REVIEW

Oral Squamous Cell Carcinoma- Deciphering the Etiology

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Abstract

Introduction: Cancer of the head and neck including oral, pharyngeal and laryngeal areas is the 6th most common cancer. About 40% of the head and neck malignancies is known to be oral squamous cell carcinoma (OSCC) occur in the oral cavity. OSCC arises as a result of multiple molecular events that develop from the combined influences of an individual's genetic predisposition and exposure to environmental carcinogens.

Materials and Methods: Recent studies confirm that oral cancer forms a large part of the cancer load in parts of India. The development of oral carcinogenesis shows multifactorial etiology - endogenous (genetic) and exogenous (environmental) factors. Tobacco and alcohol are the two most important known risk factors for the development of oral cancer. The combination of both factors seems to enhance the carcinogenic effects. Cofactors in OSCC include dietary factors, immunodeficiency and viral infections like HPV 16/18.

Conclusion: This mini-review provides a concise overview of key determinants contributing to OSCC pathogenesis. Established risk factors such as tobacco and alcohol consumption are discussed, highlighting their synergistic effects and molecular mechanisms of carcinogenesis. Additionally, the role of human papillomavirus (HPV) infection, particularly HPV-16 and HPV-18, in a subset of OSCC cases is explored.

Keywords: OSCC, Alcohol, Tobacco, Smoking, HPV

Introduction

Oral squamous cell carcinoma, or OSCC, is the sixth most common type of cancer. Approximately 95% of carcinomas in the oral cavity are of the squamous cell type[1]. A person's genetic predisposition and environmental carcinogen exposure work together to create a cascade of molecular events that eventually lead to OSCC. There are two primary known risk factors for the development of oral cancer i.e alcohol and tobacco. Both elements working together appear to intensify the carcinogenic consequences. Immunodeficiency, food factors, and viral infections such as HPV 16/18 are cofactors in OSCC[2].

Risk factors for oral cancer

Tobacco-associated carcinogens are among the risk factors; these may work in conjunction to cause oral tumorigenesis. An increased risk of head-neck cancer may result from multiple tobacco usage, alcohol intake, low socioeconomic status associated with poor diet, hygiene, and frequent virus infections.

Tobacco

Neoplasia related to tobacco chewing with betel quid is common in India, while in western countries, cigarette smoking and heavy alcohol consumption are the main risk factors[3].

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Forms of tobacco:-

(1) Smoking form

Cigarette-Tobacco smoke contains numerous compounds emitted as gases and condensed tar particles. Many organic compounds known to be genotoxic and carcinogenic. These include the known constituents, alkenes, nitrosamines, aromatic and heterocyclic hydrocarbons and amines[4].

Components of cigarette smoke:

A. Carcinogens-Cigarette smoke contains numerous known or suspected human carcinogens. The International Agency

for Research on Cancer (IARC) has listed 36 chemicals that are "known to cause cancer" in humans. Cigarette smoke contains at least 10 of these 36 compounds, plus many more mutagenic chemicals that are in the "probably carcinogenic" or "possibly carcinogenic" categories.

B. Tar- is defined as the nicotine-free, dry, particulate mass of tobacco smoke. The particulate fraction of cigarette smoke contains many harmful carcinogenic constituents, including metals, PAHs, dioxins, and some non-volatile nitrosamines[4].

C. Gases-The most widely reported of the gaseous chemicals is carbon monoxide (CO) which is emitted in high concentrations (thousands of parts per million) in cigarette smoke. The toxicity of CO is a function of its ability to form carboxyhaemoglobin, binds with haemoglobin in red blood cells to make carboxyhaemoglobin (COHb) which is then transported into the bloodstream.

Tobacco contains three main kinds of nitroso compounds. When a cigarette is burned while being used, some of the non-volatile tobacco-specific nitrosamines (TSNA) that are formed in tobacco during the post-harvest period are transferred into mainstream smoke. Four TSNAs—4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), nitrosonornicotine (NNN), N-nitrosoanabasine (NAB), and N-nitrosoanabatine (NAT)—have been extensively documented in the literature. It seems that NNK and NNN have the highest potential for mutagenesis[5].

D. Polynuclear aromatic hydrocarbons (PAHs)

Benzo(a)pyrene (BaP) is one of the most toxicologically potent of these compounds. The concentrations of PAHs in tobacco smoke are far too low to be carcinogenic in skin by themselves, and require the presence of promoters and/or co-carcinogens to induce tumours[6].

E. Chlorinated Dioxins and Furans

It has not yet been determined whether side stream smoke contains polychlorinated dibenzo-p-dioxins and dibenzofurans. Because tobacco inherently contains some chloride and hexa-, hepta- and octa-chlorodibenzop-dioxins have been found in mainstream smoke.

Cigar/cheroot/chutta- are made of air cured, fermented tobacco, usually in factories. Cheroots are small cigars made of heavy bodied tobacco. Chuttas are coarsely prepared cheroots made by rolling a tobacco leaf into a cylindrical shape and one end is tied with the thread. Cigars vary by weight and show variation in nicotine content of the tobacco[7].

Reverse chutta smoking- is a peculiar form of smoking in which the smoker puts the lit end of a chutta into his/her mouth during smoking and then inhales the smoke from the lit end. The oral mucosal lesions predominantly associated with reverse smoking are hyperpigmentation, depigmentation, stomatitis nicotina, leukoplakia, erythroplakia, and palatal cancer[8].

2. Smokeless form-

Pan Masala (PM)– is a blend of catechu, slaked lime, and areca nut combined with other flavorings. Nitrosamines, polycyclic aromatic hydrocarbons, leftover insecticides, and hazardous metals including lead, cadmium, and nickel are all present in PM mixture. An alkaloid found in areca nuts is released by the slaked lime, resulting in a euphoria and well-being feeling. When areca nut is present, slaked lime produces reactive oxygen species (ROS) that oxidatively damage DNA. As the primary component of PM, areca nut is the primary cause of oral sub-mucous fibrosis (OSMF)[9&10].

Snuff

Snuff consists of the finely ground tobacco, sold as a dry or moist powder. The moist powder is usually placed in small quantities between the cheek and the gum, in the lower part of the mouth. It is available in small sachets to be placed in the mouth. The dry powder form is used for aspiration or inhalation through the nose.

Alcohol

Oral carcinogenesis has been linked to both independent and combined effects with smoking. Alcohol might have a solvent effect, encouraging the toxins to absorb into the tissues they target. Because ethanol has previously affected the cells in the mouth epithelium, there is a theory that this makes the epithelium more susceptible to the effects of other carcinogens, such tobacco products. Alcohol is regarded more as cocarcinogen, facilitating carcinogenesis rather than initiating it.

Metabolism of alcohol- The main pathway for alcohol metabolism involves the enzyme alcohol dehydrogenase (ADH), which uses a chemical process known as oxidation to convert alcohol to acetaldehyde. Aldehyde dehydrogenase (ALDH) then further oxidizes the acetaldehyde to acetate, which results in the production of reactive oxygen species (ROS). Free radicals have the ability to interact destructively with essential cell components, possibly leading to the cell's death[11].

Betel Quid and Areca Nut

The term "quid" may be defined as "a substance or mixture of substances, placed in the mouth or chewed and remains in contact with the mucosa, usually containing one or both of the two basic ingredients, tobacco, or betel nut, in raw or any manufactured or processed form". Thus, BQ is to be considered as a specific variety of quid.

Categories of quid

1. Quid containing betel nut but without any tobacco components; it can be chewed like a regular quid or wrapped in betel leaf (paan).
2. Quid containing tobacco products but excluding betel nut (tobacco quid), such as chewing tobacco, moist snuff, dry snuff, niswar (a distinct variety of tobacco snuff),and naas (a more potent version of niswar).
3. Betel nut quid and tobacco products (betel nut and tobacco quid).

Reactive oxygen species (ROS) produced by chewing BQ are detrimental to the oral mucosa and may play a direct role in the genesis of tumors.

Reasons for using betel nut include achieving euphoria, combating fatigue, increasing salivation, attaining satiation and even seeking relief of toothaches[12].

Viruses

Numerous studies have suggested that viruses have a role in the development of oral squamous cell carcinoma. The most commonly studied viruses are Epstein-Barr virus (EBV) and Human Papillomavirus (HPV).

The human papillomavirus (HPV) is seen in malignant oral lesions, condylomas, localized epithelial hyperplasia, and squamous cell papillomas. Oral cavity (59%), pharyngeal (43%) and laryngeal (33%), tumors had higher HPV positive rates. Malignant transformation is an uncommon outcome for a small percentage of HPV-infected lesions, particularly those exhibiting HPV subtypes (16, 18)[13]. HPVs specifically target the undifferentiated proliferative basal cells of epithelial mucosa. HPV proteins, especially the oncoproteins E6 and E7 of the high risk HPVs (HR-HPVs), interact with different degrees of affinity with host cell proteins to disturb the normal epithelial differentiation and apoptosis by stimulating cellular proliferation, DNA synthesis and inhibition of cell cycle regulators. HPV DNA has been identified in primary tumours of the tonsil, larynx, hypopharynx, oral cavity, tongue, and nasopharynx, as well as in celllines derived from a variety of head and neck carcinomas and in inverted papillomas that have progressed to SCC. Precancerous lesions and metastatic lymph nodes have also been shown to contain DNA of the same HPV type as in the primary tumor in 76% of the cases, supporting the involvement of HPV in the development of SCC.

There is growing evidence that human papilloma virus (HPV) may act as a cocarcinogen, along with tobacco, in the causation of oral cancers. The role of HPV in the etiology of anogenital cancers has been firmly established, and infection with this virus has also been shown to have prognostic significance. However, there is no clear evidence to support its involvement in oral carcinogenesis.

Diet

Numerous studies have demonstrated the significance of diet and nutrition in the development of oral neoplasia. Red chili powder and meat are considered risk factors, while fruits and vegetables (high in vitamins A and C) help prevent it. Head and neck cancer risk factors include inappropriate dietary practices, such as a poor consumption of fruits and vegetables. Many micronutrients have been shown to have anti-oxidant and anticarcinogenic properties. These consist of dietary fibers, flavonoids, phytosterols, folates, and vitamins C and E.

UV rays

Ultraviolet (UV) radiation is known to cause distinct mutations in keratinocytes that ultimately contribute to the development of the non-melanoma skin cancers, which include basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). The process by which these mutations are introduced begins with the reaction of UV photons with cellular DNA. As photons are absorbed by DNA molecules, an excited state is produced which allows for the rearrangement of electrons resulting in the formation of photoproducts[14].

Candida

The weakening of the immune system changes the normal flora and Candidal infection may occur. Candida albicansis the most causal agent in oral fungal infections. It can reproduce in two forms: Hyphae (hyphal) and yeast.

Yeast is relatively harmless, but hyphae usually attack the host tissues. Consequently, the contaminated epithelial cells begin to change morphologically due to the:

a. Adhesive factors of Candida
b. Extracellular lipid lytic activities of Candida
c. The proteolytic activities of these micro-organisms

Conclusion

Oral cancer is one important public health concern. Although oral carcinogenesis has been linked to alcohol and tobacco use, the cause of approximately 20% of cases remains unexplained. It is imperative to investigate other potential factors associated with the development of OSCC in order to facilitate appropriate therapeutic therapy.

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