking and Kreyberg I cancers was shown, yet a weaker relation existed with Kreyberg II tumors (23). A study from Western Europe showed elevated lung cancer risk associated with cigarette smoking for all cell types, although a much stronger gradient in risk was noted for Kreyberg I cell types (24).

Large-scale studies of lung cancer show that squamous cell carcinoma is the most common cell type among men, and adenocarcinoma is the most common histologic type among women in the United States (25, 26). Koo and Ho (3) summarized available studies of nonsmoking women and concluded that adenocarcinoma accounts for the vast majority (64.5 percent of cases based on 16 studies) of lung cancer cases. Only a few US studies have been reported of pathologically confirmed lung cancer histologic patterns by smoking status. Two of the largest studies (27, 28) from the United States are summarized in table 1. These studies confirm that adenocarcinoma is by

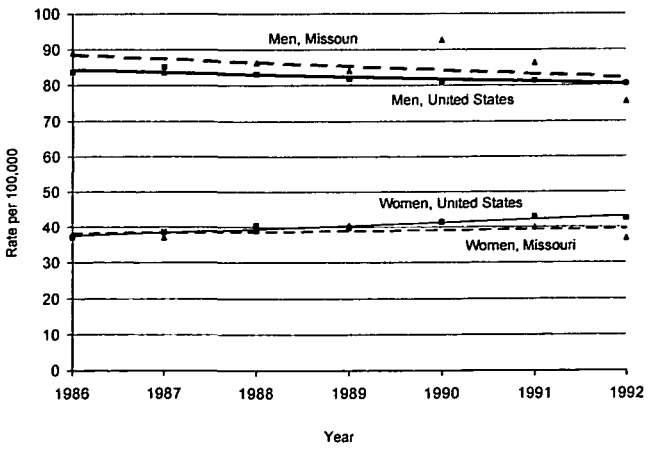

FIGURE 1. Trends in age-adjusted lung cancer incidence, United States and Missouri, 1986–1992.

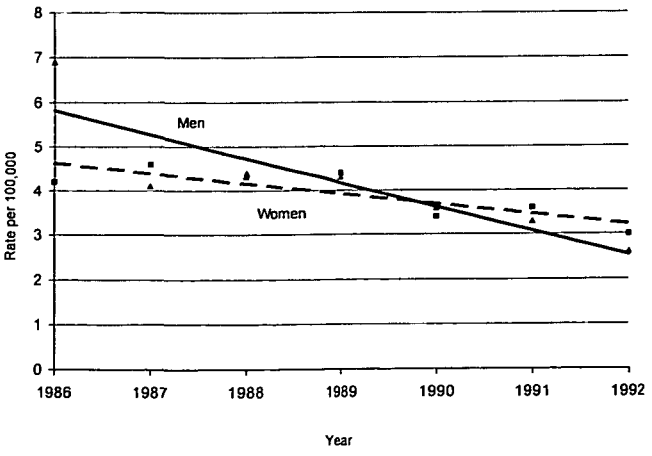

FIGURE 2. Trends in age-adjusted lung cancer incidence among nonsmokers, Missouri, 1986–1992.

TABLE 1. Histologic distributions of lung cancer among female nonsmokers in selected studies

Histologic type	Missouri*		Multicenter, United States†	
	No.	%	No.	%
Adenocarcinoma	219	66.8	497	76.1
Bronchioalveolar	17	5.2		
Large cell			74	11.3
Squamous cell	10	3.0	40	6.1
Small cell	3	0.9	24	3.7
Other	79	24.1	18	2.8
Total	328	100.0	653	100.0

* Source: Brownson et al. (28).
† Source: Fontham et al. (27).

far the dominant cell type among US female nonsmokers. In a study of lung cancer histologic patterns among nonsmokers based on a panel review by three pathologists, Brownson et al. (28) found a wide range in positive predictive values according to cell type (e.g., 0.37 for squamous cell carcinoma to 0.84 for adenocarcinoma). This suggests the importance of conducting pathologic reviews of registry-reported lung cancer cases in large studies of etiology. There also appears to be conflicting evidence of the changes in histologic distributions over time. For example, New Mexico data showed a declining proportion of adenocarcinoma among women when 1970–1972 and 1980–1981 cases were compared (25). Data from western Washington State showed a slight increase in the proportion of adenocarcinoma among women from 1974 to 1981 (26). The magnitude and reasons for temporal changes in the histologic distributions of lung cancer among nonsmokers are not well understood.

Barkley and Green (29) recently highlighted the need to examine lung cancer risk and trends by histologic subtype. Based on a literature review, researchers concluded that bronchioloalveolar carcinoma appeared to increase in incidence from 1966 to 1995. This increase may be most pronounced in young, nonsmoking women. They also suggested that three clinical subtypes of bronchioloalveolar carcinoma can be identified: mucinous, nonmucinous, and sclerotic. Bronchioloalveolar carcinoma is likely to be less related to cigarette smoking than many other cell types of lung cancer (29–31).

Age at cancer diagnosis

The age at which lung cancer is diagnosed varies according to the smoking status of the patient. In studies from the United States and Europe, lung cancer cases among smokers are generally diagnosed at a younger age than those among lifetime nonsmokers. For example, data from the Missouri Cancer Registry for 1985–1992 indicate a younger age at diagnosis for both male smokers (i.e., mean age of 64.9 years for current smokers (n = 8,831) versus 70.5 years for never smokers (n = 999); $p < 0.001$) and female smokers (i.e., mean age 63.5 years for current smokers (n = 5,137) versus 72.4 years for never smokers (n = 1,274); $p < 0.001$).

This pattern differs in Asian countries such as Japan and Hong Kong where the mean age at diagnosis is commonly lower among nonsmokers than among smokers (5, 32). There are three possible explanations for this differing pattern between Western and non-Western countries. First, the contribution of risk factors unrelated to smoking may be greater in Asian countries (3). Second, because ever smokers initiate smoking at a much later age in Asian countries, compared with the United States and Europe, the age at cancer diagnosis for Asian smokers may be higher even with induction periods similar to Western countries. And third, varying degrees of detection bias may account for part of the differences between countries.

Survival

There are few studies that have examined survival patterns for lung cancer among nonsmokers and histologically verified patients. One study has compared pathologically confirmed lung cancer survival patterns among nonsmoking women by histologic type (28). Survival rates were highest for bronchioloalveolar carcinoma, followed by adenocarcinoma, squamous cell carcinoma, and small cell carcinoma (figure 3). Others have noted that early bronchioloalveolar survival is higher but equivalent to squamous cell carcinoma after 2 years (30).

RISK FACTORS

Since nonsmoking lung cancer is a relatively rare disease, we rely mainly on epidemiologic findings

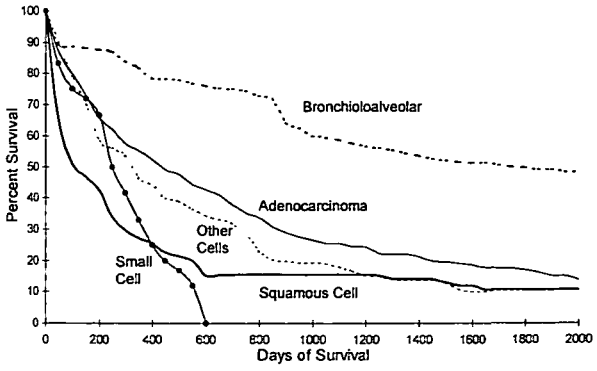

FIGURE 3. Observed survival patterns among nonsmoking women with lung cancer by histologic type based on panel review diagnosis, Missouri, 1986–1991. From Brownson et al. (28); reproduced with the permission of the publisher.

from case-control studies. Since many of these associations are relatively weak, methodological challenges are substantial when studying nonsmoking lung cancer, and these difficulties are highlighted in the context of several key risk factors. Unless otherwise noted, detailed results are described for studies that contained 50 percent or more nonsmokers among the case group or cohort being studied and/or those that presented analyses separately for smokers and nonsmokers. In studies involving nonsmokers and smokers, smoking-adjusted risk estimates are presented. A lifetime nonsmoker is commonly defined in these studies as a person who had smoked fewer than 100 cigarettes in her or his lifetime. In the tables in this section, results are presented for lifetime nonsmokers whenever possible; when data were not reported separately for lifetime nonsmokers, results are shown for adenocarcinoma since it is the predominant cell type among lifetime nonsmokers. We first discuss host and familial factors, then consider risk factors that are potentially modifiable in greater detail. It is evident for each of the risk factors noted below that relatively few studies have examined risk factors for lung cancer among large populations of nonsmokers.

Preexisting lung diseases

Several population-based studies have examined the relation between preexisting lung diseases and lung cancer risk in nonsmokers. The group of lung diseases that has been studied includes asthma, chronic bronchitis, pleurisy, pneumonia, and tuberculosis. Effect estimates from major studies are presented in table 2. Nonsmoking lung cancer risk in relation to a wide array of preexisting lung diseases has been reviewed in two large studies from the United States (33, 34). The four studies from Asia included nonsmokers and smokers combined (4, 35–37).

In a multicenter study in the United States, Wu et al. (33) found that history of any previous lung disease resulted in elevated lung cancer risk (odds ratio (OR) = 1.56; 95 percent confidence interval (CI) 1.2–2.0). Statistically significant increased risks for lung cancer were observed for prior history of asthma and chronic bronchitis. In addition, among younger cases (i.e., <55 years of age) elevated risk was noted for pneumonia (OR = 2.93; 95 percent CI 1.5–5.6) and tuberculosis (OR = 9.05; 95 percent CI 1.6–49.7). The relations observed were unchanged after adjustment for potential confounders such as environmental tobacco smoke and dietary factors.

In another large case-control study, Alavanja et al. (34) found an elevated risk of adenocarcinoma associated with any previous lung disease (OR = 1.4; 95 percent CI 1.0–2.1). Although effect estimates were not always statistically significant, each type of lung disease, except for chronic bronchitis, showed some elevation in risk (table 2).

Endocrine factors in women

The possibility that endocrine factors may play a role in the genesis of lung cancer in women is supported by several lines of evidence (38). First, as noted earlier in the section on descriptive epidemiology, there is commonly a greater proportion of nonsmokers and adenocarcinomas among women than among men with lung cancer.

Second, steroid receptors have been shown in some lung cancer tumors. Steroids such as glucocorticoids and estrogen regulate the differentiation and metabolism of pulmonary epithelial cells, and, therefore, influence lung metabolism. Chaudhuri et al. (39) have shown variation in steroid receptors according to lung cancer cell type. For example, 57 percent of adenocarcinomas were receptor positive for estrogen compared with none of the squamous cell or small cell carcinomas. Similarly, 71 percent of adenocarcinomas were receptor positive for glucocorticoid receptors compared with 7 percent of squamous cell lung can-

TABLE 2. Summary odds ratios (OR) and 95% confidence intervals (CI) from selected studies of preexisting lung disease and lung cancer in nonsmokers

Type of lung disease	Study location (reference no.)											
	Multicenter, United States (33)		Missouri (34)*		Shanghai, China (4)		Northern China (35)		Taiwan (36)*		Taiwan (37)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Asthma	1.63	1.1–2.4	1.8	0.8–4.2								
Chronic bronchitis	1.50	1.0–2.3	0.8	0.4–1.7	1.2	0.8–1.7	1.4†	1.2–1.8	2.00	0.6–6.9	1.8	0.7–4.8
Emphysema	2.86	1.1–7.6	1.5	0.4–5.2	2.0	1.0–3.7	1.4†	1.2–1.8				
Pleurisy	1.20	0.8–1.8	1.6	0.9–2.8								
Pneumonia	1.39	1.0–1.9	1.6	1.0–2.4	1.9	1.2–3.0	2.1	1.3–3.3				
Tuberculosis	1.69	0.9–3.1	2.8	0.9–8.7	1.7	1.1–2.4	1.3	0.9–1.7	2.33	0.8–6.9	4.7	1.5–14.7
Any preexisting lung disease	1.49	1.2–1.9	1.4	1.0–2.1								

* Results are shown for adenocarcinoma of the lung.
† Includes chronic bronchitis and/or emphysema.

cers. These data suggest that certain steroids may play a role in the natural history of some types of lung cancer.

Third, there is an increased risk of lung cancer among female survivors of a primary cancer of the reproductive organs. Studies from the United States (40, 41) and Denmark (42) show a 20–40 percent increased risk of lung cancer following a primary breast cancer and a 30–90 percent increased risk following a primary genital cancer (i.e., cervix, corpus, ovary). In one of the few studies conducted among nonsmokers, Kabat (43) studied 31 adenocarcinoma cases and found a fourfold increase (95 percent CI 0.9–17.6) in risk among women who had been previously diagnosed with a reproductive cancer. This risk was reduced to 1.9 (95 percent CI 0.3–11.2) after adjustment for history of radiotherapy.

Fourth, a small body of evidence has shown an association of short menstrual cycle and late age at menopause with lung cancer. Data from Shanghai suggest an elevated risk of adenocarcinoma (OR = 2.9; 95 percent CI 1.5–5.7) associated with a short menstrual cycle (<26 days compared with >33 days) (4). A strong dose-response effect was shown across quartiles of the length of the menstrual cycle. In addition, a slight elevation in risk of adenocarcinoma was shown for women whose natural menopause occurred at age 50 years or later (OR = 1.3; 95 percent CI 0.9–1.7).

Family history of cancer and genetics

There is a vast literature on somatic and inherited genetic variants in lung cancer, but studies that specifically focus on nonsmokers have been limited. At least four recent developments have begun to alter this emphasis. The first is the realization that in spite of the clear environmental component in lung cancer etiology, known lung cancer risk factors (e.g., cigarette smoking, occupational exposures, preexisting lung disease) do not entirely explain individual susceptibility. The determinants of susceptibility are especially puzzling in the subset of lung cancer that occurs in nonsmokers. The second point is, that given the universal finding of somatic genetic alterations in lung cancer, an understanding of precisely how environmental and genetic factors act to initiate and promote pulmonary carcinogenesis is a central issue. Consistent with an interplay of genes and environment, it is expected that in nonsmokers with lung cancer the genetic component might be especially prominent and, therefore, easier to detect. Third, the advances in molecular biology have rendered testing for the effects and quantitating the influences of these genes feasible. Finally, neither early detection nor treatment of lung cancer has proven to be particularly efficacious in showing large reductions in lung cancer mortality. Through genetic studies, a mechanistic understanding may be achieved that will lead to new prevention or treatment modalities.

Review of epidemiologic studies. Studies over 3 decades ago demonstrated familial clustering of lung cancer (44, 45). Since these early reports, several additional studies (primarily among smokers) have shown a smoking-adjusted two- to fourfold increased risk of lung cancer associated with a family history of cancer (primarily lung cancer). We briefly discuss seven relevant studies that present data among nonsmokers.

In a study of 57 nonsmoking cases and 297 nonsmoking controls (both genders), a study from the Texas Gulf Coast region examined lung cancer risk among individuals with a previous cancer in first-degree relatives (46). The risk of lung cancer associated with any cancer in relatives was 1.2 (95 percent CI 0.7–2.1). Having a first-degree relative with lung cancer did not increase the risk of lung cancer among nonsmoking cases (OR = 1.1; 95 percent CI 0.4–3.2).

Osann (47) reported on women who had previously received a multiphasic health checkup at Northern California Kaiser Permanente Hospitals. The nonsmoking portion of the study included 33 cases and 109 controls. No increased risk was found among nonsmokers due to family history of lung cancer, although numbers were small. Among Kreyberg II cancers, slight, nonsignificant lung cancer risks (adjusted for education and smoking) were noted for a family history of lung cancer (OR = 1.4; 95 percent CI 0.3–6.1) and a family history of any cancer (OR = 1.7; 95 percent CI 0.7–4.0).

In the largest case-control study of family history and nonsmoking lung cancer reported to date, Wu et al. (48) found a prevalence of any family history of lung cancer of 8.9 percent in female cases and 6.6 percent in population-based controls. The environmental tobacco smoke-adjusted odds ratio for any family history of lung cancer was 1.29 (95 percent CI 0.88–1.90). A statistically significant risk estimate was noted for history of lung cancer in sisters (OR = 2.78; 95 percent CI 1.0–7.4). When analyses were restricted to adenocarcinoma of the lung, the environmental tobacco smoke-adjusted risk associated with any family history of lung cancer was 1.50 (95 percent CI 1.0–2.2). There was no association between family history of other cancers and lung cancer risk in nonsmokers.

A population-based case-control study from Detroit, Michigan, found that lung cancer in a first-degree relative was associated with increased risk of lung

cancer in nonsmokers in the 40–59 year age group (OR = 6.1; 95 percent CI 1.1–33.4) (49). A positive family history of lung cancer did not increase risk among nonsmokers aged 60–84 years. For the entire group of cases and controls, the risk associated with family history of lung cancer in first-degree relatives was 1.4 (95 percent CI 0.8–2.5).

A case-control study from Missouri involved 432 female cases and 1,168 controls who were lifetime nonsmokers (50). This study found an elevated risk associated with five or more first-degree relatives having cancer (OR = 2.6; 95 percent CI 1.1–6.2). Risk was not increased due to four or fewer first-degree relatives with cancer. This relation changed only slightly after adjustment for potential confounders such as environmental tobacco smoke exposure, household radon exposure, saturated fat intake, occupational exposures, and preexisting lung disease. A history of lung cancer among first-degree relatives was not associated with lung cancer risk in nonsmokers.

Liu et al. (51) conducted a case-control study that included 54 nonsmoking female cases and 202 population-based controls from Xuanwei, China. They found that a family history of lung cancer was associated with an increased risk of lung cancer (OR = 4.18; 95 percent CI 1.61–10.85).

Yang et al. (52) have also specifically addressed the issue of genetic predisposition in nonsmokers. They identified cases from the Metropolitan Detroit Cancer Surveillance System, and obtained information (i.e., lung cancer occurrence, active smoking, environmental tobacco smoke exposure, chronic respiratory diseases in first-degree relatives) on 257 nonsmoking lung cancer probands. They performed complex segregation analysis to evaluate the role of a putative mendelian gene in smoking and nonsmoking relatives. While a role for a specific gene was not found, they determined that 0.04 percent population had a very high risk and 4.2 percent had a moderate risk of lung cancer, suggesting that virtually all the risk for lung cancer in nonsmokers would be contained in these two groups. Such a finding is consistent with a role for as yet unidentified environmental or genetic factors.

Possible genetic mechanisms. Common polymorphisms of carcinogen activating or deactivating genes have been studied in relation to lung cancer. These genes include *GSTM1* (glutathione-S-transferase), an enzyme that detoxifies carcinogenic epoxides. This enzyme is absent in 50 percent of the population, and a recent meta-analysis including 12 published studies found a consistent odds ratio of 1.4 in that segment of the population that was deficient (53). *CYP2D6* is an enzyme important in drug metabolism, and possibly the metabolism of nicotine or nitrosamines. The *CYP2D6* genotype and phenotype exhibit a tight correspondence with regard to identifying poor (deficient) metabolizers, a group hypothesized to be at lower risk of smoking-related cancer (54). It is deficient in about 7 percent of European populations, and these subjects have been postulated to be at lower risk of tobacco-related cancer. There is heterogeneity among the 15 or so published studies, with a suggestion that poor metabolizers are at slightly reduced risk. Polymorphisms of *CYP2E1*, an alcohol inducible enzyme that activated nitrosamines (55), and *CYP1A1*, an enzyme that activates polycyclic aromatic hydrocarbons, have also been studied with mixed findings. Since, for these low penetrance genes with metabolic effects, the action of the environmental component (i.e., the "external" carcinogen) is implicit, a better understanding of how genetic risk varies with the level of exposure is of great interest. Studies to date have generally been of insufficient size or failed to gather the detailed data necessary to resolve this question.

Studies of other "phenotypes" related to nutrient metabolism (56) or DNA repair may be especially plausible to consider in nonsmokers. There are some data that suggests *CYP1A1* and *NAT2* are more important in light smokers (57) while *CYP2D6* is more important in heavy smokers (58, 59). There are no data in nonsmokers, but it will be of great interest to see which factor predominates in these subjects. It can be argued that in nonsmokers who lack tobacco exposure, genes that act by activating or eliminating carcinogens are irrelevant. However, it is possible that such genes become progressively more important at lower doses, and, thus, genetic risk in these individuals might be greatest.

Ionizing radiation

Medical radiation. Although several studies are suggestive of elevated lung cancer risk due to medical exposure to radiation, there remains uncertainty about the strength and consistency of these associations and the interaction with smoking (60). In one of the few studies of lifetime nonsmokers and medical radiation, Kabat (43) found no evidence of a relation between history of radiotherapy and lung cancer risk in males. However, among females, a statistically significant increase in risk (OR = 4.4; 95 percent CI 1.3–15.1) was noted between history of radiotherapy and lung cancer. This risk decreased to 2.2 (95 percent CI 0.5–9.2) after adjustment for history of a previous reproductive cancer.

Radon gas in the home. Radon is a naturally-occurring environmental contaminant that is ubiquitous. Its decay leads to a series of short-lived, radioactive-progeny—polonium-214, polonium-218, bismuth-214, and

lead-214. Radon decays with a half-life of 3.82 days, and two of the decay products of radon, polonium-214 and polonium-218, emit α-particles. It may accumulate at extremely high levels in underground passages and mines (e.g., uranium mines) (61).

Underground miners, particularly uranium and tin miners, are potentially exposed to high levels of radon and its progeny. A causal relation has been clearly demonstrated between underground miners' exposure to radon and lung cancer occurrence (62). Radon in underground mines can reach high levels, with some cohorts receiving as much as 8,000 to 10,000 working-level months (63). For comparison, lifetime exposure in a typical US home results in 10–20 working-level months.

There are eight major studies that have investigated the relation between residential radon exposure and lung cancer. These studies contained 200 or more cases and conducted long-term radon dosimetry. Of these studies, five are shown in table 3 that provide risk estimates for nonsmokers (64–68). A fairly wide range of radon concentrations has been observed in the five studies, with the lowest readings in New Jersey (median = 0.6 pCi per liter) (64) and the highest readings in Stockholm, Sweden (mean = 3.5 pCi per liter) (66). However, comparisons in readings are problematic because the Swedish studies used winter dosimetry, and all other studies used year-long readings.

Studies conducted exclusively among nonsmokers provide inconsistent evidence of a relation between residential radon and lung cancer. Two studies are presented from the United States. In a case-control study among New Jersey women (64), smoking-adjusted elevated risk (OR = 4.2; 95 percent CI 0.99–17.5) was observed for exposure to radon concentrations of ≥4 pCi per liter, yet no trend in risk was noted for nonsmokers. Only 1 percent of study subjects had radon concentrations ≥4 pCi per liter. No clear pattern of risk by histologic subtype was observed. In a large case-control study of Missouri nonsmokers (67), the age-adjusted odds ratios for five time-weighted average levels of radon concentration were 1.00, 1.0 (95 percent CI 0.7–1.4), 0.8 (95 percent CI 0.6–1.2), 0.9 (95 percent CI 0.6–1.3), and 1.2 (95 percent CI 0.9–1.7), indicating no positive trend in risk. The highest category of radon exposure was 2.5–15.3 pCi per liter. Similar patterns in risk were observed when a cumulative measure of dose was used. Additional adjustment for potential confounders such as education, active smoking, passive smoking, previous lung disease, and saturated fat consumption had little effect on risk estimates.

Two case-control studies of residential radon and lung cancer have been reported from Sweden (66, 68). In a study from Stockholm (66), lung cancer risk tended to increase with increasing radon exposure. A relative risk estimate of 1.7 was observed for radon concentrations above 4 pCi per liter. Increasing trends in risk were noted for both never smokers and current smokers. In a second Swedish study (68), a significant positive trend in risk was observed, with a risk estimate of 1.8 at an average radon concentration of over

TABLE 3. Summary of case-control studies of residential radon exposure and lung cancer in nonsmokers with longterm α-track dosimetry

Study and year (reference no.)	Location	Population*	Radon dosimetry	Confounders examined	Summary of major findings
Schoenberg et al., 1990 (64)	New Jersey	Females: 61 cases, 213 controls	1-year α track; median of 21 years covered; 1% >4 pCi/liter	Age, respondent type, race, education, county of residence, vegetable intake, occupation	No trend for nonsmokers
Blot et al., 1990 (65)	Shenyang, China	Females: 123 cases, 225 controls	1-year α track; median of 24 years in last home; 20% >4 pCi/liter	Age, education, indoor air pollution	OR = 0.6 at ≥8 pCi/liter; no significant trends in nonsmokers
Pershagen et al., 1992 (66)	Stockholm, Sweden	Females: 38 cases, 184 controls	1-year α track; mean of 26 years covered; 28% >4.1 pCi/liter	Age, municipality of residence	OR = 3.2 for cumulative exposure ≥5,001 Bq/m^3; p = 0.04 for trend
Alavanja et al., 1994 (67)	Missouri	Females: 377 cases, 983 controls	1-year α track; median of 20 years covered; 7% >4 pCi/liter	Age, passive smoking, lung disease, diet, occupation	OR = 1.2 at ≥2.5 pCi/liter; no significant trend; slight trend for adenocarcinomas
Pershagen et al., 1994 (68)	Sweden	Both sexes; 178 cases, 1,164 controls	3-month α track during heating season; mean of 23 years covered; 20% >3.8 pCi/liter	Age, sex, urbanization, occupation	OR = 1.2 at >10.8 pCi/liter; p = 0.07 for trend

* Number of lifetime nonsmokers.

10.8 pCi per liter.

In a study from Shenyang, China, 20 percent of the homes measured had radon concentrations greater than 4 pCi per liter (65). No association between radon and lung cancer was observed, regardless of smoking status.

Recently, Lubin and Boice (69) conducted a meta-analysis of the eight published studies of radon and lung cancer. The effect estimate at 150 Bq per cubic meter (4.05 pCi per liter) for the five studies shown in table 3 was 1.24 (95 percent CI 1.0–1.5). The recent report of the Sixth Committee on the Biological Effects of Ionizing Radiations (BEIR VI) (62) used two models (exposure-age-concentration and exposure-age-duration) to estimate 1993 lung cancer deaths due to indoor radon. Total lung cancer deaths due to radon were estimated at 15,400 and 21,800 for age-concentration and age-duration models, respectively; deaths among nonsmokers were estimated at 2,900 and 2,100 (62).

There are several key methodological issues that have emerged from studies of residential radon and lung cancer. Of primary interest is the difficulty in accurate exposure assessment. Studies of radon and lung cancer seek to determine exposures as far back as 50 years. The mobility of the population makes such determination difficult. In addition, modifications to residences, such as remodeling or "tightening," may influence measurements, as noted in table 4 (70). Several studies have had relatively few subjects with high radon measurements, which increases the likelihood of type II error. There have also been small numbers of nonsmoking cases and insufficient data to control for numerous potential confounders.

Environmental tobacco smoke

Among potential risk factors for lung cancer among nonsmokers, environmental tobacco smoke is the most widely studied. The most comprehensive reviews of the health consequences of environmental tobacco smoke to date are the 1992 report of the US Environmental Protection Agency (71) and the recent risk assessment of the California Environmental Protection Agency (72). These reports follow two earlier reviews by the US Surgeon General (73) and the National Academy of Sciences (74). The current review focuses on the major studies of environmental tobacco smoke and lung cancer that have been deemed of the highest quality by the US Environmental Protection Agency review (71) and a subsequent review (75).

TABLE 4. Radon concentration (pCi/liter) for dwellings classified by insulation type*

Type of insulation	No. of dwellings	Arithmetic mean
Wall insulation	2,010	1.9
No wall insulation	652	1.5
Attic/ceiling insulation	2,451	1.9
No attic/ceiling insulation	319	1.5
Storm doors	2,595	1.8
No storm doors	344	1.4
Storm windows	2,674	1.8
No storm windows	269	1.4
Weather stripping/caulking	2,187	1.8
No weather stripping/caulking	571	1.6

* Source: Reprinted from Steenland and Savitz (70) with permission from the publisher.

Chemical composition of environmental tobacco smoke. Environmental tobacco smoke is composed of sidestream smoke, emitted by the burning tip of a cigarette, and mainstream smoke, which is inhaled by and then exhaled from the smoker. Sidestream smoke is the major component of environmental tobacco smoke, contributing nearly all of the vapor phase and over half of the particulate matter (71). A nonsmoker is typically exposed to less tobacco smoke than an active smoker, primarily because of dilution by room air. However, different toxic compounds and combustion products vary in their relative concentrations in mainstream and sidestream smoke (76). For example, twice as much nicotine is emitted in sidestream as in mainstream smoke yet the carcinogen 4-aminobiphenyl is enriched about 30-fold in sidestream smoke (76). Environmental tobacco smoke is a complex mixture of nearly 5,000 chemical compounds (77). This mixture contains 43 chemicals that have met the criteria of a known human or animal carcinogen established by the International Agency for Research on Cancer (78). Among the common carcinogens in environmental tobacco smoke are arsenic, cadmium, benz-pyrenes, nitrosamines, and vinyl chloride (78, 79).

Nonsmokers' exposure to environmental tobacco smoke. Relatively few data are available on the prevalence of nonsmokers' exposure to environmental tobacco smoke on a population basis. Based on the 1988 National Health Interview Survey, an estimated 36.5 percent of the 79.2 million US nonsmokers worked in places that permitted smoking in designated and other areas (80). Other US data showed that 37 percent of adult non-tobacco users lived in a home with at least one smoker or reported environmental tobacco smoke exposure at work (81). Among non-tobacco users, 88 percent had detectable serum cotinine levels, indicating widespread exposure to environmental tobacco smoke in the US population (81). Experimental evidence has shown the presence of a tobacco-specific lung carcinogen in the urine of nonsmokers exposed to environmental tobacco smoke (82).

Review of epidemiologic studies. Presently, there

are approximately 35 studies on the relation between environmental tobacco smoke exposure and lung cancer in nonsmokers. Most of these studies used case-control methods and were conducted among females. In its analysis of 31 studies, the US Environmental Protection Agency categorized each study in one of four tiers, based on quality scores in eight areas: never-smoker status, environmental tobacco smoke exposure criteria, lung cancer indication, interview type, proxy respondents, follow-up, design issues, and analysis issues (71). The studies presented in table 5 are those rated in the top two tiers by the Environmental Protection Agency (11, 83–100) and six additional studies (101–106) published after the Environmental

TABLE 5. Summary of selected* studies of the effects of environmental tobacco smoke and lung cancer in nonsmokers

Study and year (reference no.)	Location	Type of study (sample size)†	No. of cases	No. of controls	Size of cohort	Summary of major findings
Correa et al., 1983 (83)	Louisiana	Case-control	22	33		Spousal exposure, (RR§ = 2.07; exposure ≥41 pack-years, RR = 3.2
Hirayama, 1984 (84)	Japan	Cohort			91,540	Spousal exposure, RR = 1.6; exposure ≥20 cigarettes/day, RR = 1.9
Kabat and Wynder, 1984 (11)	New York	Case-control	24	25		Spousal exposure, RR = 0.8
Wu, et al., 1985 (85)	Los Angeles, CA	Case-control	29	62		Exposure ≥31 years, RR = 1.9
Garfinkel et al., 1985 (86)	New Jersey; Ohio	Case-control	134	402		Spousal exposure, RR = 1.7; exposure ≥20 cigarettes/day, RR = 2.1
Akiba et al., 1986 (87)	Hiroshima, Japan	Case-control	94	270		Spousal exposure, RR = 1.5; exposure ≥30 cigarettes/day, RR = 2 1
Lee, et al., 1986 (88)	England	Case-control	32	66		Spousal exposure, RR = 0.8
Humble et al., 1987 (89)	New Mexico	Case-control	20	162		Spousal exposure, RR = 2.2; exposure ≥21 cigarettes/day, RR = 1.1
Koo et al., 1987 (90)	Hong Kong	Case-control	86	136		Spousal exposure, RR = 1.6; exposure ≥21 cigarettes/day, RR = 1.2
Lam et al., 1987 (91)	Hong Kong	Case-control	199	335		Spousal exposure, RR = 1.7; exposure ≥21 cigarettes/day, RR = 2.1
Pershagen et al., 1987 (92)	Sweden	Case-control	67	?		Spousal exposure, RR = 1.2; exposure >16 cigarettes/day, RR = 3.1
Butler, 1988 (93)	California	Cohort			9,207	Spousal exposure, RR = 2.0
Shimizu et al., 1988 (94)	Nagoya, Japan	Case-control	90	163		Spousal exposure, RR = 1.1
Hole et al., 1989 (95)	Paisley Renfrow, Scotland	Cohort			1,784	Spousal exposure, RR = 2.4
Svenson et al., 1989 (96)	Stockholm, Sweden	Case-control	34	174		Spousal exposure, RR = 1.3
Janerich et al., 1990 (97)	New York	Case-control	191	191		Spousal exposure, RR = 0.8; exposure ≥50 pack-years, RR = 1.0
Kalandidi et al., 1990 (98)	Athens, Greece	Case-control	91	120		Spousal exposure, RR = 1.9; exposure ≥41 cigarettes/day, RR = 1.6
Sobue, 1990 (99)	Osaka, Japan	Case-control	144	731		Spousal exposure, RR = 1.1
Fontham et al., 1991 (100)	Five metro areas, United States	Case-control	420	780		Spousal exposure, RR = 1.3; exposure ≥80 pack-years, RR = 1.3
Brownson et al., 1992 (101)	Missouri	Case-control	618	402		Spousal exposure, RR = 1.1; exposure ≥40 pack-years, RR = 1.3
Stockwell et al., 1992 (102)	Florida	Case-control	210	301		Spousal exposure, RR = 1.6; exposure ≥40 pack-years, RR = 2.4
Liu et al., 1993 (103)	Guangzhou, China	Case-control	38	69		Exposure ≥20 cigarettes/day, RR = 2.9
Kabat et al., 1995 (104)	Four metro areas, United States	Case-control	110	304		Spousal exposure in males, RR = 1.6; in females, RR = 1.1; exposure ≥11 cigarettes/day in males, RR = 7.5; in females, RR = 1.1
Cardenas et al., 1997 (105)	United States	Cohort			133,835	Spousal exposure in males, RR = 1.1; in females, RR = 1.2; exposure ≥40 cigarettes/day in females, RR = 1.9
Nyberg et al., 1998 (106)	Stockholm, Sweden	Case-control	124	235		Spousal exposure, RR = 1.2; exposure at work, RR = 1.6; spousal and work exposure, RR = 2.5

* Studies presented are "tier 1 and tier 2" studies from the report of the US Environmental protection Agency (73) and six additional studies (101–106) published after the Environmental Protection Agency report that are likely tier 1 or tier 2.

† Limited to nonsmokers; for case-control studies (no. of cases: no. of controls); for cohort studies (size of cohort).

‡ Adjusted risk estimates are presented when available; spousal exposure refers dichotomous exposure classification, i.e., the presence or absence of a smoking spouse; data for highest exposure category adjusted for smoker misclassification when possible (71).

§ RR, relative risk.

Protection Agency report that are likely to be in the highest tiers. All of the studies in table 5 included information on environmental tobacco smoke exposure in the home environment during adulthood; fewer included home exposure during childhood or workplace exposure. Commonly, the husband's smoking status has been the exposure surrogate.

In its 1992 meta-analysis, the US Environmental Protection Agency estimated summary relative risks associated with environmental tobacco smoke exposure from the spouse by country. Pooled and adjusted relative risk (RR) estimates by country for studies in the top two quality tiers were: Greece (one study) (RR = 1.92; 90 percent CI 1.13–3.23), Hong Kong (two studies) (RR = 1.61; 90 percent CI 1.25–2.07), Japan (four studies) (RR = 1.39; 90 percent CI 1.39; 90 percent CI 1.16–1.66), United States (eight studies) (RR = 1.22; 90 percent CI 1.04–1.42), and Western Europe (four studies) (RR = 1.17; 90 percent CI 0.85–1.64) (71). The Environmental Protection Agency concluded that environmental tobacco smoke is a human lung carcinogen in adults, accounting for approximately 3,000 US lung cancer deaths in adult nonsmokers annually. The most recent meta-analysis of existing studies showed a statistically significant excess risk of 24 percent among nonsmokers who lived with a smoker (107). The conclusion that environmental tobacco smoke is a human lung carcinogen is based on the total weight of evidence (108) including: 1) evidence summarized in table 5 from dozens of epidemiologic studies conducted in eight different countries; 2) the well-established link between active smoking and lung cancer, and the absence of a threshold level of exposure below which the risk is not elevated; 3) biologic measurements of uptake and metabolism of environmental tobacco smoke by nonsmokers (82, 109); and 4) supporting evidence of the carcinogenicity of environmental tobacco smoke from animal bioassays and genotoxicity. Of note, environmental tobacco smoke is the only agent ever classified by the US Environmental Protection Agency as a known human carcinogen for which an increased risk has actually been observed at typical environmental levels of exposure. Because exposure to environmental tobacco smoke is so widespread, it is difficult to identify a truly "unexposed" reference group, which may bias effect estimates toward the null (74).

Potential for publication bias, confounding, and errors in exposure assessment. Studies of environmental tobacco smoke and lung cancer are potentially subject to several important sources of bias and confounding (110).

First, *publication bias* may be present if there is a systematic tendency to publish studies with positive findings. If null studies are not published, meta-analyses may be invalid. Research by Vandenbroucke (111), Wells (112), Bero et al. (113), and Kawachi and Colditz (110) suggests publication bias is unlikely to explain the predominance of positive studies linking environmental tobacco smoke and lung cancer. Several lines of evidence support this conclusion: 1) there appears that there are few unpublished studies of environmental tobacco smoke and lung cancer (113); 2) some of the unpublished data may actually increase risk estimates (112); and 3) some recently published studies (101, 104) have not shown elevated risk for ever versus never spousal exposure to environmental tobacco smoke.

Since the etiology of lung cancer in nonsmokers is likely to comprise a number of weak risk factors, potential *confounding* of the association between environmental tobacco smoke and lung cancer may occur. For example, it is documented that nonsmokers living with smokers have lower intakes of certain micronutrients (114). Sidney et al. (115) and Le Marchand et al. (116) estimated that the effect estimate for environmental tobacco smoke and lung cancer would decrease from 2.0 to 1.8 after adjustment for β-carotene intake. Several of the recently published studies have addressed the issue of confounding more directly (27, 100, 101, 104). For example, Fontham et al. (27) conducted the largest and most comprehensive study to date and adjusted for age, race, study area, education, fruits, vegetables, supplemental vitamin index, dietary cholesterol, family history of lung cancer, and employment in high-risk occupations. After multivariate adjustment, an increasing risk of lung cancer in nonsmoking women was observed with increasing duration of exposure (27).

Accurate *exposure assessment* in epidemiologic studies of environmental tobacco smoke and lung cancer is challenging. Misclassification is possible primarily based on whether 1) cases and controls are accurately classified as nonsmokers and 2) epidemiologic instruments can accurately classify environmental tobacco smoke exposure.

In relation to the accurate categorization of active smoking status, two earlier studies provide comprehensive data on the extent of misclassification. Fontham et al. (27) compared urine cotinine/creatinine values and questionnaire-reported smoking status for 356 cases and 665 controls. Only two cases (0.6 percent) and 25 controls (2.3 percent) had cotinine/creatinine values above 100 ng per milligram (the level commonly used to designate active smoking status). In a 10-country study (117), urine cotinine data were available for 1,369 women who were designated as nonsmokers by questionnaire. Only 26 women had cotinine values above 100 ng per milligram (1.9 percent). These data suggest that questionnaires provide

accurate assessment of active smoking status. Similarly, Nyberg et al. (118) studied discordance in smoking status among two Swedish cohorts and found misclassification occurred mainly in light smokers or long-term ex-smokers and was unlikely to substantially confound the environmental tobacco smoke-lung cancer association.

Perhaps a more challenging issue is the assessment of environmental tobacco smoke exposure in case-control and cohort studies. Because there is not a valid and reliable long-term biologic marker of environmental tobacco smoke exposure, etiologic studies have relied primarily on questionnaire assessment. Methodological studies of the accuracy of environmental tobacco smoke exposure assessment have been primarily focused in three areas: 1) validation studies comparing cotinine concentrations to current environmental tobacco smoke exposure, 2) test-retest studies among cases and controls, and 3) studies of the accuracy of spousal smoking histories.

To assess validity, the National Research Council (74) has established four criteria for a valid marker of environmental tobacco smoke. The marker should: 1) be unique or nearly unique for environmental tobacco smoke, 2) be easily detectable at low smoking rates, 3) be emitted at similar rates for a variety of tobacco products, 4) have a fairly constant ratio to other environmental tobacco smoke components of interest (e.g., suspended particulates). Recently, Benowitz (119) reviewed the literature on environmental tobacco smoke markers and concluded that cotinine is presently the best available biomarker for environmental tobacco smoke in epidemiologic studies. However, because the half-life for cotinine is about 17 hours, it does not provide a valid marker for past environmental tobacco smoke exposure. Therefore, unless a prospective study of environmental tobacco smoke exposure and lung cancer in nonsmokers is being conducted, there is presently no valid and reliable biomarker for historical environmental tobacco smoke exposure.

The reliability of environmental tobacco smoke instruments has been reported in several studies. In a test-retest study from Missouri, 110 cases and controls were reinterviewed (120). Agreement between the first and second interviews was high both for parental smoking status (94 percent concordance; $\kappa = 0.82$) and for spousal smoking status (84 percent concordance; $\kappa = 0.67$). Concordance also was relatively high for cigarette pack-years of exposure due to the parents or spouse. Two other studies are important in this area. In a Canadian study of 117 control subjects, Pron et al. (121) found relatively high agreement for residential (concordance = 88 percent; $\kappa = 0.66$) and occupational (concordance = 73 percent; $\kappa = 0.46$) environmental tobacco smoke exposure. Coultas et al. (122) assessed reliability of passive smoking histories for 149 adult nonsmokers and found concordance values for maternal and paternal smoking status during childhood of 94 and 93 percent, respectively.

Previous studies have assessed the validity of spousal smoking histories provided by cases and controls by comparing these with data from interviews with the spouses themselves (123–125). These studies showed high concordance on spousal ever smoking and lower agreement rates for duration or intensity of smoking. Since the vast majority of environmental tobacco smoke exposure among women aged 40 years and older is due to the spouse (126), these interviews help validate the active smoking and environmental tobacco smoke exposure histories self-reported by cases and controls.

Other forms of air pollution

Outdoor air pollution. Since the mid 1950s, there have been suggestions in the literature that ambient air pollution may be linked with lung cancer incidence (127). These early associations between air pollution and lung cancer were based on statistical associations among urban and rural residents, migrant studies, and studies of occupational groups exposed to by-products of fossil fuel combustion (128). The summary of studies from numerous countries suggests that after adjustment for smoking, urban areas have an approximate 1.5-fold elevation in lung cancer risk compared with rural areas (129). The polycyclic hydrocarbon, benzo-α-pyrene, has received the most attention as the potential etiologic agent in outdoor air pollution. There are few well-designed studies that have evaluated the risk between outdoor air pollution and lung cancer, controlling for cigarette smoking and other potential confounders.

In a study of mortality in six US cities, Dockery et al. (130) found a smoking-adjusted lung cancer risk of 1.37 (95 percent CI 0.81–2.31) in the most polluted city versus the least polluted city (indicated by the level of fine particulates). Katsouyanni et al. (131) reported on a case-control study ($n = 101$ cases and 89 controls) among women in Athens, Greece. Based on lifetime residential and employment addresses, exposure was estimated as mean yearly measurements of smoke and NO_2 (used as surrogates for dust, particulate matter, and polycyclic hydrocarbons). Comparing the highest quartile of air pollution exposure with the lowest quartile, a relative risk estimate of 0.81 was noted among nonsmokers. No significant linear trend in nonsmoking lung cancer risk according to air pollution was observed ($p = 0.20$).

Indoor air pollution. Several studies, particularly

research from China and Taiwan, have identified elevated lung cancer risks in nonsmoking women in relation to various cooking practices and heating devices. In Shanghai, elevated risk of lung cancer among nonsmokers has been associated with prolonged exposure to oil vapors, in particular vapor from unrefined rapeseed oil resulting from high temperature wok cooking (4). Case-control data from northern China (35) showed elevated risks due to a variety of cooking and heating (e.g., burning Kang) devices and practices. For example, 21 or more years of use of the burning Kang was associated with a 1.5-fold increase in risk (95 percent CI 1.1–2.0). Cases were also more likely to report that their homes became smokey during cooking and were more likely to develop eye irritation during cooking. Among nonsmoking women in Taiwan, lung cancer was associated with certain cooking practices, including an eightfold risk due to preparing meals without a fume extractor at cooking age 20–40 years (37). In Los Angeles, Wu et al. (85) reported an odds ratio of 3.2 (95 percent CI 0.9–11.8) associated with coal burning during the childhood and teenage years for nonsmoking women.

Occupational exposures

Several occupational exposures are well established as lung carcinogens, including arsenic, asbestos, beryllium, bis(chloromethyl)ether, cadmium, chromium, coal tar pitch, and products resulting from coal carbonization (132). These relations have been established almost exclusively among men and smokers. Over the past several years, a small body of evidence is developing on the carcinogenicity of certain occupational exposures and pursuits for lung cancer in nonsmokers.

In a study using occupational data collected during cancer reporting in Illinois, Keller and Howe (133) used case-control methods to describe occupational risks of lung cancer among nonsmokers (n = 903). Colon cancer cases comprised the control group (n = 3,226) and occupational information was extracted from the medical record. Among current occupational categories, elevated risks were noted for white males employed in bus service and urban transit (OR = 2.64; 95 percent CI 1.01–6.89); construction (OR = 1.27; 95 percent CI 1.00–2.60); and general government (OR = 2.19; 95 percent CI 1.10–4.36). Among white females, the only elevated risk for current employment was for working in eating and drinking establishments (OR = 1.92; 95 percent CI 1.21–3.07). Although there was commonly ≥50 percent missing data for longest lifetime occupation, statistically significant increases in risk were shown for white males employed in trucking services; blast furnaces, steelworks, and rolling and filling mills; and construction. Only the longest lifetime occupation of registered nurses showed elevated risk among women. The two main limitations of this study are the reliance on routinely collected data on broad occupational categories with considerable missing data and the lack of information on potential confounders such as environmental tobacco smoke or preexisting lung disease.

A case-control study of 294 lifetime nonsmoking cases from Missouri showed elevated lung cancer risks associated with employment in the dry cleaning industry (OR = 2.1; 95 percent CI 1.2–3.7) (134). In addition, occupational exposure to pesticides (OR = 3.1; 95 percent CI 1.3–7.5) was shown to increase lung cancer risk. Another recent case-control study showed a nonsignificant association between self-reported asbestos exposure and lung cancer in nonsmokers (OR = 2.0; 95 percent CI 0.9–4.6) (135).

In Taiwan, case-control analyses restricted to adenocarcinoma were suggestive of elevated risk for three job categories: those with asbestos exposure (OR = 4.33; 95 percent CI 0.82–22.82), those in the textile industry (OR = 3.00; 95 percent CI 0.85–10.63), and cooks (OR = 5.54; 95 percent CI 1.49–20.65) (36). Studies among Chinese women have shown smoking-adjusted occupational risks for glass products workers (OR = 5.1; 95 percent CI 1.3–23.5) (134) and for metal surfacers (OR = 3.1; 95 percent CI 1.1–9.0) and foundry workers (OR = 13.0; 95 percent CI 1.7–99.4) (136, 137).

Nutrition and diet

Review of epidemiologic studies. Nearly 100 epidemiologic studies have investigated the relation between nutrition and lung cancer (138). These include observational studies (retrospective and prospective) examining consumption of fruits, vegetables, carotenoids, saturated fats, and micronutrients; prospective studies of blood micronutrients; and chemoprevention trials. After adjustment for smoking, observational studies strongly suggest that increased vegetable and fruit intake is associated with lower lung cancer risk in women and men (138). For particular micronutrients (e.g., β-carotene, vitamins E and C, selenium), the epidemiologic evidence is inconsistent. A small number of studies from the United States (139–142), Hong Kong (143), Shanghai (4), and Greece (98) have been conducted exclusively among nonsmokers or have sufficient samples to analyze data in strata of smoking status. These studies are briefly summarized.

A prospective study of California Seventh-day Adventists (139) examined dietary risk factors among 61 incident lung cancer cases (nonsmokers and smokers). Among lifetime nonsmokers, nonsignificantly de-

creased risks were noted for fruit consumption of 3–7 times per week (OR = 0.23) and of ≥2 times per day (OR = 0.28). A similar inverse trend in lung cancer risk according to level of fruit consumption was noted for Kreyberg type II cancers.

In a case-control study from central Florida (140), lung cancer risk among women who were lifetime nonsmokers was assessed for dietary factors collected by the Block food frequency questionnaire (144). After adjustment for age, education, and total calories, a strong protective effect was shown for vegetable consumption and intake of β-carotene. Individuals in the highest quartile of vegetable consumption showed the smallest effect estimate (OR = 0.2; 95 percent CI 0.1–0.5). Retinol intake was not associated with a decreased risk of lung cancer.

In a study of 429 cases and 1,021 controls in Missouri (lifetime nonsmokers and former smokers who had quit 15 or more years prior to the study), a strongly increasing trend in lung cancer risk was observed in relation to saturated fat consumption (141). The odds ratio at the highest quintile of saturated fat consumption was 6.14 (95 percent CI 2.63–14.40). The effect of saturated fat was more pronounced for adenocarcinoma than for other cell types. A recent reanalysis of the Missouri data showed that the method of energy adjustment had a large effect on effect estimates (145). As noted by Willett et al. (146), the method of energy adjustment is used primarily to control for confounding and reduce extraneous variation in intake of the dietary constituent of interest. In the reanalysis, the odds ratio at the highest quintile of saturated fat consumption was reduced from the original sixfold risk to an odds ratio of 1.78 based on nutrient residual adjustment and 2.38 based on multivariate nutrient density adjustment (145). However, the positive trend in saturated fat consumption and lung cancer remained statistically significant.

Mayne et al. (142) conducted a case-control study (n = 413 case-control pairs) in New York State. Researchers found that consumption of greens, fresh fruits, and cheese were each associated with a significant dose-response reduction in risk of lung cancer in nonsmokers. Whole milk consumption was associated with a significant increase in risk. Dietary β-carotene (OR = 0.70; 95 percent CI 0.50–0.99), but not retinol (OR = 0.98; 95 percent CI 0.82–1.17), appeared to decrease risk.

A prospective study from the United States of 3,968 men and 6,100 women examined trends in lung cancer risk among never and former smokers according to quartiles of vitamin E, carotenoids, vitamin C, and fruits and vegetables (147). No statistically significant trends in risk ($p < 0.05$) were shown for any of the four variables. Another prospective study of 9,959 Finnish men and women found an inverse relation between flavenoid intake (i.e., vitamins E and C, β-carotene) and lung cancer risk in nonsmokers (RR = 0.13; 95 percent CI 0.03–0.58 for the highest versus lowest quartiles of intake) (148).

A study of 88 nonsmoking women with lung cancer and 137 matched controls from Hong Kong found a protective effect of diet—i.e., consumption of leafy green vegetables, carrots, tofu, fresh fruit, and fresh fish—confined mainly to adenocarcinomas and/or large cell cancers (143). Case-control data from Shanghai, China, examined the relation between lung cancer and dietary indexes of vitamin A, retinol, and β-carotene (4). Risk tended to decrease according to higher consumption of vitamin A or β-carotene. No relation was shown between retinol consumption and lung cancer risk.

In a case-control study from Athens, Greece, involving 91 female nonsmoking cases and 120 controls, dietary data were collected with a semiquantitative food-frequency questionnaire (98). Consumption of fruits in the highest quartile was associated with a decreased risk of lung cancer (OR = 0.27; 95 percent CI 0.10–0.74). This pattern of risk was consistent across subgroups of histologic types.

Key methodological issues. Since methods relying on repeated short-term dietary recall or diet records are generally expensive to use in the context of epidemiologic studies and somewhat unrepresentative of usual intake and inappropriate for assessment of past diet, investigators frequently use the structured food frequency questionnaire. The underlying principle of the food-frequency approach is that diet over the course of years or decades is the biologically meaningful exposure that should be sought in epidemiologic investigations rather than merely the intake on a few specific days. Food frequency questionnaires usually consist of two components, a food list and a frequency response metric to report how often a particular food is eaten and how much of it is eaten at a typical meal (i.e., portion size). A nutrient database and analysis programs then make it possible to translate the responses on a food frequency questionnaire into measure of nutrient intake.

Developing a food list for use in an epidemiologic investigation is challenging because one often wants to accomplish two conflicting goals, namely, to comprehensively and reliably assess energy intake and macronutrient and micronutrient levels while keeping the questionnaire as short as possible. Various methods to develop valid food frequency questionnaires are summarized by Willett (149).

In most nutritional epidemiologic studies, disease

cannot be considered the primary effect of diet if the quantity of nutrients consumed is simply the result of differences in body size, physical activity, and metabolic efficiency. The objective of assessing the effect of nutrient intake on disease independent of the total caloric intake can be achieved if the effect of confounding and extraneous variation can be eliminated (146). The standard multivariate technique to adjust for potential confounding is depicted:

$$\text{Logit (disease} \mid \text{nutrient intake and total calories)} = \alpha \text{ (intercept)} + \beta_1 x_{1(\text{nutrient intake})} + \beta_2 x_{2 (\text{total calories})}$$

This technique has been found to exaggerate the relative risk of an association when the analysis is performed on categorical data. Two preferred techniques which perform better in simulations of categorical data are the nutrient residual approach and the nutrient density approach (150). Although years of discourse about energy adjustment have taken place, the rationale and the appropriate method of energy adjustment remain controversial (151, 152).

Assessing the effect of surrogate sources of information is another methodological issue of considerable importance to lung cancer etiology. The literature indicates that next-of-kin dietary information may introduce misclassification bias (153) and the extent of misclassification can vary based on the source of surrogate data (154, 155). These studies suggest that it is prudent to incorporate methodological components into the study to assess the effect of including next-of-kin interviews when there is doubt about the ability of a proxy to describe the diet of a study subject.

Pet birds

Five studies have examined whether keeping pet birds in the home is an independent risk factor for lung cancer (156–160). The earliest of these studies reported a 6.7-fold risk of lung cancer associated with bird keeping, after adjustment for smoking and vitamin C intake (156). More recent studies (159, 160) have shown no evidence of excess risk. These studies have included small numbers for nonsmokers, making risk estimates for nonsmoking lung cancer unstable. In one of the recent studies (159), the adjusted lung cancer risk among nonsmokers associated with bird keeping was 1.15 (95 percent CI 0.48–2.74).

IMPLICATIONS FOR PREVENTION EFFORTS

To help in determining priorities for prevention, the population attributable risk (PAR) is a useful measure of the public health burden of a risk factor. Summary PAR values for nonsmoking lung cancer among various populations are presented in table 6. Data for Missouri are presented from a summary paper of PAR values (161). For other studies, PAR values were calculated based on the raw data presented in the respective journal articles. A history of preexisting lung disease appears to have the consistently highest PAR value, ranging from 5.4 to 15.3 percent. Envi-

TABLE 6. Population attributable risk estimates (%) from selected studies of lung cancer in nonsmokers*

Risk factor	Study location (reference no.)				
	Multicenter, United States (27, 33, 48)	Multicenter, United States (38, 43, 104)	Missouri (161)	Shanghai, China (4)	Northern China (35)
Preexisting lung disease	15.3		10.7	20.3	5.4
Environmental tobacco smoke exposure from spouse (≥40 pack-years)	3.6	Women, 1.8† Men, 11.7†	7.6	12.4‡	0.0§
Domestic radon exposure			1.9		0.0§
Occupational exposure			5.5		
Use of rapeseed oil or deep frying ≥3 times per month				15.9	7.1
Cooking with burning Kang for 21 or more years					3.3
Family history of lung cancer	1.1				2.0
Family history of any cancer			0.4		
Total¶	20.0		26.1	48.6	17.8

* Data shown are for women unless otherwise noted.
† Exposed to ≥11 cigarettes per day from the spouse.
‡ Lived with a smoking husband for ≥40 years.
§ No increase in risk was noted.
¶ Total values should be viewed as approximations because they ignore the effects of interactions of risk factors.

ronmental tobacco smoke exposure from a spouse was also an important risk factor based on PAR values. PAR estimates based on environmental tobacco smoke exposure were calculated for the highest exposure group, since this is the dose range that has consistently shown increased risk (71).

AREAS OF FUTURE RESEARCH

Future research appears warranted in several areas.

Analysis of descriptive data from cancer registries

Cancer registries have grown in number, scope, and quality in recent years. In addition to the longstanding SEER Program discussed earlier, the Centers for Disease Control and Prevention now funds state health departments in all 50 states and the District of Columbia to enhance and expand registry coverage. There are increasing opportunities for analysis of the descriptive epidemiology of lung cancer as these registries are enhanced. Efforts to describe patterns in nonsmoking lung cancer may be especially appropriate among registries that collect smoking information on patients, although these may have difficulty in distinguishing between former and current smokers (20).

Studies in diverse populations

Most studies examining risk factors for lung cancer in nonsmokers have been conducted among women, primarily among Caucasian women in the United States and Chinese women. Further studies are needed among nonsmoking men and diverse racial/ethnic groups such as African Americans and Hispanics. Among women, a better understanding of the potential role of a composite of endocrine factors is also needed.

Closer examination of certain modifiable risk factors

Certain modifiable risk factors for nonsmoking lung cancer have not been fully characterized. For example, evidence is inconclusive on whether long-term, low-level exposure to radon gas in the home is a significant risk factor among nonsmokers. Pooling of existing data from large epidemiologic studies of radon and lung cancer may assist in this area. In addition, further studies of occupational risk factors for lung cancer are needed. These factors may become increasingly important as new potential risk factors (e.g., silica exposure (162)) emerge among studies conducted primarily in smokers and among more recent cohorts of US women with greater likelihood of occupational exposures outside the home. There is also a need for a better understanding of the role of dietary factors in the etiology of lung cancer in nonsmokers.

Advances in "molecular epidemiology"

As the linkage between methods in molecular biology and epidemiology grows stronger, several areas are particularly relevant to studies of lung cancer in nonsmokers.

General methodological advances. Technical advances (i.e., polymerase chain methods to assay nanogram quantities of DNA and noninvasive approaches to obtaining DNA) are rendering large genetic studies more feasible, and opportunities to integrate these markers into well-designed field studies should increase.

Exposure assessment. New methods of assessing low-level environmental and occupational exposures can be useful for future epidemiologic studies in complementing questionnaire data and in reducing misclassification. For example, a technique has been developed to measure cumulative levels of radon daughters that become firmly attached to glass surfaces in the home. This technique was first reported by Samuelsson (163) and others (164) and has been adapted for use in epidemiologic studies by Mahaffey et al. (165). There also may be intermediate markers of exposure for specific carcinogens (e.g., DNA adducts) that will assist in determining biologic mechanisms.

Genetic studies. In an earlier section, certain "susceptibility" genes were briefly discussed (e.g., *CYP2D6*, *CYP2E1*, *CYP1A1*). Verifying roles for these genes in the etiology of lung cancer in nonsmokers will require a better understanding of the potential linkages between low-level environmental exposure and gene activation. In addition, a variety of changes in somatic genes accompany morphologic tissue changes from dysplasia to in situ cancer. While there is an understanding of how smoking is related to such changes in the lung, there is little known about the somatic gene changes in the lung as nonsmoking lung cancer progresses.

CONCLUSIONS

Despite the thousands of studies of lung cancer, particularly those of active smoking, relatively few well-designed and comprehensive studies of nonsmoking lung cancer have been conducted. By examining the "total" PAR values in table 6 (range 14–49 percent), it is clear that the largest contributors to the etiology of lung cancer in nonsmokers have not been elucidated.

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