Proceedings of the 4th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/61/20241450

Early Detection and Prevention of Oral Cancer: A Comprehensive Review

Ruiyang Zou

School of Stomatology, Nanchang University, Nanchang, China

zouruiyang@ncdx.wecom.work

Abstract. Despite significant advancements in cancer research, oral cancer remains a major global health challenge, particularly in high-risk regions such as India and Pakistan. This paper provides a comprehensive overview of various oral cancers, with a special focus on oral squamous cell carcinoma (OSCC), its risk factors, and early diagnostic methods. Key risk factors for OSCC include cigarette and cigar smoking, alcohol consumption, betel nut chewing, chronic inflammation, and human papillomavirus type 16 (HPV-16) infection. The paper evaluates various early detection methods, including self-examinations, professional screenings, biopsies, toluidine blue staining, fluorescence screening, and liquid biopsies. Additionally, the study highlights preventive measures, such as lifestyle modifications, HPV vaccination, regular health check-ups, and the dissemination of public health information. The paper emphasizes that progress in early detection and prevention strategies holds promise for reducing the incidence and mortality of oral cancer. By promoting awareness and encouraging regular screenings, the fight against this devastating disease can advance significantly, ultimately improving survival rates and quality of life for affected individuals.

Keywords: Oral squamous cell carcinoma (OSCC), Early detection, Risk factors, Prevention, HPV vaccination.

1. Introduction

Despite the significant progress in cancer research obtained over the past few decades, as of 2019, diseases classified as cancer continue to be among the primary reasons for mortality prior to reaching the age of 70 in 112 countries across the world [1]. According to the GLOBOCAN 2020 data, breast cancer is one of the most common with the proportion of 11.7% out of all new cancer cases, and lip and oral cancer are one of the most common cancers with the proportion of 2% out of all cancers. The incidence and mortality of these cancers are 2.1% and 1.8%, respectively. India and Pakistan are high-risk countries for oral cancer with oral cancer as one of the most common tumors that have been diagnosed more frequently than 25% of all other cancer cases and increase its incidence with age, reaching its highest incidence in the group of patients 60 years and older [1-3]. Oral cancer has emerged as a significant public health concern due to its high prevalence and fatality rates, and the disease has a higher incidence of in males relative to females; This situation may because of smoking and chewing betel nut, and carcinoma of the squamous cell variety represents the highest frequency within the category of oral cancer potential causes [2, 3]. For patients with oral cancer, not only the high cost of tumor treatment is an economic burden but also it leads to functional disorders such as muscles in face

DOI: 10.54254/2753-8818/61/20241450

and tongue, mandibular joint which brings inconvenience for mastication and deglutition so that intake food a shortness somewhat affects change appetite. Lack of calorie intake can also eventually result in malnutrition among patients [4]. In addition, tooth loss and poorly assembled dentures as a result of therapy-induced eating difficulties can also impact patients causing weight-loss [5]. Cancer of the mouth can also lead to a variety of psychological stress, such as face and speech difficulties caused by oral cancer that led patients fearing loss self-confidante without enough physique during talking. And even if gradually improved with treatment for many years later, various swallowing and speaking problems formed due to symptoms in head-neck region still affects patient furthermore when scar tissue generated locally after surgery will ultimately push these people into eating more hot soft food while avoiding foods which are steamy hard sour or spicy [4].

Due to its intervention nature, identification of oral cancer within all mouth cancers is essential for early detection and treatment to result has impact on reducing mortality rate of oral cancers as well as improving survival rates [6]. Oral cancer has a poor prognosis, with the 5-year survival rate only about 60%, implying that most patients are diagnosed at an advanced stage of the disease. Early diagnosis of this advanced cancer malignant tumor can save about 80% or more lives. However, if the diagnosis is delayed by more than one month before it is obtained, then it can increase for the patient to develop an advanced stage of oral cancer [3]. In addition, patients of advanced oral cancer had a poor prognosis because those are difficult to approach the tumor site especially for tumors in oropharynx [3]. Since oral cancer can develop from precancerous lesions, early detection is key to the practice of screening these patients even via a simple visual examination by an oral surgeon. Besides, the current clinical detection method for oral cancer can be divided into some categories such as biopsy, toluidine blue staining and saliva biomarker instant test; spontaneous fluorescence imaging [3, 7]. Hence, early screening and treatment can lead to a marked reduction in the incidence of invasive cancer with high quality-adjusted life years provided for at-risk populations due to decreased cost of treatments [7].

2. Types of Oral Cancer

2.1. Oral Squamous Cell Carcinoma

Oral squamous cell carcinoma (OSCC) constitutes the predominant form of cancer affecting the mouth, although we will expect to meet worse survival rate in later diagnosed cases but with improvement advance treatment technology, five years post- operative prognosis have increased notably [8]. In clinical practice, squamous cell carcinoma often has a continuous metastasis to neighboring lymph nodes and can be spread multiple places or systemic in the late stage of clinicopathology; The early symptoms may be mucosa leukoplakia, skin surface rough uneven followed by ulcers presented either dentition failure and hemorrhage or oral cavity facial pain with ulceration on top face appearance such as numbness pairs contradicting sometimes mixing together respectively that latter one is even more popular than former [9]. OCC accounts for 90% and originates from the squamous tissue, so named oral squamous epithelial cell carcinoma tumor formation by proliferating of squamous epithelial cells, which invade into superficial layer of connective tissues; pathological alteration in involved fluoride can be seen under microscope that cancer nest exists a stage process similar to classification image one with skin surface where granulation is flashing towards double wavelike [8].

HPV accounts for 2% to 8% of oral squamous cell carcinoma immune role, with HPV express viral oncoproteins that distinguishes it from other low risk and some high-risk HPV genotypes. Various studies have shown the importance of deregulating key tumor genes as means by which various tumorigenic human papillomavirus (bvHpvs) might contribute to initiation or progression in carcinogenesis. OCSCC is closely correlated with gene mutations and chromosomal abnormalities. Oncogenes like PIK3CA and the inhibitory genes such as FAT1 mutation, some other related to loss of alleles or abnormal amplification leads cancer cells lose its control effect on signal pathways maintain proliferation by acquiring unlimited cell growth. Moreover, by changing their surface antigens, they get to escape the immune system onslaught. Additionally, when the intracellular serine/threonine protein kinase MAPK is self-initiated also helping to cell growth and inhibiting endogenous cyclin-specific

DOI: 10.54254/2753-8818/61/20241450

inhibitor genes-thereby suppressing a cascade of apoptosis pathway [9]. Similar to other neoplasms, OCSCC results from the accumulation of a cascade of serial mutations leading towards cancerous growth [10].

Clinically, as only a fraction of the precancerous lesions (leukoplakia and erythroplakialike) goes on to develop into invasive cancer white or red patches [12], majority of these patients do not have previous clinic history findings regarding them, they often present directly with advanced OCSCC. Histologically, invasive OCSCC development occurs in an orderly fashion with well-defined steps beginning with epithelial hyperplasia that transitions through dysplasia and ultimately to invasion [11].

2.2. Other types of oral cancer

Mucinous epithelial carcinoma (MEC) represents a significant share of malignant tumors originating from the salivary glands, ranging from 2.8% to 15% of the total salivary gland cancer cases. Predominantly, this type of cancer develops in the parotid glands and the minor salivary glands, while the sublingual mucoid padding contributes to less than 1% of these instances. MEC is built of epithelial cells and mucus cells, usually in the parotid gland, presenting as a painless swelling at the floor of mouth with or without facial nerve involvement. MEC can occur at any age, with middle-aged men (30-60 years old) most commonly affected [12]. Bilaterally symmetrical, the usual clinical sign of MEC is an asymptomatic swelling on the floor of mouth, as an existing lesion within sublingual region may result in some discomfort. The criteria for MEC also include tongue pain and numbness.At a macroscopic level, MEC is usually small in size and partially encapsulated; under light microscopy, in addition to the epithelioid cells and intermediate cells seen in the affected area, more mucus-producing cells can be seen, and the hallmark of MEC is the presence of obvious cystic structures containing mature mucus cells, intermediate cells, or epithelioid cells, with the solid regions of the tumor not being obvious and usually containing prominent fibrous stroma [12]. MEC exhibits different biological behaviors and clinical characteristics based on tumor staging and grading, with high-grade MEC showing highly invasive behavior through lymphatic or hematogenous metastasis to the lung, liver, brain, and skin, while low-grade MEC also shows metastasis but mostly as benign tumors [12].

2.3. Oral Adenoid Cystic Carcinoma

Adenoid cystic carcinoma (ACC) is a less prevalent salivary gland tumor in both small and large glands than are other types of tumors. This condition prevails less frequently within the parotid organ, but is observed more regularly among the submandibular structures, the minor salivary tissues, and the mucous tissues. The most common malignant tumor in the sublingual gland is ACC, and mucinous epithelial carcinoma (MEC) is the next most frequent malignant growth[12,13]. ACC may also occur in other secretory glands in other tissues, such as the trachea and bronchi, esophagus, breast, lung, prostate, and skin [13]. ACC is less likely to involve regional lymph nodes but more often spreads hematogenously [13]. It invades early on neuroparenchyma, occurs locally often and has a high rate of delayed distant metastases, yet ACC is commonly seen as indolent with respect to its pathologic characteristics[13]. ACC can be subdivided into three histological groups based on the solid component of the tumor: trabecular, tubular, and solid. Some studies have shown that tumors with solid growth components are more likely to be lethal than those without solid growth components[13].

3. Risk Factors for Oral Cancer

The risk factors for oral cancer include extensive tobacco use (including electronic cigarettes), the chewing of betel nuts, excessive drinking, and persistent inflammation [3]. The occurrence of oral and oropharyngeal cancers attributed to HPV, primarily HPV16, has been rising in recent decades, especially among younger individuals [3]. There is a notable gender difference in oral cancer prevalence, often attributed to differing tobacco consumption habits and lifestyles. Individuals of the male gender are more commonly impacted, which can be attributed to their higher prevalence of tobacco and alcohol consumption, nonetheless, females who indulge in similar habits are at a higher risk of developing oral tumors in comparison to male individuals [2].

DOI: 10.54254/2753-8818/61/20241450

3.1. Smoking

Continuous exposure over an extended period to tobacco products increases the likelihood of suffering from oral squamous cell carcinoma (OSCC).Tobacco contains over 5,000 compounds, with many proven carcinogens, including polycyclic aromatic hydrocarbons (PAHs) and tobacco-specific nitrosamines (TSNAs) such as NNN (N-nitrosamine nicotine),NNK [4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone], and MNPN [3-(methylnitrosamine)propionitrile] [10, 14]. E-cigarettes also contain nitrosamines as primary carcinogens [10, 14]. These substances metabolize into reactive metabolites that form covalent DNA adducts, leading to gene mutations and other hereditary anomalies if DNA repair mechanisms fail [10]. Additionally, tobacco use induces inflammation in exposed tissues, increasing local cytokines, chemokines, and growth factors, which promote cell proliferation and carcinogenesis [10].

The use of tobacco impacts the oral microbiome composition, where certain microorganisms are capable of transforming tobacco compounds into carcinogens or procarcinogens. For instance, Candida can generate nitrosamines, while Candida, Neisseria, and Streptococcus may produce ethanol, a substance that can lead to the development of cancer [14]. Nitrate-reducing bacteria convert nitrates to nitrites, which react with alkaloids to form nitrosamines [14]. Non-tobacco smoking can transform a healthy oral microbiome into an inflammation-associated one, causing dysbiosis. This dysbiosis, particularly an increase in Streptococcus, Porphyromonas, and Fusobacterium abundance, is associated with periodontal disease and oral inflammations, contributing to OCSCC [14]. Alcohol exacerbates this process by affecting oncogenes involved in cancer development, damaging DNA repair mechanisms, and allowing the overexpression of certain oncogenes [15].

3.2. Alcohol

Alcohol dehydrates cells, enhancing the penetration of tobacco carcinogens into oral tissues. Heavy drinking also causes nutritional deficiencies, reducing the body's antioxidant defenses against cancer [15]. Certain alcoholic beverages contain chemical impurities such as N-nitrosodimethylamine in beer and PAHs in some whiskey brands, both carcinogenic [15]. The combined use of tobacco and alcohol significantly raises oral cancer risk, as alcohol dissolves carcinogenic compounds in cigarette smoke and increases the permeability of the oral epithelium [15].

3.3. HPV Infection

HPV, a DNA virus with an affinity for squamous epithelial cells, is a significant cause of OCSCC. The malignant potential of HPV types determines their classification as low-risk or high-risk. Precancerous squamous intraepithelial lesions that progress to cancer can be caused by high-risk HPV types including HPV16 and HPV18. During persistent HPV infection, the E2 protein of HPV controls the expression of the viral oncogenes E6 and E7 [16]. The proteins hinder the regulation of the cell cycle by neutralizing the tumor-suppressing functions of proteins pRb and p53. E7 protein interacts with pRb, leading to the liberation of the transcription factor E2F and thus advancing the cell cycle. Concurrently, p16 gene expression increases, making p16 a marker for high-risk HPV. Hence, p16 protein expression is used to determine the type of HPV infection in the oral cavity [16].

3.4. Other Factors

Other factors contributing to oral cancer include betel nut chewing, oral microorganisms, inflammation, and genetic predispositions. In countries like India and Southeast Asia, betel nut chewing, which involves betel alkaloids, is a leading cause of oral cancer. Betel alkaloids stimulate fibroblasts, leading to fibrosis of the reticular layer and eventually the submucosal layer, causing chronic fibrosis disorders that are precancerous lesions [3].

Oral microbial imbalance also plays a role in oral cancer development. Bacterial interactions within oral biofilms interfere with the production and utilization of E-cadherin and adhesion molecules, disrupt immune defenses, and influence proteolytic molecules and extracellular signal-regulated kinase activity. Pathogenic bacteria, such as Actinomyces, are prevalent in oral cancer patients and high-risk populations

DOI: 10.54254/2753-8818/61/20241450

[3, 17]. Genetic factors further increase oral cancer risk. For instance, individuals with Fanconi anemia (FA), a rare hereditary disease with impaired DNA repair, have a significantly elevated risk of developing OCSCC [10].

4. Early Detection of Oral Cancer

4.1. Oral self-examination

Early detection of oral cancer is feasible through visual inspection and palpation due to the frequent development of oral cancer in accessible areas.Detecting oral precancerous changes without professional healthcare assistance is possible through oral self-examination (MSE), a simple, non-invasive, and cost-effective method [18].The following nine steps are recommended for self-examination [19]:

- Observe the mucosal surfaces while closing the teeth and retracting the upper and lower lips in front of a mirror.
- Ispect the face and lips for symmetry, discoloration, or injuries.
- Open the mouth and use fingers or a palate expander to move the cheeks, examining the mucosal surfaces.
- Check the area beneath the lower teeth.
- Inspect the upper and lower surfaces by extending and retracting the tongue, then move it side to side to examine the lateral aspects.
- Using the tip of the tongue, touch the upper jaw and examine the underside and mucosal surface below the tongue.
- Move the tongue tip towards the upper jaw and examine the mucosal surface below by moving it left and right.
- Check the tongue tip towards the upper jaw and examine the mucosal surface below by moving it left and right.
- Examine the neck for any asymmetrical, lumpy, or discolored areas. Examine the Adam's apple, take a saliva sample, and check the neck for pain spots, including the jaw.

An oral surgeon can often detect suspicious lesions or symptoms in early-stage diagnosis. Professional early screening not only reduces the incidence of oral cancer but also improves survival rates. Typically, early oral cancer screening includes the detection of precancerous conditions [20].

4.2. Precancerous Conditions

Leukoplakia is categorized into homogeneous and heterogeneous types, with the latter being more common and mostly benign [3]. The early or thin leukopapa has grayish-white patches that are slightly raised and may be clearly bordered or blend in with the normal mucous membrane. As lesion progression continues, they thicken, become whiter, and may appear leathery with surface fissures [20]. Lesions with irregular surfaces are called granular or nodular leukoplakia, and verrucous leukoplakia is linked to warts or verrucas [20]. Verrucous leukoplakia has a higher chance of developing abnormal hyperplasia than thick homogeneous leukoplakia, which in turn has a higher chance of developing abnormal hyperplasia than thin leukoplakia. Hyperplasia or cancer are most likely to develop in individuals with speckled leukoplakia or mixed leukopapular lesions [20].

Oral red patches are most common in elderly men and appear as soft, velvety red patches or plaques. The soft palate, retropharyngeal area, floor of the mouth, and uvula are common sites [3, 20]. Lesion boundaries are usually well-defined but may blend into the surrounding mucosa. Some lesions may mix with white areas, forming red-white patches [20]. Although often asymptomatic, red patches can cause pain and a burning sensation, especially when mixed with white areas [3, 20]. Red patches, though less common than white patches, are more likely to show dysplasia or cancer [20].

Wickham's striae and hyperkeratotic patches or papules are the main characteristics of Wickham's striae type, which is the most common subtype of oral lichen planus (OLP)[3]. Malignant transformation is most likely to occur in Erosive OLP, followed by atrophic OLP, and network OLP has the lowest risk

DOI: 10.54254/2753-8818/61/20241450

[3]. Submucous fibrosis is a chronic fibrotic lesion of the oral mucosa, potentially a response to chronic injury and wound overhealing, with an estimated 9% malignancy transformation rate [3]. It is characterized by loss of tissue elasticity, affecting tongue mobility and limiting mouth opening. The buccal mucosa is most commonly affected, followed by the tongue, lips, palate, and gingiva [3].

4.3. Existing Detection Techniques

The biopsy remains the gold standard for diagnosing oral diseases, involving the removal of tissue samples for histopathological examination [21]. Techniques include incisional, excisional, punch, and electrosurgical or laser biopsy, with brush biopsy serving as an auxiliary method [21]. Toluidine blue staining, a cost-effective and convenient detection technique, involves staining underdeveloped epithelial areas with a pinkish-blue color using a 1% toluidine blue solution after clearing the oral cavity with 1% acetic acid [3]. Fluorescence screening technology, a non-invasive method, uses fluorescent dyes to detect abnormal tissues. This process involves spraying a fluorescent dye on the oral mucosa and capturing images under ultraviolet light with a special camera, helping identify lesions requiring biopsy by highlighting the loss of green fluorescence in abnormal hyperplasia and cancerous tissues [3].

Oral liquid biopsy, particularly saliva biomarker analysis, represents a novel, non-invasive cancer diagnostic method. This technique aims to detect various saliva molecules, including proteins, RNA, micro-RNA, metabolites, and microbiome components, which serve as cancer biomarkers [3, 22]. Despite the advantages of these advanced techniques, surgical biopsy remains essential for definitive diagnosis, although it may cause patient anxiety, tissue damage, bleeding, and infection risks [3, 21]. Toluidine blue and fluorescence techniques also have limitations in sensitivity and specificity, as benign conditions can cause similar tissue fluorescence changes [3]. Liquid biopsy offers precision with minimal harm, aiding in monitoring minimal residual disease and recurrence detection. The discovery of specific circulating biomarkers across different oral cancer stages will enhance diagnosis and prognosis [22].

5. Prevention Measures for Oral Cancer

5.1. Changing Lifestyle Habits

Globally, many cases of oral cancer are attributed to the use of tobacco and betel nut products, which are modifiable risk factors [10]. Quitting smoking can significantly reduce the risk. Personalized smoking cessation plans should be provided based on an individual's smoking history and habits, incorporating behavioral and psychological support, appropriate cessation advice, and follow-up actions [10]. Nicotine replacement therapy and non-nicotine medications such as bupropion can enhance the likelihood of successful cessation [10]. Similarly, betel nut addiction requires further research to understand its biological basis and develop effective quitting strategies. Addicts should be informed about the oral health risks of betel nut and encouraged to cooperate with treatment efforts [10].

Maintaining a healthy diet is also crucial for oral cancer prevention. Diets that promote chronic inflammation can increase cancer risk, while those rich in fruits, vegetables, vitamins, and minerals can support apoptosis initiation and tumor gene suppression. Many dietary products contain antioxidants and anti-proliferative vitamins that enhance the immune system through synthesis and DNA methylation [23]. Compounds such as sugar acids and indole-3-carboxaldehyde in vegetables are believed to have anti-cancer properties by eliminating reactive oxygen species and repairing DNA damage. For example, beta-carotene is an antioxidant that reduces reactive oxygen species and prevents DNA damage [23]. Therefore, incorporating fruits and vegetables into the diet can reduce oral cancer risk, serving as a "green prevention" method [23]. Additionally, maintaining oral hygiene is essential to preserve the stability of the oral microbiome and avoid increasing cancer risk due to microbiome instability [17].

5.2. Regular Check-Ups

The stage of oral cancer at diagnosis is a significant factor in determining the survival rate of patients. In the case of regional spread or distant metastasis, SEER data from the National Cancer Institute (1973-

DOI: 10.54254/2753-8818/61/20241450

1988) shows that the survival rate decreases by 46.4% to 46.4% and 21.1% respectively. Regular check-ups facilitate early diagnosis, significantly improving survival rates. High-risk individuals should follow targeted screening plans to detect the disease at an asymptomatic stage. A study in India found that oral cancer mortality decreased significantly among high-risk individuals who were examined by trained health care professionals. Thus, educating high-risk individuals about oral self-examination and encouraging regular professional examinations are crucial [19, 20].

5.3. HPV Vaccination

Three preventive HPV vaccines have been approved: a bivalent vaccine for women aged 9-26, a quadrivalent vaccine for women and men aged 9-26, and a nine-valent vaccine for women and men aged 9-45,all three vaccines are effective against HIV-16 and HIV-18 [10]. Studies show that HPV vaccination significantly reduces oral HPV infections. In Costa Rica, a Phase III trial found that HPV-16 or HPV-18 oral infections can be prevented with a 93% success rate. The NHANES data (2009-2014) revealed lower type-specific oral HPV infection rates among vaccinated young adults compared to unvaccinated individuals [10]. Thus, HPV vaccination, particularly with the nine-valent vaccine, can help prevent HPV-related oral diseases and reduce oral cancer incidence.

5.4. Policy Development

The World Health Organization recommends four cost-effective national policy interventions to reduce tobacco consumption: increasing taxes on tobacco products, implementing large graphic warnings on cigarette packaging, banning all tobacco advertising, and enforcing a comprehensive public smoking ban. These policies can help reduce smoking rates and control tobacco use [10]. Additionally, health education programs for the public, especially high-risk groups, can promote good oral hygiene, regular self-examinations, and early disease detection [19].

6. Conclusion

Oral cancer, including oral squamous cell carcinoma (OSCC), mucoepidermoid carcinoma, and adenoid cystic carcinoma of the salivary glands, is a significant public health concern.OSCC, the most frequent type, is highly malignant and has a high risk of metastasis, which causes a low global survival rate and poor prognosis.It is crucial to detect and prevent early.Early-stage lesions can be identified by self-examination and professional oral examinations, along with advanced detection techniques like fluorescence screening and toluidine blue staining, which can significantly reduce mortality and improve survival rates.

Preventing oral cancer involves addressing risk factors such as smoking, alcohol consumption, and betel nut use, and promoting HPV vaccination. Maintaining a healthy diet and good oral hygiene also contribute to risk reduction. Despite advances in detection technologies, public awareness about the dangers of oral cancer and the importance of oral health remains inadequate. Public education campaigns are needed to encourage high-risk individuals to avoid harmful behaviors, seek regular oral health assessments, and participate in cancer screening.

Current detection technologies have limitations, such as low sensitivity and specificity in some methods, and traditional biopsies can damage healthy tissues. While liquid biopsy technology offers high precision, it is complex, costly, and still under research. Therefore, further improvements in oral cancer detection technologies are necessary. Additionally, policies regulating tobacco and alcohol sales and raising public awareness about their risks can enhance preventive measures and reduce oral cancer incidence.

References

[1] Sung, H., Ferlay, J., Siegel, R. L., et al. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin., 71(3), 209-249.

[2] Gupta, N., Gupta, R., Siegel, R. L., et al. (2016). Changing Trends in oral cancer - a global scenario. Nepal J Epidemiol., 6(4), 613-619.
[3] Abati, S., Bramati, C., Bondi, S., et al. (2020). Oral Cancer and Precancer: A Narrative Review on the Relevance of Early Diagnosis. Int J Environ Res Public Health., 17(24), 9160.
[4] Gellrich, N-C., Handschel, J., Holtmann, H., et al. (2015). Oral Cancer Malnutrition Impacts Weight and Quality of Life. Nutrients., 7(4), 2145-2160.
[5] Nordgren, M., Hammerlid, E., Bjordal, K., et al. (2008). Quality of life in oral carcinoma: A 5-year prospective study. Head Neck, 30, 461–470.
[6] Walsh, T., Liu, J. L., Brocklehurst, P., et al. (2013). Clinical assessment to screen for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults. Cochrane Database Syst.
[7] Brocklehurst, P., Kujan, O., O'Malley, L. A., et al. (2013). Screening programmes for the early detection and prevention of oral cancer. Cochrane Database Syst.
[8] Chamoli, A., Gosavi, A. S., Shirwadkar, U. P., et al. (2021). Overview of oral cavity squamous cell carcinoma: Risk factors, mechanisms, and diagnostics. Oral Oncol., 121, 105451.
[9] Wong, T., Wiesenfeld, D. (2018). Oral Cancer. Aust Dent J., 63 Suppl 1, S91-S99.
[10] Feller, G., Khammissa, R. A. G., Ballyram, R., et al. (2023). Tumour Genetic Heterogeneity in Relation to Oral Squamous Cell Carcinoma and Anti-Cancer Treatment. Int J Environ Res Public Health., 20(3), 2392.
[11] Johnson, D. E., Burtness, B., Leemans, C. R., et al. (2020). Head and neck squamous cell carcinoma [published correction appears in Nat Rev Dis Primers. 2023 Jan 19;9(1):4. doi: 10.1038/s41572-023-00418-5]. Nat Rev Dis Primers., 6(1), 92.
[12] Maloth, A. K., Nandan, S. R., Kulkarni, P. G., et al. (2015). Mucoepidermoid Carcinoma of Floor of the Mouth - A Rarity. J Clin Diagn Res., 9(12), ZD03-ZD4.
[13] Cantù, G. (2021). Adenoid cystic carcinoma. An indolent but aggressive tumour. Part A: from aetiopathogenesis to diagnosis. Acta Otorhinolaryngol Ital., 41(3), 206-214.
[14] Saxena, R., Prasoodanan, P. K. V., Gupta, S. V., et al. (2022). Assessing the Effect of Smokeless Tobacco Consumption on Oral Microbiome in Healthy and Oral Cancer Patients. Front Cell Infect Microbiol., 12, 841465.
[15] Madani, A. H., Dikshit, M., & Bhaduri, D. (2014). Interaction of alcohol use and specific types of smoking on the development of oral cancer. Int J High Risk Behav Addict., 3(1), e12120.
[16] Hübbers, C. U., Akgül, B. (2015). HPV and cancer of the oral cavity. Virulence., 6(3), 244-248.
[17] Lim, Y., Fukuma, N., Totsika, M., et al. (2018). The Performance of an Oral Microbiome Biomarker Panel in Predicting Oral Cavity and Oropharyngeal Cancers. Front Cell Infect Microbiol., 8, 267.
[18] Shrestha, G., Maharjan, L. (2020). Mouth Self-Examination for Prevention and Control of Oral Cavity Cancer. JNMA J Nepal Med Assoc., 58(225), 360-362.
[19] Jornet, P. L., Garcia, F. J., Berdugo, M. L., et al. (2015). Mouth self-examination in a population at risk of oral cancer. Aust Dent J., 60(1), 59-64.
[20] Neville, B. W., Day, T. A. (2002). Oral cancer and precancerous lesions. CA Cancer J Clin., 52(4), 195-215.
[21] Avon, S. L., Klieb, H. B. (2012). Oral soft-tissue biopsy: an overview. J Can Dent Assoc., 78, c75.
[22] Lousada-Fernandez, F., Rapado-Gonzalez, O., Lopez-Cedrun, J. L., et al. (2018). Liquid Biopsy in Oral Cancer. Int J Mol Sci., 19(6), 1704.
[23] Rodríguez-Molinero, J., Migueláñez-Medrán, B. D. C., Puente-Gutiérrez, C., et al. (2021) Association between Oral Cancer and Diet: An Update. Nutrients., 13(4), 1299.