Aetiology and prevention of head and neck neoplasms: a review

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INTRODUCTION

Development of head and neck malignancy is a multifactorial process associated with a variety of risk factors. Tobacco and alcohol consumption have been implicated in 75% of all head and neck neoplasia.1

In the developed countries major risk factors are tobacco and alcohol consumption while in the developing countries like India, Indonesia, Iran, Bangladesh, China, Nepal, are betel quid chewing and beedi (thin, Indian cigarette filled with tobacco flake and wrapped in a tendu leaf tied with a string at one end) smoking.2 Other cofactors in development of carcinoma of head and neck include dietary factors, rampant viral infections and immunodeficiency, international agency for research on cancer 2004.3 Suspected aetiological factors likely to cause head and neck squamous cell carcinoma are tobacco and its forms, alcohol, dietary status, viral infections, occupational exposure, genetic makeup and family history.

TOBACCO

Tobacco consumption is a significant etiological factor in the development of head and neck cancer.5 6 The international agency for research on cancer (IARC) documented that smoking of various forms of tobacco (beedis, pipes, cigars and cigarettes) is carcinogenic in humans.7 Smokeless tobacco (refers to a number of tobacco products that are used by means other than smoking i.e. by chewing, inhalation and application to the skin) and “beedi smoking” has been attributed to head and neck cancer in the developing countries. Conversely, in developed countries, cigarette smoking is responsible for the majority of cancers.8 Tobacco is a name for any plant of the genus nicotiana of the solanaceae family (nightshade family) and for the product manufactured from the leaf and used in cigars, cigarettes, pipe, hookah, sniff and chewing tobacco.9

Cigar

A tightly-rolled bundle of dried and fermented tobacco that is ignited so that its smoke may be drawn into the mouth.

Cigarette

A small roll of finely cut tobacco leaves wrapped in a cylinder of thin paper.
**Pan masala / gutka**
Betel leaf filled with a mixture of chopped or coarsely ground areca nuts and other spices.

**Pipe**
Consists of a chamber for the combustion of tobacco and a thin stem ending in a mouthpiece.

**Hookah**
Also known as a water-pipe, in which the smoke is passed through a water basin (often glass-based) before inhalation.

**Snuff**
A product made from finely ground or pulverized tobacco leaves, a type of smokeless tobacco. It is generally insufflated (inhaled) or snuffed through the nose either directly from the fingers or by using specially made snuffing devices.

**Chewing tobacco**
A type of tobacco that is chewed by placing a portion of the tobacco between the cheek and gum or upper lip and teeth.

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**Figure 1: Adverse effect of smoking/ tobacco chewing.**

Processed tobacco has over 3000 compounds including 16 identified carcinogens. The smoke generated when tobacco is burnt, contains more than 4000 constituents including about 69 carcinogens, which are the byproducts of pyrolysis (i.e. the thermo chemical decomposition of organic material at elevated temperatures without the participation of oxygen).^{10}

Studies on the mechanism of tobacco carcinogenesis and dosimetry in tobacco consumers indicate that the major classes of carcinogens, polycyclic aromatic hydrocarbons (PAHs), aromatic amines and tobacco specific nitrosamines (TSNAs) play important roles in tobacco-associated cancers.\(^{11}\)

Chewing of tobacco with betel quid increases exposure of oro-digestive mucosa to carcinogenic tobacco-specific nitrosamines and to nitrosamines derived from arecanut alkaloids. Moreover, there is generation of substantial amounts of reactive oxygen species in oral cavity during chewing.\(^{12}\) The risk for head and neck cancer for tobacco users is estimated to be approximately five to twenty-five folds more as compared to that of non smokers. This risk is proportional to dose, duration and extent of tobacco consumption. On the contrary, this risk diminishes with time from cessation of exposure, although never reaching the level of a non smoker.\(^{13}\)

The byproducts of mainstream smoke can be divided into particulate phase and gaseous phase. The particulate phase contains nicotine, tobacco specific nitrosamines, TSNAs, 4-methylnitrosamino-1-3-pyridyl-1-butanone (NNK), N-nitrosonornicotine (NNN), metals (cadmium, nickel, zinc, and polonium-210), polycyclic aromatic hydrocarbons (PAHs) (benzo(a)pyrene) and carcinogenic amines (4-aminobiphenyl). The gaseous phase contains among other carbon monoxide, carbon dioxide, benzene, ammonia, formaldehyde, hydrogen cyanide, N-nitrosodimethylamine (NMDA) and N-nitrosodiethylamine (NDEA). Approximately sixty nine known carcinogens are present in tobacco smoke.\(^{14}\)

The strongest and most potent carcinogens are polycyclic aromatic hydrocarbons (PAHs), tobacco specific nitrosamines (TSNAs) and aromatic amines.\(^{15}\) On the basis of animal studies, polycyclic aromatic hydrocarbons (PAHs), 4-methylnitrosamino-1-3-pyridyl-1-butanone (NNK), N-nitrosonornicotine (NNN) are the most likely causes of oral cancer in smokers.\(^{16,17}\)

Cigarette smoking increases the vulnerability to sinonasal and nasopharyngeal cancer and is a cause of oropharyngeal, hypopharyngeal and laryngeal cancer. It is also associated with cancer of oral cavity, including lip and tongue in both genders. Alcohol consumption in combination with smoking increases the risk of oral cancer manifold, international agency for research on cancer.\(^{1}\) Smoking and drinking are independently and synergistically associated with an increased risk of oral cancer, and the risks tend to increase with an increased frequency of exposure.\(^{18}\)

**Effect of cessation of smoking**

Cessation of smoking at any age avoids the further increase in risk of cancer due to continued smoking. However, the risk of ex-smokers developing cancer remains high for years after cessation, compared with the
risk in non-smokers, international agency for research on cancer.\textsuperscript{3}

**ALCOHOL**

Alcohol remains second only to tobacco consumption as a risk factor for head and neck cancer worldwide.\textsuperscript{3} Alcohol may act independently as well as synergistically with tobacco as a co-carcinogen.\textsuperscript{19}

Alcohol is an organic compound in which the hydroxyl functional group (OH) is bound to a carbon atom. Alcohol may act as a solvent for other carcinogens or perhaps generate and exacerbate coincident inflammation, producing significant reactive oxygen species.\textsuperscript{20,21} There is evidence that the topical effect of alcohol on oral mucosa, facilitate penetration of tobacco carcinogens and leads to head and neck cancer.\textsuperscript{22-24}

Microsomal metabolism of ethanol, releases toxic acetaldehydes, hydroxyethyl radicals, ethoxy radicals and hydroxyl radicals which exhibit pronounced affinity for DNA. Acetaldehyde, the first oxidative metabolite of ethanol, is a known carcinogen.\textsuperscript{25} Moreover, alcohol influences carcinogenesis by mucosal cell proliferation and related histological changes. There is mucosal hyper-regeneration and enhanced susceptibility to carcinogenic action of tobacco. Alcohol consumption might increase the bioavailability of DNA binding tobacco components in mucosa of upper aerodigestive tract, increasing the plasma levels of these compounds or might modify the metabolism of procarcinogenic compounds by inducing specific metabolic pathways. An indirect effect of alcohol includes nutritional deficiencies and cirrhosis associated with its heavy consumption with poor intake.\textsuperscript{26}

Malnutrition can lower the body’s natural ability to use antioxidants to prevent formation of cancer whereas hepatocellular dysfunction/cirrhosis interferes with systemically active oral P carcinogens, international agency for research on cancer (IARC).\textsuperscript{27} Heavy tobacco users have a 5-fold to 25-fold higher risk of developing head and neck cancer than non-smokers. Alcohol can further increase the risk; for example, a person who has a more than 40 pack-year history of smoking and who consumes 5 alcoholic drinks per day has a 40-fold increased risk.\textsuperscript{13}

**DIETARY FACTORS**

Dietary factors are important risk factors for oral and pharyngeal cancers. Numerous epidemiological studies have shown protective effect of fruits and vegetables, whereas meat and red chilli powder head and neck cancer increase susceptibility to head and neck cancer.\textsuperscript{28,29} Although individual micronutrients responsible for protection have not been identified, fruits and vegetables are rich in beta-carotene, vitamin C and E with antioxidant properties which have been proposed to play a protective role in maintaining the thickness of the epithelium. Iron deficiency which results in oral epithelial atrophy and the Plummer-Vinson syndrome, is associated with cancer of upper air and food passages.\textsuperscript{30}

**VIRAL INFECTIONS**

Epstein-Barr virus (EBV) and human papillomavirus (HPV) are associated with cancer of head and neck region. Epstein-Barr virus (EBV) can cause nasopharyngeal carcinoma (NPC), specifically world health organization (WHO) type 2 (non-keratinizing) and type 3 (undifferentiated) NPCs, prevalent in endemic areas of Northern Africa and Asia.\textsuperscript{31,32} Human papillomavirus (HPV) is now recognized to have a role in the pathogenesis of head and neck cancer approximately 60% of oropharyngeal carcinomas are associated with HPV.\textsuperscript{33,34}

Both molecular and epidemiological studies have shown that approximately 25% of all head and neck cancers are associated with HPV. High-risk HPVs (HPV types 16, 18 and 31) are known to be tumorigenic in human, epithelial tissues. The E6 and E7 viral oncoproteins of high-risk HPV promote tumor progression by inactivating TP53 and retinoblastoma tumor suppressor gene products respectively.\textsuperscript{35} These tumors appear to be clinically and molecularly distinct from HPV-negative tumors. Tumors positive for HPV are more likely to originate in the oropharynx, be poorly differentiated, have basaloid features and present at a lower T stage than HPV-negative primaries.\textsuperscript{35-38}
Viral infection (high risk HPV types 16, 18 and 31)

E6 and E7 viral oncoproteins inactivates TP53a and retinoblastoma tumor suppressor gene

Increased risk for oropharyngeal and nasopharyngeal cancer

**Figure 3: Viral infection association with head and neck cancer.**

### OCCUPATIONAL EXPOSURE

Head and neck malignancy is seen in individuals in certain occupations. Occupational exposure to chromium, nickel, radium, mustard gas and byproducts of leather tanning and woodworking has been associated with head and neck cancer primarily sinonasal tract cancer. Hardwood dust exposure increases incidence of adenocarcinoma and softwood dust exposure of squamous carcinoma. Wood dust impairs mucociliary clearance and predispose to carcinogenesis.

Hardwood is wood from angiosperm trees, like Burma teak, and mahogany. Hardwood consists of a thin veneer (any of thin layers of wood glued to form plywood) bonded to a core of softwood, plywood or medium-density fibreboard (MDF). Hardwood is used as fuel in making tools, furniture, flooring, charcoal, etc. Softwood is wood from gymnosperm trees such as Conifers. Hardwoods are not necessarily harder than softwoods.

In both groups there is an enormous variation in actual wood hardness, with the range in density in hardwoods completely including that of softwoods.

### GENETIC MAKE UP

Cancer is a complex genetic disease derived from the accumulation of various genetic alterations like activation of proto-oncogenes and inactivation of tumor suppressor genes. Inactivation of tumor suppressor gene function requires inactivation of both parental alleles, by point mutation and a chromosomal detection. 10% of all malignancies have a strong hereditary component. Association studies show that the first degree relatives of patients with head and neck squamous cell carcinoma exhibited a two to four fold higher risk for head and neck squamous cell carcinoma.

More than 50% of all primary head and neck squamous cell carcinomas harbor p53 mutations in the conserved regions of the gene. The most commonly deleted regions of allelotype in head and neck cancer is located at chromosome 9p21-22. Homozygous deletions in this region are frequent in HNSCC and represent one of the most common genetic changes identified in all human neoplasms.

### FAMILY HISTORY

Although head and neck cancer arises sporadically, familial inheritance has also been identified as a risk factor in several epidemiological studies. The ability to detoxify tobacco carcinogens such as benzo(a)pyrenediolepoxide (BPDE) as well as to repair the DNA damage caused by these carcinogens is defective in some patients with head and neck cancer. Head and neck cancer patients show an increased susceptibility to chromosome damage by mutagens.

### PREVENTIVE MEASURES

#### Antitobacco regulations

The cigarettes and other tobacco products (prohibition of advertisement and regulation of trade and commerce, production, supply and distribution) act, 2003 (COTPA) is the principal comprehensive law governing tobacco control in India.

In 2005, in view of rise in the incidence of on-screen smoking scenes, stringent rules were framed to implement a complete ban on showing any tobacco product. Smoking scenes were to be banned in new films. The notification, which was to come into effect from November 14, 2011, makes it mandatory for all new movies, that have smoking scenes or tobacco use, to provide a valid explanation and that health warnings should be mentioned on each and every tobacco product.

The new rules which have come into force on November 14, 2011, has made it mandatory for 30-second antitobacco health spots or message to be shown at the beginning and middle of cinema and TV programmes, smoking is injurious to health, smoking causes cancer, which depict tobacco use. In addition, a scroll of prominent anti-tobacco health warnings will be run at the bottom of the screen during the duration of these scenes. All new movies with smoking scenes or showing any form of tobacco use will have to give a valid explanation for the scene and will be given universal/adult (U/A) certification.

The rules also made it mandatory for any actor displaying tobacco use in any movie or TV programme to record a 20-second anti-tobacco disclaimer explaining the ill effects of tobacco.

In 1975, the US state of Minnesota enacted the Minnesota clean indoor air act, making it the first state to restrict smoking in most public spaces. At first, restaurants were required to have no smoking sections, and bars were exempted from the act.
The resort town of Aspen, Colorado, became the first city in the US to restrict smoking in restaurants, in 1985. Smoking was first restricted in schools, hospitals, trains, buses and train stations in Turkey in 1996. On 3 December 2003, New Zealand passed a legislation to progressively implement a smoking ban in schools, school grounds, and workplaces by December 2004. Minnesota enacted a ban on smoking in all restaurants and bars state wide, called the freedom to breathe act of 2007. In 2008, a more comprehensive smoking ban was implemented, covering all public indoor venues.

Bhutan is the only country in the world to completely outlaw the cultivation, harvesting, production and sale of tobacco and tobacco products under the tobacco control act of Bhutan 2010. However, small allowances for personal possession are permitted as long as the possessor can prove that they have paid import duties. In March 2012, Brazil became the world's first country to ban all flavoured tobacco including menthols.

**Gutka /pan masala ban regulations**

In 2001 gutka and pan masala tobacco products were banned. It was notified that no person shall, by himself or using any person on his behalf, manufacture, store, distribute or sell chewing tobacco, pan masala and gutka containing tobacco in any form under whatever name or description. Under section 2.3.4 of the regulations under the food safety and standards of India, act a product is not to contain any substance which may be injurious to health: tobacco and nicotine shall not be used as ingredients in any food products.

The Punjab Government approved the proposal of the state health and family welfare department for banning the gutka and pan masala in the interest of public health. On Aug 27, 2012 the Punjab Government banned the sale, storage, manufacture and distribution of gutka and pan masala or other items with tobacco and nicotine content in the state.

In 2010, the state of Maharashtra banned the sale of gutka and cigarettes within 100 metres of schools and colleges. Maharashtra is among the highest users of tobacco in the country, with 43% adult men and 19% adult women addicted to it, as per the global adult tobacco survey, 2012. The Maharashtra Government, the Bombay high court banned tobacco flavoured gutka and pan masala in the state from July 19, 2012.

States such as Kerala, Madhya Pradesh, Goa and Bihar have already banned the sale of gutka. Assam is one among the states that register a high number of cancer cases in the country due to consumption of tobacco products with 39.3 per cent adults currently using some form of the other tobacco-based products. But inspite of high incidence of tobacco-induced cancer, the state government still has not brought about a regulation act as has been done by eight other Indian states; Madhya Pradesh, Kerala, Bihar, Maharashtra, Rajasthan, Haryana, Jharkhand and Chhattisgarh which have recently banned gutka and pan masala.

**CONCLUSION**

Awareness of the public about underlying aetiological factors of head neck neoplasia is the need of the day. Alcohol and tobacco predominate as the major avoidable aetiological agents in the developing countries thereby emphasizing the necessity of stringent implementation of regulations to control the sale and consumption of all forms of tobacco and nicotine.

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