REVIEW

# Risk Factors for Oral Squamous Cell Carcinoma in Young Adults

Deepa A G[1], Sudha S[2], Resmi G Nair[3], Indu G[4]


## Abstract

**Introduction:** Incidence of oral squamous cell carcinoma is increasing in individuals less than 45 years. Similar trend is also observed in India.

**Objectives:** To discuss the etiological factors for oral squamous cell carcinoma in young adults.

**Materials and Methods:** A literature search of electronic databases: MEDLINE, PubMed, ScienceDirect, Cochrane Database of Systematic Reviews, and Wiley InterScience was carried out from September 2019 to December 2019. Original researches and review articles regarding etiology and risk factors were included. 32 articles were selected for this literature review.

**Conclusion:** Tobacco and alcohol are the main etiological factors in young adults also. Chronic trauma, Genetic predisposition, Nutritional deficiency, Poor oral hygiene Human papilloma virus etc are the other important causative factors.


**Key words:** carcinogenesis, oral cancer, risk factors, squamous cell carcinoma of head and neck.

Oral and Maxillofacial Pathology Journal (2020): ***http://www.ompj.org/archives.***

## Introduction:

Oral squamous cell carcinoma (OSCC) is the eighth most common cancer worldwide[1]. Until recently, it was considered to be a disease more common among older adults. Nowadays, increased incidence of OSCC in younger patients is reported worldwide; majority of them affecting the tongue.[2] Llewellyn et al. reported incidence of HNSCC as 0.4-3.6% in patients younger than 40 years.[3] Most of them were also not exposed to the conventional risk factors like tobacco and alcohol.[3] In India, various studies reported varying incidence of 8-33%.[4-10] An institutional incidence of 2.8% was reported in patients less than 35 years at Regional Cancer Centre, Trivandrum.[11] This review is an attempt to discuss the risk factors associated with head and neck squamous cell carcinoma (HNSCC) in young adults.

A literature search of electronic databases: MEDLINE, PubMed, ScienceDirect, Cochrane Database of Systematic Reviews, and Wiley InterScience was carried out from September 2019 to December 2019. Search was restricted to journals of English language using key words *squamous cell carcinoma of head and neck, risk factors, oral cancer, carcinogenesis, and genetic predisposition*. These were searched as text word and as subject headings individually as well as in various combinations. The reference lists of relevant articles were also searched for appropriate studies. Original researches and review articles regarding etiology and risk factors were included. Among these articles, only 32 articles that fulfilled the inclusion criteria were considered for this literature review.

[1-4] Department of Oral and Maxillofacial Pathology, Government Dental College, Medical College P O, Thrissur, Kerala , India.

**Corresponding Author:** Deepa A G, Department of Oral and Maxillofacial Pathology, Government Dental College, Medical College P O, Thrissur, Kerala, India. Email: deepakrishna4@gmail.com, phone: 9947084244

**How to cite this article:** Deepa AG, Sudha S, Nair RG, Indu G. Risk Factors for Oral Squamous Cell Carcinoma in Young Adults. Oral Maxillofac Pathol J 2020;11(2):60-63

**Source of Support:** Nil

**Conflict of Interest:** None

| Conventional risk factors | Other risk factors |
|---|---|
| Tobacco & arecanut products | Chronic trauma |
| Alcohol | Genetic predisposition |
| | Nutritional deficiency |
| | Poor oral hygiene |
| | Human papilloma virus |
| | Sedentary lifestyle |
| | Alcohol containing mouthrinses |
| | Stress |
| | Ultraviolet radiation |

### Tobacco & arecanut products

Tobacco is considered as the most potent risk factor for OSCC even in young adults[12]. It is used in two forms: smoking and smokeless tobacco. The most important carcinogens in tobacco smoke are

aromatic hydrocarbon benz-pyrene and the tobacco-specific nitrosamines 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 cause tumors of the oral cavity, lung, esophagus, and pancreas. NNK, NNN, and their metabolites covalently bind with deoxyribonucleic acid (DNA) of keratinocyte stem cells forming DNA adducts. These adducts are responsible for critical mutations involved in DNA replication. Thus tobacco components have an important role in chemical carcinogenesis.

Tobacco consumption in any form for >21 years has shown to increase the risk for cancer. As many people begin consumption of tobacco in early adolescence, the risk for OSCC is high by the age of 40, which is thought to be the reason for occurrence of oral cancer in young adults.[10] Commercially available smokeless tobacco preparations carry a higher risk than smoking tobacco due to the combined effect of the ingredients present in them.[13] Most of the ingredients are extracts and concentrates of arecanut and tobacco.[13] Use of smokeless tobacco products causes direct contact of carcinogens with the oral epithelium for a longer period as many of these products are kept inside the vestibule.[14] The smokeless form of tobacco may be considered as a strong independent risk factor for oral cancer.[12]

Conventional betel quid contains betel leaf, areca nut, slaked lime and tobacco. International Agency for Research on Cancer (IARC) affirmed that chewing betel quid without tobacco is also carcinogenic to humans, probably due to the carcinogenicity of arecanut[15]. 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. It has been shown that reactive oxygen species, methylating agents, and reactive metabolic intermediates from betel quid induced various kinds of DNA damage[16] In a study conducted by Sharma et al in North East India, 50.8% OSCC cases occurred in younger age group, probably due to the early onset habit of tobacco & betel quid chewing. Illiteracy and lack of awareness was also associated with the increased tobacco use.[9]

**Alcohol**

Alcohol increases the risk for oral cancer by local and systemic effects. Alcohol has a synergistic role with tobacco in oral carcinogenesis as it increases the permeability of oral mucosa by causing epithelial atrophy. This allows easier penetration of carcinogens. The main metabolite of alcohol is acetaldehyde which can induce DNA damage, sister chromatid exchange and gene mutation. Gene polymorphisms of alcohol metabolizing enzymes alcohol dehydrogenase and aldehyde dehydrogenase are associated with alcohol related cancers. Acetaldehyde can inhibit the enzyme 6-methyl guanitransferase which is responsible for repair of injuries caused by alkylating agents.[17,18] Systemic effects are mainly due to nutritional deficiency and alcohol induced hepatic damage resulting in reduced immune response.[18]

**Trauma**

Trauma from sharp tooth/ ill fitting prosthesis is an underestimated cause of OSCC affecting tongue. Chronic low grade trauma from the sharp cusps may produce a potential cancerization field on the lateral border of tongue. Thus chronic trauma from sharp teeth has been suggested as a potentially malignant condition.[19]

Experimental animal studies have proposed two mechanisms for development of malignancy from chronic trauma. Persistent mechanical irritation may cause DNA damage eventually resulting in cancer formation. Increased activity of poly-ADP-ribose polymerase in cases with chronic trauma supports this mechanism.

Alternative theory suggests that chronic mucosal trauma results in inflammation. Chemical mediators such as cytokine, prostaglandins, and tumor necrosis factors are released which leads to oxidative stress. This could trigger genetic and epigenetic changes causing DNA damage, inhibiting its repair, altering transcription factors, preventing apoptosis, and stimulating angiogenesis, finally resulting in cancer.[20]

Also constant Irritations harm the epithelia and may reduce their barrier function making them more susceptible to carcinogens.[19]

**Genetic predisposition**

Genetic predisposition may be an important contributor to young-onset HSNCC.[21] The development of typical HNSCC is a result of a multistep process, which involves multiple genetic and epigenetic events. Studies show that gains at 3q, 5q, 8q, and 11q, as well as losses at 3p and 9p have been found in most of the HNSCC patients [100]. Loss of chromosome region 3p and 9p21 are common early genetic events in head and neck squamous neoplasia.[21]

Individuals with inherited syndromes like Fanconi's anaemia, Epidermolysis bullosa, Dyskeratosis congenita, Xeroderma pigmentosum, and Blooms syndrome are reported to have 700-1000 fold increased incidence of HNSCC than that of general population.[22] An increased susceptibility to viral transformation, mutagens, defective DNA repair, chromosomal instability and immune system defects are found in these persons.[23] They carry an elevated risk of secondary malignancies including HNSCC at an early age.[24] Mutations that are responsible for HNSCC in syndromic patients are same as those develop in the general population. These include inactivation of tumor suppressor genes (TP53, p16, FANCA-M ) or aberrant expression of oncogenes (ras and myc gene family, int-2, hst-1, cyclin D1, epidermal growth factor receptor and Bcl-2).[25] Researchers strongly suggest to conduct a thorough and standardised oral cavity examination and genetic consultation of young individuals with such systemic diseases.[26]

Family history may reveal important clues for HNSCC susceptibility, which is linked with its early onset. The suspicion of a genetic alteration should arise from a family history of: 1) first-degree relative with the same kind of tumour and same clinical presentation 2) two or more first-degree relatives with a tumour in the same location; 3) two or more first-degree relatives affected by rare tumours.[27] Retrospective studies have demonstrated a 3.6-fold increased risk for those individuals whose first-degree relatives are affected by other head and neck cancers.[20] It has been suggested that the offspring do not inherit cancer itself but a genetic make up that makes them easier to get cancer.[24] Several single nucleotide polymorphisms affect the genes like p53, p21 and cyclin D1 which are responsible for the repair of tobacco induced DNA damage thereby increasing the risk for OSCC. Increased prevalence of such single nucleotide polymorphisms have been reported in many young individuals, who were more vulnerable to the carcinogenic effects of smoking compared to healthy volunteers.[27]

**Nutritional deficiency**

Micronutrients act by their antioxidant effects and by binding and diluting carcinogens in the digestive tract. Chronic iron deficiency anemia can cause atrophy of mucosa and increase the susceptibility to carcinogens.[25] The anti-cancer effects of fresh vegetables and

fruits are be due to their contents of carotenoids, vitamin A, vitamin C, folic acid, flavonoids, phytosterols, fibres and other antioxidants.[28] These results may be overestimated too as many of the heavy smokers and drinkers usually tend to consume less fruits and vegetables resulting in an association. Fish and seafood contain polyunsaturated fatty acids, mineral salts and proteins which could inhibit tumor progression through their anti-inflammatory effects and inhibition of oxygen free radicals.[28]

**Poor oral hygiene**

Periodontitis and poor dental care are positively associated with increased risk of OSCC.[29] Poor oral health can lead to mucosal disruption by local irritation increasing the susceptibility to OSCC.[19] Studies have reported a 2–5 fold increase in the risk of OSCC among periodontitis patients as compared to those without the disease.[29]

**Human papilloma virus**

Human papilloma virus (HPV) types 16 and 18 are most commonly associated with OSCC. Oncogenic properties of HPV are attributed to the viral proteins E6, E7 and E5 which act through disruption of tumor suppressor genes p53 and Rb. HPV has been identified as a major contributor for oropharyngeal SCC in young adults; but only a small fraction of Oral cavity SCC is proven to be HPV-related even in young non-smoking non-alcoholic patients.[30]

In high risk HPV infection, viral genome gets integrated into the host genome. During this process, the circular viral genome breaks at the level of the E1 and E2 regions. The loss of E2 causes the loss of E6 and E7 control. E6, in combination with a ubiquitin ligase called E6 associated protein (E6AP) bind with p53 and target it for ubiquitination and proteosomal degradation. The p53 tumor suppressor gene normally regulates growth arrest and apoptosis after DNA damage. E6 also interferes with other pro-apoptotic proteins, Bak, and procaspase 8, thus preventing apoptosis. Recently, the product of the notch1 gene and telomerase also have been identified as targets of p53.[31]

E7 can to bind to the retinoblastoma tumor suppressor gene product, pRb, and its family members, p107 and p130. In the hypophosphorylated state, pRb family proteins bind to transcription factors such as E2F family members and repress the transcription of genes involved in DNA synthesis and cell cycle progression. After binding to unphosphorylated pRb, E7 disrupt pRb- E2F complexes and prematurely induce cells to enter the S phase. E7 also interact with p21, targeting it for ubiquitin and proteosomal degradation, resulting in initiation of S phase of cell cycle. The E7 protein function enables HPV replication in the upper layers of the epithelium where uninfected daughter cells normally differentiate and completely exit the cell cycle. E6 & E7 are known to activate the Wnt signalling pathway, causing the transcription of cyclin D1 and initiates the G1 phase of cell cycle.[31]

E5 is a membrane associated protein that delay the degradation of epidermal growth factor receptor (EGFR), causing progression of cell cycle into S phase, activating anti apoptotic and proliferative pathways and promoting angiogenesis. Thus the combined effect of E6, E7 and E5 lead to cell cycle progression in differentiated epithelial cells, finally leading to oral cancer.[31]

**Lifestyle risk factors- sedentary lifestyle**

There is increasing evidence suggesting the role of physical activity in prevention of cancer.[32] Reduced risk of colorectal, breast and prostate malignancies are reported in people who exercise regularly.[33] Improved survival and lower risk relapse of cancer also have been reported among them. Weight control, better immunity and improved control of endogenous hormone levels are suggested to be the factors mediating these.

Physical activity may influence head and neck carcinogenesis by modulating specific mucosal immune parameters, like salivary immunogloblin (Ig) A.[32] Regular moderate exercise improves immune function thereby decreasing susceptibility to cancer while a sedentary lifestyle or repeated exhaustive exercise suppress immune function increasing susceptibility to cancer. Long-term, regular exercise is suggested to have anti-inflammatory effect by reducing body fat, release of catecholamines and anti-inflammatory cytokines by muscles and inhibition of pro-inflammatory cytokines thereby providing protection against chronic inflammation-associated diseases.[34] The serum levels of inflammatory cytokines produced by adipose tissue such as tumor necrosis factor alpha (TNFα) and interleukin (IL)-6, are found to be decreased in physically active persons who are on low-calorie diet.[32]

**Alcohol containing mouth rinses**

Acetaldehyde, the genotoxic metabolite of ethanol mediates its carcinogenicity. Many commonly used mouthwashes also contain 5-27% of ethanol. Dirk et al found that alcohol containing mouthwashes temporarily raised the salivary acetaldehyde concentrations similar to those found after the intake of alcoholic beverages.[35] Even though mouthwash cannot be considered as an independent risk factor, it can increase the risk for OSCC in association with other carcinogenic factors.[36]

**Stress**

Chronic stress induce higher levels of catecholamines in blood via two mechanisms; hypothalamus pituitary axis (HPA) mediated release of cortisol and sympathetic nervous system mediated release of nor epinephrine. Elevated cortisol subsequently resulted in heat shock protein -70 (HSP-70) over expression. HSP-70 inhibited apoptosis, allowing tumor cells to escape immune surveillance and develop resistance to chemotherapy.[37] Chronic stress also resulted in increased tumor size, elevated levels of matrix metalloproteinase -2(MMP2) and vascular endothelial growth factor (VEGF) and more invasive growth of oral carcinoma cells in an experimentally stressed mouse model. They suggested that catecholamine and glucocorticoid might stimulate tumor progression under chronic stress.[38] Another study in tumor bearing mouse reported noradrenaline could enhance cancer stem cell like phenotype and upregulate the expression of stem cell markers. Administration of nor adrenaline increased tumor growth whereas injections of ß2-adrenaline receptor inhibitor blocked this.[39]

**UV exposure**

Oral cavity may be exposed to UV light by simple mouth opening while outdoors as well as by dental procedures like teeth whitening. Blue light irradiation generated reactive oxygen species and induced oxidative stress in oral tissues, which can be inhibited by antioxidants.[40] Researches conducted to find the correlation between UV exposure and oral cancer remains inconclusive. Experimental studies have shown that UV B exposed oral tissues have a higher carcinogenic risk than skin tissues. DNA repair and apoptosis were less in the oral cells compared to that in skin cells.[40] Several studies reported no positive correlation between UV exposure and incidence of oral cancer.[41]

## Conclusion

Incidence of OSCC is increasing in younger population. Increased habit of chewing commercial preparations of tobacco, trauma & genetic susceptibility are the commonly associated risk factors. Other risk factors such as sedentary lifestyle, chronic stress and UV exposure are also increasingly associated with oral cancer. As in conventional OSCC, prevention, early detection and timely intervention might reduce the disease burden in early age onset oral cancer too. Creating proper awareness in the general population regarding the risk factors is the key to prevention of OSCC in majority of young adults.

## References


1. Matlashewski G, Banks L, Storey A, et al. Role of a p53 polymorphism in the development of human papilloma virus associated cancer. Nature 1998;393:229-34.
2. Jefferies S, Foulkes WD. Genetic mechanisms in squamous cell carcinoma of the head and neck. Oral Oncol 2001;37:115-26.
3. Llewellyn CD, Linklater K, Bell J, Johnson NW, Warnakulasuriya S. An analysis of risk factors for oral cancer in young people: A case-control study. Oral Oncol 2004;40:304-13.
4. Ur Rahaman SM, Ahmed Mujib B R. Histopathological correlation of oral squamous cell carcinoma among younger and older patients. J Oral Maxillofac Pathol 2014;18:183-8
5. Abdulla R, Adyanthaya S, Kini P, Mohanty V, D'Souza N, Subbannayya Y. Clinicopathological analysis of oral squamous cell carcinoma among the younger age group in coastal Karnataka, India: A retrospective study. J Oral Maxillofac Pathol 2018;22:180-7
6. Acharya S, Tayaar AS.Analysis of clinical and histopathological profiles of oral squamous cell carcinoma in young Indian adults: A retrospective study. J Dent Sci. 2012;7:224-30.
7. Beena VT, Binisree SS, Ayswarya T, Paikkadan I, Padmakumar SK, Sivakumar R. Oral squamous cell carcinoma in patients younger than 40 years: A 10 year retrospective study. Int J Sci Stud 2016;4:150-3.
8. Sharma P, Deb T, Ray JG, Singh AK, Gupta G, Das A, Srivastava S. Oral squamous cell carcinoma profile in North-Eastern regions of India from habits to histopathology: A hospital-based study. Natl J Maxillofac Surg 2018;9:56-60
9. Tandon A, Bordoloi B, Jaiswal R, Srivastava A, Singh RB, Shafique U. Demographic and clinicopathological profile of oral squamous cell carcinoma patients of North India: A retrospective institutional study. SRM J Res Dent Sci 2018;9:114-8
10. Singh MP, Misra S, Rathanaswamy SP, et al. Clinical profile and epidemiological factors of oral cancer patients from North India. Natl J Maxillofac Surg. 2015;6(1):21-24. doi:10.4103/0975-5950.168215
11. Iype E M, Pandey M, Mathew A, Thomas G, Sebastian P, Nair M K. Oral cancer among patients under the age of 35 years. J Postgrad Med 2001;47:171
12. Müller S. Update from the 4th Edition of the World Health Organization of Head and Neck Tumours: Tumours of the Oral Cavity and Mobile Tongue. Head Neck Pathol. 2017;11(1):33–40.
13. Nemeth Z, Turi K, Lehner G, Veres SD, Csurgay K. The prognostic role of age in oral cancer. A clinical study. Magy Oncol2013;57:166-72.
14. van Monsjou HS, Wreesmann VB, van den Brekel MWM, et al. Head and neck squamous cell carcinoma in young patients. Oral Oncol 2013;49:1097-102.
15. Madani AH, Jahromi AS, Dikshit M, Bhaduri D. Risk assessment of tobacco types and oral cancer. Am J Pharmacol Toxicol 2010;5:9e13.
16. Sharma JD, Baishya N, Kataki AC, Kalita CR, Das AK, Rahman T. Head and neck squamous cell carcinoma in young adults: A hospital-based study. Indian J Med Paediatr Oncol 2019;40, Suppl S1:18-22
17. Goldenberg D, Lee J, Koch WE, et al. Habitual risk factors for head and neck cancer. Otolaryngol Head Neck Surg 2004;131:986e93.
18. Kumar M, Nanavati R, Modi TG, Dobariya C. Oral cancer: Etiology and risk factors: A review. J Can Res Ther 2016;12:458-63.
19. Panta P, Sarode SC, Sarode GS, et al. 'Chronic traumatic ulcer of lateral tongue' - An underestimated 'oral potentially malignant disorder'? Oral Oncol 2018;85:101-2.
20. Singhvi HR, Malik A, Chaturvedi P. The Role of Chronic Mucosal Trauma in Oral Cancer: A Review of Literature. Indian J Med Paediatr Oncol. 2017 Jan-Mar; 38(1): 44–50.
21. Liu X, Gao XL, Liang XH, Tang YL. The etiologic spectrum of head and neck squamous cell carcinoma in young patients. Oncotarget. 2016;7(40):66226–66238.
22. Romick-Rosendale LE, Lui VW, Grandis JR and Wells SI. The Fanconi anemia pathway: repairing the link between DNA damage and squamous cell carcinoma. Mutat Res. 2013; 743-744:78-88.
23. Budrukkar A, Shahid T, Murthy V, Hussain T, Mulherkar R, Vundinti BR, Deshpande M, Sengar M, Laskar SG and Agarwal JP. Squamous cell carcinoma of base of tongue in a patient with Fanconi's anemia treated with radiation therapy: case report and review of literature. Head Neck. 2010; 32:1422-1427.
24. Kaplan MJ, Sabio H, Wanebo HJ and Cantrell RW. Squamous cell carcinoma in the immunosuppressed patient: Fanconi's anemia. LARYNGOSCOPE. 1985; 95:771-775.
25. Huang SF, Chen IH, Liao CT, Wang HM, Liou SH and Hsieh LL. Combined effects of MDM2 SNP 309 and p53 mutation on oral squamous cell carcinomas associated with areca quid chewing. Oral Oncol. 2009; 45:16-22.
26. Tettamanti L, Caprioglio A, Tecco S, Barello G, Macchi A, Tagliabue A and Levrini L. Oral Squamous Cell Carcinoma in the paediatric patient: a literature review. Eur J Paediatr Dent. 2012; 13:35-40.
27. A. Paderno, R. Morello, C. Piazza. Tongue carcinoma in young adults:a review of the literature. Acta Otorhinolaryngol Ital 2018;38:175-180.
28. Petti S. Lifestyle risk factors for oral cancer. Oral Oncology, 2009;45(4–5), 340–350.
29. Javed F, Warnakulasuriya S. Is there a relationship between periodontal disease and oral cancer? A systematic review of currently available evidence. Crit Rev Onc.2016;97:197-205.
30. Mirghani H, Amen F, Moreau F, et al. Do high-risk human papillomaviruses cause oral cavity squamous cell carcinoma? Oral Oncol. 2015;51(3):229-36
31. Sathish N, Wang X, Yuan Y. Human Papillomavirus (HPV)-associated Oral Cancers and Treatment Strategies. J Dent Res. 2014;93(7 Suppl):29S-36S. doi:10.1177/0022034514527969
32. Leitzmann MF, Koebnick C, Freedman ND, et al. Physical activity and head and neck cancer risk. Cancer Causes Control. 2008;19(10):1391-1399. doi:10.1007/s10552-008-9211-0
33. Kokila G, Smitha T. Cancer and physical activity. J Oral Maxillofac Pathol 2017;21:4-7
34. Kruijsen-Jaarsma M, Révész D, Bierings MB, Buffart LM, Takken T. Effects of exercise on immune function in patients with cancer: A systematic review. Exerc Immunol Rev 2013;19:120-43.
35. Lachenmeier DW, Gumbel-Mako S, Sohnius EM,Keck- Wihelm A. Salivary acetaldehyde increase due to alohol-containing mouthwash use; a risk factor for oral cancer. Int. J .Can .2009;125(3):730-5.
36. Ustrell-Borràs M, Traboulsi-Garet B, Gay-Escoda C. Alcohol-based mouthwash as a risk factor of oral cancer: A systematic review. Med Oral Patol Oral Cir Bucal. 2020;25(1):e1-e12. Published 2020 Jan 1. doi:10.4317/medoral.23085
37. Pereira DB, Sannes T, Dodd SM, Jensen SE, Morgan LS, Chan EKL.Life stress, negative mood stress and antibodies to heat shock protein 70 in endometrial cancer. Brain Behav Immun. 2010;24(2):210.
38. Xie H, Li C, He Y, R Griffin R, Ye Q,Li L. Chronic stress promotes oral cancer growth and angiogenesis with increased circulating catecholamine and glucocorticoid levels in a mouse model. Oral Oncol 2015; 51( 11): 991-7.
39. Zhang B, Wu Chenzhou, Chen W, Qiu L, Li S, Wang T et al. The stress hormone norepinephrine promotes tumor progression through ß2-adrenergic receptors in oral cancer. Arch Oral Biol.2020; 113:104712.
40. Agrawal A, Shindell E, Jordan F, Baeva L, Pfefer J, Goder DE. UV Radiation Increases Carcinogenic Risks for Oral Tissues Compared to Skin. Photochem Photobiol 2013;89(5):1193-8.
41. Adams S, Lin J, Brown D, Shriver CD, Zhu K. Ultraviolet Radiation Exposure and the Incidence of Oral, Pharyngeal and Cervical Cancer and Melanoma: An Analysis of the SEER Data. Anticancer Res. 2016;36(1):233–237.