Lung Cancer

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Introduction

Lung cancer remains the leading cause of cancer-related deaths in both men and women worldwide.

Lung cancer was the most commonly diagnosed cancer and the leading cause of cancer death in men in 2008 globally globally.

In women, lung cancer is the fourth commonly diagnosed cancer and the second leading cause of cancer death.

Lung cancer is defined as every neoplasm of respiratory epithelial source.

It is recognized from 1930 in industrial countries.

Its incidence was 1.8 million and its mortality was 1.59 million person in the year of 2012.

58% of cases are happened in developing countries.

Its burden according to DOLY will rise from 33 in 1990 to 15 in the year of 2020 of grade.

Incidence rate

- Lung cancer is the leading cause of cancer death in the United States and around the world. Almost as many Americans die of lung cancer every year than die of prostate, breast, and colon cancer combined.

- Cancer data and estimated a total of 239,320 new cases of lung cancer and 161,250 deaths from lung cancer in the United States.

- Likely underestimate the current lung cancer burden 2010.

- Lung cancer has been the most common cancer worldwide since 1985, both in terms of incidence and mortality.

- And 17.6% of total cancer deaths. The 5-year survival rate in the United States for lung cancer is 15.6%, and although there has been some improvement in survival during the past few decades, the survival advances that have been realized in other common.

- The age-adjusted incidence rate of lung cancer is 62 per 100000 men and women per year in the United States, with the incidence rate higher in men than in women.

- In men in the United States has been decreasing since the early 1980s. The incidence and mortality rates for lung cancer tend to mirror one another because most patients diagnosed with lung cancer eventually die of it.

- In 2011, noted decreases in death rates from lung cancer in men by 2.0% per year from 1994 to 2006.

- In women, however, lung cancer death rates continued to increase by 0.3% per year from 1995 to 2005, but more recent data from 2003 to 2006 show a more encouraging trend with a start in

decline of 0.9% per year. The lung cancer incidence among women has declined over the past decades.

- 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 decreases in men.
- The lag in the decline of lung cancer rates in women compared with men has been attributed to the fact that cigarette smoking in women peaked two decades later than in men. Lung cancer mortality rates thus seem to be reaching a plateau, which is an encouraging change from the steep rise in the 1970.
- Lung cancer arises from the cells of the respiratory epithelium and can be divided into two broad categories. Small cell lung cancer (SCLC) is a highly malignant tumor derived from cells exhibiting neuroendocrine characteristics and accounts for 15% of lung cancer cases.
- Non-small cell lung cancer (NSCLC), which accounts for the remaining 85% of cases, is further divided into 3 major pathologic subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Adenocarcinoma by itself accounts for 38.5% of all lung cancer cases, with squamous cell carcinoma accounting for 20% and large cell carcinoma accounting for 2.9%. In the past several decades, the incidence of adenocarcinoma has increased greatly, and adenocarcinoma has replaced squamous cell carcinoma as the most prevalent type of NSCLC.
- In contrast, lung cancer rates in underdeveloped geographic areas, including central Amercia and most of Africa, are lower, except the rates are slowly increasing. More developed countries have higher incidence and mortality rates from lung cancers in both genders than less developed countries.
- The world health organization estimates that lung cancer deaths worldwide will continue to rise, largely as a result of an increase in global tobacco use, especially in Asia.

Risk Factor
Tobacco smoking

- Tobacco use is the principal risk factor for lung cancer, and a large proportion of all pulmonary carcinomas are attributable to the effects of cigarette smoking.
- More men (23.5%) than women (17.9%) smoke. The decline in smoking rates is steeper for black men and white than for white women and black women.
- The smoking rate has declined but has slowed of late; the smoking prevalence increased from 27.5% in 1991 to 36.4% in 1997, declined to 21.9% in 2003, and then declined less to 19.5% in 2009 the first scientific report that associated cigarette smoking with an increased risk of premature death was in 1938, when pear showed the degree of adverse effect on longevity increased with the amount of smoking.
- In a case-control study in United Kingdom, Doll and Hill described an association between carcinoma of the lung and cigarette smoking and the effect of the amount of cigarette use on the development of lung cancer.
- Cigarette smoking is the major cause of lung cancer.
- Cigarette smoke is a complex aerosol composed of gaseous and particulate compounds. The smoke consists of mainstream smoke and side stream smoke components. Mainstream smoke is produced by inhalation of air through the cigarette and is the primary source of smoke exposure for the smoker. Side stream smoke is produced from smoldering of the cigarette

between puffs and is the major south primary determinant of tobacco addiction is nicotine, and tar is the total particulate matter of cigarette smoke after nicotine and water have been removed. Exposure to tar seems to be a major component of lung cancer risk.

- He composition of mainstream smoke, however, can vary greatly depending on the intensity of inhalation by a smoker.

- Although the use of filter tips decreases the amount of nicotine and tar in mainstream smoke, the effect of filter tips also varies because the compression of the tips by lips or fingers and the depth of inhalation of the smoker. There are more than 4000 chemical constituents of cigarette smoke: 95% of the weight of mainstream smoke comes from 400 to 500 gaseous compounds.

- Mainstream smoke contains many potential carcinogens, including polycyclic aromatic hydrocarbons (PAHs), aromatic amines, N-nitrosamines, and other organic and inorganic compounds, such as benzene, vinyl chloride, arsenic, and chromium. The PAHs and N-nitrosamines require metabolic activation to become carcinogenic. Metabolic detoxification of these compounds can also occur, and the balance between activation and detoxification likely affects individual cancer risk. Radioactive materials, such as radon and its decay products, bismuth, and polonium, are also present in tobacco smoke.

- Cigarette smoking was associated with a 70% increase in the age-specific death rates of men and a lesser increase in the death rates of women (2). Cigarette smoking was causally related to lung cancer in men. The magnitude of the effect of cigarette smoking far outweighed all other factors leading to lung cancer. The risk for lung cancer increased with the duration of smoking and the number of cigarettes smoked per day. The report estimated that the average male smoker had an approximately 9-fold to 10-fold risk for lung cancer, whereas heavy smokers had at least a 20-fold risk (3). Cigarette smoking was believed more important than occupational exposures in the causation of lung cancer in the general population (4). Cigarette smoking was the most important cause of chronic bronchitis in the United States (5). Male cigarette smokers had a higher death rate from coronary artery disease than male nonsmokers.

- It is estimated that 20.6% of all American adults over age 18 years continue to smoke, a figure that has only minimally decreased since approximately 1997.

- Despite efforts to curb tobacco smoking, there are approximately 1.1 billion smokers worldwide, and it the current trends continue, that number would increase to 1.9 billion by 2025.

- As of 2008, 20.6% (46.0 million) of American adults smoke. Of these, 79.8% (36.7 million) smoke every day and 20.2% (9.3 million) smoke some days.

- During the past decade, there has been a 3.5% point decrease in the number of US adults who smoke (20.6% in 2008 and 24.1% in 1998).

- Patients with localized disease at diagnosis have a 5-year survival rate of 52%; however, the more than 52% of patients with distant metastasis at diagnoses have a dismal 5-yrear survival rate of 3.6%, which begs for the need for better screening methods to detect early-stage cancers.

- Despite the availability of new diagnostic and genetic technologies, advancements in surgical techniques, and the development of new biologic treatments, the overall 5-year survival rate for lung cancer in the United States remains at a dismal 15.6%.

- The situation globally is even worse, with 5-year survival in Europe, China, and developing countries estimated at only 8.9%.

- The international agency for research on cancer (IARC) had identified at least 50 carcinogens in tobacco smoke. The agents that seem of particular concern in lung carcinoma are the tobacco-specific N-nitrosamines (TSNAs) formed by nitrosation of nicotine during tobacco processing and during smoking. Eight TSNAs have been described, including 4-(methyl nitros amino)-1 (3-pyridyl)-1-butanone (NNK), which is known to induce adenocarcinoma of the lung in experimental animals. Other TSNAs have been linked to cancer of the esophagus, bladder, pancreas, oral cavity, and larynx.

- Of the TSNAs, NNK, which seems the most important inducer of lung cancer, has carcinogenic effects with both topical and systemic administration. TSNAs are directly delivered to the lung by inhalation of tobacco smoke. TSNAs are also absorbed systemically, and hematogenous delivery to the lung can occur by way of the pulmonary circulation.

- NNK is associated with DNA mutations resulting in the activation of K-ras oncogenes. K-ras oncogene activation has been detected in 24% of human lung adenocarcinomas and is present in adenocarcinoma of lung in ex-smokers, suggesting that such mutations do not revert necessarily with the cessation of tobacco smoking. This may in part explain the persistent elevation in lung cancer risk in smokers even years after discontinuing cigarette use. In addition, a specific chemical constituent of tobacco smoke, benzo[a] pyrene metabolite, can damage various p53 tumor-suppressor gene loci that are known to be abnormal in approximately 60% of primary lung cancer cases.

- One in 9 smokers eventually develops lung cancer. The relative risk of lung cancer in long-term smokers has been estimated as 10-fold to 30-fold compared with lifetime nonsmokers. The cumulative lung cancer risk among heavy smokers can be as high as 30% compared with a lifetime risk of less than 1% in nonsmokers. The lung cancer risk is proportional to the quantity of cigarette consumption, because factors, such as the number of packs per day smoked, the age of onset of smoking, the degree of inhalation, the tar and nicotine content of cigarettes, and use of unfiltered cigarettes, become important.

- Although more than 80% of lung cancers occur in persons with tobacco exposure, fewer than 20% of smokers develop lung cancer. This variability in cancer susceptibility is likely affected by other environmental factors or by genetic predisposition.

- Other forms of tobacco use, such as cigar smoking and pipe smoking, have been associated with increased risk for lung cancer. The risk seems weaker, however, than with cigarette smoking.

- Smoking 5 cigars a day on average is equivalent to smoking 1 pack a day of cigarettes.

- A large prospective study of more than 130000 men over 12 years showed that cigar smokers have a relative risk of lung cancer of 5.1 compared with non-cigar smokers. Another study showed a relative risk of 2.1 for lung cancer compared with nonsmokers, with men who smoked 5 or more cigars a day having the greatest risk.

- A large cohort study showed that active pipe smoking was associated with a relative risk for lung cancer of 5.0. Cigar and pipe smokers have a greater risk for lung cancer than lifelong nonsmokers of former smokers.

- Marijuana and cocaine, are less studied than the effects of tobacco smoke. Meta-plastic histologic and molecular changes similar to premalignant alterations have been described in the bronchial epithelium in habitual smokers of marijuana or cocaine.

- A clear association has not been fully established, however, between such inhalant drug use and lung cancer. A case-control study showed that there is an 8% increased risk for lung cancer for each joint-year of marijuana smoking after adjusting for tobacco cigarette smoking. Similarly, there is a 7% increased risk for lung cancer for each pack year of cigarette smoking after adjusting for marijuana smoking. The relationship between cocaine smoking and lung cancer is not well studied.
- Tobacco use was ranked as the fourth most preventable health risk behind malnutrition unsafe sex, and high blood.

Race

- Race is complex variable that often has a strong socioeconomic association. Racial differences in disease states can shed light, however, on the specific issues of a particular subpopulation. Menck showed that the incidence of lung cancer is substantially higher among blacks and native Hawaiians and other Polynesians and lower among Japanese Americans and Hispanics than among whites in the United States.
- Black Americans also have higher mortality rates from lung cancer than white Americans. This difference in mortality rates has been attributed not only to the higher incidence rates but also to the poorer survival of black patients with lung cancer than white patients

Occupational exposure

- Occupational exposure to carcinogens accounts for 9%-15$ of lung cancer cases (Alberg & Samet, 2003). Occupations with a known risk of lung cancer include uranium mining, chemical exposures, asbestos production, refineries, foundries (handling of metals), construction, painting, shipbuilding, motor vehicle manufacturing, wood-production related activities, ceramic and brick production, and exposure to diesel exhaust (taxi and but drivers).
- The risk for the development of lung cancer sharply increases when exposure in these occupations is combined with smoking. Other risk factors that have been linked with a higher risk of lung cancer are indoor pollution.
- Hormonal factors may also play a role in susceptibility. A case-control study showed that estrogen replacement therapy was significantly associated with an increased risk for adenocarcinoma (OR 1.7), whereas the combination of cigarette smoking and estrogen replacement increased that risk substantially (OR 32.4). Conversely, early menopause (age 40 years or younger) was associated with a decreased risk for adenocarcinoma (OR 0.3). More recent large randomized studies suggest that the use of hormonal therapies, such as estrogen and progestin, is associated with an increased risk for lung cancer in women.
- Lifestyle study followed perimenopausal women for 6 years and found the risk for lung cancer was increased in those who used estrogen and progestin.
- The observed risk was proportional to the duration of hormone exposure, with approximately 50% increased risk for those who used hormone replacement therapy for 10 years or longer. Two studies as part of the women's health initiative found a statistically non-significant trend toward increased incidence of NSCLC and an increased number of deaths from lung cancer in women taking hormone therapy compared with those taking placebo.

- Any exposure with: Asbestos, Radon as in door or out door exposure, corom, nickel hematite, Arsenic, Polycyclic Hydrocarbons, sulfuric acid, radioactive material, mustard, Crystalline silica, Heated Cooking Oil are risk factors for lung cancer are risk factor of lung cancer.
- Cigarette smoking may be more harmful to the pulmonary function in women than in men. In the study, changes in forced expiratory volume in the first second of expiration (FEV_1) and maximal mid expiratory flow rate increased with increasing pack-years more rapidly in women smokers than in their male counterparts. These changes were independent of age, height, and weight. Beck and colleagues.

Genetic

- Studies on familial aggregation have supported the hypothesis that there is a hereditary component to the risk for lung cancer. These familial association approaches have been used to discover high-penetrance, low-frequency genes. A meta-analysis involving 32 studies showed a 2-fold increased risk for lung cancer in persons with a family history of lung cancer with an increased risk also present in nonsmokers.
- The addition of smoking history to the effect of this inheritance was associated with a 3-fold increase risk for lung cancer.
- There have also been many studies on candidate susceptibility genes that are of low penetrance and high frequency. The approach has been to target genes known to be involved in the absorption, metabolism, and accumulation of tobacco or other carcinogens in lung tissue. For example, genetic polymorphisms encoding enzymes involved in the activation and conjugation of tobacco smoke compounds, such as PAHs, nitrosamines, and aromatic amines, have been widely studied.
- The presence of mutagen sensitivity is associated with an increased risk for lung cancer.
- Combined risk for lung cancer was greater in individuals with mutagen sensitivity who smoked than in persons with either smoking or mutagen sensitivity characteristics alone.
- Lung cancer susceptibility is determined at least in part by host genetic factors. Person with genetic susceptibility might therefore be at higher risk if they smoke tobacco. As technology advanced, it may be possible to target subgroups identified as genetically high risk for lung cancer for specific interventions, including intensive efforts at smoking cessation, screening, and prevention programs.

Preexisting pulmonary disease

- (Chronic obstructive pulmonary disease, tuberculosis, and silicosis), and treatment with alkylating agents and radiation therapy for Hodgkin's disease are significantly associated with an increased risk for lung cancer, especially in men.
- There is other evidence that airflow obstruction like asthma is a risk for lung cancer, and also
    - Chronic Bronchitis
    - Emphysema
    - Systemic Sclerosis

Diet and Obesity

- The Alpha-Tocopherol, Beta Carotene Cancer Prevention (ATBC) study was a randomized, double-blind, placebo-controlled trial designed to determine whether daily supplementation of α-tocopherol, β-carotene, or both could reduce the incidence of cancers, including lung cancer. The study enrolled 29,133 male smokers aged 50 to 60 years in Finland. Unexpectedly, a higher than expected mortality, primarily due to lung cancer and heart disease, was observed in the group receiving β-carotene and retinal efficacy trial (CARET), also a randomized, double-blind, placebo-controlled study.

- The study was intended to determine whether dietary supplementation with β-carotene, vitamin A, or both would decrease the incidence of lung cancer. It enrolled 18,314 men and women considered at increased risk for lung cancer. The CARET study was stopped 21 months early because of "clear evidence of no benefit and substantial evidence of harm" in the group that received β-carotene and retinol palmitate, especially women. The group that received both vitamin A and β-carotene had 17% increase in mortality and a 28% increase in the number of lung cancers compared with placebo. A third randomized, double-blind, placebo-controlled trial, the physician's health study, evaluated the effect of β-carotene in 22,071 male physicians 11% of the participants were current smokers and 39% former smokers at the onset of the trial. Over 12 years of follow up, neither benefit nor harm in terms of malignancy or cardiovascular disease was demonstrated. The dose of β-carotene in this trial was lower than in both the ATBC trial and the CARET study.

BMI

- A meta-analysis by Renehan and colleagues reported that there was an inverse association between BMI and lung cancer risk and obesity may even have a protective role. In the absence of cigarette smoking, however, the association between BMI and lung cancer was not significant.

- After adjusting for pack-years of smoking and other relevant covariates in a female cohort, showed that there was evidence for inverse associations of BMI and lung cancer risk in current and former smokers, whereas in never smokers, BMI was positively associated with lung cancer.

Lung cancer prevention and control

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A) <u>Primary prevention</u>
- A) Avoidance of exposure with carcinogen materials

- B) Consideration of occupational exposure
- C) Control of BMI
- D) Diet recommendations: eating more vegetable and fruits as bellow:
- 1- Terpens like cartinoids
- 2-Fenols like flavonoids
- 3-Tyols like cabbages
- 4-Lignans like wheat bran, grain
- 5-Catchines like green tea
- 6-selinium
- 7-Vitamin C and E
- 8-Probiotic
- Vitamin A, C, E, D, Foliate sometimes, especially in high level of vitamins increase lung cancer
- Beta carotene in heavy smokers can lead to lung cancer

Correctable risk factor of lung cancer

Risk factor	Importance
Smoking occupation	RR>4
Exposure with indoor radon massive smoker low β carotene diet	RR=2-4
High fat diet air pollution	Suspicion

Population-Attributable Risk

Factor	Best estimate (%)	Range 9%)
Cigarette Smoking	87	84-90
Occupation	13	10-20
Residential Radon	10	7-25
Low vegetable diet	5	-
Environmental Tobacco Smoke	2	1-6

B) <u>Secondary prevention</u>

- This can be done with screening of high risk persons: lung cancer screening with high resolution spiral CT (Low. Dose Helical) is studying by RCT in 53000 high risk individuals, more effective (7%) than CXR.

- There is challenge for screening in community due to false positive (needs follow up) and its costs.

- Target group: men and women older than 40 years who have a history of smoking at list 10 pack/year cigarette.

- The prevalence of a detectable pulmonary cancer is 2-4%.

- In last 50 years there are a lot of studies in relation between diet and genetic factor with lung cancer and will be done on biomarkers for early diagnosis of it.

- Tertiary preventions is rehabilitation and psychiatry consulting for health promotion.

- Highlighted the significantly increased risk for lung cancer specifically for persons with a family history of early-onset lung cancer (<60 years of age).