



EFFECT OF TOBACCO USE ON HEAD AND NECK CANCER

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Abstract— Nicotine is obtained from the leaves of the *Nicotiana tabacum* plant, belongs to the class of parasympathomimetic alkaloids, is metabolized by the liver, and because of its dopaminergic activity, it is very addictive. Head and neck cancer risk factors include alcohol and tobacco misuse by showing synergic effects. Smokeless tobacco products have been associated with oral cancer. This article explains how the active constituent of tobacco can cause head and neck cancer, which subtype can have a greater chance of becoming cancerous in head and neck cancer, and how we can prevent using tobacco.

Keywords— Nicotine, head and neck cancer, Tobacco

I. INTRODUCTION

Cancer is a condition in which normal body cells proliferate uncontrollably. Head and neck cancer begins in squamous cells of the mouth, throat, voice box, salivary gland, sinuses, muscles or nerves. Researchers have estimated that 70%-80% of cancers of the head and neck are linked to tobacco consumption and rank sixth in the most prevalent cancers diagnosed worldwide. [1] The clinical presentation of head and neck cancer includes white or red patches in the mouth, swelling, a mass or lump in the neck or head area with or without pain, persistent sore throat, difficulty in breathing, loosening of teeth, etc. This is the most common sign and symptom of this cancer. The different stages of head and neck carcinoma are classified based on the observations of physical exams, biopsies, endoscopies, and imaging tests like MRIs, CT scans, PET scans, and/or chest X-rays. The cancer staging system called the TNM (tumor, node, and metastasis) was developed by the American Joint Committee on Cancer to assess three essential factors of cancer treatment. Around 900,000 cases and more than 400,000 fatalities from head and neck cancer occur each year worldwide. [1] Tumours of the oropharynx have been associated with carcinogenic strains of HPV (human papillomavirus), especially HPV-18 and HPV-16. [2] The

risk of nose and salivary gland malignancies increases with Epstein-Barr virus infection that causes infectious mononucleosis. [3] Head and neck cancer risk is greater in men than in females due to the high consumption of tobacco by men. Evidence suggests that HPV transmission rates between men and women are higher compared to transmission rates in women to men, owing to women's greater immunological response to infection. [4] Most cases of neck and head cancer are diagnosed in later stages, so early detection of this cancer can lead to fast relief for the patient. [2] E-cigarettes are thought to be safer than traditional cigarettes, study has shown that when compared to tobacco smokers, e-cigarettes users had lower quantities of biomarkers of exposure to tobacco-specific nitrosamines (TSNAS), polycyclic aromatic hydrocarbons, and the most volatile compound, TSNAS like 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, are significantly lower in non-smokers than in cigarette smokers. Several studies have shown that nicotine has several harmful effects, which include cancer growth stimulation, furthermore, the chemicals and compounds produced by the heating process in e-cigarette cartridges have received much research due to their possibly hazardous and mutagenic consequences. E-cigarette aerosol also elevated the pro-inflammatory cytokines IL-6 and IL-8 while decreasing the lung glutathione levels in human and mouse lung epithelial cells. importantly results suggest that elevated IL-6 may stimulate lung cancer cell proliferation via the STAT3 signalling cascade. Every year tobacco kills almost 8 million people. Furthermore, 7 million deaths are caused by direct tobacco use, whereas around 1.2 million are caused by non-smokers who use second-hand smoke. [3] India has the world's second highest number of adult smokers. In India, the most popular tobacco product is bidis. [4]

The proportion of adults who exclusively smoked bidis climbed dramatically from 50.1% in 2009-2010 to 57.0% in 2016-2017.

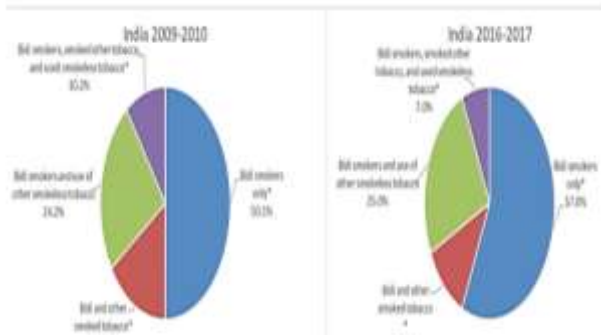


Fig.2. Tobacco uses among adults who smoke bidis in India.

TOBACCO: The death toll from tobacco is close to 8 million per year. Direct tobacco use results in more than 7 million fatalities, whereas exposure to second-hand smoke causes around 1.2 million deaths in non-smokers. [5] This is due to the presence of several mutagens and carcinogens in tobacco smoke, including tobacco-specific nitrosamines and polycyclic aromatic hydrocarbons, which are the major causes of cancer in humans.

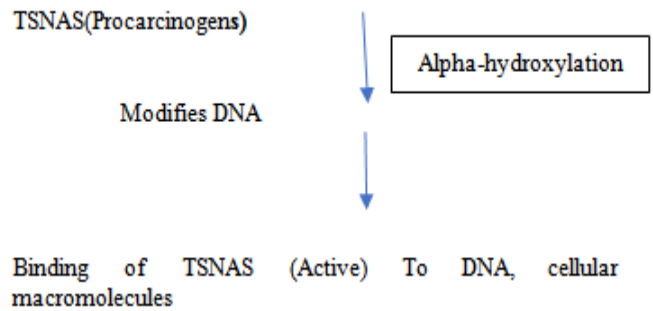
The principal nitrosamines which are tobacco-specific identified in tobacco are: [5]

1. NAB (Nitrosoanabasine)
2. NAT (Nitrosoanatabine)
3. NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone)
4. Nitrosornicotine (NNN)

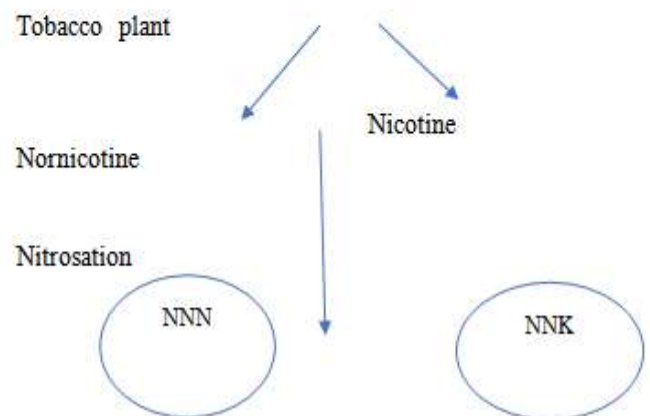
Biomarkers are divided into two types they are exposure biomarker and toxicity biomarker, exposure biomarker contains products of tobacco combustion and its chemical constituent, which includes carbon monoxide, nicotine, cotinine, 4-(methylnitrosamino)-1-(3-pyridyl) butanol and its glucuronides. toxicity biomarkers include 4-aminobiphenyl haemoglobin adducts. [6]

How Tobacco products cause cancer: Tobacco smoke from cigarettes, cigars, and pipes, has some toxic chemicals which enter the bloodstream while the inhalation process, from that toxic chemical, passes to different parts of the body, these toxic chemical damages the DNA which control the formation of new cell in the body, damage DNA makes cells to grow in an improper manner, this growth is said to be cancer. [7]

Carcinogenicity of Tobacco-specific Nitrosamines (TSNAS):



The above flow chart shows how TSNAS get activated. Among TSNAS, the strongest carcinogens were NNK and NNN. NNK is generally formed as a consequence of nicotine nitrosation during the final stages of tobacco production, such as fermentation and curing, When the methyl group on the alkaloid nicotine is lost during the curing of tobacco leaves, NNN is formed. [8] In F344 rats, NNK caused tumours in the nasal cavity and in the lung, whereas in the Syrian golden hamsters it affected mainly the liver, lung, trachea, and nasal cavity. In rats, NNN caused tumours in the nasal cavity and oesophagus, and in the Syrian golden hamsters, it affected the trachea and nasal cavity, and in mice, the lungs were affected. [8]



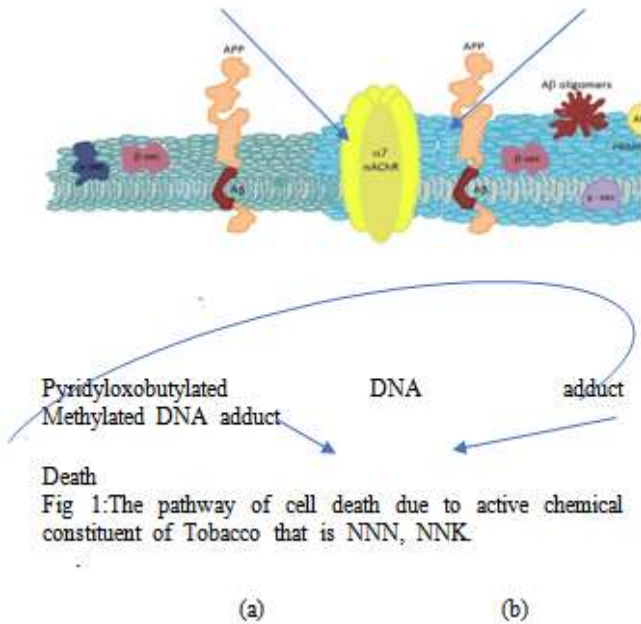


Fig 1: The pathway of cell death due to active chemical constituent of Tobacco that is NNN, NNK.

Tobacco carcinogens and their metabolites are commonly considered to bind with DNA by the formation of covalent bonds, which form DNA adducts. Unrepaired DNA adducts can result in miscoding and irreversible mutations that can activate oncogenes like K-ras or inactivate tumour suppressor genes like p53. [10] etiological factors behind the mutation of P53 are tobacco smoking and alcohol consumption. Head and neck cancer commonly involves G → T transversion.

The combined effect of tobacco smoke and alcohol would be more carcinogenic in the pharynx, followed by the larynx and lungs, where tobacco smoke's effects would predominate. Research has shown that carcinogen-metabolizing enzymes and DNA adducts in laryngeal tissue are caused by the metabolic activation of polycyclic aromatic hydrocarbons in cigarette smoke. [11] Oral cancer was 9.9 times more likely to occur in users of paan without tobacco, compared to 8.4 times more likely in people who consumed paan with tobacco. [12]

Effect of tobacco on periodontal cells: The periodontium is one of the complex structural and functional tissues that are involved in the support of teeth in the jaws. The periodontium mainly consists of fibroblasts, stem cells, and epithelial cells. [13]

Nicotine promotes human gingival fibroblast-mediated collagen breakdown, in part through activating MMPs (membrane-associated matrix metalloproteinases), which leads to periodontitis by causing the disruption of the membrane and hinders the teeth from supporting the dental alveoli via affecting the epithelial tissue. [9] Smoking cigarettes promotes the onset of harmful periodontal diseases and hinders the healing process.

Nicotine shows cytotoxic effects on periodontal stem cells. [14]

A recent comprehensive study showed that periodontitis is possibly linked with the risk of head and neck cancer. [15]

Nicotine causes vasoconstriction of gingival blood vessels. It impairs the adhesion of fibroblasts to root surfaces. Smokers show high gingival inflammation and supragingival plaque when compared to non-smokers, an acute type of necrotising ulcerative gingivitis causing bleeding and painful infection. High ulceration occurs in those individuals who smoke more than 10 cigarettes per day. Periodontitis in smokers causes severe attachment loss, higher marginal bone loss, deeper periodontal pockets, and tooth furcation

Periodontal status in smokeless tobacco: [10]

1. Ghutka Increased plaque index, probing death > 4mm
2. Betel quid Increased plaque index, probing death > 4mm
3. Shamma Increased plaque index, probing death > 4mm
4. Naswar Increased plaque index, probing death > 4mm
5. Snuff Increased gingival recession

Smokers palate (nicotine stomatitis): Heavy cigarette use turns the palate white and can cause small raised lumps covered in red dots. This condition is not cancerous and goes away when a person stops smoking, although some severe versions can eventually leads to cancer.

Effect of Nicotine on molecular and systemic health:

At the molecular level, nicotine impairs the functions of polymorphonuclear leukocytes, damages the function and structure of gingival fibroblasts, and enhances oxidative stress, inflammation, and myofibroblast differentiation.

When it comes to systemic health, it causes acute cardiac ischemia, atherosclerosis, hypertension, and pancreatic cancer. [11]

Preventive measures for Head & neck cancer in relation to Tobacco:

For people who are addicted to tobacco, it is difficult for them to stop the usage of tobacco at an early stage, so smokefree.gov provides free text messaging for encouragement, information, and advice for quitting smoking.

NRT (nicotine replacement therapy) is among the most widely used classes of smoking cessation medications. NRT improves withdrawal symptoms by providing small, controlled quantities of nicotine without containing any other harmful constituents present in cigarette smoke. This modest nicotine dose helps to satisfy a smoker's nicotine craving and lessens the desire to smoke.



Different types of NRT: gum (releases nicotine when chewed), patch (provides a steady and small amount of nicotine when placed on the skin), lozenge (placed in the mouth like hard candy), nasal spray (put into the nose and spray), inhaler (specific amount of nicotine released when inhaled). [18]

II. CONCLUSION

Tobacco, no matter in which form it is consumed, is undoubtedly associated with the development of head and neck cancers. NNK and NNN, being the main carcinogens present in tobacco, bind to DNA and cause mutation, which leads to cancer. Nicotine not only has toxic effects on periodontal cells but deteriorates molecular and systemic health as well. Even though tobacco prevention programs and various types of nicotine replacement therapies are available, tobacco usage is still high among the general population, resulting in a high prevalence of head and neck cancer, which indicates more robust planning and implementation of tobacco usage prevention programs are necessary.

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