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Review Article

Oral Cancer, Oral Health And Potentially Malignant Disorders- A Review

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ABSTRACT:
Oral cancer remains a significant global health burden, with a high prevalence and mortality rate, particularly in regions with high tobacco and betel quid consumption. The development of oral squamous cell carcinoma (OSCC) is often preceded by potentially malignant disorders (PMDs), including leukoplakia, erythroplakia, and oral submucous fibrosis. Early detection and management of PMDs play a crucial role in preventing malignant transformation. This review explores the intricate relationship between oral cancer, oral health, and PMDs, highlighting the risk factors, molecular pathways, and early diagnostic strategies. Furthermore, the role of artificial intelligence, biomarker-based screening, and preventive interventions in improving prognosis and survival rates is discussed. Understanding the pathogenesis of oral cancer and PMDs and integrating advanced diagnostic and preventive measures into routine dental practice can significantly reduce the burden of this disease.

Keywords: Oral cancer, potentially malignant disorders, oral squamous cell carcinoma, leukoplakia, erythroplakia, oral submucous fibrosis, early detection, artificial intelligence, biomarkers, prevention.

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INTRODUCTION

Oral cancer is a major public health concern, accounting for a significant proportion of head and neck malignancies worldwide. Among these, oral squamous cell carcinoma (OSCC) is the most prevalent, contributing to approximately 90% of all oral malignancies (1). Oral cancer is detected in 270,000 people per annum or around 3% of all malignancies. It ranks sixth among males and twelve among females in terms of prevalence. (2).

Several risk factors have been identified, including tobacco use, alcohol consumption, betel quid chewing, human papillomavirus (HPV) infection, and poor oral hygiene (3,4).

A crucial aspect of oral carcinogenesis is the presence of potentially malignant disorders (PMDs), such as leukoplakia, erythroplakia, oral submucous fibrosis, and lichen planus, which have a variable risk of malignant transformation (5). Early identification and intervention in PMDs can significantly improve prognosis and reduce the incidence of OSCC (6). However, challenges in clinical diagnosis, lack of standardized screening methods, and limited public awareness contribute to delayed treatment initiation (7).

Advancements in diagnostic technologies, including artificial intelligence, biomarker-based screening, and non-invasive imaging techniques, have shown promise in improving early detection rates (8,9).

Moreover, preventive strategies such as tobacco cessation programs, HPV vaccination, and routine oral health check-ups play a vital role in reducing the incidence of oral cancer (10). This review aims to provide a comprehensive analysis of the relationship between oral cancer, oral health, and PMDs, with a focus on risk factors, diagnostic advancements, and preventive approaches.

Furthermore, recent studies have emphasized the role of genetic and epigenetic alterations in the pathogenesis of oral cancer. Mutations in tumor suppressor genes such as TP53, along with dysregulation of signaling pathways like EGFR and Wnt/β-catenin, have been implicated in OSCC development and progression (1). Epigenetic modifications, including DNA methylation and histone acetylation, also contribute to the transformation of normal oral epithelium into malignant lesions. These molecular insights have paved the way for targeted therapies that hold promise in improving treatment outcomes for oral cancer patients (2).

In addition to genetic predisposition, the impact of the oral microbiome on oral carcinogenesis has gained attention. Studies suggest that chronic infections with pathogenic bacteria such as *Porphyromonas gingivalis* and *Fusobacterium nucleatum* may promote tumor progression by inducing chronic inflammation and immune evasion (3). Dysbiosis of the oral microbiota may act as a cofactor in carcinogenesis, particularly in individuals with predisposing habits like tobacco and alcohol consumption. Understanding the microbial influence on OSCC development may open new avenues for preventive strategies, including probiotic-based interventions and antimicrobial therapies (4).

Despite advancements in research and diagnostic modalities, disparities in access to early detection and treatment remain a major challenge, particularly in low-resource settings. Public health initiatives focusing on education, awareness campaigns, and community-based screening programs are essential for bridging this gap (5). The integration of artificial intelligence-driven diagnostic tools in primary healthcare settings could aid in the early detection of PMDs and OSCC, thereby improving survival rates. Future research should focus on enhancing the affordability and accessibility of these advanced diagnostic techniques to ensure equitable healthcare delivery (6).

Oral cancer, predominantly oral squamous cell carcinoma (OSCC), constitutes a significant global health challenge due to its high morbidity and mortality rates [1].

The progression of OSCC is often preceded by oral potentially malignant disorders (OPMDs), which are mucosal lesions with an increased risk of malignant transformation [2].

Risk factors for oral cancer and OPMDS[3-7]

Several etiological factors contribute to the development of oral cancer and OPMDs:

- **Tobacco Use:** Both smoking and smokeless tobacco are well-established risk factors, significantly increasing the likelihood of developing OPMDs and their subsequent transformation into OSCC. According to the Global Youth Tobacco Survey (2009) 14.6% of students were using any form of tobacco out of which 4.4% of them smoked cigarettes and 12.5% used some other forms of tobacco. The incidence of oral cancer increases with age and is highest over 60 years, even though cases in people younger than 40 years are increasing.
- **Alcohol Consumption:** Excessive alcohol intake acts synergistically with tobacco, further elevating the risk of malignant transformation in oral tissues.
- **Betel Quid Chewing:** Common in South Asian populations, betel quid chewing is strongly associated with OPMDs, particularly oral submucous fibrosis, which carries a high risk of progression to OSCC.
- **Human Papillomavirus (HPV) Infection:** High-risk HPV strains, especially HPV-16, have been implicated in the pathogenesis of a subset of oral cancers, underscoring the importance of viral factors in oral carcinogenesis.
- **Genetic and Molecular Factors in Oral Cancer and OPMDs**

In addition to lifestyle and environmental risk factors, genetic predisposition plays a crucial role in the development of oral cancer and OPMDs. Several oncogenes and tumor suppressor genes, such as *TP53*, *CDKN2A*, and *EGFR*, have been identified as key players in the molecular pathogenesis of OSCC. Mutations in *TP53*, which encodes the tumor suppressor protein p53, are found in a significant proportion of oral cancers, leading to impaired cell cycle regulation and increased genomic instability [8]. Epigenetic modifications, such as DNA methylation and histone modifications, have also been implicated in the malignant transformation of OPMDs. Studies have shown that hypermethylation of tumor suppressor genes and global hypomethylation contribute to oral carcinogenesis by promoting uncontrolled cell proliferation and evasion of apoptosis [9]. Advances in genomic research have paved the way for the identification of molecular biomarkers that can aid in early detection and targeted therapy for oral cancer.

- **Chronic Inflammation and Microbial Factors**

Chronic inflammation has been increasingly recognized as a contributing factor in oral carcinogenesis. Persistent irritation of the oral mucosa due to factors such as tobacco, alcohol, and betel quid can lead to chronic inflammation, which promotes carcinogenesis through the production of reactive oxygen species (ROS) and inflammatory cytokines.

These inflammatory mediators, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), create a tumor-promoting microenvironment that facilitates cellular mutations and malignant transformation [8]. Additionally, recent research has highlighted the role of the oral microbiome in OSCC development. Pathogenic bacteria, such as *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, have been associated with oral cancer progression due to their ability to modulate immune responses, induce chronic inflammation, and promote epithelial-mesenchymal transition (EMT), a process linked to cancer metastasis [9]. Understanding these microbial influences on OPMDs and OSCC could lead to novel preventive strategies, including probiotic therapies and antimicrobial interventions.

- **Environmental and Occupational Exposures**

Exposure to environmental and occupational carcinogens also contributes to the development of oral cancer. Prolonged exposure to polycyclic aromatic hydrocarbons (PAHs) and heavy metals such as arsenic, chromium, and nickel has been linked to an increased risk of OSCC. These substances, commonly found in industrial pollutants and certain occupational settings, induce DNA damage and disrupt cellular repair mechanisms, leading to oncogenic transformation [10]. Additionally, excessive exposure to ultraviolet (UV) radiation, particularly in outdoor workers, has been associated with an increased risk of lip cancer, a subset of oral malignancies. Measures such as workplace safety regulations, protective gear, and public awareness campaigns are essential to mitigate these environmental risks.

- **The Role of Diet and Nutrition in Oral Cancer Prevention**

Dietary factors also play a significant role in modulating the risk of oral cancer and OPMDs. A diet deficient in fruits and vegetables, which are rich in antioxidants and essential micronutrients, has been associated with an increased risk of OSCC. Nutrients such as vitamin A, vitamin C, vitamin E, and selenium possess chemopreventive properties that help neutralize free radicals and prevent DNA damage [1]. Conversely, diets high in processed foods, red meats, and fried foods have been linked to an increased risk of oral cancer due to the presence of carcinogenic compounds such as nitrosamines and heterocyclic amines. Emerging evidence also suggests that certain bioactive compounds found in green tea, turmeric (curcumin), and cruciferous vegetables have potential anti-cancer properties and may play a role in preventing the malignant transformation of OPMDs [2]. Public health initiatives promoting balanced nutrition and lifestyle modifications can serve as effective strategies for reducing the burden of oral cancer.

Common oral potentially malignant disorders (OPMDS) [3-7]

Oral potentially malignant disorders (OPMDs) represent a group of mucosal conditions that have an increased risk of progressing to oral squamous cell carcinoma (OSCC). Recognizing and managing these lesions at an early stage is crucial in preventing malignant transformation. Among the various OPMDs, leukoplakia, erythroplakia, and oral submucous fibrosis (OSF) are the most studied and clinically significant. According to the definition of "potentially malignant disorders," not all potentially malignant disorders have a high likelihood of developing into cancer.

Oral submucous fibrosis (OSF) [11-13]

Precancerous lesions, such as oral submucous fibrosis (OSMF), are clinically apparent abnormalities that are primarily noncancerous and frequently precede cancer of the oral cavity. Oral submucous fibrosis (OSF) is a chronic, progressive disorder that primarily affects individuals with a history of betel quid chewing, particularly in South Asian populationsPatients' clinical presentations vary based on the state of the illness at the time of being diagnosed, as the illness is progressive. Intolerant to hot foods, lip stiffness, tongue stiffness, and palate stiffness that reduces mouth opening, limited tongue motions, dysphagia, and diminished hearing in its advanced stages are among the most typical appearances.

The pathogenesis of OSF involves the activation of fibroblasts due to the alkaloids and areca nut in betel quid, resulting in increased collagen deposition and reduced collagen degradation. Sub-mucosal fibrosis, which affects the majority of the mouth, pharynx, and upper portion of the esophagus, is the disease's hallmark. It has been suggested that iron and vitamin deficits play a part in the genesis of OSMF. Over time, this leads to irreversible fibrosis, restricting oral function. The malignant transformation rate of OSF is estimated to be between 7% and 13%, making it one of the most serious OPMDs.

Clinically, OSF progresses through distinct stages:

- Early Stage: Burning sensation, blanching of oral mucosa, and formation of vesicles.
- Moderate Stage: Stiffening of oral mucosa, loss of elasticity, and formation of palpable fibrous bands.
- Advanced Stage: Severe trismus, restricted tongue movement, and risk of malignant transformation.

There is no definitive cure for OSF, but treatment aims to improve symptoms and halt disease progression. Management strategies include cessation of betel quid chewing, intralesional corticosteroid injections, physiotherapy, and surgical interventions in severe cases. Long-term monitoring is essential, given the high risk of OSCC development.

Leukoplakia, erythroplakia, and OSF are among the most significant OPMDs due to their potential to undergo malignant transformation. Early detection, lifestyle modifications, and appropriate clinical

management are crucial in reducing the risk of OSCC development. Regular oral screenings and biopsies of suspicious lesions are essential in preventing late-stage diagnoses and improving patient outcomes.

Leukoplakia [14]

Leukoplakia is the most common OPMD, defined by the World Health Organization (WHO) as a predominantly white lesion of the oral mucosa that cannot be characterized as any other definable disease. It presents as either a homogeneous or non-homogeneous lesion, with the latter demonstrating a higher risk of malignant transformation.

Homogeneous Leukoplakia: Uniformly white, smooth, or slightly wrinkled patches with well-demarcated borders. This form is usually asymptomatic and has a relatively lower risk of malignant transformation.

Non-Homogeneous Leukoplakia: Irregular, mixed white-and-red lesions with surface nodules, fissures, or verrucous projections. It is associated with a significantly higher risk of malignant transformation, ranging from 7% to 20% over time.

The exact etiology of leukoplakia remains unclear, but chronic irritation from tobacco, alcohol, and betel quid use is strongly linked to its development. Histopathological examination often reveals epithelial dysplasia, which is a key predictor of cancerous transformation. Treatment includes lifestyle modifications (tobacco and alcohol cessation), surgical excision, laser ablation, and photodynamic therapy, depending on the lesion's size, location, and dysplastic features.

Leukoplakia and lichen planus, as the most prevalent lesions, are consistent with their known associations with chronic irritation and autoimmune processes, respectively.

Erythroplakia [15]

Erythroplakia is a relatively rare but highly aggressive OPMD characterized by a well-defined, persistent red patch on the oral mucosa. Unlike leukoplakia, erythroplakia lacks keratin production, making it appear smooth and velvety in texture. It is often asymptomatic, leading to delayed diagnosis and an increased likelihood of being detected at an advanced stage.

Erythroplakia carries the highest risk of malignant transformation among OPMDs, with reported rates ranging from 30% to 50%. Histopathological analysis typically reveals severe epithelial dysplasia, carcinoma in situ, or early invasive OSCC at the time of diagnosis. The etiology of erythroplakia is similar to that of leukoplakia, with tobacco and alcohol being major contributing factors.

Given its high risk of malignant progression, erythroplakia requires immediate intervention. Management strategies include complete surgical excision, laser therapy, and regular follow-up to monitor for recurrence or progression. Unlike leukoplakia, erythroplakia almost always warrants biopsy and histological examination to rule out malignancy.

Diagnostic Advancements [16-24]

Early detection of OPMDs is crucial for preventing progression to OSCC. Recent advancements include:

- **Artificial Intelligence (AI):** AI algorithms have been developed to predict malignant transformation in oral epithelial dysplasia, enhancing diagnostic accuracy and aiding in early intervention.
- **Biomarker Identification:** Research into salivary biomarkers offers potential for non-invasive screening methods, facilitating early detection of malignant changes in OPMDs
- **CBCT:** radiographic examination of suspected lesions with CBCT can be extremely helpful in diagnosis.

Preventive Strategies [25-32]

Effective prevention of oral cancer involves addressing modifiable risk factors and implementing public health measures:

- **Tobacco and Alcohol Cessation:** Public health initiatives promoting cessation can significantly reduce the incidence of OPMDs and OSCC.
- **HPV Vaccination:** Immunization against high-risk HPV strains may decrease the incidence of HPV-related oral cancers.
- **Regular Oral Examinations and overall oral health maintenance:** Routine dental check-ups facilitate early detection of OPMDs, allowing for timely management and reducing the risk of malignant transformation

CONCLUSION

Understanding the complex interplay between risk factors, OPMDs, and oral cancer is essential for developing effective diagnostic and preventive strategies. Continued research and public health efforts are vital to reduce the global burden of oral cancer.

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