Epidemiology of Lung Cancer*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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Background: The objective of this study was to summarize the published literature concerning the epidemiology of lung cancer.
Methods: A narrative review of published evidence was conducted, identifying and summarizing key reports that describe the occurrence of lung cancer in populations and factors that affect lung cancer risk.
Results: In the United States, lung cancer remains the leading cause of cancer death in both men and women, even though an extensive list of modifiable risk factors has long been identified. The predominant cause of lung cancer is exposure to tobacco smoke, with active smoking causing most cases but passive smoking also contributing to the lung cancer burden.
Conclusions: The reductions in smoking prevalence in men that occurred in the late 1960s through the 1980s will continue to drive lung cancer mortality rates downward in men during the first portion of this century, but rates in women have not yet begun to decrease. Fortunately, exposures to major occupational respiratory carcinogens have largely been controlled, but the population is still exposed to environmental causes of lung cancer, including radon, the second leading cause of lung cancer death. *(CHEST 2007; 132:29S–55S)*

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

Abbreviations: BMI = body mass index; CI = confidence interval; CL = confidence limit; CPS = Cancer Prevention Study; ETS = environmental tobacco smoke; FTC = Federal Trade Commission; IARC = International Agency for Research on Cancer; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; LET = linear energy transfer; RR = relative risk; SSc = systemic sclerosis

The vast majority of lung cancer deaths are attributable to cigarette smoking. Any action that prevents cigarette smoking initiation or promotes cessation among dependent smokers is a step to preventing lung cancer. This includes tobacco control activities to affect policy, such as cigarette taxes and smoke-free workplace legislation, as well as individual-level interventions to prevent the onset or continuation of smoking.

Epidemiologic 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 inter-

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ventions or screening, are also assessed using epidemiologic approaches. For lung cancer, routine mortality statistics confirmed the clinical impression that the disease became more frequent across the first half of the 20th century. Case-control and cohort studies, the epidemiologic study designs that are used to evaluate exposure/disease associations, causally linked smoking to lung cancer in investigations reported from the 1950s onward.[1–3] 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.[4] 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, because skilled clinicians weigh alternative diagnoses depending on risk factor profiles of patients.

At the end of the 20th century, lung cancer had become one of the leading causes of preventable death.[5] It was a rare disease at the start of that century, but exposures to new etiologic agents and an increasing life span combined to make lung cancer a scourge of the 20th century. Although 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.[6] German scientists in Nazi Germany conducted some of the earliest research on the links between smoking and lung cancer.[7] By the early 1950s, epidemiologic studies in Britain and the United States using the case-control method had shown that cigarettes were strongly associated with the risk for lung cancer[8–10]; this association was corroborated by the pioneering cohort studies of British physicians, US veterans, and volunteers recruited by the American Cancer Society.[11,12] By 1964, the evidence was sufficient to support a conclusion by the US Surgeon General that cigarette smoking caused lung cancer.[11] The Royal College of Physicians had reached the same conclusion 2 years before.[12] Passive smoking, the involuntary inhalation of tobacco smoke by nonsmokers, has also been found to cause lung cancer.[13,14]

Although its predominant cause is now widely known (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, raised early in the 20th century, led to what was probably the first occupational respiratory carcinogen to be identified[15]; radon in indoor environments is now considered as the second-leading cause of lung cancer in the United States.[16] 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.[17] 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 1970s, associations of diet with lung cancer risk have been vigorously investigated with the anticipation that dietary micronutrients that modify the high lung cancer risk in smokers might be found. The biological basis for 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 has also been a need for research to track the risks of smoking over time, because 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, have also changed in the past few decades such that the frequency of adenocarcinoma has risen and that of squamous cell carcinoma has declined.[4] There is also emerging evidence on 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. Whereas 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 nonmalignant cell becomes malignant and genetic factors that possibly determine susceptibility to tobacco smoke. Biomarkers of exposure, dosage, susceptibility, and genetic damage may allow epidemiologic investigations to uncover specific pathways of human lung carcinogenesis and provide useful intermediate markers for prevention studies.

Materials and Methods

A narrative review of published evidence on the epidemiology of lung cancer was conducted. Key reports that described the occurrence of lung cancer in populations and factors that affect lung cancer risk were identified. This was accomplished using a combination of approaches that included cataloguing reports from the authors' files and augmented with MEDLINE searches. The MEDLINE searches included a term for "lung cancer" along with additional terms for various exposures that have been studied in relation to lung cancer (*eg*, "cigarette," "smoking," "asbestos," "radiation"). In the updating of recent literature, emphasis was placed on systematic reviews when these were available.

Our objective was to provide a summary of the epidemiologic evidence on lung cancer, with an emphasis on issues that are relevant to prevention. This literature is now extraordinarily large; therefore, we did not attempt 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 UK Royal College of Physicians and Scientific Committee on Tobacco and the World Health Organization's International Agency for Research on Cancer (IARC). Several relevant reports have been published, including the 2004 IARC monographs on active and involuntary smoking[18] and the 2004 report of the Surgeon General.[19]

The topics covered were agreed on by consensus of the writing committee with initial input from the ACCP Guidelines Panel. As prior versions of this article underwent several rounds of external review, additional topics were added as recommended by the external reviewers, the ACCP Lung Cancer Guidelines Panel, the Thoracic Oncology Network, the Health and Science Policy Committee, and the Board of Regents of the American College of Chest Physicians. On the basis of the agreement of all parties, we did not attempt to grade the evidence or generate formal guidelines.

Results

Patterns of Occurrence

Survival: The 5-year relative survival rate for lung cancer for the period of 1995 to 2001 was 15.7%, reflecting a steady but slow improvement from 12.5% from 1974 to 1976.[20] The 5-year relative survival rate varies markedly depending on the stage at diagnosis, from 49 to 16 to 2% for local, regional, and distant stage disease, respectively.[20] Stage at diagnosis accounts for the most marked variation in prognosis, but patient characteristics associated with poorer survival also include being older, male, and African American.[20]

Temporal Trends: Because of the high case-fatality rate of lung cancer, incidence and mortality rates are nearly equivalent; consequently, routinely collected vital statistics provide a long record of the occurrence of lung cancer. We are amid an epidemic of lung cancer that dates to the first half of the last century.

Sex: 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.[21] 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.[21] As the leading cause of cancer death among women, lung cancer is a major women's health issue. As a result of historical cigarette smoking patterns, the epidemic of lung cancer started later in women than men, but in contrast to the situation in men, lung cancer incidence rates in women have not yet begun to decrease consistently.[20] Far more men than women still die from lung cancer each year, but the gender gap in lung cancer mortality is steadily narrowing and will eventually close.[22,23] This trend is due to historical smoking patterns, with smoking prevalence having peaked approximately 2 decades earlier among men than women.[22,23]

Examination of time trends of age-specific lung cancer mortality rates in the United States further highlights the differing epidemic patterns in men compared with women. The sex- and race-specific mortality rates are now almost all decreasing.[22] The rates of lung cancer in the younger age groups have been declining during the past several decades in men and during the past decade in women.[22] As the younger birth cohorts age, their reduced risk for lung cancer foreshadows substantial reductions in the overall occurrence of lung cancer, but the reductions will be greater for men than for women. These patterns all are consistent with population patterns of smoking prevalence over time.[22]

Tobacco smoking accounts for such a large proportion of lung cancer that there have been few data on the occurrence of lung cancer among nonsmokers. Evidence from the American Cancer Society Cancer Prevention Study (CPS) I and II cohorts indicates that there has not been a strong temporal trend in lung cancer death rates among male nonsmokers, but there has been an upward trend among female nonsmokers, mostly confined to elderly women.[23] The data from these cohorts also indicate that among nonsmokers, lung cancer death rates are greater in men than in women and greater in African-American than white women.

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 minorities. Of particular note is that whereas lung cancer incidence rates are similar among African-American and white women, lung cancer occurrence is approximately 45% higher

among African-American men than among white men.[20] This racial disparity may be partially due to greater susceptibility of African-American smokers to smoking-induced lung carcinogenesis.[24] The higher mortality rates of lung cancer in African-American compared with white individuals reflect not only their higher incidence rate but also the poorer survival from lung cancer among African-American compared with white individuals. The 5-year relative survival rate was 13% lower in African-American compared with white individuals during the period 1995 to 2001.[20] This racial gap persisted within each stage at diagnosis category and for men and women.[20]

Lung cancer mortality rates among Hispanic, Native American, and Asians/Pacific Islander individuals are significantly lower than rates among African-American and non-Hispanic white individuals.[25] Nevertheless, lung cancer poses a considerable public health burden among these groups.

Socioeconomic Status: Lung cancer is more likely to occur in the poor and less educated, a pattern that is observed in many countries worldwide. For example, in Canada, the risk for lung cancer in both sexes was inversely associated with income, education, and social class, even after adjustment for cigarette smoking.[26] In China, those who were classified as low income had a sixfold increased risk of lung cancer compared with those in the high-income category.[27] In the Netherlands, the risk for lung cancer was inversely associated with attained education, an association that was not attributable to occupational exposures.[28] Lower socioeconomic status has also been observed to be associated with later stage at diagnosis.[29]

Socioeconomic status is associated with a constellation of interacting determinants of lung cancer risk, such as smoking, diet, and exposures to inhaled carcinogens in the workplace and general environment. Lower socioeconomic status is associated with an unfavorable profile for all of these factors. Advancing our understanding of the complex linkages between components of socioeconomic status and lung cancer risk is essential to effectively addressing this social class disparity and reducing lung cancer rates in the poorer segments of society.

Geographic Patterns: Lung cancer is the most commonly diagnosed cancer worldwide,[30] but its geographic distribution shows marked regional variation: age-standardized incidence rates range > 60-fold among men and 30-fold among women (Fig 1,
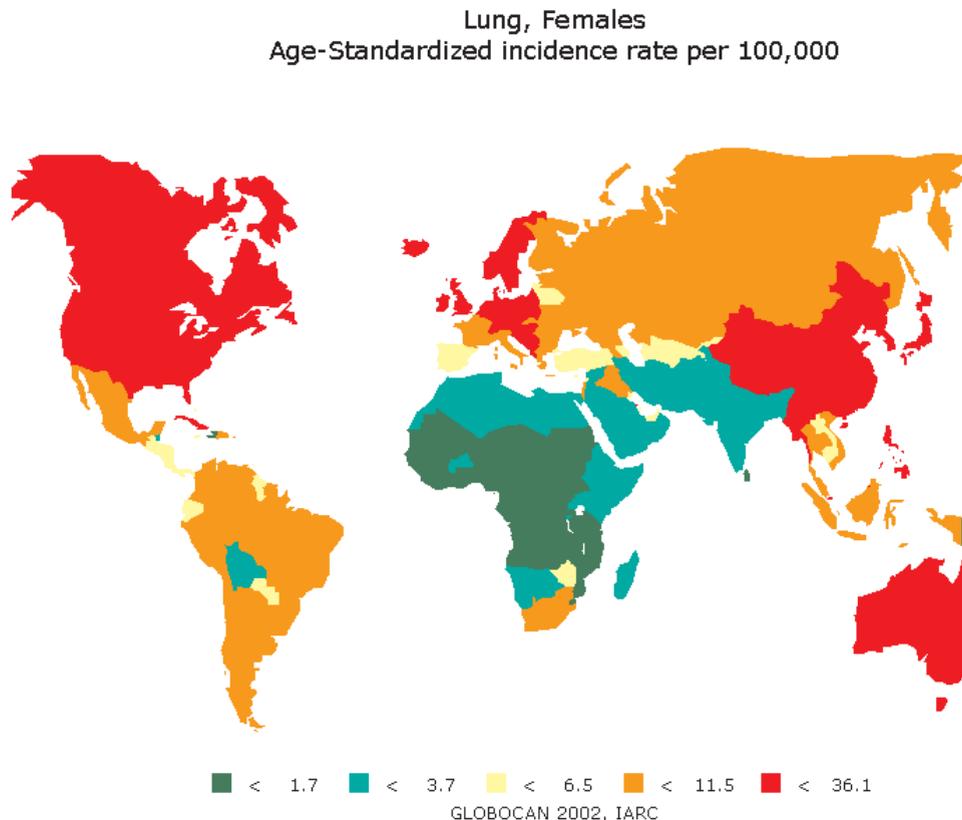

Lung, Females
Age-Standardized incidence rate per 100,000

< 1.7 < 3.7 < 6.5 < 11.5 < 36.1

GLOBOCAN 2002, IARC

FIGURE 1. Age-adjusted lung cancer incidence rates in women worldwide in 2002. Source: IARC, GLOBOCAN 2002 (www-dep.iarc.fr).

Lung, Males
Age-Standardized incidence rate per 100,000

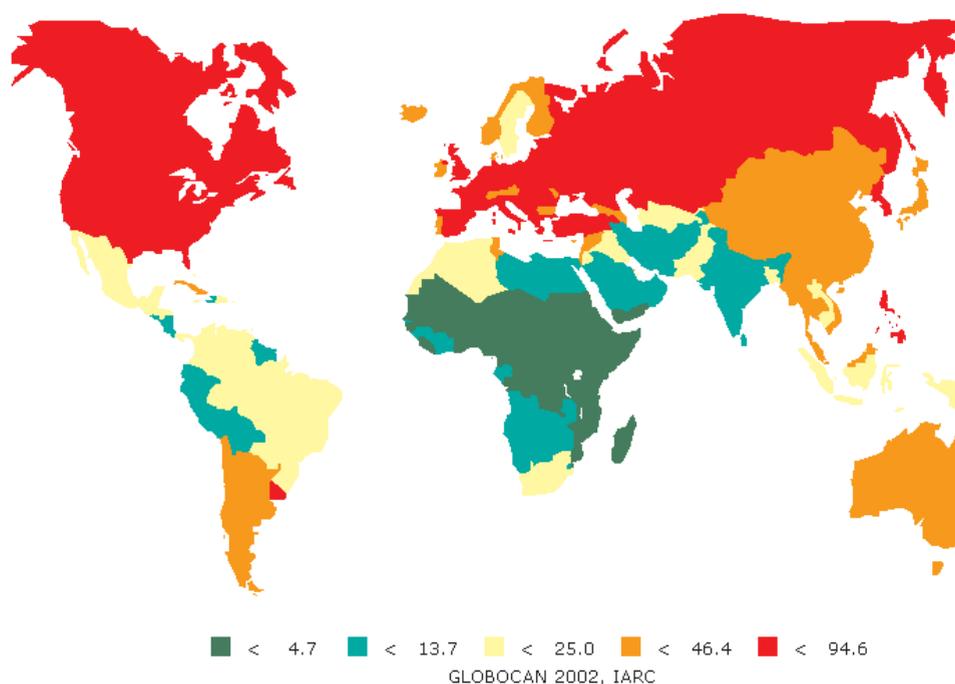|				
■ < 4.7	■ < 13.7	■ < 25.0	■ < 46.4	■ < 94.6

GLOBOCAN 2002, IARC

FIGURE 2. Age-adjusted lung cancer incidence rates in men worldwide in 2002. Source: IARC, GLOBOCAN 2002 (www-dep.iarc.fr).

2).[31] 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.[31] The low rates of lung cancer in Africa are comparable to US rates in 1930, when rates of lung cancer were < 5 per 100,000 for both sexes.[32] In contrast, African-American individuals in the United States, an epicenter, 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.[30]

Within countries, lung cancer incidence among men invariably exceeds that in women, by well more than 100% in most nations. The international rankings of lung cancer incidence of men and women from the same countries tend to differ only slightly, so 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 has also been observed within countries. For example, during the period 1997 to 2001, the age-adjusted lung cancer mortality rates varied more than threefold between the state with the highest rate (Kentucky, 78 per 100,000) and the state with lowest rate (Utah, 25 per 100,000).[20] Trends in its regional distribution can provide clues about 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.[33] Later on, several hypotheses[34,35] were prompted by patterns observed in a systematic review of US lung cancer mortality rates for the period 1950 to 1969,[36] particularly the rates among men. For example, high rates in coastal areas were postulated to reflect employment in shipyards with attendant asbestos exposure. This hypothesis was then tested in a series of population-based case-control studies that showed that employment in the shipbuilding industry was indeed associated with an excess risk for lung cancer.[37] 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.[38] This temporal fluidity in the geographic

variation underscores the need for regularly monitoring lung cancer mortality patterns.

Etiology of Lung Cancer

Although the causes of lung cancer are almost exclusively environmental, there is likely substantial individual variation in susceptibility to respiratory carcinogens. The risk for the disease can be conceptualized as reflecting the joint consequences of the interrelationship between the following: (1) exposure to etiologic (or protective) agents, and (2) individual susceptibility to these agents. The "environment" in its broadest sense may influence the risk for 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 have typically been considered on an agent-by-agent basis, such as the synergistic effect of cigarette smoking on the lung cancer risk from asbestos exposure.[39] Our emerging understanding of cancer genetics indicates the additional relevance of gene/environment interactions.

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 (RR) associated with an exposure along with the likelihood of exposure in the general population. These attributable risk estimates include joint contributions of risk factors that sometimes have synergistic relationships. For example, the attributable risk estimate for cigarette smoking includes the lung cancer risk attributed to the independent effects of cigarette smoking and further includes the risk for lung cancer from smoking as a result of its synergistic interactions with factors such as asbestos and radon. For this reason, the total percentage can be > 100%. Lung cancer has a well-characterized set of important risk factors and established synergistic interactions between risk factors, and these reasons contribute to the attributable risks summing to considerably more than 100%. As reviewed next, population attributable risk estimates for lung cancer indicate that in the United States, active smoking is responsible for 90% of lung cancer; occupational exposures to carcinogens for approximately 9 to 15%; radon for 10% of lung cancer,[16] and outdoor air pollution for perhaps 1 to 2%.[40] The contribution of nutritional factors cannot yet be precisely determined; consequently, estimates of the role of dietary factors range widely.[41]

Environmental and Occupational Agents

Smoking: 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.[42] Compared with never-smokers, smokers who have smoked without quitting successfully have an approximate 20-fold increase in lung cancer risk. 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 approximately 20 years. Analyses using statistical modeling techniques show a tight association between national mortality rates and smoking.[43] The unequivocal role of cigarette smoking in causing lung cancer is one of the most thoroughly documented causal relationships in biomedical research.[6,44]

The burden of lung cancer that is attributable to smoking has been extensively documented. Using an attributable risk approach, the annual number of deaths caused in the United States by smoking-related lung cancer during the period from 1995 to 1999 was 122,800.[19] Peto et al[42] 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, the highest in the world, with country-specific estimates ranging down to 150 for Tajikistan. The total for the developed countries was 457,371.[42] A staggering future burden of lung cancer has been forecast for China, where the numbers are predicted to reach several millions by mid-century.[45,46]

Cigar smoking is also an established cause of lung cancer.[47] The lung cancer risks associated with cigar smoking are substantial but less than the risks observed for cigarette smoking as a result of differences in smoking frequency and depth of inhalation. The same pattern holds true for pipe smoking.[48] With respect to smoking of nontobacco products, the potential role of smoking marijuana on lung cancer risk has been of interest. Despite the plausibility of marijuana as a risk factor for lung cancer, the evidence to date has not documented an association after adjusting for tobacco smoking.[49]

The risk for lung cancer among cigarette smokers increases with the duration of smoking and the number of cigarettes smoked per day.[50] This observation has been made repeatedly in cohort and case-control studies. Risk models have been derived to estimate quantitatively how lung cancer risk varies with number of cigarettes smoked, duration of smoking, and age. Such models are useful for estimating the future burden of lung cancer under various

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scenarios of tobacco control. In one widely cited analysis, Doll and Peto[50] proposed a quantitative model for lung cancer risk on the basis of 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 duration of smoking was estimated to increase the risk 100-fold.[51] These quantitative dimensions of the dosage-response relationship between smoking and lung cancer have implications concerning the now widespread smoking among youths. Those who start at younger ages have a greater likelihood of becoming a heavier smoker and remaining a smoker.[52] The exponential effect of duration of smoking on lung cancer risk markedly increases the lifetime risk for those who become regular smokers in childhood and places them at increased risk at younger ages. Prevention approaches that delay the age of onset of smoking in a population could have 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 to actual age.

Cigarette smokers can benefit at any age by quitting smoking. The likelihood of lung cancer developing decreases among those who quit smoking as compared with those who continue to smoke.[52] As the period of abstinence from smoking cigarettes increases, the risk for lung cancer decreases.[53] However, even for periods of abstinence of > 40 years, the risk for lung cancer among former smokers remains elevated compared with never-smokers.[53,54] The benefits derived from smoking cessation also depend on the duration of smoking; for a given period of abstinence, the decrease in risk increases as the duration of smoking decreases.[53] In general, studies[55] have shown comparable reductions in risk after cessation regardless of sex, type of tobacco smoked, and histologic type of lung cancer.

The benefits of physician (and other clinician) intervention for smoking cessation are well established.[56] The results of research in this area have been translated into an evidence-based clinical practice guideline for treating tobacco dependence on the basis of the "5 A's": *a*sk whether a patient smokes, *a*ssess willingness to quit, *a*dvise to quit, *a*ssist with quitting, and *a*rrange follow-up.[56]

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, whereas charcoal filters are used extensively in Japan and some other countries.[57] In the mid-1960s, ventilation holes were added to the filter, which dilute the smoke with air drawn through them. However, smokers can readily block the holes with their fingers, which are left unblocked by the machines that are used to test cigarettes. There have also been substantial changes in the design of the cigarette and in the tobacco used. Reconstituted tobacco has been used increasingly since the 1960s, there have been changes to the cigarette paper and additives used, and most cigarettes are more ammoniated in the United States.[57]

A concomitant shift toward lowered levels of "tar" and nicotine, as measured by a smoking machine, has occurred.[58] Cigarette tar refers to the condensable residue of cigarette smoke (*ie*, the total particulate matter of cigarette smoke deposited on the filter of the machine, less the moisture and nicotine). Tar is a complex mixture that includes many chemicals that are cancer initiators and/or promoters.[58] 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 and puff volume, the frequency of puffing, and the length to which the cigarette is to be smoked.[59]

Studies[59] using biomarkers of exposure to and dosage of tobacco smoke components show little relationship of levels of these markers with tar or nicotine yield as measured by the FTC protocol. These studies have been conducted in both the population context and during smoking in the laboratory setting. For example, Coultas et al[60] collected saliva for analysis for cotinine level and end-tidal breath samples for measurement of carbon monoxide level in a population sample of New Mexico Hispanic individuals who were included in a respiratory health survey. After taking account of numbers of cigarettes smoked, biomarker levels were not associated with the yields of tar and nicotine of the current brand smoked. Djordjevic et al[61] evaluated smoking pattern 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 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 who switch from higher to lower yield products. The compensation includes blocking of the ventilation holes, more frequent and deeper puffs, and an increase in the number of cigarettes smoked.[62]

The gradual reduction in machine-measured tar yield would be expected to have reduced smokers'

exposures to carcinogens if the FTC test protocol were predictive of carcinogen dosages delivered to the lung.[58] However, questions remain as to whether the FTC test method is informative with regard to lung cancer risk or risks for smoking-caused diseases more generally.[62,63] Epidemiologic studies have been conducted 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, three lines of epidemiologic data have been available on changes in products. The first comes from case-control studies that compared the smoking history profiles of people with lung cancer with those of control subjects. The second comes from cohort studies that tracked the risk for lung cancer over time, as the products smoked changed. The third comes from assessment of the temporal changes in age-specific patterns of lung cancer mortality rates in comparison with changes in cigarette characteristics.

The initial evidence came primarily from case-control studies that compared risks in people who had used filter-tipped cigarettes with people who had smoked nonfiltered cigarettes exclusively.[64,65] This evidence suggests that filtered cigarettes and cigarettes with lower tar yields slightly reduce the risk for lung cancer associated with cigarette smoking compared with nonfiltered cigarettes or with higher tar yields.[66-68] This comparison could be made among smokers in the 1960s because there was still a substantial proportion who had not used filtered cigarettes at all. For example, in one of the first studies, Bross and Gibson[64] compared lung cancer risk of smokers of filtered and nonfiltered cigarettes among patients who were seen at Roswell Park Memorial Cancer Institute in Buffalo; individuals were classified as filter cigarette smokers when they had used these products for at least 10 years.

The relevant cohort studies are the American Cancer Society CPS I and CPS II studies and the British Physicians Cohort. In a 1976 publication, Hammond et al[69] compared mortality risks from lung cancer and other diseases by tar yield of products smoked by CPS I participants. The follow-up interval spanned from 1960 to 1972. Smokers were placed into three categories of 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- 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 risk for lung cancer death increased with tar yield.[70]

Further insights have been gained by comparing the risks in the two CPS studies of the American Cancer Society; this comparison addresses whether risks have changed, comparing smokers with disease developing from 1960 to 1972 with a similar group of smokers with disease developing during the initial follow-up of CPS II, from 1980 to 1986.[71,72] If the risk for lung cancer associated with smoking is decreasing over time, then 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.[73]

In an analysis with a similar pattern of findings, Doll et al[74] compared the risks for death from lung cancer and other causes during the first and second 20 years of the 40-year follow-up of the British physician cohort. Lung cancer mortality increased among smokers in the second 20 years (from 1971 to 1991), even though products smoked during this period would have had a substantially lower tar and nicotine yield than those smoked during the first 20 years (from 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. In 2004, Doll et al[75] reported the findings at 50 years of follow-up; compared with lifelong nonsmokers, the risk for lung cancer was increased fourfold among former smokers and > 14-fold among current smokers. Among current smokers, the RRs increased from 7.7 to 13.7 to 24.5 among smokers of 1 to 14, 15 to 24, and > 25 cigarettes per day, respectively.

The third line of observational evidence comes from descriptive analyses of age-specific trends of lung cancer mortality.[18,62,76] Successive birth cohorts have had differing patterns of exposure to cigarettes of different characteristics and yields. For example, the cohort of individuals who were born between 1930 and 1940 and started to smoke in the 1950s was one of the first to have the opportunity to smoke primarily filter-tipped cigarettes. Subsequent birth cohorts would have had access to the increasingly lower yield products, whereas earlier cohorts had access initially only to nonfiltered cigarettes. Patterns of temporal change in age-specific rates of lung cancer mortality in younger men have been examined to assess whether there has been a decline greater than expected from changing prevalence, duration, and amount of smoking, thereby indicating a possible effect of cigarette yield.

Data on lung cancer mortality in younger men in the United Kingdom have been interpreted as indi-

cating a possible reduction in lung cancer risk associated with changes in cigarettes.[62,76] A sharp decline in lung cancer mortality has occurred across the past few decades in UK men < 50 years of age. The decline seems greater than anticipated from trends in prevalence and other aspects of smoking: age starting and number of cigarettes smoked. A similarly steep decline has not taken place in the United States. Given the ecologic nature of the data under consideration, uncertainty remains with regard to their interpretation, and alternative explanations have been proposed, including less intense smoking at younger ages in more recent birth cohorts.[62]

This discussion highlights the complexity of isolating the precise effect on lung cancer risk of the continually changing cigarette. The data available to evaluate these effects have limitations, particularly in capturing the experience of successive birth cohorts in either case-control or cohort studies that were appropriately designed. The UK mortality data suggest a greater effect of changes in cigarettes than is found in the case-control and cohort studies. As recommended by the Institute of Medicine,[77] surveillance is needed to track the health consequences of the changing cigarette.

Several expert panels have reviewed the findings. The Institute of Medicine[77] conducted a comprehensive review on various harm reduction strategies for reducing the disease burden caused by smoking, including lower yield cigarettes. There are also new products in various phases of development that are intended to deliver nicotine without 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 addressed in the 2004 report of the US Surgeon General,[19] with the conclusion that "although characteristics of cigarettes have changed during the last 50 years and yields of tar and nicotine have declined substantially, as assessed by the Federal Trade Commission's test protocol, the risk of lung cancer in smokers has not declined."

Results of some case-control and screening studies have suggested a potentially higher risk for smoking-associated lung cancer in women compared with men,[78–80] but methodologic issues cloud the interpretation of these studies, particularly a lack of focus on the most informative comparisons.[81] Furthermore, the evidence from prospective cohort studies fails to support the notion of a sex differential in susceptibility to lung cancer from smoking.[82] The equal rates of lung cancer mortality in younger US men and women corresponding to a time of equal smoking prevalence also provides evidence against an important sex difference in susceptibility to smoking-induced lung cancer.[22] The evidence against this hypothesis outweighs the evidence in favor of the hypothesis on the basis that the results of studies that have compared the RR estimates for men and women for a specific degree of smoking history demonstrate very similar associations.[82]

The development of menthol cigarettes was targeted specifically at African-Americans and women.[83,84] African-Americans are more likely than white individuals (69 vs 29%) to smoke menthol cigarettes,[85] and the menthol smoke delivery levels of common cigarette brands have increased significantly since the 1980's.[86,87] This has led to the hypothesis that menthol cigarettes explain the greater susceptibility to lung cancer from cigarette smoking in black vs white individuals[24] and thus the disparity in lung cancer risk between US black and white individuals, especially among men.

Menthol cigarettes may cause a greater increase in lung cancer risk than nonmenthol cigarettes, either by increasing systemic exposure to toxicants from tobacco smoke or by affecting the metabolism of nicotine and/or tobacco smoke carcinogens. Initially, this hypothesis gained currency because of the potential for increased nicotine uptake through the effects of menthol in the respiratory tract. These include an increase in the smoothness of tobacco smoke, which promotes deeper inhalation; stimulation of cold receptors, which results in airway cooling effects that mask the irritation caused by cigarette smoke, promoting deeper inhalation and altered inhalation frequency; further masking of irritation through anesthetic effects[86,88]; and increased permeability and diffusibility of smoke constituents.[87]

There is limited information on the molecular mechanisms by which mentholation might increase the health risk of smoking. Seventy to 80% of nicotine is metabolized to cotinine, and cytochrome P450 2A6 is responsible for 90% of this conversion.[89] The P450 2A6 gene has multiple functional polymorphisms that vary by race. The observation that menthol competitively inhibits cotinine metabolism by the monkey analog of a human UDP-glucuronyltransferase[90] suggested that inhibition of either CYP2A6 or UDP-glucuronyltransferase by menthol might alter nicotine and cotinine metabolism. African-American and white menthol smokers have similar baseline cotinine levels.[91] Human studies[89,91–93] have suggested that smoking mentholated cigarettes inhibits nicotine metabolism, so smokers experience higher dosages of nicotine for a given level of smoking. Menthol inhibits the microsomal oxidation of nicotine to cotinine,[92] suggesting that smoking mentholated cigarettes may lead to inhibition of nicotine metabolism. In a randomized, crossover study of seven African-American and seven white individuals, Benowitz et al[93] found that the systemic intake of

nicotine was not affected by mentholation, but smoking mentholated cigarettes inhibited the metabolism of nicotine. By slowing the metabolism of nicotine and thereby reducing the need for nicotine from smoking, menthol may reduce the number of cigarettes smoked per day. A menthol effect might explain why African-American individuals smoke fewer cigarettes per day than white individuals. It may also explain, in part, the variation by race and gender in the correlation between cotinine level and cigarettes smoked per day among smokers of menthol cigarettes,[94] possibly reflecting the effect of menthol on nicotine inactivation by P450 2A6.[89]

However, the epidemiologic data suggest that, overall, smokers of mentholated cigarettes do not have an increased risk for lung cancer compared with smokers of nonmentholated cigarettes. This evidence is based primarily on hospital-based case-control studies,[95–98] but also includes a population-based case-control study[99] and a cohort study within a health maintenance organization.[100] Furthermore, menthol cigarettes have not been associated with any specific histologic subtypes of lung cancer.[101]

Evidence that menthol cigarettes might carry greater risks were observed in one case-control study[97] in which black, male, heavy smokers of mentholated cigarettes (> 37.5 pack-years, or ≥ 21 cigarettes per day) had a higher risk than white men with similar smoking histories. In the cohort study,[100] the RR for lung cancer among men but not women was slightly elevated in menthol smokers compared with nonmenthol smokers, with a graded increase in lung cancer risk with increasing duration of menthol cigarette use.

The evidence does not indicate that menthol cigarettes are an important contributor to the high rates of lung cancer in African-American individuals. A more definitive answer to this question will emerge if future studies address several methodologic challenges, including misclassification of menthol cigarette exposure as a result of brand ambiguity; potential for selection bias in hospital-based case-control studies, as a result of lower prevalence of menthol cigarette use among African-American patients at university hospitals used for such studies than in the general population; and lack of information about compensatory mechanisms.[102]

Passive smokers inhale a complex mixture of smoke now widely referred to as secondhand smoke or as environmental tobacco smoke (ETS). Passive smoking was first considered as a possible risk factor for lung cancer in 1981, when two studies that described increased lung cancer risk among never-smoking women who were married to smokers were published. Hirayama[103] reported the findings from a cohort study in Japan that showed that among nonsmoking women, those with a husband who smoked cigarettes were at higher risk for lung cancer than those whose husband was a nonsmoker. A case-control study in Athens reported by Trichopolous et al[104] shortly thereafter replicated this finding. Additional evidence rapidly accrued, such 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 approximately 30% more likely to have lung cancer develop than nonsmoking spouses married to nonsmokers and that this relationship was biologically plausible.[105] Almost one fourth of lung cancer cases among never-smokers were estimated to be attributed to exposure to passive smoking.[105] The 1986 Surgeon General report also judged passive smoking to be a cause of lung cancer,[13] an inference corroborated by the 1992 review of the evidence and risk assessment by the US Environmental Protection Agency, which classified ETS as a known human (class A) carcinogen.[14] Estimates indicate that passive smoking accounts for approximately 3,000 lung cancer deaths per year in the United States.[14] Since these conclusions were reached, several major studies[106,107] have been conducted to characterize further 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 potential confounding factors.

Passive smoking is more weakly associated with lung cancer than is active smoking, as expected given the generally lower dosages of carcinogens that are passively received by the lung of the nonsmoker compared with the dosages received by the active smoker. Because of broad societal implications, the conclusion that this association is causal has generated controversy, some driven by the effort of the tobacco industry to maintain continued questioning of the evidence.[108,109] Questions have been raised about the method of the epidemiologic studies, including confounding and misclassification of exposure to environmental tobacco smoking. Review groups[13,14,106,110] have nonetheless concluded that the association between ETS and lung cancer cannot be attributed to methodologic 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. Metaanalyses have been conducted periodically to

summarize the evidence from the epidemiologic studies. A 2002 metaanalysis by Boffetta[111] found a 25% increased risk associated with marriage to a smoker; this excess risk seemed to be due to exposure to passive smoking because it could not be explained by confounding or misclassification. This finding was consistent with the 29% estimated increased risk among women whose husband smoked in the metaanalysis of Taylor et al,[112] who observed that the association was consistent across study designs and in Western and non-Western nations. Workplace exposure to secondhand smoke was associated with a 17% increase in lung cancer risk in the metaanalysis of Boffetta.[111]

The studies of passive smoking provide further evidence documenting the dosage/response relationship between cigarette smoke and lung cancer. The dosages extend to far lower levels than those of active smoking and increased risk is observed, suggesting that there is no threshold for tobacco carcinogenesis.[13]

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.[113] Notable shifts have taken place in the incidence rates of lung cancer by histologic type.[114] After steadily increasing occurrence during the period from 1973 to 1987, adenocarcinoma supplanted squamous cell carcinoma as the most frequent form of lung cancer.[114] Adenocarcinoma increased markedly in all race and sex subgroups.[114]

Despite extensive research, the mechanisms that lead to these different types of lung cancer remain uncertain. Hypotheses have focused on the cells of origin of lung cancers and on pathways of differentiation of malignant cells.[113] An area of active interest is characterizing the likelihood that dysplastic lesions that are detected by fluorescence bronchoscopy will progress to invasive cancer[115] and relating the distribution of these lesions *vis a vis* the distribution of invasive lung cancer tumors on the basis of epidemiologic findings. CT scans are generally being used to identify peripheral lesions (usually adenocarcinoma), whereas fluorescence bronchoscopy is being used for the detection of central airway lesions, predominantly preinvasive squamous cell carcinoma. Smoking has been shown to cause each of the major histologic types, although the dose/response relationship with number of cigarettes smoked varies across the types, being steepest for small cell undifferentiated carcinoma.[115,116] 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 are exposed to chloromethyl ethers and in underground miners who are exposed to radon progeny.[113]

In the initial decades of the smoking-caused epidemic of lung cancer, squamous cell carcinoma was the most frequent type of lung cancer observed in the population, 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,[113,117,118] and now adenocarcinoma of the lung is the most common histologic type.[112] 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.[114] In women, the Surveillance, Epidemiology, and End Results[4] data from 1973 to 1996 indicated that the incidence rates of squamous cell, small cell, and large cell carcinomas at least reached a plateau, whereas the rate for adenocarcinoma were still rising.

Although 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.[113,117,118] Beginning in the 1970s, new techniques for the diagnosis of lung cancer became available, including the fiberoptic bronchoscope and thin-needle aspiration[119]; improved stains for mucin, the hallmark of adenocarcinoma, were also introduced. Using data from the Connecticut Tumor Registry, Thun et al[119] 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 consequent changes in the dosages of carcinogens inhaled.[120] Puff volume has likely increased in the past few decades with the possibility that patterns of deposition in the lung have changed, tending toward enhanced deposition of tobacco smoke in the peripheral airways and alveoli.[120] Nitrate levels in tobacco smoke have also increased, which enhances the combustion of tobacco smoke. Although more complete combustion decreases the concentrations of polycyclic aromatic hydrocarbons, the increased production of nitrogen oxides contributes to increased formation of tobacco-specific nitrosamines. An increase in dosage of the potent tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone has been postulated as one factor leading to the increase in adenocarcinoma.[120,121] Nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone induces lung carcinomas, predominantly adenomas and adenocarcinomas, in mice, regardless of route of administration.[121,122]

Few studies can provide data to test these hypoth-

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[119] compared risks for lung cancers of the various histologic types among participants in the American Cancer Society CPS I and CPS II. They found markedly rising risks associated with smoking for adenocarcinoma of the lung in both men and women during the approximate 20 years separating the two studies. Thun et al[119] concluded, "The increase in lung adenocarcinoma since the 1950s is more consistent with changes in smoking behavior and cigarette design than with diagnostic advances." In a study[123] that compared tumor location in lung cancer patients, lower-tar cigarettes were associated with a higher likelihood of peripheral than central tumors.

Diet: Research on diet and lung cancer has now been conducted for nearly 3 decades. The possible role of diet in modifying the risk for lung cancer has been the focus of intensive investigation, driven initially by the rationale that specific micronutrients might have anticarcinogenic activity. The most thoroughly investigated dietary factors are also those that seem to have the greatest implications for prevention: fruits, vegetables, and specific antioxidant micronutrients that are commonly found in fruits and vegetables. Much of the research on diet and lung cancer has been motivated by the hypothesis that diets that are high in antioxidant nutrients may reduce oxidative DNA damage and thereby protect against cancer.[124]

The results of case-control and prospective cohort studies have tended to show that individuals with high dietary intake of fruits or vegetables have a lower risk for lung cancer than those with low fruit or vegetable intake.[125] Evidence from cohort studies[126–130] published since 2000 has tended to reinforce this notion. In the European Prospective Investigation Into Cancer and Nutrition Study,[131] a strong protective association was observed with fruit but not vegetable consumption. A stronger protective association was observed for fruit than vegetable consumption in a pooled analysis of seven cohort studies.[132]

To better understand the basis of this protective association, fruits and vegetables have been grouped into classes and also examined individually in relation to lung cancer risk. For example, tomatoes[133–135] and cruciferous vegetables[129,135] have been associated with a reduced risk for lung cancer in a number of studies, at least for the highest vs lowest categories of consumption. These food-based analyses can help to clarify whether protection against lung cancer is conferred by the complex mixture contained in fruits and vegetables or by the presence of specific biochemical constituents in particular fruits and vegetables.

Fruits and vegetables are the major dietary source of antioxidant micronutrients. Two different strategies are used to evaluate the relationship of micronutrients to lung cancer risk in observational epidemiologic studies: (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. The differences in measurement approaches may lead to different results in certain situations. A metaanalysis[136] of selenium and lung cancer found that selenium intake as measured by questionnaire showed no association (RR, 1.0; 95% confidence limit [CL], 0.8, 1.3), whereas associations in the protective direction were observed for selenium concentrations measured in toenails (RR, 0.5; 95% CL, 0.2, 0.9) or serum (RR, 0.8; 95% CL, 0.6, 1.1).

Studies of both dietary intake[137–140] and prediagnostic blood concentrations[141,142] suggested a protective association between carotenoids and lung cancer. The evidence for vitamin C is scant but suggestive of a protective association, whereas the data on vitamin A has yielded null findings.[143] Reports from cohort studies have tended to reinforce the previous findings of protective associations with intake of a variety of carotenoids[128,135,144] or an antioxidant index.[140] However, a pooled analysis[139] of seven cohort studies did not find strong protective associations with any carotenoids other than β-cryptoxanthin.

More recently, studies have examined phytochemicals such as flavonoids and isothiocyanates in relation to lung cancer risk. Phytochemicals are low-molecular-weight molecules produced by plants. Of the many classes of phytochemicals, those studied in relation to lung cancer include phytoestrogens, flavonoids, and glucosinoids. The tumor-promoting effects of steroid hormones can be blocked by phytoestrogens. Soya beans are a primary source of a specific class of phytoestrogens known as isoflavonoids. Flavonoids exhibit potent antioxidant activity. Flavonoid intake has been at least weakly associated with lung cancer in some of the preliminary studies[145,146] of this topic. Isothiocyanates are metabolites of the class of phytochemicals known as glucosinolates. Isothiocyanates could exert anticancer effects by blocking carcinogens via induction of

phase 2 detoxification enzymes, such as glutathione S-transferase. Cruciferous vegetables contain high concentrations of glucosinolates; therefore, consumption leads to higher endogenous isothiocyanate concentrations. As with cruciferous vegetables,[147] lung cancer risk is consistently lower with higher intakes or urinary levels of isothiocyanates.[148–150] When isothiocyanates have been studied in combination with a common polymorphism in the GSTM1 gene, the decreased risk for lung cancer associated with isothiocyanates has been especially pronounced in people with the GSTM1 null genotype.[148–150] This provides an example of a potential gene/diet interaction that may be relevant to lung carcinogenesis.

Studies of fruits, vegetables, and micronutrients have been the centerpiece of studies of diet and lung cancer, but a wide range of dietary and anthropometric factors have been investigated. For example, the results of a metaanalysis[151] showed that alcohol drinking in the highest consumption categories was associated with increased risk for lung cancer. Anthropometric measures have also been studied, indicating a tendency for people with lower body mass index (BMI) to have increased lung cancer risk relative to heavier people.[152,153] However, effects of both alcohol drinking and low BMI may be difficult to separate from the concomitant effects of smoking. When considering the possible relationships between lung cancer and factors such as alcohol drinking and lower BMI, cigarette smoking cannot be dismissed as a possible explanation.

The overwhelming contribution of cigarette smoking as a cause of lung cancer poses a challenge to detecting the role that other lifestyle factors, such as diet, may play in the cause of lung cancer. Cigarette smoking is now so closely associated with less healthful lifestyles in the United States and some other countries, such as less healthful diets,[154] that it is often difficult to disentangle the dietary factor(s) of interest from the effects of smoking. Cigarette smoke can directly affect circulating concentrations of dietary factors; for example, smokers tend to have lower circulating concentrations of antioxidant micronutrients even after accounting for differences in dietary intake.[154] In addition, associations between dietary factors and lung cancer risk are likely to be far weaker than the association with active smoking, and diet is measured with much greater error in general than is smoking. Even for a dietary factor, such as vegetable consumption, which is fairly consistently associated with a lower risk for lung cancer, the highest exposure category is typically associated with at most a halving in the risk for lung cancer. Therefore, in interpreting the evidence, residual confounding cannot be readily set aside as an expla-

nation for the observed associations between dietary factors and lung cancer.[155]

Chemoprevention Trials: The experimental rationale for trials of beta carotene and retinoids is offered in another article in this *Supplement* ("Lung Cancer Chemoprevention" by Gray et al). Experimental data indicated a potential for prevention with these agents; observational data were supportive of the hypothesis that beta-carotene and retinoids might have chemopreventive activity.[124] However, a protective association between beta-carotene and lung cancer was not found in three randomized, double-blind, placebo-controlled chemoprevention trials[156–158] of beta-carotene reported during the 1990s. In fact, beta-carotene supplementation was associated with an increased risk for lung cancer among the high-risk populations of heavy smokers in the α-Tocopherol β-Carotene Cancer Prevention Study,[156] and smokers and asbestos-exposed workers in the Carotene and Retinol Efficacy Trial.[158]

In summary, observational evidence suggests that smokers who eat more vegetables are at lower risk for lung cancer than those who consume fewer vegetables. The evidence is not as consistent for fruit consumption. The specific constituents of vegetables that confer protection are not known. The results of the chemoprevention trials clearly suggest a more complex role for micronutrients than previously proposed.

Physical Activity: Several studies[159–161] have reported that more physically active individuals have a lower risk for lung cancer than those who are more sedentary, even after adjustment for cigarette smoking. As with the assessment of any lifestyle factor other than smoking with lung cancer risk, potential residual confounding by cigarette smoking needs to be considered as an alternative explanation.

Occupational Exposures: Investigations of occupational groups, often heavily exposed over a long time to workplace agents, have provided 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.[162] Estimates derived from case-control studies[163–169] 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%. Although disagreement persists concerning specific estimates,[170] the message is clear: in industrialized nations, the contribution of occupational exposures

to the lung cancer burden is small compared with that of cigarette smoking, but large compared with contributions of most other exposure classes. Cigarette smoking potentiates the effect of some known occupational lung carcinogens.[40]

Lung cancer has been observed to be associated with many workplace exposures. Workers who are exposed to tar and soot (which contains benzo[a]pyrene), such as coke oven workers,[171,172] in concentrations that exceed those present in urban air[173] are at increased risk for lung cancer. Occupational exposures to a number of metals, including arsenic, chromium, and nickel, are also causes of lung cancer.[174] For many of the worker groups exposed to these agents, there were substantial increments in risk. However, in developed countries, these hazards have largely been controlled.

For some other workplace agents, the evidence has been less clear. The results of numerous case-control and cohort studies are compatible with a weak association between exposure to diesel exhaust and the development of lung cancer.[175] Although inadequate control of cigarette smoking limits the inferences that can be drawn from many of these studies, exposure to diesel exhaust remains a likely explanation for these findings.[175] This association remains a public health concern because the public is exposed to diesel exhaust in urban areas, and in some European countries diesel vehicles are increasingly used.[41]

The question of whether silica dust is a risk factor for lung cancer has been controversial.[176–178] A twofold increase in lung cancer risk was estimated from a metaanalysis[179] of the relationship between silicosis and lung cancer mortality. Effects of smoking were not well controlled in most of the studies.[179] The evidence on silica exposure, absent consideration of the presence of silicosis, is less clear.[180,181] In 1997, the IARC did classify crystalline silica as a human carcinogen[182]; however, some still continue to question its carcinogenicity[181] and the role of silica exposure vs that of fibrosis in people with silicosis.[180]

Asbestos: Asbestos, a well-established occupational carcinogen, refers to several forms of fibrous, naturally occurring silicate minerals.[183] The epidemiologic evidence dates to the 1950s, although clinical case series had previously led to the hypothesis that asbestos causes lung cancer.[184,185] In a retrospective cohort study published in 1955, Doll[186] 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 were implemented to limit asbestos dust in factories. A sevenfold excess of lung cancer was subsequently observed among insulation workers in

the United States.[187,188] The risk for lung cancer has been noted to increase with increased exposure to asbestos[189] and to be associated with the principal commercial forms of asbestos.[190] Whether asbestos acts directly as a carcinogen or through indirect mechanisms, such as causing chronic inflammation that eventually leads to cancer development, remains uncertain.[191,192]

Asbestos and cigarette smoking both are independent causes of lung cancer, but in combination they act synergistically to increase the risk for lung cancer in a manner that is compatible with a multiplicative effect.[193] Cigarette smoking may increase the lung cancer risk associated with asbestos exposure by enhancing retention of asbestos fibers.[194]

Radiation: Epidemiologic studies of populations that were exposed to high doses of radiation showed that lung cancer is one of the cancers associated with exposure to ionizing radiation.[195] However, the risks for low-dose radiation, more relevant to contemporary workers and the general population, have proved difficult to characterize.[195] Assessing the cancer risk that is associated with low-dose radiation among humans is methodologically difficult because the signal-to-noise ratio is highly unfavorable.[196] Nevertheless, large cohort studies,[16,197,198] particularly the study of Japanese atomic bomb survivors, have provided understanding of the risks of low-dose ionizing radiation.

The following two types of radiation, classified by rate of energy transfer to the tissue, are relevant to lung cancer: low linear energy transfer (LET) radiation (*eg*, x-rays, gamma rays) and high-LET radiation (*eg*, neutrons, radon). High-LET radiation produces ionization of relatively higher density in tissues than low-LET radiation, so in equivalent doses, more biological damage is produced by high-LET than low-LET radiation.[199] For both types of radiation, the majority of the epidemiologic evidence comes from cohorts that were exposed at levels substantially greater than those experienced by the general population. Risk assessment methods are then used to estimate risks to the population.

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 α particles that, by virtue of their high energy and mass, can cause damage to the DNA of cells of the respiratory epithelium. Epidemiologic studies[200,201] of underground miners of uranium and other ores have established exposure to radon daughters as a cause of lung cancer. In the miners who were exposed to radon in past centuries, very high lung cancer risks were observed; these fell for more recent workers, but the epidemiologic studies[16] still show clear evi-

dence of existing cancer risk. Cigarette smoking and radon decay products synergistically influence lung cancer risk in a manner that is supraadditive but submultiplicative.[16,201]

Radon is of broader societal interest because it is a ubiquitous indoor air pollutant that enters 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.[201] Exposure to radon in indoor air is also 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 α particle causes permanent cellular change, an assumption that leads to a nonthreshold 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 led to estimates that approximately 15,000 to 20,000 lung cancer deaths per year in the United States are caused by radon.[202] Case-control studies[203,204] concerning indoor exposure to radon as a risk factor for lung cancer, undertaken to assess risks directly, have produced findings that are generally consistent with downward extrapolation of risk models based on the underground miners. This coherence lends support to using extrapolation of the miner data to estimate the risk of indoor radon.

Epidemiologic data relating low-LET radiation to lung cancer stem from three principal populations: the atomic bomb survivors in Japan,[205] patients with diseases such as ankylosing spondylitis[206] or tuberculosis[207,208] who received multiple radiation treatments, and occupational groups in professions that expose workers to radiation.[209] The single, high-dose exposure of the atomic bomb survivors was associated with significant lung cancer risk.[205] 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,[205] and a consideration of radiation and smoking together suggests an additional relationship.[198]

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 atomic bomb survivor's data to lower doses. Patients who had tuberculosis and received radiation therapy have also 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 patients with tuberculosis suggest that if any risk for lung cancer is associated with this exposure pattern, then it is small,[207,208] suggesting that the assumptions on which the higher risk estimates that were obtained from the data of atomic bomb survivors may in actual fact not hold.[208]

Low-LET radiation therefore seems to be associated with higher lung cancer risk when exposure occurs at a higher dose rate.[208] These results contrast with those for high-LET radiation, suggesting that the two types of radiation have different dose-rate relationships.[208]

Air Pollution: During a typical day, the average adult inhales approximately 10,000 L of air.[210] 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.[162,211]

Carcinogens that are generated by combustion of fossil fuels include polycyclic aromatic hydrocarbons and metals such as arsenic, nickel, and chromium.[174] In considering respiratory carcinogenesis, the constituents of "air pollution" will vary by locale and over time depending on the pollution sources.[212] 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.[213–215] 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,[216,217] but an urban effect persists in a number of studies.[40]

Air pollution has been assessed as a risk factor for lung cancer in both case-control and cohort studies. Whereas early evidence from case-control and cohort studies was found wanting, more recently the evidence supports a causal role for air pollution.[218]

Two prospective cohort studies[219,220] that partially addressed weaknesses of earlier studies add evidence that suggests air pollution is weakly associated with the risk for lung cancer. By prospectively studying air pollution levels in relation to risk for 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 of much previous research.[221] In a study of six US cities,[219] the adjusted risk for lung cancer mortality in the city with the highest concentration of fine particles was 1.4 times (95% confidence interval [CI], 0.8 to 2.4) higher than in the least polluted city. Using data from the American Cancer Society CPS II, Pope et al[220] observed that compared with the least polluted areas, residence in areas with high sulfate concentrations was associated with an increased risk for lung cancer (adjusted RR, 1.4; 95% CI, 1.1 to 1.7) after adjustment for occupational exposures and the factors mentioned previously. However, unlike in the Six-Cities Study,[222] fine-particulate concentration was not associated with lung cancer risk. In a subsequent update, follow-up was extended to 1998. In that report, the risk for lung cancer was observed to increase 14% for each 10-μg/m^3 increase in concentration of fine particles.

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 exposure assessment for air pollution was based on proxy, less specific measures of air pollution.[221] Some case-control studies[223–225] have reported indexes of air pollution to be modestly associated with elevated risks for lung cancer, but others[226] have reported no association.

Another research approach to evaluate the risk of air pollution has been to investigate populations that reside 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[35] 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[227–229] lend support to this hypothesis by showing that the risk for lung cancer increased the nearer that people lived to nonferrous smelters, after accounting for personal cigarette smoking and employment at the smelter. Other case-control studies[230,231] did not replicate this finding but were also limited by their failure to account for smoking and employment at the smelter.

Doll and Peto,[162] in their 1981 review of the causes of cancer, estimated that perhaps 1 to 2% of lung cancer was related to air pollution. Even in light of more recent findings, this seems to remain a reasonable estimate.[232] The body of evidence linking air pollution to lung cancer is solidifying,[218] but the public health impact of this exposure is small relative to cigarette smoking, at least in developed country settings where research has been conducted. 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.

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 originate indoors from tobacco smoking, building materials, soil gases, household products, and combustion from heating and cooking.[233] A trade-off exists between energy efficiency and indoor air quality because ventilation allows heated/cooled air to escape but improves indoor air quality.[234]

As discussed, in more developed countries, two of the most important indoor pollutants that most strongly increase lung cancer risk in never-smokers are passive smoking[13] and radon.[202] Asbestos exposure may pose a risk to building occupants, but concentrations are generally very low.[183] 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.[235] Mumford et al[236] inferred that smoky coal was likely to be a major determinant of the geographic distribution of lung cancer in Xuan Wei, China, a finding corroborated by an animal model.[237] Evidence supporting a causal association was strengthened by the results of a retrospective cohort study that showed that switching from use of unvented fire pits to stoves with chimneys almost halved the risk for lung cancer.[238]

Host Factors: Genetic susceptibility to lung cancer has long been postulated. Environmental agents, even cigarette smoking, cause lung cancer in only a minority of exposed people, leading to the hypothesis that susceptibility is inherently determined. Epidemiologic studies[244] 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 report; aspects of genetic susceptibility for lung cancer have been reviewed.[239–243]

Familial aggregation of lung cancer has been primarily demonstrated in both case-control and cohort studies.[244] In these studies, a family history of lung cancer tended to be associated with increased

risk for lung cancer; most of the studies controlled for smoking, which is known to aggregate in families. In a large study in Louisiana, segregation analysis suggested that lung cancer inheritance was consistent with a Mendelian codominant autosomal gene determining early onset of disease.[245] Conversely, the largest study of lung cancer in twins reported to date did not provide evidence indicating a genetic basis for susceptibility.[246] 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 sibling died of lung cancer. The results of a linkage analysis based on 52 extended pedigrees indicated that a locus on chromosome 6q23–25 was associated with a major susceptibility to lung cancer.[247]

In a genetic epidemiology study of lung cancer in nonsmokers in Detroit, Schwartz et al[248] explored familial risk for lung cancer and found an association between risk and a history of lung cancer in a first-degree relative (odds ratio, 1.4; 95% CI, 0.8 to 2.5). The association was much stronger in those aged 40 to 59 years at diagnosis compared with older people. This pattern of risk with age suggests that genetic factors may be more important at younger ages. This general finding was confirmed by a subsequent, complex segregation analysis of the same data.[249]

Research Findings on the Genetic Basis of Lung Cancer: With 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 providing a framework for understanding the genetic and epigenetic basis of lung cancer risk. Figure 3, proposed by Hecht,[121] 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 understanding of the mechanisms by which smoking causes cancers of the lung and other organs. A rapidly expanding literature addresses dosimetry and metabolism of tobacco carcino-

gens at the cellular and molecular levels, genetic determinants of susceptibility, and patterns of genetic changes in the tissues of smokers and in the cancers that the tissues develop.[121,241] Much of the research conducted to date has been based in case-control studies that compared the genotypes of lung cancer cases with those of control subjects. Studies have also been conducted using cohort designs with affected and nonaffected people sampled from the cohort and biological samples analyzed for the markers of interest.

The understanding of the epigenetic changes that may be involved in the causal pathway to lung cancer is advancing rapidly. For example, there is increasing evidence that methylation of cytosine in the DNA, leading to hypermethylation of promoter regions, is frequent in most types of cancers, including lung cancer.[250] Promoter regions of many human genes have loci rich in CpG dinucleotides, regions referred as *CpG islands*.[250,251] Hypermethylation of the CpG islands can be detected by polymerase chain reaction methods. Cells with abnormal methylation of genes have been detected in sputum before the diagnosis of lung cancer, suggesting that hypermethylation could be a useful marker for early detection.[252,253]

In a general formulation of determinants of cancer risk, the risk depends on carcinogen exposure and the factors that determine host susceptibility, including genetic predisposition.[254] For tobacco smoking and lung and other cancers, the elements of this paradigm all are topics of inquiry, using the combination of laboratory- and population-based studies 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.[255] As research evolves within this paradigm, a more complete biological understanding of the specific events underlying the multistage model, originally proposed on a conceptual basis, can be anticipated.

This framework indicates multiple points where genetically determined host characteristics might be important: carcinogen metabolism and activation,
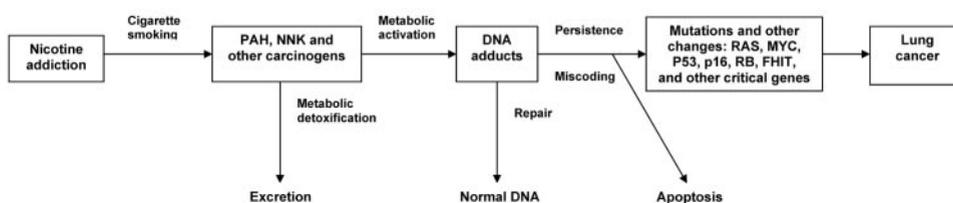

FIGURE 3. Scheme linking nicotine addiction and lung cancer via tobacco smoke carcinogens and their induction of multiple mutations in critical genes. Adapted from Hecht.[121] PAH = polycyclic aromatic hydrocarbon.

and DNA repair capacity, for example. Reviews have been published,[240,256–258] and the evidence has expanded and deepened our understanding of how smoking injures cells and causes cancer and indicates potential approaches to identification of high-risk individuals and molecular screening.

The metabolism of toxic agents, including carcinogens, generally proceeds through two phases.[259] In phase 1, unreactive nonpolar compounds are converted, usually by oxidative reactions, to highly reactive intermediates. These intermediates are then able to form complexes with conjugating molecules in phase 2 conjugation reactions, which are usually less reactive and more easily excreted. However, the intermediate metabolite may react with other cellular components, such as DNA, before conjugation occurs. This binding to DNA may be the first step in the initiation of the carcinogenic process.[259]

Many carcinogenic compounds in tobacco smoke (*eg*, polycyclic aromatic hydrocarbons) undergo metabolic activation by phase 1 enzymes of the cytochrome p450 system to form reactive intermediates that bind to DNA and cause genetic injury. Several of these enzymes have been investigated with regard to lung cancer risk, including CYP1A1. For CYP1A1, the current evidence suggests that two specific polymorphisms, the MspI polymorphism[260] and a polymorphism in exon 7,[261] are associated with increased risks for lung cancer.

Glutathione S-transferase is a phase 2 enzyme that detoxifies reactive metabolites of polycyclic aromatic hydrocarbons. There are at least four genetically distinct classes of the glutathione S-transferases: μ, α, π, and θ. The risk estimates from a metaanalysis[262] indicate that individuals with the GSTM1 null genotype have higher risk for lung cancer than those with the GSTM1 present genotype, but a pooled analysis[262] of data from 21 case-control studies did not indicate that this susceptibility was stronger among cigarette smokers than among nonsmokers. The importance of interactions between genes is highlighted by the joint assessment of the CYP1A1 Ile462Val and GSTM1 null polymorphisms in nonsmokers, which indicated that the combination of the two variant genotypes was associated with a greater than fourfold increased likelihood for lung cancer compared with the combination of the two nonvariant genotypes.[263]

There are other candidates for determinants of susceptibility to lung cancer in smokers, including oncogenes and suppressor genes and DNA repair capacity.[239] One gene of particular interest for lung cancer is p53, a tumor suppressor gene.[254,258] This gene has been described as "at the crossroads" for multiple cellular response pathways that are considered relevant to carcinogenesis.[258] The gene is frequently mutated in lung cancers, > 90% of small cell cancers and > 50% of non-small cell cancers. The spectrum of mutations in smokers seems to be different from that in nonsmokers.[254,258] In fact, Denissenko et al[264] showed binding of an activated metabolite of benzo[a]pyrene to the same p53 codons where mutations are commonly observed in lung cancers in smokers. However, epidemiologic studies[265] of common polymorphisms in the p53 gene have not shown strong associations with lung cancer risk.

Substantial research has been directed at DNA repair and susceptibility to lung cancer and other tumors.[257,266] People with specific rare, recessive traits (*eg*, xeroderma pigmentosa) have long been known to be at increased risk for cancer. DNA repair capacity has now been examined as a specific risk factor for lung cancer, with the underlying hypothesis that lesser capacity would lead to greater lung cancer risk from the multiple DNA-damaging components of tobacco smoke. Although much research remains to be done to clarify the association between variation in DNA repair capacity and lung cancer risk, the evidence suggests that this is a promising lead.[241] There are a variety of phenotypic assays for susceptibility to DNA damage. Individuals with a less proficient DNA repair capacity phenotype as measured by a nonspecific mutagen sensitivity assay have been shown to have an increased risk for lung cancer in some studies.[267,268] Studies of DNA repair genes have been conducted, including studies of *XPA*, *XPD*, radiograph repair complementation groups 1 and 3 (*XRCC1* and *XRCC3*), excision repair cross complementation group 1 (*ERCC1*), and *hoGG1*. One of the most extensively studied DNA repair genes is the nucleotide excision repair gene *ERCC2/ XPD* (*eg*, references[269,270]). The evidence to date has not yet revealed a consistent pattern of associations for the Asp312Asn or Lys751Gln polymorphisms of the *ERCC2/XPD* gene.[271] The findings of a review of polymorphisms in three genes in the base excision repair pathway (*OGG1*, *APE1/APEX1*, and *XRCC1*) showed that for the *OGG1* Ser326Cys polymorphism, individuals with the Cys/Cys genotype had an elevated risk for lung cancer (summary odds, 1.24; 95% CL, 1.01, 1.53).[272]

Presence of Acquired Lung Disease: In addition to hereditary factors, increased susceptibility to lung cancer may result from underlying lung disease. Such acquired lung diseases assume two major forms: (1) those that obstruct airflow, such as COPD; and 2) fibrotic disorders that restrict lung capacity, such as pneumoconiosis.[273] 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, even after debate for > 60 years.[274]

A substantial body of evidence suggests that COPD or impaired lung function is associated with the occurrence of lung cancer.[275] Cigarette smoking is the principal cause of both COPD[276] 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. Therefore, clarifying the relevance of COPD to the development of lung cancer awaits further proof that this association is not accounted for by cigarette smoking. One potential mechanism that is hypothesized to link COPD with lung cancer is α_1-antitrypsin deficiency, and evidence to support this notion includes the observation that the prevalence of α1AD carriers was higher in patients with lung cancer than in the general population and higher in patients who had lung cancer and had never smoked.[249] Alternatively, 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 mechanism, the presence of COPD is a clinically useful risk indicator.

Several studies[277–280] found inverse associations between asthma and lung cancer. However, a meta-analysis[281] that rigorously controlled for smoking revealed a positive association between asthma and the risk for lung cancer, especially nonadenocarcinoma lung cancer. Subsequently, asthma was found to be associated with lung cancer mortality in the Second National Health and Nutrition Examination Survey Mortality Study (from 1976 to 1992).[282] Several potential mechanisms have been proposed to explain this association: (1) mucociliary dysfunction leading to accumulation of toxicants, such as lung carcinogens, in the airway; (2) free radical damage to DNA, as a result of imbalance between oxidants and antioxidants; and (3) chronic inflammation, leading to chronic mitogenesis, and increased likelihood of conversion of endogenous DNA damage into mutations.[281] Appropriately designed studies are needed to establish whether and how asthma might increase the risk for lung cancer.

Clarifying the possible relationship between pneumoconioses and lung cancer poses particularly vexing challenges. Even for asbestos exposure, which is clearly established as a potent cause of lung cancer,[190] whether lung cancer results from asbestos *per se* or from asbestosis remains controversial.[191] Asbestos is likely to cause lung cancer via multiple mechanistic pathways.[283,284] 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 indi-

viduals has proved difficult.[285,286] The presence of silicosis is associated with an increased risk for lung cancer.[179] Understanding the basis of this association will entail isolating the independent effects of silica exposure and lung fibrosis while taking into account exposure to smoking and other lung carcinogens.[177,192]

Such differences in the pattern of associations between pneumoconioses and lung cancer emphasize that "fibrosis" is not a homogeneous exposure but one that depends 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 the potential harmfulness of an agent.[283]

In addition to pneumoconioses, two other forms of interstitial lung disease (ILD) have been most consistently linked to lung cancer: idiopathic pulmonary fibrosis (IPF) and systemic sclerosis (SSc). The potential relationship between these conditions and lung cancer is controversial, because ILD has alternatively been hypothesized to do the following: (1) cause lung cancer, (2) be caused by lung cancer, and (3) share common pathogenetic mechanisms with lung cancer.[287] Until recently, epidemiologic studies of ILD were hindered by the variable criteria used to diagnose this rare condition. However, recent improvements to an international classification system have facilitated investigation of the potential association between ILD and lung cancer.

The variability in the diagnostic criteria for IPF until 1998 probably contributed to the wide-ranging associations (from increased risk to protection) that have been observed between IPF and lung cancer.[287] The results of autopsy studies have shown high rates of lung cancer in patients with IPF.[287] However, IPF, specifically, usual interstitial fibrosis, is a histopathologic marker of inflammatory response to a variety of toxic exposures that are common in lung cancer, including connective tissue disease, chemotherapy, radiotherapy, and surgery. In the absence of clinical data, autopsy findings are prone to overestimate the role of IPF as a risk factor for lung cancer. However, estimates based on registry data may have limited validity as a result of possible misclassification of smoking status and the lack of histologic confirmation. Misclassification of IPF in such studies likely attenuates the association between IPF and lung cancer.[192] Similarly, in studies that rely on death certificates, underreporting may lead to the lower reported lung cancer prevalence among individuals who had a diagnosis of IPF, compared with the general public.

ILD may also occur in the context of SSc, a rheumatologic disorder with a myriad of local and/or

systemic manifestations. ILD, which occurs in most cases of SSc, is the major cause of morbidity and mortality as a result of SSc. Lung cancer is the most frequently reported malignancy in SSc, usually occurring in patients with SSc and concurrent ILD.

Compared with the general population, lung cancer occurs more frequently among those with SSc, especially those with ILD, even after adjustment for cigarette smoking.[287] A mechanism proposed to explain this association is genetic damage induced by inflammation and fibrosis and the subsequent repeated cellular injury and repair.[287] Another hypothesis for the increased lung cancer risk seen in patients with SSc relates to enhanced lung cancer susceptibility resulting from the frequent use of immunosuppressive drugs.[287] Alternatively, the potential role of repeated chest imaging resulting in overdiagnosis bias cannot be ruled out as an explanation for the observed associations between SSc and lung cancer.[287]

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 exposure to these agents, then this would be expected to reduce the risk for lung cancer. Preventive strategies can be pursued in the public policy arena or in public health interventions 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 has also proved to be a productive component of tobacco control strategies, as exemplified by the settlement between 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 patient 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.[288] Lung cancer is a major women's health issue. As a result of 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 have not yet begun to decrease consistently.[25] Although lung cancer remains a critical public health problem, the decrease in the overall lung cancer burden that is occurring in the United States, as 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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