ETIOLOGY AND RISK FACTORS OF ORAL CARCINOMA

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ABSTRACT: Oral cancer is the sixth most common malignancy in the world. Oral cancer is of major concern in Southeast Asia primarily because of the prevalent oral habits of betel quid chewing, smoking, and alcohol consumption. Despite recent advances in cancer diagnoses and therapies, the 5-year survival rate of oral cancer patients has remained at a dismal 50% in the last few decades. This paper is an overview of the various etiological agents and risk factors implicated in the development of oral cancer.

KEY WORDS: Etiology, genetic predisposition, nutrition, oral cancer, risk factors, tobacco, viruses.

INTRODUCTION:

Oral cancer accounts for 2%–4% worldwide of all cancer cases. The prevalence of oral cancer in India is around 45%.[1,2] Oral cancer is a common life threatening disease in India. Oral cancer is the third most common malignancy in south Asia. Oral Squamous cell carcinoma (OSCC) is the leading cancer worldwide. OSCC is one of the leading causes of morbidity and mortality in many countries. It arises anywhere in the oral cavity. The most common sites are the Tongue, Upper and Lower Gingiva, Oral floor, Palate, and Buccal mucosa. Tongue cancer incidence is increasing despite the general global trend of a slight decrease in the incidence of oral cancer. [3] Appears in patients older than 50 years of age. Several studies have shown that between 1 to 6 % of oral cancers present in patients under the age of 40 years. However, in the last decade an increase is observed in the percentage of young patients. [3]

Oral cancer is of major concern in Southeast Asia. This is because of the prevalent oral habits of betel quid chewing, smoking, and alcohol consumption. Despite recent advances in cancer diagnoses and therapies, the 5-year survival rate of oral cancer patients has remained at a dismal 50% in the last few decades.

The two main factors which influence most diseases are genetic and epigenetic factors. Development of oral or head and neck Squamous cell carcinoma (HNSCC) and minor salivary gland carcinomas is influenced by both these factors namely tobacco, alcohol, diet and nutrition, viruses, radiation, ethnicity, familial and genetic predisposition, oral thrush, immunosuppression, use of mouthwash, syphilis, dental factors, occupational risks, and mate.

GENETIC FACTORS:

Current modeling postulates that the development of cancer is driven by the accumulation of genetic and epigenetic changes within a clonal population of cells. These genotypic alterations can affect hundreds of genes, leading to phenotypic changes in critical cellular functions, such as resistance to cell death, increased proliferation, induction of angiogenesis, and the ability to invade and metastasize. Genetic predisposition has been shown to be an important risk factor in the development of OSCC. A study by Copper et al., who followed up first-degree relatives of 105 head and neck cancer patients, found that 31 of these subjects developed cancers of respiratory tract and upper aero digestive tract.[4] However, population based studies to determine the genetic or familial disposition to oral cancers are limited by the coexisting risk factors like smoking and alcohol. It is also believed that certain individuals inherit the susceptibility of inability to metabolize carcinogens or procarcinogens and/or an impaired ability to repair the DNA damage. The metabolism of tobacco carcinogens, genetic polymorphisms in the genes coding for the enzymes (P450 enzymes and XMEs) responsible for tobacco carcinogen metabolism are suspected to play key role in the genetic predisposition of tobacco induced head and neck cancers.[5]

EPIGENETIC FACTORS:

TOBACCO:

Oral neoplasia has been associated with chewing of tobacco with betel quid (BQ) in India and other Asian countries, whereas in western countries, cigarette smoking and heavy alcohol consumption are the main risk factors.[6] The international agency for research on cancer (IARC) confirmed that smoking of various forms of tobacco (e.g., bidis, pipes, cigars and cigarettes) is carcinogenic in humans.[7] Chewing of tobacco with BQ increases exposure to carcinogenic tobacco-specific nitrosamines (TSNA) and to nitrosamines derived from areca nut alkaloids. Furthermore, reactive oxygen species (ROS) implicated in multistage carcinogenesis, are also generated in substantial amounts in the oral cavity during chewing. Tobacco smoke pro-carcinogens such as benzo-[α]pyrene are metabolized by oxidizing enzymes, particularly cytochrome p450, some resulting in the production of reactive carcinogenic intermediates. Some studies link that cytochrome P450 family 1, subfamily A (CYP1A1) and CYP2E1 genotype shows susceptibility to oral cancer, but others have failed to confirm this association. [8]

BETEL QUID AND ARECA NUT:

Betel chewing is reported to be the most important etiological factor in oral sub mucous fibrosis. The use of betel quid, containing both areca nut and tobacco, is associated with a much higher relative risk of oral cancer, between 8-15 times as compared to that of 1-4 times, associated with using the quid, without tobacco.[6] BQ chewing produces ROS that is detrimental to oral mucosa and can be directly involved in tumor initiation process, by inducing mutation, or by making the mucosa susceptible to BQ ingredients and environmental toxicants. Betel quid (BQ) chewing produces reactive oxygen species (ROS), that have multiple detrimental effects upon the oral mucosa. The production and release of ROS occurs under alkaline conditions during the autooxidation of areca nut (AN) polyphenols, in the BQ chewer's saliva.[9] The ROS can be directly involved in the tumour initiation process, by inducing genotoxicity and gene mutation, or by attacking the salivary proteins and oral mucosa, leading to structural change in the oral mucosa, that may facilitate the penetration by other BQ ingredients and environmental toxicants. The nitrosation of areca alkaloids to AN-specific nitrosamines occurs in the saliva of BQ chewers.[10] These AN-specific nitrosamines are mutagenic, genotoxic and capable of inducing tumours in animal models.[11]

ALCOHOL:

Alcohol has been implicated in the development of oral cancer.Alcoholic beverages have been considered carcinogenic to humans causing in particular, tumors of the oral cavity, pharynx, larynx, esophagus, and liver. Alcohol consumption has been shown to act synergistically with Tobacco in the increased risk of development of oral cancer. In one study, alcohol has been found to be an independent risk factor for oral leukoplakia in an Indian population.[12] However, similar studies evaluatingthe oral epithelial dysplasia occurrence in alcohol drinkers who are nonsmokers, found that the role of alcohol in development of oral epithelial dysplasia is crucial only when considered in conjunction with tobacco.[13] 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.[13] Substances that have been believed to be carcinogenic to humans have been seen in alcoholic beverages. A few examples are, N-nitroso compounds, mycotoxins, urethane, inorganic arsenic, and others. The major metabolite of alcohol is acetaldehyde. Acetaldehyde causes DNA damage in cultured mammalian cells. It interferes with the DNA synthesis and repair. ill-effects of acetaldehyde which initiates or promotes tumor formation, increase in acetaldehyde accumulation in the body either due to increase in its production or due to decrease in its elimination, is considered deleterious. 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.[14] 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 systemby affecting liver and nutritional status.[15]

DIET AND NUTRITION:

The relationship between diet and nutrition to the risk of cancer development has been established by several epidemiological and laboratory studies.[16] The working group of International Agency for Research on Cancer (IARC) has affirmed that low intake of fruits and vegetables predisposes to increased risk of cancer development. More frequent consumption of fruit and vegetables, particularly of carrots, fresh tomatoes, and green peppers were associated with reduced risk of oral and pharyngeal cancer. Food and food groups other than fruits and raw vegetables that have a protective effect are fish, vegetable oil, olive oil, bread, cereals, legumes, protein, fat, fresh meat, chicken, liver, shrimp, lobster, and fiber.[16] Certain food groups have been shown to be associated with higher risk of oral cancer namely processed meats, cakes and desserts, butter, eggs, soups, red meat, salted meat, cheese, pulses, polenta, pasta or rice, millet, and corn bread. The evidence from the above studies however does not allow authoritative attribution of either the benefit or the drawback to a specific ingredient in the food.[17] Considerable evidence has shown that certain micronutrients decrease the risk of oral cancer development. They include vitamins A (retinol), C (AA), and E (α-tocopherol); carotenoids (β-carotene); potassium; and selenium (38–43). β-carotene, retinol, retinoids, vitamin C (AA), and vitamin E (α-tocopherol) are antioxidants that are essential in reducing free radical reactions that can cause DNA mutations, changes in enzymatic activity, and lipid peroxidation of cellular membranes.[16] Cultural risk factors and dietary factors seem to interplay in the development of oral cancer and precancer. Studies have shown the association between smoking and lowering of serum levels of nutrients.[18]

MATE:

Maté, which is a tea-like beverage consumed in South America and in parts of Europe has been shown to be an independent cause for development of oral and pharyngeal cancers. The exact pathogenesis of maté predisposing to oral cancer is still unknown. Many reasons that have proposed for maté's carcinogenicity are thermal injury, solvent for other chemical carcinogens, and presence of tannins and N-nitroso compounds.[19]

ENVIRONMENTAL FACTORS:

VIRAL INFECTIONS:

The impact of viruses regarding oral SCC has been studied since the beginning of the 20th century, when Ellerman and Bang, and Rous isolated an infective agent which later was shown to be a virus that had the ability to induce tumours in chickens.[20,21] HPV. Human papillomavirus (HPV) was identified as a causal agent of cervical cancer by zur Hausen and colleagues in 1983. [22] The association of HPV with oral cavity and oropharyngeal cancer was first reported by Loning et al.[23] and de Villiers et al. [24] in 1985. [25] HPV types detected were classified into (i) non-oncogenic (low-risk, such as HPV6, 11, 26) and (ii) oncogenic (high-risk, such as HPV16, 18, 31) categories, according to the World Health Organization's International Agency for Research on Cancer.[26] HPV 16 and 18 seem to be the most important viruses responsible for tumourigenesis and can be found in premalignant and malignant lesions of the oral cavity.

The Epstein-Barr virus (EBV) was the first human virus to be assigned oncogenic potential. EBV has been implicated in a wide variety of malignant and benign tumours, as well as in classic infectious diseases. . EBV infects approximately 90% of the world's adult population asymptomatically and is associated with hairy leukoplakia (HL), epithelial cancer such as Burkitt's lymphoma, immunoblastic lymphoma, nasopharyngeal cancer [27], and oral squamous cell carcinoma, as well as some benign and potentially malignant oral lesions and diseases, including oral lichen planus, gingivitis, and periodontitis. After primary infection, EBV establishes a latent infection in a small proportion of B-lymphocytes and oronasopharyngeal

and salivary gland epithelial cells. The virus periodically replicates in the oropharynx or in te salivary gland epithelium, and is then shed in the saliva.[28]

Herpes simplex virus type-1 (HSV-1) is found predominantly in oropharyngeal infections, and HSV-2 has a strong predilection for anogenital sites. Both types of viruses cause a large range of clinical symptoms. [29] HSV1 is a cytotoxic virus that readily infects and destroys human cells, including cancer cells. Infections with HSV are frequent in the general population and occur normally during early adolescence, manifesting as herpetic gingivostomatitis or pass asymptomatically. After primary infection, the virus travels along the axons of sensory nerve fibres that innervate the affected area, to the trigeminal ganglion, where it stays in a latent form. When the balance between the virus and the host is disturbed, fast replication and reactivation occurs.

FUNGAL INFECTIONS:

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. The doubt of whether Candida invasion is a secondary event or causal in oral premalignant lesions is still uncertain and debatable.Candida species are commensals in the oral cavity which become opportunistic during host's immunosuppression due to systemic diseases or drug therapy. Besides immunocompromised individuals, Candida infection can coexist or be associated with other risk factors like irondeficiency and in chronic smokers which may prove synergistic in the development of oral cancer. There is evidence that Candida possesses necessaryenzymes fromdietary substances to produce nitrosamines and chemicals that have been implicated in carcinogenesis.[30]

IMMUNOSUPPRESSION:

Immunosuppressed individuals are more prone to develop oral cancers. Human immunodeficiency 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.

OCCUPATIONAL RISKS:

Occupational risks, namely exposure to excessive solar radiation/ultraviolet (UV) light is known to cause lip cancers. UV rays also causes actinic cheilitis which may transform to OSCCs. Sulfur dioxide, asbestos, pesticide exposures, and mists from strong inorganic acids and burning of fossil fuels have also been known to cause cancers of posterior mouth, pharynx, and larynx.[31] Certain occupations have been reported to place people at increased risk for the development of salivary gland carcinomas; these include manufacturing of rubber products, plumbing (exposure of metals), and woodworking in an automobile industry.[32]

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.

SYPHILIS:

Tertiary syphilis had been known to predispose to the development of oral cancer along with other risk factors such as tobacco and alcohol.

RADIATION:

Substantial evidence exists for a relationship between exposure to ionizing radiation and the later development of
salivary gland tumors.

CONCLUSION:

Oral cancer is a relevant public health problem. The increased incidence is related to aging and to development of chronic diseases. The literature has highlighted the important role of tobacco and alcohol consumption in oral carcinogenesis, but nearly 20% of OSCC cases have shown unknown etiology. There has been an increased number of cases among individuals without history of smoking and/or alcohol consumption and in female (younger and older). Another interesting aspect refers to the potential role of HPV associated with OSCC. It is important to investigate other possible factors associated with the occurrence of OSCC, enabling appropriate clinical management and monitoring. Moreover, improving the incidence, mortality, and survival rates of oral cancer requires a multi-tier structural approach that targets society, dentists, communities, and the individual. [33]

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