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A M E R I C A N C O L L E G E O F  
 **C H E S T**  
P H Y S I C I A N S

# Epidemiology of Lung Cancer\*

Anthony J. Alberg, PhD, MPH; and Jonathan M. Samet, MD, MS

**In the United States, lung cancer remains the leading cause of cancer death in both men and women even though an extensive list of risk factors has been well-characterized. Far and away the most important cause of lung cancer is exposure to tobacco smoke through active or passive smoking. The reductions in smoking prevalence in men that occurred in the late 1960s through the 1980s will continue to drive the lung cancer mortality rates downward in men during the first portion of this century. This favorable trend will not persist unless further reductions in smoking prevalence are achieved. (CHEST 2003; 123:21S–49S)**

**Key words:** air pollution; asbestos; cigarette smoking; epidemiology; lung cancer; nutrition; passive smoking; occupation; radiation; tobacco

**Abbreviations:** CPS = Cancer Prevention Study; ETS = environmental tobacco smoke; FTC = Federal Trade Commission; IARC = International Agency for Research on Cancer; LET = linear energy transfer

**E**pidemiologic evidence is the foundation for primary and secondary disease prevention. Epidemiologic approaches are used to track the occurrence of disease, to characterize natural history, and to identify determinants of disease. The benefits of intervention programs, whether based in risk factor interventions or screening, also are assessed using epidemiologic approaches. For lung cancer, routine mortality statistics have confirmed the clinical impression that the disease became more frequent during the first half of the 20th century. Case-control and cohort studies,<sup>1–3</sup> the epidemiologic study designs that are used to evaluate exposure-disease associations, causally linked smoking to lung cancer in investigations reported from the 1950s forward. As we have continued to follow lung cancer incidence and mortality rates, we have readily shown that their rise and decline parallel past trends of cigarette smoking.<sup>4</sup> The epidemiologic evidence and the complementary biological understanding of respiratory carcinogenesis have unassailably supported the conclusion that smoking causes lung cancer. Epidemiologic findings are also relevant to patient care, as skilled clinicians weigh alternative diagnoses depending on the risk factor profiles of patients.

This article provides a summary of the epidemiologic evidence on lung cancer, with an emphasis on

issues that are currently relevant to prevention. This literature is now extraordinarily large, and we have not attempted to conduct a comprehensive review and systematic synthesis. Such syntheses have been periodically carried out by expert review groups, including the committees assembled to prepare the US Surgeon General's reports on smoking and health, and other federal documents and expert committees of other governments and organizations, including the Royal College of Physicians and the Scientific Committee on Tobacco of the United Kingdom, and the International Agency for Research on Cancer (IARC) of the World Health Organization. Several relevant reports can be anticipated from these groups, including the 2002 and 2003 reports of the US Surgeon General addressing active and passive smoking, respectively, and a planned new IARC monograph on tobacco smoking. The general topic was reviewed in a 1994 monograph.<sup>5</sup>

At the end of the 20th century, lung cancer had become one of the world's leading causes of preventable death.<sup>6</sup> It was a rare disease at the start of that century, but exposures to new etiologic agents and an increasing lifespan combined to make lung cancer a scourge of the 20th century. While tobacco had been widely used throughout the world for centuries, the present pandemic of lung cancer followed the introduction of manufactured cigarettes with addictive properties, which resulted in a new pattern of sustained exposure of the lung to inhaled carcinogens.<sup>7</sup> German scientists in Nazi Germany conducted some of the earliest research on the links between smoking and lung cancer.<sup>8</sup> By the early 1950s, epidemiologic studies<sup>9–11</sup> in Britain and the

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United States using the case-control method had shown that cigarettes were strongly associated with the risk of lung cancer. This association was corroborated by the pioneering cohort studies of British physicians, US veterans of the armed forces, and volunteers recruited by the American Cancer Society.<sup>12</sup> By 1964, the evidence was sufficient to support a conclusion by the US Surgeon General that cigarette smoking caused lung cancer.<sup>12</sup> The Royal College of Physicians had reached the same conclusion 2 years previously.<sup>13</sup> Passive smoking, the involuntary inhalation of tobacco smoke by nonsmokers, also has been found to cause lung cancer.<sup>14,15</sup>

While its predominant cause is now well-known (*ie*, tobacco smoking), there are other causes as well, some acting in concert with smoking to synergistically increase risk. The suspicion that radon was a cause of lung cancer in underground miners, which was raised early in the century, led to what was probably the first occupational respiratory carcinogen to be identified.<sup>16</sup> Radon in indoor environments is now considered to be a significant cause of lung cancer.<sup>17</sup> The list of human occupational causes of lung cancer also includes arsenic, asbestos, chromates, chloromethyl ethers, nickel, polycyclic aromatic hydrocarbons, radon progeny, and other agents.<sup>18</sup> Outdoor air pollution, which includes combustion-generated carcinogens, is also considered to contribute to the lung cancer burden in urban dwellers. Indoor air contains several respiratory carcinogens, including radon, asbestos, and cigarette smoke. In some developing countries, exposure to fumes from cooking stoves and fires is associated with lung cancer risk. Beginning in the 1980s, associations of diet with lung cancer risk have been vigorously investigated with the anticipation that dietary micronutrients might be found that modify the high lung cancer risk in smokers. The biological basis for the prevention of cancer through supplementation of micronutrients is addressed in another article in this supplement.

Even though the epidemiology of lung cancer has been extensively investigated for > 50 years, there are still active areas of research, some quite relevant to prevention. Investigation of lung cancer and diet continues, using both observational and experimental approaches, and concern remains over the risk of indoor and outdoor pollutants including, for example, radon and diesel emissions. There also has been a need for research to track the risks of smoking over time, as the cigarette has evolved in its design characteristics and yields of tar and nicotine, as assessed by standard protocol using a machine, have declined since the 1950s. The histologic characteristics of lung cancer in a number of developed countries, including the United States, also have changed

in recent decades so that the frequency of adenocarcinoma has risen and that of squamous cell carcinoma has declined.<sup>4</sup> There is also emerging evidence on the genetic determinants of lung cancer risk. A current research approach, termed *molecular epidemiology*, melds the population and laboratory tools that are used to address susceptibility to environmental carcinogens. While the evidence from the “traditional” epidemiologic approaches conclusively established the carcinogenicity of tobacco smoke, molecular epidemiology should characterize the sequence of molecular and cellular changes as a non-malignant cell becomes malignant and the factors determining susceptibility to tobacco smoke. Biomarkers of exposure, dose, susceptibility, and genetic damage may allow epidemiologic investigations to uncover specific pathways of human lung carcinogenesis.

## PATTERNS OF OCCURRENCE

### *Temporal Trends*

Because of the high case-fatality rate of lung cancer, the incidence and mortality rates are nearly equivalent, and, consequently, routinely collected vital statistics provide a long record of the occurrence of lung cancer. We are presently amid an epidemic of lung cancer that dates to the mid-20th century (Fig 1).<sup>19–21</sup> Lung cancer was rare until the disease began a sharp rise around 1930 that culminated by mid-century with lung cancer becoming the leading cause of cancer death among men.<sup>22</sup> The epidemic among women followed that among men, with a sharp rise in rates from the 1960s to the present, propelling lung cancer to become the most frequent cause of female cancer mortality.<sup>22</sup> The epidemic among women not only occurred later, but will not peak at as high a level as that among men because smoking prevalence crested at substantially higher levels among men than among women.<sup>4,23,24</sup>

An examination of the time trends of age-specific lung cancer mortality rates in the United States further highlights the differing epidemic patterns in men compared to women (Fig 2).<sup>20,21,23,25,26</sup> In the older age groups, the rates continue to increase in both sexes, but the rates of increase are decelerating more significantly in men than in women.<sup>23</sup> The rates of lung cancer are now decreasing in the younger age groups, decreases that are more pronounced for men but also now are becoming evident in women.<sup>23,27</sup> As the younger birth cohorts age, their reduced risk of lung cancer should thus translate into substantial reductions in the overall occurrence of lung cancer, reductions that will probably be more favorable for men than for women. In a recent analysis of lung

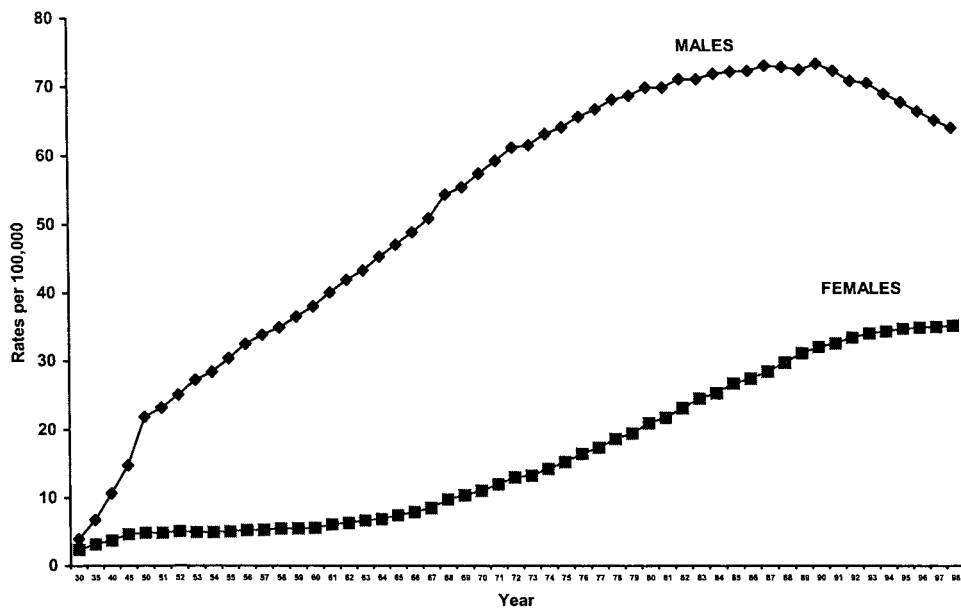


FIGURE 1. Lung cancer mortality rates for the United States from 1930 to 1998, age-standardized to the 1970 US population. Adapted from Gordon et al,<sup>19</sup> and McKay et al,<sup>20</sup> and Ries et al.<sup>21</sup>

cancer mortality in the United States from 1970 to 1997, Jemal and colleagues<sup>23</sup> found that the rates of decrease in younger men and women (*ie*, those born after 1950) were moderating, even though the decline continues. These investigators suggested that the moderation could reflect patterns of smoking

initiation. In some other countries, lung cancer rates continue to rise in all age groups.

Notable shifts have taken place in the incidence rates of lung cancer by histologic type.<sup>28</sup> After steadily increasing in occurrence during the period from 1973 to 1987, adenocarcinoma supplanted

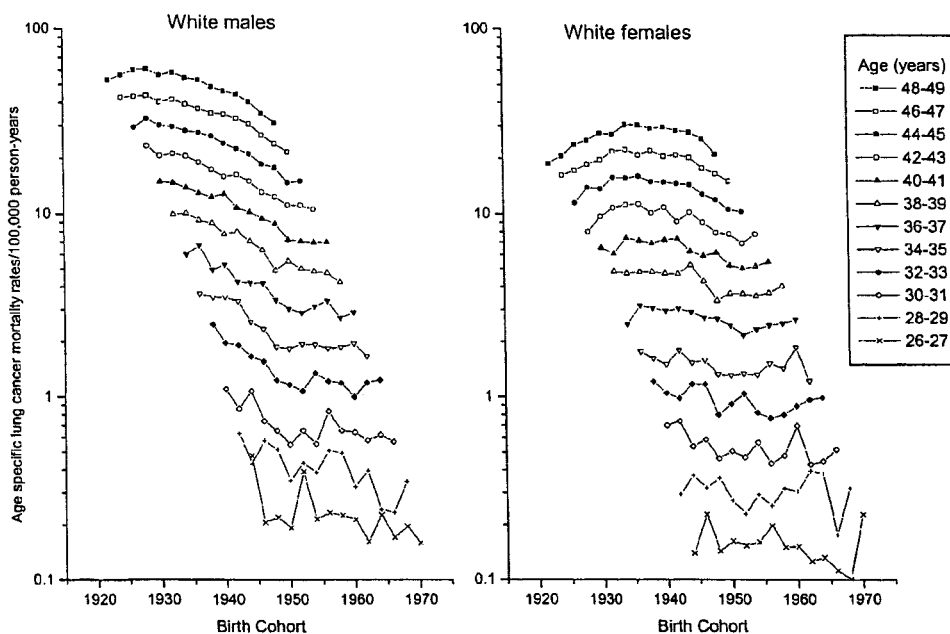


FIGURE 2. US age-specific mortality rates (white men and women) by 2-year age intervals from 26 to 27 years of age through 48 to 49 years of age, plotted against the birth cohort. Adapted from the American Cancer Society.<sup>22</sup>

squamous cell carcinoma as the most frequent form of lung cancer (Table 1).<sup>28</sup> Adenocarcinoma increased markedly in all race-sex subgroups (Table 1).

### Race and Ethnicity

The patterns of occurrence of lung cancer by race and ethnicity make lung cancer a relevant disease for those concerned with the health of women and minorities. Whereas lung cancer incidence rates are similar among African-American and white women, lung cancer occurs about 50% more frequently among African-American men than among white men.<sup>21</sup> The marked reduction in cigarette smoking that has occurred among African-American youths<sup>29</sup> forecasts a possible reversal of this trend, and, if this trend persists, declines in the incidence of lung cancer among African-Americans can be expected.

Lung cancer mortality rates among Hispanics, Native Americans, and Asians/Pacific Islanders are significantly lower than rates among African-Americans and non-Hispanic whites.<sup>30</sup> Nevertheless, lung cancer occurs sufficiently often among these groups to pose a considerable public health burden.

### Geographic Patterns

Lung cancer is the most commonly diagnosed cancer worldwide,<sup>30</sup> but its geographic distribution shows marked regional variation.<sup>31</sup> The global variation in

age-standardized incidence rates is greater than fourfold among men, and a fivefold among women (Fig 3).<sup>32</sup> Because of differences in cancer registration between countries, caution is needed in interpreting these data. However, this marked variation in rates cannot be explained on the basis of diagnostic practices and data quality alone. Lung cancer tends to be most common in developed countries, particularly in North America and Europe, and less common in developing countries, particularly in Africa and South America.<sup>33</sup> The low rates of lung cancer in Africa<sup>34</sup> are comparable to United States rates in 1930, when rates of lung cancer were under 5 cases per 100,000 for both sexes.<sup>19</sup> In contrast, African-Americans in the United States, an epicenter of the disease, now experience lung cancer incidence rates that are among the highest in the world. As the lung cancer epidemic begins to subside in the developed countries, it is on the rise in the developing world.<sup>35</sup>

Within countries, lung cancer incidence among men invariably outpaces that in women, by well over 100% in most nations. The international rankings of lung cancer incidence for men and women from the same countries tend to differ only slightly, so that the highest rates of lung cancer occur in the same regions of the world for both sexes.

Substantial geographic variation in lung cancer mortality rates also has been observed within countries. Trends in its regional distribution can provide clues

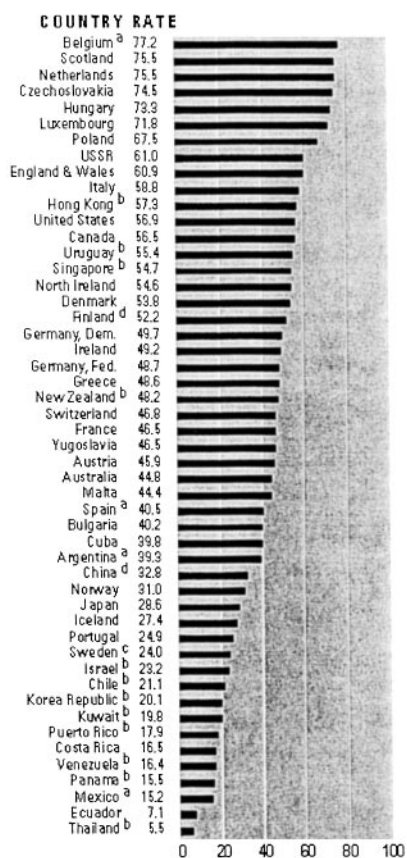
**Table 1—Age-Adjusted Incidence Rates per 100,000 Population of Lung Cancer by Histologic Subtype and Time Period**

Group	Carcinoma Subtype	1973–1977*	1978–1982*	1983–1987*	1992–1998†
Total	Total	39.5	46.8	51.4	54.0
	Squamous cell	13.4	15.1	15.3	11.5
	Adenocarcinoma	10.5	14.2	16.7	18.9
	Small cell	5.9	8.2	9.4	7.9
	Large cell	0.0	3.9	4.9	3.8
White men	Squamous cell carcinoma	24.3	26.8	25.5	17.2
	Adenocarcinoma	14.5	19.0	21.3	22.0
	Small cell	9.5	12.5	13.1	9.7
	Large cell	0.0	5.9	7.2	4.6
White women	Squamous cell carcinoma	4.0	5.5	6.6	6.8
	Adenocarcinoma	6.9	10.2	12.9	16.7
	Small cell	3.4	5.5	7.1	7.5
	Large cell	0.0	2.2	3.1	2.8
African-American men	Squamous cell carcinoma	43.9	46.3	48.5	30.8
	Adenocarcinoma	18.1	27.4	32.5	31.9
	Small cell	9.5	13.3	14.0	10.1
	Large cell	0.0	8.0	10.8	8.1
African-American women	Squamous cell carcinoma	5.6	6.8	9.5	9.3
	Adenocarcinoma	6.8	10.8	13.3	16.4
	Small cell	3.6	3.9	6.0	6.0
	Large cell	0.0	2.0	3.0	3.1

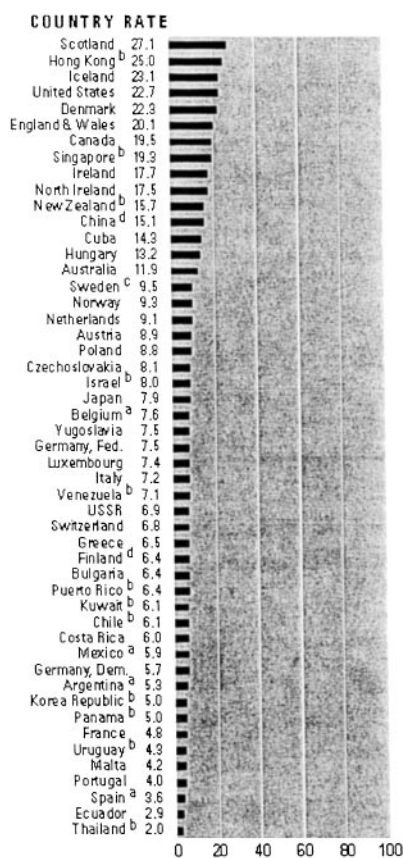
\*Adapted from Travis et al.<sup>28</sup>

†Calculated from online SEER data using Cancer Query Systems software. (National Cancer Institute; Bethesda MD; available at <http://seer.cancer.gov/canques/>.)

Lung, Males



Lung, Females



- <sup>a</sup> 1986 only
- <sup>b</sup> 1986-87 only
- <sup>c</sup> 1987 only
- <sup>d</sup> 1987-88 only

FIGURE 3. Age-adjusted lung cancer death rates from 1986 to 1988 per 100,000 population for men and women. Adapted from The National Cancer Institute.<sup>22</sup>

about the determinants of lung cancer. In the past, rates tended to be highest in urban areas, which led to conjecture that air pollution might be a cause of the lung cancer epidemic.<sup>36</sup> Later on, several hypotheses<sup>37,38</sup> were prompted by patterns observed in a systematic review of US lung cancer mortality rates for the period 1950 to 1969,<sup>39</sup> particularly the rates among men. For example, high lung cancer rates in coastal areas were postulated to reflect employment in shipyards with attendant asbestos exposure. This hypothesis then was tested in a series of population-based, case-control studies, which showed that employment in the shipbuilding industry was indeed associated with an excess risk of lung cancer.<sup>40</sup> Another shift then took

place in the distribution of lung cancer within the United States, with lung cancer mortality rates among white men becoming highest in the South and lower in the Northeast.<sup>41</sup> This fluidity in the geographic variation underscores the value of regularly monitoring lung cancer mortality patterns.

### THE ETIOLOGY OF LUNG CANCER

#### Overview

Although the causes of lung cancer are almost exclusively environmental, it is likely that there is substantial individual variation in the susceptibility to

*Smoking*

respiratory carcinogens. The risk of the disease can be conceptualized as reflecting the joint consequences of the interrelationship between (1) exposure to etiologic (or protective) agents and (2) the individual susceptibility to these agents. The term *environment* in its broadest sense may influence the risk of disease through direct exposures or indirectly by affecting the likelihood of exposure to exogenous agents. Given the multifactorial etiology of lung cancer, synergistic interactions among risk factors may have substantial consequences for lung cancer risk. These interactions typically have been considered on an agent-by-agent basis, as for example the synergistic effect of cigarette smoking on the lung cancer risk from asbestos exposure.<sup>42</sup> Our emerging understanding of cancer genetics indicates the additional relevance of gene-environment interactions.

When the environment is considered more holistically, an even broader set of interactions can be proposed. For example, socioeconomic status is associated with a constellation of the following interacting determinants of lung cancer risk: smoking; diet; and exposures to inhaled agents in the workplace and general environment. Lower socioeconomic status is associated with an unfavorable profile for all of these factors. Risk factor patterns at the individual and societal levels identify persons and populations at high risk and can be used to target prevention approaches toward those who are at greatest risk.

Given the many risk factors that have been identified for lung cancer, a practical question is the relative contribution of these factors to the overall burden of lung cancer. The “population attributable risk” approach takes into account the magnitude of the relative risk that is associated with an exposure along with the likelihood of exposure in the general population. Because of the interactions between exposures, the combined population attributable risk for diseases such as lung cancer that have a well-characterized set of important risk factors can exceed 100%. As reviewed below, population attributable risk estimates for lung cancer indicate that in the United States, active smoking is responsible for 90% of lung cancer cases, occupational exposures to carcinogens account for approximately 9 to 15% of lung cancer cases, radon causes 10% of lung cancer cases,<sup>17</sup> and outdoor air pollution accounts for perhaps 1 to 2% of lung cancer cases.<sup>43</sup> The precise contribution of nutritional factors remains to be determined, but dietary factors have been hypothesized to account for approximately 20% (range, 10 to 30%) of the lung cancer burden.<sup>44</sup>

*Overview:* A single etiologic agent, cigarette smoking, is by far the leading cause of lung cancer, accounting for approximately 90% of lung cancer cases in the United States and other countries where cigarette smoking is common.<sup>45</sup> Compared to never-smokers, smokers have about a 20-fold increase in lung cancer risk at present. Few exposures to environmental agents convey such risks for any disease. In general, trends of lung cancer occurrence closely reflect patterns of smoking, but rates of occurrence lag smoking rates by about 20 years. Analyses using statistical modeling techniques show a tight association between national mortality rates and smoking.<sup>46</sup> The unequivocal causal association of cigarette smoking with lung cancer is one of the most thoroughly documented causal relationships in biomedical research.<sup>7,47</sup>

The burden of lung cancer that is attributable to smoking has been extensively documented. Using an attributable risk approach, the Centers for Disease Control and Prevention has documented the numbers of deaths caused in the United States by smoking-related lung cancer. For 1990, that number was 117,000.<sup>48</sup> Peto et al<sup>45</sup> have used a different attributable risk method to quantify the burden of smoking-related deaths from lung cancer in the major developed countries. For 1990, the US total was 127,000 deaths, which was the highest in the world, with country-specific estimates ranging down to 150 deaths for Tajikistan. The total number of smoking-related deaths for the developed countries was 457,371.<sup>45</sup> Peto and colleagues forecast a staggering future burden for China, which now has one third of the world's smokers.<sup>49</sup> The numbers are predicted to reach several millions by mid-century.

Cigar smoking is also an established cause of lung cancer.<sup>50</sup> The lung cancer risks associated with cigar smoking are substantial, but are less than the risks observed for cigarette smoking due to differences in smoking frequency and depth of inhalation. The same pattern holds true for pipe smoking.<sup>51</sup>

*Quantitative Risks:* The risk of lung cancer among cigarette smokers increases with the duration of smoking and the number of cigarettes smoked per day<sup>48,52</sup> (Table 2). This observation has been made repeatedly in cohort and case-control studies. Risk models have been derived to quantitatively estimate how lung cancer risk varies with the number of cigarettes smoked, the duration of smoking, and age. Such models are useful for estimating the future burden of lung cancer under various scenarios of tobacco control. In one widely cited analysis, Doll

**Table 2—Age-Specific Lung Cancer Mortality Rates per 100,000 Population Among Men and Women of Comparable Smoking Levels in the CPS-II\***

Age Group, yr	Never-Smokers	Smoked 20 Cigarettes per Day		Smoked 40 Cigarettes per Day	
		30 Years	40 Years	30 Years	40 Years
<b>Men</b>					
50–59	2.5	124.6	236.8	188.4	336.5
60–69	11.9	224.3	486.8	572.8	606.6
<b>Women</b>					
50–59	5.9	93.2	150.2	152.2	159.5
60–69	9.8	200.8	264.4	257.7	552.8

\*Data from Thun et al.<sup>56</sup>

and Peto<sup>52</sup> proposed a quantitative model for lung cancer risk based on data from the cohort study of British physicians. This model predicted a stronger effect of duration of smoking than of amount smoked per day. Thus, a tripling of the number of cigarettes smoked per day was estimated to triple the risk, whereas a tripling of the duration of smoking was estimated to increase the lung cancer risk 100-fold.<sup>53</sup> These quantitative dimensions of the dose-response relationship between smoking and lung cancer have implications concerning the now widespread occurrence of smoking among youths. Those persons starting to smoke at younger ages have a greater likelihood of becoming heavier smokers and remaining smokers.<sup>54</sup> The exponential effect of the duration of smoking on lung cancer risk markedly increases the lifetime risk for those who become regular smokers in childhood. Thus, those who initiate smoking earlier in life are most likely to develop lung cancer and are most likely to do so at younger ages. Prevention approaches that delay the age of onset of smoking in a population could have a substantial impact on the incidence of lung cancer by shortening the duration of smoking. In considering the likelihood of lung cancer in a particular patient, clinicians should give more weight to the duration of smoking and less weight to actual age.

**Smoking Cessation:** Cigarette smokers can benefit at any age by quitting smoking. The likelihood of developing lung cancer decreases among those who quit smoking compared to those who continue to smoke<sup>55</sup> (Table 3<sup>56</sup>). As the period of abstinence from smoking cigarettes increases, the risk of lung cancer decreases<sup>55</sup> (Table 3). However, even for periods of abstinence of > 40 years, the risk of lung cancer among former smokers remains elevated compared to never-smokers<sup>55,56</sup> (Table 3). The benefits derived from smoking cessation also depend on the duration of smoking. For a given period of

**Table 3—Risk of Lung Cancer among Ex-Smokers Relative to Never-Smokers According to Length of Time Since Smoking Cessation and Number of Cigarettes Formerly Smoked among a Cohort of US Veterans\***

Years Since Smoked	Cigarettes Smoked per Day				Total Ex-smokers
	1–9	10–20	21–39	≥ 40	
< 5	7.6†	12.5	20.6	26.9	16.1
5–9	3.6	5.1	11.5	13.6	7.8
10–19	2.2	4.3	6.8	7.8	5.1
20–29	1.7	3.3	3.4	5.9	3.3
30–39	0.5	2.1	2.8	4.5	2.0
≥ 40	1.1	1.6	1.8	2.3	1.5

\*Relative risk compared to referent category of never-smokers (1.0).

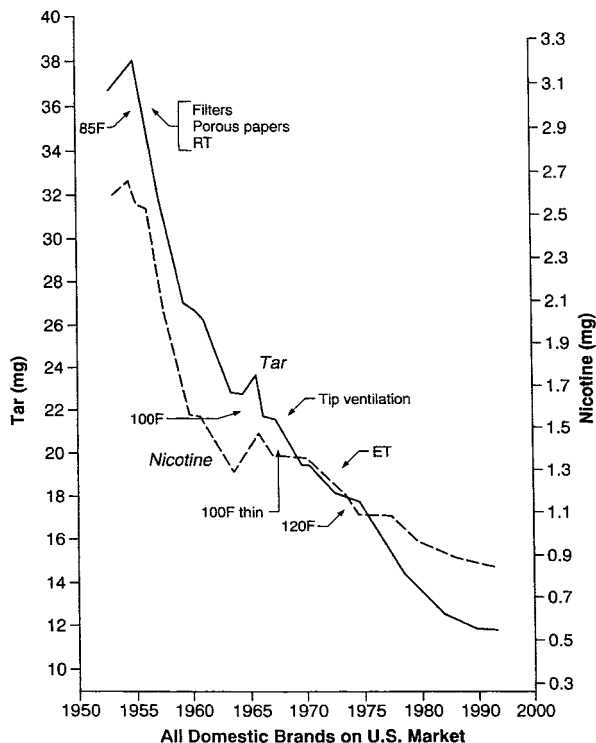
†Table adapted from Hrubec and McLaughlin.<sup>56</sup>

abstinence, the decrease in risk increases as the duration of smoking decreases.<sup>55</sup> In general, studies<sup>57</sup> have shown comparable reductions in risk following smoking cessation, regardless of sex, type of tobacco smoked, and histologic type of lung cancer.

**The Changing Cigarette:** The composition of cigarettes has evolved considerably since the 1950s. The marketplace has shifted from mainly unfiltered cigarettes to predominantly filtered cigarettes. The filters in use in the United States are predominantly cellulose acetate, while charcoal filters are used extensively in Japan and some other countries.<sup>58</sup> In the mid-1960s, ventilation holes were added to the filter, which dilute the smoke with air drawn through them. However, smokers can use their fingers to readily block the holes, which are left unblocked by the machines that are used to test cigarettes. There also have been substantial changes in the design of the cigarette and in the tobacco used. Reconstituted tobacco has been used increasingly since the 1960s, and there have been changes to the cigarette papers and additives used.<sup>58</sup>

A concomitant shift toward lowered levels of tar and nicotine, as measured by a smoking machine, has occurred (Fig 4). Cigarette tar is the label given to the condensable residue of cigarette smoke (*ie*, the total particulate matter from cigarette smoke that is deposited on the filter machine's less the moisture and nicotine). Tar is a complex mixture that includes many chemicals that are cancer initiators and/or promoters.<sup>59</sup> Tar and nicotine yields are measured with a smoking machine according to a standardized protocol established by the Federal Trade Commission (FTC) that specifies such details as puff volume, the frequency of puffing, and the length to which the cigarette is to be smoked.<sup>60</sup>





Key: RT = reconstituted tobacco; F = filter; ET = expanded tobacco.

FIGURE 4. Sales-weighted average tar and nicotine deliveries, 1954 to 1993. Adapted from US Department of Health and Human Services.<sup>59</sup>

Studies using biomarkers of exposure and dose to tobacco smoke components show little relationship of levels of these markers with tar or nicotine yield as measured by the FTC protocol.<sup>60</sup> These studies have been conducted in both the population context and during smoking in the laboratory setting. For example, Coultas and colleagues<sup>61</sup> collected saliva for the analysis of cotinine levels, and end-tidal breath samples for the measurement of carbon monoxide levels in a population sample of Hispanic persons from New Mexico who were included in a respiratory health survey. After taking account of the numbers of cigarettes smoked, the levels of biomarkers were not associated with the yields of tar and nicotine of the current brand that was being smoked. Djordjevic and colleagues<sup>62</sup> evaluated smoking patterns and biomarkers in the laboratory setting, contrasting smokers of medium-yield and low-yield cigarettes. The smokers had greater puff volumes and frequencies than are specified in the FTC protocol and had substantially greater intakes of tar and nicotine than those implied by the brand listings. The lack of association of tar and nicotine yields with biomarker levels partially reflects compensatory changes in smoking patterns for those switching from higher yield to lower yield products. The compensation

includes the blocking of the ventilation holes, more frequent and deeper puffs, and an increase in the number of cigarettes smoked.<sup>63</sup>

The gradual reduction in tar yield over recent decades would be expected to have reduced smokers' exposures to carcinogens if the FTC test protocol were predictive of carcinogen doses that are delivered to the lung.<sup>59</sup> However, questions remain as to whether the FTC test method is informative with regard to lung cancer risk, or to the risks of smoking-caused diseases more generally.<sup>63,64</sup> Epidemiologic studies have been carried out to assess whether the seemingly substantial changes in tar and nicotine yield, as measured by the FTC protocol, have resulted in parallel changes in the risk of smoking. Epidemiologic studies have been the key source of information, because they can provide direct evidence on the risks of smoking cigarettes as they are actually smoked during use, including any compensatory behavior.

For lung cancer, and for other diseases, two lines of epidemiologic data have been available on the changes in smoking products. The first line of data comes from case-control studies that compared the smoking history profiles of persons developing lung cancer over the several-year period of case accrual with those of concomitantly selected control subjects, and the second line of data comes from cohort studies that have tracked the risk of lung cancer over time, as the products being smoked changed. These studies have provided temporally cross-sectional assessments, but have not provided insights into the consequences of smoking one product or another across the full time period of smoking. In fact, smokers change the products that they smoke and the product characteristics continue to change over time as well. Consequently, researchers cannot compare the risks of smoking one type of cigarette across decades with that of smoking another. Because of these methodological issues, the epidemiologic data need to be interpreted cautiously.<sup>63</sup>

Some epidemiologic data, coming primarily from case-control studies, suggest that filtered cigarettes and lower tar yields slightly reduce the risk of lung cancer associated with cigarette smoking compared to unfiltered cigarettes (Table 4)<sup>52-62,65-75</sup> or to higher tar yields (Table 5).<sup>69,74-80</sup>

The initial evidence came primarily from case-control studies that compared risks in persons who had used filter-tip cigarettes to persons who had smoked nonfilter cigarettes exclusively.<sup>65,66</sup> This comparison could be made among smokers in the 1960s, as there was still a substantial proportion of smokers who had not used filter cigarettes at all. For example, Bross and Gibson<sup>65</sup> compared the

**Table 4—A Summary of Studies of Lung Cancer Risk According to Type of Cigarette Smoked (Non-filtered vs Filtered Cigarettes)\***

Study/Year	Location	Results	Comments
Case-control studies†			
Bross and Gibson <sup>65</sup> /1968	Roswell Park, hospital-based	1.69 (1.12, 2.57)	
Wynder et al <sup>66</sup> /1970	New York, hospital-based (Memorial Sloan-Kettering)	1.62 (0.99, 2.65)	
Wynder and Stellman <sup>67</sup> /1979	US multisite, hospital-based	Men: 1.9 (0.92, 1.55) Women: 1.29 (0.67, 2.47)	Nonfilter usage vs filter usage > 10 yr
Wynder and Kabat <sup>68</sup> /1988	US multisite, hospital-based	Men: 1.45 (0.79, 2.70) Women: 1.56 (0.74, 3.33)	Lifetime nonfilter usage vs lifetime filter usage
Lubin et al <sup>69</sup> /1984	Western Europe, multisite, hospital-based	Men: 1.6 (1.3, 1.8) 1.8 (1.5, 2.1) Women: 1.8 (1.3, 2.6) 2.5 (1.2, 5.2)	Mixed usage Lifetime nonfilter usage Mixed usage Lifetime nonfilter usage
Pathak et al <sup>70</sup> /1986	New Mexico, population-based	Whites: 1.25 Hispanics: 25.0	Lifetime nonfilter usage
Jockel et al <sup>71</sup> /1992	Germany, hospital-based	2.4 (1.2, 4.8)	All men; exclusively or partly nonfilter usage last 20 yr vs filter usage last 20 yr
Prospective studies‡			
Hawthorne and Fry <sup>72</sup> /1978	West Scotland	1.20 (0.77, 1.89)	
Rimington <sup>73</sup> /1981	England	1.67 (1.14, 2.45)	Age-adjusted relative risk = 1.54
Garfinkel and Stellman <sup>74</sup> /1988	United States (American Cancer Society, CPS II)	1.5 (1.3, 1.8)	All women; filter for ≤40% of smoking relative to lifetime filter usage
Sidney et al <sup>75</sup> /1993	Kaiser Permanente	1.24 (0.78, 1.89)	

\*The referent category of filtered cigarette smokers is equal to 1.0.

†Values given as odds ratio (95% confidence limits).

‡Values given as relative risk (95% confidence limits).

lung cancer risks for those persons smoking filter cigarettes with those smoking nonfilter cigarettes among patients seen at Roswell Park Memorial Cancer Institute in Buffalo. Persons were classified as *filter cigarette smokers* if they had used

these products for at least 10 years. These initial studies indicated that filter cigarettes provided some reduction of lung cancer risk. Subsequent case-control studies that have contrasted the use of either filter or lower yield cigarettes across the

**Table 5—A Summary of Studies of Lung Cancer Risk According to Tar Exposures or Levels in Cigarettes Smoked**

Study/Year	Location	Results*				
		1†	2	3	4	5
Case-control studies‡						
Joly et al <sup>76</sup> /1983	Havana, Cuba, hospital-based	1.0	1.75 (1.12, 2.74)	1.62 (0.99, 2.66)		
Lubin et al <sup>69</sup> /1984	Western Europe multisite, hospital-based	1.0	1.2	1.5	1.8	1.7 Male
		1.0		5.9	4.0	7.7 Female
Wilcox et al <sup>77</sup> /1988	New Jersey, population-based	1.0	1.62	1.96	1.89	
Kaufman et al <sup>78</sup> /1989	United States and Canada, multisite, hospital-based	1.0	1.9 (1.0, 3.7)	3.1 (1.3, 7.1)		
Prospective studies§						
Hammond et al <sup>79</sup> /1976	United States (American Cancer Society CPS-I)	1.0	1.21 (1.02, 1.45)	1.36 (1.15, 1.61)		
Higenbottam et al <sup>80</sup> /1982	England (Whitehall Study)	1.0	1.15 (0.77, 1.74)	1.48 (1.0, 2.18)		
Garfinkel and Stellman <sup>74</sup> /1988	US Women (American Cancer Society CPS-II)	1.0	1.17	1.36	1.59	1.85
Sidney et al <sup>75</sup> /1993	United States (Kaiser Permanente)	1.0	0.98 (0.66, 1.47)	0.87 (0.56, 1.37)		

\*The exposure categories of low to high are for summary purposes only and do not correspond to identical dosage categories.

†Referent category (low).

‡Values given as odds ratio (95% confidence limits).

§Values given as relative risk (95% confidence limits).

cumulative smoking history with nonfilter or higher yield cigarettes have had generally similar findings.<sup>64</sup>

In a 1976 publication, Hammond and colleagues<sup>79</sup> compared the mortality risks from lung cancer and other diseases by the tar yield of products smoked by participants in the American Cancer Society Cancer Prevention Study (CPS) I participants. The follow-up interval spanned the years 1960 to 1972. Smokers were placed into the following three categories of cigarette products smoked: low yield, < 17.6 mg per cigarette; high yield, 25.8 to 35.7 mg per cigarette; and medium yield, intermediate. The standardized mortality rate for lung cancer in low-yield and medium-yield smokers was approximately 80% of the rate in high-yield smokers. A further analysis of tar yield using the same data set confirmed that the risk for lung cancer death increased with tar yield.<sup>81–83</sup>

This study only provided a comparison of risks across the 12 years of follow-up from 1960 to 1972. Further insights have been gained by comparing the risks in the two CPS studies of the American Cancer Society. This comparison addressed whether the risks have changed, comparing smokers who developed the disease between 1960 and 1972 with a similar group who developed the disease during the initial follow-up of CPS II, from 1980 to 1986.<sup>84,85</sup> If the risk for lung cancer that is associated with smoking is decreasing over time, the expectation would be that risks for smokers would be less in CPS II than in CPS I. In fact, the opposite was observed, with increasing lung cancer mortality in male and female smokers in CPS II compared with CPS I (Fig 5).<sup>86</sup> While differences in smoking patterns may partially explain the increased lung cancer mortality, comparing CPS I and CPS II, male smokers in CPS II had substantially higher lung cancer mortality rates than their counterparts in CPS I.<sup>86</sup>

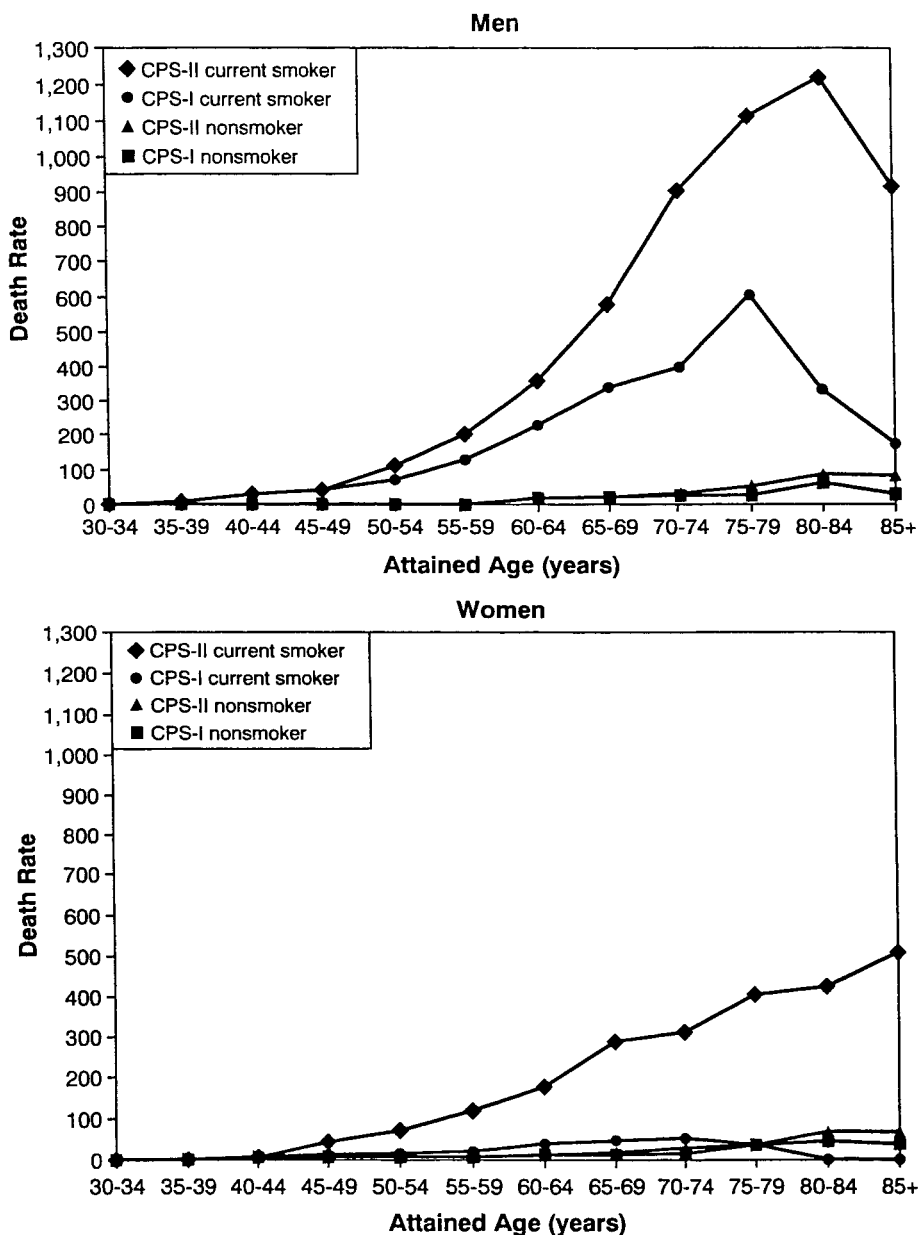
In an analysis with similar findings, Doll and colleagues<sup>87</sup> compared the risks of death from lung cancer and other causes during the first and second 20-year periods of the 40-year follow-up of the British physician cohort. Lung cancer mortality increased among smokers in the second 20-year period (*ie*, 1971 to 1991), even though the products smoked during that time period would have had a substantially lower tar and nicotine yield than those smoked during the first 20-year period (*ie*, 1951 to 1971). For the first 20 years, the annual lung cancer mortality rate among current smokers was 264 per 100,000, and for the second 20 years, it was 314 per 100,000.

Several expert panels have recently reviewed the findings. Stratton et al<sup>88</sup> for the Institute of Medicine carried out a comprehensive review on various harm-

reduction strategies for reducing the disease burden caused by smoking, including the smoking of lower yield cigarettes. There are also new products in various phases of development that are intended to deliver nicotine without the direct combustion of tobacco. The Institute of Medicine report concluded that smoking lower yield products had not been shown to benefit the health of smokers.

This topic was also addressed in the National Cancer Institute monograph, *Risks Associated with Smoking Cigarettes with Low Machine-Measured Yields of Tar and Nicotine*.<sup>63</sup> This monograph provides a comprehensive review of the topic as well as new analyses of the CPS I data. The report proposes that the net consequences of having lower yield products needs consideration, along with any change in the risk of disease to smokers. If some persons start smoking or continue to smoke because they view the smoking of lower yield cigarettes as having a more acceptable level of risk, then the success of tobacco control interventions may be lessened. The report also found that compensatory changes in smoking patterns reduce any theoretical benefit of lower yield products. Overall, the report concluded that changes in cigarette design and manufacturing over the last 50 years had not benefited public health.

*Passive Smoking:* Passive smokers inhale a complex mixture of smoke that is now widely referred to as *environmental tobacco smoke* (ETS). Passive smoking was first considered as a possible risk factor for lung cancer in 1981 when two studies were published that described increased lung cancer risk among never-smoking women who were married to smokers. Hirayama<sup>89</sup> reported the findings from a cohort study in Japan, which showed that among nonsmoking women, those whose husbands smoked cigarettes were at higher risk for lung cancer than those whose husbands were nonsmokers. A case-control study in Athens reported by Trichopoulos and colleagues<sup>90</sup> shortly thereafter replicated this finding. Additional evidence rapidly accrued so that by 1986 two important summary reports were published. The National Research Council reviewed the epidemiologic evidence and concluded that nonsmoking spouses who were married to cigarette smokers were about 30% more likely to develop lung cancer than nonsmoking spouses who were married to nonsmokers, and that this relationship was biologically plausible.<sup>91</sup> Almost one fourth of lung cancer cases among never-smokers were estimated to be attributed to exposure to passive smoking.<sup>91</sup> The 1986 report of the Surgeon General also judged passive smoking to be a cause of lung cancer,<sup>14</sup> an inference corroborated by the 1992 review<sup>15</sup> of the



\* Rate per 100,000 person-years.

FIGURE 5. Age-specific death rates from lung cancer among current cigarette smokers and lifelong never-smokers based on smoking status at enrollment in the CPS I or CPS II, according to attained age. Adapted from Thun et al.<sup>56</sup>

evidence and risk assessment by the US Environmental Protection Agency, which classified ETS as a known human (class A) carcinogen. Estimates indicate that passive smoking accounts for approximately 3,000 lung cancer deaths per year in the United States.<sup>15</sup>

Since these conclusions were reached, several major studies have been carried out to further characterize the association of passive smoking with lung cancer, while taking into account some of the

limitations of earlier studies, particularly small sample sizes, exposure misclassification, and omission of some potentially confounding factors.<sup>92,93</sup>

Passive smoking is more weakly associated with lung cancer than is active smoking, as would be expected given the generally lower doses of carcinogens that are received passively by the lung of the nonsmoker compared to the doses received by the active smoker. Because of broad societal implications, the conclusion that this association is causal

has been controversial.<sup>94,95</sup> Questions have been raised about the methodology of the epidemiologic studies, including confounding and the misclassification of exposures to environmental tobacco smoking. Review groups have concluded<sup>14,15,91</sup> that the association between ETS and lung cancer cannot be attributed to the methodological limitations of epidemiologic data.

Studies have been directed at the specific venues where nonsmokers are exposed to tobacco smoke, including the home, workplaces, and public places. Much of the literature has focused on the increased risk associated with being married to a smoker, an exposure variable that can be readily ascertained. Meta-analyses have been conducted periodically to summarize the evidence from the epidemiologic studies. A 1997 meta-analysis by Law and colleagues<sup>96</sup> found an approximately 20% increased risk associated with marriage to a smoker. This excess risk appeared to be due to exposure to passive smoking since it could not be explained by confounding or misclassification.

Reynolds<sup>97</sup> summarized the evidence on workplace exposure to secondhand smoke and lung cancer risk. In general, the estimates have indicated the existence of an increased risk associated with exposure, although they are imprecise due to a limited numbers of cases. There is also coherence between model-based estimates derived by combining risk estimates from studies of exposure to smoking by husbands and monitoring data from workplaces.<sup>98</sup>

The studies of passive smoking provide further evidence documenting the dose-response relationship between cigarette smoke and lung cancer. The doses extend to far lower levels than those of active smoking, and increased risk is observed, suggesting that there is no threshold for tobacco carcinogenesis.<sup>14</sup>

*Lung Cancer Histopathology:* Lung cancer occurs in multiple histologic types as classified by conventional light microscopy. The four major types include squamous cell carcinoma, adenocarcinoma, large cell carcinoma, and small cell undifferentiated carcinoma. Together, these four types of lung cancer account for >90% of lung cancer cases in the United States.<sup>99</sup> Despite extensive research, the mechanisms leading to these different types of lung cancer remain uncertain. Hypotheses have focused on the cells of origin of lung cancers and on the pathways of differentiation of malignant cells.<sup>17,99</sup> Smoking has been shown to cause each of the major histologic types of lung cancer, although the dose-response relationship with the number of cigarettes smoked varies across the types and is steepest for small cell undifferentiated carcinoma.<sup>57,100,101</sup> There are a few suggestive links of histologic type with

occupational agents. Small cell lung cancer has been reported to be in excess in workers who have been exposed to chloromethyl ethers and in underground miners who have been exposed to radon progeny.<sup>17,99</sup>

In the initial decades of the smoking-caused epidemic of lung cancer, squamous cell carcinoma was the most frequent type of lung cancer that was observed in the population among smokers, and small cell carcinoma was the next most frequent. In the late 1970s, the first evidence of a shift toward a predominance of adenocarcinoma was noted,<sup>99,102,103</sup> and now adenocarcinoma of the lung is the most common histologic type of lung cancer.<sup>4,28</sup> The decline in lung cancer rates has been more rapid for squamous cell and small cell carcinomas than for adenocarcinoma, which is just beginning to show a lower incidence rate (Fig 6).<sup>4</sup> In women, the Surveillance, Epidemiology, and End Results program data from 1973 to 1996 indicate that the incidence rates of squamous cell, small cell, and large cell carcinomas have at least reached a plateau while the rate for adenocarcinoma is still rising.

While the changing patterns of diagnosis and classification of lung cancers could have led to these changes over time, most observers have set aside an artifactual change.<sup>99,103</sup> Beginning in the 1970s, new techniques for the diagnosis of lung cancer became available, including the fiberoptic bronchoscope and thin-needle aspiration.<sup>104</sup> Improved stains for detecting mucin, the hallmark of adenocarcinoma, also were introduced. Using data from the Connecticut Tumor Registry, Thun et al<sup>104</sup> showed that the rise in adenocarcinoma antedated these diagnostic innovations.

Hypotheses concerning the shift in histopathology have focused on the potential role of changes in the characteristics of cigarettes and the consequent changes in the doses of carcinogens inhaled.<sup>60,101,105</sup> Puff volume likely has increased over recent decades with the possibility that patterns of deposition in the lung have changed, tending toward enhanced deposition of tobacco smoke in the peripheral airways and alveoli.<sup>105</sup> The levels of nitrate, which enhances the combustion of tobacco, also have increased in tobacco smoke. While more complete combustion decreases the concentrations of polycyclic aromatic hydrocarbons, the increased production of nitrogen oxides contributes to the increased formation of tobacco-specific nitrosamines. An increase in the dose of the potent tobacco-specific nitrosamine NNK has been postulated as one factor leading to the increase in adenocarcinoma.<sup>105,106</sup> NNK induces lung carcinomas, predominantly adenomas and adenocarcinomas, in mice, regardless of the route of administration.<sup>106</sup>

Few studies can provide data to test these hypo-

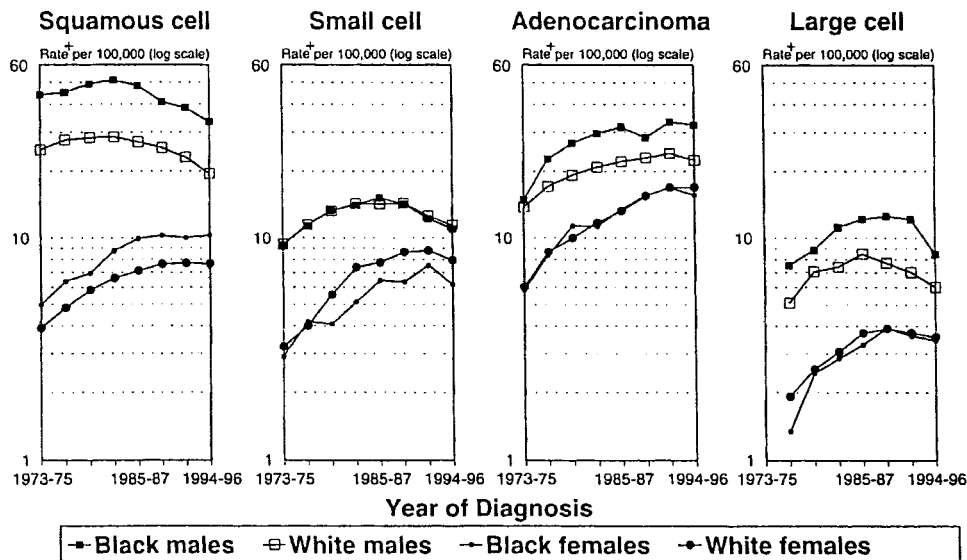


FIGURE 6. Surveillance, Epidemiology, and End Results incidence rates of cancer of the lung and bronchus by histologic type, sex, race, and ethnicity for all ages, 1973 to 1996. Adapted from Wingo et al.<sup>4</sup>

eses because of the need for longitudinal observation of lung cancer risk in relation to the characteristics of the cigarettes smoked over time. Thun et al<sup>104</sup> compared the risks for lung cancers of different histologic types among participants in CPS I and CPS II of the American Cancer Society. They found markedly rising risks for adenocarcinoma of the lung to be associated with smoking in both men and women over the approximately 20 years separating the two studies. Thun et al<sup>104</sup> concluded that “the increase in lung adenocarcinoma since the 1950s is more consistent with changes in smoking behavior and cigarette design than with diagnostic advances.”

The hypothesis has been advanced that women may have a greater risk of lung cancer than men at the same level of smoking. Hypotheses have been based on possible hormonally related differences in response to carcinogens. The evidence is limited and mixed, and the 2001 Report of the Surgeon General<sup>107</sup> did not reach a conclusion on this issue.

### Diet

*Overview:* The dietary factors that have received greatest emphasis in studies of diet and lung cancer, namely fruits, vegetables, and specific antioxidant micronutrients, are the focus of this summary. These are the research areas that also presently appear to have the greatest implications for lung cancer prevention. Much of the research on diet and lung cancer has been motivated by the hypothesis that diets high in antioxidant nutrients may protect against oxidative DNA damage and thereby protect against cancer.<sup>108</sup>

Within this limited range of topics, we have attempted to be comprehensive in our review. We omitted studies with lung cancer mortality as the end point, as different factors may be associated with survival of lung cancer than disease risk. We limited our consideration of specific micronutrients to retinol, total carotenoids,  $\beta$ -carotene, and vitamin C. For these postulated relationships, there is no reason to suspect a threshold effect in the exposure-response relationship. Rather, a dietary factor that protects against lung cancer would theoretically be expected to confer greater protection when present in greater amounts. Consequently, dose-response trends are emphasized in this review, with the presence of a monotonic dose-response relationship considered to provide strong evidence favoring an association, and measures of association in the protective direction but with no dose-response gradient providing weak evidence in favor of an association.

The overwhelming contribution of cigarette smoking as a cause of lung cancer imposes challenges to detecting the role that other lifestyle factors, such as diet, may play in the etiology of lung cancer. Cigarette smoking is so closely associated with less healthful lifestyles, such as less healthful diets,<sup>109–113</sup> that it is often difficult to discern whether the dietary factors of interest have truly been disentangled from the effects of smoking. Compounding this problem, even associations between dietary factors and lung cancer that truly exist are likely to be very weak in relation to smoking. Even for a dietary factor such as vegetable consumption (reviewed below), which is fairly consistently associated with a lower risk of lung

cancer, the highest exposure category is usually associated with, at most, a halving in the risk of lung cancer. In many instances, the potential residual confounding effects of smoking could thus plausibly be strong enough to explain the observed associations between dietary factors and lung cancer.<sup>114</sup> In the future, studies that control for cigarette smoking in the design are best suited to address the persistent concern about residual confounding by cigarette smoking. Examples are case-control studies, in which cases and control subjects are closely matched on cigarette smoking history, and studies limited to never-smokers.

*Fruit and Vegetable Consumption:* In case-control studies, fruit consumption has been clearly protective in 4 studies,<sup>115–118</sup> suggestive of a protective association in 4 other studies,<sup>119–122</sup> and not protective in 10 studies.<sup>123–132</sup> In prospective studies, fruit consumption has been clearly protective in three studies,<sup>133–135</sup> suggestive of a protective association in two other studies,<sup>136,137</sup> and not protective in two studies.<sup>138,139</sup> The combined evidence for fruit consumption is far from consistent but hints at the possibility of a protective association.

The evidence favoring a protective association is more consistent for vegetable consumption. In case-control studies, 12 studies showed a decreased lung cancer risk as vegetable consumption increased,<sup>115–117,123–125,127,129,132,140–142</sup> while 5 other studies showed a weak association in this direction.<sup>93,118,126,143,144</sup> A protective association was absent in only six studies.<sup>119–121,128,131</sup> In prospective studies, vegetable consumption was clearly protective in two studies,<sup>134,137</sup> was suggestive of a protective association in two other studies,<sup>135,138</sup> and was not protective in two studies.<sup>133,136</sup>

*Micronutrients:* Two different strategies used to evaluate the relationship of micronutrients to lung cancer are (1) using data summarized from food-frequency questionnaires to estimate micronutrient intake and (2) drawing blood samples from study participants and assaying the concentrations of micronutrients in circulation. The former approach provides a better average measure of micronutrient “exposure,” whereas the latter approach has the advantage of measuring micronutrient concentrations closer to the cellular level where the postulated biological effect occurs. As mentioned above, we focused on vitamins A and C, total carotenoids, and  $\beta$ -carotene.

Evidence consistent with higher dietary retinol intake being associated with a reduced risk of lung cancer in at least one subgroup has been observed in only 11 studies,<sup>122,145–154</sup> with 17 studies not providing

supportive evidence.<sup>118,121,124–126,129,132,133,140,143,155–161</sup> Circulating retinol concentrations also have not been consistently associated with protective associations.<sup>162–172</sup>

In contrast to the results for retinol, the results for total carotenoids,  $\beta$ -carotene, and vitamin C are more supportive of a reduction in lung cancer risk. Higher dietary intake of total carotenoids were consistent with a protective association in 18 observational studies<sup>119,121,122,125,126,132,135,139,143,146,150,153,155,156,161,173–175</sup> and were not supportive in 6 studies.<sup>124,129,133,137,157,166</sup> Circulating concentrations of total carotenoids have been linked to a reduced risk of lung cancer.<sup>163,172</sup> Similar protective associations have also consistently been observed for a specific carotenoid,  $\beta$ -carotene. Data from 16 case-control and cohort studies<sup>93,118,122,125,126,129,135,137,139,140,148,154,160,176–178</sup> of dietary  $\beta$ -carotene intake were compatible with associations in the protective direction. In only five studies<sup>121,124,134,138,152</sup> have null findings been observed. Further bolstering the evidence in favor of a protective association between  $\beta$ -carotene and lung cancer are prospective studies in which  $\beta$ -carotene is assayed from blood that has been collected from a population that was initially cancer-free and was subsequently followed-up for the occurrence of lung cancer.<sup>163,166,168,169,172,179,180</sup> The preponderance of evidence from observational studies thus has demonstrated a protective association between carotene (specifically,  $\beta$ -carotene) and lung cancer.

The evidence for the protective association of vitamin C is less abundant than for total carotenoids and  $\beta$ -carotene but also is suggestive of a protective association. For vitamin C intake, six case-control or cohort studies<sup>133,150,155–157,178</sup> were at least compatible with an inverse association with lung cancer risk, whereas three studies were not.<sup>93,124,176</sup> A serologic study of ascorbic acid concentrations and lung cancer was also compatible with a protective association.<sup>179</sup>

*Chemoprevention Trials:* The experimental rationale for trials of  $\beta$ -carotene and retinoids is offered in another article in this supplement. These data indicated a potential for prevention with these agents, as supported by observational data as well. However, a protective association between  $\beta$ -carotene and lung cancer was not found in three randomized, double-blind, placebo-controlled chemoprevention trials<sup>181–183</sup> of  $\beta$ -carotene, which indicated that  $\beta$ -carotene supplementation does not protect against lung cancer. In fact,  $\beta$ -carotene supplementation was associated with an increased risk of lung cancer among the high-risk populations of heavy smokers in the  $\alpha$ -Tocopherol  $\beta$ -Carotene Cancer Prevention Study<sup>181</sup> and of smokers and asbestos-exposed workers in the Carotene and Retinol Efficacy Trial.<sup>183</sup>

In summary, people who eat more vegetables are at lower risk of lung cancer than persons who consume fewer vegetables. The same may also apply to fruit consumption, but the evidence is less clear-cut. The specific constituents of vegetables that confer protection are not known. The results of the chemoprevention trials clearly suggest a more complex role than researchers had previously thought. These trials also emphasize that we do not know whether the associations present in observational studies are specific to the micronutrients or whether the micronutrient measurements are merely serving as a marker of the intake of other protective substances or even of more healthful dietary habits in general.

If the association is attributable to vegetable consumption, we need to determine whether this effect applies globally to vegetable consumption or to specific classes of vegetables or specific vegetables. For example, carrots<sup>115,137,140,144,146</sup> and tomatoes<sup>118,119,137,140,146</sup> are associated with a reduced risk of lung cancer, at least for the highest vs the lowest categories of consumption. Resolving this question also will help to clarify whether specific biochemical constituents that are present in vegetables confer protection against lung cancer or whether the complex mixture that comprises vegetables leads to the net protective effect. Reports from large-scale prospective cohort studies that considered overall fruit and vegetable consumption as well as classes of vegetables (*eg*, cruciferous, brassica) and also individual micronutrients<sup>138,138</sup> exemplify the comprehensive approach that affords the greatest opportunity to pinpoint the specific foods and/or nutrients that may explain the apparent protective association with vegetable consumption.

### *Environmental Exposures*

*Occupational Exposures:* Investigations of occupational groups, who often are heavily exposed over a long time to workplace agents, have provided a substantial understanding of the carcinogenicity of a number of chemicals and physical agents. Among cancers that are associated with occupational exposures, cancer of the lung is the most common.<sup>184</sup> Estimates derived from case-control studies of the proportion of lung cancer that is contributed to by occupational exposures, via independent or shared causal pathways, have ranged widely, but most point estimates or ranges have included values from 9 to 15%.<sup>185–191</sup> While disagreement persists concerning specific estimates,<sup>192</sup> the following message is clear: in industrialized nations the contribution of occupational exposures to the lung cancer burden is small compared to that of cigarette smoking, but it is large

compared to the contributions of most other exposure classes. Cigarette smoking potentiates the effect of many of the known occupational lung carcinogens.<sup>42</sup>

Lung cancer has been observed to be associated with many workplace exposures. Workers exposed to tar and soot (which contains benzo[a]pyrene), such as coke oven workers,<sup>193,194</sup> in concentrations exceeding those present in urban air<sup>195</sup> are at increased risk of lung cancer. Occupational exposures to a number of metals, including arsenic,<sup>196–198</sup> chromium,<sup>199–201</sup> and nickel,<sup>202–204</sup> are also causes of lung cancer.<sup>205,206</sup> For many persons in the worker groups that have been exposed to these agents, there were substantial increments in risk. However, in developed countries these hazards largely have been controlled.

For some other workplace agents, the evidence has been less clear. The results of numerous case-control and cohort studies<sup>207</sup> are compatible with a weak association between exposure to diesel exhaust and the development of lung cancer. Although inadequate control of cigarette smoking limits the inferences that can be drawn from many of these studies, the exposure to diesel exhaust remains a likely explanation for these findings.<sup>207</sup> This association remains a public health concern, as the public is exposed to diesel exhaust in urban areas, and in some European countries diesel vehicles are being used increasingly.<sup>43</sup>

The question of whether silica dust is a risk factor for lung cancer has been controversial.<sup>208–210</sup> A twofold increase in lung cancer risk was estimated from a meta-analysis<sup>211</sup> of the relationship between silicosis and lung cancer mortality. Effects of smoking have not been well-controlled in most of the studies.<sup>211</sup> The evidence on silica exposure, absent consideration of the presence of silicosis, is less clear.<sup>212,213</sup> In 1997, IARC did classify crystalline silica as a human carcinogen<sup>214</sup>; however some still continue to question its carcinogenicity<sup>213</sup> and the role of silica exposure vs that of fibrosis in persons with silicosis.<sup>212</sup>

*Asbestos:* Asbestos, a well-established occupational carcinogen, refers to several forms of fibrous, naturally occurring silicate minerals.<sup>215</sup> The epidemiologic evidence dates to the 1950s, although clinical case series had previously led to the hypothesis that asbestos causes lung cancer.<sup>216,217</sup> In a retrospective cohort study published in 1955, Doll<sup>218</sup> observed that asbestos textile workers at a factory in the United Kingdom had a 10-fold elevation in lung cancer risk and that the risk was most heavily concentrated during the time frame before regulations had been implemented to limit asbestos dust in



factories. A sevenfold excess of lung cancer was subsequently observed among insulation workers in the United States.<sup>219,220</sup> The peak incidence occurred 30 to 35 years after the initial exposure to asbestos (Fig 7).<sup>221</sup> The risk of lung cancer has been noted to increase with increased exposure to asbestos<sup>222</sup> and to be associated with the principal commercial forms of asbestos.<sup>223</sup> Whether asbestos acts directly as a carcinogen or through indirect mechanisms such as causing chronic inflammation that eventually leads to cancer development remains uncertain.<sup>224,225</sup>

Asbestos and cigarette smoking are both independent causes of lung cancer, but in combination they act synergistically to increase the risk of lung cancer in a manner that is compatible with a multiplicative effect (Table 6).<sup>226</sup> Cigarette smoking may increase the lung cancer risk associated with asbestos exposure by enhancing the retention of asbestos fibers.<sup>227</sup>

### Radiation

Epidemiologic studies of populations that have been exposed to high doses of radiation show that lung cancer is one of the cancers associated with exposure to ionizing radiation. However, the risks of low-dose radiation, which are more relevant to contemporary workers and the general population, have proven difficult to characterize.<sup>228</sup> Assessing the

**Table 6—Summary of the Joint Relationship Between Cigarette Smoking and Asbestos Exposure on the Risk of Lung Cancer Mortality\***

Smoking	Mortality Rates		Additive Model		Multiplicative Model	
	No	Yes	No	Yes	No	Yes
No	11.3	58.4	0	47.1	1.0	5.17
Yes	122.6	601.6	111.3	590.3†	10.85	53.24‡

\*Mortality rates are per 100,000 population. Table adapted from Hammond et al.<sup>226</sup>

†Rate difference compared to referent category of no smoking and no asbestos exposure. Expected value under model of no statistical interaction is 158.4.

‡Rate ratio compared to referent category of no smoking and no asbestos exposure. Expected value under model of no statistical interaction is 56.1.

cancer risk that is associated with exposure to low-dose radiation among humans is methodologically difficult because the signal-to-noise ratio is highly unfavorable.<sup>229</sup>

The following two types of radiation, which are classified by the rate of energy transfer to the tissue, are relevant to lung cancer: low linear energy transfer (LET) radiation (*eg*, x-rays and gamma rays); and high-LET radiation (*eg*, neutrons and radon). High-LET radiation produces ionization of a relatively higher density in tissues than does low-LET radiation, so in equivalent doses more biological damage

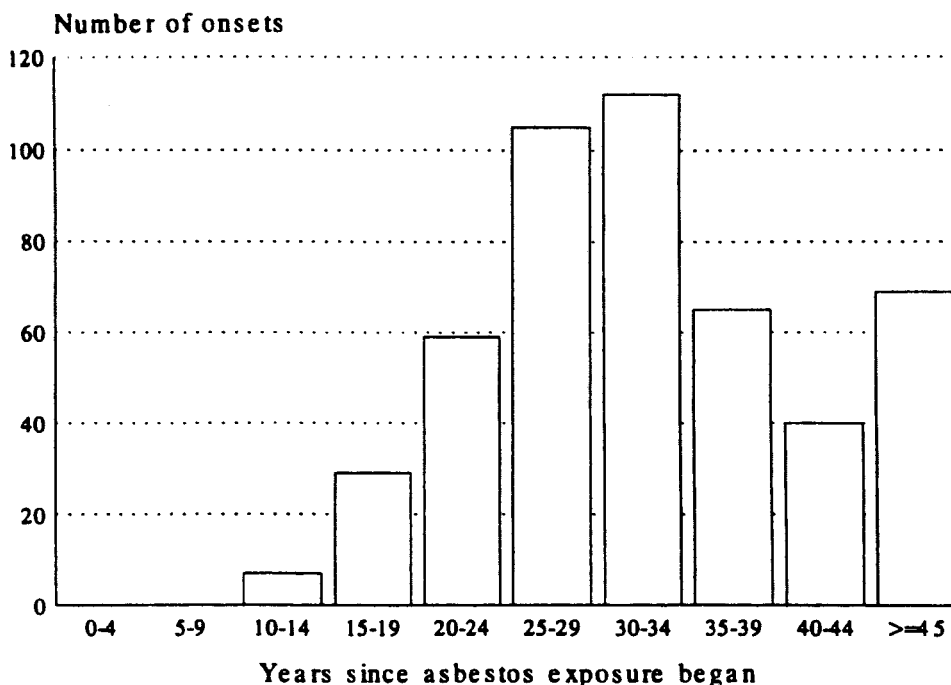


FIGURE 7. Frequency distribution of the number of lung cancer cases by time since asbestos exposure began among a cohort of asbestos insulation workers. Adapted from Selikoff.<sup>221</sup>

is produced by high-LET than by low-LET radiation.<sup>230</sup> For both types of radiation, the majority of the epidemiologic evidence comes from cohorts who have been exposed at levels substantially greater than those experienced by the general population. Risk assessment methods then are used to estimate the risks to the population.

*High-LET Radiation (Radon):* Radon is an inert gas that is produced naturally from radium in the decay series of uranium. Two of the decay products of radon emit  $\alpha$  particles that can, by virtue of their high energy and mass, cause damage to the DNA of cells of the respiratory epithelium. Epidemiologic studies of underground miners of uranium and other ores have established exposure to radon daughters as a cause of lung cancer.<sup>17,231,232</sup> In the miners who were exposed to radon in past centuries, very high lung cancer risks were observed. These risks fell for more recent workers, but some epidemiologic studies<sup>17</sup> still show clear evidence of existing cancer risk. Cigarette smoking and radon decay products synergistically influence lung cancer risk in a manner that is supra-additive but submultiplicative.<sup>17,232</sup>

Radon is of broader societal interest because it is a ubiquitous indoor air pollutant, entering buildings in soil gas. On average, indoor exposures to radon for the general population are much less than those received by occupational groups such as uranium miners. For example, even the lowest historical radon concentration in a uranium mine is roughly 50 to 100 times higher than in the average home.<sup>232</sup> Exposure to radon in indoor air also is assumed to cause lung cancer, but the magnitude of the risk is uncertain because of the assumptions underlying the extrapolation of findings from uranium miners to the generally lower exposures indoors. These assumptions relate to dose, dose-rate, and dosimetry, and also reflect the lack of information on risks of exposures of women and children. Strengthening biological evidence supports the assumption that a single hit to a cell by an  $\alpha$  particle causes permanent cellular change, an assumption leading to a non-threshold dose-response relationship.

The assumptions made by the Environmental Protection Agency and the Biological Effects of Ionizing Radiation IV and VI Committees of the National Research Council have led to estimates that approximately 15,000 to 20,000 lung cancer deaths per year in the United States are caused by radon.<sup>233</sup> Case-control studies concerning indoor exposure to radon as a risk factor for lung cancer, which were undertaken to directly assess risks, have produced findings that are generally consistent with downward extrapolation of risk models based on the underground miners.<sup>234</sup> When combined with meta-

analysis, there is a significant association between indoor radon and lung cancer in the general population that is quantitatively comparable with risk models derived from the underground miners. This coherence lends support to using extrapolation of the miner data to estimate the risk of indoor radon.

*Low-LET Radiation (X-Rays and Gamma Rays):* Epidemiologic data relating low-LET radiation to lung cancer stem from the following three principal populations: the atomic bomb survivors in Japan<sup>235</sup>; patients with diseases such as ankylosing spondylitis<sup>236</sup> or tuberculosis,<sup>237,238</sup> who received multiple radiation treatments; and occupational groups in professions who are exposed to radiation.<sup>239</sup> The single, high-dose exposure of the atomic bomb survivors was associated with a significant lung cancer risk.<sup>235</sup> Regardless of their age when the atomic bombs were dropped, the excess of lung cancer did not occur until the survivors reached older ages when cancer usually occurs.<sup>235</sup>

The risks associated with exposure to lower doses of low-LET radiation have been estimated in two ways. Statistical models have been used to extrapolate from the data of the atomic bomb survivors to lower doses. Tuberculosis patients who received radiation therapy also have been studied. They were intermittently exposed to radiation. Such intermittent, low-dose exposures may be most pertinent for the general population because this exposure pattern is the most common in technologically advanced societies. Studies of tuberculosis patients have suggested that if there is any risk of lung cancer associated with this exposure pattern, it is small,<sup>237,238</sup> implying that the assumptions on which the higher risk estimates obtained from the atomic bomb survivors data may in actual fact not hold.<sup>238</sup>

Low-LET radiation therefore appears to be associated with higher lung cancer risk when exposure occurs at a higher dose rate.<sup>238</sup> These results contrast with those for high-LET radiation, suggesting that the two types of radiation have different dose-rate relationships.<sup>238</sup>

#### *Air Pollution*

During a typical day, the average adult inhales about 10,000 L air.<sup>240</sup> Consequently, even the carcinogens that are present in the air at low concentrations are of concern as a risk factor for lung cancer. Extrapolation of the risks associated with occupational exposures to the lower concentration of carcinogens in polluted ambient air leads to the conclusion that a small proportion of lung cancer cases could be due to air pollution.<sup>184,205,241</sup>

*Atmospheric Air Pollution:* Carcinogens generated

by combustion of fossil fuels include polycyclic aromatic hydrocarbons and metals such as arsenic, nickel, and chromium.<sup>205</sup> In considering respiratory carcinogenesis, the constituents of air pollution will vary by locale and over time depending on the pollution sources.<sup>242</sup> Consequently, epidemiologic investigations of air pollution and lung cancer have been limited by the difficulty of estimating exposure. Nevertheless, descriptive evidence is consistent with a role for air pollution in causing lung cancer. Urbanization and lung cancer mortality are linked.<sup>38,243–245</sup> This association could arise from differences in the distributions of other lung cancer risk factors, such as smoking and occupational exposures, by degree of urbanization. Adjustment for these factors may considerably attenuate the effect of urban location,<sup>246,247</sup> but an urban effect persists in a number of studies.<sup>43</sup>

Air pollution has been assessed as a risk factor for lung cancer in both case-control and cohort studies. These studies have been reviewed in detail elsewhere.<sup>43,248</sup> These reviewers have found the evidence wanting because of the potential for exposure misclassification and for uncontrolled confounding.

Two prospective cohort studies<sup>249,250</sup> that partially address these weaknesses of earlier studies have added evidence suggesting that air pollution is weakly associated with the risk of lung cancer. By prospectively studying air pollution levels in relation to the risk of lung cancer, and by controlling for possible confounders such as age, smoking, and socioeconomic status at the individual level, these studies surmount some shortcomings noted in much previous research.<sup>251</sup> In a study of six US cities,<sup>249</sup> the adjusted risk of lung cancer mortality in the city with the highest fine particulate concentration was 1.4 times (95% confidence interval, 0.8 to 2.4) higher than that in the least polluted city. Using data from CPS II of the American Cancer Society, Pope and colleagues<sup>250</sup> observed that, compared to the least polluted areas, residence in areas with high sulfate concentrations was associated with an increased risk of lung cancer (adjusted relative risk, 1.4; 95% confidence interval, 1.1 to 1.7) after adjustment for occupational exposures and the factors mentioned above. However, unlike the Six-Cities study, fine particulate concentration was not associated with lung cancer risk.<sup>250</sup> By contrast, in the American Cancer Society CPS I cohort air pollution was not associated with lung cancer risk. In that study, men were stratified according to exposures in the workplace but relied only on proxy, less specific measures of air pollution.<sup>251</sup> Some case-control studies<sup>252–254</sup> have reported indexes of air pollution to be modestly associated with elevated risks of lung cancer, but others<sup>121,255</sup> have reported no association. Another

research approach to evaluate the risk of air pollution has been to investigate populations residing around point sources of pollution, such as factories and smelters. Proximity of residence to the pollution source can be used as a proxy for exposure. Many industries have been studied using this approach. Areas surrounding nonferrous smelters, which emit arsenic, have been of particular interest. An ecologic study reported by Blot and Fraumeni<sup>37</sup> in 1975 suggested that excess lung cancer occurred in US counties with copper, lead, or zinc smelting and refining industries. The results of several subsequent case-control studies<sup>256–258</sup> have lent support to this hypothesis by showing that the risk of lung cancer increased the nearer persons lived to nonferrous smelters, after accounting for personal cigarette smoking and employment at the smelter. Other case-control studies did not replicate this finding<sup>259,260</sup> but were also limited by their failure to account for smoking and employment at the smelter.

Doll and Peto,<sup>184</sup> in their 1981 review of the causes of cancer, estimated that perhaps 1 to 2% of lung cancer cases were related to air pollution. Even in light of recent findings, this appears to remain a reasonable estimate. To the extent that air pollution may contribute to the occurrence of lung cancer, and the overall epidemiologic evidence is equivocal, its contribution is minimal relative to cigarette smoking. This is to be expected, given that respiratory doses of carcinogens from active smoking are significantly greater than those received from the inhalation of atmospheric contaminants.

*Indoor Air Pollution:* An individual's total exposure to air pollution depends on indoor as well as outdoor exposures. Indoor air quality has large potential health implications because people may spend substantial amounts of time indoors. Indoor air pollution may stem from incoming outdoor air or may originate indoors from tobacco smoking, building materials, soil gases, household products, and combustion from heating and cooking.<sup>261</sup> A trade-off exists between energy efficiency and indoor air quality, as ventilation allows heated/cooled air to escape but improves indoor air quality.<sup>262</sup>

As discussed earlier, in more developed countries, two of the most important indoor pollutants that influence lung cancer risk in never-smokers are passive smoking<sup>14</sup> and radon.<sup>231</sup> Asbestos exposure may pose a risk to building occupants, but it is estimated to be minimal.<sup>215</sup> Of major concern in the developing world is the indoor air contamination resulting from the use of unprocessed solid fuels, notably coal, for cooking and space heating.<sup>263</sup> Mumford and colleagues<sup>264</sup> inferred that smoky coal was likely to be a major determinant of the geographic

distribution of lung cancer in Xuan Wei, China, a finding that was corroborated by an animal model.<sup>265</sup> Case-control studies conducted elsewhere in mainland China<sup>131,258</sup> and Taiwan<sup>149</sup> further implicated coal use as a risk factor for lung cancer. Another case-control study in Shanghai,<sup>266</sup> where most homes are unheated, reported no association between the use of coal and lung cancer risk. Exposure to coal burning in the preadult years was associated with lung cancer risk in a case-control study of women in Los Angeles County.<sup>154</sup>

## HOST FACTORS

### Overview

Genetic susceptibility to lung cancer has long been postulated. Environmental agents, even cigarette smoking, cause lung cancer in only a minority of exposed persons, leading to the hypothesis that susceptibility is inherently determined. Epidemiologic studies showing that a family history of lung cancer predicts increased risk further support a genetic basis for lung cancer susceptibility. This long-postulated hypothesis is now being actively addressed using the approach of molecular epidemiology. Full coverage of this topic is beyond the scope of this article. Aspects of genetic susceptibility have been reviewed previously.<sup>267,268</sup>

Familial aggregation of lung cancer has been demonstrated primarily in case-control studies (Table 7).<sup>266,269-278</sup> In these studies, a family history of

lung cancer tended to be associated with increased risk of lung cancer. Most of the studies controlled for smoking, which is known to aggregate in families. In a large study in Louisiana,<sup>279</sup> segregation analysis suggested that lung cancer inheritance was consistent with a mendelian codominant autosomal gene determining the early onset of disease. On the other hand, the largest study<sup>280</sup> of lung cancer in twins reported to date did not provide evidence indicating a genetic basis for susceptibility. A follow-up of 15,924 male twin pairs in the United States did not show greater concordance in monozygotic compared with dizygotic twins, and death rates from lung cancer were similar by zygosity group in surviving twins whose siblings had died of lung cancer.

Nevertheless, the evidence for aggregation and seeming susceptibility of some smokers has been viewed as a sufficient rationale for further investigation of the potential basis for lung cancer, using the new techniques of cellular and molecular biology.

### Research Findings on the Genetic Basis of Lung Cancer

With the application of the new and powerful tools of modern molecular and cell biology, research findings are now characterizing the changes in cells that are caused by exposure to tobacco smoke and are providing a framework for understanding the genetic basis of lung cancer risk. Figure 8, adapted

**Table 7—A Summary of Case-Control Studies of Lung Cancer Among Persons With a Family History of Lung Cancer Compared to Those With No Family History of Lung Cancer**

Study/Year	Location	Odds Ratio*	Comment
Tokuhata and Lilienfeld <sup>269</sup> /1963	Buffalo, NY	2.4 (1.1, 5.2)	Adjusted for cigarette smoking, age, sex, generation
Tokuhata <sup>270</sup> /1964	Baltimore, MD	2.6 (1.4, 5.4)	Adjusted for age, sex, generation
Ooi et al <sup>271</sup> /1986	10 Louisiana Parishes	2.7 (1.7, 4.2)	Adjusted for smoking, sex
Samet et al <sup>272</sup> /1986	New Mexico	Parental: 5.3 (2.2, 12.8)	Adjusted for cigarette smoking, age, sex, ethnicity
Gao et al <sup>266</sup> /1987	Shanghai, P.R.C.	Parental: 1.1 (0.6, 2.3) Sibling: 3.0 (0.7, 12.5)	Adjusted for smoking, age
Tsugane et al <sup>273</sup> /1987	Tokyo, Japan	1.0 (0.3, 3.9)	Smoking and occupational exposure data collected, but not adjusted for
Horwitz et al <sup>274</sup> /1988	New Haven, CT	2.3 (0.6, 9.7)	Adjusted for smoking
McDuffie <sup>275</sup> /1991	Saskatchewan, Canada	2.0 (1.2, 3.4)	Smoking and occupational exposure data collected, but not adjusted for
Osann <sup>276</sup> /1991	Northern California	1.9 (0.7, 5.6)	Adjusted for cigarette smoking education, matched on age and race
Shaw et al <sup>277</sup> /1991	Gulf Coast of Texas	1 1st degree relative with cancer: 1.7 (1.2, 2.4)	Adjusted for cigarette smoking, passive smoking, and number of first degree relatives
Filho et al <sup>278</sup> /1995	Sao Paulo, Brazil	2 1st degree relatives with cancer: 2.8 (1.2, 6.6) 3.2 (1.0, 11.1)	Smoking and occupational exposure data collected, but not adjusted for

\*Referent category of persons with no family history of lung cancer = 1.0. Values in parentheses are confidence limits.

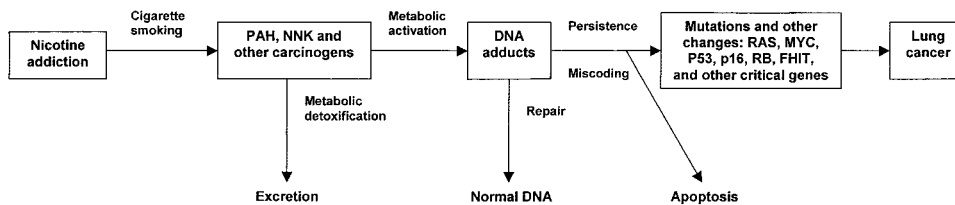


FIGURE 8. Scheme linking nicotine addiction and lung cancer via tobacco smoke carcinogens and their induction of multiple mutations in critical genes. Adapted from Hecht.<sup>106</sup>

from Hecht,<sup>106</sup> offers a general schema for the process of carcinogenesis by tobacco smoking. Viewed in the framework set by this type of model, research findings mirror the predictions of the multistage model in many respects and are enhancing the understanding of the mechanisms by which smoking causes cancers of the lung and other organs. A rapidly expanding literature, based both in the laboratory and in the observational approach often referred to as molecular epidemiology, addresses the dosimetry and metabolism of tobacco carcinogens at the cellular and molecular levels, the genetic determinants of susceptibility, and the patterns of genetic changes in the tissues of smokers and in the cancers that the tissues develop.<sup>106,267</sup>

In a general formulation of the determinants of cancer risk, the risk depends on carcinogen exposure and the factors that determine host susceptibility, including genetic predisposition.<sup>281</sup> For tobacco smoking and lung and other cancers, the elements of this paradigm are all topics of inquiry, using the combination of laboratory-based and population-based studies that are indicated in the diagram. Biomarkers are central to the molecular epidemiology approach. The term refers to making measurements of indicators of exposure and dose, susceptibility, and response in biological materials, including tissue samples, blood, urine, and saliva.<sup>282–285</sup> As research evolves within this paradigm, a more complete biological understanding of the specific events underlying the multistage model, which originally was proposed on a conceptual basis, can be anticipated.

This framework indicates multiple points at which genetically determined host characteristics might be important (*eg*, carcinogen metabolism and activation, and DNA repair capacity).

There is a rapidly expanding literature on the molecular and cellular basis of lung cancer. It is beyond the scope of this review to cover this topic. Some reviews have been published.<sup>267,286</sup> The evidence has expanded and deepened our understanding of how smoking injures cells and causes cancer.

Many carcinogenic compounds in tobacco smoke (*eg*, polycyclic aromatic hydrocarbons) undergo met-

abolic activation by phase I enzymes of the cytochrome p450 system to form reactive intermediates that bind to DNA and cause genetic injury. Two of these enzymes have been investigated with regard to lung cancer risk (CYP1A1 and CYP2D6). For CYP1A1, the evidence has varied across populations. The finding that a particular polymorphism was associated with increased lung cancer risk in Japan<sup>287</sup> was not replicated in Brazil<sup>288</sup> or in the United States.<sup>289</sup> A different and unique polymorphism found in African-Americans and Africans was associated with lung cancer in one case-control study of African-Americans<sup>290</sup> but not in another.<sup>291</sup>

Both phenotype and genotype have been examined for CYP2D6. This enzyme determines the phenotype for debrisoquine metabolism, which has been studied extensively as a risk factor for lung cancer.<sup>268</sup> The initial case-control studies found that fast metabolizers had a greater lung cancer risk, which is consistent with the hypothesized role of the rate of metabolism in determining lung cancer risk,<sup>292</sup> although a subsequent and larger study found no association.<sup>293</sup> More recent studies<sup>267</sup> that have assessed genotype have generated inconsistent results.

Glutathione S-transferase is a phase II enzyme that detoxifies reactive metabolites of polycyclic aromatic hydrocarbons. There are at least four genetically distinct classes of the glutathione S-transferases as follows:  $\mu$ ,  $\alpha$ ,  $\pi$ , and  $\theta$ . The results of several studies<sup>294,295</sup> have shown that individuals with high activity of the glutathione S-transferase  $\mu$ -polymorphism have lower risk of lung cancer. Other studies, however, have not supported this finding.<sup>296,297</sup> Nakachi and colleagues<sup>287</sup> conducted a case-control study in Japan that jointly assessed two polymorphisms of the CYP1A1 gene and the deficient genotype of glutathione S-transferase  $\mu$ . There was an indication of extremely high risk among lower exposure smokers if both high-risk genotypes were present.

There are other candidates for determinants of susceptibility to lung cancer in smokers, including oncogenes and suppressor genes and DNA repair capacity.<sup>267</sup> Much research remains to be done to clarify the association between variations in DNA

repair capacity and lung cancer risk, but the evidence to date suggests that this is a promising lead. For example, a polymorphism of the DNA repair gene XRCC1 was significantly associated with lung cancer risk.<sup>298</sup> Individuals with a less proficient DNA repair capacity phenotype, as measured by a mutagen sensitivity assay, have been shown to have an increased risk of lung cancer.<sup>299,300</sup>

### *Presence of Acquired Lung Disease*

In addition to hereditary factors, increased susceptibility to lung cancer may result from previously incurred lung damage. Such acquired lung diseases assume the following two major forms: (1) those that obstruct airflow, such as COPD; and (2) fibrotic disorders that restrict lung capacity, such as pneumoconiosis.<sup>301</sup> Associations between lung cancer and both types of acquired lung disease have been noted, but, as mentioned below, this topic is complex and many issues await resolution. These questions have been controversial for > 60 years.<sup>302</sup>

A substantial body of evidence suggests that COPD or impaired lung function is associated with the occurrence of lung cancer.<sup>303</sup> Cigarette smoking is the principal cause of both COPD<sup>304</sup> and lung cancer, being so strongly causally associated with both of these illnesses that presuming that statistical adjustment procedures “remove” the effect of cigarette smoking may not be well-founded. Thus, clarifying the relevance of COPD to the development of lung cancer awaits further proof that this association is not accounted for by cigarette smoking. The presence of COPD may indicate that the affected individual has received a greater dose of tobacco carcinogens than the typical unaffected individual. Regardless of the mechanism, the presence of COPD is a clinically useful risk indicator.

Clarifying the possible relationship between pneumoconiosis and lung cancer poses particularly vexing challenges. Even for asbestos exposure, which clearly has been established as a potent cause of lung cancer,<sup>223</sup> whether lung cancer results from asbestos *per se* and/or asbestosis remains unresolved.<sup>224</sup> Asbestos is likely to cause lung cancer via multiple mechanistic pathways.<sup>305,306</sup> For other mineral fibers, the situation is murkier. For example, determining whether silica exposure or silicosis mediates the increased lung cancer risk in silica-exposed persons has proven difficult.<sup>307,308</sup> The presence of silicosis is associated with an increased risk of lung cancer.<sup>211</sup> Understanding the basis of this association will entail isolating the independent effects of silica exposure and lung fibrosis while controlling for exposure to smoking and other lung carcinogens.<sup>209,225</sup>

Such differences in the pattern of associations between pneumoconiosis and lung cancer emphasize that “fibrosis” is not a homogeneous exposure but one that is dependent on the properties of the specific mineral fiber or other environmental agent. Properties of the agent, such as its size, shape, and durability, and the effects of other exposures, such as cigarette smoking, are important considerations in assessing its potential harmfulness.<sup>305</sup>

### CONCLUSIONS

The path to preventing lung cancer is charted by the identification of numerous exposures that are causally associated with lung cancer. If steps can be taken to reduce or eliminate the population's exposure to these agents, this would be expected to reduce the population's risk of lung cancer. Preventive strategies can be pursued in the public policy arena or in public health interventions that are directed at individual behavior. Cigarette smoking provides a useful example to illustrate the multiple levels that can form the basis of preventive strategies. In the legislative/regulatory arena, examples of tobacco control strategies include legislation that limits cigarette advertising, that reduces children's access to cigarettes, and that prohibits smoking in the workplace. Litigation against cigarette manufacturers also has proven to be a productive component of tobacco control strategies, as exemplified by the settlement of suits between the states and the tobacco industry. Behavioral interventions to prevent children and adolescents from starting to smoke cigarettes and behavioral/pharmacologic interventions to promote smoking cessation are individual-level approaches that, if successful, could be expected to reduce the occurrence of lung cancer.

In developing lung cancer prevention strategies, certain groups warrant particular attention. Steps need to be taken toward the goal of reducing the very high lung cancer incidence rates in African-American men.<sup>309</sup> Lung cancer is a major health issue for women. Due to historical cigarette smoking patterns, the epidemic of lung cancer started later in women than in men, but, in contrast to the situation in men, lung cancer incidence rates in women are still increasing.<sup>310</sup> Although lung cancer remains a critical public health problem, the decrease in the overall lung cancer burden that is presently occurring in the United States, as is the case in much of the developed world, reflects the successes of preventive strategies. A critical global priority is to prevent the uptake of cigarette smoking in developing countries where smoking prevalence is still low in order to prevent the increase in morbidity and

mortality from lung cancer that is certain to follow an increase in smoking prevalence.

A consideration of the epidemiology of lung cancer consistently reinforces one major theme. The pandemic of lung cancer is a consequence of the tragic and widespread addiction to cigarettes throughout the world. Curtailing the pandemic of lung cancer will require preventing youths from starting to smoke cigarettes and effectively promoting smoking cessation among addicted smokers. There are other causes that also need control, but fortunately there have been successes in reducing exposures to occupational carcinogens in countries of the developed world.

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