

Special Article - Oral Squamous Cell Carcinoma

A Review of Head and Neck Squamous Cell Carcinoma Risk Factors with More Focus on Oral Cancer

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Received: June 13, 2016; **Accepted:** August 14, 2016;**Published:** August 17, 2016**Abstract**

Background: Head and Neck Cancer (HNC) is the tenth most common cancer and the seventh most common cause of cancer death in the most regions of the world. Squamous Cell Carcinomas (SCCs) are the most common malignant lesion (90%) of HNC. Because, oral cancer is the most common HNC, it is a significant health problem in the world mainly in developing countries. Despite the improvement in the diagnosis and treatment, these lesions are still poor prognosis and have major morbidity and mortality. Therefore, identification of the risk factors is very important for prevention and early detection of cancer.

Methods: In this review article, the studies were identified by researchers on three databases- PubMed, MEDLINE, and Google scholar- from 2005 through 2015 in the English language for the risk factors of head and neck cancer with more focus oral cancer. We used the following search terms: «risk factors», «oral SCC», «head and neck carcinoma». We included original studies and review articles. Furthermore, case reports were excluded from this study.

Results: Recently, many researchers have been performed to study, a review of risk factors related to development and progression of SCC in head and neck which have been identified already. The important role of dietary, oral hygiene, genes was approved. Also, tobacco and alcohol consumption, denture used, fungal infection and some types of viruses have direct association with HNC.

Conclusion: It is possible to conclude that head and neck cancer development is a complex. More researches are needed for better understanding of mechanisms about HNC. Identification of the patients with the important risk factors by general dental practitioner scan is help to the prevention and early detection of cancer. Early diagnosis of oral premalignant and malignant lesions decreases tissue destruction and improves the treatment outcome and prognosis. Therefore, general dental practitioners have a key role in the early diagnosis and referral of patients with oral lesions.

Keywords: Head and neck carcinoma; Risk factors; Squamous cell carcinoma; Oral cancer

Background

Head and Neck Cancer (HNC) is the tenth most common cancer and the seventh most common cause of cancer death in the most regions of the world [1]. Head and neck cancer essentially is including cancers of the oral cavity, pharynx (oropharynx and hypopharynx) and larynx [2]. Squamous Cell Carcinomas (SCCs) are the most common malignant lesion (90%) of HNC [3]. Furthermore, more than 90% of squamous cell carcinomas are originating from the oral mucosa [4]. Because, oral cancer is the most common HNC, it is a significant health problem in the world mainly in developing countries [5,6].

Despite the improvement in the diagnosis and treatment, these lesions are still poor prognosis and have major morbidity and mortality [7,8]. Therefore, identification of the risk factors is very important for prevention and early detection of cancer developing. The etiology of Oral Squamous Cell Carcinoma (OSCC) is very

complex. It is associated with several risk factors [9]. Recently, many researchers have been performed for identification of the risk factors related to development and progression of SCC in head and neck. General dental practitioners may encounter oral lesions with a potential for malignancy during routine clinical examinations. They have a key role in the early diagnosis and referral of patients with oral lesions. The purpose of this study is a review of risk factors for HNC with more focus on oral cancer which can especially be useful for general dental practitioners.

Methods

In this review article, the studies were identified by researches on three databases- PubMed, MEDLINE, and Google scholar- from 2005 through 2015 in the English language for the risk factors of head and neck cancer with more focus oral cancer. We used the following search terms: «risk factors», «oral SCC», «head and neck carcinoma». We included original studies and review articles. Furthermore, case reports were excluded from this study.

Dietary

The most of studies showed the important role of diet in the development of Head and Neck Cancers (HNC). The effect of fruits consumption is one of the issues that examined in the literatures. Some of the studies presented that high consumption of fruits (combined) make of decrease in the risk of HNC, especially with fresh fruits consumption [10,11]. Furthermore, consumption of yellow/orange vegetables is associated with reduced risk of HNC [10-14]. But, high consumption of preserved vegetables is associated with an increased risk of HNC. Furthermore, consumption of pumki, carrots, cabbage, and tomato have inverse associated with HNC [10]. Protection effects of fruits and vegetables may be the result of many mechanisms such as inhibition of endogenous carcinogen bioavailability, stimulation of the immune system and antiviral and antibacterial activities [15,16].

Another issue were examined in this field is the effect of consumption of meat on cancer development. According to most studies, red meat consumption is with increased risk of laryngeal cancer [10]. Also, the studies showed that the high consumption of dairy (milk, yogurt, cheese) products and HNC have reverse relationship. In addition, some studies reported a protective effect of yogurt on esophageal cancer. One reason may be the presence of high level of conjugated linoleic acid in yogurt [10]. Furthermore, the immune stimulation studies have been showed anticarcinogenic properties [17].

Other investigation studied on the effect of different methods of food preparation on cancer development. Some studies showed that the consumption of fried foods once a week is associated with increased risk of HNC [18]. Furthermore, because the various production of carcinogenic heterocyclic amines by cooking meat at high temperatures (frying, broiling), it method of food preparation is risk factors for HNC [10].

Some epidemiological studies reported that nutritional deficiency has been related to an increased risk of HNC [11,19,20]. As an example, dietary intakes of folate and water-soluble B vitamin for example B6 were inversely related to HNC risk [11,20,21]. One of the reasons for this result may be explained by inducing an imbalance in DNA precursors and modification to DNA synthesis and repair and leading to chromosome breaks in humans [11]. Furthermore, relation between the Methylene Tetrahydrofolate Reductase (MTHFR) c677 T polymorphism and folate metabolism have been observed in some studies, that is increase the risk of HNC [22,23]. Some studies have been showed the high alcohol consumption can lead to decreased folate absorption and increase folate excretion by the kidney. Also, according to more studies, alcohol consumption is the strong-risk factor for HNC. The main sources of folate are fruits and vegetables, which their important role in cancer protection described before [11,20,24]. In biological reactions, vitamin B6 is a coenzyme of folate for DNA synthesis and methylation. Therefore, vitamin B6 deficiency is leading to chromosome breakage and help to cancer development [11,25].

Another subject that investigated in several studies about HNC and risk factors is tea consumption. But, the results of these studies have been conflicting. Some studies showed the significant inverse association between tea drinking and HNC especially for green tea [24,26-29]. While, a few studies have been reported positive relation

and no relation between tea drinking and HNC [28,30]. Different amount of tea consumption and different types of tea drinking in the multiple geographic regions are the reasons for the conflicting results of studies [24]. Generally, tea contains polyphenols such as catechins. These contains have antitumor properties with leading cell cycle arrest and apoptosis. Furthermore, they are inhibiting angiogenesis, proliferation, and metastasis of cancer cells [31]. On the other hand, coffee is one of the most common beverages in world wine. Because, it is contains antioxidant, polyphenols, There is reverse association between development and progression of cancer [24,31,32].

Oral hygiene, periodontal disease

Periodontal Disease (PD) has been reported in the more than 90% of worldwide population [33]. It is an inflammatory disease of the supporting tissues of the teeth. PD have been showed some symptoms such as swelling and bleeding of gingival, destruction of periodontal ligament and alveolar bone, that is loading to deep pockets formation, gingival recession, and tooth mobility [34,35].

More recently, several studies investigated the relation between PD and some systemic disease such as several types of cancers progression [36-40]. The results of studies have been found the positive association between PD and HNC. Tezal et al. reported increased risk of oral tumors and precancerous lesions in patients with more than 1.5 mm clinical attachment loss [39]. Also, the direct relationship between risk of HNC and numbers of missing teeth was found [37,41]. Guha et al. showed that missing more than 6 teeth will be two-fold increased risk of HNC [42]. Therefore, PD has association with increased the risk of HNC. Production of carcinogenic metabolic in PD can explain these results. The poor oral hygiene status have been loaded the increase acetaldehyde production in saliva by oral microorganisms especially *streptococcus salivarius*, *corynebacterium*, *stomatococcus*, and alpha hemolyzing *streptococcus* [43,44]. Furthermore, some studies showed the role of Interleukin 6 (IL6) that is produce in local and systemic inflammation including response to periopathogenic microorganisms [45]. IL6 is leading to proliferation of cancer cells, angiogenesis, metastasis and inhibition of cell apoptosis [46]. According to result of studies, the serum and saliva of HNC patients have more level of IL6 [47]. Thus, inflammatory reactions can be explained that PD is an independent risk factor for HNC.

Tooth loss, Denture used Epidemiological study investigated that several factors such as age, sex, systemic diseases, and oral hygiene status are the risk factors of tooth loss [48,49]. Some studies examined the role of tooth loss in HNC progression without other confounding factors. According to results of these studies, association between tooth loss and HNC completely undetected. But, the some studies showed which tooth loss is a significant and dependent risk factor for HNC. The patient with more than six teeth loss need to be further investigated to symptoms of HNC and losing 11 teeth or 15 teeth may be the risk of HNC is several times [48].

Some studies investigated the role of denture in oral cancer. According to results of several studies was not relationship between complete dental prosthesis and oral cancer [40,50,51]. Because, recently identified that the chronic trauma of the oral mucosa can be help to oral cancer development. Some studies assessed the role of quality of the denture fitting on oral cancer [6,52]. The recurrent

sores related to the use of ill-fitting dentures can be help to cancer development [53]. Persistent trauma from ill-fitting dentures may be inducing chronic inflammation and leading to produce reaction oxygen and nitrogen species from leukocyte and phagocytes. This production can be effect to proliferating cells, genomic damage and progress towards tumor [54]. On the other hand, by the chronic trauma can be increase the carcinogenic effect of tobacco, alcohol, and diet in the oral cavity [6]. Candida may be induced the denture-related sores (denture stomatitis) which can be related to epithelial dysplasia [55]. Furthermore, ill-fitting mandibular dentures can be reduced chewing performance and mechanical cleaning of oral mucosa that is leading to increase the carcinogens effects of diet, tobacco, and alcohol for long period [6]. Therefore, denture can be important role to the cancer development and progression.

Candida

One of the most common types of the oral microflora is candida species. According to recent studies, candida albicans is the predominant species detected in the oral cavity [56]. Several studies showed that infection of candida and epithelial dysplasia and oral cancer development have a near relationship with each other [57,58]. Candida- albicans is 78% of isolated yeasts in premalignant lesions and oral cancer [59]. Furthermore, candida-globrata and candida-tropicalis were detected in these lesions [60].

One of the premalignant lesions of oral cavity is candida-infected leukoplakia [61]. It has a high rate of malignant changes than uninfected leukoplakia [62]. Some studies have been showed that the candida produce some carcinogenic substances such as acetaldehyde, nitrosamines, and N-nitroso benzylmethylamine [62,63]. The studies observed the high nitrosation potential in the lesions that have severe advances precancerous and malignant transformation. Furthermore, the extension and penetration yeast cells to deeper epithelial cell layers caused transportation and deposition of precursors for example nitrosamines to deeper cells of epithelial layers. It is explain the role of candida in initiating cancer development. Thus, there is a strong association between candida infection and oral cancer [62].

Allergy

Most recently, some studies have been investigated the relationship between the forms of allergies and cancer risk [64,65]. The overactive immune response to the substances in the environment (allergen) is allergies that in this way produced immunoglobulin E (IgE) against allergens. The conjunction of IgE with mast cells and basophiles surfaces leads to several allergic diseases such as rhinitis, asthma, eczema, and food allergy [66]. Several studies have been showed the inverse association between history of allergies and HNC especially for rhinitis and asthma [64,67,68]. For explain this results, the «immunosurveillance hypothesis» have been suggested. In fact, the allergic symptoms are the side effect of hyper immune reactions [69]. According to some studies, IgE has anti-tumor activities. In addition, the higher numbers of IgE-positive cells in the tumor tissue observed compared to the normal tissue [67]. The IgE may participate in tumor surveillance. Furthermore, engaging the several types of effectors cells in antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis against cancer cells with IgE bind to IgE-receptor and CD23 [67]. Thelper2 assists to recognition and destruction of tumor cells [64]. Furthermore, the studies detected IgE

to specific allergens in the nasal washing in the patients with allergic rhinitis, that may be indicator for a more active local immunity reaction against foreign substances, loading to reduced HNC risk [66,67].

On the other hand, contact allergy to metal dental restorations was found a potential risk factor for oral cancer [70]. For explain the positive associations between allergy and cancer, the «antigen stimulation hypothesis» has been suggested. The increased stimulation of cell growth and chronic inflammation leads to increasing the genetic mutation of dividing stem cells and malignant changes [71].

Alcohol consumption

The third leading risk factors for disease and mortality in the worldwide is alcohol consumption [72]. The International Agency for Research on Cancer (IARC) suggested the some evidences on the alcohol carcinogenicity for low and moderate alcohol intakes [73-75]. IARC monographs indicated the consumption of alcoholic beverages is associated with HNC [73]. Furthermore, the drinking patterns have an important role in this association. Regular heavy drinking has a strongest relationship between alcohol and cancer risk [76-78]. Another hand, the combined consumption alcohol and tobacco smoking leads to synergistic effect that increases the risk of neoplasms up to 14 times [79].

Briefly, there are several mechanisms of cancer development by alcohol. Ethanol has a direct effect on the cells where conversion to acetaldehyde occurs, such as liver cells, saliva and the large intestine. It is loading to reactive oxygen species production which can be damage DNA and alter DNA methylation. Also, ethanol facilitates uptake of carcinogens from tobacco smoking in the mouth and throat. Therefore, loading to increased risk of tobacco-induced cancers [77,80]. But, without the consideration the systemic ethanol metabolism, a 30 second rinsing of the oral cavity with different alcoholic beverages, loading to increase the salivary acetaldehyde levels excessively, that before showed to be carcinogenic effect [75]. Also, genetic factors associated to the enzyme Alcohol Dehydrogenase (ADH), which oxidized ethanol to acetaldehyde that is detoxified by the Aldehyde Dehydrogenase (ALDH2) to acetate, a less toxic compound has important role for cancer risk [75]. The high salivary acetaldehyde production by the less-active or inactive ADH1B, ALDH2 enzymes explained the increased cancer risk [75,81]. Thus, the alcohol drinking has a direct association with HNC.

Age

The most epidemiological studies showed the oral squamous cell carcinoma (OSSC) is typically occurred in fifth to seventh decade of the life [82,83]. Also, 5% of all HNC involved the young age (25-40 years old), but HNC incidence is increasing in younger people especially in recent decades [84,85]. These results suggested that the different pathogenesis of HNC in young patients to compared in old patients [84]. The data from some countries showed the smoking, alcohol, and other drugs consumption in young-age have been increased in recently [86]. Furthermore, according to studies, Human Papilloma Virus (HPV) is transmitted with sexual behavior and this subject explains the increased of young-onset HNC [84]. On the other hand, the genetic predisposition and family history effect on development of HNC in young age [87]. Some inherited HNC-susceptibility syndromes such as Li-Fraumeni syndrome, Fanconi

Anemia (FA) and Bloom syndrome have relation with cancers [84]. The tongue is reported the most common location of HNC in the young patients [88]. Also, the male predominance of HNC was in young patients. According to studies, the younger patients have a more aggressive disease, and local recurrence and lymph node involvement after treatment compared with older patients [89].

All together, they explained well-known risk factors are playing a minor role in the carcinogenesis in the younger patients. But, intrinsic susceptibility to environmental genotoxic exposures plays an important role in the development of HNC in these patients. Some studies showed that the young patients have an increased sensitivity to induced chromosomal damage [90].

Viruses

Human papilloma virus: According to the most studies, Human Papilloma Virus (HPV) has been established as the important risk factor in the head and neck carcinoma, especially tonsil and base of tongue carcinoma [91]. In recent years, a significant increase in HPV prevalence in HNC observed. Furthermore, up to 15-20% of all HNC are associated with high-risk HPV infection [7,92]. Also, up to 70% of oropharynx squamous cell carcinomas especially tonsils have HPV-DNA [93]. HPV is a DNA virus which generally has an important role in many benign and malignant lesions. On the other hand, it is the most common sexually transmitted viruses [94,95]. In some epidemiological studies showed that oro-genital contact and oral sex to result in oral and cervical cancers [96]. Thus, specific sexual behaviors have strongly relation with risk of HPV-positive tumors [7]. The International Research Agency of Cancer and National Cancer Institute (USA) explained that HPV as an independent risk factor for oropharyngeal squamous cell carcinoma [7,94,97]. According to their classification HPV16 and HPV18 (Group1) infected lesions have high propensity for lesions malignant transformation which can be found in premalignant and malignant lesions of the oral cavity. HPV31 and HPV33 as probably carcinogenic effect (Group 2A), and residual HPVs as possibly carcinogenic effect (Group 2B) [5,98].

The molecular mechanism of viral oncogenesis of HPV has been explained. The HPV genome is divided into seven Early-phase genes (E) and two Late-phase genes (L). Some evolved proteins of HPV such as E6 and E7 have been controlled the growth of the infected epithelial cells. The viral oncoproteins E6 and E7 from high-risk HPV types have been prevented the cell differentiating and withdrawing [7]. Also, the studies showed that these proteins increased the proliferation, adhesion, and cell spreading [99]. After infection, integration of virus to host genome can be to malignancy initiation the E6 protein can bind the cellular P53 protein (a tumor suppressor protein) and this leads to the breakdown of P53 and loss of its concentration in cells. Thus, the lack of DNA repairs after damage by the other agents and loss of ability to cell apoptosis. Progression to malignant transformation occurs after cell cycle deregulation [5]. Furthermore, the E7 protein can bind to the cellular Retinoblastoma protein (pRB) and releasing transcription factors such as E2f [7,8,100].

On the other hand, some studies have been showed that a combination of high-risk HPV and chemical carcinogen such as tobacco and alcohol which essential for cancer development [9].

Herpes Simplex Virus (HSV): Herpes simplex virus is the other types of virus that have an important role to cancer development

and positive relation. But, the role of HSV in the development of OSCC has been less investigated. Some studies showed a possible interaction between tobacco use, alcohol consumption or HPV16 and HSV1 in the development of OSCC [92,101]. Infection with HSV is frequent in general population and common occurred during early adolescence with the herpetic gingivostomatitis or asymptotically. After primary infection, the virus travels the axons of sensory nerve fibers in affected location. Different conditions can be disturbing the balance between host and virus. Therefore, herpes labialis with the appearance of vesicles on the lips and release of viruses in the saliva have been occurred [5]. According to studies, up to 90% of the general population has antibodies against HSV and the shedding of HSV1 in many intraoral sites for brief period have been showed [92]. But, the patients with oral cancer have higher levels of IgA antibodies to a protein present in infected cells and higher levels of IgM antibody to an antigen present on the virus particle [9].

Some mechanisms of HSV1 and HSV2 for cancer development have been suggested but yet remain obscure.

Epstein-Barr Virus (EBV): The Epstein-bar virus is the first human virus to be established the oncogenic potential [5]. It has an important role to wide variety of benign and malignant tumors development. But, it less frequently associated with OSCC [9]. Approximately 90% of adult population infected asymptotically. After primary infection, EBV established a latent infection in B lymphocytes, oropharyngeal and salivary gland epithelial cells and it is replicated in the oropharynx and salivary gland epithelium and shed in the saliva [5].

According to results of studies, nearly 60% of oral SCCs were EBV genome positive. On the other hand, studies showed a positive correlation between different grade of SCC and EBV DNA positivity. In well differentiated OSCC have higher percentage positive of EBV DNA than poorly differentiated OSCC (9). The relation between EBV and HNC yet understood and necessary to more studies. But, high-risk HPV and EBV co-infections play an important role in the initiation of neoplastic change of oral epithelial cells [102].

Genes

Recently, many studies have been investigated about the role of genetic mutations and polymorphisms in the cancer development. The results of these studies showed that human genetic mutations may increase susceptibility of cancer development [5,103].

One of the genes that have an important role to in cancer initiation is P53. It is a tumor suppressor gene which is in the chromosome 17. The gene mutation, deletion, or inactivation can be load to P53 do not effective role such as cell-cycle control, apoptosis, and DNA repair [103]. Thus, the cell can be load to cancer.

Furthermore, P16 and P21 is cell-cycle regulator gene that has an important role in this regard [104]. As well as, the role of Bcl2, Keratins, FGFs, ORAOV1 in cancer have been investigated [5].

On the other hand, some genetic polymorphism such as miR-146a rs2910164, CYP1A1, GSTM1, XPA A23G, COX-2, EPHX1, MTNR1A, MTHFR C677T, TGF, AURKA Ph3111e, cyclooxygenase-2, HMGB1, RAGE, XRCC3, Matrix metalloproteinase gene, Cytochrome P-450 have been examined in the recent studies [105-118].

Table 1: The risk of oral cancer by smokeless tobacco [121].

Type of product	Relative risk
Moist snuff and chewing tobacco	Very low risk
Dry snuff	Higher risk
Other smokeless tobacco	Intermediate risk

Premalignant lesions

Some of the oral lesions have positive relation with oral cancer development. One of the most premalignant lesions is oral leukoplakia. The World Health Organization (WHO) explained that oral leukoplakia is a white patch or plaque that cannot be characterized clinically or pathologically as any other disease. A special high-risk form of leukoplakia is Proliferative Verrucous Leukoplakia (PVL). Also, erythroplakia is a premalignant lesion. Oral lichen planus is one the lesions that increased the risk of cancer especially plaque and erosive types [119].

Tobacco use

Tobacco use has been identified as a strong risk factor for oral cancer that is classified as a Group 1 carcinogen (120). Any product with tobacco is not safe for human health [121]. A recent study showed that the prevalence of oral premalignant lesions in the smokers is 10.5% [120]. The more incidence of oral cancer in Asian as compared to Western countries showed by numerous studies, that may be explained by varying types and patterns of tobacco use (122). Generally, there are two patterns of tobacco used in the worldwide that explain in this review.

Smokeless tobacco

The using of tobacco products in a way other than smoking is called «smokeless tobacco». Chewing tobacco, naswar, snuff, snus, gutka, and topical tobacco paste are the most common smokeless tobacco. Smokeless tobacco types include loose-leaf chewing tobacco, moist snuff, and dry snuff. Moist snuff is called «snus». More than twenty-five compounds in smokeless tobacco have carcinogenesis effect. Smokeless tobacco used show increased risk of oral cancer [121]. The risk of oral cancer by types of smokeless tobacco is in Table 1 [121].

The most harmful compound in smokeless tobacco are Tobacco-Specific Nitrosamines (TSNAs) and their levels in products have a direct association with risk of cancer. Other compounds in smokeless tobacco with risk of cancer are Cadmium, Polonium, Formaldehyde, Polycyclic aromatic hydrocarbons [121].

Epithemiological studies showed the risk of oral cancer from smokeless tobacco that is a result of chronic application of purified TSNAs to the oral mucous membrane [123]. According to mahapatra study, buccal mucosas, lateral part of tongue, and base of tongue are the most cancer sites in the tobacco smokeless patients. Thus, according to the most studies, there is strong evidence that gutka, supari, chewing tobacco, betel quid, and bidi are independent risk factors for oral cancer [123].

Tobacco smoking

In the most countries, the main form of tobacco use is cigarette water pipe smoking [124]. Nicotine is the major compound responsible for addiction in tobacco products. It is in the non-

ionized state at a high pH (Alkaline) and can be absorbed across the epithelium of the lung, oral mucosa, and nose and through the skin [125]. The halftime of nicotine in plasma is about 2h [126]. About 85-90% of nicotine is metabolized in the liver before elimination by renal excretion [127]. Some studies investigated about genotoxicity of nicotine. According to studies, nicotine have been showed to induce DNA damage, chromosomal aberration, and sister chromatid exchange. Furthermore, effect on DNA repair showed by recent studies [128]. The formation of micronuclei by nicotine in human gingival fibroblasts has been showed in some studies. Micronuclei formation represents an irreversible DNA damage [129].

On the other hand, the effect of nicotine on signaling pathway has been showed by some studies. According to these studies, low concentrations of nicotine stimulate cell proliferation, but high concentration is cytotoxic [129]. Thus, the nicotine's and other nicotine metabolites stimulate signaling pathway and reactions that increase cell proliferation and cell survival. The secretion of Epidermal Growth Factor (EGF), Vascular Endothelial Growth Factor (VEGF) and arachidonic caused the transactivation of acid Epidermal Growth Factor Receptor (EGFR) and activation of nitrogenic and antiapoptotic pathways [130]. Also, nicotine decreases the tumor suppressor genes, which is activated by DNA damage. Furthermore, the other effect of nicotine is Epithelial-Mesenchymal Transition (EMT) which is one of the steps for the malignant transformation that is important role for migratory properties and cancer metastasis [129]. Also, there is promotion endothelial cell migration, proliferation, survival by angiogenic growth effect of nicotine.

The all nicotine effects on human body loading to increase risk of cancer. Smokeless tobacco and poly-ingredient oral dipping products may have a stronger effect than smoking because of the direct contact of the carcinogens compounds with the oral epithelium. Maybe the reason of the cancer risk of tobacco smokeless is premalignant lesion development such as submucous fibrosis. Some studies showed strong risk of oral cancer in consumer chewing tobacco that is used with or without lime and kept in the mouth for different duration of time [130].

Solar exposure

Solar exposure is one the risk factors of potentially premalignant disorder such as (Actinic cheilitis) and lip cancer. Lip cancer is included of SCC and often arises in the epithelial layer of the vermilion, a transition zone between the inner labial mucosa and the outer skin of the lip. Many risk factors of cancer lip is resemble to risk factors of skin cancer. Although, Risk for cancer of the lower vermilion was independently positively associated with increasing year of age, a history of smoking, surrogate indices of increased exposure to solar UV radiation and immunosuppression [131].

Results

In initial step of electronic search were identified 200 original and review articles about risk factors related to development and progression of squamous cell carcinoma in head and neck. In this review article, the important role of dietary, oral hygiene, genes for increased risk factor of oral cancer were approved. Also, denture used, tobacco and alcohol consumption, candidiasis, and some types of viruses (HPV, HSV, and EBV) were cancer risk factors Table 2.

Table 2: Risk factors of head and neck cancer.

Risk factors	Comments
Diatary	Nutritional deficiency, Method of food preparation
Periodontal disease	Production of carcinogenic metabolics by microorganisms after poor oral hygien
Dentures used	Chronic trauma by ill-fitting dentures
Candidia	Candida-infected loukoplakia
Allergy	Antigen stimulation by metal dental restoration
Alcohol consumption	Direct and indirect effects
Age	Older and younger patients
Viruses	HPV, HSV, EBV
Genes	P53, P16,P21,BCL2, FGF, ORAOV...mutations
Premalignant lesions	Loukoplakia, erythroplakia, submoucos fibrosis
Tabacco use	Carcinogenic effects of tabacco products
Solar exposure	Especially for lip cancer

Generally, according to the recent studies, oral cancer incidence trend worldwide showed striking geographic and ethnic variations that are largely attributable to the practice of risk factors.

Conclusion

It is possible to conclude that head and neck cancer development is a complex. More research is needed for better understanding of mechanisms about HNC. Identification of the patients with the important risk factors by general dentist can be help to the prevention and early detection of cancer. Early diagnosis of oral premalignant and malignant lesions decreases tissue destruction and improves the treatment outcome and prognosis. Therefore, general dental practitioners have a key role in the early diagnosis and referral of patients with oral lesions.

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