

Association of Lung Cancer with Tobacco smoking; a review

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Abstract

Smoking is leading cause of lung cancer accounting for about 85% lung cancer cases. Even, illness associated with smoking caused about 5 million deaths globally every year. It is alarming that about one-third of adults globally are considered to be smokers and this rate is significantly increasing in female. It is worrisome that estimated deaths attributed to tobacco smoking will rise up to 10 million by 2025. A number of researches reported strong association between cigarettes smoking and lung cancer and cigarette smoking related deaths accounts about one-third of all adult deaths. A constant smoker has 20-40 times higher risk for the development of lung cancer as compared to non-smokers. About sixty carcinogens have been identified in cigarette in laboratory settings which are proven to induce carcinoma. This review article described the linkage of lung cancer and smoking with some etiologies for the development of cancer in tobacco consumers.

Key Words: *Smoking, DNA adducts, carcinogenic metabolites, pulmonary cancer*

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INTRODUCTION

Lung cancer is defined as an abnormal growth of epithelial cells of bronchi which is mainly caused by tobacco smoking. Tobacco is prepared from the tobacco plant. There is a strong relationship between lung cancer and smoking (Neiderhuber et al., 2013). Tobacco smoking is a well-known cause of lung carcinoma. Over the last 50 years, tobacco strains and some other distilled processes can change human histology and it becomes the most prevailing subtype. During the period of last 10 years, smoking has increased in developing countries and it left its effects more strongly on patients or people having already diseased lungs and it also changes the peculiar qualities of patients or persons. Nowadays, one-third of adult males are using different types of smoking, and its percentage is rapidly increasing in the female population. Studies revealed that there is a strong association between smoking and pulmonary cancer, and it has been reported that the mortality rate from tobacco use will rise to 10 million by 2025 (Hencht et al., 2002; Furrugh, M. 2013). Tobacco use has become more common and is reported to be the main cause of lung cancer among 90% of males and 79% of females. 90% of the mortality rate of lung cancer increases due to smoking. The probability of lung cancer development is 20-40 times more in smokers in comparison to non-smokers. Exposure to cigarette smoke in the environment also is the cause of lung carcinoma. Some progress has to be

done to understand smoking and lung cancer and actions have done to indicate the exact mechanisms of cause of tobacco carcinogenesis. There are many carcinogens and chemicals present in tobacco that cause lung carcinoma. The information shows that the components which contain nicotine acts on DNA and cause genetic changes. This link causes changes in cancer genes and tumor suppresser genes. In the period of 10 years, there has been a move from squamous and small cell lung cancer types to adenocarcinoma. After quitting smoking at the earliest the chances of death from lung cancer decreases. Due to continuous smoking, person or patients faced difficulties in their cancer treatment. Reduction in smoking also reduces the chances of lung carcinoma. Doctors should advise and give the knowledge of the benefits of smoking cessation to save the life of both healthy and diseased person (Hencht et al., 2002).

Tobacco Smoking

History and Components of Tobacco smoke

During 16th and 17th centuries, the use of tobacco spread vigorously in Europe and it was just used as a narcotic drug. While the use of tobacco in the United States also spread rapidly. In 1905, the total consumption of tobacco in the United States was 5 billion and became approximately 17 billion in 1915. After that due to the evaluation of harmful effects of tobacco use different campaigns regarding the control of tobacco use were started in the 1950s.

As a result of these campaigns, many cigarette companies started to produce cigarettes with filters to minimize the harmful effects of tobacco and saved their business. After the introduction of these cigarettes with filters Light cigarettes having the minute quantity of tar and nicotine were also introduced in the market during the 1970s (Stewart et al., 2003).

Tobacco smoke is a complex mixture of toxic and carcinogenic chemicals composed of about more than 5,000 chemicals (Talhout et al., 2011). The gaseous components of smoke included hydrogen cyanide (HCN), carbon monoxide (CO), and nitrogen oxides while volatile components present in liquid-vapor part of smoke consisted of acrolein, formaldehyde, benzene, and certain N-nitrosamines. Further, submicron-sized solid particles are composed of many toxic components like phenol, nicotine, polyaromatic hydrocarbons (PAHs), and certain tobacco-specific nitrosamines (TSNAs) (Harris, 1996). Approximately 85% of lung cancers are caused by cigarette smoking and its risk increases over time, strength, and amount of smoke inhaled. Cigarettes contain more than 60 chemicals that originate lung cancer. Polycyclic aromatic hydrocarbons (PAH) and N-nitrous chemicals or mutagens cause changes in the *p53* gene that causes lung cancer (Jazi et al., 2016).

Nicotine is an addictive compound and it is the booster for lung carcinoma. Smoking activates both sympathetic and

parasympathetic nervous systems which release neurotransmitters and hormones in the blood basically in this process nicotine plays a major role to binds with the receptors that stimulate the neurotransmitters. Nicotine releases dopamine which involves in addiction. Cigar and pipe tobacco smoking are less harmful as compared to cigarette smoking. Due to deep inhalation of cigarette smoke, particles release from this smoke can easily reach the distal airways increases the nicotine level, and then causes addiction in the person. (Warde et al., 2012)

Environmental risk factors, such as chemicals like asbestos, tar is also involved in lung cancer. Air pollution also enhances the risk of lung cancer (Pawel et al., 2004). Genetic factors are also involved in lung cancer. It is also reported that Cytochrome P-450 system may also act as influential factor in progression of lung tumor. The encoding gene for aryl-hydrocarbon hydroxylase, named as *CYP1A1*, activates pro-carcinogens (present in smoke of cigarette) which subsequently escalate the risk for lung tumor (Jazi et al., 2016).

PATHOGENESIS

Lung tumor has almost same pathogenesis as many others tumors. Chemicals or carcinogen enter into the body which initiates and progressed over time. Cigarette smoke act as an initiator for lung carcinoma. This initiation causes changes or deletion in the genes (e.g. 3p deletion, *p53* mutations). Long time exposure to

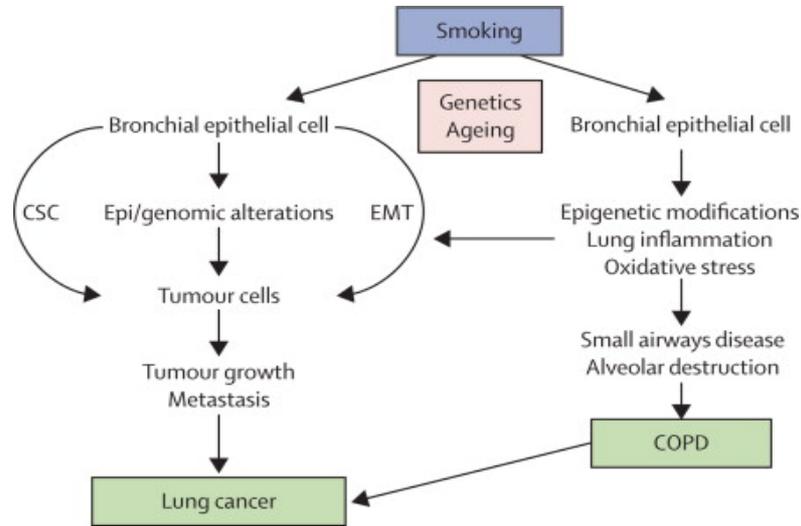


Figure 1: Effects of smoking on lung cancer. Adapted and modified from (Poomakkoth et al., 2016).

Table 1: Classification of lung cancer (Neiderhuber et al., 2013)

Lung Cancer Types		Characteristics
Adenocarcinoma	Non-Small Cell Lung Carcinoma	Most familiar kind of lung cancer. Originates from the small airway epithelial cells and type II alveolar cells.
Squamous Cell Carcinoma		Hardly connected with cigarette smoking. Originates from large airway epithelial cells. Make obstructions and failure of pulmonary alveoli.
Large Cell Lung Carcinoma		Act same as adenocarcinoma but large wounds are formed
Small Cell Lung Carcinoma		Strongly associated with smoking. Originates from the lung neuro endocrine cells, accountable for different growth factors and neurotransmitters.

smoke also causes mutations and it took time almost 20-25 years for the development of cancer (Figure 1).

The types of lung cancer, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) behave in different fashion due to different reasons. These reasons are: these cancers acquired from altered cells, variety of pathogenesis pathways are involved, and comprised on diverse genetic formations. The changes in different genes like *MYC*, *BCL2*, *c-KIT*, *p53* and *RB* are involved in SCLC. On the other side, changes in *EGFR*, *KRAS*, *CD44*, and *p16* genes are involved in NSCLC (Figure 1; Table 1). Lung cancer starts when a body exposure to any chemicals or components. Cigarette smoke has most remarkable components, which are responsible for 85% of lung cancer. Other risk factors are responsible for lung cancer, such as asbestos and tar. Sites of origin and clinical presentations are also different in SCLC and NSCLC. Central tumor formation is hall mark of small cell lung cancer forms while non-small cell lung cancer from both central and peripheral lung tumors. Small cell lung cancer spread quickly but quickly in response to chemotherapy. Non-small cell lung cancer does not spread quickly and less responsive to chemotherapy. Both small cell lung cancer and non-small cell lung cancer cause paraneoplastic syndrome (Poomakkoth et al., 2016).

Early smoking-associated molecular changes in lung cancer development

Many studies have extensively described changes at molecular level in lung cancer.

Studying these pre-deep lesions by profiling and sequencing, will no doubt improve processes which are involved in progression of lung cancer due to smoking. In a study by Ooi and colleagues, role of *myc* gene activation in progression and development of lung cancer has been established. They reported this role by sequencing the RNA of malignant and premalignant tumors which were associated with smokers (Ooi et al., 2014). Recent ongoing studies have used complete sequencing to change the regular conversions involved in the pathogenesis of squamous dysplasia in smokers (Rahal et al., 2017). Slaughter has provided information first time about "field tumor concept" and described that tumor sites have normal histological cells around (Rahal et al., 2017). Further research has examined the effects of exposure to smoking on normal epithelial cells that indicate that smoking exacerbates airway cell defects indicating "mass damage", something that may be closely related to lung oncogenesis (Kadara and Wistuba, 2012). Various cell mutations, such as genetic mutations, number of copies, and DNA methylation, have been described in the smoking-related area of the airway epithelial field and are reviewed elsewhere (Spira et al., 2015). A seminar study conducted by Spira and colleagues shows that smoking-related

smoking is associated with changes in normal cytologically airway (Spira et al., 2015). Significantly, many studies have described the importance of changes in at genetic level and its relatedness in minimal invasive sites in lung cancer at initial stages which ultimate help in early detection of tumor in smokers (Kadara et al., 2014, Gustafson et al., 2010). Recent work has shown that the epithelial portion of lung cancer-related injuries in all smokers reaches the nose and has the potential to detect early lung cancer (Perez-Rogers et al., 2017). Analysis of genome-wide DNA mutations in cancerous or malignant domains within the normally visible pattern is limited. Recent research by Jakubek and colleagues, using genome wide wide SNP arrays and critical novel tools to analyze allelic abnormalities, revealed heterozygosity loss in the driver oncogenes and tumor suppressor shared between normal air cancer and lung cancer (Rich, 2007).

Lung Cancer in Pakistan

The death rate is rising due to carcinoma of lung in Pakistan. The frequency of lung tumor has increased over time and now, it is among the most frequent tumors in Pakistani men (Hussain and Aziz, 2017). Studies have shown that there is a much lower risk of developing lung cancer e.g. 0.56%; however, the rate increases with age and in the group the rate of lung cancer is higher e.g. 64.17% which is the highest (Hussain and Aziz, 2017). In the same study, the occurrence of lung cancer was higher in men than in women. In the database, a

total of 1440 records, 1174 records were male patients and 266 records were female patients. The same study found that the lung cancer rate was 22.29% and 77.71% for non-smokers and smokers respectively. There is no doubt that lung cancer is end result of smoking in majority of cases and should be banned by the government, saving their citizens but need to focus on other causes of lung cancer in non-smokers also (Hussain and Aziz, 2017). A summary review published in 2020 by Shams et al revealed that lung cancer was the most common cancer among men, which is associated with cigarette smoke. And then followed by oral cavity cancers which are again associated with smoking. Pakistan is one of the top four smokers in the world. According to WHO 2011, 32.4% of men and 5.7% of women now smoke in Pakistan. According to some researches, the frequency of smoking in teenagers of Pakistan is 9.9% and 1% in boys and girls respectively. The situation is becoming more alarming because this habit continues to increase in Pakistan which is making region as tobacco epidemic region (Majeed et al., 2019). Tobacco use is mainly due to smoking accounts in about 90% of cases of carcinoma lung (Jha et al., 2008). Although lung cancer occurs in about 25% of smokers' other factors such as non-disclosure and exposure to work can also play a role (Subramanian and Govindan, 2007). The increase in the incidence of lung cancer in Pakistan is directly related to the increase in

smoking cases over the past few years in the country (Proctor, 2001). Shams et al also reported intake of tobacco with smoke or smokeless is at top risk factor different types of cancers including lungs, head and neck cancer (Shamsi, 2020). According to the Pakistan Health Research Council (PHRC) lung carcinoma is the tenth most common cancer of both sexes (figure 2) while the 8th most common in men (Majeed et al., 2019). Data published by GLOBOCON show very alarming picture that lung cancer is at top third position in most occurring cancers in country. Even, this also the cause of many deaths in country accounting for about 6,013 deaths (5.9%) in 2012 (Majeed et al., 2019).

TREATMENT

As lung cancer is strongly linked with smoking so following strategies could be used to handle lung cancer at different stages

Smoking Cessation

Tobacco smoking enhances lung complications after surgery. Three main interventions are used to eradicate the habit of smoking which are the following.

Nicotine replacement therapy (NRT):

The first strategy to eliminate the addiction of smoking is to alter the pulmonary route of nicotine entry into the body using nicotine replacement therapy. These are available in the forms of gum and transdermal patch; and this technique quitted smoking habit ranges from 50-70% (Osadchy et al., 2009).

Antidepressant: The second significant strategy to quit smoking addiction is to

give selective antidepressant-like *bupropion*, *nortriptyline*, etc and it was reported that it was effective NRT. It was investigated that antidepressants that selectively inhibit serotonin reuptake are not as effective as others (Piper et al., 2009).

Nicotine receptor partial agonist: The third way to abolish the desire of smoking is to use compounds which act as an agonist of nicotine like *varenicline* which is more effective than antidepressant drug and NRT (Clarke et al., 2013).

Surgery

Some normal and tumor tissue resect from the infected part. Surgery is best for non-small cell lung cancer.

Radiation Therapy and Chemotherapy

The size of tumor depends on stages of lung cancer. First three stages, I-III, remains within abdomen involving lymph node but with no dissemination of cancerous cells into different parts of the body. When cancerous cells disseminate into different parts of the body then it is referred to as "stage IV" and both surgical and chemotherapy treatment is required.

Epidermal growth factor receptor

(EGFR): Another targeted therapy is also used as first line treatment against NSCLC using EGFR mutations. Stimulation of cell growth via epidermal growth factor (EGF) and binding to EGFR subsequently gives signals to activate tyrosine kinase. It is documented that NSCLC repeatedly evades EGFR mutations making

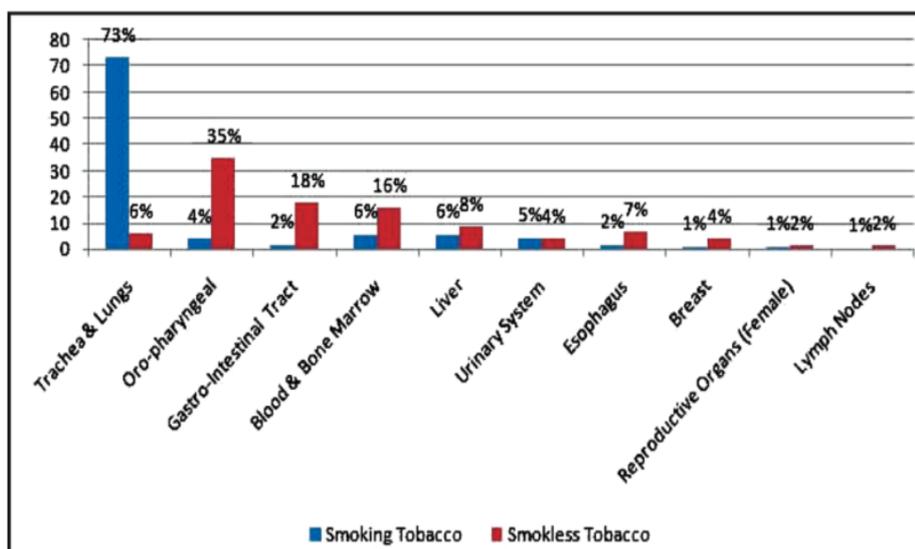


Figure 2. Figure presenting the tobacco association with the cancer of lung. Data was taken from the PHRC website (Majeed et al., 2019)

receptor active than earlier and then gives signals to activate marked growth of cancerous cells. There are remedies which specifically target specific protein: one is antibody against EGFR and other is inhibitors of tyrosine kinase. These two therapeutic agents specifically target the tissues having mutations of EGFR, but unfortunately, a number of other mutations led to marked cellular degradations (Baldwin et al., 2011).

Systematic Care

At the time of diagnosis, there are chances that an advanced and progressive disease has affected patient. In such case, treatment of lung cancers diverted towards systemic care from therapeutic treatment. In systemic

treatment, clinician treat patient with improving life style, reducing stress and suffering other than prolonging the life span of patient. Some researchers have documented that initialization of supporting therapy by improving life style at early stages ultimate increase life span. A study reported that life span of cancer patients increased by 2.7 months. The major benefit of this supportive and palliative therapy is; it reduces cost of treatment, unnecessary treatment, family stress, suffering and increase willpower (Nelson et al., 2011).

CONCLUSION

Throughout the globe, about one-third of adults are considered to be smokers and this rate is significantly increasing in

females and estimated that deaths attributed to tobacco smoking will raise up to 10 million by 2025. It is well reported that cigarette smoking-related deaths account for about one-third of all adult deaths and an association between cigarette smoking and lung cancer have been found in many studies. It was reported that lifelong smokers have a 20-40 times higher risk for the development of lung cancer as compared to non-smokers and tobacco usage caused about 90 % of male lung cancers while 79 % of female lung cancers. Overall study showed that there is a strong relationship between smoking and lung cancer. Further prospect of this study is that it provides another factor as a key diagnosis of lung cancer and all other related diseases.

Conflict of interest

Authors declare that there is no conflict of interest.

Consent for Publication

All authors approved manuscript for publication.

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