Chapter 1
US and Global Epidemiology and Incidence Rates of Lung Cancer

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Introduction

The global incidence of lung cancer in 2020 was 2.2 million cases [1]. It is the second most common cause of cancer, accounting for 11% of all cancer cases, and the most common cause of cancer-related death [1]. There were 1.8 million deaths from lung cancer in 2020, accounting for 18% of all cancer mortality [1].

The incidence and mortality of lung cancer mirror each other closely, with a reported mortality incidence ratio of 0.85. The 5-year survival rate is low, most recently 23% in the USA, but lower in low-income countries [2, 3]. For example, the 5-year survival is less than 10% in Brazil, Bulgaria, India, and Thailand. Relative to other malignancies, this is quite low [4]. The impact of lung cancer is severe, leading to 40 million disability-adjusted life years, 99% of which were due to years of life lost [5]. Lung cancer is consistently the number one type of malignancy with the highest years of life lost.

Globally, the overall number of lung cancer cases is still rising. Over 10 years, from 2007 to 2017, there was a 37% increase in cases [5]. However, the incidence rates for advanced disease over the past decade have steeply declined (6.5% annually) with a concurrent rise (4.5% annually) in incidence rates of localized disease, likely due to screening methods [4]. Higher incidence of localized lung cancer has led to an increase in 3-year survival rates from 21% to 31% (2004–2018). Overall in the USA, the incidence rate is declining, 3% annually in males and 1% annually in females.

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Influential Factors of Lung Cancer Incidence

Several factors affect the incidence rate in specific populations, including age, sex, socioeconomic background, and tobacco use.

Age

Increasing DNA damage over time and shortened telomeres lead to an increase in the incidence of cancers with age. In both males and females, the median age of lung cancer diagnosis is 70 [6]. In the USA, the probability of developing lung cancer is highest in males above age 70 (1 in 17) with successively lower probability in lower age ranges (1 in 169 for ages 50–59 and 1 in 59 for ages 60–69) [4]. Figures are slightly lower in US females. Younger patients diagnosed with non-small cell lung cancer (NSCLC) are more likely to be female and/or non-white [7]. Tumors tend to be adenocarcinoma and present with larger, later-stage disease. However, younger patients are more likely to undergo treatment with an overall improved survival due to relatively less comorbid conditions than similarly staged older patients.

Sex

Globally, lung cancer remains the second most common cancer in females, following breast cancer and the second most common cause of cancer death in females [1]. The incidence in females compared to males had a later uptrend in case rates following a delayed uptake of tobacco use comparatively [8].

In a recent analysis of a Statistics, Epidemiology, and End Results database of over 450,000 lung cancer cases in the USA, the disease remains disproportionally higher in males versus females (74 per 100,000 in males versus 52 per 100,000 in females) at all disease stages [9], and males are still more likely to be diagnosed with late-stage 3–4 lung cancer [9]. However, the incidence gap is successively getting smaller. In the USA, lung cancer rates in females are falling after a peak in the late 1990s, but at a much slower pace than in males (Fig. 1.1a) [4]. In addition, in the USA and several other countries, there has been a notable increase in the female-to-male incidence rates in successively lower birth cohorts [10, 11]. Outside of the USA, sex-related incidence rates vary widely based on geographic region (Fig. 1.2). For example, the male-to-female ratio is 1.2 in Northern America but 5.6 in Northern Africa [1].

While lung cancer deaths continue to decline in both sexes, the decline is less precipitously in females versus males (Fig. 1.1b). Comparative modeling predicts lung cancer deaths will be higher in females than males by 2045 [12].

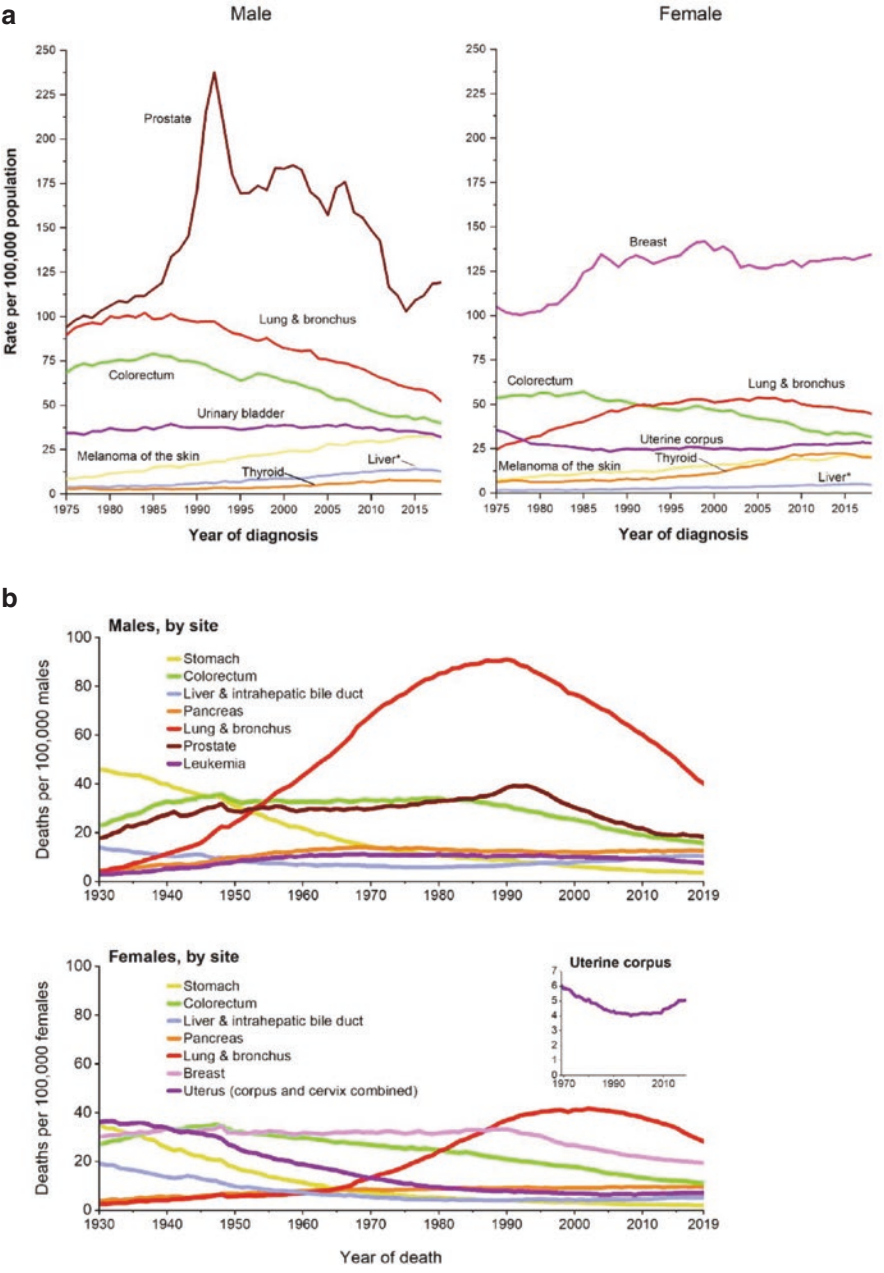

Fig. 1.1 (**a**) Trends in incidence of cancer by sex in the USA 1975–2018. (**b**) Trends in mortality rate of cancer by sex in the USA 1930–2019. (Reproduced with permission from Siegel RL, 2022)

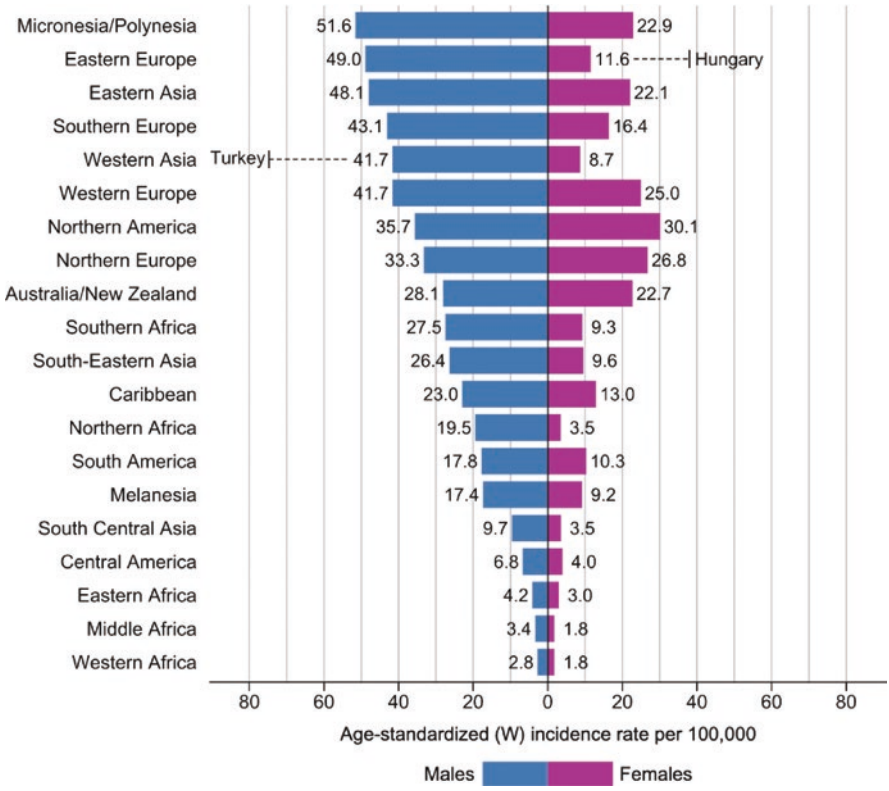

Fig. 1.2 Geographic variation in the age-standardized rates of lung cancer in males and females in 2020. (Reproduced with permission from Sung, H 2021)

Tobacco Use

As discussed above, it is expected that global trends in lung cancer incidence and death will change over time, mostly driven by trends in tobacco use. Over 80% of tobacco users currently reside in low-income countries [13]. However, tobacco use was initially highest in high-income countries such as the USA and UK, which in parallel developed a high incidence of lung cancer [14]. Subsequently, the decline in tobacco use in high-income countries has led to a decline in lung cancer deaths [15]. Tobacco smoking prevalence remains positively associated with age-adjusted incidence and mortality rates due to lung cancer [16]. Sex-specific differences in tobacco use account for a continued rise in incidence among women in many countries [17].

Socioeconomic Factors

The sociodemographic index (SDI) and human development index (HDI) can be used to stratify the global disease burden. The SDI is a composite indicator of gross national income per capita, educational attainment, and total fertility rate, whereas the HDI also incorporates life expectancy at birth. Regarding the incidence of lung cancer, it was highest in men (1 in 13), in high-middle SDI countries; highest in women (1 in 28), in high SDI countries; and lowest in men and women (1 in 45 and 1 in 142, respectively), in low SDI countries [5]. Overall, lung cancer rates are three to four times higher in high HDI countries compared to low [1]. Specifically, the rates are highest in men in Micronesia/Polynesia, Eastern and Southern Europe, and Eastern and Western Asia. In women, the highest rates are observed in Northern America, Northern and Western Europe, Micronesia/Polynesia, and Australia/New Zealand. There is a bivariate association between mortality—to—incidence ratio (MIR) and HDI; countries with higher HDI (more developed) have lower MIR (higher 5-year survival rates) [16].

Smoking-Related Risk Factors

Cigarette Smoking

In the USA, 80% to 90% of all lung cancers are caused by cigarette smoking [18, 19]. A higher proportion of lung cancer is associated with smoking in males than females. The proportion of lung cancer associated with smoking is gradually decreasing in locations where tobacco use is becoming less common; however, 72% of women and 81% of men with newly diagnosed lung cancers aged 20–49 years have a smoking history [19]. The cumulative risk of lung cancer is high in individuals who smoke up to 16% by the age of 75 years and 30% by 85 years in those with a heavy smoking history [20, 21]. This is compared to an average lifetime risk of 1% in individuals who have never smoked.

Before the twentieth century, lung cancer was rare, with only 140 published reports by 1900 [22]. However, cigarettes gained popularity at the beginning of the twentieth century due to mass production and marketing.

Tobacco smoke was first linked to lung cancer in 1912 when Issac Adler noted a marked increase of tumors in the lung and postulated that this may be due to the abuse of tobacco [23]. This theory, however, was not fully elucidated until the mid-1900s when evidence from population studies, animal experiments, cellular pathology, and the discovery of carcinogens in tobacco smoke provided additional evidence. In 1939, Franz Hermann Müller published a case-control study identifying a significantly higher rate of cancer in tobacco user [24]. Several other observational studies were published in Germany, the UK, and the USA. In 1954, Doll and Hill reported their findings regarding the incidence of lung cancer among 3093 male

doctors in the UK stratified by their smoking habits [25]. Those who smoked more than 35 cigarettes/day were found to be 40 times more likely to die from lung cancer. In the same year, similar findings were confirmed in a cohort of 187,766 men in the USA, making the association between smoking and lung cancer indisputable [26]. Additionally, research regarding the changes induced in the lungs at a cellular level provided mechanistic explanations for the association of tobacco smoke and cancer; cigarette smoke caused ciliastasis and cilia cell death leading to further concentration of the carcinogenic substances within the lungs [27]. Concurrently, experiments were underway demonstrating the carcinogenesis induced by tobacco smoke and tar in animal models [28, 29]. Polycyclic aromatic hydrocarbons in coal tar had previously been identified as carcinogenic and were soon identified in tobacco smoke [30]. Soon thereafter, several dozen carcinogens were identified in cigarette smoke. In 1954, the American Cancer Society's Board of Directors announced that tobacco smoke unequivocally led to lung cancer, which was recognized by the US Surgeon General in 1964.

Smoking is still quite prevalent globally despite 70 years since tobacco smoke was implicated with lung cancer. Tobacco smoking prevalence was still 21.6% worldwide in 2016 [16]. An estimated 1.1 billion people over the age of 15 are currently smoking [13]. There is geographic variation, with tobacco smoking being more prevalent in European countries (Fig. 1.3). Five of the top ten countries with the highest smoking prevalence are in Europe. The peak of the tobacco epidemic in the USA was in the 1950s to 1960s when approximately half of the adult males smoked cigarettes, which has decreased since then (Fig. 1.4). In 2020, 12.5% of

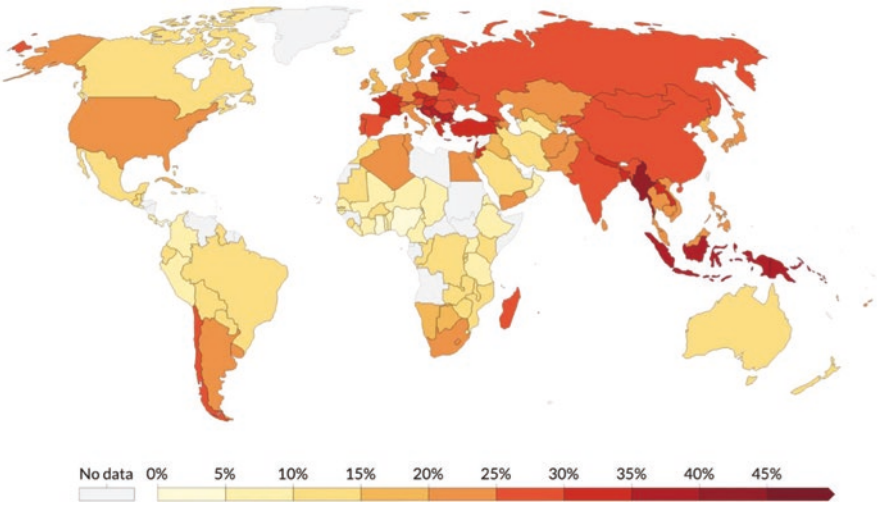

Fig. 1.3 Tobacco smoking prevalence (percent) globally in 2020 per World Health Organization Data. (Figure reproduced from Hannah Ritchie and Max Roser (2013)—"Smoking." Published online at OurWorldInData.org. Retrieved from: https://ourworldindata.org/smoking [Online Resource])

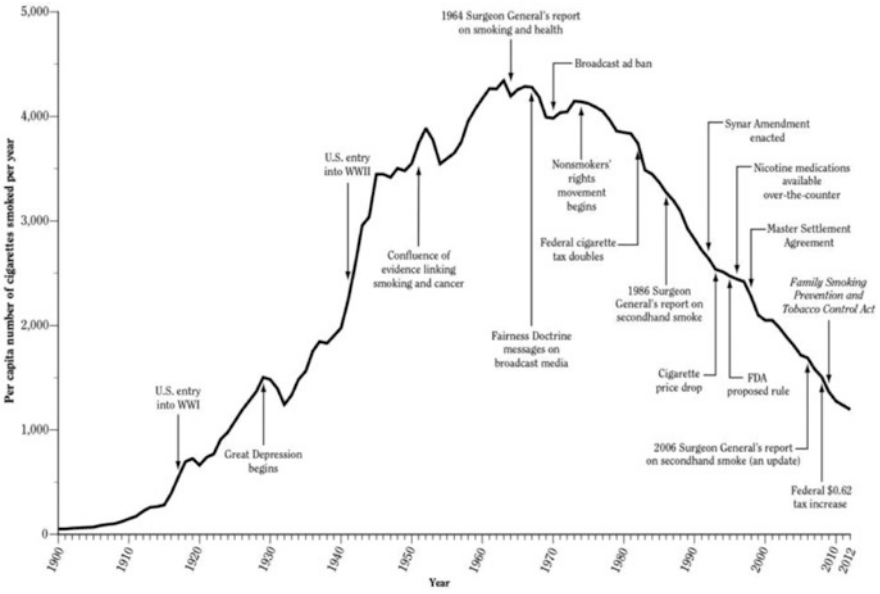

Fig. 1.4 Timeline of cigarette use in the USA. (Reproduced from US Department of Health and Human Services, The Health Consequences of Smoking-50 Years of Progress: a report of the Surgeon General, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, and Office of Smoking and Health)

adults over 18 (30.8 million people) smoked [31]. This figure is substantially less than in 2005 when 21% of American adults were currently smoking cigarettes. Tobacco use remains higher in males (14% compared to 11% of US females) and among American Indian/Alaska Natives (27%).

Secondhand Smoke

Exposure to carcinogens from burning tobacco products can also occur indirectly through secondhand smoke (SHS) or sidestream smoke. Shortly after discovering the carcinogenic properties of personal tobacco use, the effect of SHS was studied. Although exposure to the carcinogens in SHS is typically less concentrated, exposure can begin young in childhood, creating a more significant overall lifetime exposure. In the 1960s, it was demonstrated that the children of individuals who smoke were sick, primarily with respiratory illnesses, more often than those of individuals who did not smoke [32]. Later, in the 1980s, it was noted that the nonsmoking wives of heavy individuals who smoke had a higher incidence of lung cancer [33]. In 1986, SHS was recognized as a cause of lung cancer [34]. Serum cotinine can detect recent nicotine exposure and, in individuals that do not smoke, can be

used as a marker of SHS exposure. From 1988 to 2014, exposure to SHS declined from 87.5% of the nonsmoking population in the USA to 25.2% but plateaued at this level (Fig. 1.5) [35]. Highest levels of exposure were seen in children aged 3–11, non-Hispanic blacks, those living in poverty and/or with someone who smoked inside the home. In 2006, the US Surgeon General released a report entitled "The Health Consequences of Involuntary Exposure to Tobacco Smoke" [36]. In this report, it was noted that despite efforts to control exposure to SHS, 43% of individuals that do not smoke still had detectable levels of cotinine, and more than 60% of children aged 3–11 were exposed to SHS. Adverse events related to SHS exposure in children and adults were noted, including development of lung cancer. Overall, 2.7% of lung cancers can be attributed to secondhand smoke [18]. Individuals that do not smoke who are exposed to SHS at home or work increase their risk of developing lung cancer by 20–30%. Compared to individuals that do not smoke not exposed to SHS, people exposed to SHS had an odds ratio of developing lung cancer of 1.31 (95% confidence interval (CI), 1.17–1.45) [37]. A recent study investigated the in utero effects of smoking and the impact on SHS during childhood in a cohort of 432,831 participants [38]. The incidence of lung cancer was significantly increased in those exposed to tobacco earlier in life (adjusted HRs for adulthood, adolescence, and childhood (vs. never tobacco users) were 6.10 (5.25–7.09), 9.56 (8.31–11.00), and 15.15 (12.90–17.79)). Additionally, compared with participants without in utero exposure, those with in utero exposure had a higher risk of both incidence of lung cancer (HR: 1.59, 95% CI, 1.44–1.76, $p < 0.001$) as well as lung cancer mortality (HR: 1.70, 95% CI, 1.54–1.87, $p < 0.001$).

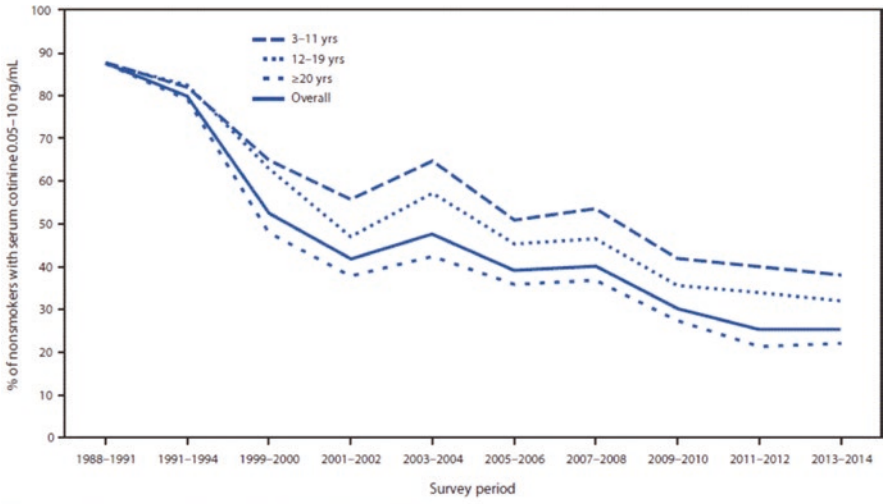

Fig. 1.5 Percentage of individuals that do not smoke in the USA over age 3 years with secondhand smoke exposure 21988–2014. (Reproduced from Tsai J, Homa DM, Gentzke AS, et al. Exposure to Secondhand Smoke Among Nonsmokers—United States, 1988–2014. MMWR Morb Mortal Wkly Rep 2018;67:1342–1346)

Due to the relative novelty, the effects from inhalation of secondhand vapors produced by e-electronic cigarettes (EC) are not yet well established.

Cigar Smoking

Cigar smoking and sales have increased over the past several decades due to taxation and regulation of cigarette sales and the perception that smoking cigars has fewer health consequences [39, 40]. Individuals who smoke cigars and cigarettes adjust their smoking habits by exposing themselves to similar amounts of nicotine and other components of mainstream smoke when smoking cigars [41]. However, cigar and pipe smoking increases the risk of developing lung cancer [42–45]. Exclusively smoking cigars and pipes is still associated with an increased risk of cancer-related mortality, although less compared to exclusively smoking cigarettes (HR, 1.61; 95% CI, 1.11–2.32; HR, 1.58; 95% CI, 1.05–2.38; and HR, 4.06; 95% CI, 3.84–4.29, respectively) [45]. Compared to those who do not smoke, the relative risk of lung cancer death, in particular, is high in those that smoke cigars (RR = 5.1; 95% CI 4.0–6.6) [44].

Cannabis Smoking

Frequent concomitant use of marijuana and cigarettes and the illegal status in many countries make directly studying the effects of marijuana on lung cancer risk challenging. Studies have shown a positive association between marijuana use and the development of lung cancer, especially in heavy users [46]. A meta-analysis of several studies demonstrated a biologic plausibility of lung cancer development in response to marijuana smoke but failed to identify an association between them [47].

Electronic Cigarette Smoking

Although initially designed as a harm-reduction product as an alternative to tobacco cigarettes, EC use has skyrocketed among prior nontobacco users, particularly the youth [48–51]. Containing a liquid mixture of nicotine and other flavorings dissolved in glycerin or propylene glycol, these devices produce vapor when heated. Given their relative novelty, longitudinal data regarding their safety is not yet known. However, in response to the increased use of EC as a “safer” alternative to tobacco cigarettes, the National Academies of Science, Engineering, and Medicine released a consensus statement in 2018 clearly delineating the health risks associated with EC use [52]. EC are known to contain both definite and probable carcinogens including nicotine derivatives, polycyclic aromatic hydrocarbons, heavy

metals, aldehydes, and other complex organic compounds. Compared to individuals who smoke tobacco, EC users have lower levels of toxic and carcinogenic metabolites in their urine, although they are still detectable [53]. EC vapor has tumorigenic properties in the lungs of animal models [54]. Additionally, it causes DNA damage in both human and animal models [54, 55]. Ongoing, longitudinal epidemiologic studies will be needed to establish the relationship between EC use and lung cancer.

Smoking Cessation

Massive public health efforts have resulted in increasing rates of smoking cessation. Cessation of smoking results in significant lung cancer risk reduction [56–58], and sustained smoking cessation increasingly reduces the risk of lung cancer; men who quit at ages 60, 50, 40, and 30 had a cumulative risk of lung cancer by age 75 of 10%, 6%, 3%, and 2%, respectively [56]. A similar trend was noted in life expectancy after smoking cessation; those that quit smoking at age 25–34 years, 35–44 years, or 45–54 years gained about 10 years, 9 years, and 6 years of life, respectively [58]. Reductions in smoking also can result in a lower incidence of lung cancer in a dose-dependent manner [59]. Resumption of smoking following quitting, even at a lower amount, results in an increased risk of lung cancer compared to sustained quitting. However, the risk remains elevated compared to those that do not smoke [57].

Even after a diagnosis of lung cancer, smoking cessation is beneficial [60]. Ongoing smoking after a diagnosis of early-stage lung cancer can result in an increased risk of all-cause mortality (hazard ratio 2.94, 95% CI, 1.15–7.54), cancer recurrence (1.86, 95% CI, 1.01–3.41), and development of a second primary tumor (4.31, 95% CI, 1.09–16.98). Cessation after diagnosis of lung cancer resulted in increased adjusted median overall survival time compared to ongoing smoking (6.6 years vs. 4.8 years, respectively; $p = 0.001$), higher 5-year overall survival (60.6% vs. 48.6%; $p = 0.001$), and progression-free survival (54.4% vs. 43.8%; $p = 0.004$) [61]. Ongoing nicotine exposure in patients with established lung cancer can increase the incidence and progression of brain metastasis [62].

Never-Smoking

Approximately 25% of newly diagnosed lung cancer occurs in individuals who have never smoked, defined as having smoked less than 100 cigarettes in a lifetime, comprise approximately 25% of newly diagnosed lung cancer [63]. Overall, the proportion of patients with lung cancer, especially non-adenocarcinoma, that have never smoked is small [19, 64]. However, the proportion of individuals who have never smoked and are diagnosed with lung cancer is increasing, particularly in women [65, 66]. In some Asian countries, 60–80% of women with lung cancer have never

smoked [63], while in the USA, women with lung cancer are much more likely to have never smoked compared with men, 19% versus 9%, respectively [67]. The highest incidence of nonsmoking-related lung cancers in the USA is among women aged 20–49 (28%) [19]. The incidence of lung cancer in individuals that have never smoked in the USA has increased from 8% in 1995 to 15% in 2013 and is independent of sex, stage at diagnosis, and ethnicity [66].

The predominant subtype of lung cancer in this group is adenocarcinoma, making up 50–60% of lung cancers. In contrast, approximately 6–8% of all cases of squamous cell carcinoma and 2.5% of small cell carcinoma are in individuals that have never smoked [68].

Driver mutations are more commonly found in lung adenocarcinomas in individuals who have never smoked. A recent study of a cohort of individuals who do not smoke with adenocarcinoma in the USA identified genetic alterations in tumors in 80% [69]. Additionally, approximately 7% of samples in individuals that never smoked had alterations in germline DNA repair genes similar to those that did smoke. Finally, several samples had genetic mutation signatures that indicated a response to passive exposure to cigarette smoke.

In the USA, epidermal growth factor receptor (EGFR) mutations are identified in approximately 40–60% of lung adenocarcinomas in individuals that never smoked, whereas this mutation is identified in only about 15% of total adenocarcinomas [70]. Low or no exposure to tobacco smoke is mainly associated with exon 19 and 21 mutations in the EGFR gene [71].

Anaplastic lymphoma kinase (ALK) mutations leading to fusion with echinoderm microtubule-associated protein-like 4 (EML4) are found in approximately 3–7% of patients with NSCLC [70]. This mutation is mutually exclusive with the EGFR and Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations. Compared to both wild-type and those with EGFR mutations, ALK mutations are found more frequently in a younger population and in men [72]. Similar to those with EGFR mutations, ALK mutations are more commonly found in light and individuals that never smoked.

In contrast, the KRAS's driver mutations are found more commonly in former and active individuals that smoke [73, 74]. However, a distinct mutational profile is observed in individuals that do not smoke; a transition mutation (G → A) rather than a transversion mutation is noted in the nonsmoking population [74].

Nonsmoking-Related Risk Factors

Sex

Early studies suggested that women may be more susceptible to lung cancer due to smoking. Several have demonstrated that women tend to be diagnosed with lung cancer at relatively younger ages and with lower tobacco use [75–77]. However,

other large studies have not demonstrated any increase in susceptibility to the carcinogenic effects of tobacco. In a large cohort study of over 460,000 Americans, there was no significant difference in the development of lung cancer in men and women with comparable smoking histories [78].

The rates of lung cancer in never-smoking women are higher than in men. Hormonal factors are postulated to be, at least in part, what drives these differences. There is differential expression of estrogen receptors in lung tissue individuals that do not smoke. Estrogen receptor-beta (ERB) expression in NSCLC specimens has a more favorable outcome than ER-alpha [79]. Higher rates of ERB expression have been noted in females who do not smoke compared to males [80].

Race

In the USA, there are notable racial disparities in the presenting stage and ultimate treatment regimens. According to the American Lung Association, white Americans are diagnosed with lung cancer in an early stage much more frequently than other racial minorities (25% compared to 21% black Americans, 21% Asian Americans, and 22% Latinos) [81]. Blacks and Latinos in America are also less likely than whites to undergo surgical treatment. The Latino group in America, in particular, is significantly less likely to undergo treatment (20% versus 15% of white Americans).

Diet and Supplements

Diet modifications and supplements have long been thought to play a preventative role in cancer development [82, 83]. However, in 2014, the US Preventive Services Task Force (USPSTF) recommended against the routine use of supplements, including beta-carotene and vitamin E, to prevent cancer [84]. This was primarily based on two large randomized placebo-controlled trials evaluating vitamin supplementation in high-risk lung cancer groups [85, 86]. In both the Alpha-Tocopherol Beta-Carotene Prevention and Carotene and Retinol Efficacy Trial of groups at high risk of lung cancer due to tobacco use or asbestos exposure, follow-up was terminated early due to excess cases of lung cancer and overall mortality in groups taking the supplements beta-carotene, vitamin E, and/or vitamin A. In post-intervention analysis, this increased risk persisted for several years following supplementation [87, 88]. A recent meta-analysis done by the USPSTF demonstrated an odds ratio of 1.2 (95% CI, 1.01–1.42) for lung cancer development associated with beta-carotene supplementation [89].

Weight

High body mass index (BMI) and obesity are associated with an increased risk of many cancers. Lung cancer risk, however, is inversely related to higher BMI. While it is challenging to differentiate the actual BMI effect from confounding factors such as tobacco use and preclinical wasting before an obvious manifestation of lung cancer, several studies demonstrate that low BMI is an independent risk factor for lung cancer [90, 91]. In a recent large cohort study, escalating BMI trajectories in adulthood led to reduced lung cancer risk [90]. This trend even applied when excluding patients who developed the disease during the first to fourth years of follow-up. In this study, several genetic foci involved in regulating cell growth, differentiation, and inflammation were identified and associated with these BMI trajectories, possibly identifying a causal relationship. In a study with a median follow-up of 20 years of over 770,000 individuals, the inverse relationship between BMI and lung cancer persisted after controlling variability in smoking [91].

Underlying Lung Disease

While the influence of benign lung diseases on lung cancer development is often confounded by concurrent tobacco, several underlying lung diseases are associated with an increased risk of lung cancer independent of smoking history. Chronic inflammation associated with various diseases creates a tumor-supporting microenvironment [92]. Additionally, activation of innate immunity and inflammation leads to the production of cytokines, which are critical for stimulating tumor growth [93].

One of the largest studies to evaluate the impact of underlying lung disease was performed with pooled analysis of 17 studies with 24,607 lung cancer cases and 81,829 controls in the International Lung Cancer Consortium [94]. Emphysema conferred the highest risk of lung cancer (relative risk (RR) = 2.44), followed by pneumonia (RR = 1.57), tuberculosis (RR = 1.48), and chronic bronchitis (RR = 1.47). In an analysis of individuals that never smoked, elevated risks were observed for emphysema (RR = 2.21), tuberculosis (RR = 1.50), and pneumonia (RR = 1.35) A dose-response relationship was noted as well, with an increasing number of underlying lung conditions being positively associated with a risk of lung cancer.

Several other studies confirmed that chronic obstructive pulmonary disease (COPD), including emphysema and chronic bronchitis, is positively associated with lung cancer and can be independent of smoking history [95–97]. In a cohort of 602 patients with lung cancer, 50% had COPD compared to 8% in a community control group [95]. In a 20-year prospective study of 448,600 individuals that do not smoke, the hazard ratio (HR) of lung cancer-related death was increased in those with emphysema or chronic bronchitis (2.44) [96]. Additionally, alpha(1)-antitrypsin deficiency carriers have up to a 70% higher risk of developing lung cancer than

noncarriers [97]. Data from 18,473 individuals that smoke in the National Lung Screening Trial demonstrated that the severity of airflow obstruction had a linear relationship with lung cancer risk [98]. The exact mechanism by which increasing airflow limitation incurs a higher risk of lung cancer is unknown. However, it is felt that premalignant transformation, or epithelial-mesenchymal transition, is promoted by the excess of metalloproteinases and growth factors found in COPD. This is correlated with airflow limitation [99, 100].

Interstitial lung disease and idiopathic pulmonary fibrosis (IPF) are associated with increased lung cancer. In a meta-analysis, the incidence rate of lung cancer in IPF was 13% [101]. In a US population of patients with IPF, lung cancer was found to be 3.34-fold higher than in the general population [102]. In this population, cancer was more often found in the lower lobes (63% in IPF versus 26% in non-IPF) and was squamous histology. There was a significant increase in the risk of lung cancer over time in IPF patients (1.1% at 1 year, 8.7% at 3 years, 15.9% at 5 years, and 31.1% at 10 years) [103].

Bronchiectasis is also an independent risk factor for lung cancer. In a non-cystic fibrosis population, the incidence of lung cancer is significantly higher in patients with bronchiectasis (2.099 vs. 0.742 per 1000 person-years, $p < 0.001$) [104]. This difference is independent of smoking status (aHR = 1.28, 95% CI, 1.17–1.41 for individuals that never smoked; aHR = 1.26, 95% CI, 1.10–1.44 for individuals that ever smoked).

Significant inflammation associated with tuberculosis infections can lead to changes within the lung that can promote tumor growth [105]. In a cohort study in Taiwan, lung cancer incidence rate was 269 per 100,000 person-years in those with a history of tuberculosis compared to 153 per 100,000 person-years in those without [106]. The highest risk was in the years just following TB infection (incidence rate ratio (IRR) = 1.98 at 2–4 years), but the risk was persistently elevated 12 years following infection (IRR = 1.59).

Radiation Therapy

A history of prior radiation therapy for other primary cancers may lead to an increased risk of developing lung cancer. The most robust data is in those with a history of mediastinal radiation for Hodgkin's lymphoma or breast cancer. Particularly in individuals that use tobacco, the risk of developing lung cancer following chemo/radiotherapy for Hodgkin's lymphoma is 50–150 per 1000 within 10–20 years following treatment [107]. Compared to those not treated with radiation therapy, patients with breast cancer who underwent radiation therapy were significantly more likely to develop primary lung cancer (2.25% versus 0.23%) [108].

Familial Risk Factors

Several studies establish that a positive family history of lung cancer increases the risk for the disease, particularly among individuals that do not smoke [109, 110]. Both genetic and shared environmental factors may be responsible. A first-degree relative with a history of lung cancer before age 50 results in a significantly higher risk of lung cancer development in a nonsmoking population (OR 1.8, 95% CI, 1.0–3.2) [109]. Similar results were demonstrated in another study with a heterogeneous population of both those that smoke and do not smoke (OR 1.63, 95% CI 1.31–2.01) [110]. Risk was further increased with lung cancer history in more than one family member (OR 3.6, 95% CI, 1.56–8.31). This positive association resulted in the inclusion of family history of lung cancer in several lung cancer risk prediction models [111, 112].

Occupational and Environmental Factors

Many occupational and environmental exposures increase the risk of lung cancer. Radon and asbestos are the two most common and will be discussed in detail below. Still, others include arsenic, hard metal dust, beryllium, chloromethyl ether, chromium, formaldehyde, nickel, polycyclic aromatic hydrocarbons, and vinyl chloride. Concurrent tobacco use may compound the risk associated with exposures.

Asbestos

Asbestos is naturally occurring fibers that are composed of hydrated magnesium silicates. The two main types of fibers are serpentine (with the most common subtype being chrysotile) and amphibole. Serpentine fibers are the most common asbestos used commercially and are considered less toxic but can still be pathogenic [113, 114]. Asbestos exposure can cause various pulmonary diseases, including asbestosis, pleural disease, and malignancies—NSCLC, small cell lung cancer, and mesothelioma. Occupational exposure can occur in multiple ways, but most commonly, mining or milling of fibers and industrial applications, including textile, cement, shipbuilding, and insulation work. Nonoccupational exposure can occur via close contact with soiled clothing of an asbestos worker, renovation/demolition work in buildings containing asbestos, and environmental exposure. In the USA, the use of asbestos has been limited since the 1970s, with use limited to automotive brake pads and roofing products.

The most common parenchymal complication of asbestos exposure is development of asbestosis or a slowly progressive diffuse pulmonary fibrosis typically in

the subpleural regions of the lower lobes. This is caused by the direct toxic effects of the fibers on the parenchyma and the release of inflammatory mediators.

Asbestos exposure is the leading occupational exposure associated with lung cancer risk accounting for up to 12% of lung cancer cases in men after adjusting for smoking status and diet [115]. In a cohort of American insulators, lung cancer was the cause of death in 19% [116]. Among individuals that do not smoke, lung cancer mortality was increased by asbestos exposure (rate ratio = 3.6) and asbestosis (rate ratio = 7.40). Cigarette smoking, in conjunction with asbestos exposure, can significantly increase the risk of lung cancer [116, 117]. In the above cohort, smoking was additive to the risk of lung cancer (rate ratio = 14.1). This risk was significantly increased in those with asbestosis (rate ratio = 36.8).

The risk of lung cancer associated with nonoccupational exposure to asbestos is debated. A study performed in a mining town in Canada judged to have an intermediate environmental exposure to asbestos showed no increased risk of lung cancer in women [118]. However, a recent study demonstrated an increased risk of lung cancer in those that live near a source of asbestos (risk estimate 1.48) [119].

Radon

Radon is a natural gas that is colorless and odorless. It results from the decay of naturally occurring uranium-238 in rock and soil. It damages the respiratory epithelium via alpha particles. Typically found in high concentrations in mines from the ore or water, it was first linked to lung cancer in miners, but it also can be found in high concentrations in the home. Radon enters homes as gas from the soil through cracks in the foundation. The association of radon with lung cancer was established in the 1960s in a mining population [120].

While concentrations in residential homes are typically less than that in mines, high concentrations can develop. Radon is the second leading cause of lung cancer in the USA, and 1 in every 15 homes in the USA has radon levels above the Environmental Protection Agency's recommended threshold [121]. The risk of lung cancer increases proportionally with the amount of residential radon, 11%, with each 100 Bq/m^3 increase [122]. In Europe, it is estimated that 2% of lung cancer deaths can be attributed to radon exposure [123].

Environmental Pollution

In approximately half of the world, unprocessed biomass fuels and coal are used for heating or cooking [124]. Emissions from indoor combustion of coal are carcinogenic to humans [125]. Emissions include polycyclic aromatic hydrocarbons (PAHs), methylated PAHs, and nitrogen-containing heterocyclic aromatic compounds [126]. These compounds and others can be found in high concentrations,

especially in unvented areas. In a large cohort study of over 27,000 people in China, the absolute risk of death from lung cancer was 18–20% among users of smoky coal, compared to 0.5% among users of smokeless coal [127].

Ambient air pollution, especially particulate matter with high amounts of absorbed polycyclic aromatic hydrocarbons and other toxic chemicals, is associated with an increased risk of lung cancer [128]. In a large analysis of 17 European studies, the long-term effect of exposure to particulate matter in the air on lung cancer development was assessed [128]. With both exposure to particulate matter of aerodynamic diameters less than 10 μm and 2.5 μm (PM_{10} and $PM_{2.5}$, respectively), the hazard ratio for developing lung cancer, particularly adenocarcinoma, was increased in a combined cohort population of over 300,000 people. In the US population, for every 10 $\mu g/m^3$ increase in particulate air pollution, there was an 8% increase risk of lung cancer death [129]. Additionally, diesel motor exhaust can increase the risk of lung cancer in a dose-dependent manner [130].

Conclusion

While many factors may influence the development of lung cancer, tobacco use remains the primary etiology of lung cancer in the USA and globally. While lung cancer prognosis is overall improving with earlier detection, lung cancer remains the leading cause of cancer death. In the USA, tobacco use and associated secondhand smoke exposure have dramatically decreased due to successful public health efforts; however, tobacco use remains high globally. Nontobacco smoking is rising, particularly in the USA, where ECs are largely unregulated, and cannabis use is regionally legalized. The impact of this trend is yet to be realized.

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