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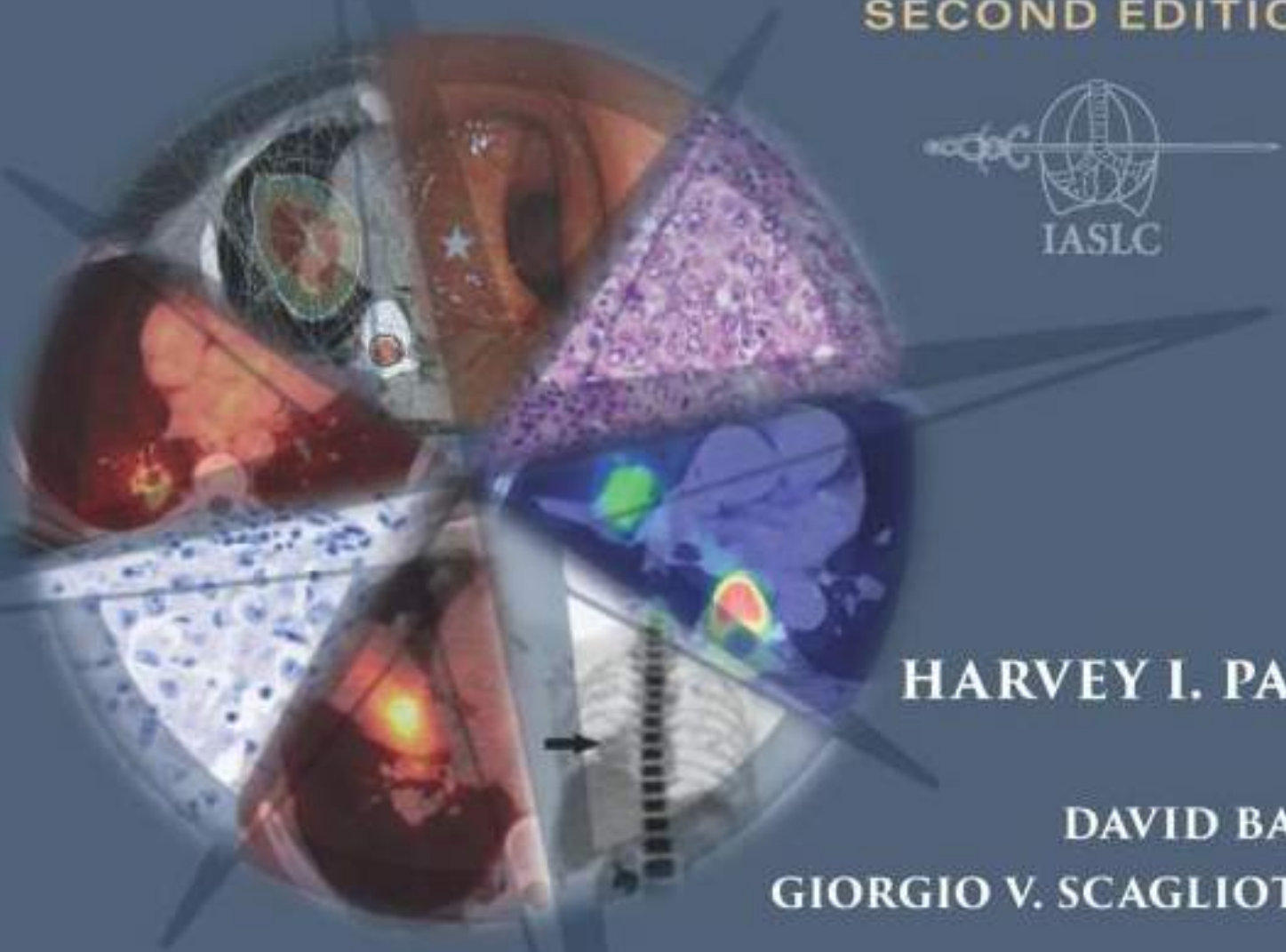
SECOND EDITION



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Preface

Reference texts for the management of cancer are only as good as their information, and the information must be relevant to clinical practice and must be current. Moreover, lung cancer and other thoracic malignancies remain an international problem. Lung cancer is not only the greatest cause of cancer death but also a major cause of disability and suffering.

For the past 40 years the **International Association for the Study of Lung Cancer** has remained the only society totally dedicated to the study and treatment of lung cancer and other thoracic malignancies. These cancers are notoriously complicated, as was recently pointed out by their mutational burdens and histologic heterogeneity. New discoveries, novel trials, and changes in the standard of care are happening at an extraordinary rate, and medical, surgical, and radiation oncologists, as well as respiratory physicians, nurses, physician's assistants, and social workers, need reliable and up-to-date sources of information filtered by experts in the field. The IASLC represents international and multidisciplinary expertise at every level: basic science, epidemiology, respiratory medicine, medical and radiation oncology, surgery, and palliative care, as well as nursing and advocacy. The IASLC, however, has recognized that this expertise must be channeled toward a mission of education. At the foundational level of education is a reference text that is thorough, timely, and readily available to all practitioners who are confronted with patients with thoracic malignancy.

That is why the organization published the first edition of *The IASLC Multidisciplinary Approach to Thoracic Oncology* in 2014 with the hope that this would be the first step in consolidating this information in one comprehensive source. The plan was always to be able to update, amend, and incorporate new ideas in later editions so that the basics were retained but new discoveries were discussed by the "discoverers" themselves. That is the reason why we now have a new edition of the reference text, *IASLC Thoracic Oncology*. However, we never imagined the explosion of information that would happen over a 2-year period that would need to be presented to the reader. The genomic phenotyping of lung cancer has expanded remarkably, necessitating the discovery and validation with new trials of third-generation targeted agents. The staging system for the disease has been modified and externally validated. Histologic classification of the disease has helped to define high-risk patients in early-stage disease. Radiation techniques are being expanded with greater implementation in oligometastatic disease as well as for early-stage patients, and, most dramatically, immunotherapeutic strategies, not limited solely to check point inhibition, now dominate many of the novel trials for metastatic disease as well as for neoadjuvant and adjuvant therapy.

Can you cover everything and be "au courant" with a textbook? It's a formidable task; however, the editors, along with our previous dedicated group of chapter writers, have been extraordinarily fortunate to add new experts and the most recent data from meetings in the fourth-quarter of 2016. The textbook remains a "work in progress" with online capabilities, which the IASLC and its publishing partner, Elsevier, hope to use to get information to the "treaters" in the future as early as "real time." Future updates available for selected chapters online will give readers access to the latest news as well as innovations for many of the disciplines. Just as the IASLC has matured and is growing, it is hoped that these chapters will mature so that the reader will alter his or her practice quickly due to a more rapid delivery of timely evidence-based information.

But for now, this second edition, which represents updated material for more than 50 percent of the book, will help manage the wealth of new data so that the word gets out in a comprehensive multispecialty coordinated fashion. Novel findings are presented "hot off the press" in a way that academics and nonacademics alike can keep up with thoracic cancer diagnostics and therapeutics so that the ultimate beneficiary is the patient. This endeavor calls for one international society and one book or information source that is born and keeps on growing, just like the society

As with the first edition, there is absolutely no way that this project would have been completed essentially in less than 2 years without our managing editor, Deborah Whippen. Deb has always been the binding glue for this book, as well as every single IASLC publication, and without her, every page would have scattered to the wind. Physicians are notoriously unorganized, and physician editors fall right into that category. Therefore the momentum for getting this task accomplished, from keeping updates about the status of the chapters to copyediting to indexing to even organizing what the cover would look like, fell to Deb and her cadre of book-producing experts at Elsevier including Taylor Ball and Sharon Corell. We are the luckiest editors in the world to be able to work with and listen to these dedicated manuscript aficionados.

The editors are also indebted to the Board of the IASLC for allowing us to expand this portion of the IASLC educational portfolio. Although the IASLC has been extraordinarily successful with conferences, webinars, consensus meetings, and publications, including the *IASLC Staging Manual in Thoracic Oncology* and the *IASLC Atlas of ALK and ROS1 Testing in Lung Cancer*, the updating of this 62-chapter textbook has proceeded on schedule for many reasons. We felt that our authors are dedicated to the mission, and this devotion is very different from the usual heartaches that come with editing a book. The commitment of the authors to write the most informative chapters was obvious from the beginning to the end of the task.

IASLC Thoracic Oncology is meant to provide both the practitioner and the fellow with an updated reference source that will be useful in dealing with lung cancer. It is also meant to further unify the international community through recognition that wars are won by forming allies, and in the battle against lung and other thoracic cancers, the IASLC stands for such an alliance. The battle is not only fought in the clinics and the hospitals but also on the educational front in order to supply the troops with successful plans for therapy. The editors' most profound wish is that the knowledge available in the book and all of its associated future ventures will help to move the survival curves upward and toward the right.

Harvey I. Pass
Giorgio V. Scagliotti
David Ball

1 Classic Epidemiology of Lung Cancer

Paolo Boffetta

SUMMARY OF KEY POINTS

- Lung cancer incidence and mortality has declined among men in many countries, following a decline in the prevalence and level of smoking. Among women, lung cancer incidence and mortality is still increasing in many countries and has become the main cause of cancer death.
- Despite important advances in lung cancer screening, primary prevention through tobacco control remains the main approach in the fight against lung cancer, especially in low-income countries.
- Occupational factors, passive smoking and other indoor pollutants, including radon, and air pollution are other important modifiable causes of lung cancer; nutritional factors and infectious agents are additional potential risk factors. Control of exposure to lung carcinogens other than tobacco, in both the general and the occupational environment, has had a substantial impact in several high-risk populations.
- Lung cancer in never-smokers is not an uncommon disease. While there is an interaction between tobacco smoking and other lung carcinogens, several agents have been shown to cause lung cancer also in never-smokers.
- Lung cancer was the most important epidemic of the 20th century, and it is likely to remain a major public health problem in the 21st century. It is also a paradigm of the importance of primary prevention and a reminder that scientific knowledge is not sufficient per se to ensure human health.

The history of lung cancer epidemiology parallels the history of modern chronic disease epidemiology. In the 19th century, an excess of lung cancer was observed among miners and some other occupational groups, but otherwise the disease was very rare. An epidemic increase in lung cancer began in the first half of the 20th century, with much speculation and controversy about its possible environmental causes.

Among both women and men, the incidence of lung cancer is low in persons under 40 years of age, it increases up to age 70 or 75 years (Fig. 1.1), and it declines thereafter. The decline in incidence in the older-age groups can be explained, at least in part, by incomplete diagnosis or by a generation (birth cohort) effect.

Methodologically, epidemiologic studies of lung cancer have been straightforward because the site of origin is well defined, progressive symptoms prompt diagnostic activity, and the predominant causes are comparatively easy to ascertain. Novel approaches to the classification of lung cancer based on molecular techniques will likely bring new insights into its etiology, especially among nonsmokers.

DESCRIPTIVE EPIDEMIOLOGY

Lung cancer, a rare disease until the beginning of the 20th century, has become the most frequent malignant neoplasm among men in most countries and the main neoplastic cause of death in both men and women. In 2012, lung cancer accounted for an estimated 1,242,000 new cancer cases among men, which is 17% of all cancers excluding nonmelanoma skin cancer, and 583,000, or 9%, of new cancers among women. After nonmelanocytic skin cancer, lung cancer is the most frequent malignant neoplasm in humans and the most important cause of neoplastic death. Approximately 58% of all cancers occur in developing countries.[1]

The geographic and temporal patterns of lung cancer incidence are determined chiefly by consumption of tobacco. An increase in tobacco consumption is paralleled a few decades later by an increase in the incidence of lung cancer, and a decrease in consumption is followed by a decrease in incidence. Other factors, such as genetic susceptibility, poor diet, and indoor air pollution, may act in concert with tobacco smoking in shaping the descriptive epidemiology of lung cancer.

The pattern found today in men (Fig. 1.2) is composed of populations at high risk, in which consumption of tobacco has been persistently high for decades, and populations at low risk, either because tobacco consumption has not been increasing for long (e.g., China, Africa) or because a decrease in consumption has been present for several decades (e.g., Sweden).

In countries with populations made up of different ethnic groups, differences in lung cancer rates are frequently observed. For example, in the United States, the rates are higher among black men than among other ethnic groups (Table 1.1).

Over the past 25 years, the distribution of histologic types of lung cancer has been changing. In the United States, squamous cell carcinoma, which was formerly the predominant type, is decreasing, whereas adenocarcinoma has increased in both genders.[2] In Europe, similar changes are occurring in men, whereas in women, both squamous cell carcinoma and adenocarcinoma are increasing.[3] Although the increase in the incidence of adenocarcinoma may be due, at least in part, to improved diagnostic techniques, changes in composition and patterns of tobacco consumption (deeper inhalation of low-nicotine and tar tobacco smoke) are additional explanations.[4]

RISK FACTORS

Tobacco Smoking

The evidence is very strong that tobacco smoking causes all major histologic types of lung cancer. A carcinogenic effect of tobacco smoke on the lung has been demonstrated in epidemiologic studies conducted since the early 1950s and has been recognized by public health and regulatory authorities since the mid-1960s. Tobacco smoking is the main cause of lung cancer in most populations, and the geographic and temporal patterns of the disease largely reflect tobacco consumption during the previous decades. Because of the high carcinogenic potency of tobacco smoke, a major reduction in tobacco consumption would result in the prevention of a large fraction of human cancers.[5,6]

The excess risk among continuous smokers relative to the risk among never-smokers is on the order of 10-fold to 20-fold. The overall relative risk reflects the contribution of the different aspects

of tobacco smoking: average consumption, duration of smoking, time since quitting, age at start, type of tobacco product, and inhalation pattern, as well as the absolute risk in never-smokers.

Several large cohort and case–control studies have provided detailed information on the relative contributions of duration and amount of cigarette smoking to excess lung cancer risk. Doll and Peto[7] analyzed data from a large cohort of British doctors and concluded that the excess lung cancer risk rises in proportion to the square of the number of cigarettes smoked per day but to the fourth power of the duration of smoking. Therefore duration of smoking should be considered the strongest determinant of lung cancer risk in smokers. Analysis of the same cohort after 50 years of follow-up confirmed these results.[8]

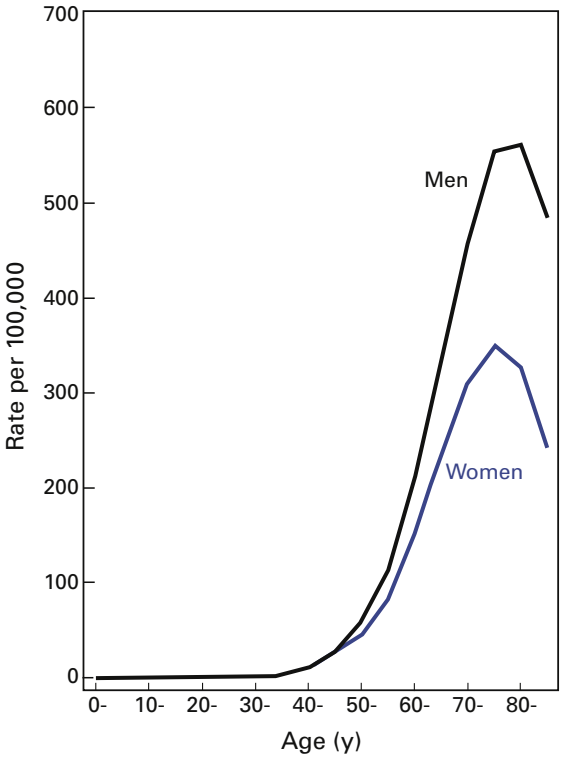

Fig. 1.1. Age-specific incidence rate of lung cancer per 100,000, by gender, according to the US Surveillance, Epidemiology End-Result (SEER) database for 2003–2007.[1]

An important aspect of tobacco-related lung carcinogenesis is the effect of cessation of smoking. The excess risk sharply decreases in ex-smokers, starting approximately 5 years after quitting, and an effect is apparent even for cessation late in life. However, an excess risk throughout life likely persists even in long-term quitters.[6]

The risk of lung cancer is lower among smokers of low-tar cigarettes than among smokers of high-tar cigarettes and lower among smokers of filtered cigarettes than among smokers of unfiltered cigarettes. Smokers of black (air-cured) tobacco cigarettes are at twofold to threefold higher risk of lung cancer than smokers of blond (flue-cured) tobacco cigarettes.[6] Tar content, the presence or absence of a filter, and the type of tobacco are not independent, however. High-tar cigarettes tend to be unfiltered, and in countries where both black and blond tobacco are used, cigarettes are more frequently made from black tobacco.

Although cigarettes are the main tobacco product smoked in Western countries, an exposure–response relationship with lung cancer risk has also been shown for cigars, cigarillos, and pipes, indicating a carcinogenic effect of these products as well.[6] An increased risk of lung cancer has also been shown after consumption of local tobacco products, such as bidi and hookah in India, khii yoo in Thailand, and water pipe in China.[6] Limited data suggest an increased lung cancer risk after consumption of other tobacco products, such as narghile in western Asia and northern Africa and toombak in Sudan.

Differences in the Effect of Tobacco Smoking According to Histology, Gender, and Race

Although the evidence is abundant that tobacco smoking causes all major histologic types of lung cancer, the associations appear to be stronger for squamous cell and small cell carcinoma and weaker for adenocarcinoma. The incidence of adenocarcinoma has greatly increased during the past decades. Some of the increase may be attributable to improved diagnostic techniques,

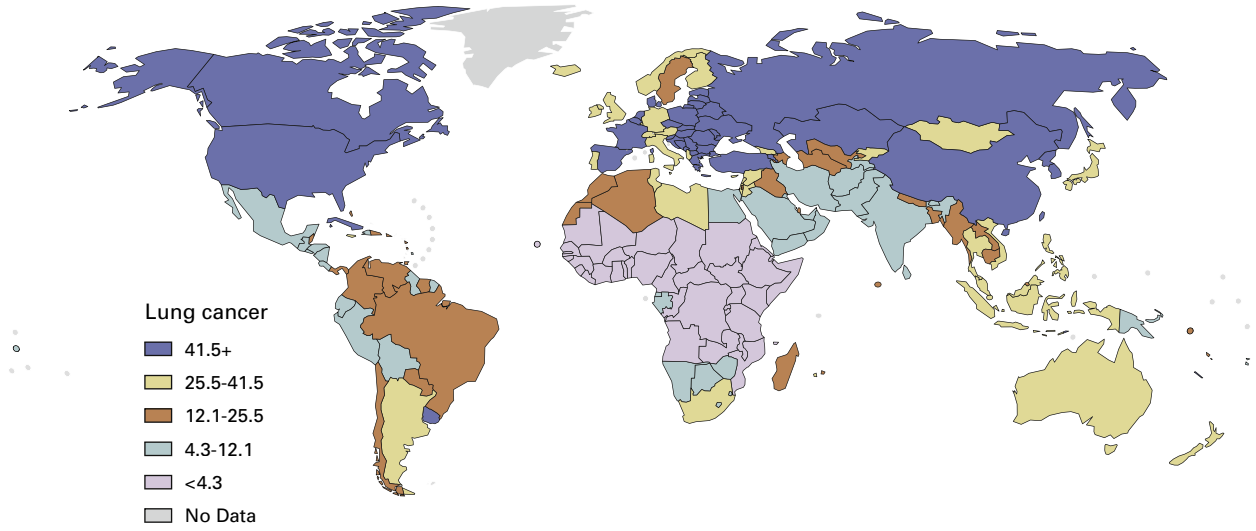

Fig. 1.2. Estimated age-standardized rate (ASR) of lung cancer in men per 100,000 men, by country, 2012
Ferlay J1, Steliarova-Foucher E., Lortet-Tieulent J., et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. *2013 Apr;49(6):1374–1403. http://dx.doi.org/10.1016/j.ejca.2012.12.027. Epub 2013 Feb 26. (Reprinted from International Agency for Research on Cancer. GLOBOCAN 2012. Estimated Cancer Incidence, Mortality, and Prevalence Worldwide in 2012.* http://globocan.iarc.fr/Default.aspx*. 2012.)*

but aspects of tobacco smoking may also have played a role; it is unclear, however, which aspects of smoking might explain these changes.

A few studies have suggested a difference in the risk of lung cancer between men and women who have smoked a comparable amount of tobacco,[9] but most of the available evidence does not support this gender difference.[6]

The higher rate of lung cancer among the black population compared with the rates in other ethnic groups in the United States is probably explained by the higher tobacco consumption in that population.[10] The lower risk of lung cancer among smokers in China and Japan compared with the risks among smokers in Europe and North America may be due to the relatively recent beginning of regular heavy smoking in Asia, although differences in the composition of traditional smoking products and in genetic susceptibility may also play a role.[11]

Secondhand Tobacco Smoke

The epidemiologic evidence and biologic plausibility support a causal association between secondhand exposure to cigarette smoke and lung cancer risk in nonsmokers.[12] The evidence of a high relative risk in the original studies[13,14] has been challenged on the basis of both possible confounding by active smoking, diet, or other factors and possible reporting bias. However, when these factors were taken into account, the association was confirmed, and the excess risk was on the order of 20% to 25%.[12,15]

The effect of involuntary smoking appears to be present for both household exposure, mainly from the spouse, and workplace exposure.[16,17] By contrast, little evidence has been found for an effect of childhood involuntary smoking exposure.[18]

Confounding Effects of Tobacco Smoking

The importance of tobacco smoking in the causation of lung cancer complicates the investigation of the other causes of this disease because tobacco smoking may act as a powerful confounder. For example, a population of industrial workers exposed to a suspected carcinogen may smoke more than the unexposed comparison population. An excessive lung cancer risk in the exposed group, especially if small, might be due to the difference in smoking rather than to the effect of the occupational agent. One solution is to restrict the investigation to lifetime nonsmokers. However, they may represent a selected group, with low prevalence of exposure to many agents of interest. An alternative is to collect detailed information on smoking habits and to compare the effect of the suspected carcinogens across different groups of smokers. This approach has shown that tobacco smoking as a confounder rarely completely explains excess risks larger than about 50%.[19]

Interaction Between Tobacco Smoke and Other Lung Carcinogens

Other carcinogens may interact with tobacco smoke in the determination of their carcinogenic action on the lung. In other words, the absolute or relative risk from exposure to another agent may be greater (or smaller) among heavy smokers compared with the corresponding risk among light smokers and nonsmokers. The interaction may take place at the stage of exposure; that is, the other agent has to be absorbed on the tobacco particles to penetrate the lung. Or it may take place at some stage of the carcinogenic process, for example, on induction of common metabolic enzymes or activation of common molecular targets. The empirical evidence for an interaction between tobacco smoking and other agents is scanty, mainly because of lack of data among light smokers and nonsmokers.[20] The interaction between asbestos exposure and tobacco smoking falls between the additive and the multiplicative model.[21] The interaction between radon exposure and tobacco smoking best fits a submultiplicative model; data for other agents are too sparse to allow conclusions.

TABLE 1.1 Age-Standardized Incidence Rates of Lung Cancer per 100,000 by Gender and Ethnic Group[a]

Ethnic Group	Men	Women
Asian and Pacific Islander	31.6	17.5
Black	66.8	35.5
Hispanic white	25.0	16.5
Non-Hispanic white	51.2	38.1

[a]Data from the US Surveillance, Epidemiology End-Result database for 2003–2007.[1]

Use of Smokeless Tobacco Products

Few studies have investigated the risk of lung cancer among users of smokeless tobacco products. In two large cohorts of US volunteers, the relative risk of lung cancer associated with spit tobacco use among nonsmokers was 1.08 (95% confidence interval [CI], 0.64–1.83) and 2.00 (95% CI, 1.23–3.24).[22] In a Swedish cohort, the relative risk of lung cancer for every use of snus was 0.80 (95% CI, 0.61–1.05).[23] In a large case–control study from India, the relative risk of lung cancer for every use of tobacco-containing chewing products was 0.74 (95% CI, 0.57–0.96).[24] Overall, the evidence of an increased risk of lung cancer from use of smokeless tobacco products is weak; the apparent protective effect detected in studies including smokers may be due to uncontrolled negative confounding.

Dietary Factors

Vegetables and Fruits

There is some evidence that a diet rich in vegetables and fruits probably exerts a protective effect against lung cancer.[25] Although a protective effect of high vegetable and fruit intake was found in most case–control studies, results of prospective studies with detailed information on dietary intake are less consistent in showing a similar effect. Possible reasons for the inconsistent results include bias from retrospective dietary assessment, misclassification and limited heterogeneity of exposure in cohort studies, residual confounding by smoking, and variability in food composition. Among specific types of fruits and vegetables, the evidence is stronger for cruciferous vegetables,[26] but even in this case it is unlikely that this group of foods represents a strong protective factor against lung cancer.

Meat and Other Foods

It has been suggested that high intake of meat, in particular fried or well-done red meat, increases the risk of lung cancer,[27] although the available evidence does not support this hypothesis.[25] If real, the association may be explained by the formation of nitrosamines during cooking of the meat,[28] as well as by the saturated fat content of meat (as discussed later). Although risk estimates for the intake of other foods, such as cereals, pulses, eggs, milk, and dairy products, have been specified in some studies, these results are inadequate for a judgment of the evidence of an effect.[25]

Coffee and Tea

In a few studies, high consumption of coffee has been associated with an increased risk of lung cancer.[29] However, residual confounding by tobacco smoking is a distinct possibility, and no conclusion can be drawn at present.[25] There is some evidence of a chemopreventive effect of tea, notably green tea, in smokers.[30] The overall evidence, however, is not consistent.

TABLE 1.2 Preventive Trials on Supplementation of Beta-Carotene and Lung Cancer Risk

Author	Setting, Population, Age (y)	Follow-up	Daily Dose (mg)	RR	95% CI
Kamangar et al. (2006)[30a]	Linxian (China), 29,584, 40–69	1986–2001	15[a]	0.98	0.71–1.35
ATBCCP Study Group (1994)[30b]	Finland, 29,133 male smokers, 50–69	1985–1993[b]	20	1.18	1.03–1.36
Hennekens et al. (1996)[30c]	United States, 22,071 male physicians, 40–84	1982–1995	25[c]	0.93	NA
Omenn et al. (1994)[30d]	United States, 18,314 smokers or asbestos workers, 45–74	1985–1995	30	1.28	1.04–1.57

[a]Combined with selenium (50 μg) and alpha-tocopherol (30 mg).
[b]Follow-up for cancer incidence.
[c]50 mg on alternate days.
CI, confidence interval; *NA*, not available; *RR*, relative risk.

Lipids

In several ecologic studies, a positive association was found between total lipid intake and lung cancer risk that appears to be independent of the risk of tobacco consumption.[31] The analytic studies that have addressed this association, however, have produced mixed results. Although no study has provided evidence of a protective effect of total lipid intake, an increased risk was shown only in case–control studies, whereas a pooled analysis of eight cohort studies provided no evidence of an increased risk of lung cancer for high intake of either total fat or saturated fat.[32]

Carotenoids

Many studies have addressed the risk of lung cancer in relation to estimated intake of either beta-carotene or total carotenoids (which in most cases correspond to the sum of alpha- and beta-carotene).[33] Five cohort and 18 case–control studies published up to 1994 provided 28 risk estimates in different populations; with one notable exception,[34,35] 25 of these estimates indicated a protective effect of high beta-carotene intake. The protective effect provided a 30% to 80% reduction in the risk of lung cancer between the highest and lowest intake categories.[31] The risk decreased for all major histologic types of lung cancer in many countries, in both genders, and in both smokers and nonsmokers. Similar results have been obtained in studies based on measurement of beta-carotene in prospectively collected sera.[36] The evidence of a protective effect from most observational studies has been refuted by the results of randomized intervention trials based on beta-carotene supplementation (Table 1.2). In two of these trials, which included smokers or workers exposed to asbestos, a significant increase in the incidence of lung cancer was observed in the treated groups; in the remaining studies, no effect was ascertained. The difference in results between observational studies and preventive trials can be explained by confounding by cancer-protective factors in fruits and vegetables other than beta-carotene or by the possibility that high, nonphysiologic doses of beta-carotene may cause oxidative damage, especially among smokers.[37]

Other Micronutrients

For none of the antioxidant vitamins or the other micronutrients is there conclusive evidence of a protective effect against lung cancer. The data for selenium, vitamin A, lutein, and lycopene, in particular, are inconclusive.[25,38] The results of studies of serum level of these micronutrients are insufficient for an evaluation. There is evidence from observational studies that low levels of vitamin D are associated with lung cancer risk;[39] results of randomized trials, however, do not provide supportive evidence, arguing for caution in drawing conclusions.

Isothiocyanates

Isothiocyanates are a group of chemicals with cancer-preventive activity in experimental systems and may be responsible for the possibly reduced risk of lung cancer associated with high intake of cruciferous vegetables. The enzymes glutathione S-transferase M1 and T1 are involved in their metabolism. As indicated, these enzymes are polymorphic, with 5% to 10% of Europeans and 30% to 40% of Asians being carriers of a deletion in both. In four studies it has been shown that the protective effect of a high intake of isothiocyanates is stronger in carriers of both deletions than in other noncarriers (Fig. 1.3).[40–43] No final conclusions can be drawn, but this effect is an example of a possible gene–environment interaction in lung carcinogenesis.

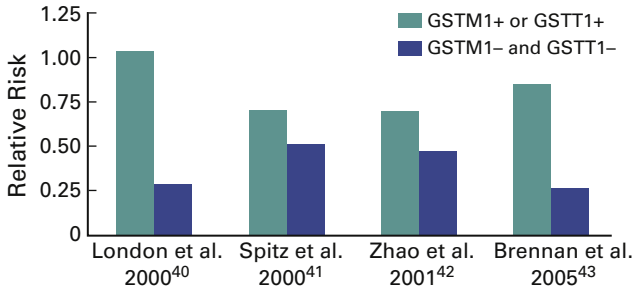

Fig. 1.3. Interaction between high intake of isothiocyanates and polymorphism in glutathione S-transferase mu 1 (GSTM1) and glutathione S-transferase theta 1 (GSTT1) in four case–control studies of lung cancer.

Alcohol

Given the strong correlation between alcohol drinking and tobacco smoking in many populations, it is difficult to disentangle the contribution of alcohol to lung carcinogenesis while properly controlling for the potential confounding effect of tobacco. Meta-analyses have demonstrated that the increased risk of lung cancer observed among alcoholics is mainly attributable to such residual confounding, but some evidence of a smoking-adjusted association with high alcohol consumption was found.[44,45] This conclusion was confirmed by a pooled analysis of seven cohort studies.[46] Overall, it may be premature to conclude that an association between alcohol drinking and lung cancer has been confirmed by the available data. If the association is causal, alcohol may act as a solvent for carcinogens such as the ones in tobacco smoke. In addition, alcohol can induce metabolic enzymes or act through direct DNA damage via the active metabolite acetaldehyde.[47]

Hormones

Estrogen and progesterone receptors are expressed in the normal lung and in lung cancer cell lines, and estradiol has a proliferative effect on lung cancer cells. Although an effect of estrogens on lung carcinogenesis has not been demonstrated, estrogens may act via formation of DNA adducts and activation of growth factors.[48] Data on risk of lung cancer after the use of hormone

replacement therapy have been reported from five case–control studies, two cohort studies, and one randomized trial.[49–56] A small increased risk of lung cancer has been found in the early studies, whereas a decreased risk was detected in the more recent studies. No effect was observed in the only randomized trial.[53] Although the different results may be explained by changes in the formulations used for replacement therapy, the lack of an effect in the only study with an experimental design argues against an effect of this type of exposure on lung cancer.

Three cohort studies and one case–control study were included in a meta-analysis of serum insulin-like growth factor 1 level and lung cancer. The overall relative risk was 1.01 (95% CI, 0.49–2.11).[57] The results for insulin-like growth factor–binding protein 3 level were also negative (summary relative risk, 0.83; 95% CI, 0.38–1.84), although exclusion of a deviant study resulted in a decreased risk of lung cancer for a high level of insulin-like growth factor–binding protein 3 (relative risk, 0.53; 95% CI, 0.34–0.83).

Anthropometric Measures

There is some evidence for association between a reduced body mass index and an increased risk of lung cancer.

However, this inverse association can be explained, at least in part, by negative confounding by smoking,[58] and no clear association has been demonstrated among never-smokers. Subsequent studies have supported this conclusion that the apparent association is due to confounding.[59]

Evidence suggests a direct association between height and lung cancer risk.[60] Subsequent studies have supported this finding,[61,62] although the evidence is not fully consistent.[63,64]

Infections

People with pulmonary tuberculosis have been found to be at increased risk of lung cancer.[65] A similar association was reported from community-based studies among smoking and nonsmoking women.[49,66–68] In the most informative study, involving a large cohort of people with tuberculosis from Shanghai, China,[69] the relative risk of lung cancer in the whole cohort was 1.5 and it was 2.0 20 years after the diagnosis of tuberculosis; a correlation was also seen with the location of the tuberculosis lesions. Whether the excess risk is caused by the chronic inflammatory status of the lung parenchyma or by the specific action of the *Mycobacterium* is not clear. A role of isoniazid, a widely used tuberculosis drug that causes lung tumors in experimental animals, was excluded in one large study.[70]

Chlamydia pneumoniae is a cause of acute respiratory infection. Six studies have been published on the risk of lung cancer among individuals with markers of *C. pneumoniae* infection. A positive association was detected in all six studies.[71] However, studies based on prediagnostic samples had lower risk estimates than studies based on postdiagnostic samples. An association between infection with human papilloma virus and lung cancer, in particular the adenocarcinoma type, has been suggested by the results of an analysis of series of cases and by the growing evidence of an increased risk among workers potentially exposed to this agent, such as butchers.[72] The results are insufficient to draw a conclusion about the presence or absence of a causal association. Other biologic agents that have been suggested as playing a role in lung carcinogenesis include simian virus 40 and the fungus *Microsporum canis*.[73,74]

Ionizing Radiation

There is conclusive evidence that high exposure to ionizing radiation increases the risk of lung cancer.[75] Atomic bomb survivors and patients treated with radiotherapy for ankylosing spondylitis or breast cancer are at moderately increased risk of lung cancer (relative risk, 1.5–2.0 for cumulative exposure in excess of 100 rad).[76] The association with high doses of ionizing radiation was stronger for small cell carcinoma than for other histologic types of lung cancer. Studies of nuclear industry workers exposed to relatively low levels of ionizing radiation, however, provided no evidence of an increased risk of lung cancer.[75]

Underground miners exposed to radioactive radon and its decay products, which emit alpha particles, have been consistently found to be at increased risk of lung cancer.[77] The risk increased with estimated cumulative exposure and decreased with attained age and time since cessation of exposure.[78] In a pooled analysis of 11 cohorts, an apparently linear, approximately 6% risk increase per working-level year of exposure was estimated.[78] Evidence was also found that for comparable cumulative exposure, the risk is greater for lower rates over a longer period and that smoking modifies the carcinogenic effect of radon.[78,79] Today the main concern about lung cancer risk from radon and its decay products comes from residential rather than occupational exposure. In a pooled analysis of 13 European case–control studies, a relative risk of 1.084 (95% CI, 1.030–1.158) per 100 Bq/m^3 increase in measured indoor radon was found.[80] After correction for the dilution caused by measurement error, the relative risk was 1.16 (95% CI, 1.05–1.31). The exposure–response relationship was linear with no evidence of a threshold. The same conclusion was reached from a similar analysis of North American studies.[81] These results suggest that indoor radon exposure may be an important cause of lung cancer, in particular among nonsmokers unexposed to occupational carcinogens.

Occupational Exposures

The important role of specific occupational exposures in lung cancer etiology has been well established in reports dating back to the 1950s. The risk of lung cancer is increased among workers employed in a number of industries and occupations (Table 1.3).[82,83] The responsible agents have been identified for several, but not all, of these high-risk workplaces. Evidence for the carcinogenicity of many occupational agents has been reviewed.[19] Estimates of the proportion of lung cancer cases attributable to occupational agents in France (12.5% in men and 6.5% in women) and the United Kingdom (14.5% overall) have been reported in two studies, published in 2010 and 2012, respectively.[84,85] Although asbestos remains the most important occupational lung carcinogen, the precise role of silica, radon, heavy metals, and polycyclic aromatic hydrocarbons (PAHs) in the burden of occupational cancer is uncertain. The remaining occupational lung carcinogens are likely to play a lesser role in terms of disease burden.

Asbestos

The first evidence of increased risk of lung cancer after inhalation of asbestos fibers dates back to the 1950s.[86] All forms of asbestos—chrysotile and amphiboles, including crocidolite, amosite, and tremolite—are carcinogenic to the human lung, although chrysotile's potency may be lower than that of other types.[87] Although asbestos has been banned in many countries, a substantial number of workers are still exposed, mainly in the construction industry. In many low-resource and medium-resource countries, occupational exposure is widespread. Asbestos is responsible for a large number of occupationally related lung cancers in many countries.

Metals

Exposure to inorganic arsenic, known as a lung carcinogen since the late 1960s, occurs mainly among workers employed in hot smelting; other groups at increased risk are fur handlers,

TABLE 1.3 Occupational Agents, Groups of Agents, Mixtures, and Occupations Classified as Human Carcinogens (Group 1) by the IARC Monographs Program, Volumes 1–100, Which Have the Lung as Target Organ (Cogliano et al.[82])[a]

Agents, Mixtures, Occupations	Main Industry, Use
AGENTS AND GROUPS OF AGENTS	
Arsenic and inorganic arsenic compounds	Glass, metals, pesticides
Asbestos	Insulation, filters, textiles
Beryllium and beryllium compounds	Aerospace
Bis(chloromethyl)ether and chloromethyl methyl ether	Chemical intermediate
Cadmium and cadmium compounds	Dye/pigment
Chromium-b compounds	Metal plating, dye/pigment
Involuntary tobacco smoking	Hospitality
Nickel compounds	Metallurgy, alloy, catalyst
Plutonium	Defense
X-ray radiation and gamma radiation	Medical
Radon-222 and its decay products	Mining
Silica, crystalline	Stone cutting, mining, glass, paper
MIXTURES	
Coal-tar pitch	Construction, electrodes
Soot	Pigments
OCCUPATIONS	
Aluminum production	NA
Coal gasification	NA
Coke production	NA
Hematite mining (underground)	NA
Iron and steel founding	NA
Painting	NA
Rubber production industry	NA

[a]Since the publication of this source, diesel engine exhausts (mainly used in mining and transportation) have been added to the list (Benbrahim-Tallaa et al.[83]).
IARC, International Agency for Research on Cancer; *NA,* not available.

manufacturers of sheep-dip compounds and pesticides, and vineyard workers.[88] Chromium VI compounds increase the risk of lung cancer among chromate-production workers, chromate-pigment manufacturers, chromium platers, and ferrochromium producers. No such risk has been detected among workers exposed only to chromium III compounds. An increased risk of lung cancer has been found in studies of nickel miners, smelters, electrolysis workers, and high nickel alloy manufacturers.[88] Agreement is lacking on whether all nickel compounds are carcinogenic for humans; the available evidence does not allow a clear separation of the effects of the different nickel salts to which workers are exposed. An increased risk of lung cancer has been demonstrated among workers in cadmium-based battery manufacturing industries, copper–cadmium alloy industries, and cadmium smelters. The increased risk does not seem to be attributable to concomitant exposure to nickel or arsenic. In US studies, an excess risk of lung cancer has been found among workers exposed to beryllium in the early technologic phase of the industry,[89] although the relevance of these results to the current exposure situation has been debated.[90]

Silica

An increased risk of lung cancer has been consistently reported in cohorts of people with silicosis.[91] Many authors have investigated workers exposed to crystalline silica in foundries, pottery making, ceramics, diatomaceous earth mining, brick making, and stone cutting, in some of whom silicosis may have developed. An increased risk of lung cancer was found in some, but not all, studies, and in the positive studies the increase was small, with evidence of an exposure–response relationship.[92]

Polycyclic Aromatic Hydrocarbons

PAHs are a complex and important group of chemicals formed during combustion of organic material. They are widespread in the human environment; for most people, diet and tobacco smoke are the main sources of exposure to PAHs. A number of occupational settings entail exposure to high levels of PAHs. These chemicals, however, occur inevitably as complex mixtures of variable composition; an assessment of the risk from individual PAHs is therefore difficult. An increased risk of lung cancer has been demonstrated in several industries and occupations entailing exposure to PAHs, such as aluminum production, coal gasification, coke production, iron and steel founding, tar distillation, roofing, and chimney sweeping.[93] An increase has also been suggested in a few other industries, including shale oil extraction, wood impregnation, road paving, carbon black production, and carbon electrode manufacture, with an exposure–response relationship found in the studies with detailed exposure information. Motor vehicle and other engine exhausts represent an important group of mixtures of PAHs because they contribute significantly to air pollution. The available epidemiologic evidence shows an excess risk among workers with high occupational exposure to diesel engine exhaust.[94]

Medical Conditions and Treatment

In addition to tuberculosis and lung fibrosis from chronic exposure to high levels of fibers and dusts (both discussed in earlier sections), chronic respiratory diseases have been associated with lung cancer risk. People with chronic bronchitis and emphysema are at moderately increased risk, and after adjustment for tobacco smoking, this risk is greater for squamous cell carcinoma than for other cancers.[66,94,95] The roles of shared exposures, namely, tobacco smoking and chronic inflammation, have not been fully elucidated. A meta-analysis of studies of lung cancer and asthma in never-smokers showed a summary relative risk of 1.8 (95% CI, 1.3–2.3);[96] the results were similar when the analysis was restricted to studies that controlled for smoking. However, because the evidence is based mainly on case–control studies, selection and recall bias cannot be fully excluded.[97]

The risk of lung cancer is increased in individuals surviving other tobacco-related and lifestyle-related cancers.[98] Commonality of risk factors, long-term effects of radiotherapy, and increased susceptibility probably interact in the causation of second primary cancers. The effect of chemotherapy and radiotherapy on the risk of a second primary lung cancer has been extensively investigated among long-term survivors of breast cancer; lung cancer develops in 2% to 9% of this group.[99] The increased risk is restricted to patients receiving radiotherapy. Among them, a clear exposure–response relationship has been shown, together with an interactive effect of tobacco smoking.

Several studies have assessed lung cancer risk among regular users of aspirin and other nonsteroidal anti-inflammatory drugs. A meta-analysis of 15 studies resulted in a pooled relative risk of 0.86 (95% CI, 0.76–0.98).[100] However, there was heterogeneity among the different studies, likely owing in part to differences in the definition of the exposure. The protective effect was stronger for case–control studies (relative risk, 0.74; 95% CI, 0.57–0.99) than for cohort studies (relative risk, 0.97; 95% CI, 0.87–1.08), suggesting a role for recall bias. In particular, in a large cohort study of 1 million US volunteers, a reduction in risk was not found.[101] However, in a meta-analysis of eight aspirin trials, the risk of lung cancer was reduced during the first 10 years after the end of the trial (relative risk, 0.68; 95% CI, 0.50–0.92).[102]

Indoor Air Pollution

Indoor air pollution is thought to be the main determinant of the elevated risk of lung cancer among nonsmoking women living in

TABLE 1.4 Results of Selected Cohort Studies on Fine Particle Exposure and Risk of Lung Cancer

Study; Population; Reference	No. and Sex	RR	95% CI	Exposure Contrast[a]	Basis for Exposure Assessment	Range or Mean (SD) or Both, μg/m³
Seventh-Day Adventists; USA, 1977–1992 (McDonnell et al., 2000)[102a]	6338, M	2.23	0.56–8.94	per 24.3 μg/m³ $PM_{2.5}$	Residential history 1966–1992 and local monthly pollutant estimates based on airport visibility data 1966–1992	Mean (SD) $PM_{2.5}$, 59.2 (16.8)
ASC/CPS-II; USA, 1982–1998 (Pope et al., 2002)[102b]	500,000, M + F	1.08	1.01–1.16	per 10 μg/m³ $PM_{2.5}$	City of residence in 1982. Pollutant average of 1979–1983	Mean (SD) $PM_{2.5}$, 21.1 (4.6); range, roughly 5–30 μg/m³
Six Cities; USA, 1975–1998 (Laden et al., 2006)[102c]	8111, M + F	1.27	0.96–1.69	per 10 μg/m³ $PM_{2.5}$	City of residence in 1975. Pollutant average 1979–1985	Range $PM_{2.5}$, 34.1–89.9 μg/m³
ESCAPE; Europe; 1990s–2000s[a] (Raaschou-Nielsen, 2013)[102d]	273,838, M + F	1.18	0.96–1.46	per 5 μg/m³ $PM_{2.5}$	Place of residence at enrollment. Pollutant average 2008–2011	Range of cohort-specific mean $PM_{2.5}$, 6.6–31.0 μg/m³

[a]Pooled analysis of 14 cohorts, enrollment mainly in the 1990s, follow-up until late 2000s.
CI, confidence interval; *F,* female; *M,* male; *NA,* not available; *PM,* particulate matter; *RR,* relative risk; *SD,* standard deviation.

several regions of China and other Asian countries. The evidence is stronger for coal burning in poorly ventilated houses, but evidence also exists for burning of wood and other solid fuels, as well as for the fumes from high-temperature cooking using unrefined vegetable oils, such as rapeseed oil.[103] A positive association between various indicators of indoor air pollution and lung cancer risk has also been reported in populations exposed to less extreme conditions than the ones encountered by some Chinese women, for example, populations in Central Europe and Eastern Europe and other regions.[104,105]

Outdoor Air Pollution

There is abundant evidence that lung cancer rates are higher in cities than in rural settings.[106] However, this pattern, may result from confounding by other factors, notably tobacco smoking and occupational exposures, rather than from air pollution. Cohort and case–control studies are limited by difficulties in assessing past exposure to the relevant air pollutants. The exposure to air pollution has been assessed either on the basis of proxy indicators—for example, the number of inhabitants in the community of residence, residence near a major pollution source—or on the basis of actual data on pollutant levels. These data refer to total suspended particulates, sulfur oxides, and nitrogen oxides, which are not likely to be the agents responsible for the carcinogenic effect, if any, of air pollution.[107] Furthermore, the sources of data may cover quite a wide area, masking small-scale differences in exposure levels.

The combined evidence suggests that urban air pollution may confer a small excess risk of lung cancer on the order of 50%, but residual confounding cannot be excluded. In four cohort studies, assessment of exposure to fine particles was based on environmental measurements (Table 1.4). The results of these studies suggest a small increase in risk among people classified as most highly exposed to air pollution. In 2013, the International Agency for Research on Cancer classified outdoor air pollution as an established cause of lung cancer in humans.[108]

Drinking Water Contamination

An increased risk of lung cancer has been consistently reported among people exposed to arsenic in drinking water. Investigations include ecologic studies from Argentina, Chile, and Taiwan and case–control and cohort studies from Taiwan—in particular, in areas endemic for blackfoot disease, caused by chronic arsenic poisoning—Japan, the United States, and Chile.[109] An exposure–response relationship was observed in most of these studies. In particular, in a cohort study from a contaminated area in Taiwan, the relative risk of lung cancer according to cumulative estimated exposure to arsenic from drinking water was 4.0 for 20 or more milligrams per liter of drinking water contamination compared with uncontaminated water.[110]

CONCLUSION

Given the poor prognosis of lung cancer and the lack of effective screening procedures, primary prevention remains the main weapon against this neoplasm and control of tobacco smoking is by far the most important preventive measure. Although the effects of tobacco control on the incidence of the disease can be demonstrated in several populations, much remains to be done, especially among women and in low-income countries. Control of exposure to other lung carcinogens, in both the general and the occupational environment, is another measure that has been taken and, at least in some instances, has had substantial effects. Priorities for the prevention of lung cancer, in addition to tobacco control, include understanding the carcinogenic and preventive effects of dietary and other lifestyle factors, control of occupational exposures, avoidance of high exposure to outdoor and indoor pollution, and elucidation of conditions that entail increased genetic predisposition to lung cancer.

Lung cancer in never-smokers is not a rare disease. Occupational factors, passive smoking, and indoor exposure to radon explain a portion of these cases, and nutritional, infectious, and genetic factors are receiving attention as additional risk factors.

Lung cancer was the most important epidemic of the 20th century, and it is likely to remain a major public health problem in the 21st century. It is ironic that this cancer causes more deaths than any other malignancy in the world, even though epidemiologic research has led to the identification of more than 10 causes of the disease, including the quantitatively dominant cause, tobacco smoking. Lung cancer is also a paradigm of the superiority of prevention over treatment and a reminder that scientific knowledge is not sufficient per se to ensure human health.

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2 Tobacco Control and Primary Prevention

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SUMMARY OF KEY POINTS

- Smoking is the predominant risk factor for development of lung cancer. As tobacco is introduced to societies, common patterns emerge. Typically, it is first used in men, then later in women. A 20- to 25-year lag between smoking rates and lung cancer rates reflects this.
- The World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC) provides a comprehensive global tobacco-control strategy. Six key concepts are described with the mnemonic "MPOWER."
  - **M**onitor Tobacco Use and Prevention Policies: The WHO has standardized surveys and metrics to make comparisons possible between societies and over time.
  - **P**rotect People from Tobacco Smoke: Secondhand smoke is a risk factor for lung cancer. Implementation of public smoking bans has been linked to decreased disease from tobacco smoke (asthma exacerbations, acute coronary events, etc.).
  - **O**ffer to Help Quit Tobacco Use: Physician advice, pharmacotherapy, and tobacco quitlines improve cessation rates, but are underutilized.
  - **W**arn About the Dangers of Tobacco: Public service messages are effective. Written and graphic warning labels on tobacco packages reach each user and are effective at decreasing use.
  - **E**nforce Bans on Tobacco Advertising, Promotion, and Sponsorships: Often tobacco marketing targets youth and socioeconomically disadvantaged populations. Restricting marketing prevents initiation and decreases use.
  - **R**aise Taxes: Taxation suppresses use while raising money; unfortunately, most tobacco tax funds do not support other tobacco-control measures.

Many lives have been saved by tobacco control over the past 50 years. However, due to ongoing use of tobacco, millions of preventable deaths have occurred. Tobacco use has steadily grown and spread across the globe to such a degree that tobacco-induced death and disability have attained epidemic proportions. Many diseases and conditions attributable to smoking, such as cerebrovascular disease, heart disease, emphysema, and cancer—especially lung cancer—have led to death and disability. This chapter highlights the growth, spread, and current status of the tobacco epidemic worldwide; global efforts to curb the use of tobacco; and the potential impact of control measures on outcomes, specifically lung cancer–related mortality.

As tobacco use is encouraged, promoted, and perpetuated with a variety of mechanisms, there is a need to intervene and provide tobacco prevention and cessation in multiple dimensions. Various tobacco-control strategies have been used in the past, with varying degrees of success across different populations. The WHO FCTC provides a unified multidimensional approach to tobacco control for the 21st century, with a structure to discuss implementation of comprehensive tobacco control. Although societies around the globe differ widely in terms of language, cultural norms, economic resources, and smoking rates, nearly all societies are afflicted with the tobacco epidemic, and a concerted effort involving the use of evidence-based strategies has the potential to save millions of lives.

HISTORICAL CONTEXT OF THE TOBACCO EPIDEMIC

Tobacco is indigenous to the Americas, and, prior to its European discovery in 1492, tobacco was unknown in the rest of the world. After Europeans were introduced to tobacco—and nicotine addiction—consumption steadily grew in Europe. Despite its popularity, King James I of England issued "A Counterblaste to Tobacco" as one of the first documented efforts of tobacco control. In 1604, he not only stated the harm to the smoker as being "… hatefull to the Nose, harmefull to the braine, dangerous to the Lungs …" but also discussed the implications of second-hand smoke in the context of a woman whose husband smokes and "resolve[s] to live in a perpetuall stinking torment."[1] One of the first documented tobacco-control policies was his accompanying "Commissio pro Tabacco," which levied a tax on tobacco importation.[2] In these early years of the spread of tobacco, much of its use was in the form of chew tobacco, pipe tobacco, cigars, or snuff. Tobacco was even touted as medicinal. Despite the proclamation from King James I, government taxation, and various religious edicts, tobacco use continued to grow throughout Europe.

The Industrial Revolution included the development of cigarette-rolling machines in the late 1800s, which not only spawned mass production and increased the use of tobacco but also shifted the bulk of tobacco use to cigarette smoking. Cigarettes are smoked with deeper inhalation than pipe tobacco or cigars, leading to absorption in the pulmonary parenchyma rather than in buccal and pharyngeal parenchyma. As a result of pulmonary delivery, a much more rapid and intense peak in nicotine levels leads to a greater addiction potential. This more addictive product, combined with industrialization, global transportation, and aggressive marketing to men, women, and children across the globe, led to an explosion in tobacco use and a highly profitable industry.

The epidemiologic relationship between smoking rates in a population and death rates attributable to smoking has been extensively analyzed on a global scale, and fascinating patterns tend to recur predictably from one society to another. Lopez et al.[3] noted that the rise in the prevalence of cigarette smoking was reflected in the rise in the death rate caused by smoking-related illnesses, with an approximately 20-year to 25-year lag.[3] Overall, it has been demonstrated that death rates from tobacco-induced disease occur at a rate of roughly half of the smoking rate, given this time lag (e.g., for a population with a 60% smoking rate, 30% of the deaths 20 years later are secondary to smoking). Stage I of a smoking epidemic represents initiation, with low smoking rates and very low death rates due to smoking (Fig. 2.1). Stage II consists of a rapid rise in the smoking prevalence among men to its peak, with the beginning of a rise in deaths. During this time, smoking among women just starts to increase, but there are few deaths. Stage III consists of a decline in smoking among men, with a continued increase in smoking among women. During this time, the death rate among men continues to rise following the 20-year to 25-year lag from the peak in smoking, and the death

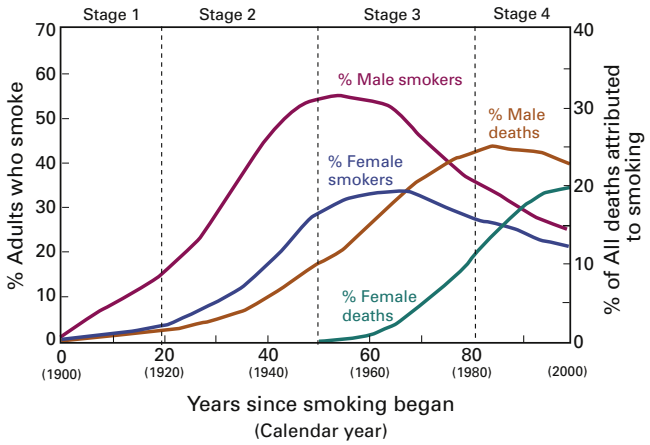

Fig. 2.1. Lopez curve from 1994 demonstrating the stages of the tobacco epidemic in countries with developed economies as indicated by the rates of smoking and smoking-attributable deaths (based on lung cancer data) for men and women. *(Reprinted with permission from Thun M, Peto R, Boreham J, Lopez AD. Stages of the cigarette epidemic on entering its second century.* Tob Control. *2012;21(2):96–101.)*

rate among women also begins to increase. Stage IV consists of a decline in smoking rates among men and a plateau or fall in smoking rates among women, with an eventual decline in death rates. The Lopez model has been applied to many societies, and, in general, developing nations tend to be represented by stages I and II, whereas many industrialized nations have experienced their peak in smoking rates and deaths, particularly among men, and are in stages III or IV.

This rise and fall in the number of smoking-related deaths closely parallels the rise and fall in lung cancer incidence and mortality rates in the United States. Smoking was relatively uncommon before 1900, correlating with Lopez stage I. The smoking rate among men in the United States increased from the 1900s and peaked around 1965 (stage II). After the Surgeon General's report of the link between smoking and cancer,[4] smoking rates among men decreased, yet smoking-related deaths among men continued to increase (stage III). This increase in male smoking prevalence eventually led to a peak and decrease in lung cancer–related deaths among men approximately 20 years later. During this time, the smoking rate among women rose and plateaued. In the late 1990s and beyond, the death rate among women was just beginning to decrease (stage IV). According to the Lopez model, the incidence of lung cancer and lung cancer–related mortality should continue to fall for men and women in the United States as smoking rates have declined.

This descriptive model has also been applied to many other societies. Rates of smoking in China and Japan have risen for men, and the rates of smoking-attributable deaths continue to rise in these societies (stage II). However, countries such as Australia, New Zealand, the United Kingdom, and Sweden have progressed through all phases of the Lopez model and are in stage IV, with declining rates of smoking-related deaths among men and women. Despite the decrease in tobacco use in some of the aforementioned countries, tobacco use is growing in other countries, particularly India, Japan, and China, where societal and cultural shifts are leading to growing numbers of people who smoke, particularly women. The growth of the global population, the spread of tobacco use to more countries, and the rising rates of smoking among women are all contributing to a projected rapid global increase in tobacco use and tobacco-induced deaths. The toll of tobacco is considerable, with an estimated 100 million deaths globally in the 20th century; currently, 5 million deaths are reported annually, with 1 billion deaths projected globally in the 21st century if the trajectory is not changed.[5]

TABLE 2.1 Measures to Assist With Implementation of Effective Tobacco Control

Monitor tobacco use and prevention policies
Protect people from tobacco smoke
Offer help to quit tobacco use
Warn about the dangers of tobacco
Enforce bans on tobacco advertising, promotion, and sponsorship
Raise taxes on tobacco

As smoking rates have declined in some countries, they have stabilized or increased in other countries as a result of aggressive marketing by the tobacco industry and lax or nonexistent tobacco-control policies. With the irrefutable evidence that this aggressively marketed, addictive product leads to premature death and disability among people who smoke (with one in two people who continue to smoke dying of tobacco-related disease) and illness in people exposed to secondhand smoke, tobacco control not only can be seen as a public health crisis but also can be viewed from ethical and human rights perspectives.[6,7] By the end of the 20th century, the tobacco epidemic had steadily grown into a massive global crisis in which, currently, 5 million people die annually as a result of its use. Attempts at tobacco control have varied among different countries, and often by state or province within a country. The production, marketing, and distribution of cigarettes are predominantly controlled by a few international corporations: Philip Morris, Altria, British American Tobacco, Japan Tobacco, R. J. Reynolds, and China National Tobacco. The production, marketing, and distribution of cigarettes had become a globally organized network, and although the battle was being fought on many fronts, there was no global consensus on measures of tobacco control, and unified countermeasures to combat this problem were lacking.

21ST CENTURY TOBACCO-CONTROL MEASURES

The need for a comprehensive, unified, and enforceable global strategy to combat this global epidemic was initially conceptualized by Roemer and Taylor in 1993.[8] These authors subsequently presented a strategy for a FCTC to the WHO in 1995. Persistent efforts led to adoption of the WHO FCTC at the World Health Assembly in 2003. The WHO FCTC came into force in 2005 as the first international treaty adopted under the WHO and was ratified by 177 parties in 2013. The United States notably remains a nonparty. This unprecedented agreement between party nations became the first international legal instrument for a unified approach to combat the global tobacco epidemic. The multidimensional treaty delineates universal standards declaring the dangers of tobacco and outlines strategies for limiting its use worldwide through provisions regarding education, production, advertisement, distribution, sale, and taxation.

The details of the entire WHO FCTC are beyond the scope of this chapter, but the WHO produced an internationally applicable summary of the essential elements of a tobacco-control strategy, publicized as the mnemonic "MPOWER," which includes six components (Table 2.1). Examples of successful tobacco-control strategies are discussed here using these categories as a construct.

Monitor Tobacco Use and Prevention Policies

If an epidemic is to be treated, it must first be measured. It is crucial to dramatically improve global surveillance of tobacco use among adults and youths. Until recently, the extent of the epidemic has not been well documented, particularly in developing countries. Differences among nations with regard to the tools

that have been used to measure this epidemic have made comparisons difficult. The WHO Global Tobacco Surveillance System is a uniform comprehensive format for measuring the epidemic and gauging the impact of measures when implemented. The system comprises three school-based components (the Global Youth Tobacco Survey, the Global School Personnel Survey, and the Global Health Professions Student Survey) and one adult component (the Global Adult Tobacco Survey). These surveys contain the same basic data fields in all queries, and individual countries can add other specific points if they wish. Uniformity is necessary to compare one society and/or time point with another. The system involves three sequential phases: a survey workshop, data analysis, and a programmatic workshop that is designed to determine the needs and priorities to suit that area at that time. The surveys are intended to be conducted shortly after the implementation of control measures and then repeated every few years. Monitoring with reliable tools to obtain accurate data is the only way to truly determine where tobacco control is most needed, what type of tobacco control is most appropriate, who the target audience should be, and the outcomes of any implemented policies.

Protect People From Tobacco Smoke

The harm that smoking causes to people who smoke has been a driving force for tobacco control, but the effects of smoking on nonsmokers has led to another arm of tobacco control: protecting all people from tobacco smoke. Secondhand smoke, also known as environmental tobacco smoke or passive smoking, is a risk factor for asthma, bronchitis, and respiratory infections and also has been demonstrated to be a risk for the development of lung cancer and cardiovascular disease. Rates of lung cancer are higher for women who have never smoked but have husbands who smoke, with a relative risk ranging from 1.3 to 3.5.[9] Rates are higher for women with husbands who are "heavy" smokers (>20 cigarettes per day), suggesting a dose–response relationship.[9]

Mackay et al. [10] and Pell et al. [11] reported on the effect of a 2006 policy to prohibit smoking in all enclosed places in Scotland on health conditions related to secondhand smoke. In analyzing hospital data, the authors found that the rate of hospitalizations for childhood asthma was increasing 5.2% per year before the policy and fell by 18.2% per year after the policy took effect; this change was noted for both preschool and school-age children. In addition, after implementation of the policy, the rate of admissions for acute coronary syndrome decreased by 14% among active smokers, by 19% among former smokers, and by 21% among individuals who had never smoked. When the 12-month periods before and after implementation of the policy were compared, the rate of admissions for acute coronary syndrome fell by 17%. In comparison, during that time in England (where there were no smoke-free laws), the rate fell by only 4%, and during the preceding decade in Scotland, the rate decreased by an average of 3% per year. Serum cotinine was measured in patients during this time. The self-reported exposure to secondhand smoke decreased among nonsmokers, and this decrease was validated on the basis of lower cotinine levels in those individuals.[11] Many other examples demonstrate the impact of smoke-free laws on public health, and it is not surprising that improved outcomes are seen among nonsmokers, but it is encouraging that improved outcomes can be found among smokers as well, likely as a result of a reduction in tobacco use despite the fact that they are still smoking.

Offer Help to Quit Tobacco Use

Many people who use tobacco may not actively seek assistance with cessation because of either a lack of interest in quitting, the perceived futility of cessation efforts, the stigma associated with tobacco use, or a lack of willingness to invest the time and financial resources to support their desire to quit. The International Association for the Study of Lung Cancer conducted a survey regarding the smoking-cessation practices among its members (response rate, 40.5%).[12] According to the survey, 90% of respondents believe that current smoking affects clinical outcomes and that cessation should be a standard part of care; 90% ask their patients about smoking at the time of the initial visit; 81% advise their patients to quit (but only 40% discuss pharmacotherapy); and 39% provide cessation assistance. These survey results likely represent a best-case scenario for cancer providers, as the respondents were members of an international multidisciplinary lung cancer organization who were motivated to respond to the survey and because the survey responses were self-reported. By contrast, the rates of primary physician queries about smoking and advice on cessation have been disappointingly low, likely driven by the perceived of lack of efficacy of such efforts among practitioners.

However, although many people who smoke may not quit on the basis of their physician's advice, brief counseling from primary physicians at every visit could have a substantial impact. In one of the first landmark studies on this subject, published in 1979, researchers from London found that physician practices such as asking patients about tobacco use, advising patients to stop smoking, providing informational pamphlets, and telling patients they will be called for follow-up yielded a 5.1% quit rate at 1 year.[13] Although this quit rate was modest, it was significantly higher than the rate for the control group (0.3%; $p < 0.001$). This finding suggests that active cessation interventions by primary care physicians could substantially impact the number of people who would quit. Unfortunately, as yet, primary care providers often do not follow the most basic steps of asking patients about smoking, advising them to stop smoking, and referring them to a cessation service such as a telephone quitline or other resource.

In many countries, quitlines are able to offer assistance with cessation. In the United States, many, but not all, of the quitlines run by individual states provide pharmacotherapy such as nicotine-replacement therapy. However, most countries are not able to afford this type of intervention. For many people who smoke, the cost of the nicotine-replacement therapy can exceed the cost of cigarettes. The convenience of the quitline, the availability of nicotine-replacement therapy, and the free-of-charge service would lead one to think that quitlines are popular, but the penetrance of quitlines is low, even in developed countries. For example, Australia has extremely aggressive and successful tobacco-control programs, with the quitline number displayed in all retail outlets, on every package of cigarettes, and in advertisements as part of a mass media campaign, yet one study demonstrated that only 3.6% of people who smoke used the service in 1 year, suggesting that many people who smoke may not initiate the call for help in quitting and may not be interested in asking for help.[14]

Compared with face-to-face counseling with a physician or other health-care provider, quitlines are more convenient, less costly, and more easily approached by reluctant smokers. A cost analysis of a national quitline in Sweden demonstrated a 31% self-reported 1-year quit rate with an estimated cost of $1052 to $1360 per quitter and of $311 to $401 per life year saved, indicating that the quitline was less costly than other modalities that were analyzed, such as counseling by a general practitioner, a community mass media campaign, and bupropion treatment.[15]

Warn About the Dangers of Tobacco

Education regarding the addictive and harmful nature of smoking can be delivered in multiple ways, including (but not limited to) physician–patient interactions, education in schools, public announcements on television and radio, warning labels on cigarettes, and print and outdoor advertisements related to the effects

of tobacco. One of the simplest and least expensive ways to distribute education about tobacco is through mandatory warning labels on tobacco packaging. A 2006 study conducted in four countries (the United States, the United Kingdom, Australia, and Canada) demonstrated that larger warnings and graphic warnings were more effective for communicating the risks of smoking compared with the very inconspicuous United States warnings.[16] Another report on warnings in these same countries was published in 2009, after the use of graphic warnings had been implemented in Australia. The impact of health warnings was evaluated by comparing graphic warnings from Australia and Canada with text-only warnings from the United Kingdom and the United States.[17] The new graphic warnings in Australia increased smokers' salience (reading and noticing), cognitive reactions (thinking about harm and quitting), and behavioral responses (forgoing cigarettes and avoiding the warnings).

Clearly, graphic warning labels are important means of communication in areas with lower literacy rates, but, even for populations with higher literacy rates, the graphic labels have greater impact and are associated with lower smoking rates. While public media campaigns and advertisements that warn about the dangers of tobacco have been shown to be effective, they do require financial resources for the creation and distribution of the messages and ongoing funding for maintenance. The implementation of policies regarding enlarging warning labels and including graphic warnings does not require ongoing cost to the government and literally puts an effective warning message in the hands of every tobacco user.

Enforce Bans on Tobacco Advertising, Promotion, and Sponsorship

The tobacco industry spends tens of billions of dollars annually to promote its product, which in turn kills up to half of its users. The industry depends on promotion to maintain its current customer base and to recruit "replacement smokers," that is, to replace the minority of smokers who successfully quit and the masses who die of tobacco-related diseases. An Article of the WHO FCTC states that all parties must implement comprehensive restrictions on tobacco advertising, promotion, and sponsorship within 5 years.[13] In many countries, particularly those with developing economies, tobacco use among women traditionally has not been high and women are viewed as a growth market by industry because of growing financial and social independence. It is unsurprising that women and minors have been the targets of many tobacco advertising, promotion, and sponsorship activities, with the rate of smoking among women expected to double between 2005 and 2025.[18] Because of this selective targeting, tobacco control also needs to be gender and age based in its approach. Exposure to tobacco advertising, promotion, and sponsorship is associated with a higher prevalence of smoking, and a comprehensive ban on such activities leads to lower exposure to these messages, a finding that has held true across different socioeconomic groups.[19] Bans on tobacco advertising, promotion, and sponsorship have been shown to decrease smoking rates in both developed and developing countries.[20,21]

Raise Taxes on Tobacco

"Of all the concerns, there is one—taxation—that alarms us the most. While marketing restrictions and [restrictions on] public and passive smoking do depress volume, in our experience taxation depresses it much more severely."[22]

These words from the tobacco industry, written more than 25 years ago, still hold true today. A 10% rise in retail price will result in a 4% decrease in cigarette sales through both increased cessation and reduced consumption by active smokers in developed nations and in an estimated 8% decrease in middle- to lower-income countries.[23] The fact that tobacco disproportionately affects lower socioeconomic groups that are linked with a greater elasticity (i.e., reduced sales with increased price) makes increasing the cost a logical tobacco-control strategy, particularly with respect to these lower socioeconomic groups. While some tobacco-control policies (e.g., media campaigns and cessation-support services) require ongoing financial resources and others (e.g., clean indoor air policies and policies banning advertisement) are fairly inexpensive to implement, taxation has the unique ability to effectively suppress tobacco use and generate revenue. Unfortunately, of the $133 billion globally generated by tobacco taxation, less than 1% of revenues collected in tobacco taxes are reinvested in prevention or cessation efforts.[24] A progressive approach to tobacco taxation was implemented in Costa Rica in 2012, with a rise in tobacco taxes of approximately $0.80 per pack. This change increased total taxes from approximately 56% to 71% of the cost of a pack of cigarettes, and all of the new tax revenue was earmarked for cancer treatment, tobacco-prevention and cessation services and research, support of the nation's Health Promotion Act, and other health-related measures. Although not all of these measures are directly related to tobacco control, some of the increased funds will directly benefit prevention, cessation, treatment, and patient-support efforts. A provision of this act is that taxes will automatically increase annually to keep pace with inflation.[25] Taxes passed as a flat tax amount per quantity of tobacco will be eroded by inflation over time unless levied as a percentage of the price or adjusted for inflation.

Combinations of Measures

Typically, successful tobacco control is implemented not as a single measure but rather as part of a more comprehensive multifaceted approach involving several of the aforementioned concepts; therefore it may be difficult to distill the impact of one measure on smoking rates when several are implemented in combination. For example, in California, clean indoor air legislation was accompanied by increased tax and antitobacco advertising. This combination resulted not only in a lower smoking prevalence but also lower per capita cigarette consumption. Reducing smoking is the aim of these programs, but the deeper overall goal is to improve public health, and therefore outcomes such as the lower mortality from heart disease and the decreased rates of bladder cancer and lung cancer that were found following the implementation of the California comprehensive tobacco program[26,27] further strengthen the need for multidimensional tobacco-control programs.

Some of the strongest tobacco-control measures that have an impact on several of the aforementioned categories have been developed in Australia. For example, the implementation of plain packaging regulations in Australia acts in several dimensions by providing health warnings and the quitline number while also eliminating brand image and advertising and promotion on the packaging itself. This approach not only has resulted in the distribution of warnings and the promotion of quitlines but has also been shown to decrease the appeal of smoking and to increase thoughts about quitting.[28]

Impact of Tobacco Control on Lung Cancer Mortality

As described in the previous section, effective tobacco-control efforts have been well defined and have a strong evidence base. The MPOWER strategy was developed by the WHO to assist countries in implementing the FCTC. The impact of tobacco-control efforts on the incidence of and mortality resulting

from lung cancer is demonstrated by the Lopez curves describing the stages of the smoking epidemic and the consequent epidemic of lung cancer (Fig. 2.1).[29] Unfortunately, only a few of the more economically developed countries heeded the epidemiologic news from the 1950s that smoking causes lung cancer.[30,31]

Doll et al.[32] demonstrated significantly improved survival for British male physicians who were nonsmokers (Fig. 2.2) and also significant benefits for physicians who had smoked but quit. Predominantly because of this cessation, Britain was also the first country to have a drop in lung cancer rates among men (Fig. 2.3).[29] Australia and the United States were close behind, but, interestingly, the decline was slower. Unfortunately, the lung cancer rates among women do not replicate the rates among men in different countries because of the variety of cultural influences on smoking prevalence. These changes in the United States and the United Kingdom were primarily driven by smoking cessation as a result of epidemiologic evidence linking disease to smoking. In the United States, the peak prevalence of male smokers started to decline after the 1930 birth cohort as a result of smoking cessation (Fig. 2.4).[33] In the United Kingdom, the rates of smoking among both male and female individuals and the annual rates of lung cancer–related death (Fig. 2.5) declined.[34] These changes indicate that smoking cessation occurs as a result of public education about the risks of smoking in the years following these early epidemiologic studies on lung cancer.

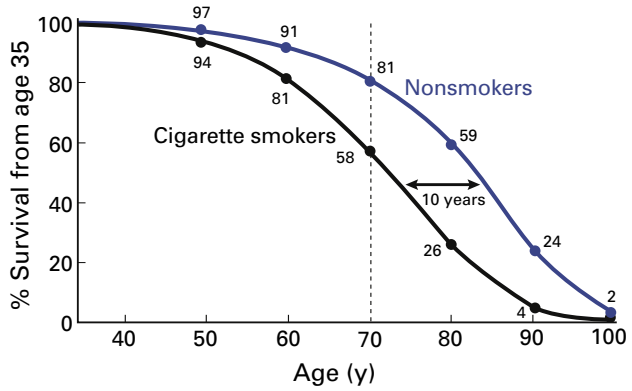

Fig. 2.2. Survival after 35 years of age for continuing smokers and nonsmokers among male physicians in the United Kingdom (born between 1900 and 1930). The values indicate the percentage of individuals in each group who were still alive at each decade of age. *(Reprinted with permission from Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors.* BMJ. *2004;328(7455):1519.)*

In both the United Kingdom and the United States, large-cohort epidemiologic studies were established to quantify the risk of lung cancer with continued smoking and the markedly decreased risk with cessation. Data from the United Kingdom demonstrate that the decrease in lung cancer mortality depends on the age at the time of tobacco cessation (Fig. 2.6).[34] These data indicate that even middle-aged individuals who stop smoking before they have incurable lung cancer or another fatal disease avoid most of their risk of being killed by tobacco. Smoking cessation before middle age reduces the risk further.[33]

As already noted, education can lead to cessation, which results in fewer people smoking and a decrease in the incidence of lung cancer. Sharing of educational information with the public was the first demonstration of how tobacco-control efforts could affect the incidence of tobacco-related disease, such as lung cancer. Subsequently, other countries implemented policies that have an impact on the incidence of lung cancer.

Another mechanism to reduce smoking levels was introduced in Sweden, where the GOTHIATEK standard for the manufacturing of a smokeless tobacco product (Swedish snus) was instituted in the 1980s and 1990s.[35] The transition to the GOTHIATEK standard was an incremental process and was influenced by regulatory oversight by the Swedish Food

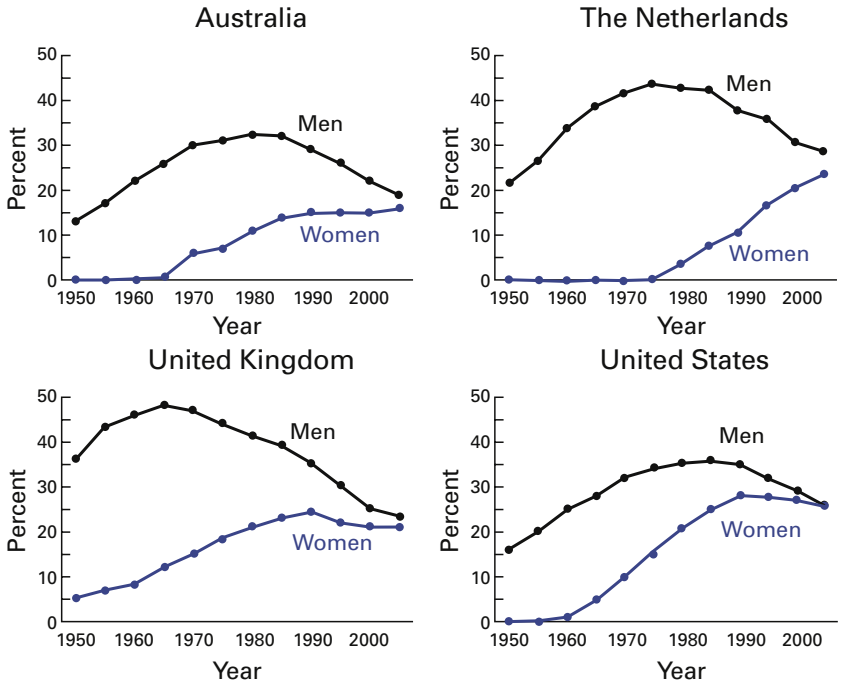

Fig. 2.3. Smoking-attributable deaths as estimated from lung cancer rates. The values are expressed as the percentage of all deaths. *(Reprinted with permission from Thun M, Peto R, Boreham J, Lopez AD. Stages of the cigarette epidemic on entering its second century.* Tob Control. *2012;21(2):96–101.)*

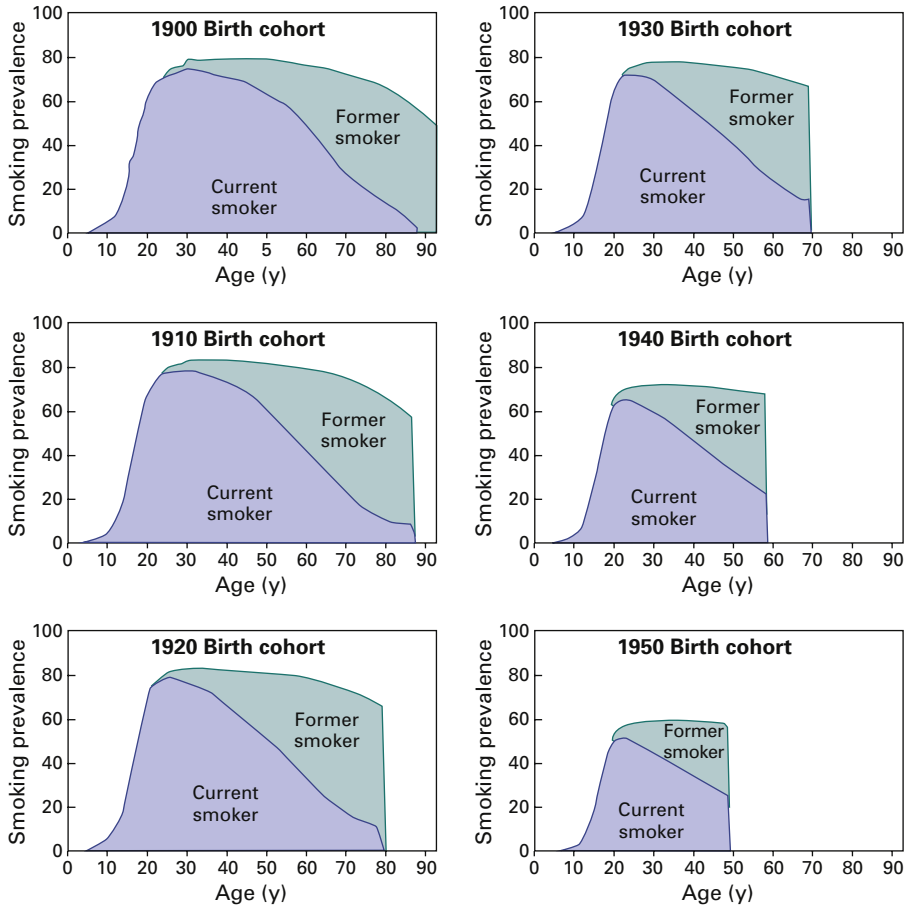

Fig. 2.4. Age-specific prevalence of current and former smoking according to birth cohort for white male individuals in the United States. *(Reprinted with permission from International Agency for Research on Cancer (IARC).* IARC Handbooks of Cancer Prevention, Tobacco Control, Vol. 11, Reversal of Risk After Quitting Smoking. *Lyon, France: IARC Press; 2007.)*

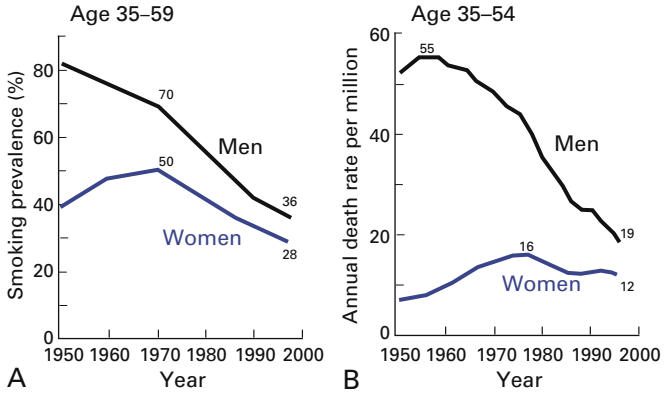

Fig. 2.5. (A) Trends in smoking prevalence and (B) change in the annual rate of lung cancer–related deaths.[34] *(Reprinted with permission from Peto R, Darby S, Deo H, Silcocks P, Whitley E, Doll R. Smoking, smoking cessation and lung cancer in the UK since 1950: combination of national statistics with two case-control studies.* BMJ. *2000;321(7257):323–329.)*

Authority in the 1970s. Smokeless tobacco products were initially manufactured by the government-controlled Swedish tobacco industry, but, since the 1990s, the manufacturing was privatized into the company Swedish Match North Europe AB. As a result of marketing efforts, lower price, social pressure, or, most likely, some combination of these influences, men in Sweden began to use more Swedish snus than combusted tobacco (as in cigarettes).

Snus is a smokeless product that has been manufactured in Sweden since the 1800s and has since spread to other, mostly Scandinavian, countries. Snus also has migrated to the United States and is now manufactured by several different tobacco companies, although Swedish Match notes that these products are not analogous to Swedish snus because they are not made with adherence to the GOTHIATEK standard. The GOTHIATEK standard was developed to be consistent with Swedish food standards and, through the adherence to several manufacturing standards, provides for low levels of microbiologic growth, heavy metals, and nitrosamines. As a result of Swedish men switching to snus in the 1970s, the rate of smoking among Swedish men decreased (Fig. 2.7).[35] Between 1980 and 2010, smoking rates in Sweden dropped from 36% to 12% among men and from 29% to 13% among women.[36,37] During those same years, the prevalence of snus use increased from 16% to 20% among men and from 1% to 4% among women,[36,37] which subsequently had an effect on the incidence of lung cancer and the trend in lung cancer–related mortality (Figs. 2.8 and 2.9).[38,39] Switching to a tobacco product that causes fewer deaths among men, particularly deaths from lung cancer, is a type of smoking cessation, but this change resulted from both educational awareness of tobacco-induced mortality and the marketing of a smokeless tobacco product manufactured according to GOTHIATEK standards, which allowed for a substantial change of the addictive habit

from a combusted to a noncombusted nicotine-delivery product. Women in Sweden have been slower than men to switch to snus or to stop smoking.

The next movement in tobacco control was the push for smoke-free environments. The rationale for smoke-free environments was based on data demonstrating that exposure to secondhand smoke is also detrimental to health, with increased asthma attacks and more deaths from conditions related to secondhand combusted tobacco or from lung cancer–related deaths among individuals exposed to secondhand smoke than individuals not exposed. The intention of these laws was built on the evidence that eliminating exposure to secondhand smoke would benefit the health of those who had been previously exposed. Although many localities established second-hand smoke laws, Ireland was the first country to implement a comprehensive ban on smoking in the workplace. Other regions restrict where smoking is allowed, specifying that smoking is not allowed in such locations as the workplace, public spaces, or outdoor venues (e.g., stadiums, parks, or beaches). These restrictions have had an impact on how much individuals smoke; as a result of smoke-free workplace policies, cigarette consumption has decreased in the United States, Germany, and Japan.[40–42] It is important to note, however, that the risk of lung cancer is more strongly related to the duration of smoking than to the number of cigarettes smoked per day.[43,44] Other tobacco-control policies as delineated by MPOWER also will decrease the number of people who smoke or use other tobacco products. Price controls (usually through increased taxes), restrictions prohibiting advertising and marketing, and measures designed to help people to quit are a few of the major policies that have been recommended. Different countries are in various stages of implementing these policies, and the strength and breadth of their implementation and enforcement will have an impact on the rates of smoking and, as a direct consequence, the rates of lung cancer.

Various grading systems have been developed to illustrate the relationship between the degree of tobacco-control implementation and lung cancer. A tobacco-control scorecard was proposed by Levy et al.[45] in 2004 to assess the success of implemented policies. Joossens and Raw,[46] in a report prepared for the Association of European Cancer Leagues, described the use of The Tobacco Control Scale to examine policies across countries in the European Union. Interestingly, the United Kingdom and Ireland were considered to have the best tobacco-control policies among the participating countries in the European Union, whereas Sweden was ranked ninth, despite having the lowest rates of male individuals who smoke and the lowest rates of lung cancer for men among developed countries. Thus the correlation between tobacco-control policies and smoking prevalence is not yet tight.

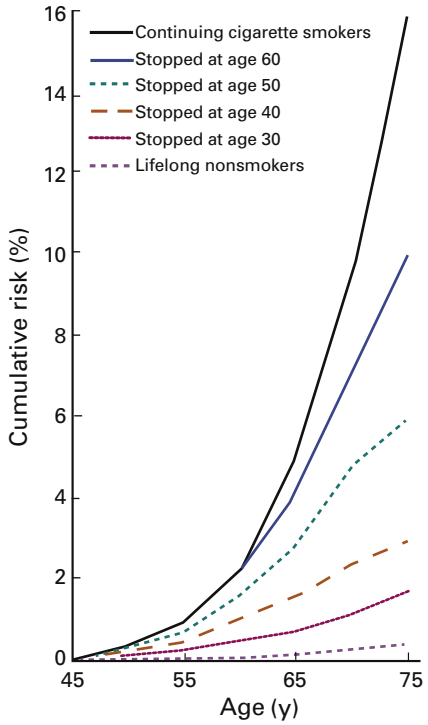

Fig. 2.6. Cumulative risk of smoking cessation at different ages in the United Kingdom. *(Reprinted with permission from Peto R, Darby S, Deo H, Silcocks P, Whitley E, Doll R. Smoking, smoking cessation and lung cancer in the UK since 1950: combination of national statistics with two case-control studies.* BMJ. *2000;321(7257):323–329.)*

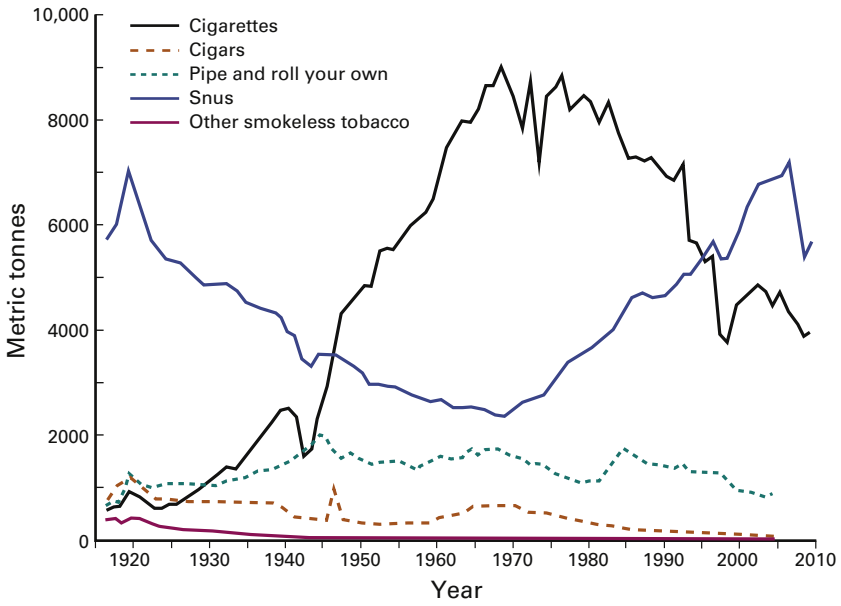

Fig. 2.7. Changes in Swedish smoking and snus use over time.

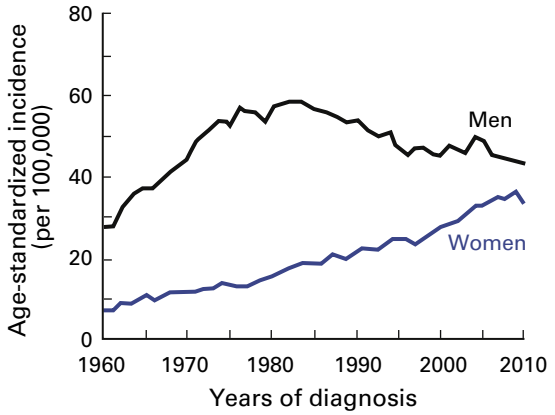

Fig. 2.8. Age-standardized incidence of lung cancer in Sweden. *(Reprinted with permission from Cancer Incidence in Sweden. http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/18530/2011-12-15.pdf. 2010.)*

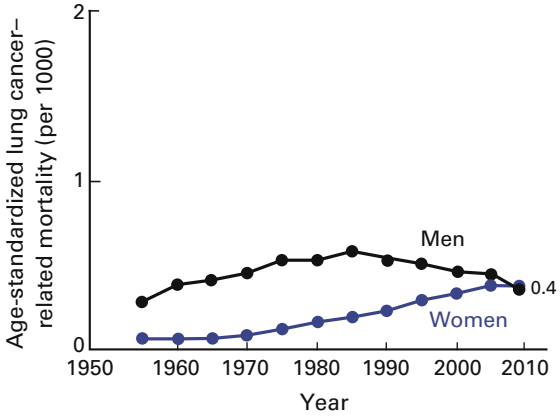

Fig. 2.9. Age-standardized rate of lung cancer–related deaths among individuals aged between 35 years and 69 years in Sweden. *(Reprinted with permission from Peto R, Lopez AD, Boreham J, et al. Mortality from smoking in developed countries 1950–2005. [The additional appendix to this article (and www.ctsu.ox.ac.uk) updates these 1990–2000 estimates to the years 2005–2009]. New York, NY: Oxford University Press; 1994.)*

More recently, denormalization of tobacco use has been considered as a potential powerful driver for decreasing tobacco use (smoking or using smokeless tobacco) and increasing support for tobacco-control policies. Willemsen and Kiselinova[47] compared the European Union Tobacco Control Scale with each country's smoking rates, and the only significant finding was the correlation between concern for the health effects of secondhand smoke and stronger tobacco-control policies (Fig. 2.10). In turn, there was an association between strong tobacco-control policies and lower smoking rates, although the association was not significant. The achievement of significance was based entirely on the data from the United Kingdom and Ireland. Both of those countries have strong tobacco-control polices and lower smoking rates. As noted earlier, the decline in smoking in the United Kingdom, particularly among male individuals, started as a result of the epidemiologic studies from the 1950s, and Ireland was the first country to institute a strong secondhand smoking law (in 2004) that had strong societal support. Willemsen and Kiselinova[47] suggested that denormalization of tobacco use in a society is a result of education and internalization of the harms of secondhand smoke and leads to stronger tobacco-control policies and, probably, to lower smoking rates.

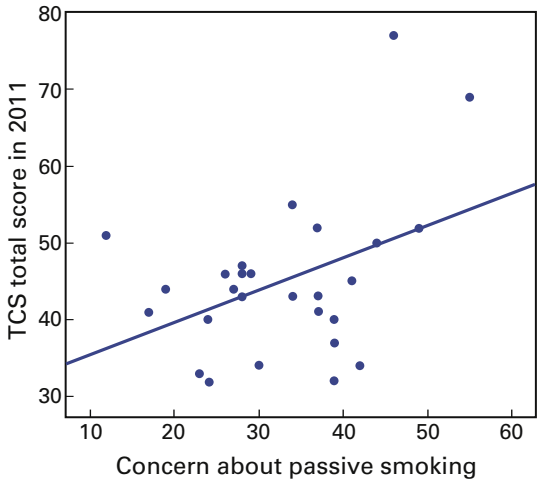

Fig. 2.10. Correlation between concern for health effects of secondhand smoke and stronger tobacco-control policies ($p = 0.006$). *TCS,* Tobacco Control Scale. *(Reprinted with permission from Willemsen MD, Kiselinova N. Concern about passive smoking and tobacco control policies in European countries: an ecological study.* BMC Public Health. *2012;12:876.)*

To address the question of whether tobacco-control policies, which do decrease tobacco use, also will decrease the incidence of lung cancer, Thun and Jemal[48] estimated that decreases in smoking rates in the United States resulted in 146,000 fewer lung cancer–related deaths among men between 1991 and 2003. Building on that study, six universities developed models to address the impact of tobacco-control policies on smoking rates and lung cancer mortality.[49] In the development of these models, the authors considered what would have happened if there had been no tobacco-control efforts and the smoking rates of the 1950s had persisted. Next, they considered the impact of the changes resulting from tobacco-control efforts and the actual decreases in smoking rates in the United States. Lastly, they considered what the lung cancer mortality rates would have been if there had been so-called complete tobacco control; that is, all smoking stopped abruptly as of the 1965 Surgeon General Report. The findings are striking (Fig. 2.11). The results of this modeling suggested that 795,851 deaths were prevented between 1975 and 2000 (552,574 in men and 243,277 in women) as a result of actual tobacco-control efforts. Although the number of deaths prevented alone is remarkable, the total number of preventable deaths with optimal tobacco control is threefold greater. If complete tobacco control had been achieved, 2,504,402 deaths from lung cancer could have been prevented between 1975 and 2000.

CONCLUSION

Various tobacco-control strategies have been used with various degrees of success across populations. The WHO FCTC outlines an international collaborative front to this globally spreading epidemic. Although societies around the globe differ widely in language, cultural norms, economic resources, and smoking rates, nearly all societies are afflicted with the tobacco epidemic, and a concerted effort using evidence-based strategies can alter the future course of this epidemic, with the potential to save millions of lives. One cannot truly consider the magnitude of the effect of good tobacco control (or even complete tobacco control) and its impact on global morbidity and mortality from lung cancer without questioning why we are not doing much, much more than we already are.

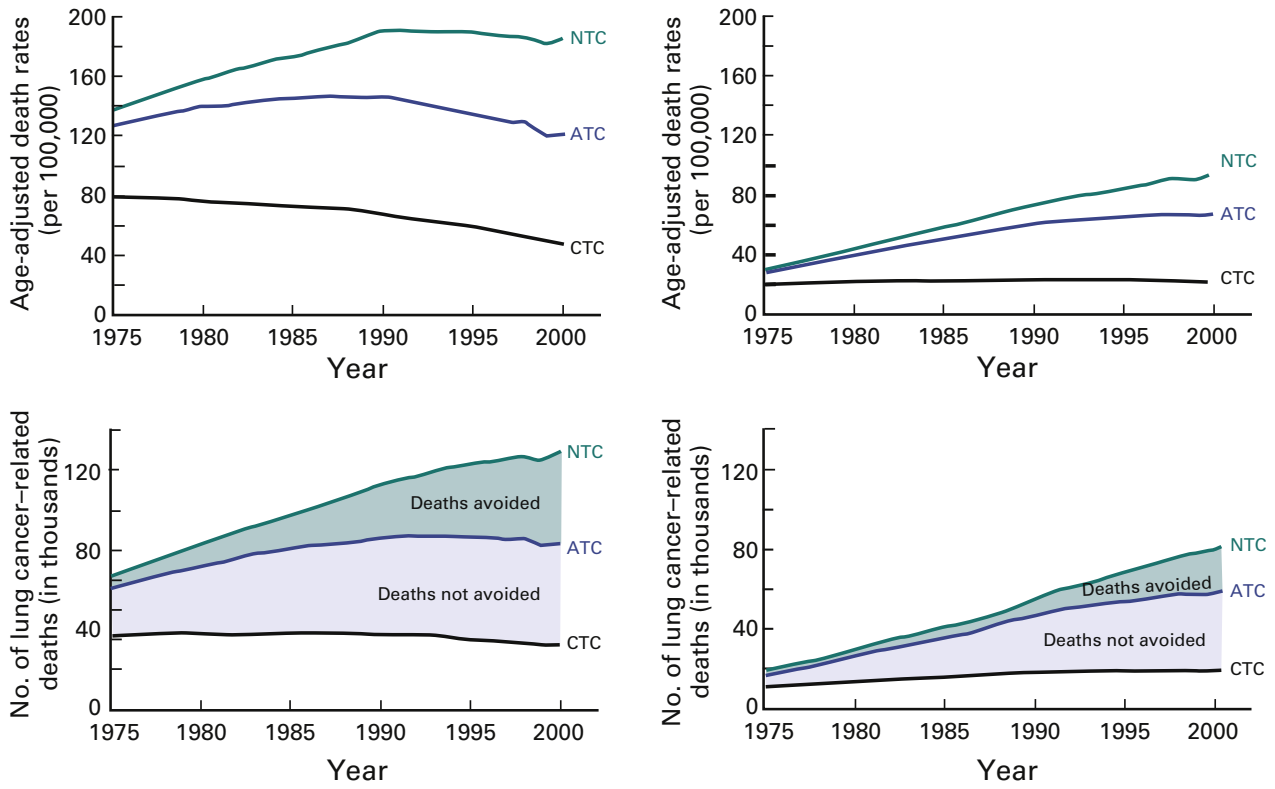

Fig. 2.11. Lung cancer–related deaths among men (left) and women (right) aged between 30 years and 84 years in the United States. *ATC,* actual tobacco control; *CTC*, complete tobacco control with no smoking after 1965; *NTC,* no tobacco control. *(Reprinted with permission from Moolgavkar SH, Holford TR, Levy DT, et al. Impact of reduced tobacco smoking on lung cancer mortality in the United States during 1975–2000.* J Natl Cancer Inst. *2012;104(7):541–548.)*

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3 Assessing and Treating Tobacco Use in Lung Cancer Care

Jamie S. Ostroff and Elyse R. Park

SUMMARY OF KEY POINTS

- Addressing tobacco dependence in patients with cancer increases the quality of care by reducing their risk for treatment complications, improving their prognosis, and reducing the risk of disease recurrence and second primary cancers.
- Smoking cessation after a diagnosis of lung cancer has been shown to have a beneficial effect on performance status.
- Many patients with cancer who smoke want to quit but unfortunately do not receive support and evidence-based tobacco treatment.
- Further provider training and research are needed to determine strategies to implement best practices for treating tobacco dependence among patients with cancer.
- In the absence of tobacco cessation interventions, lung cancer specialists are encouraged to follow general clinical practice guidelines for treating tobacco use and dependence.
- Lung cancer screening provides an invaluable opportunity to promote tobacco cessation.
- There is much debate and little data as to whether e-cigarettes or other electronic nicotine delivery devices will facilitate or impede smoking cessation.

In 1964, the landmark US Surgeon General's report, Smoking and Health, first linked smoking to lung cancer. This irrefutable knowledge about the harms of tobacco spawned five decades of tobacco prevention and control research and policy, resulting in a rich compendium of comprehensive national and international evidence-based, population-based, and clinical practice guidelines aimed at reducing tobacco-related morbidity and mortality.[1–3] Smoking not only has a causal link with disease and death but also has adverse effects on outcomes for patients with a wide range of chronic diseases, including cancer.[4] Now more than ever, tobacco cessation is firmly within the purview of modern oncology. By highlighting the specific adverse effects of persistent tobacco use on cancer outcomes, this chapter provides justification for why lung cancer specialists should assess and treat tobacco use and direction for how lung cancer specialists can help their patients stop smoking.

WHY LUNG CANCER SPECIALISTS SHOULD HELP THEIR PATIENTS STOP TOBACCO USE

Cigarette smoking is the primary risk factor responsible for 87% and 70% of lung cancer deaths in men and women, respectively,[5] making tobacco prevention and cessation essential goals for lung cancer prevention and control. Despite five decades of national and international public health accomplishments in reducing the morbidity, mortality, and economic costs of tobacco-induced diseases, there are currently an estimated 42.1 million current smokers (18.1% of all adults) in the United States alone and at least one billion smokers worldwide.[6,7] Tobacco kills nearly six million people each year; more than five million of those deaths are the result of direct tobacco use, and more than 600,000 are the result of nonsmokers being exposed to secondhand smoke. Unless urgent action is taken, the annual death toll could rise to more than eight million by 2030.[8]

Risks of Persistent Smoking and Benefits of Cessation on Lung Cancer Outcomes

Health-care providers who treat patients with cancer may assume that it is too late after diagnosis to intervene about smoking. However, an emerging body of evidence demonstrates that smoking is associated with several adverse outcomes for patients with cancer, such as increased complications from surgery, increased treatment-related toxicity, decreased treatment effectiveness, poorer quality of life, increased risk of recurrence, increased risk of second primary tumors, increased noncancer-related comorbidity and mortality, and decreased survival.[9–11] Although the number of clinical studies on the effects of smoking cessation in patients with cancer is limited, the existing data suggest that many of the adverse effects of smoking can be reduced with cessation.[12]

Although these adverse outcomes are applicable to patients diagnosed with a wide range of cancers, much of this research has focused on identifying the adverse effects of smoking for patients diagnosed with lung cancer.[12,13] Continued smoking after the diagnosis of lung cancer has been associated with treatment delays and increased complications from surgery, radiotherapy, and chemotherapy.[14] Adverse effects from continued smoking at the time of surgery include complications from general anesthesia, increased risk of severe pulmonary complications, and detrimental effects on wound healing. Complications from smoking while receiving radiotherapy include reduced treatment efficacy and increased toxicity and side effects. Smoking while receiving chemotherapy alters the metabolism of many chemotherapy drugs, decreases the effectiveness of treatment, and increases drug toxicity.[15–20] Smoking cessation before lung cancer treatment reduces the risk of recurrence and the development of additional smoking-related cancers.[21,22] Although further research is needed to examine the beneficial effects of smoking cessation in patients with cancer, smoking cessation after a diagnosis of lung cancer has been shown to have a beneficial effect on quality of life and performance status.[23,24]

Prevalence of Persistent Smoking Among Patients With Lung Cancer

Despite these risks, at least 15.1% of all adult cancer survivors report current cigarette smoking.[25] Patients with lung cancer tend to be motivated to quit smoking at higher rates than patients diagnosed with other cancers.[26,27] Focusing exclusively on the prevalence of smoking in lung cancer, 90.2% of patients with lung cancer report ever-smoking. At the time of diagnosis, 38.7%

of patients with lung cancer report current smoking, whereas 5 months after diagnosis, at least 14.2% of patients with lung cancer report current smoking.[28] Despite heavy encouragement to quit smoking and strong intentions to quit, continued tobacco use after diagnosis and resumption of smoking after initial quit attempt remains a problem in this patient population, with an estimated 10% to 20% of all patients with lung cancer smoking at some point after diagnosis.[28–32]

FACTORS ASSOCIATED WITH PERSISTENT SMOKING AMONG PATIENTS WITH LUNG CANCER

Physicians who treat patients with cancer, especially lung cancer specialists, may not understand why some patients continue to smoke. A few studies have examined factors associated with persistent smoking and smoking relapse after quit attempts.[33–35] For patients with lung or head and neck cancer who were smoking within the week before surgery, smoking relapse in the following year was predicted by lower baseline quitting self-efficacy, higher tendency for depression, and greater fears about cancer recurrence; whereas among patients who had stopped smoking before surgery, higher perceived difficulty quitting and lower cancer-related risk perceptions predicted smoking relapse.[33] In another longitudinal study of patients with early-stage lung cancer, low household income, exposure to environmental tobacco smoke at home, and evidence of depression were positively associated with return to smoking.[34] In a particularly noteworthy study, Park et al.[28] also examined factors associated with continued smoking among patients with lung cancer enrolled in the national, population-based Cancer Care Outcomes Research and Surveillance (CanCORS) cohort; at 4 months after diagnosis, younger age, more advanced disease, history of cardiovascular disease, lower social support, poorer perceived health, higher fatalism, greater pain, and depression were all identified as significant factors associated with continued smoking ($p < 0.05$).

ASSESSING TOBACCO USE AND INTEGRATING EVIDENCE-BASED TOBACCO TREATMENT IS AN INDICATOR OF HIGH-QUALITY ONCOLOGY CARE

Addressing tobacco dependence in patients with cancer increases the quality of care by reducing their risk for treatment complications, improving their prognosis, and reducing the risk of disease recurrence and second primary cancers. Clinicians have a responsibility to their patients to provide them with the best quality of care possible, and this care should include cessation treatment for those patients who smoke.[36,37] Growing awareness of the cancer-specific health risks, the emerging lines of evidence that quitting smoking may improve the prognosis for patients with cancer, and the prevalence of persistent smoking provide a strong argument for providing evidence-based treatment of tobacco dependence as a standard of quality care in cancer settings.[35,38,39] In fact, there is a growing consensus among oncology leadership organizations that assessment of tobacco use and treatment should be a metric for quality of care.[40–43] As such, oncologists are encouraged to assess smoking status and advise cessation for patients who smoke.[10,44,45] In keeping with this quality-of-care perspective, the American Society of Clinical Oncology's Quality Oncology Practice Initiative (ASCO QOPI) includes documentation of current smoking status and counseling for all smokers, by the second office visit, as a core quality indicator.[42,46,47] In recognition of the few number of clinical trials that assess tobacco use, a National Cancer Institute-American Association for Cancer Research (NCI-AACR) Task Force on Tobacco Use and Assessment has recommended assessment of tobacco use in cancer clinical trials.[48]

DELIVERY OF EVIDENCE-BASED TOBACCO DEPENDENCE TREATMENT IN CANCER SETTINGS IS CURRENTLY SUBOPTIMAL

Many patients with cancer who smoke want to quit but do not receive support and evidence-based tobacco treatment. During cancer treatment, many smokers are not even advised to quit, and after cancer treatment is completed, tobacco use is often not addressed.[49,50] In a recent survey of ASCO members, the ASCO Tobacco Subcommittee found that oncologists provide quitting advice to 25% of their patients.[51] In addition, most cancer care settings have not yet established tobacco cessation treatment as standard care; a 2012 survey found that 97% of NCI-designated comprehensive cancer centers in the United States said that having a tobacco treatment program was "very important," but only half had any type of tobacco treatment program.[52]

Most germane to determining the current status of assessing and treating tobacco dependence among patients with lung cancer are the findings of an online survey of International Association for the Study of Lung Cancer (IASLC) members, which addressed the practices, perceptions, and barriers to tobacco assessment and cessation in patients with thoracic cancer.[53] More than 90% of the 1507 physician respondents (representing 40.5% of all IASLC members) said that current smoking affects outcome and that cessation should be a standard part of clinical care. At the initial patient visit, 90% said they ask patients about tobacco use, 79% said they ask patients whether they will quit, and 81% said they advise patients to stop tobacco use, but only 40% said they discuss medication options, and 39% said they actively provide cessation assistance; fewer respondents said they address tobacco use at follow-up. Respondents identified pessimism regarding their ability to help patients stop using tobacco (58%) and concerns about patient resistance to treatment (67%) as the leading barriers. Only 33% said they felt adequately trained to provide cessation interventions.

These survey findings highlight the need to examine barriers to tobacco treatment delivery in cancer care. Barriers to addressing tobacco use include patient-related factors (shame, helplessness, addiction), physician-related barriers (lack of training and referral options, beliefs about patients' lack of interest or ability to quit), and system-level factors (inadequate identification of smokers, costs) that impede the delivery of effective tobacco programs.[54] In recognition of this problem, the NCI convened a conference to review the state of tobacco treatment at NCI-designated comprehensive cancer centers and formulate recommendations for improvement.[55] The survey findings underscore the considerable need for further provider training and research aimed at determining strategies to implement best practices for treating tobacco dependence among patients with cancer.

TREATMENT OF TOBACCO DEPENDENCE IN LUNG CANCER CARE

As summarized in a recent review, randomized controlled trials of pharmacologic and counseling interventions for cessation conducted with tobacco-dependent patients with cancer have generally not shown significant treatment effects, with 6-month point abstinence rates ranging from 14% to 30% among patients assigned to the intervention conditions.[56] Few randomized controlled trials have been conducted to test the effectiveness of cessation pharmacotherapy for patients with cancer who smoke. Schnoll et al.[57] conducted a placebo-controlled trial to evaluate the efficacy of bupropion and found benefit (reduced withdrawal symptoms and increased abstinence rates) only for the subset of patients with cancer who had symptoms of depression. In a pilot study, Park et al.[58] found significantly higher quit rates among patients with thoracic cancer who received varenicline and intensive counseling than among patients who received usual

(unspecified) care (smoking abstinence at 3 months: 34.4% vs. 14.3%; $p = 0.18$). Ostroff et al.[27] examined the utility of adding a presurgical tapering regimen to nicotine-replacement therapy and cessation counseling by telephone and found a 32% rate of smoking abstinence at 6-month follow-up for both interventions. In terms of optimal timing for the delivery of tobacco treatment, it appears that the closer to the time of diagnosis that smoking cessation treatment is delivered, the higher the likelihood for continued smoking abstinence.[59,60] These findings illustrate the need for continued development and evaluation of novel smoking cessation interventions that are acceptable and efficacious for patients with cancer and are feasible to deliver across a wide range of cancer care settings. In the absence of tobacco cessation interventions tailored and targeted to patients with cancer, lung cancer specialists are encouraged to follow general clinical practice guidelines for treating tobacco use and dependence.[61]

Guidelines for Treating Tobacco Use

Most recently updated in 2008, the US Public Health Service Treating Tobacco Use and Dependence Clinical Practice Guideline (PHS guideline) recommends that evidence-based tobacco treatment be delivered to all smokers in health-care settings.[3] Specifically, these guidelines recommend that a combination of medication and counseling be used, that counseling involve multiple sessions, and that clinicians use the five As: ask, assess, advise, assist, and arrange. Clinicians, especially thoracic cancer specialists, are encouraged to ask all their patients about their smoking status at every encounter. Once current smokers are identified, clinicians should assess their readiness to quit in order to determine what forms of assistance are needed. Smokers' quitting readiness is commonly classified as either precontemplation (no immediate plans to quit), contemplation (plan to quit within 6 months), preparation (planning to quit within a month), action (quitting for less than 6 months), or maintenance (staying quit for at least 6 months). Clinicians should strongly advise their patients against smoking, providing a personalized risk of persistent smoking and benefits of cessation in relation to the patient's disease and treatment. The next A, assist, speaks to the active role the clinician should play in his or her patients' cessation efforts by providing education, addressing barriers to quitting (such as concerns about coping), suggesting behavioral strategies that may help them overcome these barriers, developing a quit plan, and prescribing pharmacotherapy, as needed. For patients who are reluctant to quit, clinicians need to provide motivational counseling in an effort to encourage them to at least reduce their daily cigarette consumption. Considering the high rate of smoking relapse, patients who have recently quit (maintenance phase) should be reassessed for smoking lapses and given prolonged support and encouragement to remain abstinent from smoking. Lastly, clinicians are encouraged to arrange follow-up support, such as reevaluation of the smoking status during subsequent visits or referrals to other resources, such as quit-lines or onsite tobacco treatment specialists.

Pharmacotherapy

The PHS guideline strongly recommends that pharmacotherapy be used along with counseling in order to optimize cessation outcomes. Several medications are safe and effective for smoking cessation: nicotine-replacement therapies (in the form of a patch, gum, lozenge, nasal spray, or inhaler), bupropion, and varenicline (Table 3.1).

Because they are well-tolerated and acceptable to most patients, nicotine-replacement therapies should be recommended to all smokers except for patients in whom these treatments are contraindicated. Bupropion is an antidepressant that reduces withdrawal symptoms and, although it is not limited to patients with cancer, it may be especially useful in such patients who have depression. Varenicline is a partial nicotinic agonist that reduces the urge to smoke by binding to the nicotine receptors in the brain. Neuropsychiatric adverse events (e.g., depression, agitation, suicidal ideation) are rare, but patients should be monitored closely for this and other adverse effects.

It has been shown that combination pharmacotherapy may be more effective than single-agent treatment for tobacco dependence. Nicotine-replacement therapies may be combined, with a long-acting treatment such as the patch, used to maintain a steady level of nicotine and thus decrease cravings and withdrawal symptoms throughout the day, and a short-acting treatment, such as a lozenge, gum, or inhaler, used as needed. In comparison to monotherapy, the use of combination nicotine-replacement therapies increases the likelihood of achieving long-term smoking abstinence.[3] Nicotine-replacement therapies may also be used in conjunction with sustained-release bupropion.

After completion of cancer treatment, resumption of smoking is common and therefore it is essential for clinicians to reassess smoking status during follow-up visits and provide motivational counseling to help patients remain abstinent. For patients who decline pharmacotherapy support or in whom cessation drugs are contraindicated, counseling should still be included as part of treatment.

SPECIAL CONSIDERATIONS IN TREATING TOBACCO DEPENDENCE IN PATIENTS WITH CANCER

Considering the negative effects of smoking for patients with cancer,[62] oncologists should include cessation as part of treatment planning and address barriers to quitting. Because most patients will have made prior quit attempts, clinicians must provide empathy and support for their patients' quitting efforts. Some unique barriers that may exist for patients are ambivalent motivation, self-blame and internalized stigma, nihilism ("why bother?"), psychologic distress, and living with other smokers. Encouraging patients to seek psychosocial support services acknowledges the need for assistance in developing alternative strategies for coping with the stress of cancer and its treatment. Little progress has been made to integrate these guidelines into cancer care settings and there is a paucity of data on how best to promote cessation among patients with cancer.

FUTURE DIRECTIONS

Two emerging hot topics relevant to tobacco treatment and lung cancer warrant further attention from lung cancer specialists: lung cancer screening and e-cigarettes.

Lung cancer screening provides an invaluable opportunity to promote tobacco cessation. The findings from the National Lung Cancer Screening Trial and the release of the US Preventive Services Task Force recommendations for annual low-dose computed tomography screening for lung cancer for adults aged 55 to 80 years old who are at high risk for lung cancer because of their age and smoking history provide a compelling opportunity for the delivery of smoking cessation treatment.[63,64] Because lung cancer screening programs are being developed for people with a longstanding history of heavy tobacco use, these programs provide an exciting vehicle for integrating smoking cessation efforts into lung cancer screening protocols. Several studies have reported cessation rates ranging from 6.6% to 42% following enrollment in lung cancer screening programs.[65–73] The authors of a 2012 review describe these studies as collectively providing much promise for lung cancer screening as a so-called teachable moment for reaching smokers and promoting cessation through the delivery of evidence-based tobacco cessation treatment.[74] Although smokers seeking lung cancer screening appear motivated to quit,[71] the use of evidence-based smoking cessation

TABLE 3.1 Pharmacotherapy for Smoking Cessation

Pharmacotherapy	Dosage	Duration (wks.)	Availability	Precautions/ Contraindications	Adverse Effects	Patient Education
Nicotine patch	If smoking ≥11 cigarettes/d: 21 mg/24 h 14 mg/24 h 7 mg/24 h If smoking ≤10 cigarettes/d: 14 mg/24 h 7 mg/24 h	6 2 2 6 2	Over the counter	Uncontrolled hypertension	Skin irritation (redness, swelling, itchiness) Sleep disruptions (nightmares, vivid dreams)	Rotate patch site daily Remove patch before bedtime if sleep is disrupted and bothersome
Nicotine polacrilex gum	If smoking ≤24 cigarettes/d: 2 mg If smoking ≥25 cigarettes/d: 4 mg	Up to 12	Over the counter	Poor dentition Xerostomia	Hiccups Upset stomach Jaw ache	Chew gum on a fixed schedule Chew each piece of gum and then place between the gums and cheek for 30 min (so-called chew and park) Avoid eating or drinking anything except water 15 min before chewing and during chewing Do not exceed 24 pieces of gum in 24 hours
Nicotine lozenge	If smoking first cigarette more than 30 min after waking up: 2 mg If smoking first cigarette within 30 min after waking up: 4 mg	Up to 12	Over the counter	Xerostomia	Local irritation to mouth and throat Upset stomach	Avoid eating or drinking anything except water 15 min before and during use of a lozenge The lozenge will take 20–30 min to dissolve Do not use more than 20 lozenges in 24 h
Nicotine inhalation system	6–16 cartridges/d	Up to 26	Prescription		Local irritation to mouth and throat Upset stomach	Each cartridge will take 80–100 inhalations over 20 min Puff on inhaler like a cigar
Nicotine nasal spray	0.5 mg/inhalation/ nostril 1–2 times/h (or as needed)	Up to 12	Prescription	Sinus infections	Irritation to nose, eye, or upper respiratory system	Nasal irritation may become less bothersome with continued use
Bupropion	Days 1–3: 150 mg daily Thereafter: 150 mg twice daily	12	Prescription	History of seizures History of eating disorders (bulimia, anorexia)	Insomnia Xerostomia Restlessness Dizziness	Overlap with smoking for 1–2 weeks Do not need to be tapered off drug
Varenicline	Days 1–3: 0.5 mg daily Days 4–7: 0.5 mg twice daily Day 8–end of treatment: 1 mg twice daily	12[a]	Prescription	Kidney problems or treatment with dialysis Pregnancy or plan to become pregnant Breastfeeding	Mild nausea Sleep problems Headaches	Take medication with a full glass of water after eating a meal Allow 8 h between each dose Take medication a few hours before bedtime to avoid restlessness

[a]If the patient has quit smoking, treatment for another 12 weeks may be given to prevent smoking relapse.

treatments among screening enrollees is low, and the rate of persistent smoking is high 1 year after enrollment. All smokers seeking lung cancer screening should be advised to quit and provided with access to evidence-based cessation treatments.[75] Further research examining the development and evaluation of tobacco treatment interventions for smokers seeking lung cancer screening is needed.

Identified as a so-called disruptive technology in the field of tobacco control,[76] e-cigarettes are battery-powered devices that mimic the hand-to-mouth sensory experience of smoking and typically deliver nicotine to the user. Cigarette smokers report using e-cigarettes to manage nicotine cravings and withdrawal symptoms, to reduce daily smoking consumption, and to quit smoking or avoid smoking relapse.[77] Given the increasing popularity and availability of e-cigarettes in the general population and the strong advice to quit smoking traditional cigarettes at the time of diagnosis, patients with cancer are likely to consider use of e-cigarettes.

There is much debate and little data as to whether e-cigarettes will facilitate or impede smoking cessation and reduction of known hazards of traditional cigarettes and other combustible tobacco products.[66] One recent observational study found no evidence that the use of e-cigarettes promoted smoking cessation among patients with cancer who were referred to a hospital-based smoking cessation program.[78] On the other hand, promising results were reported in two clinical trials conducted among smokers from the general population. Cessation outcomes were comparable with those observed in trials of nicotine replacement therapies.[79,80] Until more is known about the risks and benefits of e-cigarettes for patients with cancer, oncologists are likely to struggle with these complexities and face challenges in how to respond to patient inquiries. In 2014, the IASLC Tobacco Control and Smoking Cessation Committee published a commentary providing guidance to oncologists about what to recommend to their patients who may be struggling to stop smoking or wondering about e-cigarettes.[81] According to this guidance, oncologists should advise smokers to

quit smoking traditional cigarettes, encourage the use of FDA-approved cessation medications, refer patients for tobacco-cessation counseling, and provide education about the potential risks and lack of known benefits of e-cigarette use with regard to long-term cessation. These recommendations are quite similar to those made by an AACR-ASCO Task Force on electronic cigarettes and other electronic nicotine delivery systems.[82]

CONCLUSION

There is a strong rationale for assessing tobacco use and promoting smoking cessation among patients with cancer. The risks of persistent smoking for patients diagnosed with lung cancer are well established and include adverse outcomes such as treatment toxicities, cancer recurrence, second primary malignant tumors, decreased survival, and poorer quality of life. Given the cancer-specific health risks and the availability of clinical practice guidelines for treating tobacco dependence, oncologists are encouraged to assess smoking status and advise cessation for patients who smoke. Further research examining patient-, provider-, and system-related strategies for engagement and retention of smokers into evidence-based tobacco treatment is needed.

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4 Lung Cancer in Never-Smokers: A Different Disease

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SUMMARY OF KEY POINTS

- The known or suspected etiologic factors for lung cancer arising in never-smokers are weak carcinogens or rare factors, which cannot explain the relatively high frequency of cancer in never-smokers. This also applies to environmental tobacco smoke.
- Genetic factors play an increasing role in the etiology of lung cancer in never-smokers. These include rare high penetrance mutations in crucial genes such as the T790M mutation in the *EGFR* gene. However, high-frequency, low-penetrance variations in susceptibility genes are playing an increasingly prominent role. These include loci that predispose to smoking as well as those that may contribute directly to cancers arising in smokers and never-smokers.
- The molecular alterations in lung cancers arising in smokers and never-smokers are very different. Smoke related tumors are associated with high numbers of mutations, especially C:G>A:T transversions, while never-smoker tumors are associated with low numbers of mutations targeting C:G>T:A transitions.
- The specific mutational targets are also different in smoker and never-smoker tumors. Thus *KRAS* mutations are more frequent in ever-smoker tumors, while *EGFR* mutations and *ALK* translocations are more frequent in never-smokers. Paradoxically, the number of therapeutic actionable mutations is more frequent in never-smoker tumors.
- Lung cancers arising in never-smokers show major differences based on ethnicity, gender, and histology. The ethnic differences point out the importance of genetic susceptibility loci in the development of lung cancers.
- The major clinical, ethnic, gender, and histology differences between lung cancers arising from smokers and never-smokers, coupled with their different etiologic factors and major molecular differences, indicate that they represent very different tumor types, confirming that lung cancers in never-smokers represent a different form of cancer.

Lung cancer is the leading cause of cancer-related mortality worldwide, with about 1.4 million deaths each year.[1] In 2008, lung cancer was the most commonly diagnosed cancer globally, the leading cause of cancer-related death in men, and the fourth most commonly diagnosed cancer and second leading cause of cancer-related death in women.[1] The lung cancer incidence rate for men in East Asia ranks as the fifth highest in the world, after Eastern and Southern Europe, North America, Micronesia, and Polynesia, with an age-standardized incidence rate by gender and area of the world of 45.0 per 100,000 cases.[1] For women, the third highest lung cancer incidence rate is found in East Asia, Australia, and New Zealand, with 19.9 per 100,000 cases.[1] Interestingly, the lung cancer incidence rate for women is higher in China (21.3 cases per 100,000 women) than in Germany (16.4) and Italy (11.4), although adult smoking prevalence is substantially lower in China (4% vs. 20%).[2]

The World Health Organization estimates that lung cancer is the cause of 1.37 million deaths globally per year, or 18% of all cancer deaths.[1] An estimated 71% of lung cancers are caused by smoking, indicating that about 400,000 deaths each year are caused by lung cancer in lifetime never-smokers.[1] It has been estimated that 15% of men and 53% of women with lung cancer worldwide are never-smokers.[3] Thus, lung cancer in never-smokers is among the seven or eight most common causes of cancer death. However, lung cancer in never-smokers is often grouped together with lung cancer in ever-smokers. In this chapter, we describe the clinical-pathologic and molecular differences between these two types of lung cancer. Although several review articles have addressed this topic,[4–6] this chapter focuses on lung cancer in never-smokers in East Asian countries, where the incidence rate is higher than in other geographic regions. In addition, we discuss molecular differences between lung cancer in never-smokers and ever-smokers. For these purposes, we use standard definitions as follows:

KEY TERMS

Ever-smoker. An individual who has smoked 100 or more cigarettes during his or her lifetime.

Never-smoker. An individual who has smoked fewer than 100 cigarettes during his or her lifetime.

Current smoker. An individual who is currently smoking or who has quit smoking during the past 12 months.

Former smoker. An ever-smoker who quit more than 12 months earlier.

EPIDEMIOLOGY OF NONSMOKING-RELATED LUNG CANCER

Although numerous articles on lung cancer in never-smokers in Asia have been published, some data are inconsistent and other data are suspect, as the definitions of never-smokers are not uniform, and the quality of some of the data is questionable. Also, smoking incidence rates differ among women even within a single country. For example, the smoking incidence rates among women in northeastern China are considerably higher than the rates among women in southern China.[7] For these reasons, we extensively cite reviews or meta-analyses that combine data from multiple published reports and from cancer registries. By doing so, we can avoid some of the biases from small, individual studies, and we can place ethnic, gender, and geographic differences in their proper context. Findings from a case–control study on epidemiologic risk factors for lung cancer in never-smokers are described in a 2010 article by Brenner et al.[8]

A review of published studies on the epidemiology of lung cancer (18 studies, comprising 82,037 people) showed a marked gender bias that lung cancer among never-smokers appears to affect women more frequently than men, irrespective of geography ($p < 0.0001$).[5] The proportion of women with lung cancer who reported never having smoked regularly is particularly high in East Asia (61%)[9–14] and South Asia (83%),[15,16] whereas only

15% of women with lung cancer in the United States are never-smokers.[17–21] In contrast, only 11% of men with lung cancer in East Asia are never-smokers.[5]

Thun et al.[7] published an analysis of 13 cohorts and 22 cancer registry studies with data from nearly 2.5 million never-smokers and from cancer registries in 10 countries covering several decades. Some of the key findings from this comprehensive analysis regarding lung cancer in never-smokers include the following:

- death rates from lung cancer were higher among men than women across all age and racial groups
- incidence rates among men and women were similar, with some variation by age
- death rates were higher among East Asian individuals (but not among those living in the United States) and black Americans than among white Americans
- no temporal trends were seen for American women
- lung cancer incidence rates were higher and more variable among East Asian women.

KNOWN OR SUSPECTED ETIOLOGIC FACTORS FOR LUNG CANCER IN NEVER-SMOKERS

Because tobacco use is a powerful carcinogen and the major cause of lung cancer, most attention has focused on environmental tobacco exposure as the major cause of lung cancer in lifetime never-smokers. Although environmental tobacco exposure has been identified as a contributing factor for lung cancer in never-smokers since 1986, the Surgeon General of the United States 2006 report confirmed that environmental tobacco exposure modestly increased the risk of lung cancer.[22] However, the odds ratios for the development of lung cancer in the United States indicated that such exposure is a very weak carcinogen compared with active smoking, as cited in the Surgeon General's report.[22,23] According to that report, the odds ratio is 1.0 for never-smokers who do not have environmental tobacco exposure and 1.2 for never-smokers who do have such exposure; in contrast, the odds ratio is 40.4 for ever-smokers.[23] Thus, if environmental tobacco exposure is a weak carcinogen and cannot be the major cause of lung cancer in never-smokers, other known or suspected factors should be considered, such as indoor air pollution, environmental and occupational toxins (e.g., arsenic, radon, asbestos), and human papillomavirus (HPV) infection (and possibly other infections). Genetic factors should also be considered, and these are discussed later.

Indoor Air Pollution

The relatively high burden of lung cancer among women in China who have no history of regular smoking is attributed to indoor air pollution from coal smoke generated by unventilated coal-fueled stoves, volatilization of oils from cooking at high temperatures in open woks, and secondhand smoke.[7,24–29] A meta-analysis of seven studies from China and Taiwan of never-smokers found that cooking oil vapors are the risk factor associated with lung cancer for women, and indoor coal and wood burning is a risk factor for both women and men.[30] Indeed, a retrospective study on the association of household stove improvement and risk of lung cancer in rural China indicated that changing from unvented fire pits to stoves with chimneys was associated with a subsequent reduction in the lung cancer incidence rate.[31] Other factors thought to contribute to higher lung cancer incidence among rural Chinese women who are never-smokers include a higher prevalence of nonsmoking women in Asian countries and viral factors of HPV infection.[32]

Environmental and Occupational Toxins

Exposure to some environmental and occupational toxins has been shown to increase the risk of lung cancer for smokers and, to a lesser extent, for never-smokers.[11,29,33] These toxins include arsenic, radon, asbestos, chromium, organic dust, and others.[34–36]

As summarized in a meta-analysis,[34] several studies indicate that high levels of arsenic in the major source of drinking water of highly defined geographic regions (southwestern Taiwan, the Niigata Prefecture, Japan, and northern Chile) were associated with increased incidence of lung cancer, both for smokers and never-smokers. The authors of the meta-analysis concluded: "Despite methodologic limitations, the consistent observation of strong, statistically significant associations from different study designs carried out in different regions provide[s] support for a causal association between ingesting drinking water with high concentrations of arsenic and lung cancer."[34]

Present in soil and groundwater, radon is a gaseous decay product of uranium-238 and radium-226, which is capable of damaging respiratory epithelium by emitting alpha particles.[40,41] The increased risk of lung cancer among uranium miners has been more clearly established and is thought to be caused by radiation from radon,[42] although most miners are ever-smokers.[40] The role of radon in the home is more difficult to assess.

An analysis of occupational asbestos exposure in the Netherlands found a relative risk of lung cancer of 3.5 after controlling for age, smoking, and other factors.[37] In a French study of 1493 cases, some occupational exposure was identified in 9.4% and 48.6% of female and male never-smokers, respectively, in whom lung cancer developed.[38] In a Canadian case–control study, the odds ratio for lung cancer risk from occupational exposures in never-smokers was 2.1 (95% confidence interval [CI], 1.3–3.3) but was higher for exposure to solvents, paints, or thinners (odds ratio, 2.8; 95% CI, 1.6–5.0).[8] A meta-analysis that focused on lung cancer risk for painters demonstrated a relative risk of lung cancer for all painters of 1.35 (95% CI, 1.29–1.41), but 2.0 (95% CI, 10.9–3.67) among never-smokers.[39]

Human Papillomavirus

Several studies have found that HPV infection is associated with lung cancer, particularly in China and Taiwan. Cheng et al.[44] reported a high incidence of HPV infection among never-smoking women in Taiwan. Results of a case–control study (141 cases and 60 controls) in Taiwan showed that the prevalence of HPV16 and HPV18 infection was significantly higher among never-smoking women with lung cancer who were older than 60 years; HPV 16 and HPV 18 infection was thought to be associated with the high lung cancer incidence and death rates among never-smoking women in Taiwan.[44] Results of a similar study in Wuhan, China, indicated that no association with clinical-pathologic features was noted.[45] However, the role of HPV infection in lung cancer pathogenesis in never-smokers might be restricted to certain geographic areas because the incidence rate of lung cancer associated with HPV infection varies widely based on geographic location and is reported to be low in Australia, Europe, and North America.[46–48]

CLINICAL-PATHOLOGIC FEATURES OF LUNG CANCER IN NEVER-SMOKERS

Adenocarcinoma is the most common form of nonsmall cell lung cancer (NSCLC) in most parts of the world and the predominant form of lung cancer in never-smokers worldwide,[5] followed by large cell carcinoma, which may represent an undifferentiated form of adenocarcinoma. Squamous cell carcinoma is rare among never-smokers with lung cancer, and small cell lung cancer almost never occurs. However, another neuroendocrine tumor, the bronchial carcinoid, may be slightly more common among never-smokers, although no relationship to smoking status has been shown.[49]

The age at which lung cancer is diagnosed varies according to geographic location and smoking status. Studies from East Asian countries, such as Singapore and Japan, as well as Hong Kong, demonstrate an earlier age at the time of diagnosis among never-smokers compared with smokers,[9,12,33] whereas the same or older age at the time of diagnosis among never-smokers has been found in studies from the United States and Europe.[1,18,21,50–52] The possible reasons for this geographic variation include the greater contribution of risk factors other than active smoking in East Asian countries, much later age of initiation of smoking among East Asians with a smoking history compared with individuals from Western countries, and different degrees of detection bias between countries.[53]

A retrospective study in Singapore comparing differences in the epidemiologic characteristics and survival outcomes between never-smokers and former and current smokers showed that never-smoker status was associated with a significantly better performance status, younger age at the time of diagnosis (10 years and 5 years earlier, respectively), higher proportion of women (68.5% vs.12% to 13%), and more advanced stage at the time of diagnosis.[9] The variation in disease stage at the time of diagnosis might be explained by late presentation of symptoms and delayed diagnosis by physicians. The survival outcome for never-smokers was significantly better than that for smokers, with a 5-year overall survival rate of 10.8% and 7.7%, respectively (p = 0.0003).[9] Differences in treatment response and survival outcome between never-smokers and smokers with lung cancer may be attributed to differences in pathogenesis and tumor biology.

THE GENETICS OF LUNG CANCER

Inherited cancer syndromes are associated with rare and highly penetrant single-gene mutations, but genetic factors also play a role in sporadic cancers, as reported in numerous family-based studies. About 100 genes with mendelian inheritance cause an even smaller number of cancer syndromes, but these syndromes provide an explanation for only a minor part of the familial clustering of common cancers.[54] Linkage analyses of high-risk families may identify other rare high-penetrance genes, and such studies have identified a lung cancer susceptibility locus on chromosome 6q.[55] Smoking appeared to increase the susceptibility. Further studies indicated that the regulator of G-protein signaling 17 (*RGS17*) gene at this location was a major candidate for lung cancer susceptibility.[56]

The major mechanism of acquired resistance to tyrosine kinase inhibitors in lung cancers with epidermal growth factor receptor (*EGFR*) gene mutations is the appearance of a second activating mutation, T790M (substitution of threonine 790 with methionine).[57] However, T790M may be inherited as a rare familial mutation.[58] Our recently published study of a large family with an inherited T790M mutation and lung cancer, combined with analysis of published cases, indicates that inherited T790M predisposed lifetime never-smokers (and women) to lung cancer.[59] These findings have, in part, been independently confirmed.[60] Of interest, although *EGFR* mutations occur more frequently among East Asians, no case of an inherited T790M mutation has been described among East Asians. However, V843I, an even rarer inherited *EGFR* gene mutation that predisposes to lung cancer, has been reported in both Asian and non-Asian families.[61,62] Another recent report described a Japanese family with an autosomal inherited germline mutation in human epidermal growth factor receptor 2 (*HER2*) associated with lung cancer risk, which may also target women and light or never-smokers.[63]

It is now believed that alleles with high frequency (typically greater than 10%) and low penetrance (typically less than a two-fold increased lifetime risk) contribute substantially to susceptibility to many diseases, including lung cancer. Genome-wide association studies (GWAS) using population-based designs have identified many genetic loci associated with risk of a range of complex diseases, including lung cancer;[54] however, each locus exerts a very small effect, and combinations of genes are required to exert a significant effect on risk. GWAS are often based on large microchip analyses of single nucleotide polymorphisms (SNPs), and more than one million SNPs can be analyzed on a single microchip. These studies of weak associations often consist of many thousands of cases and controls, and meta-analyses may be required for confirmation. In lung cancer, more than 150 GWAS have been published. Although some findings are widely accepted, others are controversial or require confirmation. In 2008, three studies identified three potential susceptibility loci for lung cancer.[64,65] Two of these loci, on chromosomes 15q25 and 5p15.33—the site of the telomerase reverse transcriptase (*TERT*) gene, essential for telomerase activation—have been confirmed, but the cancer-associated role of the locus on 6p21-6p22 remained more controversial; however, it may be histology related.[64] Additional studies, including a meta-analysis, confirmed that the major susceptibility locus was on 15q25, encoding several genes, including the nicotinic acetylcholine receptor (nAChR) genes: cholinergic receptor, nicotinic, beta 4 (neuronal) (*CHRNB4*), alpha 5 (neuronal) (*CHRNA5*), and alpha 3 (neuronal) (*CHRNA3*).[66] Because the variants at 15q25 are also associated with nicotine dependence, they may influence lung cancer risk at least in part through an effect on smoking behavior rather than a direct effect on lung carcinogenesis. A large meta-analysis of lung cancer in female never-smokers in six Asian countries showed no evidence of association for lung cancer at 15q25 in that population, which the authors said provided "strong evidence that this locus is not associated with lung cancer independent of smoking."[67] Other studies, including meta-analyses, have identified additional variants associated with increased risk, such as smoking, ethnicity, gender, and histology.[64,66–71] Thus, although genetic variation of the *TERT* locus appears to be involved in susceptibility to all lung cancers, the 15q25 locus predisposes to smoking, the cyclin-dependent kinase inhibitor 2A (*CDKN2*) locus at 9p21 may influence susceptibility to squamous cell carcinomas, and the tumor protein p63 (TP63) locus may influence susceptibility to lung adenocarcinoma in East Asian populations.

As confirmed by the GWAS cited previously, nicotine and its derivatives, by binding to nAChR on bronchial epithelial cells, can regulate cellular proliferation and apoptosis by activating the protein kinase B (PKB/Akt) pathway. Lam et al.[72] found different nAChR subunit gene expression patterns between NSCLCs from smokers and nonsmokers, and a 65-gene expression signature was associated with nonsmoking nAChR alpha-6 beta-3 expression.

MOLECULAR CHARACTERISTICS OF NONSMOKING EAST ASIAN INDIVIDUALS WITH LUNG CANCER

With the development of molecular genetic therapies for lung cancer, the molecular profile of East Asian individuals with lung cancer was found to differ from that of white individuals with lung cancer. Mutations in Kirsten rat sarcoma viral oncogene homolog (*KRAS*) and *EGFR* genes are mutually exclusive and demonstrate striking frequency differences related to ethnicity. *EGFR* mutation is the first specific molecular alteration associated with lung cancers arising among never-smokers. A relatively high incidence of somatic mutations in *EGFR* has been found in a specific subpopulation: women, never-smokers, patients with adenocarcinoma, and Asians. In the First Line Iressa versus Carboplatin/Paclitaxel in Asia (Iressa Pan-Asia Study [IPASS]) study, with 1214 (99.8%) of 1217 patients of East Asian origin and 1140 (93.7%) of 1217 never-smokers, the incidence rate of *EGFR* mutation was 59.7% in the 437 patients evaluable for *EGFR* mutation.[73] A recent multinational study demonstrated variations in the *EGFR* gene mutation rates in Asian countries, with the lowest frequencies from India.[74,75]

Nevertheless, a review of nine published studies showed that the frequency of *EGFR* mutation among US never-smokers with NSCLC was substantially lower (20%).[76] In addition, even in an unselected population, the frequency of *EGFR* mutation among East Asian individuals with NSCLC was also considerably higher than that for white individuals. In the review, which included an analysis of data on 2347 patients for whom ethnicity was noted, the frequency of *EGFR* mutations among East Asian patients was significantly higher compared with non-Asian patients (33% vs. 6%; $p < 0.001$).[77] Unlike *EGFR* mutations, *KRAS* mutations occur less commonly in lung cancers among individuals from East Asia and more frequently in lung cancers among smokers.[76]

In pooled data summarizing three published studies comprising 1536 patients with NSCLC, *EGFR* and *KRAS* were shown to be mutually exclusive in the same tumors.[76,78,79] *KRAS* mutations were detected in 20% of patients with NSCLC, particularly patients who smoked or who had adenocarcinoma.[77] A study investigating the *EGFR* and *KRAS* status of 519 unselected patients with NSCLC showed that *KRAS* mutations were present more frequently in smokers than never-smokers (10% vs. 4%; $p = 0.01$), among non–East Asians than East Asians (12% vs. 5%; $p = 0.001$), and among patients with adenocarcinoma than patients with nonadenocarcinoma histologies (12% vs. 2%; $p < 0.001$).[76] Several studies found that *KRAS* mutations were present in 20% to 30% of white patients with lung adenocarcinoma but only 5% of patients with lung adenocarcinoma from East Asia.[80–82] In addition, in previous studies from Hong Kong and Taiwan, *KRAS* mutations were found in 13% to 19% of men with adenocarcinoma but in none of the women studied.[83,84] A potential explanation for the distinction between genders may be that the vast majority of Chinese female patients were never-smokers.

A Japanese case–control study assessing the impact of smoking and gender on the risk of NSCLC with or without *EGFR* mutation demonstrated that ever-smoking was a substantial risk factor for NSCLC without *EGFR* mutation but not for NSCLC with *EGFR* mutation.[85] Cumulative exposure to smoking was associated with a linear increased risk of NSCLC without *EGFR* mutation only. This finding was consistent for both men and women. Age at the start of smoking among ever-smokers and years since quitting smoking among former smokers also showed a strong correlation between NSCLC without *EGFR* mutation and smoking. *EGFR* mutation was present more frequently among patients who smoked no more than 20 pack-years. Similarly, in another Japanese study, *EGFR* mutation was found more frequently among patients who quit smoking at least 20 years before the date of lung cancer diagnosis.[86] These findings suggest an inverse correlation between *EGFR* mutation and exposure dose of cigarette smoking.

Smoking status is a risk factor affecting not only *EGFR* mutations but other somatic mutations as well. The authors of a Korean study screened genetic tests for *EGFR* mutations, *KRAS* mutations, and enchinoderm-microtubule-associated protein-like 4-anaplastic lymphoma kinase (*EML4-ALK*) fusions in 200 fresh surgical specimens of primary lung adenocarcinoma by polymerase chain reaction (PCR), Sanger sequencing, and fluorescence in situ hybridization. They then performed high-throughput RNA sequencing in 87 lung adenocarcinoma specimens that were negative for the three known driver mutations (three samples with insufficient RNA quality were excluded). The results showed that people who had a smoking history of at least 40 pack-years harbored significantly more somatic point mutations than did people who had a smoking history of fewer than 40 pack-years or of never-smoking. In addition, important differences in mutation patterns exist between lung cancer in never-smokers and ever-smokers.[87]

Given the difference in the incidence rate of *EGFR* mutations between East Asian and white populations, several studies have investigated ethnic differences in *ALK*, c-ros oncogene 1 receptor tyrosine kinase (*ROS1*), and ret proto-oncogene (*RET*) fusions after these three novel driver fusions were identified in NSCLC. Most studies showed that *ALK* fusions occurred in 2.4% to 5.6% of NSCLC cases,[88–91] and no differences in incidence rate between Asian and non-Asian populations have been identified to date. However, a Chinese study screening *ALK* fusions by rapid amplification of complementary DNA ends (RACE)-coupled PCR sequencing found that *ALK* fusions existed in 12 (11.6%) of 103 individuals with NSCLC, 10 (16.13%) of 62 individuals with adenocarcinomas, and 10 (19.23%) of 52 never-smokers.[92] This high incidence of *ALK* fusions in a selected East Asian population may be explained by the relatively small sample size and use of a different screening method. Unlike ethnicity, smoking status is regarded as an important factor affecting the incidence rate of fusion genes. Similar to *ALK* fusions, *ROS1* and *RET* fusions appear to occur more frequently among never-smokers.[93,94] Given a very low frequency of *ROS1* as well as *RET* fusions identified in NSCLC, a large sample study is warranted to prove the role of smoking status in the occurrence of fusion genes.

Several Chinese studies have demonstrated the previously described differences in the molecular profile of lung cancer between never-smokers and smokers. An et al.[95] screened for candidate driver genes in 524 Chinese patients with NSCLC with the use of several methods, including sequencing, high-resolution melt analysis, quantitative PCR, or multiplex PCR and RACE, and analyzed the differences in driver gene alterations among a subgroup based on histology and smoking status (Table 4.1).[95] The findings demonstrated that the driver gene alterations in nonsmokers differ completely from driver gene alterations in smokers, irrespective of histologic type. In adenocarcinoma, *EGFR*, phosphatase and tensin homolog (*PTEN*), and phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (*PIK3CA*) mutations and *ALK* fusions were present more frequently among never-smokers, whereas *KRAS* and serine/threonine kinase 11 (*STK11*) mutations were present more frequently among smokers. The met proto-oncogene methylated CpG (mCpG) sequences (*MET*) and v-raf murine sarcoma viral oncogene homolog B (*BRAF*) mutations did not differ substantially by smoking status. As expected, fewer squamous cell carcinomas were present, and discoidin domain receptor tyrosine

TABLE 4.1 Driver Mutations in Lung Cancers Among Chinese Never-Smokers and Ever-Smokers Adjusted for Histologic Type and Smoking Status[95]

Adenocarcinoma (n = 347)		
Gene	**Never-Smokers (66%)**	**Ever-Smokers (34%)**
EGFR	49.8	22.0
PTEN	9.9	2.6
ALK	9.3	4.5
PIK3CA	5.2	2.1
STK11	2.7	11
KRAS	4.5	12
C-MET	4.8	4
BRAF	1.9	3.1
Squamous Cell Carcinoma (n = 144)		
Gene	**Never-Smokers (35%)**	**Ever-Smokers (65%)**
DDR2	0	4.4
FGFR2	0	2.2

ALK, anaplastic lymphoma receptor tyrosine kinase; *BRAF*, v-raf murine sarcoma viral oncogene homolog B; *C-MET*, growth factor receptor c-Met; *DDR2*, discoidin domain receptor tyrosine kinase 2; *EGFR*, epidermal growth factor receptor; *FGFR2*, fibroblast growth factor receptor 2; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; *PTEN*, phosphatase and tensin homolog; *STK11*, serine/threonine kinase 11.

kinase 2 (*DDR2*) and fibroblast growth factor receptor 2 (*FGFR2*) mutations, although infrequent, were present only in tumors from smokers.

In another Chinese study limited to lung cancers from never-smokers, Li et al.[96] identified driver mutations in 89% of the tumors (Table 4.2). Of interest, these mutations were mutually exclusive, consistent with their driver status. Although the mutation figures may be lower among lung cancers in never-smokers in Western countries, most of these tumors contain potentially actionable driver mutations. In conclusion, driver gene alterations in NSCLC are shown to be associated with smoking status rather than gender.

GENOME-WIDE MOLECULAR CHANGES

Although we have discussed specific genes mutated in lung cancer in never-smokers or ever-smokers, some genome-wide changes also are characteristic of both forms of lung cancer. Point mutations may represent changes involving purine to pyrimidine or pyrimidine to purine (transversions) or purine to purine or pyrimidine to pyrimidine (transitions). At the turn of the 21st century, it was noted that the point mutations in the tumor protein p53 (*TP53*) gene present in lung cancer were of a different pattern than the point mutations seen in most other types of solid tumor. The most frequent mutation change in the *TP53* gene in lung and other tobacco-associated cancers (head and neck or bladder) represented a G to T transversion.[97–99] These mutations frequently occur at mCpG hotspots. 5-Methylcytosine in DNA is genetically unstable, and mCpG sequences frequently undergo mutation resulting in a general depletion of this dinucleotide sequence in mammalian genomes. In human genetic disease-relevant and cancer-relevant genes, mCpG sequences are mutational hotspots.[99] Although initial attention focused on the *TP53* gene, whole genome sequencing studies have confirmed that G to T transversions are the most frequent type of point mutation in tobacco-associated cancers, and G to A transitions are the most common type of point mutation in lung cancers among never-smokers.[87,100]

Seo et al.[87] extensively analyzed the transcriptomes of 87 lung adenocarcinoma specimens from Korean patients. The authors found that the expression signature, as well as the mutation pattern, was highly related to active smoking. In another study of nontumorous lung tissues, Bosse et al.[101] compared gene expression levels between never-smokers and current smokers, as well as time-dependent changes in gene expression in former smokers. A large number of genes (3223 transcripts) were differentially expressed between the groups. Moreover, some genes showed very slow or no reversibility in expression, including serpin peptidase inhibitor, clade D (heparin cofactor), member 1 (*SERPIND1*), which was found to be the gene that was most consistently permanently altered by smoking. Thus, their findings indicate that smoking deregulates many genes, many of which reverse to normal after smoking cessation. However, a subset of genes remains altered even decades after smoking cessation and may account, at least in part, for the residual risk of lung cancer among former smokers. In another study, Lam et al.[102] evaluated the expression patterns of a small number of cell lines established from smokers and never-smokers in Hong Kong. These authors identified 71 genes that were differentially expressed or showed class predictive significance.

Whole genome sequencing has shown that the number of synonymous and nonsynonymous mutations in lung cancer in ever-smokers is remarkably high and that this lung cancer is among the cancers with the highest number of such mutations.[103]

However, major differences exist between lung cancer in never-smokers and ever-smokers with respect to the number of mutations and complexity of molecular changes, with this number being 10-fold or less in never-smokers.[87,100] These findings indicate that exposure to tobacco carcinogens induces DNA instability, resulting in the formation of numerous driver and passenger mutations. By contrast, although the number of driver mutations may be similar, the etiologic agents associated with lung cancer in never-smokers induce a more modest total number of changes.

TABLE 4.2 Driver Mutations in Lung Adenocarcinomas Among Chinese Never-Smokers[96]

Driver Mutation[a]	Percentage (%) of Patients (*n* = 202)
EGFR	75
HER2	6
ALK fusion	5
KRAS	2
ROS1 fusion	1
BRAF	0
No mutation	11
Any mutation	89

[a]Mutations were mutually exclusive.
ALK, anaplastic lymphoma receptor tyrosine kinase; *BRAF*, v-raf murine sarcoma viral oncogene homolog B; *EGFR*, epidermal growth factor receptor; *HER2*, human epidermal growth factor receptor-2; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; *ROS1*, c-ros oncogene 1, receptor tyrosine kinase.

PRENEOPLASTIC CHANGES

For more than a decade, we have known that the development of invasive lung carcinoma is preceded by numerous and widespread molecular alterations in the respiratory tree that commence in histologically normal epithelium.[104,105] However, similar studies on the development of *EGFR* mutant lung cancers indicate a far more modest field effect, largely limited to the field immediately surrounding the invasive carcinoma.[106] Although these observations may be partly due to differences in the field effects of centrally arising squamous cell carcinomas compared with peripherally arising adenocarcinomas, they also suggest that smoking induces much or all of the respiratory epithelium to undergo molecular changes very early in lung cancer pathogenesis, whereas lung cancers arising in never-smokers have much more restricted field effects.

DNA METHYLATION

Although most molecular studies have focused on genetic changes, epigenetic differences in lung cancer between ever-smokers and never-smokers demonstrate multiple differences in the overall methylation pattern and in methylation (and occasionally downregulation) of several genes. However, some studies describe contradictory findings and others are unconfirmed. One study of 59 matched lung adenocarcinoma/nontumor lung pairs, with genome-scale verification on an independent set of tissues, used the older Infinium HumanMethylation27 platform (Illumina, San Diego, CA, USA).[107] Although more than 700 genes were found to be differentially methylated between tumor and nonmalignant lung tissue, comparison of DNA methylation profiles between lung adenocarcinomas of current smokers and never-smokers showed modest differences, identifying only the lectin, galactoside-galactoside binding, soluble, 4 (*LGALS4*) gene as significantly hypermethylated and downregulated in smokers. *LGALS4*, encoding a galactoside-binding protein involved in cell-cell and cell-matrix interactions, is a known tumor suppressor. Other studies have examined individual or small numbers of genes, which have included Ras association (RalGDS/AF-6) domain family member 1 (*RASSF1A*), cyclin-dependent kinase inhibitor 2A (*CDKN2A*), and others (Table 4.3).[108–115] The association between *CDKN2A* methylation and active smoking was confirmed by meta-analysis.[116] The association between inactivation of *CDKN2A* and inactivation by any mechanism and its

TABLE 4.3 Summary of Major Differences Between Lung Cancers Arising in Ever-Smokers and Never-Smokers

FACTOR	LC IN EVER-SMOKERS	LC IN NEVER-SMOKERS
Clinical and Pathologic Factors		
Major etiologic factor	Cigarette smoking	Unknown or diverse
Major histologic types	NSCLC and SCLC	Largely adenocarcinoma
Field effects	Widespread	More limited
Stage at time of diagnosis	More advanced in never-smokers	
Response to therapy and overall survival	Improved in never-smokers	
Age at time of diagnosis	Younger for never-smokers (especially in East Asia)	
Gender	Higher ratio of women among never-smokers (worldwide)	
Genetics		
RGS17 locus (chromosome 6q)	Lung cancer susceptibility locus for ever-smokers	
Polymorphisms	Patterns differ according to smoking status and ethnicity. *CHRNA5* predisposes to smoking	
Molecular Changes		
Total number of mutations	Much higher in ever-smokers	
Most frequent mutation	G to A transitions	G to T tranversions
Specific mutations	*KRAS, STK11, SMARCA4*	*EGFR, ALK, PTEN, PIK3CA*
Percentage of cancers with potential targets for treatment	Approximately 60% (East Asia)	More than 90% (East Asia)
Gene expression signatures	More deregulation of gene expression in lung tumors and adjacent tissue in ever-smokers	
DNA methylation	Multiple genes show differential methylation, predominantly affecting cancers in never-smokers	
Methylated genes (some are unconfirmed)	*RASSF1A, CDKN2A, MTHFR, HtrA3, LGALS4*	*NFKBIA, TNFRSF10C, BHLHB5, BOLL*

ALK, anaplastic lymphoma receptor tyrosine kinase; *BHLHB5*, basic helix-loop-helix domain containing, class B5; *BOLL*, boule-like RNA-binding protein; *CDKN2A*, cyclin dependent kinase inhibitor 2A; *CHRNA5*, cholinergic receptor, nicotinic, alpha 5 (neuronal); *EGFR*, epidermal growth factor receptor; *HtrA3*, HtrA serine peptidase 3; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; *LC*, lung cancer; *LGALS4*, lectin, galactoside-binding, soluble, 4; *MTHFR*, methylenetetrahydrofolate reductase (NAD(P)H); *NFKBIA*, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha; *NSCLC*, nonsmall cell lung cancer; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; *PTEN*, phosphatase and tensin homolog; *RASSF1A*, Ras association (RalGDS/AF-6) domain family member 1; *RGS17*, regulator of G-protein signaling 17; *SCLC*, small cell lung cancer; *SMARCA4*, SWI/SNF (switching/sucrose nonfermenting) related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4; *STK11*, serine/threonine kinase 11; *TNFRSF10C*, tumor necrosis factor receptor superfamily, member 10c, decoy without an intracellular domain.

relationship to smoking has been demonstrated, with one interesting study examining gene promoter methylation assayed in exhaled breath and finding differences between smokers and individuals with lung cancer.[117]

CONCLUSION

We focused on lung cancer in never-smokers in East Asia because this type of lung cancer occurs most frequently in this geographic region. However, East Asia is a vast region, containing 10 countries and the Asian Pacific islands. It encompasses more than one-fifth of the world's population. Thus, lung cancer differences among heterogeneous East Asian subpopulations may also occur. We believe that the observations and findings summarized in this chapter demonstrate conclusively that lung cancers arise as a result of complex interactions among several factors, including exposure to tobacco through either active smoking or secondhand smoke, gender, ethnicity, and genetic predisposition. For lung cancer in never-smokers, other largely unknown environmental carcinogens or lifestyle factors may be contributors; however, no single factor or combination of factors identified to date can be responsible for the majority of cancers.

As a result, major clinical, pathologic, demographic, gender, ethnic, molecular, and genetic predisposition factors differ between lung cancers in smokers and never-smokers. We summarize many of the important differences between these two groups of lung cancers (Table 4.3). Studies have conclusively demonstrated that lung cancers arising in ever-smokers and never-smokers are very different and should be regarded as separate tumors with different pathogeneses and their own clinical, genotypic, and phenotypic features.

However, many questions remain, in particular regarding the major etiologic cause or causes of lung cancer in never-smokers. There may be no simple or universal answers, with this type of cancer remaining a heterogeneous cancer with a pathogenesis influenced by genetics, ethnicity, environmental tobacco exposure, other environmental or occupational carcinogens, and geography.

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