Clinical Cancer Investigation Journal-ISSN: 2278-0513

Environmental and genetic risk factors of oral cancer: an updated review

Abstract

Oral cancer poses a significant public health concern throughout the world. In terms of cancer incidence rates, it is ranked among the top ten. The risk of oral cancer increases with age, with the majority of cases occurring in people over 50. Since most patients do not have symptoms in the earliest stages, they do not seek medical attention unless they experience obvious symptoms like bleeding and pain. Generally, prognoses deteriorate as the condition worsens and the tumor's location becomes more difficult to reach. Heavy tobacco use (which includes smokeless tobacco), betel chewing, alcohol drinking, and persistent inflammatory conditions pose risks to the oral cavity and increase cancer risk. Tobacco usage has been associated with changes in functions and proliferation of periodontal cells, including gingival fibroblasts, periodontal membrane cells, periodontal ligament cells, et cetera, leading to cell apoptosis. Interference with the host cell cycle machinery in latent or chronic viral infections leads to malignant transformation. Also, numerous studies have been conducted to determine how chronic trauma affects the development of cancer. Finally, we provided a narrative review of the main genetic and non-genetic risk factors for oral cancer with new insight.

Keywords: *Risk factors, Oral cancer, Genetic, Tobacco, and Trauma*

Hanieh Mohammadpour[1], Arash Bakhshi[1], Naeim Norouzi[1], Amir Fallah[1], Sirous Gharib[2, *]

[1] Student Research Committee, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

[2] Assistant professor, Department of Internal Medicine, Guilan University of Medical Sciences, Rasht, Iran

Hanieh.Mohammadpour2022@gmail.com
A.bakhshi.b13@gmail.com
Naem.norozi@gmail.com
amirssign@gmail.com
Dr.cygharib@gmail.com

Corresponding:
Sirous Gharib, Oncologist Assistant professor, Department of Internal Medicine, Guilan University of Medical Sciences, Rasht, Iran
Email:
Dr.cygharib@gmail.com
https://orcid.org/0000-0002-0642-4651

Introduction

Oral cancer has become a major public health concern around the world. It has one of the top ten cancer incidence rates. While scientific advances and treatments have improved significantly in recent years, survival rates have not increased substantially, presenting an ongoing dilemma to the biomedical sciences (1). Currently, it is ranked as the 16th most prevalent malignancy and the 15th most common cause of death globally, with an age-adjusted incidence of four cases per 100,000 people worldwide. It varies widely depending on gender, age group, country, race, ethnic groups, and socioeconomic conditions (2). Men are more likely than women to develop oral cancer (3). An individual is more likely to develop oral cancer as they age, with the majority of cases occurring in people over 50 (4). Over 90% of oral cancers are squamous cell carcinomas, with two-thirds occurring in developing countries and half in South Asia (4); other oral cavity tumors include salivary minor gland tumors, lymphomas, and melanomas. OSCC may exhibit different degrees of differentiation and usually causes glandular metastases. T stage and invasion depth, as well as tumor thickness, are all directly related to lymphatic spread in the neck (5). Oral cancer is associated with unfavorable prognoses, often resulting in a 5-year survival rate of only 40%; however, survival rates can exceed 80% in the event of an early diagnosis (stages I and II) (6). Since most patients do not have symptoms at the beginning of the disease, patients generally do not seek medical attention until they demonstrate symptoms, including pain, bleeding, or a lump in the oral cavity or neck. In cases where lymphatic invasion has already occurred, almost half of oral cancer cases are diagnosed during advanced stages (stage III and IV) (7). Typically, patients are responsible for the majority of diagnostic delays; nevertheless, delays may result from an ineffective medical strategy, such as not anticipating oral cancer or failing to diagnose and treat it in a timely and appropriate manner (5). In general, prognoses worsen as the condition deteriorates and the tumor site becomes more difficult to reach (8). Heavy tobacco use (including smokeless tobacco), betel chewing, alcohol drinking, and chronic inflammation are risk factors for oral cancer (5). The chronic irritation of mucosal tissues resulting from improperly fitted dentures may increase the risk of oral malignancies. These cancers occur more frequently in females than in males and non-addicted patients (9). Additionally, genetic diseases such

as xeroderma pigmentosum, Fanconi anemia, and ataxia telangiectasia are associated with a higher risk due to the lack of DNA repair mechanisms (10). Thus, primary prevention of oral cancer entails educating people about reducing factors associated with behavioral risk, promoting the reduction of tobacco use and addiction, and restricting alcohol consumption (5). Standardized population-based screening for oral cancer, unlike other common cancers, does not have high cost-effectiveness and is not recommendable (11). Conversely, screening programs in high-risk groups (heavy smokers and drinkers) or in patients with a history of cancer outside the head and neck region may be helpful (12).

Tobacco and alcoholic beverages

Tobacco and alcohol are the two main risk factors for oral cancer (13, 14). The risk of oral cavity cancer (OCC) is 8.4 times greater among smokers than non-smokers (15, 16). Smokeless tobacco (SLT) users have a five-to-seven-fold greater chance of developing OCC than non-users. There are pan masala, chewing tobacco, betel quid, areca nut, gutka, khaini, and other forms of SLT. Chewing betel quid and areca nut on their own or in combination with tobacco increases the chance of developing oral cancer and is thus regarded as a carcinogen in group one. Tobacco smoke, SLT products, betel quid, and areca nut all consist of carcinogenic agents, which increase the likelihood of OCC (17, 18). Tobacco use has been associated with changes in functions and proliferation of periodontal cells, including gingival fibroblasts, periodontal membrane cells, periodontal ligament cells, and other cell types, leading to cell apoptosis. Additionally, it may impact the spread of periodontitis, impair immune system defenses and increase the inflammatory response, leading to alveolar bone damage and destruction (19). Smoking is epidemiologically significant for OCC and is linked with its development as well as progression (15, 16). The deadly connection between tobacco substances and human cancer is the result of the combined impact of two contributors: nicotine and carcinogens. Although nicotine is toxic and addictive, it has not been proven that nicotine causes cancer, and the IARC does not recognize nicotine as carcinogenic. Nevertheless, due to their dependence, individuals often consume products that are full of carcinogens. Unburned tobacco is known to contain at least 16 carcinogens, and tobacco smoke contains at least 60 substances that cause cancer. Tobacco-specific nitrosamines like 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N'-nitrosonornicotine (NNN), polycyclic aromatic hydrocarbons like benzoapyrene, and aromatic amines like 4-aminobiphenyl have been implicated as a cause of OCC (20, 21).

Group 1 carcinogens include alcohol (22, 23). An increased risk of developing other types of head and neck cancer, such as throat and laryngeal cancer, is also linked to excessive consumption of alcoholic beverages (24). The enzyme alcohol dehydrogenase (ADH) converts ethanol to acetaldehyde, an intermediate metabolite capable of interacting with DNA to form DNA adducts, thought to be involved in alcohol-related carcinogenesis. Mutations or disruptions in DNA synthesis are caused by these adducts, leading to the development of cancer (22, 23). According to biochemical and epidemiological studies, acetaldehyde, the initial metabolic component of ethanol, is an essential component in alcohol-induced carcinogenicity in the mouth, throat (pharynx), laryngitis, and esophageal cancers (14). In comparison to abstaining or occasional drinkers, heavy drinker groups have a tenfold greater risk of alcohol-related risks. The risk is strongly influenced by the amount of ethanol in alcoholic beverages, which correlates with dosage (13, 14). The risk of developing OCC increases with the combination of alcohol and tobacco acting together (22, 23). The risk of oral cancer increases when smoking and alcohol consumption are combined. Assessing the impact of these factors separately is a daunting task, given that approximately 75% of oral cancers are associated with both alcohol and tobacco consumption (24).

Viral infection

Interference of the host cell cycle machinery in latent or chronic viral infections leads to malignant transformation. Viral genes and gene products play a vital role in determining cell growth and proliferation. Some viral genes function as proto-oncogenes. Once incorporated into host DNA, proto-oncogenes undergo oncogenicity and result in malignant transformation (25). Cell cycle checkpoints caused by genotoxic stress can be disrupted by oncogenic viruses. The downstream roles of P53 and cellular connecting proteins are significant. Viral antigens render them inactive by releasing them from cell cycle checkpoints or by preventing them from entering apoptotic pathways mediated by p53 (26). Several investigations have revealed a significant positive correlation between oral cancer, precancer, and different viruses. The occurrence of oral cancer can be linked to precancerous and oncogenic conditions, as well as viruses like HSV, HPV, and EBV (27). The human papillomavirus, also known as HPV, is a tiny DNA virus with a squamous epithelia tropism. HPV types that infect the mucosa are additionally divided into high-risk and low-risk categories according to the extent of their potential for malignancy (28). Recent studies have found an increased prevalence of HPV infection (approximately 50%) in squamous cell carcinoma of the head and neck. In at least 90% of these instances, HPV 16 was discovered to be the most prevalent type (29, 30). In the last decade, HPV has been shown to cause both genital and anal cancers, as well as to be an etiologic factor for a type of head and neck squamous cell

carcinoma (HNSCC) (31). HPV has been implicated as a risk factor for OSCC, with the most common subtype being HPV16 (32). E6 and E7 are early HPV proteins important in HPV-associated OPSCC. E6 is a p53 inhibitor, and E7 binds to pRb, the retinoblastoma protein (33). In oropharyngeal cancers, HPV positivity was found primarily on the tonsils (94%), followed by the base of the tongue (62%) (34, 35). There is some evidence that HPV is an independent risk factor for the development of OSCC (36). HPV is the cause of 2-8% of OCC (22).

Epstein-Barr virus (EBV) belongs to the gamma subfamily of the human herpesvirus family, which is divided into two genera, lymphocryptovirus and rhadinovirus. Because of its latent infection of B lymphocytes, EBV is the prototypical lymphocryptovirus (37). The EBV genome is stored as a 172 kbp double-stranded linear DNA molecule. Two subtypes of EBV are known, namely EBV-1 and EBV-2 (38). EBV has a biphasic life cycle that is enabled by its dual tropism for B lymphocytes and epithelial cells, allowing transmission in oral lymphoid tissues. EBV has been linked to a variety of lymphomas and carcinomas that occur in the oral cavity and other sites, although the infection is often mild (39). Numerous reports show an association between the development of EBV and OSCC (40, 41). However, no definitive conclusions can be drawn from these reports. Moreover, many reports show no connection. There is a need for larger population-based studies in order to establish the oncogenic potential of EBV in OSCC (36). According to a detailed analysis of EBV/HPV coinfection in squamous cell carcinoma of the tonsils and base of the tongue, the rates were 25% and 70%, respectively (42).

Herpes simplex virus (HSV) is a member of a family of eight related viruses. These include HSV-1 and HSV-2, varicella-zoster virus, EBV, and cytomegalovirus (36). HSV is involved in the activation of chromosomal mutations, the amplification of genes, and the overexpression of pre-existing oncogenes with neoplastic tissue (43). Both animal models and in vivo experiments have investigated the significance of HSV in the development of OSCC. Studies suggest that smokeless tobacco and HSV-1 may interact to cause OSCC (44). In summary, to date, there is no evidence of a direct carcinogenic role of HSV in OSCC. Most of the studies on transformation were conducted two or three decades ago, and results from more recent studies have been inconclusive and conflicting (36).

Oral microbiome

In symbiosis with their host, the human body is home to more than 100,000 billion microbes. The genome of all microorganisms, including oral microorganisms (viruses, fungi, and bacteria), and their interactions and byproducts is called the microbiome (45). The lumens of the gut and oral cavity host diverse microbiota, as do the skin and vagina (46). Human microbiomes have been linked to various types of cancer (47). At the cellular and molecular level, the squamous epithelium of the oral cavity is constantly in contact with various microbiological threats (32). In addition to driving the chronic inflammation that may predispose OSCC, the oral microbiome is involved in directly influencing the host cell response (48, 49). Certainly, periodontitis, which is considered a polymicrobial condition, is associated with alterations in the microbiome of the mouth. Alterations in the oral bacterial and fungal microbiome have been associated with oral precancerous and cancerous lesions. Persistent bacterial infections may increase the risk of OCC or contribute to its development (32). Since bacteria constitute the major component of the oral microbiome, there has been a substantial amount of research conducted concerning the bacterial component of the oral microbiome, the oral bacteriomes. Nevertheless, attention has been drawn to lesser-known microbial communities, including fungi and viruses (50).

Streptococcus, Peptostreptococcus, Prevotella, Porphyromonas gingivalis, and Capnocytophaga gingivitis are some of the specific bacteria found to be highly correlated with OSCC (49). Bacterial mechanisms in oral cancer: The primary bacterial mechanism in oral cancer is the stimulation of persistent inflammation. Cell proliferation, mutagenesis, oncogene activation, and angiogenesis are all caused or helped by the production of inflammatory mediators during this process. Concerning the second mechanism, bacteria can influence cancer pathogenesis by affecting cell proliferation, cytoskeletal restructuring, NF-κB activation, and inhibition of cell apoptosis. As for the third mechanism, bacteria produce several potentially carcinogenic substances (49, 51).

Candida species are known to be normal oral commensals in up to 50% of the healthy population (52). The tubular hyphal structure of C. albicans is thought to play a critical role, allowing the entry of salivary precursors and release of nitrosamine product to keratinocytes, potentially initiating OSCC (53).

Candida species are known to be normal oral commensals in up to 50% of the healthy population (52). The tubular hyphal structure of C. albicans is proposed to play a role because it permits entry of precursors from saliva and the release of the nitrosamine products to keratinocytes, potentially triggering OSCC (53). The alcohol dehydrogenase enzyme is present in Candida species found in the oral cavity. Under aerobic or microaerophilic conditions, this enzyme catalyzes the production of mutagenic levels of acetaldehyde (47). Compared to non-Candida leukoplakia, Candida leukoplakia has significantly increased malignant transformation rates. Histologically, Candida leukoplakia is characterized by fungal hyphae invading superficial epithelial layers and chronic

(sometimes acute) intraepithelial inflammation (52). Candida is commonly found in histological sections of leukoplakia. According to some studies, Candida spp. N-nitroso benzyl methylamine, a potent carcinogen, can be produced by cells isolated from leukoplakia lesions (54).

Chronic trauma and irritation of mucous membranes

Numerous studies have been conducted to determine how chronic trauma affects the development of cancer. Animal studies have suggested two possible mechanisms by which chronic trauma can lead to the development of cancer. According to some theories, DNA damage due to prolonged mechanical irritation leads to the development of cancer. This is evidenced by increased poly-ADP-ribose polymerase activity in chronic trauma (9). It has also been reported that repetitive or prolonged damage to the oral mucosa caused by repeated and long-term mechanical stimulation by oral toxins alone or coupled with other risk components may be responsible for OSCC occurrence (55). Persistent irritation has been implicated as a risk factor (56). Over the past decade, it has been hypothesized that there is an association between the development of OSCC and repetitive mechanical trauma to the oral mucosa. This is defined as repetitive mechanical stimulation of various diseases. Chronic trauma may be suspected, particularly in the presence of sharp or rough teeth, ill-fitting dentures, or dysfunctional habits (57, 58). Chronic mechanical irritation (CMI), one of these understudied risk factors for oral cancer, is one example (59). There have been cases where OSCC developed in an oral site with a history of HCM. CMI can be caused by poor dental health, poor dentition, missing teeth, and prosthetic factors (57, 59). Chronic mechanical irritation (CMI), one of these understudied risk factors for oral cancer, is one example (59). In some cases, an oral site with a history of HCM has experienced the development of OSCC. CMI can be caused by poor dental health, poor dentition, missing teeth, and prosthetic factors (57, 59). CMI-related prosthetic factors are intraoral restorations that do not fit well, have a sharp/rough surface, or lack lasting stability. Poorly positioned, sharp/broken/rough natural tooth surfaces are among the dental factors associated with CMI. Parafunctional habits such as cheek biting and tongue thrusting are among the functional factors associated with CMI. The mucosal pathologies associated with CMI vary in severity and duration, from frictional keratosis in mild cases to fibrosis in moderate and severe cases (59). These cancers are more common in women in non-addictive patients (9). For carcinogens like tobacco and alcohol, a correlation between dose, duration, and cancer risk has been demonstrated. Furthermore, some studies have explored the possibility that the duration of denture use plays a role in the development of cancer (60). However, no link could be established between the duration of use of prostheses and the incidence of cancers. The prognosis and outcome of these cancers have not been studied individually, although they may be associated with early nodal disease. No clear association was found between broken/sharpened teeth, dental implants, the type of denture material, and the development of oral cancer (9).

Chronic inflammation

Periodontitis involves chronic inflammation affecting the tissues that support the teeth, including the gums and, in more severe forms, the periodontal ligaments and alveolar bone (61). Inflammatory mediators resulting from periodontitis, in addition to subgingival species and bacteria, may spread from the oral cavity and contribute to a variety of extraoral conditions, such as cancer, even though inflammations in the oral cavity occur locally (62, 63). Several stomatitis conditions have been suggested to be involved in the pathogenesis of oral squamous cell carcinoma: oral submucosal fibrosis, oral lichen planus, discoid lupus erythematosus, mouth ulcers associated with repetitive tissue damage, and chronic periodontitis (64). It has been established that infiltrates of cytokines, reactive oxygen species, and transcription factors that can induce proliferation, epithelial-mesenchymal transition, and invasion are present in the microenvironment of chronic oral inflammatory conditions such as oral lichen planus (65). Prostaglandins, reactive oxygen, nitrogen radicals, cytokines, and chemokines build up in the microenvironment of tissues that are chronically inflamed. By activating oncogenes and inactivating tumor suppressor genes, these inflammatory factors can prolong cell survival. Therefore, Genetic instability and increased cancer risk could result (66). Some infectious and environmental components, as well as inflammatory factors, can activate the nuclear signaling transducers of transcription-3 (STAT-3), activator protein-1 (AP-1), and nuclear factor kB (NF-kB), and some studies have shown that pro-inflammatory mediators such as interleukin, IL6, IL8, and tumor necrosis factor (TNFα) elevations have been reported among oral cancer patients (67, 68). These transcription factors then activate oncogenes that regulate apoptosis, cell proliferation, and angiogenesis, as well as genes that regulate the production of inflammatory mediators, which include growth factors, cytokines, prostaglandins, and proteases (66). Oxidative stress results from such inflammation. This could result in genetic and epigenetic changes that harm DNA, impede repair, alter transcription factors, prevent apoptosis, and stimulate angiogenesis, which can promote the growth of cancerous cells. To summarize, inflammation can act in multiple steps to cause cancer (69, 70).

Genetic

Genetic studies have demonstrated a strong correlation between the development of OCC and the accumulation of genetic alterations. Various chromosomal alterations have been linked to OCC (71). There are two types of genetic damage in oral cancer cells. Gain-of-function mutations are most common in proto-oncogenes but also in some TSGs. Loss of function is caused by recessive changes, most often observed in mutations of TSGs or genes involved in the growth inhibitory pathway (72). Characterization of OSCC at the molecular level has also been proposed, as has lung SCC. Signaling pathways affected include PIK3CA and EGFR mutations, differential use of lineage markers SOX2 and TP63, and dysregulation of the KEAP1/NFE2L2 oxidative stress pathway. Different patterns of EGFR pathway activation are associated with different clinical behaviors (73). Oral cancer is also associated with specific germline mutations. For instance, early-onset oral cancer is more likely in people with Li-Fraumeni syndrome (TP53 germline mutation) 12. In addition, aggressive oral cancer has been reported at a young age in patients with Fanconi anemia, which is caused by defective DNA repair, resulting in chromosomal instability (74). Most HPV-negative OSCCs contained TP53 loss-of-function mutations and CDKN2A inactivation in The Cancer Genome Atlas (TCGA) database. Furthermore, integrated genomic analyzes revealed a high degree of heterogeneity in HPV-negative OSCC. Whole-exome sequencing, a transcriptomic technique used to sequence all expressed genes in a genome, has revealed new mutations missed in previous studies. NOTCH1 mutations occurred in approximately 15% of cases, and NOTCH2/3 mutations and focal copy number changes were identified in an additional 11% of OSCC cases (75, 76). More than 80% of OSCC tumors overexpressed BGH3, MMP9, and PDIA3, suggesting the importance of ECM cell receptor interactions in the development of OSCC (77). Some genes have been found to have frequent mutations in HNSCC patients, including TP53, CDKN2A, NOTCH1, FBXW7, HRAS, and PIK3CA (75, 76). TP53 is a common mutation associated with various cancers. Only subgroups of OCC that are HPV-negative have TP53 mutations, the frequency of which ranges from 35.9% to 81.9% (78). Missense mutations are the most common type of mutation found in TP53 (78). Mutational associations with HPV have been evaluated in numerous studies (79, 80). TP53 mutations were more common in HPV-negative OSCC than in HPV-positive OSCC, although there was no clear association between p53 and HPV status (80). Furthermore, mutated TP53 was infrequently found among OSCC samples harboring HPV 16 DNA (81). The fragile histidine triad (FHIT) is a TSG on chromosome 3p14.2, and carcinogen damage leads to abnormal transcription of this gene. In 65% of OCCs, the FHIT is suppressed, which correlates with poor survival. Additionally, p16 and FHIT methylation has been reported in smokers with lung squamous cell carcinoma, suggesting that methylation in OCC regulates FHIT and p16 expression in humans exposed to tobacco smoke (82). The cancerous damage results in an abnormal transcription of the fragile histidine triad (FHIT), a TSG on chromosome 3p14.2. FHIT is suppressed in 65% of OCCs, which is associated with low survival. Furthermore, methylation of p16 and FHIT in smokers with squamous cell lung cancer has been documented, indicating that methylation in OCC controls FHIT and p16 expression in humans exposed to tobacco smoke (82). An oncogene with a mutation in the OCC is PIK3CA. PIK3CA mutations were reported in 8% of HPV-negative tumors and 21% of HPV-positive tumors. Additionally, stage IV OCC has PIK3CA mutations that negatively impact survival. Exons 9 and 20 of the tyrosine kinase domains contain the common PIK3CA mutation sites (83).

Conclusion

According to the above review, oral cancer is associated with several risk factors. Tobacco, smoking, viral infections, and trauma are the most prevalent and established. However, most patients who abstain from known lifestyle and environmental risks are diagnosed with oral cancer. Several of these factors, such as genetic susceptibility, are thought to play a role in the process. It is, therefore, imperative that the public and doctors are aware of the risk factors associated with oral cancer, and dentists should be on the lookout for early signs. It is crucial to examine the oral cavity routinely, especially in patients with known risk factors.

Authors' contributions

All three authors were involved in the design and formulation of the argument.

Conflict of interests

The authors declare that they have no conflicts of interest.

Ethical declarations

I now declare all ethical standards have been respected in the preparation of the submitted article.

Financial support

Self-funding

References

1. Rivera C. Essentials of oral cancer. International journal of clinical and experimental pathology. 2015;8(9):11884.

2. Inchingolo F, Santacroce L, Ballini A, Topi S, Dipalma G, Haxhirexha K, et al. Oral cancer: A historical review. International Journal of environmental research and public health. 2020;17(9):3168.
3. Montero PH, Patel SG. Cancer of the oral cavity. Surgical Oncology Clinics. 2015;24(3):491-508.
4. Warnakulasuriya S, Kerr A. Oral cancer screening: past, present, and future. Journal of dental research. 2021;100(12):1313-20.
5. Abati S, Bramati C, Bondi S, Lissoni A, Trimarchi M. Oral cancer and precancer: a narrative review on the relevance of early diagnosis. International Journal of environmental research and public health. 2020;17(24):9160.
6. Silverman S, Kerr AR, Epstein JB. Oral and pharyngeal cancer control and early detection. Journal of Cancer Education. 2010;25:279-81.
7. McCullough M, Prasad G, Farah C. Oral mucosal malignancy and potentially malignant lesions: an update on the epidemiology, risk factors, diagnosis, and management. Australian dental journal. 2010;55:61-5.
8. Laura Q, Chow M. Head, and neck cancer. N Engl j med. 2020;382:60-72.
9. Singhvi HR, Malik A, Chaturvedi P. The role of chronic mucosal trauma in oral cancer: A review of the literature. Indian Journal of Medical and Paediatric Oncology. 2017;38(01):44-50.
10. Van der Waal I. Oral potentially malignant disorders: is malignant transformation predictable and preventable? Medicina oral, patología oral y cirugía bucal. 2014;19(4):e386.
11. Lingen MW, Kalmar JR, Karrison T, Speight PM. Critical evaluation of diagnostic aids for the detection of oral cancer. Oral oncology. 2008;44(1):10-22.
12. Van der Waal I, de Bree R, Brakenhoff R, Coebegh J. Early diagnosis in primary oral cancer: is it possible? Medicina oral, patologia oral y cirugia bucal. 2011;16(3):e300-e5.
13. Gandini S, Negri E, Boffetta P, La Vecchia C, Boyle P. Mouthwash and oral cancer risk quantitative meta-analysis of epidemiologic studies. Annals of Agricultural and Environmental Medicine. 2012;19(2).
14. Ustrell-Borràs M, Traboulsi-Garet B, Gay-Escoda C. Alcohol-based mouthwash as a risk factor of oral cancer: A systematic review. Medicina oral, patologia oral y cirugia bucal. 2020;25(1):e1.
15. Esfahrood ZR, Zamanian A, Torshabi M, Abrishami M. The effect of nicotine and cotinine on human gingival fibroblasts attachment to root surfaces. Journal of Basic and Clinical Physiology and Pharmacology. 2015;26(5):517-22.
16. Warnakulasuriya S, Sutherland G, Scully C. Tobacco, oral cancer, and treatment of dependence. Oral oncology. 2005;41(3):244-60.
17. Khan Z, Tönnies J, Müller S. Smokeless tobacco and oral cancer in South Asia: a systematic review with meta-analysis. Journal of cancer epidemiology. 2014;2014.
18. Lin W-J, Jiang R-S, Wu S-H, Chen F-J, Liu S-A. Smoking, alcohol, and betel quid and oral cancer: a prospective cohort study. Journal of oncology. 2011;2011.
19. Sutton JD, Salas Martinez ML, Gerkovich MM. Environmental tobacco smoke and periodontitis in United States non-smokers, 2009 to 2012. Journal of Periodontology. 2017;88(6):565-74.
20. Zhang Y, He J, He B, Huang R, Li M. Effect of tobacco on periodontal disease and oral cancer. Tobacco-induced diseases. 2019;17.
21. Hecht SS. Tobacco carcinogens, their biomarkers, and tobacco-induced cancer. Nature Reviews Cancer. 2003;3(10):733-44.
22. Chamoli A, Gosavi AS, Shirwadkar UP, Wangdale KV, Behera SK, Kurrey NK, et al. Overview of oral cavity squamous cell carcinoma: Risk factors, mechanisms, and diagnostics. Oral Oncology. 2021;121:105451.
23. Stornetta A, Guidolin V, Balbo S. Alcohol-derived acetaldehyde exposure in the oral cavity. Cancers. 2018;10(1):20.
24. Reidy J, McHugh E, Stassen L. A review of the relationship between alcohol and oral cancer. The surgeon. 2011;9(5):278-83.
25. Kumar M, Nanavati R, Modi TG, Dobariya C. Oral cancer: Etiology and risk factors: A review. Journal of cancer research and therapeutics. 2016;12(2):458-63.
26. Gupta A, Kheur S, Shetty L, Kheur M. Unconventional causes of conventional oral cancer. J Integr Oncol. 2015;4(152):2.
27. Jalouli J, Ibrahim SO, Mehrotra R, Jalouli MM, Sapkota D, Larsson P-A, et al. Prevalence of viral (HPV, EBV, HSV) infections in oral submucous fibrosis and oral cancer from India. Acta oto-laryngologica. 2010;130(11):1306-11.
28. Hübbers CU, Akgül B. HPV and cancer of the oral cavity. Virulence. 2015;6(3):244-8.
29. Majchrzak E, Szybiak B, Wegner A, Pienkowski P, Pazdrowski J, Luczewski L, et al. Oral cavity and oropharyngeal squamous cell carcinoma in young adults: a review of the literature. Radiology and oncology. 2014;48(1):1.
30. He Y, Zhang M, Feng L, Yin Y, Zhang R, Di W. Risk of cervical cancer and precancerous diseases in the oral HPV carriers. Zhonghua fu chan ke za zhi. 2013;48(8):611-6.
31. Rautava J, Syrjänen S. Human papillomavirus infections in the oral mucosa. The Journal of the American Dental Association. 2011;142(8):905-14.

32. Deo PN, Deshmukh R. Oral microbiome and oral cancer–the probable nexus. Journal of Oral and Maxillofacial Pathology: JOMFP. 2020;24(2):361.
33. Irani S. New insights into oral cancer—Risk factors and prevention: A review of the literature. International Journal of Preventive Medicine. 2020;11.
34. Yete S, D'Souza W, Saranath D. High-risk human papillomavirus in oral cancer: clinical implications. Oncology. 2018;94(3):133-41.
35. Elrefaey S, Massaro M, Chiocca S, Chiesa F, Ansarin M. HPV in oropharyngeal cancer: the basics to know in clinical practice. Acta Otorhinolaryngologica Italica. 2014;34(5):299.
36. Sand L, Jalouli J. Viruses and oral cancer. Is there a link? Microbes and infection. 2014;16(5):371-8.
37. Braz-Silva PH, de Rezende NPM, Ortega KL, de Macedo Santos RT, de Magalhaes MHCG. Detection of the Epstein–Barr Virus (EBV) by in situ hybridization as definitive diagnosis of hairy leukoplakia. Head and Neck Pathology. 2008;2:19-24.
38. Jalouli J, Jalouli MM, Sapkota D, Ibrahim SO, Larsson P-A, Sand L. Human papillomavirus, herpes simplex virus and epstein barr virus in oral squamous cell carcinoma from eight different countries. Anticancer research. 2012;32(2):571-80.
39. Guidry JT, Birdwell CE, Scott RS. Epstein–Barr virus in the pathogenesis of oral cancers. Oral diseases. 2018;24(4):497-508.
40. Al Moustafa A-E, Chen D, Ghabreau L, Akil N. Association between human papillomavirus and Epstein-Barr virus infections in human oral carcinogenesis. Medical Hypotheses. 2009;73(2):184-6.
41. Sand LP, Jalouli J, Larsson P-A, Hirsch J-M. Prevalence of Epstein-Barr virus in oral squamous cell carcinoma, oral lichen planus, and normal oral mucosa. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology. 2002;93(5):586-92.
42. Jiang R, Ekshyyan O, Moore-Medlin T, Rong X, Nathan S, Gu X, et al. Association between human papillomavirus/Epstein–Barr virus coinfection and oral carcinogenesis. Journal of Oral Pathology & Medicine. 2015;44(1):28-36.
43. Jain M. Assessment of correlation of herpes simplex virus-1 with oral cancer and precancer-a comparative study. Journal of Clinical and diagnostic research: JCDR. 2016;10(8):ZC14.
44. Meurman JH. Infectious and dietary risk factors of oral cancer. Oral oncology. 2010;46(6):411-3.
45. Zhao H, Chu M, Huang Z, Yang X, Ran S, Hu B, et al. Variations in oral microbiota associated with oral cancer. Scientific reports. 2017;7(1):11773.
46. Sami A, Elimairi I, Stanton C, Ross RP, Ryan CA. The role of the microbiome in oral squamous cell carcinoma with insight into the microbiome–treatment axis. International Journal of Molecular Sciences. 2020;21(21):8061.
47. Perera M, Al-Hebshi NN, Speicher DJ, Perera I, Johnson NW. The emerging role of bacteria in oral carcinogenesis: a review with special reference to perio-pathogenic bacteria. Journal of oral microbiology. 2016;8(1):32762.
48. Lee W-H, Chen H-M, Yang S-F, Liang C, Peng C-Y, Lin F-M, et al. Bacterial alterations in salivary microbiota and their association in oral cancer. Scientific reports. 2017;7(1):16540.
49. Karpiński TM. Role of oral microbiota in cancer development. Microorganisms. 2019;7(1):20.
50. Al-Hebshi NN, Borgnakke WS, Johnson NW. The microbiome of oral squamous cell carcinomas: a functional perspective. Current Oral Health Reports. 2019;6:145-60.
51. Zhang Y, Wang X, Li H, Ni C, Du Z, Yan F. Human oral microbiota and its modulation for oral health. Biomedicine & Pharmacotherapy. 2018;99:883-93.
52. Bansal R, Pallagatti S, Sheikh S, Aggarwal A, Gupta D, Singh R. Candidal species identification in malignant and potentially malignant oral lesions with antifungal resistance patterns. Contemporary clinical dentistry. 2018;9(Suppl 2):S309.
53. Glažar I, Prpić J, Muhvić-Urek M, Pezelj-Ribarić S. Identification of Candida spp. in the oral cavity in patients with malignant diseases. Vojnosanitetski pregled. 2017;74(11):1066-70.
54. Gall F, Colella G, Di Onofrio V, Rossiello R, Angelillo IF, Liguori G. Candida spp. in oral cancer and oral precancerous lesions. New Microbiol. 2013;36(3):283-8.
55. Piemonte ED, Lazos JP, Brunotto M. Relationship between chronic trauma of the oral mucosa, oral potentially malignant disorders, and oral cancer. Journal of oral pathology & Medicine. 2010;39(7):513-7.
56. Radoï L, Luce D. A review of risk factors for oral cavity cancer: the importance of a standardized case definition. Community dentistry and oral epidemiology. 2013;41(2):97-109.
57. Gupta AA, Kheur S, Varadarajan S, Parveen S, Dewan H, Alhazmi YA, et al. Chronic mechanical irritation and oral squamous cell carcinoma: A systematic review and meta-analysis. Bosnian Journal of basic medical sciences. 2021;21(6):647.
58. Pentenero M, Azzi L, Lodi G, Manfredi M, Varoni E. Chronic mechanical trauma/irritation and oral carcinoma: A systematic review showing low evidence to support an association. Oral diseases. 2022;28(8):2110-8.

59. Anura A. Traumatic oral mucosal lesions: a mini-review and clinical update. Oral Health Dent Manag. 2014;13(2):254-9.
60. Manoharan S, Nagaraja V, Eslick GD. Ill-fitting dentures and oral cancer: a meta-analysis. Oral oncology. 2014;50(11):1058-61.
61. Choi J-I, Seymour GJ. Vaccines against periodontitis: a forward-looking review. Journal of Periodontal & Implant Science. 2010;40(4):153-63.
62. Gholizadeh P, Eslami H, Kafil HS. Carcinogenesis mechanisms of Fusobacterium nucleatum. Biomedicine & Pharmacotherapy. 2017;89:918-25.
63. Hoare A, Soto C, Rojas-Celis V, Bravo D. Chronic inflammation as a link between periodontitis and carcinogenesis. Mediators of inflammation. 2019;2019.
64. Feller L, Altini M, Lemmer J. Inflammation in the context of oral cancer. Oral oncology. 2013;49(9):887-92.
65. Niklander SE. Inflammatory mediators in oral cancer: pathogenic mechanisms and diagnostic potential. Frontiers in Oral Health. 2021;2:642238.
66. Aivaliotis IL, Pateras IS, Papaioannou M, Glytsou C, Kontzoglou K, Johnson EO, et al. How do cytokines trigger genomic instability? Journal of Biomedicine and Biotechnology. 2012;2012.
67. Kim S-K, Park S-G, Kim K-W. Expression of vascular endothelial growth factor in oral squamous cell carcinoma. Journal of the Korean Association of Oral and Maxillofacial Surgeons. 2015;41(1):11.
68. Lee JJ, Chang YL, Lai WL, Ko JY, Kuo MYP, Chiang CP, et al. Increased prevalence of interleukin-17–producing CD4+ tumor-infiltrating lymphocytes in human oral squamous cell carcinoma. Head & neck. 2011;33(9):1301-8.
69. Keibel A, Singh V, Sharma MC. Inflammation, microenvironment, and the immune system in cancer progression. Current pharmaceutical design. 2009;15(17):1949-55.
70. Kawanishi S, Hiraku Y, Pinlaor S, Ma N. Oxidative and nitrative DNA damage in animals and patients with inflammatory diseases concerning inflammation-related carcinogenesis. 2006.
71. Madhura MG, Rao RS, Patil S, Fageeh HN, Alhazmi A, Awan KH. Advanced diagnostic aids for oral cancer. Disease-a-month. 2020;66(12):101034.
72. Jurel SK, Gupta DS, Singh RD, Singh M, Srivastava S. Genes and oral cancer. Indian Journal of human genetics. 2014;20(1):4.
73. Walter V, Yin X, Wilkerson MD, Cabanski CR, Zhao N, Du Y, et al. Molecular subtypes in head and neck cancer exhibit distinct patterns of chromosomal gain and loss of canonical cancer genes. PloS one. 2013;8(2):e56823.
74. Li C-C, Shen Z, Bavarian R, Yang F, Bhattacharya A. Oral cancer: genetics and the role of precision medicine. Surgical Oncology Clinics. 2020;29(1):127-44.
75. Ghias K, Rehmani SS, Razzak SA, Madhani S, Azim MK, Ahmed R, et al. Mutational landscape of head and neck squamous cell carcinomas in a South Asian population. Genetics and Molecular Biology. 2019;42:526-42.
76. Agrawal N, Frederick MJ, Pickering CR, Bettegowda C, Chang K, Li RJ, et al. Exome sequencing of head and neck squamous cell carcinoma reveals inactivating mutations in NOTCH1. Science. 2011;333(6046):1154-7.
77. He Y, Shao F, Pi W, Shi C, Chen Y, Gong D, et al. Large-scale transcriptomics analysis suggests over-expression of BGH3, MMP9, and PDIA3 in oral squamous cell carcinoma. Plos one. 2016;11(1):e0146530.
78. Kim S, Lee JW, Park Y-S. The application of next-generation sequencing to define factors related to oral cancer and discover novel biomarkers. Life. 2020;10(10):228.
79. Chen T-W, Lee C-C, Liu H, Wu C-S, Pickering CR, Huang P-J, et al. APOBEC3A is an oral cancer prognostic biomarker in Taiwanese carriers of an APOBEC deletion polymorphism. Nature communications. 2017;8(1):465.
80. Nakagaki T, Tamura M, Kobashi K, Omori A, Koyama R, Idogawa M, et al. Targeted next-generation sequencing of 50 cancer-related genes in Japanese patients with oral squamous cell carcinoma. Tumor Biology. 2018;40(9):1010428318800180.
81. Hong A, Zhang X, Jones D, Veillard A-S, Zhang M, Martin A, et al. Relationships between p53 mutation, HPV status, and outcome in oropharyngeal squamous cell carcinoma. Radiotherapy and Oncology. 2016;118(2):342-9.
82. Joo Y-H, Park S-W, Jung S-H, Lee Y-S, Nam I-C, Cho K-J, et al. Recurrent loss of the FHIT gene and its impact on lymphatic metastasis in early oral squamous cell carcinoma. Acta oto-laryngologica. 2013;133(9):992-9.
83. Cai Y, Yousef A, Grandis JR, Johnson DE. NSAID therapy for PIK3CA-Altered colorectal, breast, and head and neck cancer. Advances in biological regulation. 2020;75:100653.