

The Epidemiology of Lung Cancer- How **Much Have We **Discovered?****

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Abstract

Lung Cancer has become a global health burden in the past years due to being the second largest contributor to new cases and the high mortality rates worldwide which is around 1.8 million patients. There are two main histological groups of Lung Cancer, however non-small cell lung cancer is more prevalent and is composed of three histologic subtypes of which adenocarcinoma represents the highest prevalence. It is calculated that the incidence in male is higher than female. Cigarette smoking is the main risk factor for developing lung cancer, however, other risk factors contribute to the increasing cases. Studying the epidemiology of lung cancer is essential to establish robust surveillance system and establish policies to reduce this global concern. In this article we will review the epidemiological data, the history of the disease, and the associated risk factors.

Keywords

Lung cancer, Prevalence, Secondhand smoking, Cancer Prevention NSCLC and smoking,

Introduction

The global figures calculated that lung cancer is ranked as the second largest contributor to new cancer diagnosis and the most common cause of death^{1,2}. Lung cancer causes excess burden worldwide, accounting for the death of approximately 1.8 million individuals with mortality in males 2-folds higher than females³. Most cases are of the non-small-cell type (NSCLC), which represents 84% of all cases^{4,5}. Cigarette smoking is the greatest risk factor for lung cancer, and the risk increases for both smokers and second-hand smokers^{6,7}. Family history, exposure to air pollution, lung disease, and oncogenic viruses can also be some of the risk factors of lung cancer⁶.

A historical overview

Lung Cancer was historically considered a non-existing disease, as reported by Le Roux, fellow of Bichat in 1798⁸. **During the World War I, smoking became popular within soldiers who smoked to relieve stress**⁹. Smoking rates dramatically increased in the U.S. and Europe with claims from tobacco companies that smoking was safe, supported by physicians advocating it in advertisements¹⁰.

The world did not wake up until 1964, after the report of the U.S. Surgeon general which warned that smoking was hazardous and is correlated to lung cancer^{9,11}. However, lung cancer existed as early as 1500 when a particular attention was given to miners in two regions of Germany and Czechoslovakia who developed a deadly lung disease and was named “Bergkrankheit” or mountain sickness⁹. The disease lasted for 25 years and killed 60-80% of all miners, resulting in lung cancer recognized as an occupational disease and suspecting that arsenic might be involved in the disease etiology⁹. Furthermore, there was a surge in the demand for uranium following the World War II, when politicians called for the development of nuclear weapons, resulting in the death of more miners without any accountability for protecting them^{9,12}.

Lung Cancer Histology

Lung Cancer has two main histological groups: small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC).¹³ NSCLC comprises three main histological subtypes: adenocarcinoma (ADC), squamous cell carcinoma (SCC), and large cell carcinoma representing 40%, 25%, and 10% respectively^{5,14}.

Adenocarcinomas have a high frequency of histologic heterogeneity with five variants recognized by the World Health Organization and the International Association for the Study of Lung Cancer⁵. SCC are most commonly located centrally in the larger bronchi, while large cell carcinoma is undifferentiated and lacks the cytologic features of the latter two types^{5,15}.

20,561 lung cancer cases in women were studied in Poland and found that squamous cell carcinoma was the most common subtypes among never smokers and current smokers¹⁶.

Conversely, Adenocarcinoma was the most common subtype among never smokers, previous smokers, and current smokers in an analysis of 437,976 Korean of which 1357 cases of lung cancer were diagnosed¹⁷.

Development of lung cancer incidence for women versus men over time

Vital statistics data for women aged 40-69 years in the United States in 1935-1940 show that female lung cancer death rates before the dawn of female smoking were similar to those of women of the same age who have conveyed no history of active smoking in cohort studies carried out since 1960¹⁸⁻²¹. The absolute rates are 20-25 times¹⁸⁻²¹ more for the male current smokers

than never smokers, and 10-12 times higher for female current smokers than never smokers²². Because of the change in lung cancer incidence in women, recent figures show that lung cancer death rates decreased in women for the first time, more than a decade after it decreased in men²³. The lag in the declining rates of lung cancer in women compared to men has been attributed to the uptake of cigarette smoking in women which peaked two decades later than men²⁴. According to the global cancer statistics 2020, cancer is the third mostly common diagnosed cancer in women, and the second leading cause of cancer death^{25,26}.

Lung cancer surpassed breast cancer as the leading cause of cancer deaths in women in the late 1980s, and in 2022 around 1.5 as many women are estimated to die from lung cancer versus breast cancer in the United States².

The American Cancer Society Cancer Prevention Study II, which followed 1 to 2 million people between 1982 and 1988, reported an overall risk for lung cancer in women smokers of 11.94, compared with an overall risk of 22.36 in male smokers, after considering the intensity of smoking²⁷.

In order to clinically quantify cigarette smoking, pack-years are used, which measure the amount a person has smoked over a long period of time by multiplying the number of cigarette packs smoked daily by the number of years a person smoked²⁸.

For example, 1 pack-year means consuming 40 cigarettes daily for 6 months, or 20 cigarettes daily for one year²⁹.

A Canadian case-control study of male-female differences in lung cancer covering the period 1981 to 1985 showed that with a history of 40 pack-years of cigarette smoking relative to lifelong nonsmoking, the overall risk for women developing lung cancer was 27.9 versus 9.6 in men³⁰.

The etiology has been studied and showed that mutations in tumor suppressor gene p53 and the proto-oncogene K-RAS as well as DNA adduct levels were higher in women, suggesting that there is an interaction between tobacco carcinogens and endogenous/exogenous sex hormones³¹⁻³³.

Descriptive Epidemiology

Age as a risk factor

Lung Cancer incidence rises with age in both smokers and never smokers. The national cancer institute's surveillance, epidemiology, and end results program showed that the median age of cancer diagnosis is 66 years³⁴. Patients older than 80 years constitute 14% of all patients with lung cancer in the United States, but account for almost a quarter of all lung cancer mortality^{35,36}. The high incidence in old age is correlated to smoking frequency, e-cigarettes use, time since quitting, and smoking 100 cigarettes in a lifetime³⁷.

Genetic Factors

The genetic component is associated with susceptibility to the pathogenesis of lung cancer, owing to familial aggregation, host susceptibility, pathogenic genetic variants, and individual's response to biologics therapies, which is with or without the exposure to cigarettes³⁸⁻⁴⁰. Smokers with a history of early commencement of lung cancer in their first-degree relatives have an increased risk for lung cancer with growing older in age than smokers lacking such a family history⁴¹. This might speak both for genetic and environmental factors since the inhalation of second-hand smoke cannot be excluded here.

The age-standardized death rate from lung cancer was roughly 40% higher among African American than white women who reported never smoking, but a statistically significant racial difference was not seen for never smoking women; there were insufficient data to measure the risk in black men⁴².

Studies showed that there is an association between Human papillomavirus (HPV) and the development of lung cancer due to E6 and E7 oncogene protein that regulates the expression of multiple target genes and promotes the proliferation of lung cells⁴³.

Primary lung cancer diagnostics

An essential part in staging NSCLC is assessing the mediastinum for lymph node involvement. Endoscopic ultrasound along with endobronchial ultrasound are both minimally invasive endosonographic procedures that involve insertion of an ultrasound probe in the esophagus or airways⁴⁴⁻⁴⁶.

The early diagnosis of lung cancer is necessary because the 5-year survival rate for treated stage I lung cancer is substantially better than for stages II to IV⁴⁷.

The US preventive services task force recommends annual low-dose Computed Tomography scan screening for high-risk individuals who are of 50-80 years of age, with a 20 pack-year smoking history, and are current smokers or quit within the last 15 years⁴⁸. Screening high-risk population has been analyzed and showed reduction in mortality, however, false-positive results led to unnecessary invasive procedures and other harmful outcomes⁴⁹.

Correlation between NSCLC and smoking

Overwhelmingly, the major risk factor for lung cancer is cigarette smoking with a relative risk of 20 to 25 and an attributable risk of 85% to 90%⁵⁰.

Smoking contains 60 carcinogens that bind to DNA forming DNA adducts, which can lead to errors during replication causing tumor initiation and progression^{51,52}. Studies showed that 80% of lung cancer patients with squamous subtype were former smokers, and research confirmed that these genetic and immune microenvironment mutations caused by cigarette smoking are key factors in the altered response to immunotherapy⁵¹.

The primary factors of lung cancer in never smokers are linked to exposure to carcinogens including radon gas, second-hand smoke, and other indoor air pollutants such as incense burning^{53,54}.

In five studies, investigators explored indoor contact to smoke from wood, straw, and further solid fuel and lung cancer risk amongst never smoking women⁵⁴. In a multicenter case-control study that was conducted during 1998–2001, Lissowska et al. found a similar association of solid

fuel use for heating and cooking with lung cancer risk, where the odds ratio of lung cancer in lifetime users of solid fuel was 1.80 and switching to nonsolid fuels resulted in a lowered risk⁵⁵. It has been suggested that the lung cancers that arise from wood smoke may behave differently from lung cancers due to tobacco smoke, by having different carcinogenic mechanisms that are translated as divergences in the clinical and mutation profile⁵⁶.

Smoking would be associated with more mutational load, which might make tumors more immunogenic⁵⁷. The causal relationship between cigarette smoking and lung cancer has been well known, with a stronger association with squamous (SQ) cell carcinoma than adenocarcinoma⁵⁷.

Lung Cancer Occurrence in Never Smokers

Roughly 10-15% of all lung cancers arise in never smokers, making lung cancer one of the major causes of cancer-related mortality in never smokers^{58,59}. The excessive and extended use of tobacco was an imperative influence in the initiation of lung cancer, putting in consideration that lung cancer in a nonsmoker was infrequent; and there could be a lag period of 10 years or more between cessation of smoking and the clinical onset of carcinoma⁶⁰.

Although more than 80% of lung cancers occur in persons with tobacco exposure, fewer than 20% of smokers develop lung cancer⁴⁷.

The overall global statistics estimation is that 15-20% of lung cancers in men, and over 50% in women are not attributable to smoking, with never smokers accounting for 25% of all lung cancer cases globally⁶¹. If lung cancer in never smokers was considered unconnectedly, it would rank as the seventh most common cause of cancer death globally before cervical, pancreatic, and prostate cancer⁶². However, the demographics of lung cancer in non-smokers differ geographically. For instance, Asian non-smoking women comprise 60-80% of lung cancer cases, while the US study showed 19% in women versus 9% in men, both non-smoking^{63,64}.

A series following 12,000 patients with lung cancer in California found a dramatic increase in broncho-alveolar carcinoma in never smokers from 19% during 1995 to 1999 to 26% during 1999 to 2003⁶⁵. The percentage of other types of lung cancer in never smokers also increased from 8.6% to 9.4%.⁶⁴ Another study in the United States found a small but statistically significant increase in the mortality rate in women with non-smoking associated lung cancers from 12.3% in the years 1959 to 1972 to 14.7% in the years 1982 to 2000⁶⁶⁻⁶⁹.

A population-based case-control study in Canada instituted that job-related exposures, a history of lung disease, and a family history of early smoking commencement cancer were important risk factors for lung cancer amongst never smokers⁶⁹.

An amplified risk of lung cancer has been steadily shown amongst never smoking women exposed to indoor biomass smoke and cooking vapors. Less reliable outcomes were found for different types of oils used for cooking and exposure to smoke from coal and risk of lung cancer among never smokers⁷⁰.

With little exceptions, research established the increased risk of lung cancer among asbestos occupationally exposed never smokers compared to unexposed non-smokers evaluation groups.

Although the accurate nature of the interaction between asbestos and tobacco smoking in lung carcinogenesis is still a topic to argument, the indication of a carcinogenic effect of asbestos independent from smoking is very robust⁷¹.

Overall, the conclusions on occupational risk factors in never smokers are corresponding to those in smokers, although the measure of the scale of the smoking interaction is complexed by the insignificant number of cases of lung cancer amongst never smokers involved in most studies⁶².

Secondhand smoking

Second-Hand smoke (SHS) is also known as environmental tobacco smoke, which an individual inhales in a form of a mixture of side stream smoke or exhaled mainstream smoke^{20,72}.

Side stream smoking is the indirect inhalation of smoke that comes from the tip of cigarettes and contributes for 80% of secondhand smoke⁷³. It is known to exert genotoxic and carcinogenic effects because it yields by-products of tobacco including tobacco-specific nitrosamines known as the major cause of adenocarcinoma and has been detected in the urine of patients exposed to secondhand smoking⁷⁴.

Strong evidence from multiple sources supports the causal association of SHS exposure with lung cancer in never smokers. Reports published in 1981 from Asia (Japan) and Europe (Greece) showed a larger lung cancer risk in never smoking wives whose husbands are cigarette smokers^{75,76}.

Epidemiologists have verified the association between lung cancer and involuntary smoking using case-control and cohort designs and have steadily found that secondhand smoking contact is connected with lung cancer risk in never smokers⁷⁷.

Another pooled investigation of large-scale studies to evaluate the risk of lung cancer of never smokers exposed to spouse and workplace sources of secondhand smoking found an additional risk of 23% from exposure to spousal smoking and 27% from exposure to workplace sources of Secondhand smoking⁷⁸.

Studies that investigate the relationship between secondhand smoke focused on identifying the threshold amount of smoke exposure that can cause or explain the underlying biological mechanism⁷⁴. A recent meta-analysis was conducted on the epidemiological studies worldwide showed that there was an increased risk of all cancers by 16% and up 20% of cancer deaths could be prevented by smoking cessation⁷⁴.

Another case control study following 2400 families' relatives of 316 never smoker patients with lung cancer cases uncovered a 25% excess risk for cancer in first-degree relatives of patients with lung cancer pointing to a genetic risk⁷⁹. A summary analysis of a large number of epidemiologic studies on the risk for lung cancer in nonsmokers found an excess risk for lung cancer of 24% in nonsmokers who lived with a smoker⁸⁰.

The correlation between other diseases, smoking and lung cancer

Interestingly, one study that examined lung cancer risk among 2640 participants of non-smokers, ex-smokers, and current smokers who have had pulmonary tuberculosis, the hazard ratios of lung cancer were 3.52, 2.16, and 3.71 compared to controlled groups respectively⁸¹.

Combustion of coal or solid fuels for cooking, and heating in inadequately ventilated spaces are among the forms of indoor air pollution that have been noticeably associated with an increased risk of lung cancer in never smokers and may be a particularly important factor contributing to the high incidence of lung cancer in never smokers in East Asia⁸².

Asbestos has a known carcinogenic effect, and in a large cohort among the US insulation workers, smoking increased the lung cancer risk by 10 folds, asbestos increased risk by 5 folds, and the two together increased the risk around 50 folds⁸³.

Oncogenic viruses, including HPV and HIV have been central to research in lung cancer among smokers and nonsmokers⁸⁴. Currently, studies testing lung cancer specimens for HPV have yielded mixed results, and such variability of the frequency of HPV-positive lung cancer may be due to genetic susceptibility; methodologic approaches to detect HPV, such as those that involve the use of polymerase chain reaction; in situ hybridization and immunohistochemistry; and environmental and high-risk behavior variables⁵³.

Similar to the concerns related to the evidence for various viruses as causes of lung cancer further investigations are needed to solidify the evidence for a causal role of Chlamydia in lung cancer⁸⁵.

More recent studies after adjusting for pack-years of smoking and other relevant covariates in a female cohort showed that there was evidence for inverse associations of body mass index (BMI) and lung cancer risk in current and former smokers, whereas in never smokers, BMI was positively associated with lung cancer⁸⁶.

Some non-malignant diseases have been associated with an increased risk for lung cancer, the strongest association being with chronic obstructive pulmonary disease (COPD). Tobacco smoking is the primary cause of both lung cancer and COPD. A study of female never smokers with lung cancer showed a statistically significant association between the presence of airflow obstruction and the development of lung cancer⁸⁷.

More recent studies in large cohorts have shown that COPD is significantly associated with an increased risk for lung cancer, especially in men^{88,89}. Because COPD affects an estimated 40% to 70% of patients with lung cancer, a coexistence of lung cancer and COPD likely reflects a common smoking exposure⁹⁰.

Cancer Prevention Studies I and II on Lung Cancer mortality

Comprehensive death data was published regarding lung cancer mortality rates amongst never smokers enrolled in two large American Cancer Society cohorts, the Cancer Prevention Studies I and II, which were initiated in the late 1950s and early 1980s, respectively, to characterize the risks of smoking. Scientists have followed the vital status of the enrolled participants longitudinally through the present and have published thorough information on age-, sex-, and race-specific lung cancer death rates in never smokers for the entire 12-year follow-up of Cancer Prevention Studies -I and 18-year follow-up of Cancer Prevention Studies -II⁴².

The greatest indication on time trends of lung cancer in never smokers originates from Cancer Prevention Studies -I and Cancer Prevention Studies -II. At least for the time period covered by these two studies, lung cancer mortality does not appear to be increasing in never smokers⁵³.

Conclusion

The global incidence and prevalence rates of lung cancer are increasing over the years, which calls for a deep understanding of the epidemiological patterns, and the etiology behind this global disease burden. While there are continuous public health efforts to reduce the consumption of cigarettes, there is an urgent need to address this global burden at a universal level and develop policies to eliminate the controllable risk factors attributing to lung cancer, given the risk it imposes to individuals, and consequently the environment, besides the high economic burden on the healthcare sector.

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