Epidemiology of lung cancer and the gender differences in risk

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Abstract

Background: Lung cancer has progressed from an exceedingly rare disease to the leading cause of all cancer-related deaths, a phenomenon largely attributed to the impact of tobacco smoking and resulting global epidemic. Methods: A thorough literature search was conducted to identify relevant factors in the epidemiology of lung cancer with a focus on recent studies and developments that had the most significant impact on the current understanding of lung cancer. Results: Most recent data suggests the global burden of lung cancer is continuing to rise with 2.2 million new cases in 2020 alone. Although no difference is noted among men, a higher rate of lung cancer deaths among women in the industrialized nations are observed compared to developing nations. Incidence and deaths are closely linked to cigarette smoking. Other risk factors include occupational hazards, increasing air pollution with pulmonary infectious diseases and inflammatory conditions, and genetic factors. Tobacco continues to cause approximately 90% of all lung cancer deaths with a markedly wide variety of incidence rates both geographically and between males and females. Lung cancer incidence has been falling in US and UK since 1990 largely due to comprehensive tobacco control programs. In contrast higher rates of cigarette smoking among emerging nations is a concern. The unprecedented, widespread adoption of electronic-cigarette use among adolescents may pose major obstacles in the prevention and treatment of lung cancer. Conclusions: While the vast majority of current lung cancer cases and deaths continue to be caused by tobacco consumption, shifts in population behaviors, geographical location, and potential new causes may alter this distribution. Further work is crucial in order to better understand the risk factors for lung cancer in the modern world so that a more holistic proactive approach, rather than a reactive approach, can be taken.

Keywords: lung cancer; epidemiology; smoking; tobacco

1. Introduction

Despite its greater than 240-year presence in scientific literature, lung cancer remains as the leading cause of cancer death worldwide and imposes one of the lowest 5-year cancer survival rates [1–3]. Indeed, in the United States (US) alone, lung cancer is expected to lead to an estimated 131,880 deaths in the year 2021, more than any other cancer [3]. On a global scale, a similar trend can be observed in that lung cancer remains as the leading cause of death when compared to any other cancer and is accountable for 1.8 million deaths, or 18% of the global total number of cancer deaths [4].

Nevertheless, this global pandemic has brought upon extensive efforts aimed at reducing the morbidity and mortality of lung cancer in the modern era and, as a result, massive influxes of research have allowed notable advances to be made in regard to understanding lung cancer’s incidence, etiology, risk factors, and treatment efficacies [3]. In addition, significant work has been recently done in elucidating the nuances of patient sex within lung cancer which has led to various new proposals regarding patient education efforts, diagnostic approaches, and treatment plans [5].

2. Patterns of occurrence

2.1 Temporal trends

Although, quantitatively, the global number of lung cancer patients continues to reach new plateaus year after year, the change in global incidence has actually been outpaced by the global population growth rate [4,6–9]. However, in taking into consideration the two-times increased incidence in men than women and the majority of studied nations reporting decreasing incidence rates for men, the worldwide population growth rate of approximately 1.17% suggests an overall decrease in global lung cancer incidence [3,8,9]. Despite this, determining the true overall incidence rate poses several obstacles as not only do the majority of nations, pending data availability, report a counting increase in female lung cancer incidence, but also different risk factors, social determinants, and smoking habit development throughout the 20th century hamper the determination of the true incidence rate [8,10]. Indeed, in their study of lung cancer in 38 countries/regions, Wong et al. [8] found that, among men, only one country, Brazil, showed an increasing incidence while, in women, only one country, The United States, reported a decreased incidence.

Although a variety of factors have been implicated in causing this phenomenon, many have proposed the differences in peak smoking frequencies amongst men and women are the main contributors [5,11,12]. More re-
cently, Wensink et al. [13] analyzed data from the WHO (World Health Organization) Mortality Database and the Human Mortality Database and determined that, amongst females within North America, there was a 30-year delay in smoking-attributable mortality relative to males. In combination with the findings of Rafiemanesh et al. [14], who determined the worldwide lung cancer mortality incidence ratio (MIR) to be 0.85, and Islami et al. [15], who determined a male peak smoking-attributable lung cancer mortality within North America to have occurred around 1990, these findings overall correspond to the recently determined rate within lung cancer among various races and ethnicities [13–15]. Contrasting, as developing countries have just recently begun seeing decreasing incidences in males, the expected peak incidence and corresponding associated mortality rates for women are not expected to reach their peaks until several years [8].

2.2 Race and ethnicity

The association between lung cancer and race and ethnicity has also been further studied in the modern era, leading to significant advancements in smoking risk assessments, lung cancer prevention, and educational efforts, among others [16,17]. For example, in their study analyzing 1979 patient cases in the US, Haiman et al. [18] found that African Americans and Native Hawaiians with low levels of smoking, defined as 10 cigarettes per day, were approximately three times more likely to develop lung cancer than Whites, Latinos, and Japanese Americans ($p < 0.001$), however, this finding became nearly negligible with higher levels of smoking, defined as 30 cigarettes per day. In 2019, Stram et al. [17] conducted a follow-up to their 2006 study by analyzing 4993 cases which further ratified their initial findings. In their meta-analysis filtered from 1877 initial studies consisting of 17,021 cases and 20,885 controls. Although it was similarly found that lower SES and increased smoking were associated with higher lung cancer incidence, Hovanec et al. [24] also found low SES to be associated with increased lung cancer rates independent of smoking behavior when compared to individuals with high SES (OR = 1.84, CI: 1.61–2.09). While the precise attributing factors leading to an increase lung cancer rate in individuals with self-reported low SES have yet to be fully elucidated, several variables such as the financial stresses of cancer, inadequate access to high-quality healthcare, screening, and treatment combined, and lower treatment compliance have been implicated [25–31].

2.3 Socioeconomic factors

Repeatedly, data has suggested an inverse relationship between overall socioeconomic status (SES) and lung cancer incidence. First noticed in the 1970s, various markers of SES such as income, education level, and occupation were found to be inversely associated with lung cancer incidence rates while at the same time strongly associated with tobacco use in the US [22,23]. Just recently, Hovanec et al. [24] evaluated the associations between lung cancer and SES by conducting a pooled analysis of case-control studies consisting of 17,021 cases and 20,885 controls. Although it was similarly found that lower SES and increased smoking were associated with higher lung cancer incidence, Hovanec et al. [24] also found low SES to be associated with increased lung cancer rates independent of smoking behavior when compared to individuals with high SES (OR = 1.84, CI: 1.61–2.09). While the precise attributing factors leading to an increase lung cancer rate in individuals with self-reported low SES have yet to be fully elucidated, several variables such as the financial stresses of cancer, inadequate access to high-quality healthcare, screening, and treatment combined, and lower treatment compliance have been implicated [25–31].

2.4 Geographic patterns

Another critical component complicating current efforts of education, prevention, and treatment is the dynamic nature of lung cancer incidence among the nations of the world and all of the variables dictating lung cancer’s evolution within them. Most commonly, the extent to which a nation has developed and undergone industrialization has been found to be closely associated with lung cancer incidence [32–34]. This phenomenon has largely been attributed to the notion that, as countries industrialize and wages increase, the general population is available to afford tobacco products and develop smoking habits, thus leading to the increase in lung cancer incidence that has been observed in developing nations [33,35].

Indeed, nations in which the peak incidence of lung cancer has already passed tend to be those that have most extensively undergone industrialization such as New Zealand, the US, and Australia [11,36,37]. In contrast, it is anticipated that an increase from 50% to 70% of the global burden of tobacco-related deaths, of which approximately 25% are attributable to lung cancer, is expected to occur in the world’s poor and middle-income nations and emerg-
ing economies by the year 2030 [33,38]. Nonetheless, determining the true incidence patterns among many of the developing nations remains unfeasible as holistic registries have yet to be established and access to adequate healthcare and screening are hurdles that have yet to be overcome [11,39].

3. Etiology

3.1 Overview

Although the link between lung cancer and tobacco consumption has long been established, a plethora of other risk factors have been implicated in increasing the risk of developing lung cancers such as infectious diseases and inflammatory conditions impacting the lungs. In addition, recent advancements have allowed more insight into genetic factors, biomarkers, and proteomics in lung cancer risk-assessment and screening [40–42].

3.2 Environmental factors

3.2.1 Smoking

3.2.1.1 Overview. Smoking has extensively been found to be the most common risk factor in the development of lung cancer amongst both males and females and has been found to be responsible for up to 90% of all lung cancer cases [43]. Indeed, in a meta-analysis representing 7 million patients, O’Keeffe et al. [44] determined the pooled, multiple-adjusted lung cancer RR in smokers to be 6.99 (95% CI = 5.09–9.59) in women and 7.33 (95% CI = 4.90–10.96) in men. However, despite the magnitude of the previously conducted studies, the multiple components factoring into the development of lung cancer, exceedingly complex dynamic nature of the disease, and rapidly evolving tobacco and nicotine industries thoroughly obscure attempts to ratify proposed risk factors, establish guidelines, and develop effective preventative measures [12]. There is a notable difference in cancer incidence throughout the world that reflect geographic trend in the tobacco epidemic.

3.2.1.2 Quantitative risk. In order to accurately assess a patient’s risk of developing lung cancer, data more granular than simple smoking status must be taken into consideration as various factors, such as starting age, overall smoking exposure, types of tobacco products consumed, and smoking method, all significantly contribute to lung cancer risk [44–46].

For example, Peto et al. [47] determined that, when compared to individuals who first started smoking at the age of 20 or older, those who started before the age of 15 had an age-adjusted approximate doubling in lung cancer development risk amongst both men and women. Furthermore, Hegmann et al. [48] analyzed data from a case-control study with 282 histologically-confirmed lung cancer cases matched to 3282 random controls and determined that, even after controlling for amount of tobacco exposure and age, males who took up smoking prior to the age of 20 had an OR of 12.7 (CI = 6.39–25.2) whereas males who began after the age of 20 demonstrated an OR of 6.03 (CI = 2.82–13.9). Furthermore, the OR for female lung cancer development risk was also significantly increased in those who started smoking at an earlier age (OR = 9.97, CI = 4.68–21.2), however, this increased risk continued until the age of 25, after which the OR was found to be 2.58 (CI = 0.53–12.4), suggesting a longer time period for which preventing smoking initiation remains crucial [48].

Overall smoking exposure, commonly reported as packs per day, is also extensively linked to lung cancer risk, however, a more holistic metric of overall exposure, the comprehensive smoking index (CSI), has more recently been developed with the intention of incorporating smoking intensity, duration, and time since cessation [49,50]. Nevertheless, both metrics demonstrate similar trends in that, as the individual metric increases, the predicted risk of lung cancer initially increases several-fold but slows down in risk accumulation with increasing smoking exposure [50].

Despite both of these metrics predicting ORs of approximately 30 in individuals with the heaviest smoking habits relative to never-smokers, recent studies have found that, regardless of overall smoking exposure, all individuals who stop smoking at some point stand to benefit from a decrease in lung cancer risk [50,51]. Indeed, in analyzing data from the Framingham Heart Study Original and Offspring cohort, Tindle et al. [51] found that just 5 years after smoking cessation, former smokers reduce their lung cancer risk by 39.1%, a figure that continues to increase as the time since cessation increases [51]. Furthermore, in their landmark prospective cohort study of 410,231 participants, Thomson et al. [52] found that the age at which smokers quit plays a major role in lung cancer risk mitigation. Indeed, former smokers who quit prior to the age of 45 avoid up to 87% of the excess cancer mortality imposed by smoking, however, the reduction in risk specific to lung cancer mortality has not been determined using these same parameters [52].

In regard to types of tobacco consumption and nicotine delivery methods, available data suggests varying lung cancer development risks between using cigarettes, cigars, or pipe tobacco [53]. In their study analyzing the smoking behaviors of 357,420 patients, Christensen et al. [53] found tobacco use in the form of cigarettes, cigars, or pipe tobacco to be associated with HRs of 11.82 (CI = 10.73–13.03), 3.26 (CI = 1.86–5.71), and 1.51 (CI = 0.61–3.74), respectively, when compared to never-smokers following multivariate analysis. Currently, nicotine delivery methods, such as electronic cigarettes, are sharply rising in use, however, given the recency of their development and incorporation into mainstream use, unequivocal data regarding their lung cancer risk has yet to be produced [54,55].

3.2.1.3 Tobacco and nicotine consumption methods. By and large, the vast majority of tobacco and nicotine products
are consumed via inhalation, however, the variety of methods and devices widely available has markedly increased over just the last 15 years [56–58]. Currently, two main categories of products exist, combustible inhalatory delivery methods and electronic inhalatory delivery methods, the former of which contains both tobacco and nicotine while the latter tends to contain only nicotine and no actual tobacco leaves [56].

The most common form of combustible tobacco consumption occurs through the use of cigarettes, the peak of which has already occurred in many developed countries such as the US and New Zealand [37,57]. On the other hand, the consumption of electronic inhalatory methods, i.e., e-cigarettes, has been on the rise in the US, with drastic adoption and normalization of use amongst adolescents between the 8th and 12th grade, evidenced by an approximate 7% increase in use over the course of just one year (2017–2018, 7.6%–14.4%) [58]. This increase in usage continued the following year [59]. Indeed, in a 2019 cross-sectional analysis of 19,018 students in grades 6–12, 8837 of which were in middle school and 10,097 of which were in high school, an overall rate of 19.5% of students (27.5% of high-schoolers vs 10.5% of middle-schoolers) self-identified as current e-cigarette users despite a study response rate of only 66.3% [60]. To put it into perspective, the US National Health Interview Survey analyzed by the Centers for Disease Control and Prevention reported that, in 2019, 4.5% of all adults were current e-cigarette users, indicating adolescents were current e-cigarette users at a rate approximately 4 times greater than adults [61].

3.2.1.4 Second-hand smoke exposure. Passive inhalation of smoke generated by the combustion of tobacco products, both indoors and out, colloquially referred to as second-hand smoke (SHS), has not only been associated with increased lung cancer risk, but also more recently in adverse growth outcomes of children in addition to a variety of other disease processes [62,63]. Indeed, the notion of adverse health effects brought upon by SHS has been established since the late 20th century, however, despite its prolonged observation, new associations continue to be discovered [62,64]. For example, while SHS has been shown to cause respiratory infections, sudden infant death syndrome, ear infections, and asthma attacks among others, the associations between SHS exposure and increased risk of obstructive sleep apnea along with SHS exposure and mental health issues among children and adolescents [64,65].

3.2.1.5 Cannabis. The association between cannabis consumption and lung cancer risk has yet to be thoroughly investigated as a result of federal prohibition, resulting in a lack of research funding, studies with limited cohort sizes, lack of a reliable use metric, among other reasons [66]. Nonetheless, studies have been conducted. For instance, in a study of 49,321 males, Callaghan et al. [67] found marijuana use to be associated with an increase in HR of 2.12 (CI = 1.08–4.14) for the development of lung cancer, however, this observation was only noted for “heavy” users of cannabis, which the authors defined as lifetime marijuana use more than 50 times, of which only 813 subjects met. Furthermore, Lapham et al. [68] studied the habits of 29,857 adult patients and found that 15.3% reported cannabis use within the past year and 3.1% reported daily use, suggesting that 20.3% of cannabis consumers are daily users [68]. Thus, it is likely the classification of “heavy” cannabis users as merely 50 or more lifetime uses, reported as 813 out of a total of 49,321 (1.7%) within the Callaghan et al. [67] study, strongly suggests potentially significant heterogeneity and sampling inconsistencies between the two studies [67,68]. Currently, a significant association between cannabis consumption and an increased risk for developing lung cancer has not yet been found. However, multiple interacting variables, such as federal prohibition, inconsistent use metrics and classifications, and temporal delay in the development of lung cancer in conjunction with only very recent widespread use and access, continue to hamper efforts aimed at elucidating the effects of cannabis use on lung cancer [66,69,70].

3.2.2 Occupational exposure

3.2.2.1 Overview. The association between cancer risk and occupation was initially brought to widespread attention during the 1970s, and since then, a variety of occupations have been found to significantly increase the risk of developing lung cancer [71,72]. The current literature implicates a variety of contributory occupations in the development of lung cancer such as those which expose employees to asbestos, radon, silica, diesel engine exhaust, smelting within foundries, and polycyclic aromatic hydrocarbons, with asbestos and radon contributing most to lung cancer risk and the risks for which evidence is most clear [72–75]. Although recent meta-analyses large population studies have yet to be conducted focusing on the US, large studies focusing on nations in Europe have approximated an overall occupational contribution of 15.0% towards the overall lung cancer burden [72,74,76].

3.2.2.2 Asbestos. First considered as a contributory agent in the development of lung cancer in the 1930s, asbestos has continuously maintained its status as the occupational exposure hazard that most significantly increases lung cancer risk [72,77,78]. In a study that analyzed asbestos exposure among 3002 adults working in textile manufacturing in the US between 1940 and 2001, Cole et al. [79] found asbestos exposure among textile manufacturing employees resulted in a 9.44% lung cancer mortality rate by age 90. However, with the new Occupational Safety and Health Administration standard of <0.1 fiber/mL, this rate was reduced to 7.17% with no discernable reduction following even further reductions in exposure standard [79].
In regard to attributing a lung cancer diagnosis to asbestos exposure, Henderson and Leigh proposed an initial prerequisite criterion of asbestos exposure with a minimum 10-year latency since exposure initiation followed by a workup analyzing a combination of the patient’s social history and lung tissue counts of asbestos bodies or uncoated amphibole fibers [78,80].

3.2.3 Radiation. High-linear energy transfer (LET) particles have extensively been implicated in inducing the accumulation of DNA damage and genetic mutations, potentially augmenting genetic predispositions to a variety of cancers [81–83]. Radon, colloquially referred to as, “the silent killer”, is the most common source of High-LET radiation implicated in increasing lung cancer risk [84,85]. Indeed, in a comprehensive review of 11 studies that investigated the association with radon exposure and lung cancer risk among 65,000 miners, pooled data evaluated by Lubin et al. [86] revealed radon exposure may be responsible for 40% of lung cancer deaths among miners. Furthermore, radon was estimated to be accountable for approximately 10% of the overall lung cancer burden in the US [85,86]. Despite the known risk and widely available radon levels testing devices, the proportional burden radon exposure contributes to lung cancer has largely remained the same [87,88].

With the common implementation of low-LET radiation, such as X-rays and computed tomography, in medical imaging, a great amount of attention has been brought to the potential for these modalities to increase the risk of cancer development. Commonly known as, “the bystander effect”, radiation which indirectly irradiates cells and simply damages them has long been implicated in eliciting tissue damage and predisposing tissue to malignancies [89]. Despite its extensive history, data regarding the association between low-LET radiation and lung cancer development within otherwise healthy individuals is limited and remains equivocal, a finding further complicated by advancements in radiotherapy that allow for reductions in radiation dose needed without hampering image quality [89–92]. Correspondingly, data regarding the potential occupational risks associated with employees working with low-LET radiation, given the thorough preventative methods using radiation barriers, has yet to suggest any clear evidence of an increased cancer risk [93].

3.2.3 Atmospheric air pollution

Global atmospheric levels of particulate matter rose by 38% from 1990 to 2009, and in 2015 alone, exposure to particulates (PM$_{2.5}$) smaller than 2.5 μm in size was responsible for 4.2 million deaths worldwide [94,95]. In regard to cancer risk, the ESCAPE study, a prospective analysis of data from 17 cohort studies across 9 European countries composed of 312,944 patients, determined increases in PM$_{10}$ of 10 μg/m$^3$ corresponded to increases in lung cancer risk (HR = 1.22, CI = 1.03–1.45) [96]. Correspondingly, subsequent comprehensive studies revealed significant increases in lung cancer mortality concordant with increasing concentrations of particulate matter in the atmosphere [11,97,98]. In their meta-analysis examining the relationship between air pollutants and cancer mortality, Kim et al. [99] analyzed 30 cohort studies and found every increase of 10 μg/m$^3$ in PM$_{2.5}$ resulted in a corresponding increase in lung cancer mortality of 1.14 (CI = 1.07–1.21) while the same increase in PM$_{10}$ resulted in a corresponding increase in lung cancer mortality of 1.07 (CI = 1.03–1.11) regardless of smoking status [97–99].

3.3 Individual factors

3.3.1 Overview

Despite smoking being responsible for approximately 90% of all lung cancer cases, the immense number of new cases worldwide corresponds to the remaining 10% portion representing approximately 220,677 non-smokers newly developing lung cancer in 2020 alone [4,43,100,101]. Outside of environmental risk factors, lung cancer in non-smokers without tobacco exposure is most commonly attributed to a history of pulmonary disease processes and their infections etiologies and genetic predisposition [102,103].

3.3.2 Infections

Several infectious diseases have been found to be associated with an increase in lung cancer risk, most notable are pulmonary HIV, tuberculosis, and HPV manifestations [104–106].

The association between HIV and lung cancer has been investigated for more than four decades, however, only recently were large cohort studies available due to the chronic nature of HIV infection progression and long-term observation needed to track patient outcomes [105,107,108]. In a study composed of 37,294 HIV-infected patients and 75,750 uninfected patients that were prospectively tracked until date of last follow up, death, or cancer diagnosis, Sigel et al. [105] found HIV infection to be independently associated with lung cancer development with an adjusted incidence rate ratio (IRR) of 1.7 (CI = 1.5–1.9). Similarly, Hessol et al. [109] performed multivariable analysis on the data of 2549 women from the Women’s Interagency HIV Study (WHIS) and 4274 men from the Multicenter AIDS Cohort Study (MACS) and found that, relative to HIV-uninfected individuals, HIV-infected individuals with a previous AIDS pneumonia diagnosis had an IRR of 3.56 (CI = 1.67–7.61).

In regard to tuberculosis, a systematic review conducted by Liang et al. [103] in 2009 found TB to be an independent risk factor for lung cancer development with an RR of 1.74 (CI = 1.48–2.03) among combined data from 31 cohort studies. In a population cohort study consisting of 716,872 healthy subjects and 4480 patients newly
diagnosed with tuberculosis who were tracked for 7 years revealed that, following multivariate analysis, tuberculosis patients had an adjusted HR of 3.32 (CI = 2.70–4.09) for lung cancer [106].

HPV infection has also been implicated in increasing lung cancer development risk, however, evidence is still equivocal. For example, in their systematic review and meta-analysis of 36 case-control studies composed of 6980 lung cancer cases, 7474 healthy controls, 24,162 HPV-exposed individuals, and 1,026,986 HPV unexposed individuals, Xiong et al. [110] reported HPV infection increases the risk of developing lung cancer with a pooled OR of 3.64 (CI = 2.60–5.08). Similarly, a meta-analysis of 9 studies conducted by Zhai et al. [111] reported an overall lung cancer OR of 5.67 (CI = 3.09–10.40) in HPV-infected individuals. Despite this, the change in lung cancer risk among HPV-infected individuals has yet to be clearly determined as a result of significant heterogeneity among the analyzed studies and a lack of individual studies composed of a cohort size large enough to provide convincing evidence [110–113].

3.3.3 COPD and other pulmonary diseases

While epidemiological studies report that approximately 20–30% of smokers develop COPD and 10–15% develop lung cancer, COPD is by far the most common comorbidity in patients with lung cancer, with a varying prevalence between 30 and 70%. A recent pooled analysis of almost 25,000 cases from the International Lung Cancer Consortium also showed both lung cancer incidence and mortality to be significantly associated with emphysema [114]. In a large meta-analysis, never-smokers with a history of chronic bronchitis, interstitial lung disease, tuberculosis, or pneumonia were found to have an increased risk of lung cancer [115].

3.3.4 Gender

Lung cancer incidence is rising in women and has in fact more than doubled since the mid1970s. In a study from UK an increased susceptibility was suggested among women compared with men. Data from the UK’s Health Improvement Network showed that female heavy smokers (>20 cigarettes daily) had a greater odds of developing lung cancer than men with comparable smoking histories, with an adjusted OR of 19.2 (95% CI: 17.1–21.3) in women versus 13.0 (95% CI: 11.7–14.5) in men [54]. However, a large prospective cohort study in the US disputed this increased susceptibility to lung cancer given equal smoking exposure. Rising rates of lung cancer in women have also been attributed to genetic variants, environmental exposures, hormonal factors, and oncogenic viruses [116,117]. Although adenocarcinoma is the most common histologic subtype in both genders, women have an even higher predominance of this cell type particularly in never smokers [118,119]. In South Asia, it is estimated that 83% of women with lung cancer may be never-smokers. It is unclear if never-smoking Asian women who immigrated to the US and adopt western lifestyles continue to have elevated risks of lung cancer [120]. Additionally, women with lung cancer have been shown in multiple studies to have better survival rates than men across different age groups, disease stage, and treatment types [121].

3.3.5 Genetic predisposition

First-degree relatives of patients with lung cancer are at increased risk, even after adjusting for smoking habits. Recent genomic studies have shown genetic variation that is associated with increased risk of lung cancer and tobacco smoking behavior. These genes appear to play a role in nicotine dependence and susceptibility for lung cancer [122–124]. Additional genetic loci had been identified using genomic wide association studies that are associated with lung cancer suggesting inherited susceptibility to lung cancer [124–126]. Furthermore, heterogeneity of these associations within specific racial subgroups and histological sub types of lung cancer had been also observed [127–129]. Several gender differences in lung cancer mutations have been described. EGFR mutations are more prevalent in women, especially in non-smokers. In particular, the L858R mutation has been shown to be associated with genetic polymorphisms related to estrogen biosynthesis and metabolism in never-smoking females with lung adenocarcinomas [118,119].

Author contributions

Authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Analysis and interpretation—MJ, WTV. Drafting the manuscript—MJ, WTV. Critical revision—MJ, WTV. Final Approval—MJ, WTV.

Ethics approval and consent to participate

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Conflict of interest

The authors declare no conflict of interest.

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