# AETIOLOGY AND RISK FACTORS FOR ORAL CANCER – A BRIEF OVERVIEW

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## ABSTRACT

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

Key words: etiology, risk factors, oral cancer, oral precancer, carcinogenicity, tobacco, alcohol, nutrition, viruses, genetic predisposition.

## INTRODUCTION

The three main factors which influence most diseases are lifestyle, environmental factors and genetic susceptibility (1). Oral or head and neck squamous cell carcinoma (SCCHN) development is influenced by all these factors namely tobacco (smoking & smokeless), alcohol, diet and nutrition, viruses, radiation, ethnicity, familial and genetic predisposition, *Candida* infection, immuno-suppression, the use of mouthwash, syphilis, dental factors, occupational risks and maté (2).

## LIFESTYLE FACTORS

### Tobacco:

Tobacco consumption continues to prevail as the most important cancer risk and tobacco accounts for millions of cancer deaths annually (3). The neoplastic diseases caused by smoking include cancers of the lung, oral cavity, pharynx, larynx, esophagus, urinary bladder, renal pelvis and pancreas (4). The oral consumption of smokeless tobacco in various forms also causes cancer, particularly in the oral cavity (5).

The relationship between smoking and oral cancer has been established firmly by epidemiological studies (6). The most important carcinogens in tobacco smoke are the aromatic hydrocarbon benz-pyrene and the tobacco specific nitrosamines (TSNs) namely 4-(nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) and N'-nitrosonornicotine (NNN). Animal studies have shown that NNK and NNN in the tobacco products causes tumours of the oral cavity, lung, esophagus and pancreas (7). NNK, NNN and their metabolites covalently bind with DNA of keratinocyte stem cells forming DNA adducts. These adducts are responsible for critical mutations involved in DNA replication (8). The metabolism of these carcinogens involves oxygenation by P450 enzymes in cytochromes and conjugation by glutathione-S-transferase (GST). Genetic polymorphisms in the genes coding for these enzymes are suspected to play a key role in the genetic predisposition to tobacco induced head and neck cancers (9). Certain other classes of enzymes are involved in the activation or degradation of carcinogens and procarcinogens and they are termed xenobiotic metabolizing enzymes (XMEs). These enzymes are found mainly in the liver and also in the upper aero-digestive tract mucosae. Many of the XMEs are polymorphic and they strongly influence the individual's biological responses to carcinogens by formation of DNA adducts. Hence, certain XME genotype may increase individual susceptibility to cancer through erroneous carcinogen metabolism leading to increased carcinogen exposure. The ability to repair damaged DNA by carcinogens, has also been found to be reduced in head and neck cancer patients (1).

Marijuana is a popular name for dried flowering leaves of the plant *Cannabis Sativa* and is also called *bhang* or *ganja*. It is smoked as cigarettes and the cannabinoids release potent carcinogens like benz(o)pyrene, phenols, phytosterols, acids and terpenes when burnt. Studies have shown that marijuana smoking is not an independent risk factor for oral cancer development. However, a theoretical risk exists because of composition of marijuana. Moreover, tobacco usually forms a part of marijuana smoking mix (10).

The use of smokeless tobacco (tobacco consumed without combustion) has become prevalent all over the world (11). Smokeless tobacco is placed inside the oral cavity in contact with the mucous membranes where the nicotine is absorbed to provide the pharmacological effect (9). 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 whereas betel quid chewing with a variety of forms and ingredients is widespread in Asia where it is a custom and cultural habit since ancient era. Consumption of smokeless tobacco causes mainly oral precancer and cancer (9).

In Western Europe and North America, the main types of chewing tobacco are plug, loose-leaf and twist. Their use is declining in these regions, albeit still prevailing in certain sub-populations (12). Moist snuff (ground tobacco) is particularly common in North America and Scandinavia. The habit has become extremely popular among youth in these countries especially Sweden (12, 13). The habit of oral snuff (referred to as snuff-dipping) causes a condition called 'snuff-dipper's cancer' which was the basis of classical description of verrucous carcinoma (9). Snuff as manufactured in Europe and North America is very different from snuff-like products used in the Middle East, which are made by small-scale industries. Swedish *snus* (snuff) is not fermented and contains very low nitrosamine levels compared to those produced elsewhere. To date there are still conflicting views on the carcinogenic potential of Swedish snuff (9, 14, 15).

**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. Other ingredients are often added namely, spices such as cardamom, cloves or aniseed are added in betel quid from India and turmeric in betel quid from Thailand (10). Some of the common forms of these mixtures are *khaini* (tobacco and lime), *mishri* (burned tobacco), *zarda* (boiled tobacco), *gadakhu* (tobacco and molasses) and *mawa* (tobacco, lime and areca) consumed in different parts of India; *nass* (tobacco, ash, cotton or sesame oil), *naswar*/*niswar* (tobacco, ash and lime) in Central Asia and Middle East; s*hammah* (tobacco, ash and lime) in Saudi Arabia and *toombak* (tobacco and sodium bicarbonate) in Sudan (9). Studies have shown the association of these products with oral cancer development. For instance, *shammah* is associated with leukoplakia-like lesions and oral cancer (16).

Studies have shown the association of tobacco chewing with oral cancer (6) and precancer namely leukoplakia, erythroplakia and oral submucous fibrosis. (17-19).

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. *In vitro* studies on oral mucosal fibroblasts using DNA damage, cytotoxicity and cell proliferation assays have shown that some essential betel quid ingredients are genotoxic, cytotoxic and also stimulate cell proliferation (20). It has been shown that reactive oxygen species (ROS), methylating agents and reactive metabolic intermediates from betel quid induced various kinds of DNA damage (21). A recent IARC evaluation affirmed that chewing betel quid without tobacco is also carcinogenic to humans and areca nut, a common component of many chewing habits is carcinogenic to humans (22).

**Alcohol:**

Alcohol has been strongly implicated in the development of oral cancer. Based on the results of cohort and case-control studies, the consumption of alcoholic beverages has been considered carcinogenic to humans causing in particular, tumours of the oral cavity, pharynx, larynx, oesophagus and liver, although ethanol *per se* has not been proven carcinogenic in animal studies (17, 23-25).

Several epidemiologic studies (17, 23-26) done to determine the direct cause-effect relationship between alcohol consumption and development of oral cancer have found difficulty in establishing the same affirmatively due to other coexisting risk factors within the same individual such as smoking and quid chewing habits. However, alcohol consumption has been shown to act synergistically with tobacco in the increased risk of development of oral cancer (17, 23, 24, 26). Few studies (27-29) have managed to do analysis with patients who drink alcohol but are non-smokers and in patients who smoke but are non-drinkers. In one such study, alcohol has been found to be an independent risk factor for oral leukoplakia in an Indian population (27). However, similar studies evaluating the oral epithelial dysplasia occurrence in alcohol drinkers who are non-smokers, found that the role of alcohol in development of oral epithelial dysplasia is crucial only when considered in conjunction with tobacco (28, 29). Hence, the role of alcohol as an independent factor in oral carcinogenesis is still unclear albeit epidemiological evidence (23-26) establishes the synergistic role played by alcohol with tobacco.

The pathogenic mechanism of alcohol causing cancer has been difficult to establish. There have been many studies (30, 31) supporting possible mechanistic pathways of alcohol inducing carcinogenesis. Ethanol 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. For instance, concentrations of ethanol of 25% and above significantly increased the permeability of porcine oral mucosa to nitrosonornicotine (NNN) (30). Substances that have been believed to be carcinogenic to humans have been seen in alcoholic beverages, a few examples being, *N*-nitroso compounds, mycotoxins, urethane, inorganic arsenic and others (25). The major metabolite of alcohol is acetaldehyde whose transformation is mainly carried out by the enzyme alcohol dehydrogenase (ADH). Acetaldehyde is then oxidized to acetate by means of aldehyde dehydrogenase (ALDH). Acetaldehyde causes DNA damage in cultured mammalian cells. It interferes with the DNA synthesis and repair. It also induces sister chromatid exchanges and specific gene mutations. Acetaldehyde inhibits the enzyme 06-methylguanitransferase which is responsible for repairing injuries caused by alkylating agents. With all the above ill-effects of acetaldehyde which initiates or promotes tumour 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 (31). Accumulation of acetaldehyde can occur due to increased activity of alcohol dehydrogenase (ADH) enzyme activity which is present in oral microflora and in the oral mucosa. Poor oral hygiene with increasing microbial flora can increase ADH production thereby increasing acetaldehyde accumulation. ADH type-3 genotypes cause rapid oxidation of alcohol to acetaldehyde and these individuals are predisposed to oral cancer. Alternately, reduction in aldehyde dehydrogenase (ALDH) enzyme can also lead to accumulation of acetaldehyde (31). Genetic polymorphisms have been reported in these two enzymes ADH and ALDH, which have been related to the increased risk of alcohol-related cancers. Cytochrome P450 IIE1 (CYP2E1), a xenometabolising enzyme (XME) present in smooth endoplasmic reticulum participates in the oxidation of ethanol and also in the metabolism of tobacco-associated *N*-nitrosamines. Two genetic polymorphisms known in this enzyme predisposes to increased accumulation of acetaldehyde and indirectly by means of activating procarcinogens and increasing the production of radical toxins (31).

The systemic effects of alcohol are mainly due to the hepatic damage. Heavy alcohol consumption leading to cirrhosis and other diseases inhibits the detoxification of carcinogenic compounds such as *N*-nitrosodiethylamine (25). 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, nutritional status and other body functions (25).

**Diet and Nutrition:**

The relationship between diet and nutrition to the risk of cancer development has been established by several epidemiological and laboratory studies (32-35). The earliest evidence was that of the iron deficiency caused Plummer-Vinson syndrome which led to the development of oral cancer in Swedish women. It was believed that patients with this syndrome also had deficiencies of vitamins B and C (36).

The working group of IARC has affirmed that low intake of fruits and vegetables predisposes to increased risk of cancer development (37). In Europe, diet has been accounted for 10-15% of oral cancer cases. 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 (32). 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 (33, 34). 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 (34). 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. This has contributed to the significant interest in studies focusing on the macronutrients (proteins, carbohydrates, fat, cholesterol) and micronutrients (vitamins and their analogues, trace elements) present in the food groups that are protective against cancer (38).

Considerable evidence has shown that certain micronutrients decrease the risk of oral cancer development and they include vitamins A (retinol), C (ascorbic acid) and E (α-tocopherol), carotenoids (β-carotene), potassium and selenium (38-43). β-carotene, retinol, retinoids, vitamin C (ascorbic acid) 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 (44). However, some studies have also shown that β-carotene (45), vitamin E (46) and vitamin C (ascorbic acid) (47) may promote tumour development.

Carotenoids are a large group of yellow to red colored substances with various structural and biological characteristics that are present virtually everywhere in nature. Green leafy vegetables and many colored fruits are rich in carotenoids. Human serum contains β-carotene, alpha-carotene,

cryptoxanthin, lycopene and lutein as major forms of carotenoids. β-carotene is the major form of provitamin A, which are converted to vitamin A in the body. There are over 600 carotenoids in the human body of which only 10% are precursors of vitamin A. Although all the mechanisms involved in the anti-carcinogenic activity of carotenoids are not known, these agents serve as antioxidants, pro-oxidants, enhances the immune response, inhibits mutagenesis, reduces the induced nuclear damage (micronuclei), prevents sister chromatid exchanges, protects from various neoplastic events and protects against photo-induced tissue damage (48).

Retinol or the preformed vitamin A and its analogues are found in liver, egg yolks and other animal products (40, 48). Studies have shown that retinoids have the ability to suppress malignancy development in cultured cells and in animals, retinoid deficiency has led to increased risk of cancer development (38). Systemic or topical retinoid treatment has shown to cause regression of oral leukoplakia (49, 50). The major drawback of retinoid therapy are the side effects of hepatotoxicity and hypervitaminosis A (38).

β-carotene or the provitamin A, is the most nutritionally active carotenoid and comprises 15-30% of total serum carotenoids. Oxygen-dependent central cleavage of β-carotene and other carotenoids leads to formation of vitamin A. β-carotene and certain carotenoids quench highly reactive singlet oxygen and can block free-radical mediated reactions. *In vitro* studies have shown that β-carotene protects against sister chromatid exchange and other nuclear damage. A direct cause-effect relationship between β-carotene and risk of oral cancer has not been elucidated. This is not feasible as the cancer prevention activity of any substance could be proven only by large scale randomized, controlled clinical trial lasting for decades (39). Indirect evidence through short term case-control and cohort studies (43, 51, 52) and laboratory studies (39) has clearly established the link between β-carotene and risk of oral cancer. However, β-carotene supplements has been shown to increase the incidence of lung cancers in smokers (45). Owing to the difficulty in conduction of large scale prevention trials, considerable interest was shown in the search for intermediate biomarkers which are usually measurable histologic, biochemical, genetic or other markers that occur during cancer development and which when displayed, places an individual at a higher risk. One such marker is the presence of micronucleated cells in the premalignant lesions and cancer which reflects the genotoxic damage produced by carcinogens (49). Several treatment trials with β-carotene have been done in oral precancer and cancer and have shown considerable success rates. Remission or regression of oral leukoplakia using β-carotene only or with vitamin A have been shown in many studies (49, 50, 53). β-carotene is a non-toxic antioxidant to humans and is highly suitable for chemoprevention trials than retinoids such as 13-*cis*-retinoic acid which exhibit toxicity (39).

Alpha-tocopherol, the most active form of vitamin E is a powerful lipid-soluble antioxidant in cellular defense systems (54) and is found in green leafy vegetables, plant oils, margarine and wheat germ. Alpha-tocopherol protects cellular membranes from lipid peroxidation and enhances the mitogenic response, inhibit certain prostaglandins, and improves T-cell mediated responses (44). Vitamin E has been shown to prevent tumor formation in hamsters and this has been attributed to the stimulation of potent immune response by vitamin E (42) and vitamin E has also been shown to have the potential to reduce oxidative damage caused by hydroxyl radicals (54). Clinical intervention trials with alpha-tocopherol which is a non-toxic antioxidant like β-carotene have shown much promise with oral cancer and precancer. Regression of oral leukoplakia have occurred using vitamin E (55). Alpha-tocopherol with β-carotene and/or ascorbic acid have shown to regress oral leukoplakia (56). However, treatment trials with alpha-tocopherol has to be done with caution as high concentrations (80μmol) of vitamin E has been shown to promote skin tumour formation (46).

Vitamin C (L-ascorbic acid/ L-AA) is found in citrus fruits, cruciferous vegetables and other fruits like mangoes, kiwi, strawberries, honeydew, papaya and cantaloupe. Ascorbic acid is an antioxidant, decreases nitrosation by preventing the formation of nitrosamines thereby acting as a chemo-preventive agent. It also affects the activity of leukocytes and macrophages. Ascorbic acid (AA) is also involved in the activity of cytochrome P-450 which is important in the inactivation of potent carcinogens and metabolic activation of procarcinogens (38, 44). Laboratory studies have shown that ascorbic acid inhibited tumour development (38). In contrast, Schwartz *et al.* (47) had shown that oral administration of L-ascorbic acid dissolved in heavy mineral oil enhances tumour development in the hamster buccal pouch experimental model. Serum vitamin C was decreased along with other antioxidants in leukoplakia patients as compared to controls (51). There has been no study reported on the sole use of ascorbic acid in the treatment of oral leukoplakia. However, Tuovinen *et al.* (1992) showed that the prevalence of leukoplakia was higher when smoking was combined with AA deficiency (41). The association between ascorbic acid 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 (44).

Trace elements like selenium and potassium have been studied in relation to cancer development. Serum levels of selenium was increased in oral cancer patients (57) whereas potassium showed strong

inverse association with oral cancer (43). There is no evidence for direct cause-effect relationship. Selenium has antioxidant activity and is essential for glutathione peroxidase, an enzyme that protects against oxidative tissue damage (38).

Cultural risk factors and dietary factors seems to interplay in the development of oral cancer and precancer (58). Studies have shown the association between smoking and lowering of serum levels of nutrients. For instance, cigarette smokers had lower levels of β-carotene than non-smokers (59) and also smoking modified the association between dietary and serum β-carotene (60). The habit of quid chewing also has been shown to reduce serum levels of vitamins A, C, B12, folate and β-carotene in quid chewers than non-quid-chewers (51). A population-based case-control study in Malaysia comparing the cultural habits including quid chewing habit, serum micronutrients and oral leukoplakia in two ethnic groups concluded that quid chewing habit masked the protective effect of other serum micronutrients (61). These studies show the inter-association between certain cultural habits and dietary patterns in the development of oral cancer.

**Mouthwash:**

The use of mouthwash has been implicated to cause oral cancer (62). Mouthwashes usually contains alcohol as a solvent for other ingredients or as a preservative. Epidemiological evidence demonstrate that the risk of mouthwash causing oral cancer is attributed to the frequency and duration of use and its alcohol content (62). However, there is no cause-effect relationship found between mouthwash and oral cancer. Nevertheless, the dental clinicians must be prudent while advocating mouthwashes/rinses with high alcohol content.

**Maté:**

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 (63). 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 (63).

## ENVIRONMENTAL FACTORS

**Viral Infections:**

Viruses have been strongly implicated in the development of malignant tumours of the squamous epithelia including the oral squamous epithelium (64). Viral infections of latent or chronic nature are usually responsible for inducing malignant transformation by interfering with the host's cell cycle machinery. For instance, certain viruses can become permanent fixtures and integrate their genome in the host's nucleus, producing factors which cause cellular immortalization. Sometimes, the viruses may produce their own genes by integrating with the host's genes. These viral genes and gene products may affect cell growth and proliferation. Certain viral genes are proto-oncogenes which become oncogenes when inserted into the host's DNA and ultimately resulting in malignant transformation (65). The prototypic viruses implicated in oral cancer development are Human Herpes Virus (mainly Epstein Barr Virus, EBV), Human Papilloma Virus (HPV) and Herpes Simplex Virus (64, 65).

EBV causes oral hairy leukoplakia and "lymphoproliferative disease" in immuno-suppressed patients (65). The causal relationship of EBV with oral squamous cell carcinoma is still unclear. Prevalence studies have shown presence of EBV in oral squamous cell carcinoma (OSCC) patients but it does not prove a causal association (66). Cruz *et al.* (2000) showed that there is no causal role for EBV in oral carcinogenesis. They analysed EBV-DNA positive OSCCs for EBV viral products which are known to be pathogenic in other EBV associated malignancies. They used a variety of techniques including RT-PCR (Reverse Transcription – Polymerase Chain Reaction), *in situ* hybridization and immunohistochemistry and found that none of the pathogenic EBV transcripts were seen in the OSCC samples. They rationalised the presence of EBV DNA detected by PCR in these OSCC patients as reflecting the increased shedding of the virus in the saliva due to associated immunosuppression (67).

HPV are the most common viruses implicated in oral carcinogenesis. HPV are DNA viruses and are epitheliotropic, especially for squamous epithelia. They cause benign proliferative lesions such as papillomas, condyloma acuminatum, verruca vulgaris and focal epithelial hyperplasia (Heck's Disease). Certain HPV types, referred to as 'high-risk' types are associated with oral squamous cell carcinoma and oral premalignant lesions. They are HPVs 16, 18, 31, 33, 35 and 39.

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 (64, 65, 68).

HPV has been detected in oral squamous cell carcinoma, 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. Recently, a large-scale multinational, case-control study to determine the role of HPV in cancers of oral cavity and oropharynx was carried out by IARC (69). In this

study, HPV DNA was detected using PCR and it was shown that only 3.9% of 766 oral cancers were positive for HPV DNA, which is relatively a low prevalence rate compared to previous studies. However, the prevalence of HPV DNA was higher in cancers of oropharynx with 18.3% of 142 cancers being positive for HPV DNA. HPV DNA was found to be higher in subjects who either had many sexual partners or practiced oral sex. 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 (69).

HPV has been shown only to play a dependent causative role in oral carcinogenesis in an *in vitro* study by Park and Kang in 2000. The authors attempted to immortalize normal human oral keratinocytes by HPV genome but failed. Later, upon exposure of the same cells to tobacco-related chemical carcinogens, the cells underwent spontaneous mutations and ultimately malignancy. Additionally, this study also showed that the mutation frequency increased with E6 and E7 expression (70). This study revealed that HPV infection alone is not tumourigenic but aids in carcinogenesis when combined with other risk factors like tobacco.

Herpes Simplex Virus (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 titres 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 pre-existing oncogenes such as c-myc and c-erb-B-1 (65).

**Fungal Infections:**

Fungal infections caused by *Candida* species, in particular, *Candida albicans* has been implicated in the pathogenesis of oral premalignant lesions (71). 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 common 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 iron-deficiency and in chronic smokers which may prove synergistic in the development of oral cancer. There is evidence that Candida possesses necessary enzymes from dietary substances to produce nitrosamines and chemicals that have been implicated in carcinogenesis (72). A recent study showed relationship between oral yeast carriage and epithelial dysplasia (73). Again, the actual role of yeast in the development of epithelial dysplasia is uncertain.

**Immunosuppression:**

Immunosuppressed individuals are more prone to develop oral cancers. HIV infected patients are predisposed to developing Kaposi's sarcoma and lymphomas, although not to oral squamous cell carcinoma. Immunosuppressed organ transplant patients have been shown to develop lip cancers (74) and the possible reason was attributed to increased exposure to solar radiation and other risk factors such as smoking. However, the direct role of immunosuppression with lip cancer development was not proven in this study (74). A recent study showed that there is a rapid progression from oral leukoplakia to OSCC in an immunosuppressed liver transplant recipient (75). The liver transplant patient who was on immunosuppressive treatment regimen developed a homogenous leukoplakia 4 months post-transplant surgery, which transformed to OSCC within next 4 months. This raises the idea that immunosuppression may indeed be a major risk factor for OSCC and warrants more studies on the actual pathogenesis.

**Occupational Risks:**

Occupational risks, namely exposure to excessive solar radiation/ ultraviolet light is known to cause lip cancers. UV rays also causes actinic cheilitis which may transform to oral squamous cell carcinomas. Sulfur dioxide, asbestos, pesticide exposures and mists from strong inorganic acids, burning of fossil fuels have been known to cause cancers of posterior mouth, pharynx and larynx (76).

**Dental Factors:**

Poor oral hygiene, poor dental status (sharp/ fractured teeth due to caries/trauma), chronic ulceration from an ill-fitting denture has been suggested to promote neoplasm in the presence of other risk factors (10). 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 (77). Nevertheless, an experimental study in hamsters (78) has shown that chronic trauma in addition to carcinogen application could promote tumour development. In this study, mechanical irritation by scratching with a pulp cleaner has been shown to significantly increase the incidence of a chemical carcinogen induced tongue carcinoma (78). In addition, Lockhart *et al.* (77) observed that all 28 intra-oral carcinomas included in their study were seen in areas in contact with teeth

and/or appliances (77). Although the second finding suggests a relationship between dental factors and oral carcinogenesis, dental status at the time of patient examination is a static observation and only a large prospective trial would resolve this issue (77). Therefore, it is prudent to closely monitor patients with known risk factors for signs and symptoms of irritation from teeth and appliances.

**Syphilis:**

Tertiary syphilis had been known to predispose to the development of oral cancer along with other risk factors such as tobacco and alcohol. However, nowadays, tertiary syphilis is rare in clinical practice as the infection is diagnosed and treated before the onset of tertiary stage (10).

## GENETIC PREDISPOSITION

Genetic predisposition has been shown to be an important risk factor in the development of oral squamous cell carcinoma. 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 aerodigestive tract (UADT) (79). However, population based studies to determine the genetic or familial disposition to oral cancers are limited by the co-existing risk factors like smoking and alcohol. It is also believed that certain individuals inherit the susceptibility of inability to metabolise carcinogens or pro-carcinogens and/or an impaired ability to repair the DNA damage. As discussed earlier about the metabolism of tobacco carcinogens, genetic polymorphisms in the genes coding for the enzymes (P450 enzymes, xenometabolising enzymes: XMEs) responsible for tobacco carcinogen metabolism are suspected to play key role in the genetic predisposition to tobacco induced head and neck cancers (9).

## 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. Hence, it is important for the public and the clinicians to be completely aware of the risk factors for oral cancer and it is prudent for dentists to look carefully for early signs of oral cancer while routine examination of the oral cavity especially in patients with history of known risk factors.

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