

LUNG CANCER IN THE WORLD: THE INCIDENCE, MORTALITY RATE AND RISK FACTORS

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Abstract – Objective: Lung cancer (LC) is one of the most common cancers in both sexes. It is also one of the deadliest forms of cancer in the world. An increase in the incidence rate of LC, coupled with the nature of its recurrence, has led to massive burden on health care system. Study findings have shown that the geographical and ethnical distribution of LC varies in different parts of the world, as in men of the Americas living in Europe, East Asia and North America it is significantly higher than sub-tropical Africa. On the other hand, most studies in this area focus mainly on LC therapies. Considering the limitations of publishing a comprehensive study with emphasis on epidemiological aspects and LC risk factors in the world, the need for studies in this field is felt. Therefore, the aim of this study is to determine the incidence and mortality rates and risk factors of LC in the world.

KEYWORDS: Lung cancer, Incidence, Mortality, Risk factors, World.

INTRODUCTION

LC is one of the most common cancers in both genders¹. LC accounted for 14% of the total cancer diagnosis in 2012 with 1.8 million of new cases². Because of the lack of clinical symptoms in the early stages, most LC cases are detected in advanced stages³. The five-year survival rate of this cancer is only 17% (1). It is also one of the deadliest forms of cancer in the world⁴. In 2012, LC formed 20% of all deaths from cancer in the world with about 1.5 million deaths⁵. Also, 27% of deaths from cancer in the United States in 2015 and 20% of deaths from cancer in the EU in 2016 were related to LC⁶. More than 60% of diagnosed LC cases occur at the age of 65

or older. Less than 2% of cases occur in people under the age of 45 years. In other words, the average age of LC diagnosis is at the age of 70⁷. The incidence of LC in developed countries is higher than less developed ones². Almost all LC cases occur in low to middle income countries⁸. Study findings have shown that the geographical and ethnical distribution of LC varies in different parts of the world, as in males of the Americas living in Europe, East Asia and North America it is significantly higher than sub-tropical Africa². Also, a remarkable geographical change in the incidence rate of LC indicates that various factors influence the increasing rates of LC⁹. On the other hand, most studies in this area focus mainly on LC therapies¹⁰⁻¹². Considering the limitations of



publishing a comprehensive study with emphasis on epidemiological aspects and LC risk factors in the world, the need for studies in this field is felt. Therefore, the aim of this study is to determine the incidence and mortality rates and risk factors of LC in the world.

MATERIALS AND METHODS

A rapid literature search strategy was conducted for all English language literature published before March 2017. We searched on PubMed, Scopus and Web of Sciences. The keywords included 'lung cancer', 'epidemiology', 'incidence', 'mortality', 'risk factor, and 'world'. The search strategy was adjusted according to different requirements for each database. The studies that clearly described the incidence and mortality rates of lung cancer and (or) related risk factors were included in the review.

INCIDENCE AND MORTALITY RATES OF LC IN THE WORLD

LC with a standardized incidence rate of 23.1 cases per 100,000 is one of the most common cancers in the world, and is the most commonly occurring cancer in the world in terms of case frequencies¹³. In 2012, out of a total number of 1825,000 new LC cases in the world, the rates for new LCs has been 1242,000 cases in men and 583,000 in women¹⁴. Also, among all new LC cases in the world in 2012, 103,388 new cases of LC (56 %) have been recorded in both sexes in Asian countries¹. The incidence rate of LC is various in different parts of the world. The average incidence rate of LC varies from 0.06 to 31.5 per 100,000 cases¹⁵. In 2012, the highest standardized rate of LC has been in Central and Eastern Europe with 53.5 cases¹⁶ and 50.4 in Eastern Asia per 100,000 cases¹. Also, the lowest incidence rate has been seen in Central and Western Africa by 0.2 and 1.7 cases per 100,000 cases, respectively¹⁷. LC is the most important and most common cancer in men with an incidence of 34.2%¹³. In men, the highest rates of LC are in Europe¹⁶, East Asia¹ and North America¹⁸, and the lowest are in suburban Africa². In women, LC has the highest incidence rates in North America, North and West Europe, Australia/New Zealand, and East Asia¹⁵. The incidence rates of LC have decreased in men by 3% and in women by 2.2% per year¹⁹ between 2011 and 2007. Despite the decline in the incidence rate of LC in North American males, Australian and European countries²⁰, the in-

cidence rate of LC in Asia and Africa¹, as well as in women, has been increased²¹. It seems that the causes of changes in LC rate and its trends are the difference in the pattern of smoking²²⁻²⁴ and the difference in the level and degree of tobacco epidemic²². In some Western countries, such as Denmark, the United States and Great Britain, the tobacco epidemic has begun long times ago and has reached its peak by the middle of the last century, and then the mortality rate has declined in men and had a plateauing in women^{25,26}. In countries where the tobacco epidemic has reached its peak later, such as Spain and Hungary, LC rates are descending in men, but ascending in women²⁵. On the contrary, in countries where the tobacco epidemic has peaked or is rising more recently, such as Indonesia, China and several African countries, LC rates are likely to increase for several decades unless interventions be implemented to stop smoking^{27,28}. The LC, with 19.7 per 100,000 cases of the standard mortality rate (ASMR) is the first and most common cause of death from cancer in the world¹³. Sexually, mortality rate of LC was significantly higher in men than women. As of the total of 158,992 deaths in 2012, 1098702 cases were estimated in males (69.1%) and 491223 cases in females (30.9)¹. LC in men with ASMR of 30 cases is known to be the first and most common cause of cancer deaths in the world; while in women with ASMR of 11.1% of cases is in the second place of deaths from cancer^{16,29}. In 2012, the mortality rate of LC was 936051 in Asia, accounting for 58% of the world's deaths from cancer. Of these numbers, 668765 cases (71.45%) were estimated in men and 267286 (28.55%) cases in women^{18,30}. The maximum ASMR of LC in the European Union (EU) in the late 1980s has been with a rate of more than 53 cases per 100,000, and then in the early 2000s has reduced to 44 per 100,000 cases³¹. The LC mortality rate varied through all over the Europe at the early 2000s, which has reached to a number between 35-45 cases per 100,000 in the largest western European countries (France, Germany, Italy and Great Britain), and in Hungary, Poland, Russia and it has reached to 55-80 cases per 100,000 in a few Eastern and Central European countries⁷. In terms of gender, the total mortality rate of LC has increased in women in most European countries as well as in all the world in recent years^{29,32}. In few countries (such as Denmark, UK and USA), the mortality rate has dropped in recent years³³. Also, in middle-aged men, mortality rates have been higher between the years of 1980-2000, and have reached to 61 from 80 cases per 100,000³⁴. Table 1 shows risk factors of lung cancer.

TABLE 1. Factors related to the lung cancer.

Factor related to LC		Protective	Risk factor	Controversial
Smoking	Cigarettes		•	
	Pipes		•	
	Cigars		•	
	Cigarillos		•	
	Hookah		•	
	Marijuana			•
Diet and alcohol	Beta Carotene		•	
	Arsenic		•	
	Fruits, vegetables and micro nutrients	•		
Alcohol				•
Occupational complications		•		
Pulmonary diseases	COPD			•
	TB	•		
	Asthma	•		
Radiation	Chest radiotherapy		•	
	Low radiation			•
Air pollution			•	
Lower Socio-economic status			•	
Family history	Asthma		•	
	TB		•	
Gender	Men	•		
	Women		•	
Ethnics	Black men		•	
	White men	•		
	Black women	•		
	White women		•	

LC INCIDENCE RISK FACTORS

Smoking

Smoking, and in particular tobacco smoke, is one of the main causes of the various LC cases⁶. Smokers are exposed to LC approximately 20 times more than people who have never smoked regularly. Smoking is responsible for 80% of LC in men and 50% of LC in women^{35,36}. LC is up to 90% attributed to smoking in countries with a history of tobacco use³⁷. Investigating the cause of promoting LC in patients with a history of smoking is very complicated, because in these patients smoking is considered as a moderator or a strong confounder factor⁶. Studies' findings have shown that non-smoker individuals exposed to cigarette smoke are also at increased risk of LC³⁸. As, the LC risk for non-smokers who marry smokers is 20-30% higher than others^{39,40}. The smoke of burning tobacco has more than 4,000 compounding containing 50 carcinogens⁴¹. Studies have shown that three main carcinogens including polycyclic aromatic hydrocarbons (PAHs), tobacco specific nitrosamines (TSNAs), and aromatic amines play an important role in

cigarette-related cancers⁴². The risk of LC in heavy and continuous smokers is more than 20 to 50 times higher compared with non-smokers⁴³. The most important indicator of LC's risk is the duration of smoking⁴⁴. Findings from the study in the United States showed that LC rates are higher in African-Americans compared to other races, which can be due to more smoking⁴⁵. Other study findings showed that the risk of promoting LC is lower in Japan and China compared to North America and Europe. It seems that one of the major causes of this difference is due to regular and lower smoking in Asian countries compared to other countries⁴⁶. Despite the fact that cigarettes as one of the main tobacco products cause LC, there is a risk of LC incidence with other tobacco products including pipes, cigars and cigarillos^{47,48}. The risk of LC with cigar is also high, but lesser than smoking and this is due to the difference in smoking frequency and the depth of the respiration. There is a similar pattern for pulling the pipe and hookah⁴⁹. Regarding the use of non-tobacco products, the potential impact of marijuana on the risk of LC is interesting. Despite the acceptance of marijuana as a risk factor for LC, current



evidence with adjusting the smoking does not confirm this association⁵⁰. LC risk has also been reported too high in people who use hookah⁵¹.

Diet and alcohol

BETA CAROTENE

The findings of a clinical trial showed that LC risk in smokers receiving high levels of beta-carotene supplementation has been increased⁵². Cancer society experts (2007) also reported that there are convincing evidence of an increased risk of LC in recipients (smokers) of high doses of beta-carotene⁵³.

ARSENIC

There are sufficient evidence about the relation between arsenic in drinking water and increased risk of LC⁵⁴. High levels of arsenic in drinking water of residents of Southeast Asia⁵⁵ and South America⁵⁶ has caused increased risk of LC in residents of these areas. In most of these studies, the water arsenic level is several times higher than the United States and even higher than those regions where the level of arsenic is higher than normal level⁵⁷. Most Americans using the public water system are drinking water without a major arsenic source⁵⁶.

FRUITS, VEGETABLES AND MICRONUTRIENTS

Vegetables, fruits, and micronutrients contain certain antioxidants which prevent the incidence of LC. Most studies in this area are based on the assumption that antioxidant-rich diets may reduce DNA damage and as a result protect the body against LC⁵⁸. Findings from cohort studies in this field showed that people who consume a lot of foods containing fruits and vegetables are at lower risk of developing LC⁵⁹. In a more recent study, a strong protective relationship was seen with fruit consumption but, not with the consumption of vegetables⁶⁰. The findings showed that increased consumption of tomatoes reduced the risk of LC^{61,62}. Findings from studies have shown that a diet rich in vitamin C and carotenoid plays a protective role against LC both in smokers and non-smokers^{63,64}. The systematic review findings showed that cruciferous vegetables play as a protective factor against LC⁶⁵. Among the effective cruciferous vegetables, in reducing the incidence of LC, we can point out to broccoli, cabbage, cauliflower, Brussels sprout, and kale. Cruciferous vegetables are rich in isothiocyanate. Isothiocyanate inhibits the bio-activation of pro-carcinogens found in tobacco smoke⁶⁶. Isothiocyanates also plays a significant role in in-

creasing the excretion of carcinogenic metabolites before they damage DNA^{67,68}. There are many epidemiological studies about on the relationship between LC and cruciferous vegetables^{68,69}.

ALCOHOL

About the alcohol consumption and LC risk, a positive association has been reported between alcohol and LC in several studies⁷⁰. On the other hand, Fernández-Somoano et al⁷¹ findings showed that high dose alcohol intake is one of the main risk factors among individual smokers. Also, the findings of a meta-analysis study showed that due to the lack of favorable correlation between alcohol intake and risk of LC in non-smokers, it was found that increased risk of LC in alcohol users is mainly due to residual confounders⁷⁰. Therefore, due to the existence of confounding factors of smoking, the impact of alcohol intake on LC has become a controversial discussion, and there is a need for further studies in this field after controlling the confounding factors.

Occupational complications

Several studies have confirmed the relationship between occupational exposure and LC^{72,73}. The risk of LC increases in workers employed in certain industries and occupations⁷⁴. Two studies also found that the LC ratio attributed to occupational factors was 14.5 in Great Britain⁷⁵, and 12.5% in France⁷⁶. The most important occupational lung carcinogens are asbestosis, radon, silica, aromatic hydrocarbons, and heavy metals⁷⁷. Among the metals that exposing them can cause LC, we can refer to nickel, arsenic, and chromium⁷⁸. Despite the increased risk of LC in employees exposed to such metals, this risk has been significantly controlled in developed countries⁷⁹. Two studies have reported that workers, who are exposed to mustard gas and soot for long periods of time in higher concentrations of urban air, are at higher risk of LC^{80,81}. Various studies have reported the correlation between exposure to diesel engine smoke and LC^{82,83}.

According to silica, the findings of a systematic review study showed that LC risk had increased noticeably in silicotic patients⁶. Among the jobs that expose workers to crystalline silica, we can be point out to pottery, ceramics, brick products, and stone cutter companies⁸⁴. Meta-analysis study findings also showed that the mortality risk is twice more than other people from LC due to exposure to silicon⁸⁵. Findings related to exposure to silica and increased risk of LC is not consistent among studies, and on the

other hand, in most of these studies the effect of smoking has not been controlled well. Therefore, there is need for further studies and controlling confounders to confirm the relationship between exposure to silica and increasing risk of LC.

Asbestos is a general term used for several different types of mineral silica and asbestosis is referred to fibrosis of lung parenchyma, which is due to inhalation contact with asbestos fibers. People who deal with asbestos include workers in mines, mills, manufacturing companies, asbestos string textile, construction workers, plumbers, welders, people who work with cement, and brick and brake pads who are suffered more than others from LC⁸⁶. Also, LC risk is higher in workers exposed to asbestos and smoke⁸⁷. Findings of Aljunid's et al⁸⁸ showed that the LC risk among workers exposed to asbestosis was seven times higher than others. Radon is a kind of odorless, invisible, tasteless radioactive gas that is produced from the decomposition of uranium from rocks and soil. Two products of radon decomposition cause distribution of alpha particle, which their high energy cause damage to the DNA of the lung epithelium cells⁷³. In the United States, the second major cause of LC, and the main cause of LC among non-smokers, is radon⁸⁹. Findings of the epidemiological studies showed that exposure of uranium miners to radon has led to LC⁹⁰. The concentration of radon in mines is 100 to 50 times higher compared to house inside radon⁷³. According to low levels of radon in the open air, there is no threat to people in the open environment. In the indoor environment, especially in underground floor, the risk of LC increases due to the increased concentration of radon⁹¹.

Pulmonary diseases

One of the conditions that increases the risk of LC is depended to smoking, is chronic obstructive pulmonary disease (COPD), and several studies have shown this relationship^{92,93}. On the one hand, smoking is one of the main causes of COPD and LC^{94,95}. Such a strong correlation with both of these diseases can cause statistical methods eliminating the effect of smoking clearly to fail. Therefore, in order to show the relationship between COPD and LC, further studies are needed after eliminating such confounding variables. Pulmonary tuberculosis patients are also at risk of LC⁹⁶. The findings of a meta-analysis study showed that there was a relationship between asthma and LC risk after the control of smoking⁹⁷. The cohort study findings in China also showed that the relative risk of LC in patients with tuberculosis

was 1.5 and it was 2 after twenty years of TB⁹⁸. Findings of an epidemiological study also showed that there is a significant relationship between the infection of Chlamydia pneumonia and LC risk, but more studies are needed in this regard⁹⁹.

Radiation

Exposure to large quantities of ionizing radiation is a factor which increases developing LC¹⁰⁰. The finding of studies have shown that people exposed to chest radiotherapy due to cancers such as breast and Hodgkin's disease in particular, smokers and atomic attack survivors are at high risk of LC⁶. However, the exposure to low radiation levels, especially in radiotherapy staffs, cannot be easily verified and there is a need for more extensive studies in this regard⁷⁷.

Air pollution

In populated cities with high traffic loads, LC's risk is higher than other areas⁷⁰. Researchers have estimated that about 5% of all deaths from LC is due to air pollution. This risk is lower than the LC risk from smoking¹⁰¹. Also, indoor air pollution caused by in appropriate inside ventilation, which use coal fuel, wood and other solid fuels, is a risk factor for LC in several regions of Asia, especially in non-smoker women¹⁰².

Socio-economic status

Study findings have shown that mortality rates and incidence of LC are lower in groups belonging to lower socioeconomic status^{6,103}. Some studies have also shown that there is a relationship between SES and LC survival^{9,10}. Findings from a study in Canada showed that there is an inverse relationship between the level of education, family income, and LC risk in both genders¹⁰⁴. The risk of LC in low income individuals and from low level society level is associated even after smoking¹⁰⁵. In the Netherlands, after adjusting occupational exposure, there was an inverse relationship between education level and LC¹⁰⁶. People with lower socioeconomic status are diagnosed at a later stage, which is associated with an increase of LC rates¹⁰⁷. Also, lower social and economic status is associated with the interaction between a set of LC risk factors, such as exposure to carcinogens at work, inappropriate diet, and smoking. All of these factors are related to lower socioeconomic status¹⁰⁸.



Family, Individual and Genetic History of the LC

If a person develops LC, the risk of developing other LC type is higher in this person⁶. The risk of LC in children and siblings of people with LC is higher than other people¹⁰⁹. Also, LC risk is higher in people with a family history of LC or those who have already been diagnosed with benign pulmonary diseases, such as asthma and TB¹¹⁰. The findings of a study showed that family risk of LC was seen in non-smokers, and the relationship between LC risk and the history of LC was seen in the first-degree relatives. This finding was more pronounced in people aged 40-59 years old, so genetic factors seem to be more important in younger ones¹¹¹.

In some people, DNA changes inherited from parents, increases significant distribution risk of special diseases. However, inherited mutations do not cause LC alone. However, some genes seem to play an important role in some families with the history of LC. For example, individuals who inherit specific DNA changes in chromosome 6 are at higher risk of LC even if they are not smoking¹⁹. Also, some people do not inherently have the ability to decompose and dispose carcinogenic chemicals such as tobacco from their bodies, which itself increases the risk of LC¹¹⁰.

Gender

The incidence of LC was rare until the 1930s, after which an increasing trend occurred, as in 1950s LC was one of the causes of death from cancer in men¹¹². The LC epidemic began in women after men, and its rate is rising rapidly since 1960. Because of the pattern of smoking in the past, the LC epidemic started in men earlier than women, but unlike men, the incidence of LC in women has not declined yet¹¹³. Although still the annual mortality rate of LC is higher in men than women, but this sexual difference in the mortality from LC is decreasing constantly and finally this difference will diminish¹¹⁴. This trend is due to patterns of smoking in the past, that the smoking peak has been higher in men than women over two past decades¹¹⁵. The incidence and prevalence of LC has decreased in younger age groups over the past few decades in men and has decreased in women through the past decade. Overall, the incidence of LC has declined in recent years, but this decline in men was higher than women. These trend patterns are consistent with patterns of smoking prevalence over the time¹¹⁴.

Ethnic

LC in black men is 45% more common than in whites. While, LC in black women develops less than whites¹⁹. Most black smokers appear to be more susceptible to cigarette smoking carcinogens than whites¹¹⁶. The higher death rate of the blacks caused by the LC not only indicates a higher incidence of LC in them, but also suggests a lower survival rates of them, as 5-year survival rate in black people between 1995-2001 was 13% lower than whites¹¹⁷.

CONCLUSIONS

The purpose of this review was investigating the incidence and mortality rate of LC in the world and the relationship between environmental risk factors and LC incidence. Due to knowledge about the LC risk factors, preventing LC is a possible performance by reducing or eliminating risk factors. Smoking is one of the main risk factors of LC. Therefore, quitting smoking greatly reduces the risk of LC. Also, other risk factors reducing LC are; preventing job exposures, controlling air pollution, following appropriate diet, and life style correction.

CONFLICT OF INTEREST:

The authors declare that there is no conflict of interests regarding the publication of this paper.

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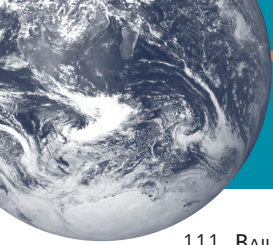
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