Oral Cancer: An Integrated Preventive Dentistry and Oral Medicine Approach

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Abstract

Oral cancer represents a significant global health problem with increasing incidence and mortality worldwide. Despite advances in diagnostic and therapeutic strategies, survival rates remain relatively low, primarily due to late diagnosis and insufficient awareness of risk factors. This review aims to highlight the importance of prevention, early detection, and comprehensive management of oral cancer through an integrated preventive dentistry and oral medicine approach. The article discusses the epidemiology of oral cancer, major etiological factors such as tobacco use, alcohol consumption, human papillomavirus infection, poor oral hygiene, and dietary influences. Additionally, it reviews oral potentially malignant disorders (OPMDs), which represent an important stage in the development of oral malignancies. Diagnostic approaches including clinical examination, vital tissue staining, biopsy, imaging techniques, and emerging diagnostic tools such as salivary biomarkers and spectroscopy are also discussed. Furthermore, current treatment modalities including surgery, radiotherapy, chemotherapy, and immunotherapy are summarized. Early diagnosis and preventive strategies remain essential for improving survival outcomes and reducing disease burden. Enhancing public awareness, promoting healthy lifestyles, and strengthening screening programs are critical steps in controlling oral cancer and improving patient prognosis.

1.Introduction

ancer of the oral mucosa originates from the mucosa lining of various structures within the oral cavity, including the lips, cheeks, teeth, gums, anterior two-thirds of the tongue, the floor of the mouth, the hard palate, and the retromolar trigone posterior to the wisdom teeth. The oral cavity shares a close anatomical relationship with the oropharynx, delineated by key boundaries such as the lower edge of the soft palate, the division between the anterior two-thirds and posterior one-third of the tongue, and the anterior pillars of the tonsils. This helps distinguish oral cavity structures, particularly the soft palate, from oropharyngeal structures, such as the faucial and lingual tonsils (the tongue base), aiding in accurate diagnosis and treatment planning. [1]

2. Overview of Oral Cancer

Cancers of the lip and oral cavity are a significant global health concern, with 389,485 new diagnoses and 188,230 deaths estimated in 2022 [**2**]. In addition, general awareness of the formation of this type of cancer and its risk factors in developing countries is low. A survey conducted in Beijing in the years 2018–2019 showed that about half of the respondents had never heard of this type of cancerous lesion, which should be alarming [3]. In developed countries, the situation is better, with 81% aware of oral cancer among the population [**4**]. It is a very important factor, as up to 46% of oral cancer cases are preventable [**5**]. An essential preventive measure is to also spread awareness about risk factors such as poor oral hygiene, smoking cigarettes, and low-nutritional diet [**6**]. Data show that annual medical examinations and early diagnosis of malignant lesions provide up to 90% chances of survival after treatment, stressing the importance of raising public awareness [**7**]. A study in Brazil involving 505 oral cancer patients highlighted a significant difference in outcomes: The five-year survival rate was 74.0% for those diagnosed at stage 1 or 2 but dropped to just 36.2% for patients at stage 3 or 4 [**8**]. Therapy commonly involves complete surgical removal of the tumor [**9**,**10**,**11**]. Even though the 5-year survival rate is increasing, it remains between 50% and 60%, which is still low compared to other types of cancer and indicates the need of improvement in the areas of spreading awareness, enhancing diagnostics, and creating new effective forms of medical therapy [**12**].This gap in organized programs can be attributed to various knowledge deficiencies concerning the natural progression of oral precancer and the clinical handling of individuals with precancerous conditions [**13**]. One of the most common lip cancers is *Squamos cell carcinoma*, with its typical location on the lower lip, between midline and mouth corner[**14**].

3.Oral Potentially Malignant Disorders (OPMD)

Compared to healthy oral mucosal tissue, potentially malignant oral disorders show a higher risk of cancer transformation, especially into squamous cell carcinoma [15]. Patients diagnosed with OPMDs exhibit an elevated probability of developing oral cancer at any site within the oral cavity over the course of their lifetime. Although the majority of these OPMDs may not progress to carcinoma, they represent a field of abnormal cellular changes, within which the likelihood of cancer development is higher compared to clinically normal mucosa and significantly greater than in individuals without these disorders [16] The most common observed lesions can be divided into leukoplakias (OL), oral leukoerythroplakias, oral erythroplakias, and actinic keratosis [17]. Over the years, many definitions have emerged to define the condition known as leukoplakia [**18**]. In 2007, Warnakulasuriya et al. proposed that any white patch on the mucosa that cannot be characterized as any other abnormality should be described as such a lesion [**19**]. Based on the clinical appearance, there are three types of oral leukoplakia: homogeneous, non-homogenous, and verrucous, considering the fact that the first one occurs most often [**20**]. The formation of these lesions can be linked to such risk factors as smoking tobacco or drinking alcohol [**21**]. The OL prevalence in the general population is approximately 2%. This figure tends to rise in higher proportions among older age demographics [**22**]. In most cases, these lesions do not cause symptoms. In the remaining situations, patients experience rough spots on the mucosa and sometimes some burning sensations [**23**]. Proliferative verrucous leukoplakia stands out as a specific type of oral lesion with an unusually high risk of developing an oral malignant neoplasia [**24**,**25**]. It was confirmed that patients with multiple oral cancers are more likely to be diagnosed with new malignments in a shorter period of time than previously healthy patients or those with a single cancer [25]. To assess the risk of malignant transformation in oral precancerous lesions, an evaluation of the degree of dysplasia can be used. More than half of the potentially malignant lesions show no signs of abnormality at the level of the structural and cytological characteristics of the epithelium [**20**,**26**]. Individuals falling into this group may undergo a comprehensive monitoring initiative administered by dentists as part of their regular check-up routine [**27**]. Lesions occurring on the tongue and floor of the mouth should merit special attention and thorough diagnostics due to the fact that a large number of neoplastic transformations occur in these locations. This can also be linked to the greater percentage of OPMD with a high degree of dysplasia, such as a moderate or severe stage, at these sites [**28**].Erythroplakia is acknowledged as a highly critical oral premalignant condition, demonstrating a significant likelihood of severe dysplasia or carcinoma, with prevalence rates typically falling within the range of 80% to 90% [**29**]. Fortunately, this type of lesion occurs very rarely [**17**,**30**].

4. Epidemiology

The difficulty in systematizing data on the epidemiology of oral cancers is that they belong to the group of head and neck cancers (HNC), which means that a large amount of research is focused not only on oral cancer but also on that of the nasopharynx, oropharynx, salivary glands, tonsils, and others.

The growing number of cases in European countries, particularly in developed nations, could be attributed to improved early cancer detection and increased exposure to risk factors. It has been observed that cancer incidence and mortality rates tend to be higher in countries with a low and medium Human Development Index (HDI), as rapid socio-economic growth leads to the adoption of unhealthy lifestyles, behaviors, and environmental factors. A review of substance use across different regions found that tobacco smoking and alcohol consumption are major risk factors for oral cavity cancer in Europe. In Melanesia, South-Central Asia, and South-Eastern Asia, the widespread practice of betel quid chewing may contribute to the high prevalence of this cancer. Meanwhile, in parts of Oceania, particularly Australia and New Zealand, sun exposure has been identified as the most significant risk factor associated with the region [31]. A significant role in the increased incidence of head and neck cancer in European countries and USA has been attributed to oropharyngeal cancers linked to HPV infections [32]. The variability in incidence in highly developed countries is interesting.

5. Risk Factors and etiology

Understanding the multifaceted etiology of oral cancer is paramount for effective prevention and early detection. Various risk factors, including tobacco and alcohol use, HPV infection, and stem cell transplants, contribute to the development of oral malignancies, highlighting the importance of comprehensive awareness and intervention strategies.

5.1. Tobacco

Smoking tobacco is the greatest risk factor for developing oral cancer due to carcinogenic chemicals, including nitrosamines, benzopyrenes, and aromatic amines [33]. The risk of developing oral cancer is 3 times higher in smokers compared with non-smokers. Individuals are also at risk from secondary passive smoking environments, particularly with chronic second-hand exposure. [34] The results of studies demonstrate a synergistic relationship with alcohol consumption, resulting in a higher risk of malignancy.[35] Chewing betel quid, also known as "pan" or "paan," involves a mixture of betel leaf, areca nut, slaked lime, and tobacco, which is then chewed. This widespread practice in South Asia and parts of Micronesia is linked to a higher risk of malignancy compared to smoking tobacco alone due to prolonged exposure of carcinogens to cells in the mouth.[36] Snuff/snus is a moist form of smokeless tobacco often placed under the upper lip for extended periods. This habit is prevalent in Scandinavia and North America.[37]

5.2. Alcohol

Alcohol consumption, especially when combined with smoking, elevates the risk of oral cancer. Although ethanol is not a carcinogenic substance, it enhances the permeability of the oral mucosa, making it more susceptible to damage from other carcinogens.[38]

5.3. Human Papillomavirus

HPVs, mainly types 16 and 18, are associated with malignancies, notably cervical cancer and oropharyngeal cancer, especially tonsillar and base of tongue tumors. Although the association with oral cancers is not as well-established, some evidence supports such a connection. In the oral cavity, HPV infection is 4 times more likely in individuals with squamous cell carcinomas compared to those with healthy mucous membranes.[39] The primary mode of infection transmission is through oral sexual contact.

5.4. Stem Cell Transplants

Individuals who have undergone hematopoietic stem cell transplants face a significantly increased risk of developing oral cancer, ranging from 4 to 7 times higher than that of the general population. The development of graft-versus-host disease in the oral cavity often precedes the onset of cancer. Common symptoms include mucositis, xerostomia, and lichenoid changes. Notably, oral cancers most frequently arise in the tongue and salivary glands approximately 5 to 9 years after transplant.[40] Moreover, due to the immunosuppressive nature of the regimen, solid organ transplant recipients also experience heightened susceptibility to oral cavity malignancies.[41]

5.5. Diet

Increased risk of oral cancer is also related to eating certain foods, mostly including those rich in pro-inflammatory factors. A pro-inflammatory diet causes prolonged inflammation, which may promote developing cancer in different parts of the body and also in the oral cavity [**42**]. Diets with high DII (dietary inflammatory index) increase levels of cytokines and other inflammatory biomarkers that intervene in the initiation and promotion of the cancer [**43**]. Thus, products that may contribute to the development of cancer include, for example, red and processed meat, refined grains, simple sugars, eggs, and high-fat dairy [**44**,**45**]. It has been proven that drinking very hot tea or eating spicy food also may increase risk of oral cancer [**6**]. On the other hand, there is a group of foods that may prevent oncogenesis. These include citrus fruits, yellow fruits and vegetables, blackberries, cranberries, products rich in omega 6 and 3 acids, garlic, curcumin, and many more [**6**,**46**,**47**,**48**,**49**].

5.6. Oral Hygiene

Inadequate oral hygiene leads to the accumulation of pathological plaque, of which bacteria are a major component [**50**].The results show that tooth brushing is associated with a reduced risk of oral cancer. Moreover, with each additional daily brushing, the risk of oral cancer has been shown to decrease by 6% [**51**].

6. Diagnostics

It is widely known that diagnostic delay is related to lack of public knowledge about precancerous lesions, oral cancer symptoms, and risk factors. The World Health Organization has indicated early detection as a fundamental effort to control the risk of oral cancer [52]. Unfortunately, it is quite difficult and requires a lot of knowledge, awareness, and experience from the examiner to diagnose this type of lesion during a standard clinical oral examination (COE) [53].

6.1.History and Physical

Oral mucosal cancer presents with varied clinical manifestations depending on its location. In its early stages, it may manifest as irregular white, red, or mixed patches on the mucosa. As the cancer progresses, more advanced cases often exhibit an indurated raised nodule with an ulcerated surface. Location-specific symptoms may include dysarthria or difficulty protruding the tongue fully if the cancer affects the tongue area, causing tethering or pain. Cancer situated in the alveolar ridge may lead to loose adjacent teeth. Furthermore, as the cancer spreads locally or systemically, patients may experience dysphagia, odynophagia, hoarse voice, otalgia, weight loss, and lymphadenopathy.

6.2. Vital Tissue Staining

Toluidine blue (TB) staining is an auxiliary, non-invasive technique commonly used during the COE. The dye utilized in this method stains cells that contain an increased amount of DNA or RNA, which is useful to identify lesions with possible malignant changes on the oral mucosa. This staining involves using a dye of 1% methylene blue, 1% malachite, 0.5% eosin, glycerol, and dimethyl sulfoxide. The more DNA there is in the cell, the more intensely the lesion will be stained [**55**].. Due to certain limitations regarding the probability of false-negative results and the questionable specificity and sensitivity of this method, it was suggested to consider for biopsy every lesion that tests positively with TB stain [**55**,**56**]

6.3. Biopsy

A biopsy is a crucial step in the initial investigation of oral lesions. Many lesions can be biopsied in an outpatient clinic if they are well-tolerated and easily accessible. Ultrasound-guided fine-needle aspiration may be performed for associated lymphadenopathy. However, for lesions located at the tongue base or more posterior regions, an examination under general anesthesia is necessary to obtain a tissue sample for histological analysis.[54]

6.4. Salivary Biomarkers

Salivary biomarkers are substances or molecular entities present in saliva that can serve as indicators of various physiological or pathological conditions, including oral cancer. The study of salivary biomarkers in oral cancer diagnostics is an area of active research and may hold promise for non-invasive and early detection of oral cancer [**57**,**58**]. Among the studied salivary biomarkers, various types of substances, such as proteins, DNA, RNA, and exosomes, are being investigated [**59**]. Specific biomarkers, e.g., CA 125, CA 15-3, IL-8, p53, and microRNA, have undergone analysis to determine their diagnostic potential. Standardizing analysis methods, eliminating confounding factors, and validating results are crucial for the success of salivary biomarkers in the diagnosis of oral cancer [**60**].

6.5. Colposcopy

While colposcopy is traditionally employed for examining the cervix and vaginal tissues, recent studies have brought attention to its potential application in the field of oral oncology. Given the similarities in anatomy and cancer types between the oral cavity and cervix, acetic acid appears to be a suitable clinical marker for detecting oral cancer as well.

6.6.Imaging

Computed tomography (CT) scans with intravenous (IV) contrast are essential for thorough assessment. They evaluate the local extent of the tumor and its involvement in the bone or adjacent structures, lymph nodes, and chest.

6.7. Spectroscopy

Spectroscopy plays a significant role in oral cancer diagnostics, offering a non-invasive and rapid method for analysing tissues and detecting abnormalities. Importantly, spectroscopy contributes to early cancer detection by identifying pre-cancerous lesions and detecting cancers in their initial stages [**61**,**62**]. Moreover, it assists in surgical procedures by offering real-time assessment of surgical margins during tumor removal surgeries, ensuring the comprehensive removal of cancerous tissue. As technology advances and becomes more accessible, spectroscopy may play a crucial role in population-wide screening programs for oral cancer, further emphasizing its potential impact on improving early detection and treatment outcomes [**61**].

7.Treatment / Management

Early-stage cancers (stage I or II) typically undergo single-modality therapy, which may involve surgery (excision of the primary tumor with margins along with elective or therapeutic neck dissection) or radiation therapy (targeting the primary tumor site and at-risk nodal basins of the neck). Primary surgery offers improved local control and reduced morbidity in oral cavity cancers compared to non-surgical treatments, which is not often seen in other head and neck cancer sites.[62]. Late-stage cancers (stage III or IV), on the other hand, necessitate multimodality therapy. Surgical intervention may be followed by radiation therapy (with or without chemotherapy or immunotherapy) or a combination of chemotherapy and immunotherapy, as well as radiation therapy.

7.1. Surgery

The extent of surgical intervention is contingent upon factors such as tumor size, location, and stage. Typically, it involves a wide local excision with an oncologic margin. Tumors affecting the tongue are treated with glossectomy, which can be partial or total. Tumors located in the buccal mucosa or soft palate are managed with wide local excision, while tumors of the hard palate require maxillectomy. Mandibular alveolar tumors are addressed with wide local excision and mandibulectomy; marginal mandibulectomy suits superficial tumors, whereas segmental mandibulectomy is reserved for deep or advanced tumors. Lip tumors are managed with wide local excision or wedge excision.

7.2. Radiotherapy

Radiotherapy is a primary treatment modality used alongside surgery and chemotherapy or immunotherapy. This targets the primary tumor site and any nodal basins at risk for metastasis. However, radiation in the head and neck region often results in significant mucositis, leading to odynophagia and potential nutritional challenges.

7.3. Chemotherapy

The cornerstone of treatment for head and neck cancer involves platinum-based chemotherapy, such as cisplatin or carboplatin. Chemotherapy is not used as a standalone curative treatment but rather in conjunction with radiation therapy. Additionally, chemotherapy is commonly utilized as an adjunct to palliative care interventions.

7.4.Immunotherapy

Cetuximab, an epidermal growth factor receptor inhibitor, can be combined with radiotherapy for treatment. Additionally, monoclonal antibodies such as pembrolizumab target specific genetic receptors on tumor cells. This approach is commonly applied to locally advanced, recurrent, or metastatic diseases. Similar to chemotherapy, immunotherapy is not used as a standalone curative treatment but is valuable for palliative care interventions.[63]

7.5. Immunotherapy and Chemotherapy Combination

The tumor immune microenvironment can be categorized as “hot” or “cold” by observing the distribution of immune cells. An immunologically “hot” tumor has distributed immune cells, while a “cold” tumor lacks them [**64**]. Immune checkpoint inhibitors alone are most effective against “hot” tumors. “Cold” tumors require other therapies, such as chemotherapy, to recruit the immune cells to the tumor tissue (convert the tumor from “cold” to “hot”), making immunotherapy effective [**65**]. In line with this theory, new combinations of immuno- and chemotherapy (pembrolizumab + docetaxel and pembrolizumab + lenvatinib) have been tested and expressed promising positive effects with minimal side effects in oral cancer treatment [**66**,**67**,**68**]

7.6. Palliation

When aggressive or advanced tumors or significant comorbidities prevent curative treatment, a palliative approach is the most suitable option for patients. This typically includes palliative radiotherapy alongside anticipatory medications aimed at symptom management and optimizing end-of-life care.

7.7.Posttreatment Follow-Up

Patients with oral cancer are at risk for developing loco-regional recurrences and second malignancies. After completion of the treatment, patients should be followed up at regular intervals to detect any signs of recurrence. Patients should be encouraged to give up tobacco and alcohol and know the signs and symptoms of recurrence.

8. Prognosis

Prognosis and survival rates in cancer depend significantly on the stage at diagnosis, timely and appropriate treatment, and the expertise of local healthcare providers. Patients' 5-year survival rates decrease notably when the disease spreads locally and even further if distant metastases develop. These trends underscore the critical importance of early detection and diagnosis in improving outcomes and survival rates.Recurrence is associated with significantly high mortality rates, and early recurrence is typically indicative of a poorer prognosis.[70]

9. Complications

Complications in oral mucosal cancer can arise from untreated disease progression or commonly from the adverse effects of treatment interventions. Surgical procedures, such as tumor excision, neck dissection, and free flap reconstruction, carry inherent risks, which include flap failure, wound dehiscence, damage to local motor and sensory nerves, vocal cord paralysis, trismus, dysarthria, and potential long-term reliance on tracheostomy and/or feeding tubes. These complications may necessitate an extended stay in intensive care for some patients. [71]

10. Prevention of Oral Cancer

STEPS TO PREVENT ORAL CANCER:

1. Avoid Tobacco in All Forms: The single most effective step to prevent oral cancer is to avoid tobacco use. For those who currently use tobacco, quitting is crucial. Numerous resources, including counseling, nicotine replacement therapies, and medications, are available to help individuals quit.
2. Limit Alcohol Consumption: Moderating alcohol intake can significantly reduce the risk of oral cancer. For those who drink, it is recommended to do so in moderation, which means up to one drink per day for women and up to two drinks per day for men.
3. HPV Vaccination: The HPV vaccine is highly effective in preventing infections from the strains of HPV most commonly associated with cancer. Vaccination is recommended for preteens but can be given up to age 45.
4. Maintain a Healthy Diet: A diet rich in fruits and vegetables can help protect against oral cancer. These foods provide essential nutrients that support the immune system and help prevent cellular damage.[72]
5. Protect Against UV Exposure: To prevent lip cancer, it is important to use lip balms with SPF, wear hats, and avoid excessive sun exposure, especially during peak hours.
6. Regular Dental Checkups: Regular visits to the dentist play a crucial role in the early detection of oral cancer. Dentists can spot early signs of cancer, such as white patches (leukoplakia) or unusual sores, which can be further investigated.
7. Oral Hygiene: Good oral hygiene practices, including regular brushing and flossing, help maintain overall oral health and can reduce the risk of infections and other conditions that may contribute to cancer development.[73]
8. Avoid Excessive Use of Mouthwash with Alcohol: Some mouthwashes contain high levels of alcohol, which may increase the risk of oral cancer with excessive use. Opt for alcohol-free mouthwash or use it sparingly.[74]

Oral cancer prevention involves a combination of lifestyle choices, regular screenings, and awareness of risk factors. Avoiding tobacco products, including smoking and chewing tobacco, is crucial as these are the leading causes of oral cancer. Limiting alcohol consumption also reduces risk, especially when combined with tobacco use, which significantly increases the likelihood of developing the disease.[75] A diet rich in fruits and vegetables, particularly those high in antioxidants, can help protect oral tissues from damage. Regular dental checkups and self-examinations are essential for early detection as they allow for the identification of precancerous conditions or lesions. Additionally, practicing good oral hygiene and protecting lips from excessive sun exposure with lip balm containing SPF can further reduce the risk of oral cancer. Public awareness and education about these preventive measures play a vital role in reducing the incidence of oral cancer.

Nicotine replacement therapy (NRT) is a valuable tool in the prevention of oral cancer, particularly for individuals seeking to quit smoking or using other tobacco products.

Noncoding RNAs (ncRNAs) play a crucial role in the regulation of gene expression and have emerged as significant players in the molecular mechanisms underlying oral cancer.

Preventing oral cancer requires a proactive approach, focusing on lifestyle changes, regular medical and dental checkups, and awareness of the disease's risk factors. By making informed choices and adopting healthy habits, individuals can significantly reduce their risk of developing oral cancer, leading to a longer, healthier life.[76]

Conclusion

A multifaceted approach that integrates health education, tobacco and alcohol control, early detection, and early treatment is needed to reduce the burden of this eminently preventable cancer. How to accomplish this is known; astonishingly, it has not been applied in most countries, and not at all in the high-burden countries. Improving awareness among the general public and primary care practitioners, investing in health services to provide screening and early diagnosis services for tobacco and alcohol users, and providing adequate treatment for those diagnosed with invasive cancer are critically important oral cancer control measures. Imaging, histopathology, cancer surgery and radiotherapy infrastructure and services, trained professionals, and the availability of chemotherapeutic agents are inadequate in many LMICs, seriously compromising early detection and optimum treatment.

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