Chapter

Oral Cancer: Epidemiology, Prevention, Early Detection, and Treatment

Ali Khani Jeihooni and Fatemeh Jafari

Abstract

One of the most common types of cancer is head and neck cancer. Head and neck cancers are the sixth most common cancer worldwide and the most common cancer in developing countries. Oral cancer, which is a subset of head and neck cancers, refers to any cancerous growth in the oral cavity. Risk factors for oral cancer include age, malnutrition, genetic factors, family history, X-rays, papilloma virus, alcohol, smoking, tobacco, which three last are the strongest risk factors. The destructive link between tobacco products and human cancers stems from a powerful combination of two factors - nicotine and carcinogens. The highest incidence of tobacco related oral cancer is seen in low and middle income countries. The chance of curing oral cancers increases if they are diagnosed and treated early. At least three-quarters of all oral cancers can be prevented by quitting smoking and drinking alcohol. Screening programs can be valuable in patients from high-risk groups (smokers and alcoholics) or in patients with a previous diagnosis of cancer outside the head and neck.

Keywords: head and neck cancer, oral cancer, smoking, tobacco, screening

1. Introduction

In the present century, the rapid growth of non-communicable diseases is considered as a serious health challenge that threatens the socio-economic development of communities and people's health [1]. The most common types of non-communicable diseases are cardiovascular disease, diabetes, chronic respiratory disease and cancer [2]. Cancers have been known as life-threatening conditions all over the world [3] and recognized as one of the most significant reasons of death around the world and every year, more than 10 million infections and 6 million deaths caused by cancers are reported [4].

One of the most common types of cancer is head and neck cancer [5]. Head and neck cancers are the sixth most common cancer worldwide and the most common cancer in developing countries. While head and neck cancers are one of the most common cancers in South and Southeast Asia, they account for only 1% -4% of all cancers in the Western world [6].

Oral cancer, which is a subset of head and neck cancers, refers to any cancerous growth in the oral cavity. This cancer includes tumors of the lips, tongue, cheeks, gum, floor of the mouth, soft and hard palate, sinuses, tonsils, salivary glands and

throat that can be fatal if left untreated. More than 90% of types of oral cancers originate in the squamous cells that line the inside of the mouth. When the growth of these cells gets out of control, it causes a cancer called squamous cell carcinoma or squamous cell carcinoma. Other types of oral cancers, such as partial malignancies of the salivary glands, sarcomas, odontogenic malignancies, melanoma, and lymphoma, make up less than 10% of oral cancers [7] and approximately 1% of metastatic cancers are lung, breast, prostate and kidney [8]. Squamous cell carcinoma can have various levels of differentiation and often give rise to node metastases. Lymphatic spreading into the neck is directly related to the T stage as well as the depth of invasion and tumor thickness [9].

2. Clinical forms

Tumors may appear in various forms of ulcers, prominent fungal masses, papillary, wart-like, white and red plaques, or a combination of both. Many primary

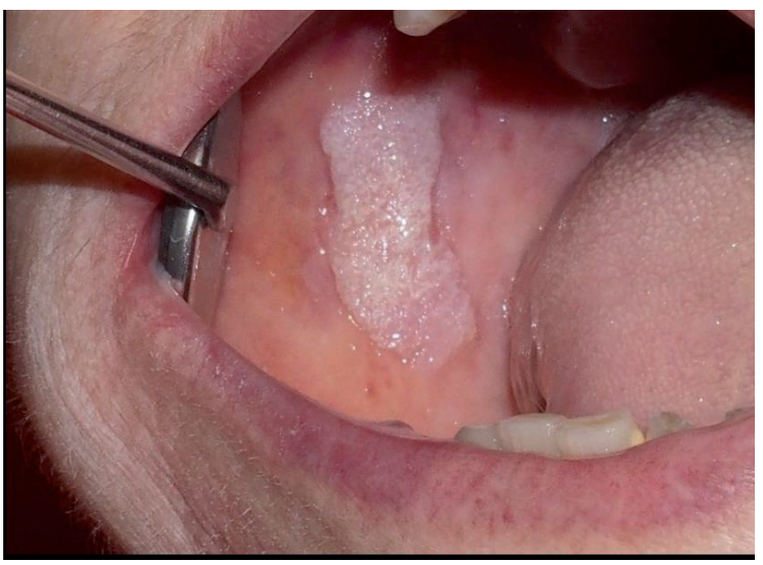

Figure 1.
Verrucous leukoplakia in the right buccal surface of a 72-year-old woman.

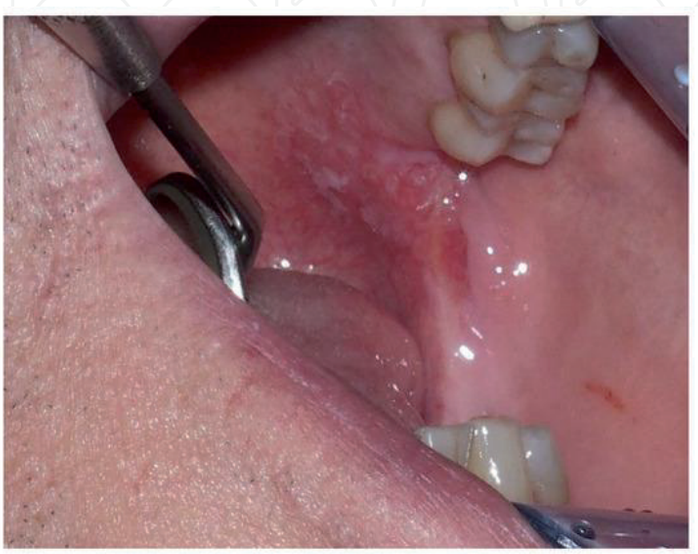

Figure 2.
Erythroplasia of the posterior hard palate, on histopathological examination in a 61-year-old man.

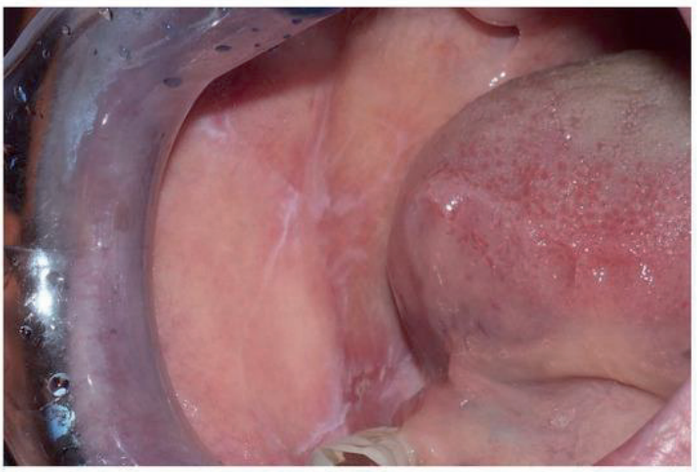

Figure 3.
White reticular striae on the right cheek mucosa of a 52-year-old man with oral lichen planus.

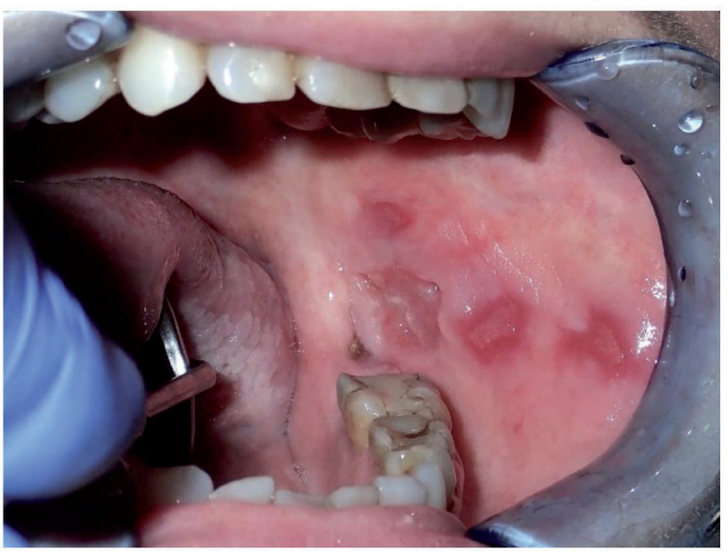

Figure 4.
Multiple areas of erythroplakia with ulceration in the left buccal mucosa because of chronic traumatic ulcer from self-biting in a 53-year-old woman.

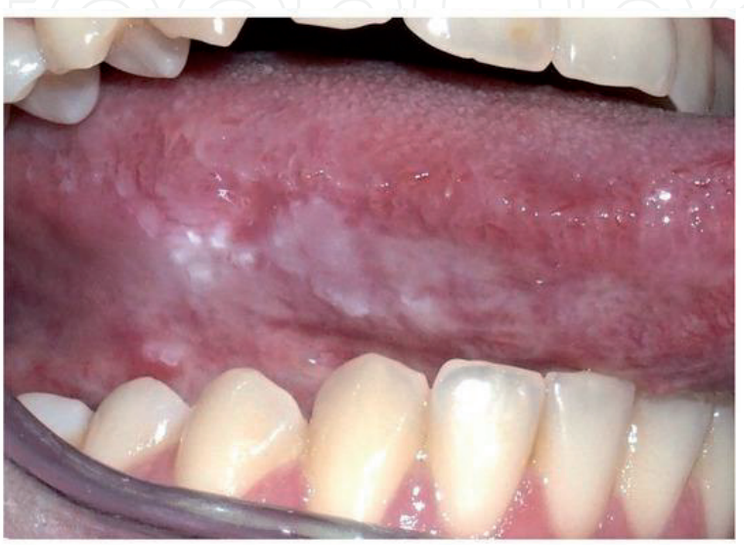

Figure 5.
Leukoplakia in the right border of the tongue with severe dysplasia in a 25-year-old woman.

cancers of the mouth are asymptomatic, while advanced lesions are often ulcerative and have prominent, hard margins. Pain is often absent in the later stages of the disease [8]. Potentially malignant oral epithelial lesions (PMOEL) are a group of oral diseases that may exist before the onset of oral squamous cell carcinoma (OSCC) and include a group of clinically oral mucosal lesions such as leukoplakia, erythroplakia, submucosal fibrosis, and lichen planus. However, most PMOELs do not progress to cancer (**Figures 1**–**5**) [10].

3. The place of conflict

The most common site of oral cancer is the lip. Lip cancer often occurs in light-skinned older men and most often affects the lower lip. Risk factors for lip cancer include sun exposure, certain occupations such as agriculture, socioeconomic status, smoking and pipe. Inside the mouth, the high-risk sites for cancer are the abdominal surface, the posterior sides of the tongue, the floor of the mouth, and the soft palate. Tongue cancer is the most common malignancy in the mouth. Tongue cancer is more common in men in their sixth and seventh decades of life. Tongue lesions are often aggressive. The second most common intraoral site for cancerous changes is the floor of the mouth. Tumors in this area occur in older men, especially in smokers and alcoholics. Involvement of the cheeks and gums is also common, especially in areas where there are certain habits such as chewing tobacco [8].

4. Risk factors

Oral cancer usually occurs in people over the age of 40 with an average age of 60, and their risk increases with age. It affects most men, but may increase as women smoke. Racially, black Americans are at higher risk for oral and throat cancer than whites. This increase in risk seems to be due to the influence of environmental factors, because the role of genetic factors in its occurrence has not been determined. Patients who smoke or chew a lot of tobacco and people who drink a lot of alcohol are at higher risk for oral cancer. Exposure to UV rays in people who stay in the sun for long periods of time is more likely to develop lip cancer. This is why the incidence of lip cancer is high in Australia. Other factors such as immunosuppression (such as AIDS and organ transplantation), viral papillomavirus infection (especially type 16, which accounts for 63% of new cases of oral cancer), Plummer–Vinson syndrome, and vitamin A deficiency also increase the risk of oral and pharyngeal cancer. The prevalence of HPV-related oral and pharyngeal cancers (mainly HPV type 16) has been increasing in North America and Northern Europe [11]. Other factors, including arsenic compounds used to treat syphilis, nutritional deficiencies, exposure to compounds such as wood and metal particles, and Candida infection, play a lesser role in cancer [8].

4.1 Hookah

In recent years, hookah has spread to Europe and the United States. In most countries, the increasing trend of hookah consumption is due to the increase in fruit and flavored tobacco products [12]. In a study conducted in Iran, the prevalence of hookah use among young people was reported to be 33.9%, which is higher than the number of people who smoke [13]. The side effects of hookah are many because the smoke produced from tobacco is composed of 4000 different chemicals and more than 40 carcinogens [14]. Tobacco smoke and hookah use are the most

important risk factors for oral cancers and dysplastic lesions [3]. Cigarettes or other tobacco-related compounds are associated with about 75% of oral cancers. Tobacco contains more than 60 known carcinogens. The use of tobacco, whether in a smoky or chewable form alone, and especially with heavy alcohol consumption, is a very important risk factor for oral cancer. Smokers are 7 times more likely to develop oral cancer than non-smokers. The relative risk of developing cancer in people who consume a lot of alcohol is 6 times higher, and this risk is 38 times higher for patients who use alcohol and tobacco together [8].

The association of tobacco with the risk of cancer may differ among the head and neck cancer subtypes [15]. In some studies, it was demonstrated that smoking had a stronger association with larynx and pharynx than the oral cavity. This may be due to the higher exposure of larynx and pharynx to smoke than the oral cavity [15, 16].

The destructive link between tobacco products and human cancers stems from a powerful combination of two factors - nicotine and carcinogens. Nicotine is addictive and toxic, but there is no scientific evidence that nicotine is carcinogenic, and the IARC does not classify nicotine as a carcinogen. However, this addiction causes people to use tobacco products constantly, and these products contain many carcinogens. Cigarette smoke contains more than 60 carcinogens and unburned tobacco contains at least 16 carcinogens. Among these, tobacco-specific nitrosamines such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N′-nitrosonornicotine (NNN), polycyclic aromatic hydrocarbons (such as benzoapyrene) and aromatic amines (such as 4-aminobiphenyl) seem to play an important role as causes of oral cancer [17].

Some believe that filtering hookah smoke through water reduces nicotine. However, contrary to popular belief, studies have shown that only 5% of nicotine is removed by water. In addition, hookah users may tend to increase the duration of smoking, thereby increasing the concentration of nicotine in their bloodstream. Therefore, considering the aforementioned harmful effects of hookah use and the results of a recent study, it seems that the use of this smoking device may cause changes in the oral mucosa [3].

Studies have shown that tobacco users, including slaked lime in the betel quid or with areca nut, experience carcinogenic and genotoxic effects on human oral epithelial cells. These products produce reactive oxygen species (ROS) in the chewing mouth [18]. Areca nut is composed of phenolic compounds and tobacco releases various nitrosamines in the mouth that are responsible for proliferative abrasions and damage to DNA and fibroblasts [19, 20]. The N-nitroso compound extracted from Areca nuts, which contains the active ingredient 3- (methyl nitrosamino) proprionityl, has been shown to cause gene poisoning and cytotoxicity responsible for tumors in the buccal cavity of smokeless smokers [21].

The long-lasting and frequent presence of paan and gutkha in the mouth around the gums leads to inflammation of the oral mucosa, which causes the activation of T-cells and macrophages, and ultimately the release of prostaglandins.

Prostaglandin production in buccal keratinocytes occurs due to Arka nut extract, which plays an important role in oral tissue fibrosis and cancer. Cytokines such as interferon-α, tumor necrosis factor (TNF), interleukin-6, and growth factor-like transforming growth factor-beta have been found to be produced at the sites of irritation [22]. The nitrosamine in tobacco is metabolized by cytochrome P450 enzymes, which may lead to the formation of N-nitrosonornicotine, a major carcinogen, which can lead to DNA damage and eventually oral cancer [23].

The consumption of tobacco is closely associated not only with the development of oral cancer, but also with the course of disease evolving a poor prognosis. The most widespread form of tobacco is chewing of betel-quid with tobacco and this has been demonstrated as a major risk factor of cancer of oral cavity [24].

Evidence from many studies shows that smoking in any way doubles the risk of oral cancer in men and women. The risk increases significantly with the duration and frequency of smoking. The risk among former smokers is consistently lower than current smokers, and the risk decreases as the years of quitting increase [25].

The highest incidence of tobacco related oral cancer is seen in low and middle income countries. People in the lower socioeconomic strata are more commonly affected. In India almost 21 people per 100 000 of the population are affected [26]. Data from a pioneering study by Taiwanese researchers show that people with a habit of smoking, drinking and chewing betel nuts at the same time are 123 times more likely to develop oral cancer than the general population [27]. More than 50 percent of oral cancers in India, Sudan and the Republic of South Sudan and about four percent of oral cancers in the United States are due to smokeless tobacco products. Smoking smoke-free tobacco is on the rise among young people in South Asia with the marketing of well-packaged products made from areca nuts and tobacco. As a result, oral precancerous conditions are significantly increased in young adults [28, 29].

4.2 Cigarette

Smoking helps to spread the tumor by suppressing immunity and tumor suppressor genes, most importantly p53 and PTEN [5]. The benefit of quitting smoking may be a time-dependent advantage. It was found that the risk of oral cancer among non-smokers is similar to that of former smokers after 10 years of smoking cessation. In addition, quitting smoking later or in middle age may significantly reduce the risk of oral cancer [30, 31].

A study in China, which included 210 cases, reported a strong association between long-term smoking and OSCC [32]. In the study by Ahmed et al. they have reported an increase in nuclear size, nuclearcytoplasmic (N/C) ratio and multi-lobed nuclei, while a decrease in size of cytoplasm in smokers as compared to non smokers [33]. The study of Woyceichoski et al. has also revealed an increase in cytoplasmic size and N/C ratio, while a decrease in size of cytoplasm in cocaine users as compared to the control group [34].

4.3 Alcohol

Tobacco and alcohol are the most well-known reasons for oral and throat cancers [35]. The synergistic effects of alcohol and tobacco smoke increase the risk of OSCC by increasing the permeability of the oral epithelium, tobacco solution, and increasing its permeability [36]. However, chronic alcohol use alone may lead to OSCC through several mechanisms, including the formation of DNA adducts, the production of ethanol-related reactive oxygen species, and interference with the DNA repair mechanism [37].

4.4 Shammah

Shamma consumption is increasing in many countries [38]. It is a combination of smokeless powder tobacco with ingredients such as lime, pepper, ash and flavorings, and people use it by placing it in the buccal cavity until the taste penetrates [39]. Another study of Yemeni shammah users found that there was a strong link between daily consumption of leukoplakia [40].

4.5 Chewing of khat

Khat is a plant that is mostly used for chewing and is amixture of cathine and norephidrine [41]. In an earlier case report of one patient, a strong affiliation

between khat chewing and growth of OSCC was reported [42]. Sawair *et al*. also reported a strong association between khat chewing and OSCC development in their study, which included 649 Yemeni patients [43].

4.6 Shisha (water pipe) smoking

Shisha is commonly available in restaurants, cafes, and other eatery shops in many countries and it contains a high concentration of nicotine, tar, and carbon monoxide [44].

Smoking with water (WPS) is a type of smoking that has traditionally been used for many years in Asia and the eastern Mediterranean. However, in the 1990s, it became global with increasing popularity in other parts of the world, including Western countries [45].

A recent study found a strong link between water pipe smoking and head and neck cancers [45]. In a study from Syria and Lebanon, Zaid et al. Reported that mutations in the p53 gene are smoking in the water tube at OSCC63 [46].

Al-Amad conducted a study in Jordan that found that 36% of those with oral cancer had a habit of smoking in a water pipe [47].

5. Protective factors

Recent studies show that the consumption of coffee, vegetables, fruits, folic acid have a protective effect [8]. A study by Ding et al. In 2013 shows that the use of polyphenols, especially in black and green tea, is effective in preventing oral cancer [48].

6. Disease epidemiology in the world

Oral cancer is a serious and growing problem in many countries. Epidemiological studies show that the incidence of oral cancer and its mortality varies in different parts of the world [49]. In Australia, more than 4,000 new cases of head and neck cancer (including lip cancer) are diagnosed each year. Over 600 of these cancers are oral cavity cancers. In developing countries, oral cancer is the sixth cancer among men and the tenth cancer in women. Worldwide, more than 400,000 new cases of oral cancer are diagnosed each year, two-thirds of which occur in Asian countries such as Sri Lanka, Indonesia, India, Pakistan and Bangladesh [50]. In these high-risk countries, oral cancer is the most common malignancy, accounting for over 25% of all new cases of cancer each year [51]. According to the International Agency for Research on Cancer, some countries in Asia and the Pacific had the top three rates of oral cancer in 2018 [52].

7. Control and prevention measures

Due to recent developments in the diagnosis and treatment of cancers, the survival of patients with cancers of the breast, colon and ovary has increased. However, over the past 50 years, the survival of patients with oral cancer has not changed [53]. In other words, oral cancer has a poor prognosis and the overall 5-year survival rate is 40%, although if diagnosed at an early stage (I and II), the survival rate can exceed 80% [54]. Up to 50% of oral cancers are diagnosed at an advanced stage (stages III and IV) because most patients are asymptomatic in the early stages

and do not seek medical help until they see clear symptoms such as pain, bleeding or a mass in the mouth or neck [55]. When the diagnostic delay is more than a month, the risk of having an advanced stage of oral cancer increases significantly [56]. In most cases, the patient is responsible for a large part of the diagnostic delay. However, delays can also be the result of an incorrect medical approach, as there is no suspicion of oral malignancy and it is not diagnosed and treated in a timely and sufficient manner [56, 57]. Clinical and pathological stage in diagnosis is the most important factor in prognosis [11].

Prevention of this devastating disease can be due to fundamental changes in the socio-economic situation, as well as measures to reduce demand, production, marketing and use of tobacco and alcohol products [58]. A healthy diet, oral hygiene and awareness of the signs and symptoms of the disease are important. Success depends on the political will, intersectoral actions, and culturally sensitive public health messages that are disseminated through educational campaigns and mass media initiatives [59].

Primary prevention of oral cancer therefore consists in education of people on the lifestyle changes such as non-smoking and alcohol consumption and protection from sunlight can reduce the risk of oral cancer [8]. Despite the increasing awareness of oral cancer in the general population, in the last 40 years the percentage of patients seeking medical attention with advanced disease has not changed significantly [51]. At least three-quarters of all oral cancers can be prevented by quitting smoking and drinking alcohol. Eliminating these two known factors also reduces cancer recurrence. In India and Sri Lanka, non-smoking tobacco education programs are designed specifically for adolescents to reduce the incidence of oral cancer. HPV vaccination can also be of importance, even though its effectiveness in not as well defined as it is in the prevention of anogenital and cervical cancer [11].

The goal of secondary prevention is early detection of cancer in the oral cavity in one of accessible places. The chance of curing oral cancers increases if they are diagnosed and treated early. Treatment of early-stage oral cancer increases patient survival. Unfortunately, most oral cancers are diagnosed at a more advanced stage and when they become symptomatic, which greatly reduces a person's chances of recovery, so early detection of precancerous lesions or early-stage oral cancer is very valuable. Diagnosis of suspected cases of oral cancer is made by assessing the patient's demographic characteristics and assessing specific habits, especially tobacco and alcohol consumption and other irritating factors that may play a role in causing oral cancer.

Routine biopsy in people with clinically characteristic precancerous lesions may lead to early detection of the underlying cause of oral cancer. In addition to history, physical examination, and biopsy, simultaneous evaluation of the upper aerodigestive tract is essential because patients with oral cancer are at risk for cancer of other parts of the head, neck, and lungs [25].

Oral health status and family history should also be evaluated for any syndromes that may increase the risk of oral cancer. In addition to the history, a complete examination of the head and neck is performed to carefully examine the location and spread of the primary tumor and identify metastases. It is noteworthy that early-stage cancerous lesions may be red or white plaques and non-ulcerative. More advanced cancers are ulcerative, aggressive, fungal, and prominent, or both. Cancer may develop within precancerous lesions such as leukoplakia or erythroplakia. Therefore, increasing the awareness of dentists is very important in getting a complete history and examination of the head and neck. Symptoms to consider include:

- Swelling or lumps on the lips or inside the mouth
- Wounds on the face, neck or mouth that do not heal within 2 weeks.

- Wounds under the denture
- White, red lesions
- Bleeding in the mouth for no reason
- Numbness or tenderness and unexplained pain in any area of the face, mouth and neck
- Difficulty swallowing, chewing, talking or moving the jaw or tongue
- Hoarseness, persistent sore throat or voice change
- Weight Loss [8].

Unlike other frequent cancers (for example, colon or cervical cancer), a standard population-based screening program for oral cancer is not cost-effective and cannot be recommended [51]. Screening programs can be valuable in patients from high-risk groups (smokers and alcoholics) or in patients with a previous diagnosis of cancer outside the head and neck [60]. In countries with regular dental practice attendance, opportunistic screening for oral mucosal lesions (early-stage cancer or precancerous lesions) in general dental practice could also be relevant in reducing diagnostic delay [61].

Visual screening involves regular visual and physical examination of the intraoral mucosa under intense light to observe the symptoms of oral potentially malignant disorders (OPMD) as well as early oral cancer, followed by careful examination and digital palpation of the neck for lymph node enlargement. This is a provider-dependent mental test. Accordingly, its performance in detecting lesions varies among providers. Comprehensive knowledge of oral anatomy, natural history of oral carcinogenesis, and clinical-pathological features of OPMDs and preclinical cancers are important prerequisites for effective oral vision screening providers [59]. A significant 34% reduction in oral cancer mortality among a high-risk group of smokers and alcoholics after three rounds of oral vision screening has been shown in a randomized controlled cluster trial in India [62, 63]. A 15-year follow-up showed a steady decline in oral cancer mortality, with a further decline in those who adhere to frequent screening courses. 38% reduction in oral cancer incidence (95% CI 8–59%) and 81% reduction in oral cancer mortality (95% CI 69–89%) in tobacco and /or alcohol users who They were screened four times [62].

Known risk factors, long natural history, easy diagnosis of precancerous lesions by oral examination make oral cavity cancer very suitable for population screening. Oral cancer usually occurs in accessible places, which can be diagnosed early by visual inspection and touch. Therefore, oral self-examination is possible for everyone because it is a method for early detection of precancerous oral lesions without the need for a simple, non-invasive and inexpensive healthcare professional [64]. It should be strongly supported for ordinary people, especially high-risk people [52]. A quasi-experimental study in Australia found the importance of oral self-examination in reducing the incidence and mortality of oral cancers [65].

Also, prompt treatment is essential for successful secondary prevention. Secondary prevention is also called cancer control [66]. Surgery and radiation therapy are widely used to treat premature oral cancer, either alone or in combination. The choice of method depends on the location of the tumor, cosmetic and functional outcomes, patient age, comorbidities, patient preference, and specialization [59].

The third prevention targets the final stages. More than 70% of advanced cancers have severe pain and other distressing symptoms. Pain control and palliative care are the third most important prevention strategies [67].

8. Conclusion

Since oral cancer is the sixth most common cancer in men and the tenth most common cancer in women and puts a lot of burden on health care providers and the public, and on the other hand many of its risk factors such as smoking and hookah can be controlled, including screening and diagnosis Early in the health care system and educational intervention programs are recommended.

Conflict of interest

The authors declare no conflict of interest.

Abbreviation

PMOEL	Potentially malignant oral epithelial lesions
OSCC	oral squamous cell carcinoma
OPMD	observe the symptoms of potentially malignant oral disorders

Author details

Ali Khani Jeihooni[1*] and Fatemeh Jafari[2]

1 Department of Public Health, School of Health, Shiraz University of Medical Sciences, Shiraz, Iran

2 Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran

*Address all correspondence to: khani_1512@yahoo.com

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