Cancer Progress and Priorities: Lung Cancer

Matthew B. Schabath[1,2,*], **Michele L. Cote**[3,4]

[1]Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida USA

[2]Department of Thoracic Oncology; H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida USA

[3]Wayne State University School of Medicine, Department of Oncology, Detroit, Michigan, USA

[4]Barbara Ann Karmanos Cancer Institute, Detroit, Michigan, USA.

Background

In the United States, lung cancer is the second most common diagnosed cancer and the leading cause of cancer-related death. Though tobacco smoking is the major risk factor accounting for 80 to 90% of all lung cancer diagnoses, there are numerous other risk factors that have been identified as casually associated with lung cancer etiology. However, there are few causally-linked risk factors for lung cancer diagnosed among never smokers which, if considered a unique reportable category, is the 11th most common cancer and the 7th leading cause of cancer-related death. Lung cancer survival has only marginally improved over the last several decades, but the availability of screening and early detection by low-dose computer tomography and advances in targeted treatments and immunotherapy will likely decrease mortality rates and improve patient survival outcomes in the near future.

Keywords

Lung cancer; epidemiology; statistics; disparities; risk factors; prevention early detection; lung cancer screening; epidemiology of lung cancer

Descriptive Epidemiology

Incidence

Globally, lung cancer has been the most common diagnosed cancer for the last several decades [1, 2]. In 2018, there was an estimated 2.1 million new lung cancer diagnoses accounting for 12% of the global cancer burden [1, 2]. Among men, lung cancer remains the most common cancer diagnosis with approximately 1.37 million diagnoses in 2018, with the highest incidence rates in Micronesia (54.1 per 100,000), Polynesia (52.0 per 100,000), Central and Eastern Europe (49.3 per 100,000) and Eastern Asia (47.2 per 100,000). Among

*Corresponding Author: Matthew B. Schabath, Ph.D., H. Lee Moffitt Cancer Center and Research Institute, 12902 Magnolia Drive MRC-CANCONT, Tampa, FL 33612, Fax: (813) 745-6525 | Matthew.Schabath@Moffitt.org.

women, incidence rates are generally lower than men with approximately over 725,000 new lung cancer diagnoses in 2018. Geographical variations in incidence rates differ for women compared to men (Figures 1a and 1b) which are attributed to historical differences in cigarette smoking. Among women, the highest incidence rates occur in North America (30.7 per 100,000), Northern Europe (26.9 per 100,000), and Western Europe (25.7 per 100,000).

In the United States, lung cancer is the second most common cancer in men after prostate cancer and the second most common cancer in women after breast cancer [3, 4]. In 2019 an estimated 228,150 new cases of lung cancer are expected. The incidence rate among men is 71.3 per 100,000 and for women it is 52.3 per 100,000. Although the incidence rate has been declining in men since the mid-1980s, incidence rates did not start declining for women until the mid-2000s because of historical sex-specific differences of smoking uptake and cessation. The decline in incidence has gained momentum in the past decade with rates decreasing from 2011 to 2015 by nearly 3% per year in men and 1.5% per year in women. Geographically, lung cancer incidence is higher the Midwest, East, and South with highest rates observed in the South for both men and women (Figures 2a and 2b).

Mortality

The global geographical patterns in lung cancer deaths closely follow those in incidence because of poor survival and the high fatality rate of this disease (Figure 3a and 3b). Worldwide, lung cancer is the leading cause of cancer death in men and the second-leading cause in women. In 2018, with an estimated 1.8 million deaths occurred (1.2 million in men and 576,100 in women), accounting for 1 in 5 cancer deaths worldwide [1, 2]. The geographical variations by country/region and between men and women are largely attributed to historical patterns in tobacco smoking and maturity of the tobacco epidemic [2].

In the United States, lung cancer is the leading cause of cancer-related death among both men and women [3, 4]. In 2019, an estimated 142,670 deaths are expected to occur, or about 23.5% of all cancer deaths. The mortality rate among men is 51.6 per 100,000 and 34.4 per 100,000 for women. Due to reductions in smoking, the lung cancer death rate has declined 48% since 1990 in men and by 23% since 2002 in women. From 2012 to 2016, the death rate dropped by about 4% per year in men and 3% per year in women. Geographically, lung cancer mortality follows a pattern similar to incidence including the highest rates observed in the South (Figures 4a and 4b).

Survival—Despite substantial improvements in survival in recent years for most other cancer types in the United States, there have only been small improvements in 5-year survival among patients diagnosed with lung cancer (Figure 5). This lack of improvement is primarily due to the majority of patients are diagnosed with last stage disease where the survival rates are dismal (Figure 6). The five-year relative survival rate for all lung cancers (non-small cell lung cancer [NSCLC] and small cell lung cancer combined) is 19% and the five-year survival is higher for non-small cell lung cancer (23%) than small cell lung cancer (6%) [3, 4].

Despite the high mortality rates and poor survival outcomes associated with a lung cancer diagnosis, the next-generation of targeted therapies and the emergence of immune

checkpoint inhibitors have demonstrated durable long-term survival in subsets of patients. As such, these therapies may hold the key in improving lung cancer patient outcomes leading to curable lung cancer among early-stage diagnoses and a chronic and manageable disease for patients with advanced and metastatic disease.

Histological Classification—Lung cancer tumors are divided into two broad histological categories: non-small cell lung carcinoma (NSCLC) and small-cell lung carcinoma (SCLC). NSCLC represents more than 80 to 85% of lung cancers of which approximately 40% are adenocarcinoma, 25 to 30% are squamous cell carcinoma, and 10 to 15% are large cell carcinomas (Figure 7) [5-7]. Bronchioloalveolar carcinoma (BAC) was a distinct histologic classification representing a sub-group of adenocarcinomas and has been replaced with adenocarcinoma *in situ*, minimally invasive adenocarcinoma, and invasive adenocarcinoma of the lung [8]. Other less common histologic subtypes include adenosquamous carcinoma, pleomorphic sarcomatoid carcinoma, large cell neuroendocrine carcinoma, and carcinoid tumor.

Among women, adenocarcinoma has been the most frequently diagnosed histological subtype since at least the 1970s (Figure 8a). Among men, the incidence rate of lung adenocarcinoma has been on the rise since the 1970s and the incidence rate for lung adenocarcinoma surpassed squamous cell carcinoma around 1994 (Figure 8b). The incidence rate for squamous cell carcinomas has been on the decline since the early 1980s. This temporal shift in histological diagnoses is largely attributed to the widespread use of filtered cigarettes and increasing amounts of tobacco-specific nitrosamines in tobacco [9]. Regarding the former, earlier in the 20th century, most mass-produced cigarettes were non-filtered which discouraged deep inhalation and combusted tobacco smoke exposed primarily the trachea and bronchus resulting in observed higher rates of squamous cell carcinoma diagnoses especially among men [10]. When filtered cigarettes were introduced, combusted tobacco smoke dispersed deeper into the respiratory tree due to deeper inhalation resulting in adenocarcinomas with a more peripheral distribution [11]. The introduction of so-called "light" filtered cigarettes and changing tobacco blends, which decreased nicotine but increased nitrate and N‑nitrosamines, had the paradoxical effect of increasing, rather than decreasing, lung cancer risk due to promotion of deeper and more frequent inhalation of combusted tobacco smoke [10, 11].

Although the binary division of lung cancer into NSCLC and SCLC is still widely applied and relevant, advances in genomic profiling has resulted in a paradigm shift whereby lung cancers are also characterized and classified by tumor biomarkers and genetic alterations, such as gene expression, mutations, amplifications, and rearrangements (Table 1), that are critical to tumor growth and survival and can be exploited with specific targeted agents or immune-checkpoint blockades [12-14].

Disparities

Males vs. females: Though the terms "sex" and "gender" have been historically interchangeable in medical research, their uses are distinct as sex is conventionally based on anatomy and physiology while gender typically refers to identity, behavior, or socially

constructed roles. As such, research in potential lung cancer disparities has not disentangled sex vs. gender. Nonetheless, the established differences in lung cancer incidence and mortality rates between males and females are attributed to historical patterns in tobacco smoking as noted above. To address potential sex-specific differences in lung cancer risk, O'Keeffe *et al* [15] conducted a systematic review and meta-analysis of prospective cohort studies on the sex-specific association of smoking with the risk of fatal and non-fatal lung cancer. By restricting the analyses to cohort studies, the goal was to minimize bias often present in case-control studies. Data from 99 cohort studies representing more than 7 million individuals and over 50 000 incident cases of lung cancer found no evidence for sex-specific differences for risk of smoking-related lung cancer. Specifically, the authors reported a pooled adjusted lung cancer relative risk of 6.99 for females and 7.33 for males and found no evidence of publication bias or differences across major pre-defined participant and study subtypes. The female-to-male ratio of relative risk was 0.99, 1.11, and 0.94, for light, moderate and heavy smoking, respectively. The authors acknowledge that "…*these data may yet underestimate the true relative risk of smoking-related lung cancer in women, given later uptake and lower intensity of smoking in women.*"

Regarding sex-specific lung cancer among never smokers, there is compelling historic evidence [16-18] that suggests a higher risk, incidence, and mortality among never-smoking females versus never-smoking males. Conversely, a multi-institutional registry-based study [19] of over 12,000 lung cancer patients found that the proportion of lung cancer patients who reported themselves as never smokers increased over time, but the observed increase was independent of sex.

Race and Ethnicity: Racial and ethnic differences in lung cancer incidence, mortality, and survival outcomes are well-documented and are largely attributed to inequalities in wealth (i.e., socioeconomic status) leading to differences in risk factor exposures and barriers to high-quality prevention, early detection, and treatment [4]. Analyses from the American Cancer Society [4] revealed that lung cancer incidence for non-Hispanic Black men (85.4 per 100,000) is higher than non-Hispanic White men (74.3 per 100,000) and Hispanic men (39.2 per 100,000). However, the incidence for non-Hispanic Black women (49.2 per 100,000) and Hispanic women (24.6 per 100,000) are lower than non-Hispanic White women (57.4 per 100,000). Similar trends were noted for lung cancer mortality. Black lung cancer patients (16%) have overall lower 5-year relative survival rate than Whites (19%) which is consistent for localized (52% vs. 56%) and regional disease (27% vs 30%), but not for distant disease (5% vs. 5%). Black lung cancer patients are more frequently diagnosed with distant disease compared to White patients (61% vs. 57%) and less frequently diagnosed with localized disease (13% vs. 17%).

Socioeconomic Status: Socioeconomic status (SES) is a broad term for the social standing or "class" of an individual or group of people and is often measured based on highest attained education, income, and occupation. SES is associated with health and disease through multiple interacting pathways in terms of resources, physical and psychosocial stressors, and health-related behaviors and risk factors. SES is strongly associated with some lung cancer risk factors including tobacco smoking behavior, whereby uptake may be higher

among those with low SES and quit attempts are less likely to be successful [20]. Results from the American Cancer Society found that cancer mortality is 28% higher overall in poor counties than affluent counties in the United States and >40% higher among men in poor counties [4]. A pooled analysis of 17,021 cases and 20,885 controls found, after adjusting for smoking, low SES based on International Socio-Economic Index was associated with an 84% increased risk of lung cancer among men and a 54% increased risk among women [21]. Lung cancer risk was still elevated but somewhat attenuated when SES was assessed using the European Socio-economic Classification. The authors concluded that the strong associations emphasizes the need for further exploration of the pathways from SES to lung cancer and "*clarifying these pathways could then contribute to further understanding of lung cancer etiology and shape prevention approaches*".

LGBTQ Individuals: The lesbian, gay, bisexual, transgender, and queer/questioning (LGBTQ) community, also referred to as sexual and gender minorities, is a diverse and medically underserved population that has been historically marginalized [22-25]. The sparse but growing body of evidence demonstrates the LGBTQ population may an ignored epidemic [26] associated with increased risk and poorer outcomes for certain cancers including lung cancer [27-32]. Prior studies linking Surveillance, Epidemiology and End Results (SEER) data with the United States Census [31] and California Cancer Registry with the California Health Interview Survey [30] provided evidence that gay men have higher incidence and mortality rates for lung cancer and lesbian females have lower incidence and mortality rates from lung cancer compared to the general population. In the bisexual community, men have a lower incidence of lung cancer, whereas bisexual women have higher incidence of lung cancer. The lung cancer disparities among LGBTQ individuals may be attributed, in part, to higher prevalence of tobacco smoking among this population [33-35]. To date there are no published risk estimates for the association between tobacco smoking and lung cancer among LGBTQ individuals. Another potential risk modifier is HIV infection where gay and bisexual individuals account for over 67% of all HIV diagnoses [36] and incidence of lung cancer among HIV-infected patients is significantly higher than the general population [37]. HIV and lung cancer is discussed below.

Risk Factors—A summary of causative and putative lung cancer risk factors that are discussed below are summarized in Table 2.

Tobacco smoking: Unequivocally, tobacco smoking is the most important and prevalent lung cancer risk factor. A rare disease at the beginning of the 20th century, lung cancer was one of the first diseases to be causally linked to tobacco smoking [38]. Throughout most of the 20th century in the United States, lung cancer incidence and mortality increased as the *per capita* in cigarette consumption increased (Figure 9) and as successive generations of first male and then female smokers began smoking at earlier ages. Men predominantly began smoking manufactured cigarettes earlier in the 20th century, during and after World War II. Though few women smoked regularly before World War II, average age at initiation continued to decrease and per capital in cigarette consumption increased through the 1960s [39]. Tobacco consumption fell drastically in the United States following publication of the

landmark 1964 U.S. Surgeon General's Report that concluded cigarette smoking is causally related to lung cancer in men [40].

Tobacco smoke contains more than 7,000 chemicals including at least 69 established carcinogens and other toxicants associated with major diseases [20]. Although only around 15% of smokers develop lung cancer, 80 to 90% of lung cancer diagnoses are attributed to tobacco smoking in the United States [3]. The relative risk of lung cancer is estimated to be about 20-fold higher than that of a lifetime never smoker and the magnitude of lung cancer risk is related to smoking intensity (i.e., cigarettes smoked per day and number of years smoked) [40-42]. Numerous lung cancer risk models [43-48] are available as web-based tools [49] that provide risk assessment based on demographic information including smoking history and intensity.

Exposure to secondhand smoke: Secondhand smoke, or side-stream smoke, is an indirect carcinogenic exposure resulting from the burning of tobacco products. From 1988 to 2014, secondhand smoke exposure among never smokers in the United States significantly declined from 87.5% to 25.2% attributed to tobacco control efforts and smoke-free laws and policies in workplaces and public places [50]. However, there has been no change in secondhand smoke exposure between 2011 to 2012 and between 2013 to 2014 with an estimated 1 in 4 never smokers, or about 58 million people, exposed to secondhand smoke from 2013 to 2014 [50]. Carcinogens that have been measured in secondhand smoke include polycyclic aromatic hydrocarbons, nitrosamines, and aromatic amines. Studies have shown that nicotine and its metabolite cotinine as well as DNA adducts from tobacco carcinogens are present the urine of never smokers who are exposed to secondhand smoke [51]. A 2006 report from the United States Surgeon General on *The Health Consequences of Involuntary Exposure to Tobacco Smoke* [52] concluded there is no safe level of exposure to secondhand tobacco smoke and stated, "*The evidence is sufficient to infer a causal relationship between secondhand smoke exposure and lung cancer among lifetime nonsmokers. This conclusion extends to all secondhand smoke exposure, regardless of location.*" A meta-analysis published in 2018 of twelve studies found that secondhand smoke exposure compared to never smokers without such exposure was associated with a 25% increased risk of lung cancer [53]. A separate meta-analysis that assessed the association between secondhand smoke and lung cancer in Japanese non-smokers found a 28% increased risk [54].

Electronic-cigarettes: Electronic nicotine delivery systems, also referred to as electronic-cigarettes and E-cigarettes, allow for the delivery of nicotine to the lung epithelium via an electronic device. Though a patent for this type of device was first issued in 1965, mass production of electronic-cigarettes did not occur until 2003 and became widely available in 2005 in the United States. Today in the United States, there are over 460 different brands on the market with over 7,700 flavors [55, 56] and prevalence of e-cigarette use among adults is estimated to be between 2.6% and 4.5% [57-61]. Of particular concern is the uptake of e-cigarette use among youth ages 12-18, with the 2017 National Youth Tobacco Survey reporting 11.7% of high school students and 3.3% of middle school students using e-cigarettes within the last month. One year later, 20.8% of high school students and 4.9% of middle school students reported using e-cigarettes within the last month, representing

increases of 78% and 48%, respectively [62]. Additionally, e-cigarette use among US youths is associated with increased risk of initiation of traditional cigarette use [63, 64]. Within the next 10 years, it is anticipated that total sales of e-cigarettes are anticipated to exceed tobacco products [65]. Although there are various configurations, these devices typically include a mouthpiece and a battery-operated heating element to heat fluid contained in a replaceable cartridge or reservoir that contains a mixture of liquid nicotine, flavorings, and other chemical solvents [66]. Propylene glycol and vegetable glycerin are the two major solvents in electronic-cigarettes and studies have shown that vapors from these solvents contain toxic and carcinogenic carbonyl compounds including formaldehyde, acetaldehyde, acetone, and acrolein [62, 67]. Studies have also shown that e-cigarette use is associated with increased oxidative stress, which seems to mediate the adverse effects of e-cigarettes. Oxidative stress develops in e-cigarette-exposed human bronchial and lung epithelial cell which can result adverse intermediate events including inflammation, cytotoxicity and increased endothelial cell permeability [68, 69]. A model has been proposed for the role of oxidative stress in mediating adverse effects of electronic-cigarettes leading to cancer, cardiopulmonary pathogenesis, and neurodegenerative disorders [65]. Furthermore, studies have demonstrated that e-cigarettes generate have acute deleterious effects on lung function [70, 71]. Cumulatively, data suggests that vapor produce from electronic-cigarettes contains potentially harmful compounds and may lead to adverse effects on human health. Although data suggest that electronic-cigarettes may less harmful alternative to conventional cigarettes, at present there are no data regarding the long-term cancer risk associated with low-level exposure to the detected carcinogens [72].

Other Tobacco Use: Although cigarettes remain the most prevalent form of tobacco use in the United States, other tobacco products including pipes, cigars, and water pipes (e.g., hookah) are still common and have been associated with increased risk and mortality of lung cancer. Christensen et al [73] identified 357,420 individuals who were never, current or former users of cigars, pipes and cigarettes by linking data from the National Longitudinal Mortality Study and the Tobacco Use Supplement of the Current Population Survey. After excluding nearly 49,000 individuals who reported multiple tobacco product use, risk of lung cancer death among daily users was highest among cigarette users (12.7-fold increased risk), followed by daily cigar use (4.2-fold increased risk), and then daily pipe users (1.7-fold increased risk). A meta-analysis [74] of 287 epidemiological studies of lung cancer found that pipe use only was associated with a 3.3-fold increased risk of lung cancer and cigar use only was associated with a 2.95-fold increased risk. A recent pooled-analysis [75] of five prospective cohort studies from U.S. National Cancer Institute (NCI) Cohort Consortium and that had collected data on cigar and pipe smoking found 2.7-fold increased risk of lung cancer cigar use only and 1.9-fold increased risk for pipe use only. A meta-analysis [76] of 13 case-control studies reported a 4.6-fold increased risk of lung cancer among those using water pipes only. While risk of lung cancer and death is lower for individuals using these products compared to those who smoke cigarettes, it should be noted that these are not safer alternatives to cigarette smoking as the lower point estimates are likely attributed to lower smoking intensity and perhaps lesser degrees of inhalation of these products.

Cannabis: Though the terms cannabis and marijuana are frequently used interchangeably, cannabis is the generic term that includes cannabinoids, hemp, and marijuana derived from the *Cannabis sativa* plant [77]. In the United States, smoked cannabis is estimated to be the most commonly inhaled drug after tobacco with an estimated 7,000 new users a day [78]. As of early 2019, thirty states, the District of Columbia, Guam, and Puerto Rico have legalized marijuana use for medical purposes and twenty states and the District of Columbia have decriminalized the possession of small amounts of marijuana for personal use [79]. However, smoked cannabis contains many of the same chemical toxins and carcinogens as tobacco smoke including acetaldehyde, acrolein, ammonia, carbon monoxide, formaldehyde, phenols, nitrosamines, and polycyclic aromatic hydrocarbons [80]. Additionally, regular smoking of marijuana alone is associated with adverse effects on the respiratory system similar to that of cigarette smoking [81, 82]. However, despite the evidence of adverse biological effects, to date there is no conclusive evidence that suggests cannabis smoking is associated with an increased incidence of lung cancer. A pooled analysis from [83] the International Lung Cancer Consortium of 2,159 lung cancer cases and 2,985 controls found little evidence for an increased risk of lung cancer among habitual or long-term cannabis smokers. However, it should be noted that studies to date have been limited by sample size, self-report, and confounding (e.g., many marijuana users also report tobacco use). Marijuana use is prevalent among youth in the United States as data from the National Survey on Drug Use and Health reported that prevalence of past-year use was between 12% and 16% for adolescents ages 12 to 17 between 2002 and 2014 [84]. In addition, over the last decade, fewer adolescents perceive "moderate" or "regular" use of marijuana as a health risk [85, 86]. As the association between smoked cannabis and lung cancer is still undefined and marijuana use is prevalent, more research will be required in the future to characterize the association between smoked cannabis and risk of lung cancer and for other diseases.

Radon: Because tobacco smoking is a potent and prevalent risk factor, secondary causes of lung cancer are often diminished in perceived importance. However, there are numerous other exposures that are causally linked to lung cancer risk. Radon is an invisible, odorless, tasteless radioactive gas that is found in soil and produced naturally during the radioactive decay of thorium and uranium. All humans are exposed to radon gas and there are substantial geographic variations globally and throughout the United States. Worldwide, 3% to 14% of lung cancers are attributed to radon exposure and the variance is attributed to geographic differences in radon concentration and on the method of calculation [87]. In the United States, radon exposure is estimated to be the second leading cause of lung cancer and responsible for over 21,000 or 13% of lung cancer deaths each year [87, 88]. Published meta-analyses have reported that indoor radon exposure is associated with a 14 to 29% increased risk of lung cancer [89-91].

Occupational Exposures: Occupational exposure to carcinogens is estimated to account for 5 to 10% of lung cancers [41, 88, 92, 93] of which asbestos exposure is historically the most common. Asbestos is a commercial term for a group of naturally occurring mineral silicate fibers, including amphiboles (crocidolite, amosite, tremolite, anthophyllite, and actinolite) and chrysotile (the sole serpentine fiber). Asbestos is found on all continents, use has been used commercially since the 19th century, and is still used in some countries today in

numerous applications including insulation, textile, cement, and roofing [94]. Although the mechanisms involved in asbestos-associated diseases are complex and the molecular pathways involved are not fully established, direct and indirect cellular and molecular effects likely contribute to lung cancer etiology including oxidative stress, chronic inflammation, genetic and epigenetic alterations, and cellular toxicity and fibrosis [95]. A meta-analysis of 14 case-control studies conducted in Europe and Canada that included 17,705 lung cancer cases and 21,813 controls found ever-exposure to asbestos was associated with a 24% increased risk in men and 12% increased risk in women [96]. There is substantial synergistic effects [97] between asbestos exposure and tobacco smoking on lung cancer risk and morality [96, 98, 99].

The International Agency for Research on Cancer (IARC) evaluates carcinogenicity for a wide range of human exposures. Agents classified as "carcinogenic to humans" (Group 1) [100] that have sufficient evidence of causing lung cancer in humans include numerous occupational-related exposures including arsenic, beryllium, cadmium, chromium, and diesel exhaust and specific occupations including aluminum production, coal gasification, coke production, underground hematite mining, iron and steel founding, painting, and rubber production (reviewed in [101]).

<u>History of Non-Infectious Related Respiratory Diseases:</u> History of chronic obstructive pulmonary disease (COPD), which includes emphysema, or chronic bronchitis, is an irreversible chronic inflammatory condition that leads to fixed narrowing of small airways and alveolar wall destruction. The long-standing inflammatory reaction in the bronchi is accompanied by a continual cycle of injury and repair and therefore could play a key role in lung carcinogenesis. In the United States, over 15 million people reported ever receiving a diagnosis of COPD in 2015 and is the third leading cause of death behind heart disease and cancer [102]. Tobacco smoking is the major risk factor for COPD [103] so it is unexpected to find a positive association between COPD and lung cancer. Published meta-analyses have reported a 2 to 3-fold risk of lung associated with a history of COPD, emphysema, or chronic bronchitis [104-106]. A pooled analysis from the International Lung Cancer Consortium found that a history of emphysema conferred a 2.44-fold increased risk of lung cancer [107].

Asthma is a common childhood disease affecting approximately 300 million people worldwide [108]. Asthma is characterized by chronic inflammation of the lungs and presents with airway hyper-reactivity, excessive mucous formation, and respiratory obstruction. Asthma has been suspected as a potential risk factor for lung cancer since inflammation also plays a pivotal role in the lung cancer pathogenesis. A pooled analysis published in 2012 of 16 studies in the International Lung Cancer Consortium concluded that increased risk between asthma and lung cancer may not reflect a causal effect since the increased incidence of was largely observed in small cell and squamous cell lung carcinomas, primarily within 2 years of asthma diagnosis, and the association was weak among never smokers [109]. However, a meta-analysis published in 2017 that included 18 studies with over 16 million individuals [110] found that asthma was significantly associated with a 44% increased risk of lung cancer and a 28% increased risk among never smokers. Subgroup analyses also demonstrated significant increases for non-Hispanic Whites, Asians, males, and females.

History of Infectious-Related Respiratory Diseases: Pneumococcal disease is an umbrella term for a group of syndromes caused by a variety of organisms resulting in varied manifestations and sequelae [111, 112]. Most commonly, pneumococcal disease is an infection caused by the *Streptococcus pneumoniae* bacterium which can infect the lungs (pneumonia), bloodstream (bacteremia), and tissues and fluids surrounding the brain and spinal cord (meningitis). In the United States, approximately 400,000 hospitalizations from pneumococcal pneumonia occur annually [113]. Pneumonia is a putative lung cancer risk factor through several possible mechanisms from mediators of chronic local inflammation including elevated reactive oxygen species that can cause DNA damage and somatic mutations, anti-apoptotic signaling, and increased angiogenesis [113]. Published meta-analyses have reported a history pneumonia was associated with a 30 to 40% increased risk of lung cancer risk [105, 114] and a pooled analysis from the International Lung Cancer Consortium reported a 57% increased risk [107]. However, such findings should be interpreted with caution since reverse causality cannot be ruled out since pulmonary infections can be a result of a weakened immune system due to lung cancer [105]. Furthermore, the timing of a pneumonia diagnosis can coincide with or confound the diagnosis of lung cancer and pneumonia may be a complication of lung cancer such as post-obstructive pneumonia [115].

Chlamydia pneumonia (*C. pneumoniae*) is the most commonly occurring intracellular bacterial pathogen and is responsible for sinusitis, pharyngitis, and pneumonia [116]. It is transmitted occurs via respiratory secretions and may increase risk of lung cancer through mediators of inflammation similar to those speculated for pneumonia [117] as described above. A meta-analysis [118] of 12 studies including 2,595 lung cancer cases and 2,585 controls reported that *C. pneumoniae* infection was associated with a 1.5-fold increased risk of lung cancer. *C. pneumoniae* infection was significantly associated with a 1.2-fold increased risk of lung cancer in prospective studies and 2.2-fold increased risk in retrospective studies. When definition of chronic infection was defined by antibody titre, the IgA 16 cutoff group was associated with a 1.2-fold increased risk and the IgA 64 cutoff group was associated with a 2.4-fold increased risk. Tuberculosis is a communicable infectious disease transmitted by cough aerosol and is caused by the *Mycobacterium tuberculosis* bacterium. Although tuberculosis primarily affects the lungs, it can affect other parts of the body. Worldwide incidence of tuberculosis has slowly declined over the past decade; in 2013 an estimated 9 million incident cases of tuberculosis (126 cases per 100,000) were reported with more than 60% of the burden concentrated in the 22 high-burden countries [119]. The United States is a low-incidence country with an annual incidence of 30 tuberculosis cases per 1 million [120]. Tuberculosis can induce chronic inflammation and pulmonary fibrosis leading to higher rates of genetic alterations and mutations which have been suggested mechanisms regarding the role of tuberculosis on lung cancer risk [121]. A pooled analysis from the International Lung Cancer Consortium and a meta-analysis reported that previous history of tuberculosis was associated with a 48% and 76% increased risk of lung cancer, respectively [105, 107].

Human Immunodeficiency Virus (HIV): Individuals who are infected with HIV are at increased for many cancers, attributed to many factors including HIV-related

immunosuppression which impairs control of oncogenic viral infections, mediators of inflammation, and co-infection with oncogenic viruses such as Hepatitis B and C [122-124]. Lung cancer is a leading non-Acquired Immunity Deficiency Syndrome (AIDS) defining cancer (NADC) and is the most frequent cause of cancer-related death among persons infected with HIV [125]. Though adults with HIV are more likely to smoke cigarettes than the general adult population [126], when accounting for smoking elevated incidence of lung cancer among HIV-infected persons has been observed [127]. The HIV/AIDS Cancer Match (HACM) Study used linked data collected by US HIV and cancer registries to describe cancer risk in HIV-infected people in the United States relative to the general population [128]. Standardized incidence ratios (SIRs) were used to test for differences by AIDS status and over time. Among 448,258 HIV-infected people, lung cancer was the second common individual cancer type (11.6%) was lung cancer risk was elevated 2-fold.

Other Lifestyle Factors: There is also compelling evidence that other factors may be associated with an increased risk of lung cancer for both smokers and never smokers including poor diet and low body mass index [129-137].

Inherited Genetics: In 2004, the Genetic Epidemiology of Lung Cancer Consortium revealed the first evidence for a major susceptibility locus influencing lung cancer risk to a region on 6q23–25 [138]. With the arrival of genome-wide association (GWA) studies about 17 years ago, it is now possible to interrogate the human genome more comprehensively for associations between inherited single-nucleotide polymorphisms (SNPs) and human disease. GWA studies have successfully identified genetic factors significantly associated with lung cancer susceptibility with varying strengths of association evidence and some loci have been refined to specific subgroups including sex, ethnicity, smoking status, and histological subtypes [139, 140]. Data from these large GWA studies could be leveraged towards development of risk models based on polygenic risk scores defined by the combination of SNPs that yield the best predictive model [141].

Lung Cancer among Never Smokers—Globally, approximately 25% of lung cancer diagnoses are among never smokers (LCANS) [142] and approximately 60 to 80% of women diagnosed with NSCLC are never smokers. In East and South Asia, a high proportion of female lung cancers occur among never smokers [143]. In the United States, although smoking rates and the incidence of lung cancer has declined over the last several decades, the incidence of lung cancer among never smokers (LCANS) has been on the rise. Approximately 10 to 20% of all lung cancer diagnoses occur in never smokers in the United States, and if considered a separate reportable category, LCANS is the 11th most common cancer and the 7th leading cause of cancer-related deaths.

Many of the exposures associated with lung cancer risk have been found to be risk factors for both smokers and never smokers. Nonetheless, risk factors found to be associated with LCANS include second-hand smoke, cooking fumes, ionizing radiation, radon gas, inherited genetic susceptibility, occupational exposures, preexisting lung disease, and oncogenic viruses (reviewed in [144]). Among all risk factors, advanced age is the most significant contributor to LCANS. Even if the incidence of LCANS remains constant over time, the number of lung cancer deaths among never smokers is expected to increase significantly in

the following decades as the prevalence of smoking continues to decline as the population age-structure continues to shift to older ages [144]. Thus, lung cancer will continue to be a substantial public health burden in the United States in spite of the significant improvements in tobacco control and early detection.

The histology of LCANS is most likely to be adenocarcinoma and molecular profiling studies have found that the tumor genome of LCANS is significantly different from the genome of lung cancers arising in smokers. Mutations in *TP53, KRAS,* and *STK11* are more frequent in tobacco smokers with lung cancer, whereas *EGFR* and *HER2* mutations and the *ALK-ELM4* fusion are more common among LCANS [145]. Revealing and understanding differences at the molecular level among LCANS may identify the etiological processes involved in tumorigenesis and reveal important therapeutic strategies for targeting key oncogenic events. As such, the National Cancer Institute has launched "*Sherlock Lung: A Molecular Epidemiologic Study of Lung Cancer in Never Smokers*" [146] with the goal of tracing lung cancer etiology in never smokers by analyzing molecular data in conjunction with histological features to develop an integrated molecular, histological, and radiological classification of LCANS.

Prevention—Most lung cancers are preventable and could be mitigated by reducing smoking initiation among adolescents and increasing smoking cessation among adults. Fortunately, smoking rates have steadily declined in the United States since the 1960s [10]. In 2016, the prevalence of current cigarette smoking among adults was 15.5%, which was substantially declined from 20.9% in 2005 [147]. Though primary prevention (smoking prevention and cessation) mitigates risk and mortality, former smokers remain at significant risk of dying from lung cancer (Figure 10) [148]. As such, early detection is currently the only option for those who have already quit smoking and among those individuals who are at high-risk. Lung cancer will likely remain a major public health burden globally throughout the 21st century and advances in risk assessment, early detection, diagnosis, and treatment will be imperative in improving outcomes of this disease [149].

Screening and Early Detection—As described earlier, the majority of lung cancer patients are diagnosed with advanced stage disease, where the prospects for cure are limited. However, local therapy for early stage disease is associated with substantially improved overall survival. Until recently, a modality for the successful detection of early stage lung cancer has been elusive. In 2011, results from the National Lung Screening Trial (NLST) demonstrated a 20% relative reduction in lung cancer mortality for individuals screened by low-dose helical computed tomography (LDCT) compared to standard chest radiography in a high-risk population of 53,454 current and former smokers aged 55–74 years [150]. Screen-detected incidence lung cancers diagnosed following a positive screen at 1 or 2 years after the baseline screen accounted for 58% of all LDCT-detected lung cancers in the NLST, were 2.7-fold higher in the LDCT arm versus the chest radiography arm, and were associated with a favorable stage shift from advanced to more early stage lung cancers [150]. Additionally, in the LDCT arm, a subset of screen-detected incidence lung cancers where their antecedent screens were positive prior to the screen of the cancer diagnosis were associated with improved 5-year survival compared to prevalent lung cancers [151] that are

usually diagnosed when patients develop symptoms in a "real world setting". Following publication of the NLST results, the United States Preventive Services Task Force (USPSTF) in December 2013 and the Centers for Medicare and Medicaid (CMS) in February 2015 issued recommendations for annual LDCT screening for eligible high-risk individuals. [152, 153]. Both the USPSTF and CMS guidelines recommend smoking cessation interventions for individuals who enter a lung cancer screening program. Novel smoking cessation strategies tailored to the lung cancer screening setting will likely amplify the survivorship gains expected from screening alone [154].

Despite the conclusive benefits shown by the NLST and the recommendations and implementation of lung cancer screening in the United States, European nations have not yet issued similar recommendations because of the absence of proven benefit in randomized clinical trials conducted in Europe [155]. However, in 2018 the initial results of the Nederlands-Leuvens Longkanker Screenings ONderzo ek (NELSON) trial [156] were presented at the 19th World Conference on Lung Cancer of the International Association for the Study of Lung Cancer and indicated significant reductions in lung cancer mortality. Moreover, two additional randomized trials conducted in Italy [157] and Germany [158] were published in 2019 providing additional confirmation of lung cancer screening efficacy. The Multicentric Italian Lung Detection (MILD) trial [157], in which 4,099 participants aged 49–75 years with a smoking history of 20 pack-years were prospectively randomized to undergo LDCT screening for a median period of 6 years ($n = 2,376$) or to a control arm with no screening intervention ($n = 1,723$). Landmark analysis that considered only individuals alive with no lung cancer diagnosis after 5 years from randomization revealed a 58% reduction in lung cancer mortality and a 32% reduction in all-cause mortality after the fifth year of screening. The German Lung cancer Screening Intervention (LUSI) was a randomized trial [158] of 4,052 long-term smokers aged 50–69 years comparing five annual rounds of LDCT screening (n = 2,029) versus a control arm without screening (n = 2,023) found a 26% in lung cancer mortality over an average observation time of 8.8 years after randomization. The cumulative evidence based on the results of the NLST, the MILD trial, the LUSI trial, and anticipated publication of the NELSON trial, has demonstrated substantial beneficial mortality reductions associated with LDCT screening.

Future Directions—Over the last several decades substantial progress has been made across the cancer control continuum in terms of etiology, prevention, early detection, diagnosis, treatment, survivorship, and end of life; however, lung cancer is still a major public health burden globally and in the United States. Etiologically, concerted efforts are needed to identify causal risk factors for lung cancer among never smokers and identify never smokers at the greatest risk for lung cancer that perhaps can benefit from a lung cancer screening program. Additionally, the impact of marijuana and electronic-cigarettes on lung cancer risk needs to be clarified. From a prevention standpoint, additional research is needed to identify potential agents that can reduce lung cancer risk especially among former smokers. Precision-based risk and screening should be explored to identify individuals who would benefit most from entering a lung cancer screening program. Advancements in screening technology and biomarkers in the screening setting could reduce false positives and overdiagnosis and improve nodule management. Further, research is needed on the

feasibility and efficacy of providing smoking cessation treatment in the lung cancer screening setting. Biomarkers that are highly predictive of negative responses to targeted therapies and immunotherapy are a significant unmet clinical since there are subgroups of that may not respond to these specific treatments. This is particularly salient in the subsets of patients that may experience treatment-induced rapid disease progression which can be rapid and lethal. Finally, more research is needed to personalize treatment plans that minimize adverse survivorship issues and lead to improved quality of life for lung cancer survivors.

Acknowledgements:

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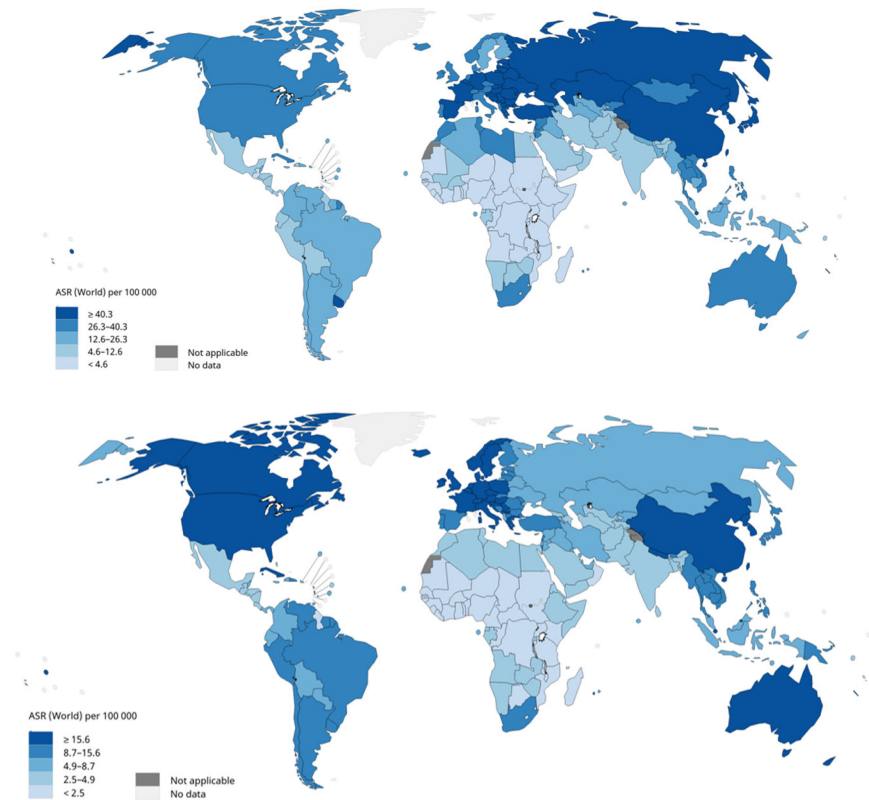
Figure 1.

Age-standardized rates (ASR) for lung cancer incidence worldwide. Figure 1a shows age-standardized incidence rates for lung cancer among males using data from GLOBOCAN, 2018. Lung cancer incidence among males is highest in Micronesia, Polynesia, Central and Eastern Europe, and Eastern Asia and lowest in most of Africa. Figure 1b shows age-standardized incidence rates for lung cancer among females using data from GLOBOCAN, 2018. Lung cancer incidence among females is highest in North America, Northern Europe, Western Europe, and Australia/New Zealand and lowest in most of Africa. Data source: GLOBOCAN 2018. Graph production: IARC (http://gco.iarc.fr/today), World Health Organization.
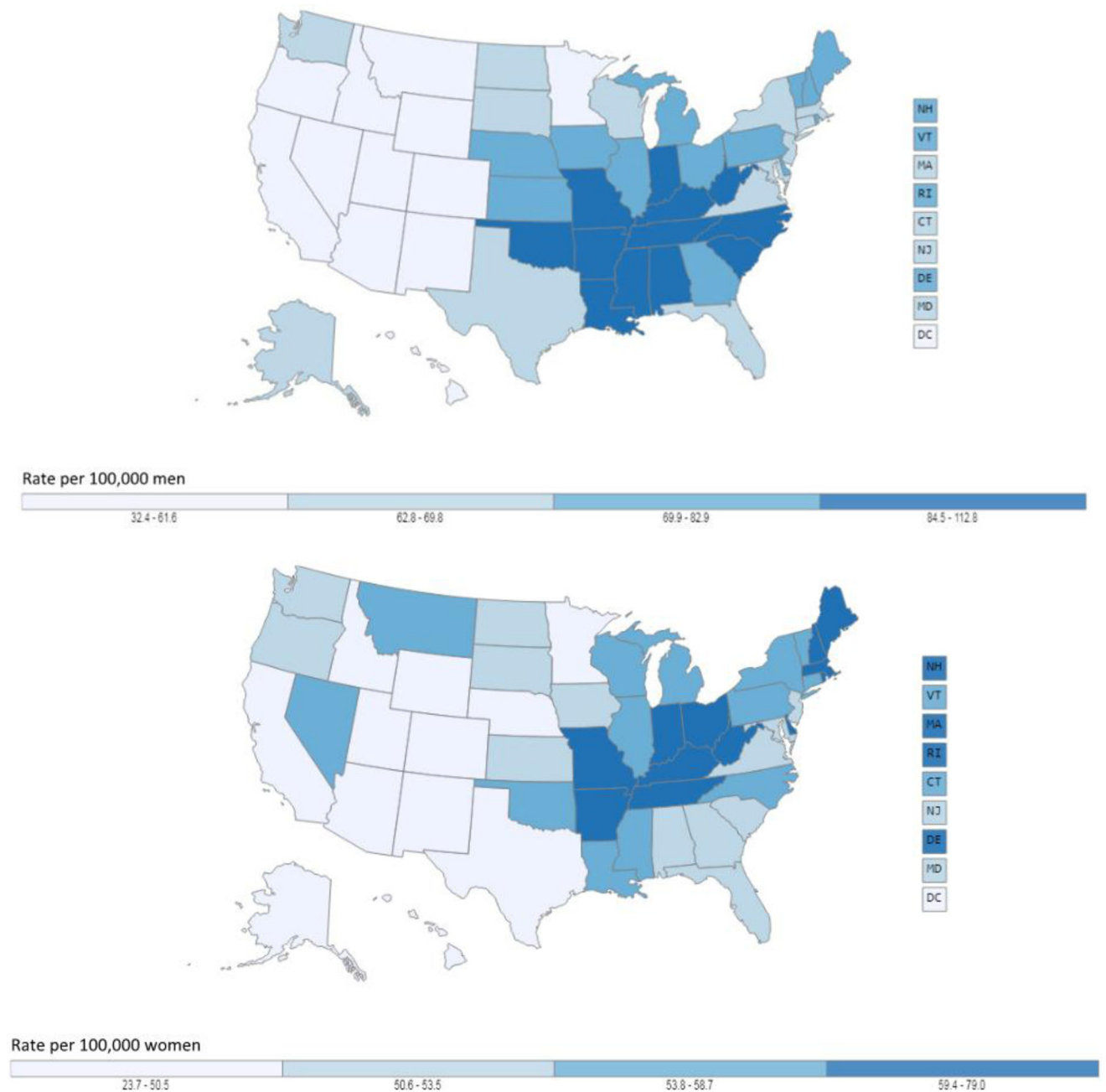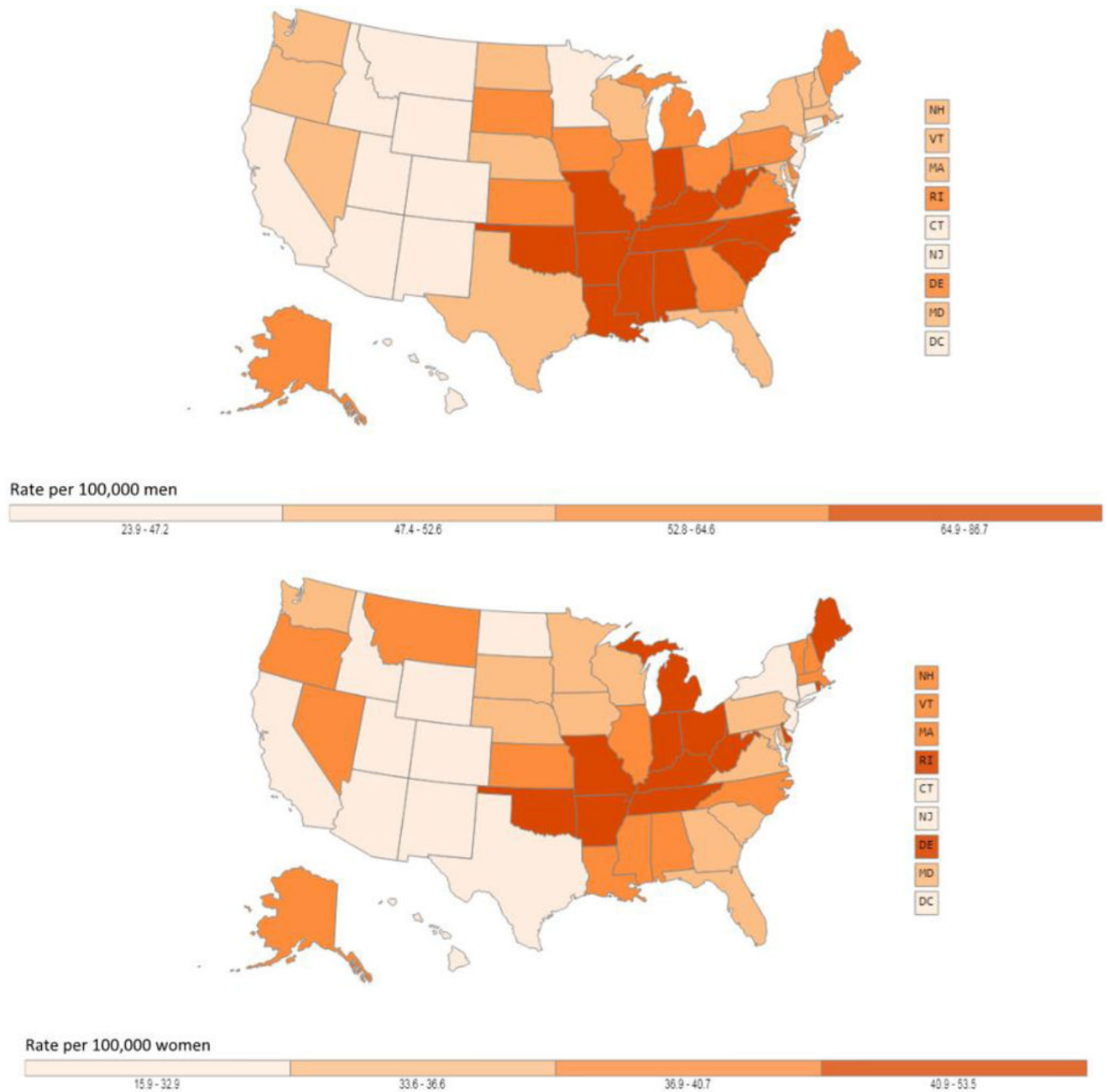
Figure 2.
Age-adjusted lung cancer incidence rates in the United States. Figure 2a shows age-adjusted lung cancer incidence rates for males in the United States, 2011 –2015, using data from U.S. Cancer Statistics Working Group. Figure 2b shows age-adjusted lung cancer incidence rates for females in the United States, 2011 –2015, using data from U.S. Cancer Statistics Working Group. Among both males and females, lung cancer incidence is higher in the Midwest and East and the highest rates are observed in the South while the lowest rates are generally found in Western states. Data source: U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on November 2017 submission data

(1999-2015): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute (www.cdc.gov/cancer/dataviz), June 2018
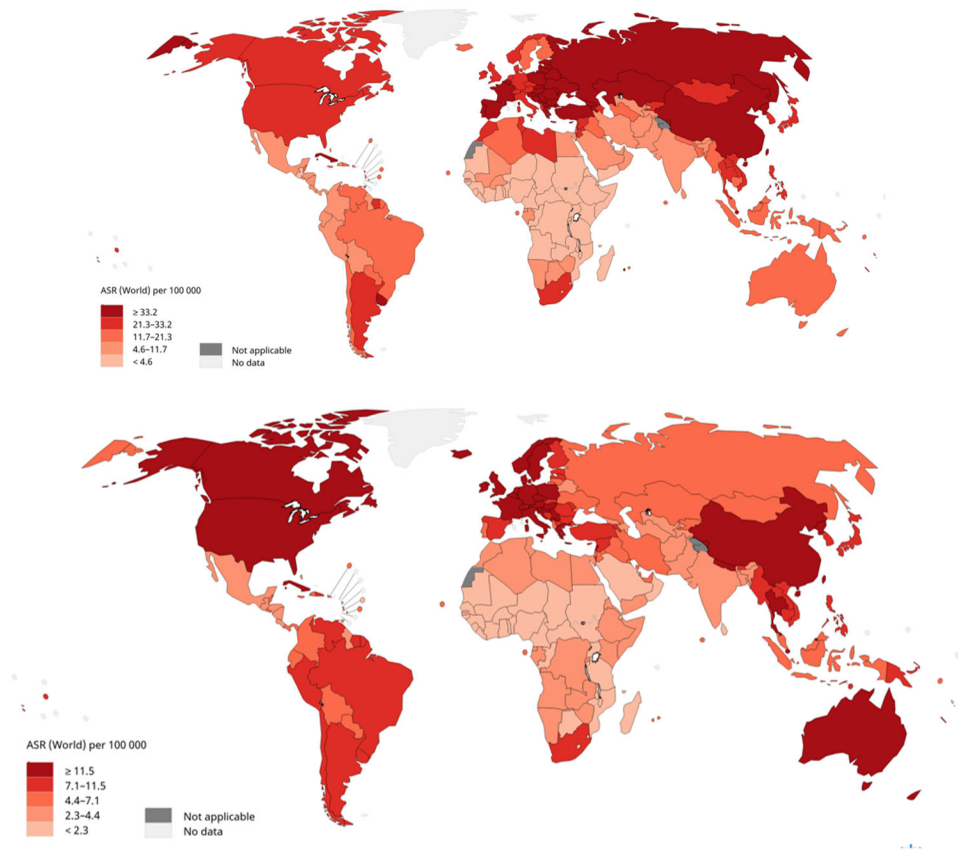
Figure 3.
Estimated age-standardized rates (ASR) for lung cancer mortality worldwide. Figure 3a shows age-standardized mortality rates for lung cancer among males using data from GLOBOCAN, 2018. Lung cancer mortality among males is highest in Eastern Europe, Western Asia, Northern Africa, and specific countries in Eastern Asia and lowest in most of Africa. Figure 3b shows age-standardized mortality rates for lung cancer among females using data from GLOBOCAN, 2018. Lung cancer mortality among females in North America, Northern Europe, Western Europe, and Australia/New Zealand and lowest in most of Africa. Data source: GLOBOCAN 2018. Graph production: IARC (http://gco.iarc.fr/today), World Health Organization.

Rate per 100,000 men

| 23.9 - 47.2 | 47.4 - 52.6 | 52.8 - 64.6 | 64.9 - 86.7 |

Rate per 100,000 women

| 15.9 - 32.9 | 33.6 - 36.6 | 36.9 - 40.7 | 40.9 - 53.5 |

Figure 4.

Age-adjusted lung cancer mortality rates in the United States. Figure 4a shows age-adjusted lung cancer mortality rates for males in the United States, 2011 −2015, using data from U.S. Cancer Statistics Working Group. Figure 4b shows age-adjusted lung cancer mortality rates for females in the United States, 2011 −2015, using data from U.S. Cancer Statistics Working Group. Among both males and females, lung cancer morality is higher in the Midwest, East, and South and lowest in most Mountain states and California. Data source: U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on November 2017 submission data (1999-2015): U.S. Department of Health and

Human Services, Centers for Disease Control and Prevention and National Cancer Institute (www.cdc.gov/cancer/dataviz), June 2018.
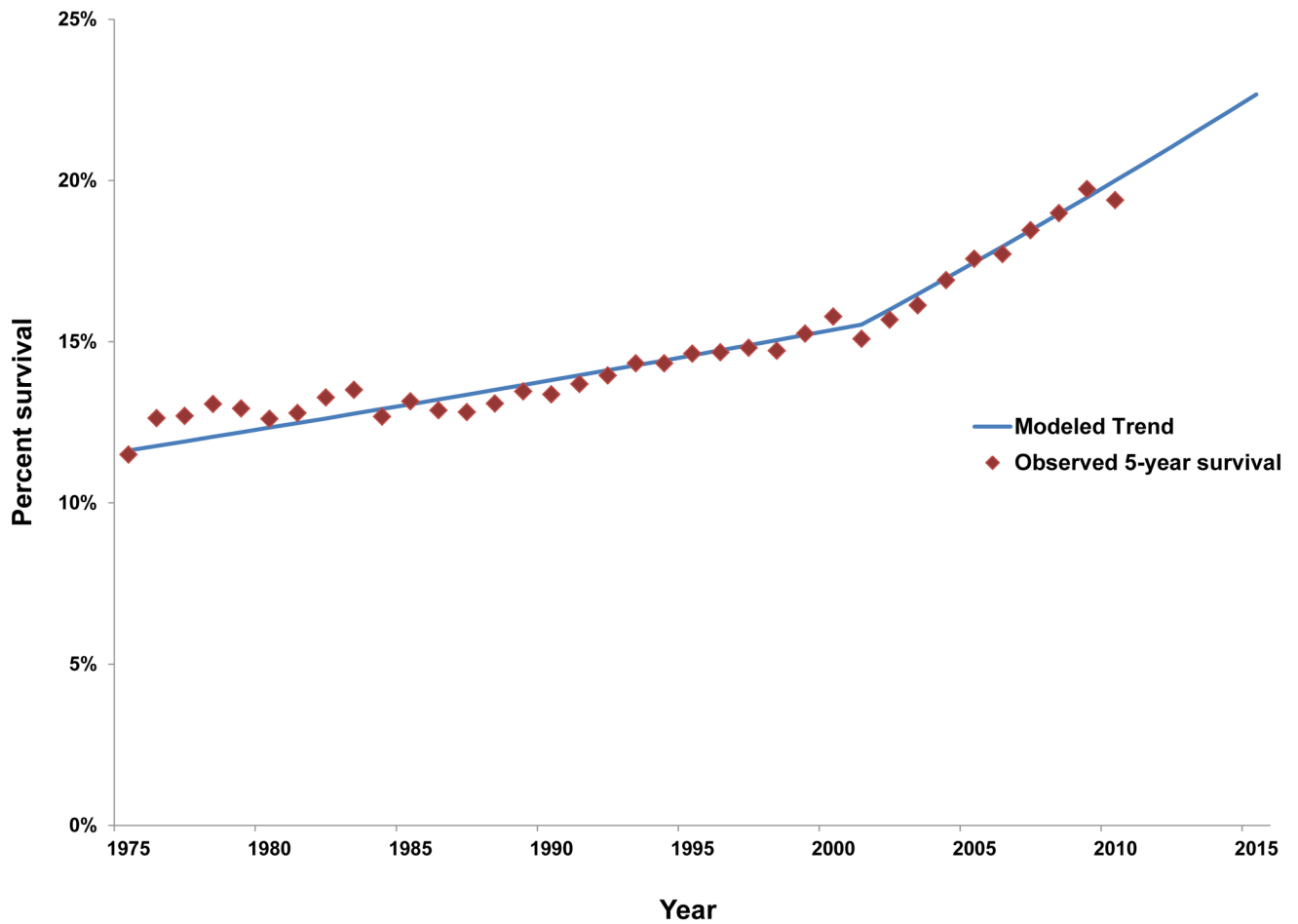
Figure 5.
Temporal trends in 5-year relative percent survival for lung and bronchus cancer. Figure 5 shows observed and modeled trends in lung and bronchus cancer 5-year survival from 1975-2015 using data from SEER 18 (https://seer.cancer.gov/statfacts/html/lungb.html).
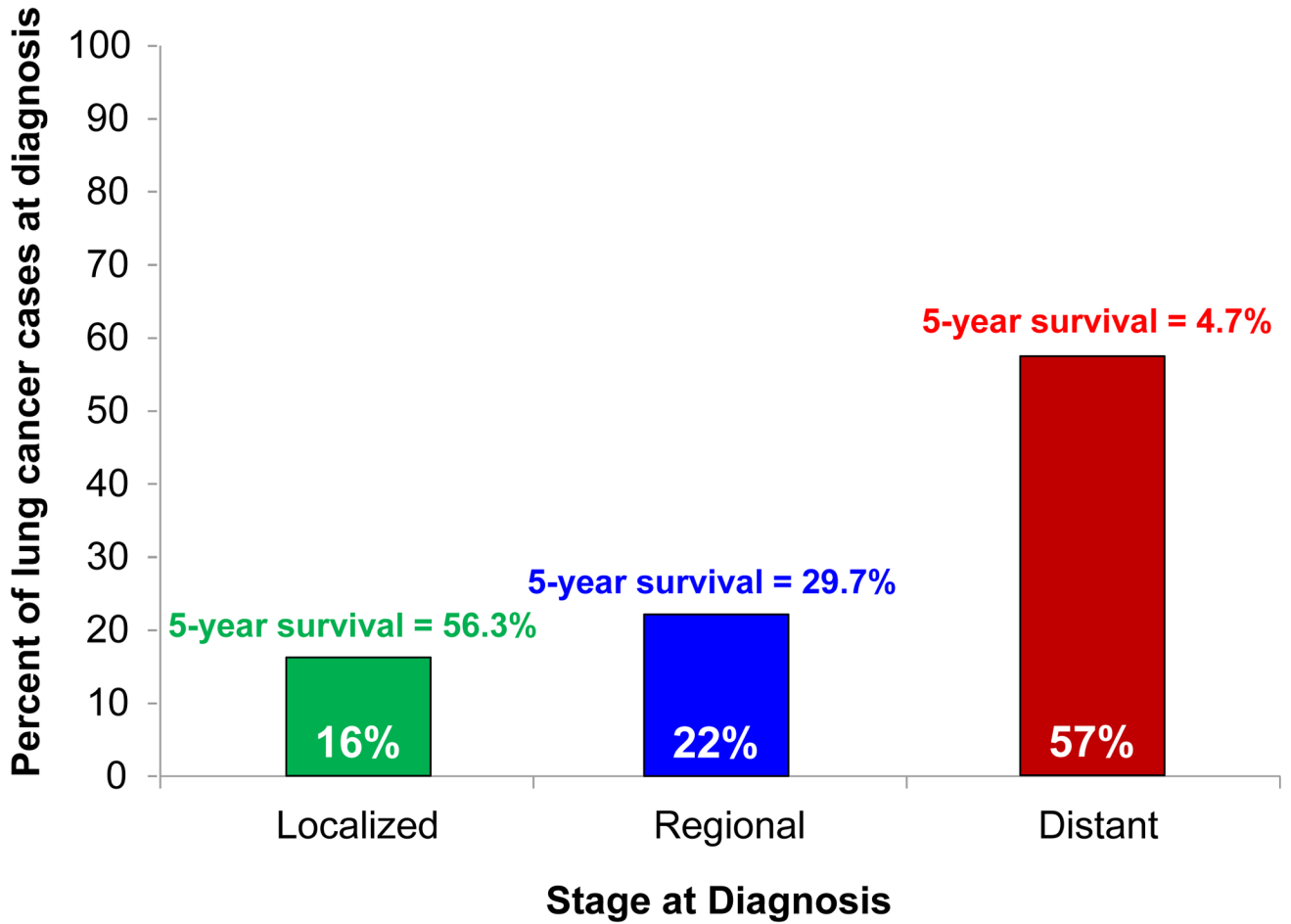
Figure 6.
Percent of lung cancer cases at diagnosis and 5-year relative survival by stage. Figure 6 shows the percentage of lung cancer cases diagnosed in the U.S. by stage and their respective 5-year survival rates using data from SEER 18 (https://seer.cancer.gov/statfacts/html/lungb.html). "Localized" is confined to the primary sites, "regional" has spread to the regional lymph nodes, and "distant" is a cancer that has metastasized. "Unknown", which accounts for 4% of diagnoses and has an 8.2% 5-year survival, is not shown.

Lung cancer histological categories

Non-small cell lung cancer subtypes

Small cell lung carcinoma 15%

Non-small cell lung carcinoma 85%

Others and not otherwise specified 20%

Large cell carcinoma 15%

Adenocarcinoma 40%

Squamous cell carcinoma 25%
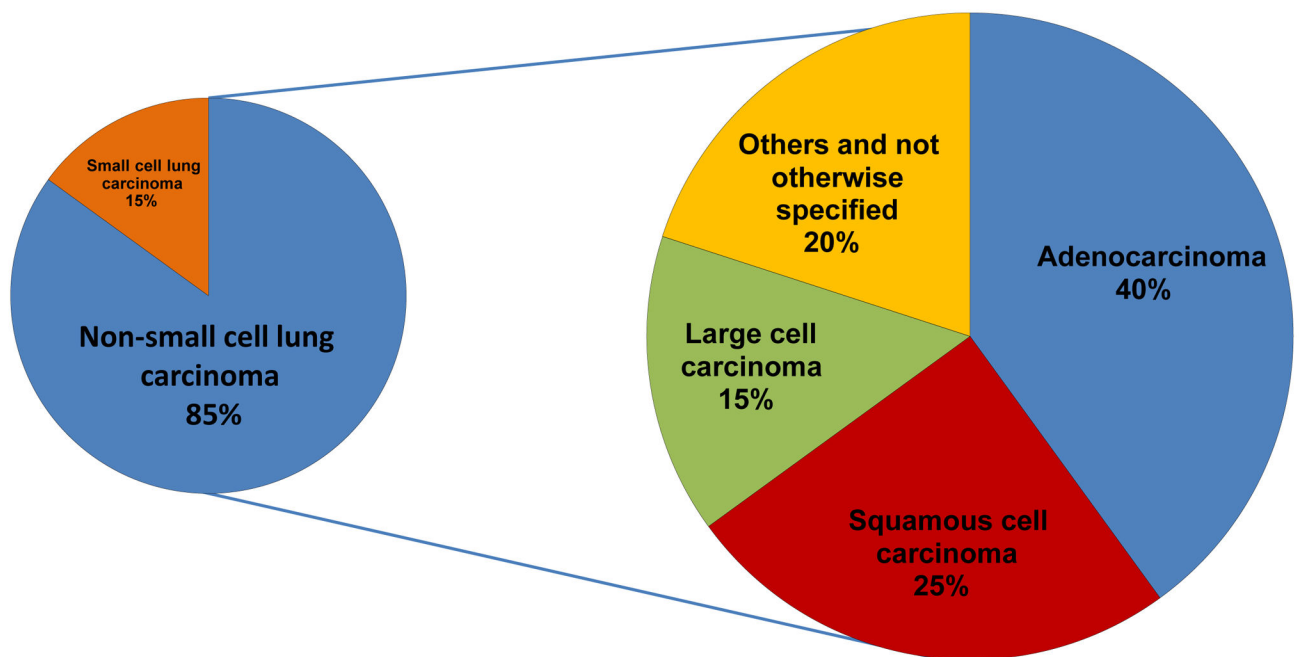
Figure 7.
Histological classification of lung cancer. Figure 7 shows the two major lung cancer histological categories (non-small cell lung carcinoma [NSCLC] and small-cell lung carcinoma) and the most common histological subtypes among NSCLC (adenocarcinoma, squamous cell carcinoma, and large cell carcinoma).
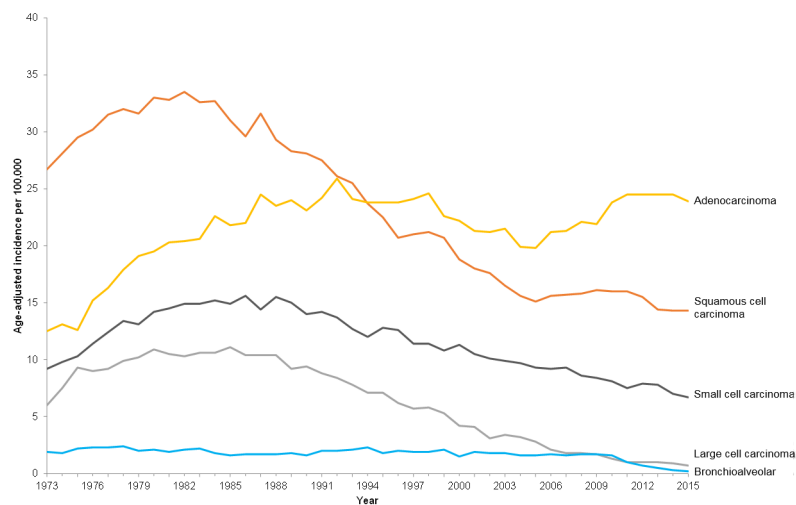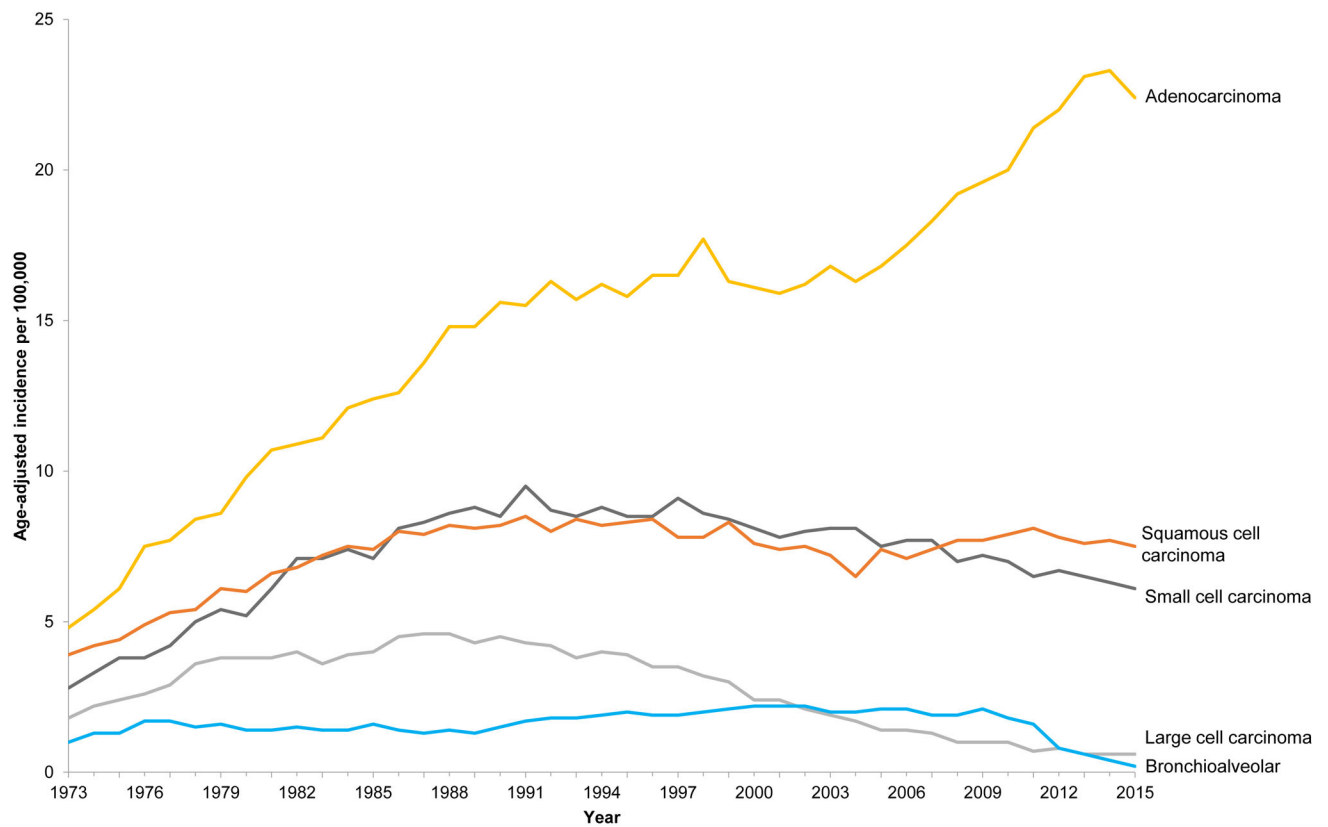
Figure 8.
Age-adjusted incidence rates (per 100,000) for lung and bronchus cancer by year of diagnosis and histology. Figure 8a shows age-adjusted incidence rates among females for lung and bronchus cancer by year of diagnosis and histology using SEER 9, 1973-2015. Figure 8b shows age-adjusted incidence rates among males for lung and bronchus cancer by year of diagnosis and histology using SEER 9, 1973-2015. The incidence rates are age-adjusted to the 2000 U.S. population.
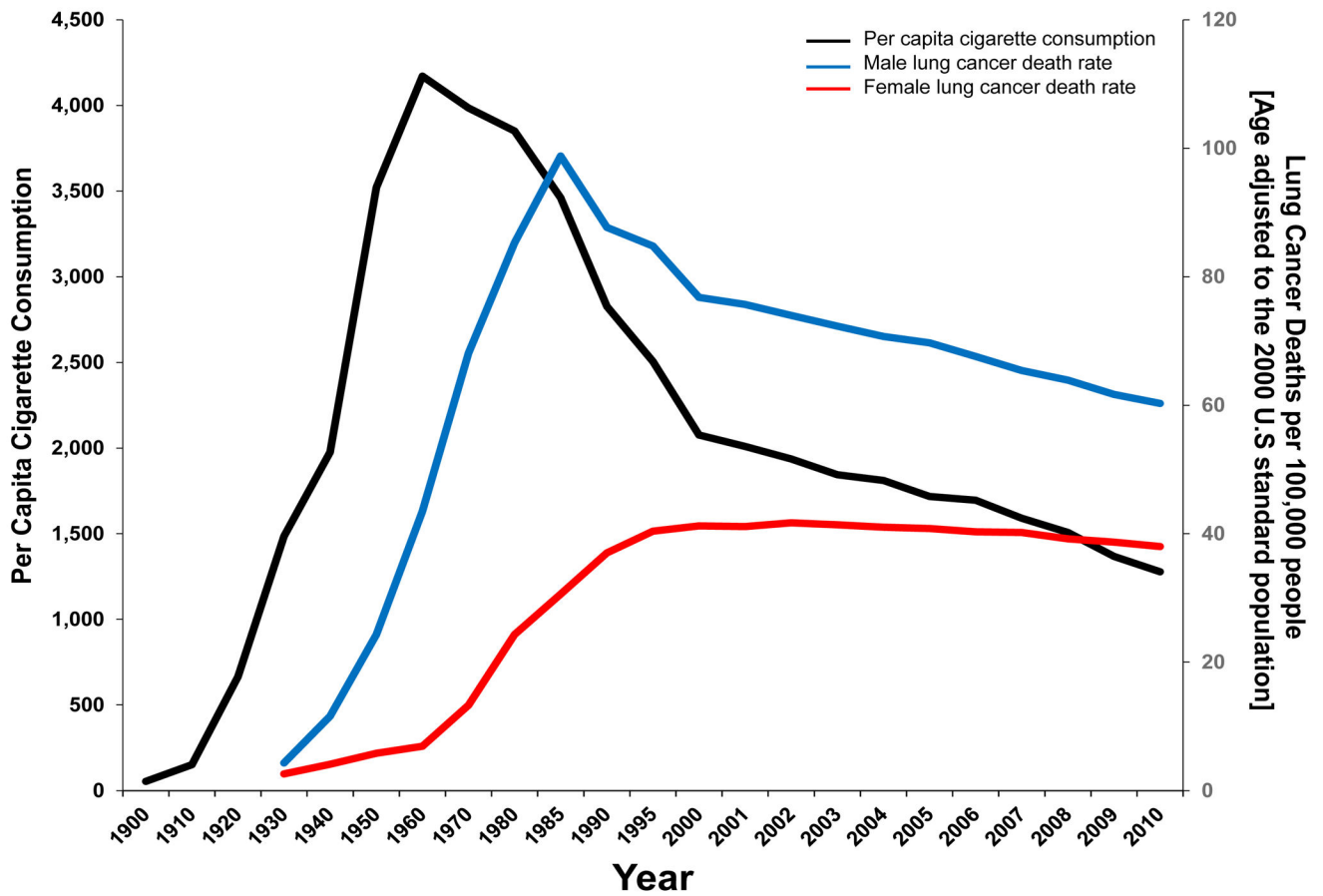
Figure 9.
Trends in cigarette and lung cancer death rates. Figure 9 shows the temporal trends in cigarette use versus lung cancer death rates for both males and females in the U.S. using data from the Centers for Disease Control and Prevention. Data sources from: National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention, 2017 and CDC Report on Consumption of Combustible and Smokeless Tobacco — United States, 2000-2015, page 1359.
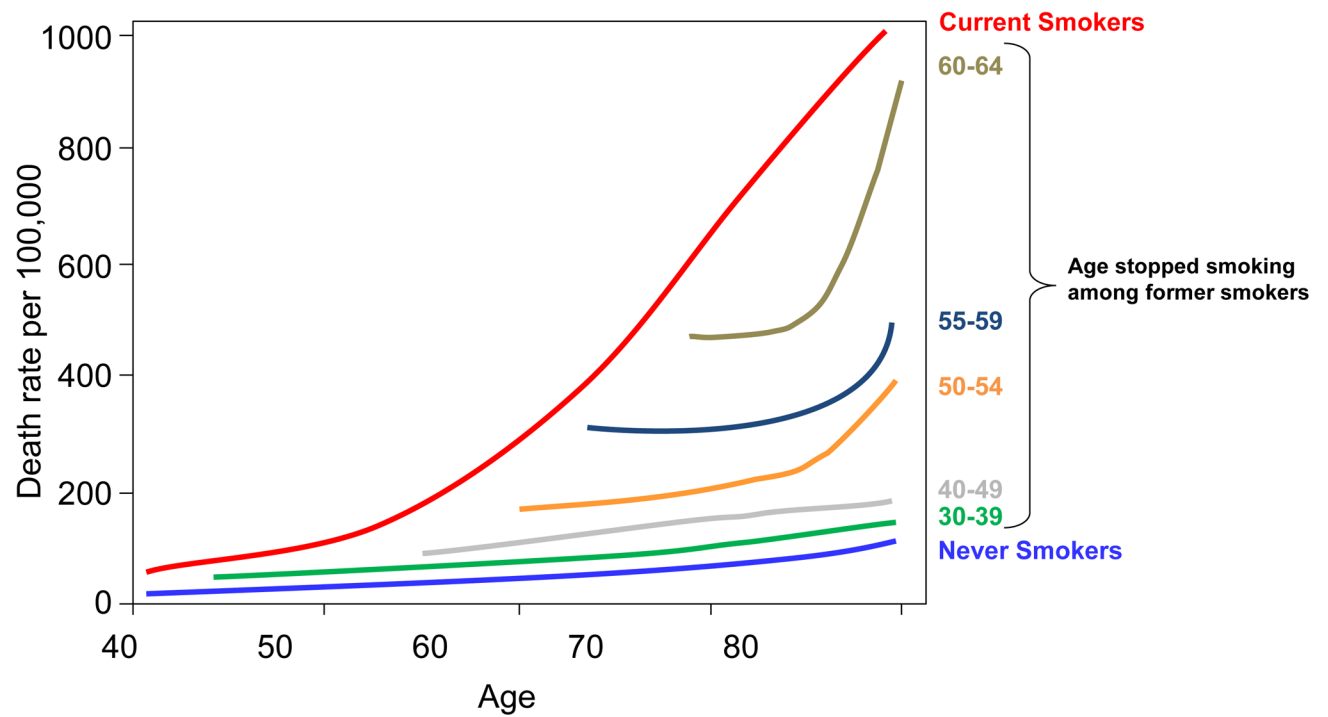
Figure 10.
Lung cancer mortality by smoking status. Figure 10 shows lung cancer mortality (per 100,000) among current smokers, former smokers, and never smokers based on published figures that were adapted from Halpern et al ([reference 148] J Natl Cancer Inst 1993; 85:457-464). Former smokers are presented by age-at-quit.

Table 1.

Frequency of Somatic Mutations and Alterations in NSCLC

Gene	Alteration type	Frequency in NSCLC
EGFR	Mutation	10–35%
KRAS	Mutation	15–25%
FGFR1	Amplification	20%
PTEN	Mutation	4–8%
DDR2	Mutation	~4%
ALK	Rearrangement	3–7%
HER2	Mutation	2–4%
MET	Amplification	2–4%
BRAF	Mutation	1–3%
PIK3CA	Mutation	1–3%
AKT1	Mutation	1%
MEK1	Mutation	1%
NRAS	Mutation	1%
RET	Rearrangement	1%
ROS1	Rearrangement	1%

Table 2.

Established and putative risk lung cancer risk factors

Risk factor	Magnitude of association
Tobacco smoking	20-fold increased risk vs. never smoker
Secondhand smoke	25% to 28% increased risk vs. never smoker
Electronic cigarettes	Presently unknown
Other tobacco use (cigars, pipes, water pipes)	1.9 to 4.6-fold increased risk
Smoked cannabis	Presently no known risk
Radon	14% to 29% increased risk
Asbestos	12% to 24% increased risk
History of COPD, emphysema, or chronic bronchitis	2 to 3-fold increased risk
History of asthma	28% to 44% increased risk
History of pneumonia	30% to 57% increased risk
History of *Chlamydia pneumoniae*	1.2 to 2.4-fold increased risk
History of tuberculosis	48% to 76% increased risk
HIV	2-fold increased risk