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Review Article

Carcinoma of Oral Cavity Causative and Risk Factors: A Review

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Abstract

Carcinoma of the oral cavity is one of the most common cancers and it's a major health problem particularly in developing countries. Misuse of cigarette smoking and alcohol consumption are main risk factors for oral carcinoma. Among Asian people, increases the risk of oral carcinoma due to regular use of betel quid (with or without smokeless tobacco). Rather than this factor the other associated factors for developing oral malignancy is a multistep process involving the accumulation of genetic and epigenetic alterations in genes. Some controversies of causative factors oral carcinoma also need clarification. This paper will provide an opinion on this major disease about the debated controversies.

Keywords: *Carcinoma; Oral Cavity; Cigarette; Tobacco*

Introduction

Oral carcinoma is most common carcinoma among the malignancy and is a major problem in world. Leading causes of death oral malignancy one of them [1]. The main factors of oral carcinoma which influences are genetic and epigenetic factors [2]. The common site of oral cancer of the lip and oral cavity (buccal mucosa, gingiva, cheek, hard palate, tongue and floor of mouth) [3] and this malignancy is considered as sixth most common type of carcinoma of world [4]. Oral malignancy or head and neck squamous cell carcinoma (HNSCC) and major and minor salivary gland carcinomas is influenced by factors namely tobacco, alcohol, diet and nutrition, viruses, radiation, ethnicity, familial and genetic predisposition, oral thrush, immunosuppression, syphilis, dental factors such as sharp teeth, ill fitting dentures, occupational risks, and mate.

Causative factors

Tobacco

Consumption of tobacco is an important factor for developing cancer risk and also causes millions of deaths annually. Adequate evidences suggesting that various forms of tobacco like cigarette/Biri/Pipe smoking, smokeless tobacco chewing and betel quid etc. can produce carcinogenic impact in oropharynx [5]. Smoking causes neoplastic diseases including cancers of lung, pharynx, oral cavity, esophagus, larynx, urinary bladder, renal, pelvis, and pancreas. Aromatic hydrocarbon benz-pyrene and the tobacco-specific nitrosamines (TSNs) namely 4-(nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) and N'-nitrosonornicotine (NNN) are the most pre-dominant carcinogenic factors. NNK and NNN in the tobacco products can cause tumors of the oral cavity, lung, esophagus, and pancreas have been

found in animal studies. NNN, NNK and metabolites of them covalently bind with deoxyribonucleic acid (DNA) of keratinocyte stem cells forming DNA adducts. These adducts can be responsible for critical mutations. P450 enzymes in cytochromes and conjugation. Enzymes of other varieties are also responsible for initiation or degradation of carcinogenic and procarcinogenic factors. They are termed xenobiotic metabolizing enzymes (XMEs). These enzymes are found mainly in the liver and also in the mucosa of the upper aerodigestive tract. Many of the XMEs are polymorphic and they strongly influence the individual's biological responses to carcinogens by formation of DNA adducts. These enzymes are found mainly in the liver and also in the mucosa of the upper aerodigestive tract. Hence, certain XME genotype may increase individual susceptibility to cancer through erroneous carcinogen metabolism leading to increased carcinogen exposure [6]. Tobacco- induced head and neck carcinoma genetic alteration in the genes coding for these enzymes are suspected to play the key role in genetic predisposition [7]. The use of smokeless tobacco (tobacco consumed without combustion) has become prevalent all over the world. Smokeless tobacco is placed inside the oral cavity in contact with the mucous membranes. Where the nicotine is absorbed to provide the desired effect. Smokeless tobacco has been used in many forms in different parts of the world. For instance, the use of oral snuff (wet or moist snuff) is more common in the west and the Middle-East [8].

Betel quid

Betel quid chewing with different ingredients is the most common habit in Southeast Asia, especially in the Indian subcontinent. Betel quid (also referred to as pan or paan) usually contains betel leaf (leaf of Piper betel vine), areca nut, slaked lime and tobacco. Studies have shown the association of tobacco chewing with oral cancer and pre-cancer namely leukoplakia, erythroplakia and oral submucous fibrosis [9].

Considerable research has been focused in the recent past on the carcinogenic, mutagenic, and genotoxic potential of betel quid ingredients, especially tobacco and areca nut [10]. Arecoline, an alkaloid present in areca nut, causes cell death, apoptosis, and cell cycle arrest of epithelial cells contributing to the pathogenesis of oral carcinogenesis [11]. Toxicity of areca nut ingredients: Activation of CHK1/CHK2. induction of cell cycle arrest, and regulation of MMP-9 and TIMPs production in SAS epithelial cells [12].

Alcohol

Numerous studies have suggested alcohol to be a major risk factor for OC. There is a certain degree of controversy whether alcohol alone may have carcinogenic impact. Studies have shown that individuals consuming more than 170g of whisky daily have ten times higher risk of OC than the light drinkers [13]. Alcohol may have additive effect and it has been suggested that it facilitates the entry of carcinogens into the exposed cells, altering the metabolism of oral mucosal cells. Hence, the role of alcohol as an independent factor in oral carcinogenesis is still unclear albeit epidemiological evidence establishes the synergistic role played by alcohol with tobacco. Alcohol is shown to increase the permeability of oral mucosa producing an alteration in morphology characterized by epithelial atrophy, which in turn leads to easier penetration of carcinogens into the oral mucosa [14]. The systemic effects of alcohol are mainly due to the hepatic damage. Alcohol addiction leading to cirrhosis and other diseases (e.g. cardiomyopathy, stroke, and dementia) inhibits the detoxification of carcinogenic compounds such as N-nitrosodiethylamine [15]. Chronic alcoholics tend to have reduced intake of nutrients due to the metabolic processes being occupied in the transformation of ethanol and the proper metabolism of nutrients is altered. This enhances nutritional deficiencies thereby increasing the risk of cancer. Chronic alcohol intake also leads to suppression of immune system by affecting liver and nutritional status [16].

Hamsters and this have been attributed to the stimulation of potent immune response by vitamin E and vitamin E has also been shown to have the potential to reduce oxidative damage caused by hydroxyl radicals. Clinical intervention trials with tocopherol, which is a non-toxic antioxidant like carotene have shown much promise with oral cancer and precancer. However, treatment trials with tocopherol have to be done with caution as high concentrations (80 mol) of vitamin E has been shown to promote skin tumor formation [19]. Antioxidant, decreases nitrosation by preventing the formation of nitrosamines, thereby acting as a chemopreventive agent. It also affects the activity of leukocytes and macrophages. AA is also involved in the activity of cytochrome P450 which is important in the inactivation of potent

carcinogens and metabolic activation of procarcinogens. There has been no study reported on the sole use of AA in the treatment of oral leukoplakia. The association between AA and oral cancer is based on the dietary assessments that low intake of fruits and vegetables which are usually rich in vitamin C predisposed to increased risk of oral cancer [20]. Controversial data exists on the effect of coffee and tea consumption and OC. A study revealed that they may decrease the risk of OC through antioxidant components [21]. While another showed that the long term exposure of molecules present in coffee and tea may affect the anticarcinogenic action of saliva [22], high fruit and vegetable consumption have shown to have a protective effect on the development of OC due to the dietary antioxidants and folate [23,24]. Intake of fruit and vegetables may protect against oral cancer, especially the groups of Leguminosae (beans and peas), rosaceae (apples, peach, nectarines, plums, pears and strawberries), Solanaceae (peppers and tomatoes) and umbelliferae (carrots) [25].

Environmental factors

Viral infections

Although the association between HPV infection and oro-pharyngeal cancer is now well established, it is still unclear whether HPV infection may lead to OC as well. Several studies suggest an association between human papillomavirus (HPV) infection and oro-pharyngeal cancers [26]. Role of oncogenic viruses in human cancer is an emerging area of research. Viruses are capable of hijacking host cellular apparatus and modifying DNA and the chromosomal structures and inducing proliferative changes in the cells. HPV [27] Herpes simplex virus (HSV) have been established in recent years as causative agents of OC. HPV has been identified in approximately 23.5% of OC cases [28]. HSV-1 or ''oral herpes'' is commonly associated with sores around the mouth and lip and has been suggested to be a causative agent of OC [29]. Epidemiological studies showed higher level of IgG and IgM antibodies to OC patients compared to control subjects [30]. Risk of oral cavity and pharyngeal cancer is two-fold higher among human immune deficiency virus (HIV) patients indicating a link between HIV and OSCC [31,32]. Epstein Barr Virus (EBV), human herpesvirus-8 (HHV-8) and cytomegalovirus have also been reported as risk factors of OSCC in different studies [33,34]. The major evidence of the role of HPV in cancer development is that their genes and gene products are capable of disturbing the cell cycle machinery. HPV encodes two major oncoproteins namely, E6 and E7. The E6 and E7 proteins have been shown to bind and destroy p53 and Rb tumor suppressor genes, respectively, thereby disrupting the cell cycle with loss of control on DNA replication, DNA repair, and apoptosis. HPV has been detected in OSCC, dysplasia, and other benign lesions using various techniques. Some studies have shown HPV presence in normal oral mucosa making the role of HPV in oral carcinogenesis speculative [35]. Moreover, HPV 16, which is the most common type found in genital cancers were also the most common in oral cancers, which clearly indicates the possible source of HPV infection in the oral cavity. HSV has not been proven to be the direct cause of oral cancer, although several studies show that oral cancer patients have high serum antibody titers to HSV. The available evidences are circumstantial and are rationalized that reactivation of HSV infection is due to immunosuppression, specifically of natural killer lymphocyte activity. Based on the evidence of *in vitro* studies, the possible role of HSV in carcinogenesis has been proposed as the enhancement of activation, amplification, and over expression of preexisting oncogenes such as c-myc and c-erb-B-1 [36].

Fungal

Fungal infections caused by *Candida* species, in particular, *Candida albicans* has been implicated in the pathogenesis of oral premalignant lesions. Superficial fungal hyphae of *Candida albicans* have been found superimposed on leukoplakia, especially nodular leukoplakia, many of which have undergone malignant transformation. *Candida* species are commensals in the oral cavity which become opportunistic during host's immunosuppression due to systemic diseases or drug therapy [37]. It has also been shown that epithelium of the chick embryo, when infected with *Candida albicans* show squamous metaplasia and higher proliferative phenotype [38].

Immunosuppression

Immunosuppressed individuals are more prone to develop oral cancers. Human immune deficiency virus (HIV)-infected patients are predisposed to developing Kaposi's sarcoma and lymphomas, although not to OSCC. Immunosuppressed organ transplant patients have been shown to develop lip cancers and the possible reason was attributed to increased exposure to solar radiation and other risk factors such as smoking. However, the direct role of immune suppression with lip cancer development was not proven in the studies [39].

Dental factors

Poor oral hygiene, poor dental status (sharp/fractured teeth due to caries/trauma), and chronic ulceration from an ill-fitting denture has been suggested to promote neoplasm in the presence of other risk factors. There has been difficulty in obtaining the evidence whether dental factors influence oral cancer development. This is due to the presence of coexisting risk factors like smoking and alcohol consumption [40].

P53

It is one of the most important tumor suppressor genes. Tumor suppressor genes work normally in cellular growth control by regulating the cell cycle, apoptosis, cell adhesion, and DNA repair. Silencing of tumor suppressor genes occurs in carcinogenesis. P53 mutation was also found to have an association with tobacco smoking and alcohol drinking. Inactivation of P53 by mutations is a critical molecular event in the upper aero-digestive tract carcinogenesis [41]. TP53 and EGFR mutations in combination with lifestyle risk factors in tumours of the upper aerodigestive tract from South America. Alteration of P53 expression is related to increased genomic instability in oral intraepithelial neoplasia and may accelerate the genetic modifications during oral tumorigenesis [42]. P53 codon 72 polymorphism was found to be associated with a higher risk for contracting oral cancer [43].

Genetic factors

More than 50% of all primary HNSCC harbour p53mutation [44]. Inactivation of p53 represents the most common genetic change in all human cancers [45]. The most commonly deleted region in HNC is located at chromosome 9p21-22 [46]. Loss of chromosome 9p21 occurs in the majority of invasive tumors in head and neck cancer [47]. Homozygous deletions in this region are frequent and represent one of the most common genetic changes identified p16 (CDKN2) present in this deleted region, is a potent inhibitor of cyclin D1 [48]. Loss of p16 protein has been observed in most advanced pre-malignant lesions also [49,50]. Have identified an alternative RNA transcript for p16 termed as Alternative Rating Frame (ARF; or p16b). Introduction of p16 orp16ARF into HNC cell lines result in potent growth suppression [51]. Loss of chromosome 17p is also frequent in most human cancer including OC. It is seen in approximately 60% of invasive lesions. Although p53 inactivation correlates closely with loss of 17p in invasive lesions, p53 mutations are quite rare in early lesions that contain 17p loss. Loss of chromosome arm 10 and 13q are also noted in primary tumors [52].

Conclusion

It is clear from the above review that several risk factors are implicated in the development of oral cancer, of which the most common and established are tobacco smoking and betel quid chewing. Nevertheless, many patients are diagnosed with oral cancer despite abstaining from known lifestyle or environmental risk factors where factors like genetic susceptibility are believed to play the causative role. Increasing knowledge of molecular genetic alterations in OC has lead to a better understanding of molecular pathways in the development of OC. This new knowledge is expected to generate new lead for prevention, early diagnosis and devising new therapy for OC. A robust progress has been made in our understanding of molecular basis of oral carcinoma, but there is lot more to be understood.

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