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LUNG CANCER AND SMOKING

Medicine

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ABSTRACT

One of the leading cause of cancer related deaths worldwide is Lung Cancer. Over 1 million people die due to Lung cancer each year worldwide. Almost 90% of Lung cancer in men & 70 %-80% in women is explained by cigarette smoking. Non small cell lung cancer (NSCLC) represents the most frequently diagnosed subtype of this morbid malignancy. Various genetic & epigenetic abnormalities contributes to clinically evident lung cancers. These abnormalities lead to activation of oncogenes and inactivation of tumor suppressor genes .Both smoking and genetic abnormality leads to chronic inflammation, which promotes cancer. These mediators in turn may be responsible for increased macrophage recruitment, delayed neutrophil clearance, and increase in reactive oxygen species (ROS). Thus, the pulmonary environment presents a unique milieu in which lung carcinogenesis proceeds in complicity with the host cellular network.

KEYWORDS

INTRODUCTION

IT IS ESTIMATED THAT ONE THIRD OF THE world's adult population, and around 1.1 billion individuals, smokes tobacco, which makes every sixth human being a smoker.(1) Smoking-related illness is estimated to cause ~ 5 million deaths per annum around the globe, but is considered a leading preventable cause of death.(2) In developed countries, the rates of smoking have either leveled off or declined, but smoking-related deaths are on the rise in developing countries and are most common among the least-educated people.

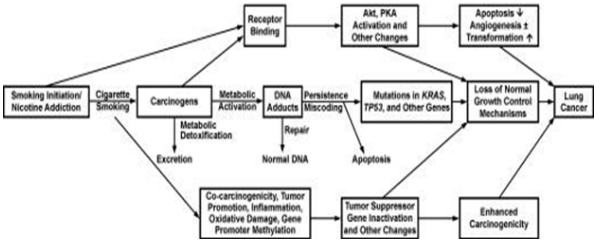
Cigarette smoking is accounting for more than 480,000 deaths every year, or about 1 in 5 deaths in United Sates. In 2017, 14 of every 100 U.S. adults aged 18 years or older (14.0%) currently smoked cigarettes. This means an estimated 34.3 million adults in the United States currently smoke cigarettes. More than 16 million Americans live with a smoking-related disease. Current smoking has declined from 20.9% (nearly 21 of every 100 adults) in 2005 to 14.0% (14 of every 100 adults) in 2017, and the proportion of ever smokers who have quit has increased.

SMOKING, INFLAMMATION, AND LUNG CANCER

Tobacco smoking remains the most established cause of lung carcinogenesis and other disease processes. Genetic basis of Lung cancer has been studied extensively. However, the molecular pathogenesis of lung cancer remains incompletely defined. Because inflammation appears to play an important role in the pathogenesis of lung cancer, a thorough understanding of lung cancer pathogenesis requires consideration of the tumor microenvironment (TME) and the inflammatory pathways operative in carcinogenesis (3).

The tobacco-induced pulmonary cellular network presents a unique environment in which carcinogenesis proceeds in complicity with surrounding lung inflammatory, structural, and stromal cells. The pulmonary diseases that are associated with the greatest risk for lung cancer are characterized by abundant and deregulated inflammation (4-6). Pulmonary disorders such as COPD are characterized by profound abnormalities in inflammatory pathways (7–9). For example, among the cytokines, growth factors, and mediators released in these lung diseases and the developing TME, interleukin (IL)-1β, prostaglandin (PG)E_2, and transforming growth factor (TGF)-β have been found to have deleterious properties that simultaneously pave the way for both epithelial–mesenchymal transition (EMT) and destruction of specific host cell–mediated immune responses against tumor antigens (10–14).

The commonalities in smoking, COPD, and lung cancer begin with the profound alterations induced by cigarette smoke, which contains known carcinogens as well as high levels of reactive oxygen species (ROS). The ready induction of ROS after tobacco smoke exposure leads to impairment of epithelial and endothelial cell function as well as inflammation. The ongoing inflammatory processes in COPD may be persistent even after smoking cessation and have been quantified and related to disease progression (15). As COPD progresses, the percentage of the airways that contain macrophages, neutrophils, T cells, B cells, and lymphoid aggregates containing follicles increases (15).



MOLECULAR PATHOGENESIS

The exposure of Tobacco smoking , industrial hazards like asbestos , high dose ionizing radiation and to some air pollution are thought to act by causing genetic alteration in lung cells which accumulate & eventually lead to neoplastic phenotype. It has been estimated that 10 to 20 genetic mutations have occurred by the time the tumor is clinically apparent .The dominant oncogenes that are frequently involved in lung cancer include c-MYC , KRAS , c-MET , & c-KIT . The commonly deleted or inactivated tumor suppressor genes include p53 , RBI, p16 (INK4a), & multiple loci on chromosome 3p.

In addition , recent studies show that LKB1 , P10, and TSC, all relating to the m-TOR pathway are also mutated in upto 30% of lung cancers (mostly non small cell lung carcinoma).

There are several signal transduction molecules that are activated in lung cancer, such as AKT, phosphatidylinositol-3-kinase, ERK1/2, STAT5, and focal adhesion proteins such as Paxillin.

It should also be noted that 25% lung cancers worldwide arise in non-smokers and these are pathogenetically distinct . They are more common in women , & are mostly adenocarcinomas .They tend to have EGFR mutations , almost never have KRAS mutations and p53 mutations , although common , occur less commonly. (16).

CLASSIFICATION

Tumor classification is important for consistency in patient treatment and because it provides a basis for epidemiologic & biologic studies .The WHO classification has gained wide acceptance . (17)

HISTOLOGICAL CLASSIFICATION OF MALIGNANT EPITHELIAL TUMORS

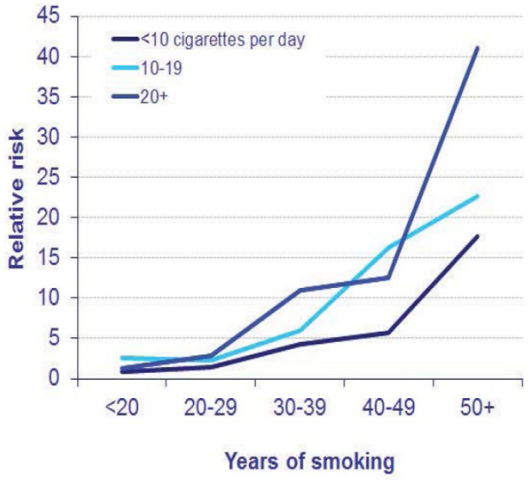
- Squamous cell carcinoma
- Small cell carcinoma
  Combined small cell carcinoma
- Adenocarcinoma
  Acinar; Papillary , bronchioalveolar, solid, mixed subtypes

- Large-cell carcinoma
  Large-cell neuroendocrine carcinoma
- Adenosquamous carcinoma
- Carcinoma with pleomorphic, sarcomatoid , or sarcomatous elements
- Carcinoid tumor
  Typical or atypical
- Carcinomas of salivary gland type
- Unclassified carcinoma

Tobacco Smoking and Lung Cancer

Smoking is strongly associated with small cell lung carcinoma (SCLC)and squamous-cell carcinoma (SCC). There has been a gradual change in the way cigarettes are manufactured which has resulted in a shift in the histology from SCC which was more frequent in the 1970s to adenocarcinoma subtypes which are currently more frequent. The impact of low tar cigarettes, introduced in the 1950s, on adenocarcinoma rates has been due to the introduction of filter vents in these cigarettes, making it easier for the smoker to draw in smoke, and allowing deeper inhalation than older, unfiltered cigarettes. Inhalation transports tobacco-specific carcinogens more distally toward the bronchoalveolar junction where adenocarcinoma often arises. Secondly, blended reconstituted tobacco releases a higher concentration of N-nitrosamines from tobacco stems.(19) Lung cancer risk increases with the duration and intensity of tobacco consumption [as shown in the figure] illustrates the prevalence of various subtypes of lung carcinoma in smokers and never-smokers.

Fig 1

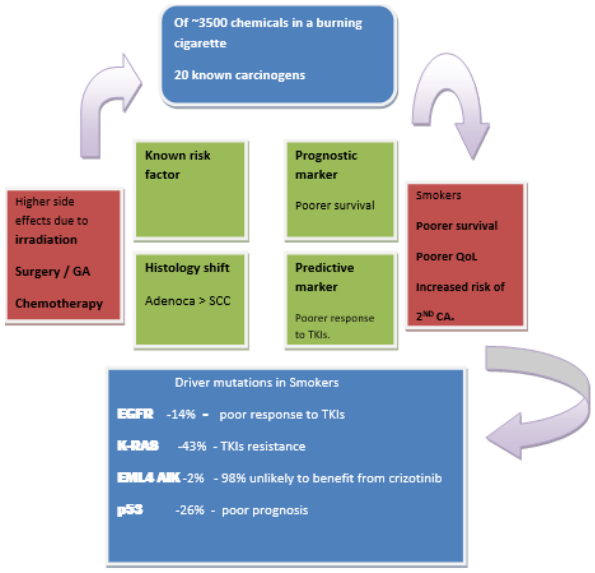


In a burning cigarette approximately 20 potential carcinogens of nearly 3500 chemicals have been detected . The most well known chemicals are the polycyclic aromatic hydrocarbons (PAH) like benzo(a) pyrenes, and the tobacco-specific N-nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), while others include Asz-arenes, Dibenz(a,h)acridine, inorganic compounds like cadmium, chromium, nickel, arsenic, radioactive polonium (Po210) and organic compounds like butadiene.(20) While smoking nitrates in the tobacco are reduced to NH2−and NH3 . Air-cured tobacco contains higher concentrations of aromatic amines as compared to flue-cured tobaccos (e.g. the urinary bladder carcinogens β2-naphthylamine and 4-aminobiphenyl).(22)

High levels of acrolein are present in cigarette smoke which is toxic to the ciliated lining of the lungs. Other agents such as nitrogen oxides, acetaldehyde, phenols, and formaldehyde, contributes indirectly to pulmonary carcinogenicity in animals and humans.(23)

Cigarette smoke also contains free radicals (FR) (e.g. hydrogen peroxide [H2O2], hydroxyl ion [OH−], sulfoxide anion) which induce oxidative damage in animal models as well as humans, while catechol and hydroquinone play their roles in single strand DNA breaks caused by the release of Free radicals further contributing to carcinogenicity .(18) Smoking has multidimensional effects on lung cancer (as shown in the figure). Tobacco smoking remains the most consistent causative agent in lung carcinogenesis in animal and human models, yet, over the past decade or so, it has also emerged as a prognostic and predictive clinical characteristic.

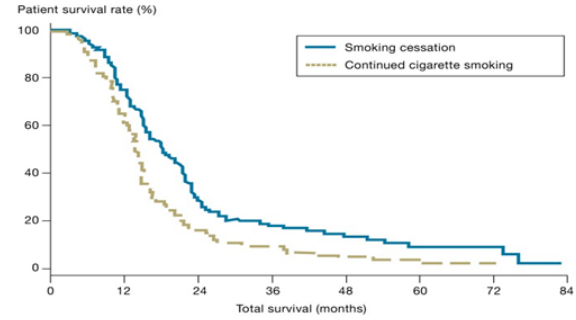
Fig 2



Impact of smoking cessation on Lung Cancer

Many studies have shown that patients with lung cancer benefit from smoking cessation. It is also been seen that after resection with curative intent second tumors are 2.3 times more common in patients who continue to smoke. Also , recurrent tumors are 1.9 times more common, in patients who continue to smoke than in those who stop. The overall mortality in smokers is 2.9 times higher. Smoking cessation also lowers the rate of radiation pneumonitis and infection during radiotherapy and prolongs the median survival after chemoradiotherapy for small-cell lung cancer. For patients with non-small-cell lung cancer, smoking cessation is associated with a better general state of health (77.5% vs. 57.6%). For the many patients with lung cancer who are treated palliatively, smoking cessation offers the advantages of improved pulmonary function, weight gain, and better overall quality of life.

Fig 3



The positive effects of smoking cessation in lung cancer patients

- Better quality of life
- Improved pulmonary function
- Improved response to chemotherapy
- Better wound healing
- Reduced surgical complications
- Less frequent radiation pneumonitis following radiotherapy
- Better radiochemotherapy outcomes
- Greater efficacy of targeted therapy
- Lower recurrence rate following resection

CONCLUSIONS

The deleterious effects on lung cells of genotoxic carcinogens in cigarette smoke has horrible mutagenic effects that have been demonstrated in many studies. This clearly stands out as the greatest voluntary human exposure to a mixture of chemical carcinogens, with horrific consequences in terms of lung cancer mortality. Many aspects of the general mechanism of carcinogenesis as discussed above are firmly established but there are still some areas that could profit from further investigation. These include structural analysis of DNA adducts in smokers' lungs, a better understanding of the role of non-

genotoxic tobacco smoke constituents in the lung cancer process, the role of polymorphisms in genes involved in nicotine and carcinogen uptake and metabolism, and the identification of smokers at high risk for lung cancer. A better understanding of mechanisms of lung cancer induction by cigarette smoke can provide new insights on prevention of lung cancer in smokers, and possibly on cancer prevention generally.

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