Review Article

The epidemiology of lung cancer

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Abstract: The incidence and mortality from lung cancer is decreasing in the US due to decades of public education and tobacco control policies, but are increasing elsewhere in the world related to the commencement of the tobacco epidemic in various countries and populations in the developing world. Individual cigarette smoking is by far the most common risk factor for lung carcinoma; other risks include passive smoke inhalation, residential radon, occupational exposures, infection and genetic susceptibility. The predominant disease burden currently falls on minority populations and socioeconomically disadvantaged people. In the US, the recent legalization of marijuana for recreational use in many states and the rapid growth of commercially available electronic nicotine delivery systems (ENDS) present challenges to public health for which little short term and no long term safety data is available.

Keywords: Lung cancer; epidemiology; smoking; e-cigarettes

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Introduction

In the last century carcinoma of the lung has progressed from an uncommon and obscure disease to the most common cancer in the world and the most common cause of death from cancer. In the late 1840s, the British author Hasse could find no more than 22 ever-published cases of lung cancer (1,2). In 1912, Adler identified only 374 published cases (3,4). In the current era, the most recent global statistical analysis estimates 1.8 million new cases were diagnosed worldwide in 2012, with 1.6 million deaths in the same year (5). This is increased from 1.6 million new diagnoses and 1.4 million lung cancer deaths in 2008 (6). Incidence trends and geographical patterns are different for men and women and primarily reflect historical, cultural and regional differences in tobacco smoking (5). In the United States, an estimated 234,030 persons, a little less than a quarter of a million, will be newly diagnosed with lung cancer in 2018 (7). The known risk factors for lung cancer include behavioral, environmental and genetic risk factors, all of which play a part in tumor development and also affect individual patients' capacity for response. The low overall 5-year survival rate for lung cancer has changed only minimally in decades (7-9).

Lung cancer statistics

Incidence

The estimated new cases of lung cancer in the US for 2018 are 121,680 for men and 112,350 for women, for a total of 234,030 (7), the equivalent of 641 lung cancers diagnosed per day. Lung carcinoma is the 2nd most common cancer diagnosis by gender, behind prostate cancer for men and breast cancer for women (7). In 2018, lung cancer accounts for 14% of new cancers in men and 13% of new cancers in women in the US (7).

Age-adjusted lung cancer incidence rates for men in the US have declined per 100,000 population since 1982 (7), reflecting changes in risk behaviors following the

promulgation of information about the risks of tobacco smoking in the 1950s and 1960s and later governmental tobacco control measures. In the last few decades, the incidence rate in men has decreased at twice the decline of incidence in women, due to differences in smoking uptake and cessation (7,10). The incidence rates for US women did not plateau until the early to mid-2000s, and saw a modest decline between 2006 and 2014 (7). It should be noted that while the incidence rates for new lung cancer diagnoses per 100,000 population have trended down, the actual number of incident cases of lung cancer has increased: there were 161,000 new lung cancer cases in 1991 (3,11), compared with an estimated 234,101 new diagnoses in 2018 (7).

Mortality and survival

In the US, a hard-won decline in lung cancer deaths follows decades of tobacco control initiatives. There was a 45% decrease in male lung cancer deaths between 1990 and 2015 and lung cancer deaths in women declined 19% from 2002–2015 (7). Estimates of mortality in 2018 are 83,550 deaths for men and 70,500 for women, around 25% of annual cancer fatalities (7). Lung cancer has one of the lowest survival rates, along with liver and pancreatic cancer. The 5-year relative survival rate for all stages combined was 12% for lung cancers diagnosed from 1975–1977. It is now 18% for new cancer diagnoses between 2003 and 2009 (9,12). Lung cancer is often not diagnosed until advanced stage disease is present, even more so in black Americans compared with white Americans (7,13). Advanced lung cancer has extremely poor prognosis, with a 5-year survival of only 5% (7).

Global trends in lung cancer epidemiology

Lung cancer rates vary around the world, reflecting geographical differences in tobacco use and air quality (12). Worldwide, lung cancer incidence is increasing (5,14). Rates of lung cancer in men are considerably higher in developed countries than in less-developed ones, predominantly related to smoking habits, but overall incidence is decreasing in men from developed countries due to tobacco control policies (12,14). Lung cancer in women is also more prevalent in the developed world and linked with cigarette smoking (12). Worldwide, rates of female lung cancer are increasing (14). For instance, female lung cancer incidence in Europe has been rising for most of the 21st century and in 2017 exceeded breast cancer mortality rates for the first time, 14.6 lung cancer deaths per 100,000 compared with 14 per 100,000 for breast cancer (15). In some regions, particularly Asia, indoor air pollution and occupational exposures play a greater role in female lung cancer (12). Similar to the US, there is significant geographical and ethnic variation in lung cancer incidence and mortality within regions. Higher income countries have comparatively improved survival rates than low income countries (12). Of particular concern for the future is the recent rise of cigarette consumption in countries like China, where 65% of men initiate smoking by their mid-20s, presaging an epidemic of lung cancer in the next few decades (16).

Demographic factors in US lung cancer

Lung cancer incidence and mortality in the US have racial and ethnic disparities as well as geographical differences. They are inversely proportional to the level of education attained by segments of the population. Education levels correlate with socioeconomic factors, including employment opportunities and income. As a result of this entwined set of factors, the burden of lung cancer in the 21st century is disproportionately borne by minorities and those living in poverty. Age and gender also influence patterns of disease.

Race/ethnicity

Non-Hispanic black (NHB) men have the highest incidence at 87.9 per 100,000. Non-Hispanic white (NHW) men and American Indian/Alaska native (AI/AN) have incidences of 75.9 and 71.9, respectively. These are considerably higher than 45.2 per 100,000 for Asian/Pacific Islanders (A/PI) and 40.6 for Hispanic men (7). In US women, incidence rates are highest in NHW, 57.6 per 100,000, and AI/AN, 55.9 per 100,000. Lung cancer is diagnosed in NHB women at a somewhat lower rate, 50.1, which is nevertheless almost twice that of A/PI women, 27.9, and Hispanic women, 25.2 (7).

Nevertheless, substantial variation exists within these broad categories. For instance, lung cancer incidence rates within the Asian population from 2004–2008 are significantly different for Indian and Pakistani men, 30.1 per 100,000, than for Vietnamese men at 73.4 per 100,000 (12). Hawaiian men have an incidence of lung cancer similar to NHW men, even though A/PI rates overall are lower. Within the NHB population, foreign born immigrants have a lower cancer incidence than native African Americans due to divergent smoking habits (7). Cuban Hispanic men have

almost twice the lung cancer mortality of Mexican men, also related to cultural smoking trends (17).

Geography

Geographic patterns in lung cancer diagnosis are also evident, attributable to differences in the percentage of smokers in the population. The incidence of lung cancer in men in the state of Kentucky is 116.3 per 100,000, compared with 73 for the US overall and 32.7 for the lowest state, Utah. The same is true for women; the incidence rate of 79.7 per 100,000 in Kentucky is more than 3 times that in Utah, 24.1. Other states with higher incidence and mortality rates from lung cancer are Mississippi, Arkansas, West Virginia, Tennessee, Alabama and Louisiana (7). The lung cancer mortality rates for women in some Southern and Midwestern states have been reported to be unchanged or even increased despite the overall national trends (18). So far 18 states have declined to expand Medicaid, which is a joint federal and state program for low income individual and families to help with medical expenses; this is leading to reduced access to health care (19).

Education/occupation/income

Cigarette smoking is much more prevalent in individuals with less than a high school education, 32.1%, compared with 9.1% in college graduates (7). Lung cancer incidence is similarly disproportionate by education level. Incidence rates range from 166.6 per 100,000 in men who didn't graduate from high school to 57.6 in college graduates (12). Individuals with more education are less likely to start smoking and more amendable to quitting (12). Smokers with low educations levels are less likely to even attempt to quit (12). Better educated people also have more resources with greater access to healthcare, leading to disparities in mortality and survival (7).

Smoking prevalence is 24% in the active military, and 29% of male veterans are smokers (20,21). Cigarette use in the military is linked with young Caucasian men without college education. Career enlisted individuals are more likely to be heavy smokers than officers (21). Tobacco use is highest in the Army, 37.3%, and Marine Corps, 35.7%. The Air Force has the lowest rate at 23.2% (21). The military services have been specifically targeted by tobacco company advertising (20,22).

Approximately 27.9% of people below the poverty threshold smoke (12). Although there is a strong association between lower income and cigarette smoking, some studies have shown a correlation between lower socioeconomic status and lung cancer incidence regardless of smoking status, suggesting contribution of other environmental factors including housing accommodations and occupational exposures (23,24).

Age

Older age is associated with cancer development due to biologic factors that include DNA damage over time and shortening telomeres. Accordingly, the median age of lung cancer diagnosis is 70 years for both men and women (12). Approximately 53% of cases occur in individuals 55 to 74 years old and 37% occur over 75 years old. The highest incidence of lung cancer in men is 585.9 per 100,000 in 85–89 years old, while the highest incidence in women is 365.8 per 100,000 in 75–79 years old (12). Lung cancer is the leading cause of death by any means in men over 40 years and in women over 59 years of age (7).

Nevertheless, lung cancer is seen in very young adults. Ten percent of cases occur in patients less than 55 years. Studies of non-small cell lung cancer (NSCLC) in patients 20–46 years of age have reported that young lung cancer patients are more likely to be female, to have adenocarcinoma histology, to be non-smokers, and to present at a more advanced stage of disease (25). Young patients usually have few co-morbidities and genetic factors are thought to play a large role in this patient population. Younger patients are more likely to receive more aggressive treatment at all stages of the disease and to have improved survival at every stage, although this margin is very small for advanced disease (25).

Gender

Historically more men than women smoke tobacco and have higher rates of incidence and mortality. Women took up smoking at a later period, mostly after the Second World War, and their rates of cessation have lagged behind those of men, leading to a much later peak in lung cancer incidence in women (7). Height at maturity has been reported to be linked with invasive cancer diagnosis and may be a factor in gender disparity (26).

There are conflicting data regarding the possibility that women may be more susceptible to developing lung cancer (27). There is a higher rate of lung cancer in non-smoking women compared with non-smoking men, a

higher proportion of epidermal growth factor receptor (EGFR) mutations in female NSCLC, and a higher incidence of adenocarcinoma with lepidic features in women (28,29). Some genetic mutations found to be more common in female smokers may predispose toward lung cancer development in women, including over-expression of the *CYP1A1* gene, mutation of the glutathione S-transferase M1 enzyme, mutations of the *p53* tumor suppressor gene, and over-expression of X-linked gastrin-releasing peptide receptor (27-29). Women also have a higher family risk of lung cancer, even adjusting for smoking status (30).

The question of hormonal influence is also debated. Estrogen receptor (ER)α, which is not present in normal lung tissue, has been shown to be overexpressed in lung adenocarcinoma of women, but some studies also demonstrate overexpression in cancers of men (27). One study has found that estradiol promoted growth of female but not male adenocarcinoma cells *in vitro* (31). Anti-estrogen compounds have been shown *in vitro* to have anti-tumor effects (30). Other variables studied include parity, age at menarche, length of menstrual cycle, age at menopause, and exogenous hormone replacement therapy, in some cases with conflicting results (30,32).

Overall, women have some unique risk factors for lung cancer compared with men, and lung tumors in women have different pathologic behavior, outcomes and prognosis in comparison with lung cancer in men (30).

Lung cancer incidence in transgender men and women has not yet been addressed. Transgender adults have higher prevalence of cigarette smoking than the general population, 35.5% (33,34). Lesbian, Gay, Bisexual, Transgender, Queer or Questioning (LGBTQ) adolescents are reported to have equally high smoking rates as well as earlier smoking initiation (35). Questions about the role of endogenous and exogenous hormones in lung cancer in cisgender women will also need to be examined for this population group.

Behavioral risk factors for lung cancer

Tobacco and smoking: historical perspective

The use of tobacco cigarettes is the single greatest risk factor in the development of lung cancer, with up to 90% of lung cancers attributed to smoking. An understanding of this causal relationship developed only slowly and gradually, not least because of the decades-long latency period between smoking initiation and lung cancer occurrence (16). Prior to the 20th century, tobacco had been used for centuries without significant disease burden (16). In the pre-Columbian Americas, tobacco was used primarily for medicinal and ritual purposes (36,37). Tobacco was brought to Europe at the end of the 15th century and utilized in various forms including snuff, pipes and cigars. Cigarettes were, until the late 19th century, expensive, hand-rolled, and not considered acceptable in polite society or around women (16,38,39).

Several technological developments in the mid to late 1800s precipitated the increased popularity and wide use of cigarettes. Flue curing of tobacco, which was introduced in the 1840s, produced a higher sugar content in dried tobacco with a smoother smoke that was easier to inhale. The safety match was invented in 1844, creating a quick and convenient method of lighting a cigarette. The automated cigarette rolling machine was invented in 1880 and the improved capacity for production led to a decline in prices and mass availability (16,40).

Cigarette smoking increased dramatically in the US and Europe during the world wars, first in men and then in women. Soldiers were given free cigarettes and developed a nicotine habit, subsequently bringing the practice back home at the end of the war (16). At that time, there was no detailed knowledge of harmful effects from tobacco smoking or understanding of nicotine addiction, and many healthcare professionals smoked. Some authors suggested a link between cigarette smoking and the increasing cases of lung cancer in the 1920s and 1930s, but these reports did not have a tangible effect on consumption (2,41-47). Major epidemiological studies published in 1950 by Doll and Hill (48) and Wynder and Graham (49) definitively established that cigarette smoking causes lung cancer; additional confirmatory studies followed. Subsequently, reports were issued by the Royal College of Physicians in Great Britain in 1962 and the US Surgeon General in 1964 to warn the public about the dangers of smoking (50,51). Concerted efforts since the 1960s to decrease tobacco consumption have had success in reducing the percentage of smokers in the US population, from 42.4% of the adult population in 1965 to 15% in 2015 (52,53). The absolute number of tobacco users in the US was 48.1 million in 1970 (54), 42.1 million in 2012 (55), and 37.5 million in 2015 (53). An estimated 6.8 million people in the US meet eligibility criteria for lung cancer screening, although only 4% of them have pursued it (7,56). This may be at least partly because of the concentration of current smokers within groups of lower socioeconomic status (7) and the inverse relationship between socioeconomic standing and participation in medical screening programs (57,58).

Tobacco and smoking: carcinogenesis

The addictive component of tobacco is nicotine, a natural alkaloid that acts as an acetylcholine agonist and binds to nicotinic acetylcholine receptors (nAChR) in the nervous system, causing release of neurotransmitters into the blood stream, including dopamine, serotonin, norepinephrine, endorphins, and gamma-aminobutyric acid (GABA). While nicotine itself is not a carcinogen, it upregulates nicotinic receptors and produces alterations in gene expression that foster tobacco dependence and is associated with progression of existing lung tumors (59-61).

Tobacco combustion produces at least 60 known carcinogens. The most significant are polycyclic aromatic hydrocarbons (PAH), including benzo[a]pyrene; nitrates; and tobacco-specific N-nitrosamines (TSNAs), such as 4-(methylnitrosamino)-1-(13-pyridyl-1-butanone) (NNK) (62,63). Tobacco smoke has a vapor phase and a particulate phase, which respectively produce 10^{15} and 10^{17} free radicals per gram (61). The mechanisms of carcinogenesis from tobacco include formation of DNA adducts by carcinogens and their metabolites as well as free radical damage (64). While tar emissions and the amount of benzo[a]pyrene have decreased in cigarette smoke over several decades, there is no convincing evidence that lower tar cigarettes have improved safety (65). Meanwhile, the concentration of nitrates and TSNAs in cigarettes has increased since 1978 (62). Laboratory studies have demonstrated the relationship of NNK to lung cancers, specifically adenocarcinomas (66). The amplified concentration of NNK in tobacco smoke likely correlates with the increase in lung adenocarcinomas relative to squamous non-small cell lung cancer in recent decades.

Menthol as a cigarette additive has been in use since the 1920s. Menthol cigarette advertising in the US has been directed particularly toward women, African Americans and youth (67,68). Menthol, a derivative of the peppermint plant, has the effect of decreasing irritation of mucosal tissues in the hypopharynx and lung as well as producing a minty flavor (69). In addition to making cigarette smoke more palatable, it affects nicotine binding to nicotinic acetylcholine receptors and it upregulates expression of nicotinic cholinergic receptors, producing increased addiction and reduced ability to quit (70,71). Up to 90% of the tobacco merchandise currently on the market contains some percentage of menthol, even if not marketed as a menthol-containing product (67,68).

Other smoking products

Cannabis sativa

In 2013, marijuana was the most commonly used illegal substance in the US, with up to 12% of adolescents and adults admitting use (72). The number of users is likely to increase as states legalize personal recreational use of the drug. At this moment, the states of Maine, Massachusetts, Colorado, Washington, Oregon, Nevada, California, Alaska and Vermont and the District of Columbia permit recreational marijuana use. Medical marijuana is legal in up to 30 states. Studies on the health effects of marijuana, including risk for lung cancer, have been limited due to previous illegal status and the confounding effects of frequent combined use with tobacco (73,74).

The main psychoactive ingredient in cannabis, Δ^9-tetrahydrocannabinol (THC), is not known to be carcinogenic but like nicotine, produces addiction. Up to 17% of people who initiate marijuana in their teens will become dependent, and an estimated 25–50% of daily smokers are addicted (72,75). Also similar to nicotine, there is evidence that THC has a deleterious effect on adolescent brain development (72). The constituent percentage of THC in marijuana products has been increasing over the last 20 years (72). There is an association between marijuana smoking and initiation of tobacco use in young people (76-78).

The combustion of organic material while smoking marijuana does produce carcinogenic substances. The tar levels in marijuana smoke are much higher than those in tobacco, as are the concentrations of polyaromatic hydrocarbons (73,79-81). Inhalation of marijuana smoke causes inflammation of the distal airways with subsequent release of cytokines. There is evidence that marijuana produces molecular histologic changes to the bronchial epithelium that mimic those of tobacco use and are known to be premalignant (80,82,83).

Some case controlled studies in 3 North African countries have suggested a 2.4-fold increased risk for lung cancer in men after adjusting for tobacco smoking and occupational exposures (73). A case control study in New Zealand found a 5.7-fold increased risk of lung cancer in the highest one-third of marijuana consumers, after adjustment for confounding variables (80). Epidemiologic studies to date have not found a strong association between cannabis use and lung cancer (84,85). However, it has been noted that the relatively low prevalence of marijuana use pre-

legalization is similar to that of tobacco prior to the 20th century and that impending industrialization of marijuana in the US may have unforeseen consequences (86).

Electronic nicotine delivery systems (ENDS)

Electronic technology for delivery of nicotine to the lung epithelium via an electronic device became available for sale in 2007. The basic mechanism consists of a battery-operated heating coil that heats fluid contained in a replaceable cartridge, usually a mixture of flavorings, a solvent, and liquid nicotine (87). When evaporated, this produces an aerosol vapor that is inhaled by the smoker, or vaper. Nicotine-containing aerosols can achieve peak serum nicotine levels in under 5 minutes (87). ENDS, also called electronic cigarettes or e-cigarettes, have evolved at a rapid rate in the last decade, with 466 brands and thousands of flavorings available as of 2014 (87,88). The diversity of available products as well as individual variations in vaping practices have made it difficult to effectively evaluate the safety of these devices and their use. The disparity in content and quality of the cartridges, especially, is substantial (89,90).

ENDS products are currently unregulated in the US except with respect to mandatory age and photo ID checks to prevent sales to minors. In 2016, the US Food and Drug Administration (FDA) claimed jurisdiction and regulatory authority over the manufacture, promotion, sale and distribution of ENDS and associated merchandise as newly deemed tobacco products. However, in 2017 the compliance dates for these regulations were extended to 2021–2022, and the registration of entities that manufacture, prepare, compound, or process a newly deemed finished tobacco product now applies only to those corporations that commence those activities on or after August 8, 2016 (91,92).

The prevalence of ENDS usage is 3.2% of adults in 2016. ENDS users fall into three categories: current smokers who use them as an intentionally transitory cigarette smoking cessation device, current smokers who practice continued use and dual use, and previous non- smokers of traditional tobacco (87). The last category is particularly prevalent in young adults; 40% of e-cigarette users between the ages of 18–24 were not previous smokers (93).

Randomized controlled trials have found that e-cigarettes containing nicotine are more effective for smoking cessation than e-cigarettes that do not contain nicotine (94). However, there is no proven benefit over other cessation aids with nicotine (87,95). Dual use is defined as the continued smoking of traditional tobacco cigarettes and electronic cigarettes; there is no evidence of health benefit (87,95). Smokers who converted to exclusive ENDS use were evaluated in a 2-year study that reported no significant adverse events within a 24-month period after switching to an electronic cigarette with nicotine (96). However, there is a lack of short- or long-term safety data. The particles in e-cigarette vapor are different from those in traditional tobacco cigarettes, but available data suggests that formaldehyde, acetaldehyde and reactive oxygen species are present in sufficient concentrations to cause inflammatory damage to the airway and lung epithelium. Microscopic particles from e-cigarettes can deposit in the distal bronchioles or alveoli (87). E-cigarette aerosol can also contain polycyclic aromatic hydrocarbons, nitrosamines, and trace metals, although concentrations vary (97). Further, nicotine is present in e-cigarette vapor and can cause new addictions in users who are not already smokers (98).

The rise of ENDS use in previous non-smokers is predicated on consumer understanding of the devices as "safer". Television and magazine advertisements for e-cigarettes utilize traditional marketing ploys of the tobacco industry, such as appeals to freedom, courage and individuality (99). Most troubling is the 900% increase in e-cigarette use in high school students between 2011 and 2015, with over 2 million middle and high school students using ENDS in 2016 (93,100,101). There is evidence that nicotine can damage brain development in adolescents (98). People with depression and anxiety are reported to have higher rates of ENDS usage and may also be a vulnerable population (87). Other at risk populations include rural, low income and LGBTQ individuals (100). Recent studies have shown that use of ENDS and other tobacco products by adolescents and young adults is independently associated with smoking of traditional tobacco cigarettes within a year (102,103).

The recommendations of the CDC at this time with regard to electronic cigarettes are that non-pregnant adult smokers may benefit from ENDS use when completely substituted for previous tobacco habits. E-cigarettes are considered not safe for adolescents, young adults, pregnant women and non-smokers (93).

Environmental risk factors for lung cancer

Radon

An association between mining and lung disease has been known in Europe since the 15th century, when miners in

the Erzgebirge mountain range along the Germany-Czech border suffered high incidence and mortality from what was then known as *bergkrankheit*, or mountain disease. Mines in that part of the world produced copper, iron, silver, cobalt, arsenic, bismuth, and, in the 20th century, radium. We now know that the German and Czech mining population had extremely high rates of lung cancer, mostly squamous cell carcinoma (3). In the modern medical era, epidemiologic studies of underground workers in uranium mines have provided the framework for our understanding of radon exposure as a cause of lung cancer (104-106).

Residential radon from soil accounts for the second most common risk factor for lung cancer, estimated 10% of cases (106). Radon is a naturally occurring radioactive gas produced by uranium decay in the earth's crust. It emits alpha particles, decaying to polonium and then bismuth. The average environmental concentration of radon is 0.2pCi/L (107), but indoor levels can be quite variable depending on soil composition, building foundations and ventilation. Radon can accumulate to unsafe levels in basements and lower building levels (106,108). The US Environmental Protection Agency provides resources for assessing and reducing radon levels in homes. Radon exposure in underground workplaces is regulated in the US (107). Concurrent tobacco smoking increases the relative risk of lung cancer from radon (106,109).

Asbestos

Occupational exposure to carcinogens is estimated to account for 5–10% of lung cancers (69,110-112). Of these, asbestos is the most common. A naturally occurring silicate mineral, asbestos has amphibole (amosite, crocidolite, trenolite) and serpentine (chrysotile) subtypes, and the use of asbestos in construction has been ongoing since the 19th century. Chrysotile fibers have the greatest association with thoracic malignancies (107). Occupational exposure to asbestos correlates with a 5-fold excess risk of lung cancer (69). Asbestos exposure and tobacco smoking have a synergistic effect on the risk for lung cancer (107).

Pollution and air quality

Ambient air quality was suggested as a potential risk factor for lung cancer as early as the 1920s (41). There are two main areas of concern for both outdoor and indoor air quality: carcinogens produced by combustion of fossil fuels and particulate matter in the air (69). Atmospheric carcinogens in the outdoor environment can include PAH, sulfur dioxide and trace metals (69,113). The risk of lung cancer is elevated in occupations that have prolonged exposure to these elements. In this regard, occupational exposures in the trucking industry, for instance, are associated with up to 50% increase in the relative risk of lung cancer (107).

Particular matter in the air increased with industrialization and it began to be regulated in the 1950s (107). The US Environmental Protection Agency in 1997 increased the legal limits on fine particles less than 2.5 μm in diameter ($PM_{2.5}$) due to evidence of adverse health effects at even low levels of particulate concentration in the air (114). A study of large urban environments in the US found a 40% increased risk of lung cancer in the 6 US cities with the highest levels of particulate matter (69). The risk of lung cancer from fine particulate pollution is increased regardless of smoking status, and the association is greatest in nonsmokers. These is also a correlation with lower levels of education which may influence housing options (114). Particulate matter has been designated a Group I carcinogen by the International Agency for Research on Cancer (IARC) (115). The risk of lung cancer from pollution is potentiated with tobacco smoking.

Indoor air pollution from the use of unprocessed fossil fuels such as soft coal and biomass fuels, which include wood, other plant-based materials and solid waste, for heating and cooking is implicated in lung cancer risk, primarily in the developing world. In some parts of Asia it is linked with lung cancer in never smokers (69,116,117). Studies have shown that proper ventilation of previously unvented cooking areas can reduce the risk of lung cancer by 50% (69).

Second hand, or side-stream, tobacco smoke is also an environmental pollutant with a dose response relationship between exposure and lung cancer risk (118). The carcinogens in side-stream smoke include PAH, nitrosamines and aromatic amines. Benzo[a]pyrene concentrations are 4 times higher in side-stream smoke compared with filtered mainstream cigarette smoke (119). Studies have shown the presence of nicotine and its metabolite cotinine as well as DNA adducts from tobacco carcinogens in the urine of nonsmokers with passive exposure to tobacco smoke (119). Nonsmoking spouses of smokers have a 20–30% increased risk for developing lung cancer (119-121). The US Surgeon General has declared that there is no safe level of exposure to second hand tobacco smoke (118).

More recently, questions of second hand exposure to e-cigarette vapor have arisen. While some studies of simulated indoor air quality with ENDS have found no significant levels of chemicals in the environment (122), a non-simulated real life evaluation of indoor air quality at a vaping convention found high levels of air nicotine, particulate matter, total volatile organic compounds (TVOCs), and carbon dioxide in the air that raises concerns for workers and others exposed to second hand vapor (123). Serum cotinine levels in non-smokers from e-cigarette vapor were comparable to those exposed to second hand cigarette smoke in a recent study (124). The US Surgeon General has determined that second-hand e-cigarette aerosol contains harmful and potential harmful components and urges the inclusion of ENDS in comprehensive smoke-free regulations to both reduce involuntary environmental exposure and prevent re-standardization of tobacco use (98,125). To date, very few states have included e-cigarettes in such laws (125).

Infection

Damage to the lung from inflammation and infection is implicated in carcinogenesis. In the past, infections such as tuberculosis conferred an odds ratio up to 1.76 for the development of lung cancer, irrespective of smoking status and with considerable latency (126). There is decreased prevalence of TB in the developed world.

Lung cancer is the most common non-AIDS defining malignancy in people with HIV infection (127). In the era of more effective antiretroviral therapy, lung cancer has become the leading cause of mortality in HIV-infected patients, accounting for nearly 30% of cancer deaths (128). Despite the increased lung cancer incidence with highly active antiretroviral therapy (HAART) (129), there is no evidence that antiretroviral medication itself increases the risk (69). The HIV virus also has not been implicated in oncogenesis, but studies suggest that immunosuppression plays a role, as HIV patients and organ transplant recipients have similarly increased rates of cancer (130). Declining CD4 counts are associated with a higher rate of lung cancer (131). The higher smoking prevalence in the HIV population, with 42% current cigarette smokers in HIV-positive adults in 2009, may be a contributing factor (132). Nevertheless, HIV-infected individuals have a 2.5-fold increased risk of lung cancer regardless of smoking status (69). Lung cancer patients with HIV have lower levels of cigarette smoking and present at younger ages than the general population, are diagnosed at more advanced stages, and have lower survival than the general population (69,128,133,134).

Genetic risk factors for lung cancer

Not all tobacco users develop lung cancer, reinforcing a genetic susceptibility to lung malignancy. A positive family history for lung cancer has been associated with a 1.7-fold increase in risk of lung cancer development (135). Some studies have shown lung cancer risk is increased 2 to 4 times in first degree relatives of lung cancer patients, controlled for personal smoking history (136,137).

Genome wide association studies (GWAS) have associated chromosome regions 5p15, 15q25-26 and 6q21 with increased risk for lung cancer (138,139). The 5p15 region encodes telomerase reverse transcriptase (TERT), involved in cell replication. In the development of lung cancer, it is associated with adenocarcinomas in smokers and nonsmokers (140). Mutations at the 15q25-26 chromosome locus are positively linked to both nicotine dependence and susceptibility for lung cancer (141). Chromosome locus 6p21 regulates G-protein signaling, and variants confer markedly increased risk on never-smokers (142). GWAS in the Han Chinese and Japanese populations have also found a locus at 3q28, among others, linked with increased lung cancer risk (138).

Tumors acquire intrinsic genetic driver mutations, most of which involve cell signaling pathways including the ErbB protein family (EGFR/HER1-4) and the GTP-ase Kirsten rat sarcoma virus (*K-ras*) gene (139). Mutations rarely occur in the same signaling pathway (143). Other genetic and epigenetic changes can cause inactivation of tumor suppressor genes such as *p53*, *p16* and *PTEN* (139). Some mutations have consistent associations with lung tumor histology; for example, EGFR and EML4-ALK mutations are associated with adenocarcinomas in nonsmokers (139).

Lung cancer in never smokers (LCINS)

Lung cancer in nonsmokers is a major cause of mortality, now the 7th leading cause of cancer deaths (30). It accounts for approximately 10–15% of lung cancer cases in the US (144). The proportion of LCINS has increased in recent years, even after controlling for gender and race or ethnicity (144). Worldwide, it is estimated that 25% of lung cancer patients are never smokers (145). LCINS occurs predominantly in women and younger patients.

The histology is most likely to be adenocarcinoma, often with specific driver mutations like EGFR mutation and ELM4-ALK fusion protein which respond well to targeted therapy (139,145,146). The proportion of female LCINS cases is particularly high in East and South Asia, where 60–80% of women with NSCLC are never smokers (116,117,147). In the US, African American nonsmokers are more likely to develop lung cancer than Caucasian nonsmokers (116).

Environmental risk factors are reported to play a predominant role in LCINS, including second hand smoke exposure, environmental particulate matter, occupational exposures, indoor air pollution, and radon (115,148). Some studies suggest up to 30% of lung cancers in non-smokers are caused by residential radon exposure (149). Genetic susceptibility is also a factor, including genes associated with metabolic syndrome (145,148).

Conclusions

Smoking prevalence and lung cancer incidence have decreased in the US over the last several decades as a result of committed tobacco control policies. However, the morbidity and mortality of the tobacco epidemic remain high in the US, and the global epidemic has just started. The history of modern tobacco smoking and the slow and reluctant understanding of its long-term fatal effects should provide a cautionary tale for the healthcare profession as we attempt to understand the safety and potential delayed consequences of marijuana smoking and e-cigarette vaping, both of which are gaining in popularity, access and consumption.

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