Review Article

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Tobacco and Tobacco-Related Oral Lesions: Current Concepts and Updates

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ABSTRACT

Tobacco use remains a leading preventable cause of morbidity and mortality worldwide and is strongly linked to numerous oral mucosal lesions, ranging from reversible keratotic changes to Oral squamous cell carcinoma. Both smoked and smokeless tobacco damage oral tissues through chemical, thermal, and immunologic mechanisms. Emerging products such as electronic cigarette and heat-not-burn device present new challenges for dental professionals. Tobacco-related lesions include smoker's palate, tobacco pouch keratosis, oral leukoplakia, erythroplakia, oral submucous fibrosis, and OSCC, many classified as oral potentially malignant disorders. Early detection is essential to reduce malignant transformation and improve prognosis. Advances in molecular biology and salivary diagnostics, including biomarker and immunologic testing, have enhanced early identification. Dental professionals play a vital role in screening, patient education, tobacco cessation counseling, and timely intervention to improve overall oral and systemic health outcomes.

Introduction

In India, oral cancer constitutes nearly 30% of all cancer cases, and its prevalence continues to increase each year. The estimated incidence rate is approximately 20 cases per 100,000 population. Major risk factors contributing to the development of oral cancer and potentially malignant disorders include tobacco chewing, tobacco smoking, and alcohol consumption.[1] Continued use of tobacco leads to cellular alterations in the oral cavity, thereby increasing the risk , it is primarily the molecular interactions between tobacco constituents and oral tissues that drive damage to the mucosal lining and gums. [2]

Tobacco smoke and smokeless tobacco products contain more than 7,000 chemical substances, including over 70 established carcinogens such as nitrosamines, polycyclic aromatic hydrocarbons, benzene, heavy metals, and nicotine, which are released during use.[3] These harmful agents trigger DNA damage, oxidative stress, and persistent inflammation, ultimately leading to epithelial dysplasia, oral potentially malignant disorders (OPMDs), and Oral squamous cell carcinoma.[4]

India bears a significant burden of tobacco-related oral diseases, largely driven by the extensive use of smokeless products such as gutkha, khaini, pan masala, and betel quid with tobacco, habits that are strongly linked to potentially malignant disorders including oral submucous fibrosis and leukoplakia, both of which carry a considerable risk of malignant transformation.[5] Evidence suggests that

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approximately 90% of oral cancer cases in India are linked to tobacco use, highlighting the critical need for dental professionals to prioritize preventive measures and early detection, while also recognizing and addressing the factors that contribute to delayed diagnosis in order to reduce disease incidence and improve outcomes. [6]

In recent years, newer nicotine delivery systems—including electronic cigarette, heat-not-burn device, and nicotine pouches—have gained popularity. Although frequently promoted as safer alternatives, emerging research suggests they may also induce oxidative stress, epithelial injury, and alterations in the oral microbiome. Therefore, dental clinicians must stay informed about the evolving patterns of tobacco-related oral lesions.[7]

This review presents an updated and comprehensive discussion of tobacco-induced oral lesions, focusing on their pathogenesis, classification, clinical manifestations, and recent diagnostic and preventive advancements, with particular attention to OPMDs and the expanding role of oral healthcare professionals in cessation counseling and early intervention.

Global and Indian Burden of Tobacco Use

Oral squamous cell carcinoma (OSCC) accounts for approximately 90–95% of oral malignancies and remains a significant global cause of morbidity and mortality, while tobacco use continues to be a major preventable contributor to disease and death worldwide. [8,9] According to the World Health Organization, tobacco use accounts for more than 8 million deaths each year, including about 1.3 million deaths resulting from exposure to second-hand smoke. Although several international tobacco control initiatives have been implemented, the burden is increasingly concentrated in low- and middle-income countries, where nearly 80% of tobacco users live.[10]

The South-East Asian region demonstrates particularly high prevalence rates. India is the second-largest consumer of tobacco globally, with widespread use of both smoked and smokeless forms across diverse socioeconomic groups. Data from the Global Adult Tobacco Survey (GATS) indicate that approximately 28–30% of Indian adults consume tobacco in some form. [11] In India, the tendency of consuming smokeless tobacco increased until 2005, and then somewhat decreased in 2017. Smokeless tobacco use, however, is still a risk factor and raises the chance of dying from cancer.[12]

The widespread and growing use of tobacco products and areca nut in India, across both genders and all age groups, has led to a notably high prevalence of oral submucous fibrosis (OSMF). [13] OSMF was the most frequent lesion among people who consumed gutkha, betel quid, with or without tobacco. [14] Over 90% of patients with oral cancer in India reported using smokeless tobacco products, such as pan (areca nut bits), slaked lime, betel nut, or nut wrapped in the betel vine leaf. Gutka, panparag, zarda, mawa, kharra, and khaini are also included. [15]

Oral cancer is among the most prevalent malignancies globally and is ranked as the 12th most common cancer worldwide. [16] Oral squamous cell carcinoma is the most prevalent malignancy among Indian men and is increasingly observed in younger individuals due to early initiation of tobacco habits.

Tobacco is strongly associated with oral potentially malignant disorders such as leukoplakia, erythroplakia, and oral submucous fibrosis, which demonstrate variable malignant transformation rates.[17] Premalignant conditions are typically seen in the oral cavity's mucosa, including the gingiva, tongue, buccal mucosa, and floor of the mouth. [18] The growing popularity of electronic cigarette, heat-not-burn device, and nicotine pouches among youth further complicates the epidemiological scenario, as emerging evidence indicates their potential to induce mucosal injury and carcinogenic changes.[7] A large proportion of preventable cancer-related deaths are linked to smoking and tobacco chewing, with lung cancer followed by oral cancer being the most significantly affected. [19] These trends highlight the urgent need for prevention strategies and active dental involvement in cessation counseling.

Pathogenesis of Tobacco-Induced Oral Damage

Tobacco-related oral lesions arise through a complex and multifactorial process involving chemical carcinogens, thermal injury, oxidative stress, immune alterations, and genetic susceptibility. Both smoked and smokeless tobacco expose the oral mucosa to numerous toxic substances that initiate and promote carcinogenic changes.

●Chemical Carcinogenesis

Tobacco products contain thousands of harmful chemicals, including highly potent tobacco-specific nitrosamines such as N-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). These carcinogens form DNA adducts and induce mutations in critical genes regulating cell growth and apoptosis, particularly tumor suppressor genes like p53. Additional compounds—including polycyclic aromatic hydrocarbons, benzene, formaldehyde, arsenic, cadmium, and lead—further contribute to genetic instability and impairment of DNA repair mechanisms. Persistent exposure results in progressive epithelial dysplasia

and may culminate in Oral squamous cell carcinoma.[20]

●Oxidative Stress and Free Radical Damage

By producing more reactive free radicals and active oxygen species, which influence phenotypic and genotypic changes and result in DNA mutations that cause carcinogenesis, tobacco use also plays a clear role in the etiopathogenesis of oral malignancies. Chronic oxidative injury promotes increased epithelial proliferation, abnormal differentiation, reduced apoptosis, and accumulation of genetic mutations—key events in the development of oral potentially malignant disorders.[18]

●Thermal Injury in Smokers

In smokers, repeated exposure to high temperatures produces chronic thermal irritation of the oral mucosa. This commonly leads to palatal keratinization, clinically recognized as smoker's palate. Heat exposure also enhances mucosal permeability, facilitating deeper penetration of carcinogens and accelerating dysplastic changes. [21]

●Effects of Smokeless Tobacco

Smokeless tobacco results in prolonged, localized contact between carcinogens and the oral epithelium. The inclusion of slaked lime raises salivary pH, increasing nicotine absorption and mucosal permeability. When combined with areca nut, which contains arecoline, fibroblast stimulation and excessive collagen deposition may occur, contributing to oral submucous fibrosis. Chronic exposure leads to epithelial atrophy, submucosal fibrosis, decreased vascularity, and elevated malignant potential. [22]

●Oral Microbiome Alterations

Toxic substances in cigarette smoke disrupt the oral immune response and contribute to diseases such as periodontitis and oral cancer, while also overwhelming detoxifying enzymes and altering bacterial survival and metabolic activity, with smokers showing increased amino acid and sugar-related enzyme metabolism compared to non-smokers.[24]

Classification of Tobacco-Related Oral Lesions

Tobacco use produces a broad range of oral mucosal alterations, varying from reversible keratotic changes to invasive malignancies. Many of these conditions are classified as oral potentially malignant disorders (OPMDs) because of their risk of progression to cancer. Prompt identification and early management are essential to prevent malignant transformation.

Smoker's Palate (Nicotinic Stomatitis)

Smoker's palate is a benign and reversible lesion typically observed in heavy smokers, especially pipe and reverse smokers. Cigarette smoke has over 4000 chemical products, amongst which are nicotine and carbon monoxide, as well as different cytotoxic agents that can hinder neutrophil function, hurting the way these cells work at the infection site, reducing oxygen diffusion and disturbing normal inflammatory pathways. [24] Clinically, it presents as a diffuse greyish-white discoloration of the posterior hard palate with multiple small papules containing central red dots representing inflamed salivary gland openings. Although not premalignant, it reflects prolonged tobacco exposure and usually resolves after cessation. [21]

Tobacco Pouch Keratosis

Also known as smokeless tobacco keratosis, this lesion appears at the habitual placement site of chewing tobacco, commonly the buccal vestibule or labial mucosa. It manifests as a localized white or grey wrinkled plaque with a corrugated surface and indistinct borders. The lesion is generally reversible once the habit is discontinued, though persistent cases may develop epithelial dysplasia. [25]

Oral Leukoplakia

Oral leukoplakia is the most common tobacco-associated OPMD and is defined as a white patch that cannot be attributed to any other diagnosable condition. It is strongly linked to smoking, smokeless tobacco, alcohol use, and chronic irritation. Clinically, it may appear as homogeneous or non-homogeneous (speckled, nodular, or verrucous) forms. The risk of malignant transformation ranges from 1–20%, particularly in non-homogeneous lesions, sites such as the tongue or floor of the mouth, and those exhibiting dysplasia. [26]

Erythroplakia

Erythroplakia is an uncommon but high-risk premalignant lesion associated with tobacco and alcohol. It presents as a bright red, velvety plaque, frequently affecting the tongue, floor of the mouth, or soft palate. Histopathologically, most lesions show severe dysplasia or carcinoma in situ, necessitating immediate biopsy. [27]

Oral Submucous Fibrosis

Oral submucous fibrosis is a chronic, progressive disorder strongly associated with smokeless tobacco and areca nut use, particularly prevalent in India. It is characterized by mucosal burning, blanching, stiffness, reduced mouth opening, and palpable fibrous bands. Malignant transformation occurs in 7–13% of cases.[22]

Oral squamous cell carcinoma

This represents the end stage of tobacco-induced carcinogenesis and accounts for over 90% of oral cancers. Commonly affecting the buccal mucosa, tongue, and floor of the mouth, it presents as a non-healing ulcer, indurated mass, or bleeding lesion. Despite therapeutic advances, survival rates remain limited due to delayed diagnosis. [27]

Newer Tobacco Products and Emerging Concerns

In recent years, the tobacco industry has introduced alternative nicotine delivery systems that are frequently promoted as safer substitutes for conventional tobacco. These include electronic cigarette, heat-not-burn device, and nicotine pouches. Their growing acceptance—especially among adolescents and young adults—poses new challenges for oral health professionals.

Electronic Cigarettes

Electronic cigarettes are battery-powered devices that generate an aerosol by heating a liquid composed of nicotine, flavoring agents, propylene glycol, and glycerin. Although they avoid combustion, research shows that their aerosols may contain nicotine, heavy metals such as nickel and lead, formaldehyde, acetaldehyde, and reactive oxygen species. [7,28] Reported oral effects include xerostomia, increased susceptibility to dental caries, periodontal inflammation, delayed wound healing, and cytotoxic changes in oral epithelial cells. Emerging evidence indicates that vaping can induce oxidative stress and DNA damage, raising concerns regarding its possible long-term carcinogenic potential. [11]

Heat-Not-Burn Products

Heat-not-burn devices warm processed tobacco at lower temperatures than conventional cigarettes, producing an inhalable aerosol rather than smoke. Despite being marketed as reduced-risk products, they still release nicotine, tobacco-specific nitrosamines, and volatile organic compounds. Preliminary findings suggest potential adverse effects such as disruption of the oral microbiome, elevated inflammatory markers, and epithelial cell injury. Consequently, their long-term safety profile remains uncertain.[28]

Nicotine Pouches and Dissolvable Products

Nicotine pouches are smokeless products placed in the oral vestibule and are increasingly used by younger populations. Although they do not contain tobacco leaf, they deliver concentrated nicotine along with flavoring additives. Possible oral consequences include localized mucosal irritation, gingival recession, keratotic changes at placement sites, and heightened nicotine dependence.[28]

An alarming development is the concurrent use of traditional cigarettes with newer nicotine delivery systems. Many users combine conventional smoking with electronic cigarette and other novel products, resulting in increased overall exposure to nicotine and potentially harmful carcinogens.

Young people are especially at risk due to targeted marketing campaigns, the wide range of appealing flavors, and the widespread belief that these alternatives are safer than conventional tobacco. This growing pattern of dual use poses a significant threat to the advances made in global tobacco control initiatives and public health efforts.

Recent Advances in Diagnosis and Biomarkers

Detecting cancer at an early stage is crucial for improving patient outcomes, as it enables timely intervention, expands treatment options, and significantly increases survival rates. [29] While thorough clinical examination and histopathological biopsy remain the gold standard for diagnosis but are time-consuming [30], recent developments in molecular biology and salivary diagnostics have introduced valuable non-invasive and adjunctive approaches for early detection and risk evaluation.

Salivary Biomarkers

Recent advances in biomarker research have led to an

investigation into saliva as a diagnostic medium for OSCC. Enzymes, metabolites, and proteins present in saliva are an abundant indicator of both systemic and local physiological alterations.It has several advantages over blood and tissue samples, including as patient compliance, noninvasiveness, and ease of collection. Several salivary biomarkers, such as tissue polypeptide-specific antigen (TPSA), matrix metalloproteinase-9 (MMP-9), and interleukin-6 (IL-6), have emerged as promising choices for early OSCC identification. [30]

Immunological and Molecular Markers

Alterations in serum immunoglobulins (IgG, IgM, IgA) reflect immune dysregulation and chronic inflammation linked to tobacco use. Studies report increased IgG and IgA levels in oral cancer patients, supporting their potential role as adjunctive diagnostic tools.[8] Additionally, genetic and epigenetic changes—such as p53 mutations, Cyclin D1 overexpression, EGFR activation, and abnormal DNA methylation—highlight the importance of molecular susceptibility in carcinogenesis and enable personalized risk assessment. [17]

Nanotechnology

In order to increase accuracy and precision, nanoparticles are being used more and more in dental imaging and diagnostics. Early detection of dental pathologies, malignancies and structural anomalies is made easier by the improved resolution and target specificity provided by nanoscale contrast mediums and imaging probes. [31]

Adjunctive Diagnostic Technologies and AI

Chairside techniques including toluidine blue staining, autofluorescence imaging, chemiluminescence devices, and brush biopsy assist in identifying suspicious lesions for further evaluation. [32,33] Moreover, artificial intelligence–based image analysis and machine learning models show promising accuracy in detecting early dysplasia and predicting malignant transformation, offering significant potential to enhance early screening strategies. Oral squamous cell carcinoma has been effectively detected through remote monitoring using simple methods such as intraoral photography. [34]

Conclusion

Tobacco consumption remains a primary etiological factor in the development of a broad range of oral mucosal lesions, varying from reversible keratotic changes to life-threatening malignancies such as Oral squamous cell carcinoma. [35] The disease burden is especially pronounced in countries like India, where the widespread use of smokeless tobacco significantly contributes to oral pathology. Oral potentially malignant disorders—including leukoplakia, erythroplakia, and oral submucous fibrosis—constitute crucial transitional stages in the progression of tobacco-related carcinogenesis.

Furthermore, the growing popularity of alternative nicotine delivery systems such as electronic cigarette and heat-not-burn device introduces additional complexities in oral healthcare. These evolving trends highlight the necessity for heightened clinical vigilance, continuous professional education, and proactive preventive strategies among dental practitioners.

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