The Epidemiology of Lung Cancer*
Jonathan M. Samet, M.D.

Lung cancer rates and mortality have risen in epidemic proportions in the United States and other industrialized nations during the 20th century. Case-control and cohort studies performed in the 1950s and 1960s firmly established cigarette smoking as the single greatest risk factor for lung cancer. In the United States, overall lung cancer mortality rates in men and women rose progressively from the 1950s. Fortunately, lung cancer incidence and mortality are now declining in middle-aged men. Smoking has significantly increased lung cancer rates among women and is on the rise in developing countries. Environmental agents found in the home and workplace, including radon and asbestos, have also been shown to increase lung cancer risk in both smokers and nonsmokers. Government regulations have helped curtail quantities of these and other atmospheric carcinogens. Efforts to reduce lung cancer risk must be continued and their scope expanded in order to have a global impact on the incidence and mortality of this fatal malignancy. *(Chest 1993; 103:205-295)*

During the 20th century, the incidence of and mortality from lung cancer have risen in an epidemic pattern in the United States and other developed countries. Whereas lung cancer was a rare disease at the turn of the century, approximately 150,000 cases now occur annually in the United States. This increase was observed by physicians early in the century.1,2 In 1939, for example, Ochsner and DeBakey4 presented seven cases of primary pulmonary malignancy treated by pneumonectomy; they opined that the increase in lung cancer incidence was related to increasing smoking with consequent irritation of the bronchial mucosa.

Despite the growing number of lung cancer deaths, controversy as to the reality of the increase continued through the mid-20th century;8 explanations for a possibly artifactual increase cited improved diagnostic procedures and the increasing lifespan of the general population. However, as a consensus on the reality of the increase developed, research was initiated to determine the causes. In the early 1950s, the publication of three case-control studies provided firm evidence that cigarette smoking was associated with an increased risk of lung cancer.4 Additional case-control studies and cohort studies supplied conclusive evidence during the 1950s and 1960s.1

![Figure 1. Age-adjusted cancer death rates for selected sites, rate per 100,000 women, United States, 1930-1986. (Age adjustment of rates was to 1970 US population.) Reprinted from US DHHS.7](image_url)
A number of expert groups reviewed the data on smoking and health as a basis for making public health decisions. The most prominent of these reports in the United States was prepared by an advisory committee to the Surgeon General in 1964; it concluded that "Cigarette smoking is causally related to lung cancer in men; the magnitude of the effect far outweighs all other factors. The data for women, though less extensive, point in the same direction." Sharply increasing lung cancer mortality rates in the United States throughout the 20th century provided indisputable documentation of the new epidemic (Fig 1 and 2). Clinical observations and early epidemiologic findings had suggested that tobacco smoking was associated with lung cancer, but hypotheses related to air pollution, occupation, and other factors were also extant. By 1964, however, the epidemiologic data were conclusive: smoking could be causally related to lung cancer. Further support for this conclusion was obtained from animal studies showing that condensates of tobacco smoke were carcinogenic and from the analytic demonstration that tobacco smoke contained carcinogens.

Newer evidence has continued to support the causal relationship between smoking and lung cancer. Recent findings have established that smoking also causes lung cancer in women; more comprehensive epidemiologic data have provided expanded descriptions of exposure-response relationships between smoking and lung cancer risk and have addressed the risks associated with smoking various types of cigarettes. Research has also been directed at environmental and host factors that may determine susceptibility to tobacco smoke. New investigative techniques in molecular and cellular biology are providing insights into the molecular mechanisms of carcinogenesis by tobacco smoke.

**Occurrence of Lung Cancer**

**Temporal Trends**

In the early decades of this century, lung cancer was an uncommon cause of death (Fig 1 and 2). By the early 1950s, however, lung cancer became the leading cause of cancer.
mortality among American men. Fortunately, lung cancer incidence and mortality rates began to drop among middle-aged white American men during the early 1980s (Table 1), and a similar pattern of decline has been documented in England, Wales, and Scandinavia.  

In 1964, at the time of the first Surgeon General's Report, lung cancer was only the fifth leading cause of cancer mortality among women. In 1964, the male-to-female ratio of death rates from lung cancer was 6.7:1. Subsequently, lung cancer mortality has increased dramatically in women; by the late 1980s, lung cancer caused approximately as many deaths as breast cancer among women. Lung cancer mortality for women now equals that observed for men 200 years ago, and the male-to-female ratio of death rates has fallen to 2.1. Lung cancer death rates in women are climbing faster than for any other cancer and have not yet begun to plateau.

**Racial and Ethnic Variation**

The occurrence of lung cancer also varies among racial and ethnic groups in the United States (Table 2). Mortality rates have been higher in black men than in white men since the 1970s, although among black and white women, the mortality rates have been comparable. In the West and Southwest, lung cancer mortality has been lower in Hispanic men than in white men, although a rapid increase from the late 1950s through the early 1980s in lung cancer rates in Hispanic men in New Mexico has been reported.

**Table 1—Age-Specific Lung Cancer Incidence Rates (per 100,000) in US White Men, 1973-1983**

<table>
<thead>
<tr>
<th>Year</th>
<th>45-54 yr</th>
<th>55-64 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1973</td>
<td>76.3</td>
<td>221.0</td>
</tr>
<tr>
<td>1974</td>
<td>83.1</td>
<td>222.8</td>
</tr>
<tr>
<td>1975</td>
<td>89.0</td>
<td>226.8</td>
</tr>
<tr>
<td>1976</td>
<td>85.6</td>
<td>238.4</td>
</tr>
<tr>
<td>1977</td>
<td>86.9</td>
<td>231.6</td>
</tr>
<tr>
<td>1978</td>
<td>90.4</td>
<td>242.3</td>
</tr>
<tr>
<td>1979</td>
<td>87.6</td>
<td>240.3</td>
</tr>
<tr>
<td>1980</td>
<td>88.7</td>
<td>243.7</td>
</tr>
<tr>
<td>1981</td>
<td>83.9</td>
<td>244.2</td>
</tr>
<tr>
<td>1982</td>
<td>78.0</td>
<td>244.1</td>
</tr>
<tr>
<td>1983</td>
<td>77.1</td>
<td>227.6</td>
</tr>
</tbody>
</table>

*Adapted from Horm and Kessler.*

**Table 2—Average Annual Age-Adjusted Lung Cancer Incidence Rates (per 100,000) by Sex and Racial-Ethnic Group, 1978-81**

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whites</td>
<td>81.0</td>
<td>28.2</td>
</tr>
<tr>
<td>Blacks</td>
<td>119.0</td>
<td>30.5</td>
</tr>
<tr>
<td>Hispanics</td>
<td>34.3</td>
<td>13.0</td>
</tr>
<tr>
<td>Japanese</td>
<td>45.1</td>
<td>14.1</td>
</tr>
<tr>
<td>Chinese</td>
<td>62.6</td>
<td>31.2</td>
</tr>
<tr>
<td>Filipinos</td>
<td>38.1</td>
<td>18.4</td>
</tr>
<tr>
<td>Native Hawaiians</td>
<td>100.9</td>
<td>38.6</td>
</tr>
<tr>
<td>Native Americans</td>
<td>14.6</td>
<td>3.10</td>
</tr>
</tbody>
</table>

*From the Surveillance, Epidemiology and End Results (SEER) Program. Adapted from Baquet et al.*

**Table 3—Results of Selected Case-Control Studies of Smoking and Lung Cancer in Men**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Location/Years</th>
<th>Ever Smoked</th>
<th>Current Smokers</th>
<th>Former Smokers</th>
</tr>
</thead>
</table>

*Calculated as crude odds ratios from data provided or extracted from published tables and figures.*

Few publications describe the incidence of lung cancer in American Indians. A nationwide mortality study conducted during the 1950s and 1960s showed that lung cancer was rare among American Indians, and more recent population-based data for New Mexico continue to support this finding.

**Geographic Variation**

Substantial geographic variation in the occurrence of lung cancer exists within the United States. Before 1970, analyses of lung cancer rates on a county-by-county basis documented regional variation that was most prominent for men. The incidence tended to be higher in the urban areas of the Northeast and along the south Atlantic and Gulf coasts. This pattern changed during the 1970s; by 1975, rates were similar in men residing in urban and rural counties in the Northeast. Lung cancer mortality among white men tended to be highest in urban and rural counties of the South.

**Risk Factors for Lung Cancer**

**Cigarette Smoking**

This section selectively reviews the evidence on the overall risks of lung cancer associated with cigarette smoking, drawing on particularly important or illustrative studies. The reports of the Surgeon General provide more comprehensive reviews of this large literature.

Overall risk estimates for smokers integrate multiple aspects of smoking behavior, including age at starting, number of cigarettes smoked, the products smoked, and inhaling pattern. Changes in overall patterns of risk in broad smoking groups (never smokers, current smokers, and former smokers) may reflect changes in one or more aspects of smoking behavior.

Three hospital-based case-control studies published during the early 1950s provided evidence that is now regarded as conclusive in establishing the causal link between cigarette smoking and lung cancer. Doll and Hill compared the smoking habits of lung cancer patients from London and
consistent with the time trends of differences in smoking by men and women throughout the mid-20th century: women tended to start smoking at an older age and to smoke fewer cigarettes.\(^7\) Reports from the 1970s and 1980s show that odds ratios have increased since the initial studies.

The original case-control studies were followed by prospective cohort studies of mortality, initiated partially in response to criticism of the case-control approach.\(^3\) Large studies performed in the United States, United Kingdom, and other countries examined mortality from lung cancer and other diseases within strata defined by use of cigarettes on enrollment, and in some studies, on subsequent follow-up (Table 5).\(^3,12-20\) These studies primarily addressed the risks of smoking in men. The three studies initiated in the United States during the 1980s (the American Cancer Society's 9-state and 25-state studies, now known as Cancer Prevention Study I, and the study of US Veterans\(^21-25\)) provided closely parallel estimates of overall risk that were in close agreement with results of contemporaneous case-control studies (Table 3). In a subsequent study by the American Cancer Society (Cancer Prevention Study II) initiated in 1980, levels of risk were much higher.\(^26\)

Less evidence is available from cohort studies on the risk of smoking in women. In the American Cancer Society's Cancer Prevention Study I,\(^27\) the mortality rate from lung cancer was 7 per 100,000 in women who had never smoked and 16 per 100,000 in women with a history of cigarette smoking. Among 6,194 women included in the study of British physicians,\(^28\) the annual death rate from lung cancer was 7 per 100,000 in never smokers; it increased progressively with amount of smoking in current smokers and was 23 per 100,000 in former smokers. In women in a Japanese study,\(^29\) the relative risk of death from lung cancer was 2.3 in a comparison of daily smokers with nonsmokers.

Expedite the data for women are now available from the American Cancer Society's Cancer Prevention Study II. The cohort includes 619,225 women; findings have been reported for 1982 through 1986.\(^30\) The standardized mortality ratio was 12.7 for current smokers and 4.8 for former smokers. For women older than 35 years of age, the relative risk for current smokers in Cancer Prevention Study I was 2.7, whereas the newer study showed 11.9.\(^7\)

** Exposure-Response Relationships: Early retrospective and

<table>
<thead>
<tr>
<th>Reference</th>
<th>Location/ Years</th>
<th>Odds Ratios*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doll and Hill, 1955(^a)</td>
<td>UK, 1948-1951</td>
<td>2.1</td>
</tr>
<tr>
<td>Wynder et al, 1956(^b)</td>
<td>US, 1953-1955</td>
<td>4.3</td>
</tr>
<tr>
<td>Haenszel and Shimkin, 1956(^c)</td>
<td>US, 1955-1957</td>
<td>2.4</td>
</tr>
<tr>
<td>Lubin et al, 1984(^e)</td>
<td>Western Europe, 1976-1980</td>
<td>3.9</td>
</tr>
<tr>
<td>Higgins and Wynder, 1988(^f)</td>
<td>US, 1977-1984</td>
<td>7.8</td>
</tr>
<tr>
<td>Pathak et al, 1986(^g)</td>
<td>New Mexico, US, 1980-1982</td>
<td>9.4</td>
</tr>
<tr>
<td>Wu et al, 1985(^h)</td>
<td>California, US, 1981-1982</td>
<td>4.1†</td>
</tr>
</tbody>
</table>

*Calculated as crude odds ratios from data provided or extracted from published tables and figures.
†For squamous cell carcinoma cases.
§For small cell carcinoma cases.

For squamous cell carcinoma cases. Among 6,194 women included in the study of British physicians, the annual death rate from lung cancer was 7 per 100,000 in never smokers; it increased progressively with amount of smoking in current smokers and was 23 per 100,000 in former smokers. In women in a Japanese study, the relative risk of death from lung cancer was 2.3 in a comparison of daily smokers with nonsmokers.

For women older than 35 years of age, the relative risk for current smokers in Cancer Prevention Study I was 2.7, whereas the newer study showed 11.9.\(^7\)

** Exposure-Response Relationships: Early retrospective and
Table 6—Standardized Mortality Ratios for Lung Cancer in Women in ACS-CPS II by Number of Cigarettes Currently Smoked and Duration of Smoking*

<table>
<thead>
<tr>
<th>Duration of Smoking, yr</th>
<th>Cigarettes per Day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-10</td>
</tr>
<tr>
<td>21-30</td>
<td>2.9</td>
</tr>
<tr>
<td>31-40</td>
<td>7.9</td>
</tr>
<tr>
<td>41-70</td>
<td>10.0</td>
</tr>
</tbody>
</table>

*In comparison with nonsmoking women. ACS-CPS II = American Cancer Society Cancer Prevention Study II. Adapted from Garfinkel and Stellman.26

prospective epidemiologic investigations documented exposure-response relationships between lung cancer risk and measures of exposure to tobacco smoke. Investigation of dose-response relationships for lung cancer has subsequently been extended, and mathematical models have been used to gain insights into the biology of respiratory carcinogenesis. The cigarette has evolved substantially since 1964 with modifications designed to reduce tar and nicotine yields. Recent research has addressed the risks of smoking the newer products. Studies of lung cancer and involuntary smoking have examined lung cancer risks at low-dose levels.27

Abundant epidemiologic evidence has shown dose-response relationships of lung cancer risk with duration of smoking and cigarettes smoked per day. In smokers who continue to smoke, the risk of lung cancer depends strongly on the duration of smoking (Table 6).20,26,28 For example, in the American Cancer Society's Cancer Prevention Study II, the risk of lung cancer approximately doubled, comparing the shortest duration with the longest duration (Table 6). Age at starting to smoke is tightly linked to duration of smoking and appears to influence lung cancer risk by determining duration of smoking rather than by differential susceptibility with age.19,20

Dose-response relationships between the numbers of cigarettes smoked and risk of lung cancer have been found in numerous case-control and cohort studies (Table 6). The evidence is limited for low numbers of cigarettes smoked daily. However, recent studies of passive smoking show that even the exposure of never smokers to environmental tobacco smoke, defined as the combination of mainstream smoke exhaled by active smokers with the sidestream smoke emitted by the smoldering cigarettes, causes lung cancer.26,27 The exposure of never smokers to smoking by a spouse is associated with an approximately 30 percent increment in risk.26,41

Since the 1950s, commercial cigarettes have been modified to reduce tar yield, as assessed by a smoking machine. The sales-weighted average tar yield has dropped substantially, from 35 mg in 1957 to about 13 mg at present.2 This has been accomplished with the addition of filters and modifications to the filter design, reduction in the amount of tobacco in cigarettes, and changes in the length of the cigarette and the porosity of the paper.28 These changes have apparently been designed to reduce tar yield in the artificial circumstances of machine smoking, and their impact on the dose of carcinogens delivered to target sites in the lung is uncertain. In fact, changes in smoking patterns may compensate for the lower tar and nicotine yields of the newer cigarettes.49

Evidence from prospective and case-control studies and assessment of temporal trends of lung cancer mortality indicate somewhat lower lung cancer risks associated with smoking cigarettes with reduced tar and nicotine yield, although the risks remain markedly higher than for non-smokers.44 Doll and Peto45 examined trends of lung cancer mortality in men in the United States, Britain, and other European countries. They concluded that the international differences and the temporal trends were generally consistent with the tar yields and tar intakes across time and across countries.

Studies of lung cancer cases during the 1960s and 1970s addressed the consequences of switching from nonfiltered, high-tar cigarettes to the lower-tar filter cigarettes that were introduced from the 1950s on. These studies showed a modest reduction of risk associated with switching.26,46 More recent studies have provided data on lifetime use of filter cigarettes. In these studies risk of lung cancer was higher among lifelong nonfilter smokers than among lifelong filter smokers, but there was an inconsistent trend of increasing risk with increasing years of nonfilter smoking.26,46

Smoking Cessation: The 1990 Report of the US Surgeon General provides a comprehensive review of the evidence on smoking cessation and lung cancer.48 Numerous cohort and case-control studies conducted in different countries have documented a 20 to 90 percent reduction in lung

Table 7—Standard Mortality Ratios of Lung Cancer Among Former Male Smokers in ACS-CPS II (Relative to Never Smokers)*

<table>
<thead>
<tr>
<th>No History of Chronic Disease</th>
<th>All Respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-20</td>
</tr>
<tr>
<td>Current smokers</td>
<td>23.5</td>
</tr>
<tr>
<td>Former smokers (yr since stopped)</td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>16.8</td>
</tr>
<tr>
<td>1-2</td>
<td>16.7</td>
</tr>
<tr>
<td>3-5</td>
<td>19.7</td>
</tr>
<tr>
<td>6-10</td>
<td>8.6</td>
</tr>
<tr>
<td>11-15</td>
<td>6.3</td>
</tr>
<tr>
<td>≥16</td>
<td>3.3</td>
</tr>
</tbody>
</table>

*By years of smoking abstinence, daily cigarette consumption at time of cessation, and history of chronic disease. ACS-CPS II = American Cancer Society Cancer Prevention Study II. Adapted from US DHHS.48

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cancer risk among former smokers compared with current smokers (Tables 7 and 8). In most studies, the benefit becomes apparent about 5 years after cessation and increases as the period of abstinence increases. These studies generally showed a similar pattern of risk reduction for men and women, for all histologic types of lung cancer, and for different types of tobacco smoked.

The risk of lung cancer among former smokers appears to remain elevated above the risk of never smokers, even at the longest durations of abstinence, approximately 20 to 25 years, evaluated to date.  

Modifiers of Risk and the Concept of Susceptibility

Substantial epidemiologic and experimental research has been directed at the determinants of susceptibility to tobacco smoke, both environmental exposure and host characteristics have been investigated. The identification of such determinants would not only further understanding of the mechanisms of carcinogenesis by tobacco smoking but could offer new approaches for lung cancer prevention through identification of smokers at higher risk. In a disease of multifactor etiology such as lung cancer, synergistic interactions of risk factors may place certain persons at particularly high risk. This section briefly reviews current evidence on host characteristics and environmental agents that may modify lung cancer risk in cigarette smokers.

Familial Factors: The 1964 Report of the Advisory Committee to the Surgeon General considered and dismissed the "constitutional hypothesis" that predispositions to cigarette smoking and to lung cancer share a common genetic origin. The report did state that genetic factors might determine susceptibility for a minority of cases. Subsequent epidemiologic studies have provided empirical evidence of possible genetic or familial determinants of susceptibility.  

For example, in a recent case-control study in New Mexico, a parental history of lung cancer was associated with a fivefold increase in lung cancer risk after adjustment for cigarette smoking. Clinical studies of selected families have also indicated familial aggregation.

Research has not yet identified the mechanisms underlying the familial aggregation of lung cancer. In 1973, Kellerman and coworkers reported that patients with lung cancer had a higher degree of inducibility of aryl hydrocarbon hydroxylase than did control subjects. Because this enzyme converts polycyclic aromatic hydrocarbons to more active carcinogens and because enzyme concentrations are under genetic control, this observation suggested a possible genetic determinant of lung cancer risk. Not all subsequent studies have been confirmatory, however, and the inheritance of inducibility in humans has not yet been fully described.  

More recently, Ayesh and coworkers reported that the phenotypes for debrisoquin metabolism differed in patients with lung cancer from those in control subjects matched for age, sex, and smoking. The evolving fields of molecular and cellular biology will undoubtedly contribute further insights concerning the role of genetic factors in lung cancer.

Other Host Factors: Acquired host characteristics have also been examined as determinants of lung cancer risk, including pulmonary tuberculosis, chronic bronchitis, chronic obstructive pulmonary disease, disorders associated with interstitial fibrosis of the lung, and peripheral pulmonary scars. The evidence related to these disorders, however, is incomplete and frequently derived from case series rather than epidemiologic investigations. Recent epidemiologic evidence has indicated increased lung cancer risk for smokers with chronic obstructive lung disease in comparison with unexposed smokers.

Occupational Exposure: Diverse agents inhaled in the workplace have been shown to cause lung cancer, even in never smokers. The cumulative impact of occupational exposure and smoking on lung cancer risk was the focus of the 1985 Report of the Surgeon General. That report concluded, "For the majority of American workers who smoke, cigarette smoking represents a greater cause of death and disability than their workplace environment." The report also highlighted limitations of the evidence supporting risk-influencing interactions between smoking and occupational exposure.

Little new information has become available since the 1985 report. The evidence remains strongest for interactions of smoking with exposure to radon and its progeny and with exposure to asbestos. For both exposures, the preponderance of data indicates synergism, but the results of some individual investigations are contradictory.

Ambient Air Pollution: Although ambient air pollution has been considered as a potential cause of lung cancer for smokers and nonsmokers in the general population, the epidemiologic evidence is limited. In fact, at current air
pollution levels in most developed countries, respiratory
doses of carcinogens from active smoking are several orders
of magnitude greater than those of inhaled atmospheric
contaminants.

Indoor Radon: Radon is an inert gas formed from radium
during the natural decay of uranium. The predominant
source of radon in indoor air is the soil beneath structures.
Radon diffuses through the soil and enters basements and
crawl spaces, and from there spreads throughout the air
in the home; it also penetrates cracks and other small spaces
in homes erected on concrete slabs. Radon and its decay
products are invariably present in indoor air, and a wide
range of concentrations has been observed in homes.9 Some
homes have levels comparable with those measured in
uranium mines, but the majority probably have levels
acceptable by current guidelines of the US Environmental
Protection Agency.

Radon decomposes into short-lived particulate decay
products. Two of these products emit alpha particles, which
are highly effective in damaging cells because of their high
energy and high mass. When these alpha emissions take
place within the lung, the epithelial lining of the tracheo-
bronchial tree may be damaged and lung cancer may
ultimately result. Extensive epidemiologic data from studies
of miners have established a causal association between
exposure to radon progeny and lung cancer.10 The Committee
on the Biological Effects of Ionizing Radiation IV
concluded that these studies indicated synergism between
cigarette smoking and radon decay products,11 implying that
cigarette smokers should be considered more susceptible
than nonsmokers to carcinogenesis by exposure to such
products.

Although definitive data are lacking, it must be assumed
that radon decay products are carcinogenic in the indoor
environment as they are in the mining environment. How-
ever, dosimetric analyses indicate that radon may be some-
what less carcinogenic in homes than in mines.12 Neverthe-
less, indoor radon is one of the most prevalent factors
interacting with cigarette smoking with the potential to
increase lung cancer risk. In fact, the US Environmental
Protection Agency estimates that approximately 14,000 lung
cancer deaths, mostly in smokers, are caused annually in
the United States by radon, making radon the second most
important cause of lung cancer.

Diet: Diet has recently been considered a potential
influence on lung cancer risk in smokers. Nutrients of
particular interest include preformed vitamin A, carotene,
vitamin E, selenium, and vitamin C.13

A growing body of experimental and epidemiologic
evidence supports the hypothesis that risk for certain cancers
varies inversely with consumption of preformed vitamin A
or beta carotene, its precursor.14-17 The biologic plausibility
of this hypothesis derives from the known effects of vitamin
A deficiency on the differentiation of epithelial surfaces
from in vitro and in vitro models, which show that retinoids
can suppress the development of malignancy, and from
possible anticarcinogenic activity of beta carotene, the
principal dietary precursor of vitamin A.18,19 Epidemiologic
data show a protective effect of dietary vitamin A intake
from vegetable sources, but not of preformed vitamin A,
which is derived from meat and dairy sources, or of vitamin
supplements. Clinical trials on vitamin A and lung cancer
risk are in progress.

Vitamins E and C are antioxidants that might have
anticancer effects. To date, the epidemiologic data on these
vitamins are sparse and inconclusive.20 Only a few small
studies have been reported on selenium intake and lung
cancer risk.

Involuntary Smoking: The evidence on environmental
tobacco smoke and cancer was comprehensively reviewed
in the 1986 Report of the Surgeon General21 and by the
National Academy of Sciences.22 A major conclusion of both
reports was that involuntary smoking can cause lung cancer
in nonsmokers. The association of involuntary smoking with
lung cancer derives biologic plausibility from the presence
of carcinogens in sidestream smoke and the lack of a
documented threshold dose for respiratory carcinogenesis
in active smokers. This is further supported by the finding
of substantial concentrations of tobacco combustion products
in indoor spaces and in body fluids of nonsmokers.23 More-
ever, epidemiologic studies demonstrate increased risk of
lung cancer in nonsmokers married to smokers, although
this finding may be partly attributable to bias, particularly
from classification of smokers as nonsmokers.24,25,41,70 With
the usual assumption of a nonthreshold relationship between
dose of a carcinogen and lung cancer risk, exposure to
environmental tobacco smoke must be presumed to convey
some such risk.26 In the United States, estimates of lung
cancer cases attributable annually to involuntary smoking
have ranged from 2,000 to 4,000.71

Nonsmoking Risk Factors

Although lung cancer is the most common cause of death
from cancer among men and women in the United States
today,27 it remains a rare cause of death in nonsmokers. The
data show that lung cancer is more common among non-
smoking men than nonsmoking women; this finding may
reflect occupational exposure of men to known carcinogens
or misclassification of smokers as nonsmokers. Because
cigarette smoking has been more prevalent among men,
random misclassification of smoking status would produce
an apparent excess of lung cancer in nonsmoking men
compared with nonsmoking women.

Environmental factors may increase the nonsmoker's risk
for lung cancer. Familial factors and acquired host charac-
teristics, including pulmonary tuberculosis,28 peripheral pul-
monary scars,29 and interstitial pulmonary fibrosis,30,31 have
also been proposed as risk factors. However, the number of
reported nonsmoking patients with these conditions is small,
and the evidence has been derived primarily from case
series rather than epidemiologic investigations.

Ambient Air Pollution: Many potential cancer-causing
agents are released into the atmosphere from natural sources
and from the industrial and nonindustrial activities of
humans. Polycyclic hydrocarbons are generated by fossil
fuel combustion and industrial activities and can be identi-
fied in the air of urban locations. Other respiratory carcino-
genoms include metals, radionuclides, diesel exhaust, and
asbestos fibers. Descriptive data have demonstrated urban-
rural gradients of lung cancer mortality consistent with an
effect of urban air on lung cancer occurrence. Throughout
the 1950s and 1960s, lung cancer mortality in more devel-

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oped countries was generally higher in urban locations, even after adjustment for differences in the cigarette smoking habits of urban and rural residents.26 Studies of migrants have also been interpreted as showing a lasting effect of urban residence on lung cancer risk.16,26 Few direct epidemiologic studies of air pollution and lung cancer have been conducted, particularly among nonsmokers. Recent investigations57,60,61 have not shown a strong correlation between the two, although one study in the Buffalo, New York area did identify potentially important effects of air pollution.62 Doll and Peto,40 in their 1981 review of the causes of cancer, estimated that only 1 to 2 percent of lung cancer cases was related to air pollution.

Indoor Air Pollution: As the hazards posed by ambient air pollution from conventional fossil fuels have diminished in some countries, the relevance of indoor air quality for health has become increasingly apparent. Studies of time-activity patterns demonstrate that residents of more developed countries, including the United States, spend, on average, little time outdoors.7,16 Indoor spaces may be polluted by the entry of contaminants in outdoor air and by indoor sources, including those related to human activity, such as tobacco smoking, building materials, combustion devices, personal care and other household products, and other sources. A trend toward reduced building ventilation in the aftermath of the energy problems of the 1970s may have worsened indoor air quality.

At present, the two indoor pollutants of greatest public health concern with regard to respiratory carcinogenesis in never smokers are environmental tobacco smoke (see above)7 and radon.41 Other indoor pollutants such as asbestos, man-made fibers, and formaldehyde are established (asbestos) or possible (man-made fibers and formaldehyde) respiratory carcinogens, but the evidence is incomplete and tends to suggest a much smaller public health hazard than environmental tobacco smoke and radon.4,44

Occupational Agents: Many workplace agents that increase the risk of lung cancer have been identified through epidemiologic investigation.4,44 Unfortunately, many of these investigations have not included information on cigarette smoking; because of this, evidence on risks in nonsmokers and on interaction between the occupational agent and cigarette smoking is limited. Nevertheless, it has been clearly demonstrated that some occupational agents can cause lung cancer in nonsmokers. In addition to radon, increased lung cancer risk has been described in never smokers exposed to arsenic, asbestos, chloromethyl ethers, and nickel.

Conclusions

A worldwide lung cancer epidemic has occurred during the 20th century. Although the incidence of lung cancer is presently declining among middle-aged men in some countries, it is increasing among women in many developed countries. The rise of smoking in developing nations will inevitably be followed by spread of the lung cancer epidemic. Epidemiologic research has convincingly established that cigarette smoking is a cause of lung cancer, accounting for the majority of lung cancer cases in most regions. Other remediable causes, including exposure to occupational agents and indoor air pollutants, have been identified. This evidence has provided a strong impetus for the implemen-

tation of a broad range of strategies to reduce the occurrence of lung cancer. Smoking prevention and cessation programs have been implemented by governmental and nongovernmental organizations, and workplace exposures to atmospheric carcinogens have been reduced through regulatory and other actions. It is encouraging that lung cancer mortality is beginning to decline among middle-aged men in the United States, and further reductions are projected for both men and women. On the other hand, smoking remains prevalent throughout the world, and the association of smoking with lung cancer has not stopped nonsmoking youths from becoming smokers.

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