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REVIEW PAPER

Oral cancer in the aging population: molecular mechanisms, major risk factors, and preventive strategies

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Abstract

Oral cancer represents a major public health challenge worldwide and disproportionately affects older adults due to cumulative exposure to carcinogens combined with age-related biological changes, including genomic instability, chronic inflammation, impaired immune surveillance, and epigenetic dysregulation, all of which increase susceptibility to oral carcinogenesis. The burden of disease is further amplified by comorbidities and age-associated functional decline, which may complicate both prevention and treatment in geriatric populations. This review synthesizes current knowledge on molecular mechanisms linking aging biology with oral cancer development and discusses major etiological risk factors prevalent in geriatric populations, including tobacco use, alcohol consumption, dietary deficiencies, oral microbiome dysbiosis, obesity-associated inflammation, and human papillomavirus infection. The review also outlines evidence-based strategies for prevention and early detection, emphasizing lifestyle modification, smoking cessation, improved oral hygiene, and emerging chemopreventive approaches. Finally, we highlight current challenges in oral cancer screening and early diagnosis and discuss the diagnostic relevance of novel molecular biomarkers, which may support earlier detection and more accurate risk stratification.

Keywords: oral cancer, oral health, carcinogens, aging, screening

Introduction

Oral cancer is a malignant neoplasm arising most commonly in the lip, tongue, gingiva, floor of the mouth, hard and soft palate, and buccal mucosa [1]. The predominant histological subtype of oral cancer is oral squamous cell carcinoma (OSCC), which represents the most ubiquitous malignancy within the spectrum of head and neck cancers [2].

Oral cancer constitutes a significant global public health challenge. According to recent worldwide analyses, between 1990 and 2021, the number of incident cases of lip and oral cavity cancer increased by nearly 162%, while disability-adjusted life-year (DALY) rates rose by approximately 100%, reflecting not only rising incidence but also a considerable disease burden [3]. Importantly, a strong age dependence has been consistently observed for both incidence and mortality, with older age identified as a predominant risk factor. The highest incidence and mortality rates occur in individuals aged 50 years and above across all world regions and in both genders, with a marked male predominance [3]. Moreover, epidemiological projections indicate that this upward trend is likely to persist in the coming decades, largely driven by demographic shifts and population aging [4].

These data, together with a reported mean age at diagnosis ranging from 62 to 70 years, underscore the critical role of aging as a determinant of oral cancer risk and outcome [5]. As global populations continue to age, understanding the biological mechanisms underlying age-related susceptibility to oral cancer, as well as identifying modifiable risk factors and effective preventive strategies, becomes increasingly important for reducing disease burden in geriatric populations.

Aim of the work

In this review, we aim to provide a synthetic overview of the age-related molecular mechanisms predisposing older adults to oral oncogenesis, discuss key etiological risk factors prevalent in the geriatric populations, and shortly summarize both current and emerging preventive and screening approaches.

Methods

This article was designed as a narrative review aimed at providing a comprehensive overview of the topic. A literature search was conducted in PubMed, Medline, and Google Scholar databases using controlled vocabulary and keywords. The main search strategy included the search for “oral cancer” in combination with related terms, such as “aging”, “molecular mechanisms”, “risk factors”, “screening”, or “prevention”. To narrow the search outcome, the following filters were applied: inclusion of studies published in English and primarily published between 2022 and 2025, with selective inclusion of earlier landmark studies where relevant. Furthermore, this process excluded studies that did not address the primary search concepts or those written in languages other than English. The literature search period spanned from September to December 2025. Retrieved records were screened qualitatively based on titles and abstracts, and full texts were assessed for relevance to the scope of the article by independent reviewers. In addition, a manual search of reference lists and citation tracking was performed to identify further eligible studies. Final inclusion decisions were made collaboratively, and any disagreement was resolved through discussion. The studies were included based on their relevance to oral cancer in the aging population, with priority given to original research articles and high-quality reviews. Following these processes, a total of 50 articles were included in this narrative review. The included literature was subsequently organized into three thematic domains: (1) age-related molecular and biological mechanisms of

oral carcinogenesis; (2) major etiological risk factors with particular relevance to aging populations; and (3) preventive, screening, and early detection strategies, to enable a structured synthesis of the literature.

Literature review results

Age-related molecular mechanisms predisposing to oral cancer

Genomic instability and cellular senescence

Older age is associated with the gradual accumulation of molecular and cellular alterations that increase general susceptibility to oncogenesis. One of the most critical processes is genomic instability caused by lifelong exposure to endogenous and exogenous stress factors, resulting in increased genotoxic stress, oxidative damage, and a decline in DNA-repair efficiency [6]. Defects in DNA damage response (DDR) systems, including double-strand break repair pathways, have been linked to malignant transformation of oral epithelial cells and progression from potentially malignant lesions to OSCC. Telomere shortening and chromosomal instability further promote genomic fragility, facilitating oncogenic mutations [7].

Cellular senescence represents another hallmark of tissue ageing that contributes to oral carcinogenesis. Senescent cells accumulate with age and, through the senescence-associated secretory phenotype (SASP), release pro-inflammatory cytokines, growth factors and matrix-remodeling enzymes, such as interleukin-1α (IL-1α), IL-6, transforming growth factor β (TGF-β), prostaglandin E2 (PGE2), and matrix metalloproteinase-2 (MMP-2). These molecules modify the tumor microenvironment, enhance epithelial invasiveness, and support malignant progression, including OSCC [8,9].

Immunosenescence, impaired antitumor defense and epigenetic changes

Ageing also significantly affects immune surveillance. Immunosenescence and "inflammaging" together are major contributors to impaired antitumor defense. Thymic involution and reduced production of CD8+ naïve T cells, together with diminished NK-cell cytotoxicity and an increased proportion of tumor-associated macrophages and regulatory T

cells, contribute to impaired immune recognition and clearance of premalignant cells, while chronic low-grade inflammation provides a pro-tumorigenic milieu [10].

Additionally, age-related epigenetic alterations significantly contribute to oral carcinogenesis. Aberrant DNA methylation and histone modifications can silence tumor-suppressor genes and dysregulate transcriptional programs, leading to activation of oncogenic pathways. These changes, together with altered microRNAs expression profiles that are commonly observed in OSCC, may promote oral epithelial transformation and consequently contribute to oral cancer development [11].

Major risk factors of oral cancer in the geriatric population

Tobacco smoking and smokeless tobacco

The International Agency for Research on Cancer (IARC) classifies both smoked and smokeless tobacco as Group 1 carcinogens for humans [12]. Tobacco use, in all its forms, is therefore recognized as one of the most strongly established risk factors for oral cavity cancer. Notably, smokers are associated with an approximately 8.4-fold higher risk of developing oral cancer compared with non-smokers [13].

The carcinogenicity of tobacco arises from multiple mechanisms. Thermal injury and chemical irritation contribute to chronic mucosal inflammation, creating a microenvironment conducive to the development of potentially malignant lesions [14]. Tobacco also impairs periodontal tissue homeostasis by disrupting the proliferative capacity of gingival fibroblasts, as well as periodontal membrane and ligament cells, inducing their apoptosis and aggravating periodontal disease, which is an independent oral cancer risk factor further amplified by smoking [15].

Exposure to tobacco-specific nitrosamines (TSNAs) is considered a major molecular driver of tobacco-induced carcinogenesis, particularly the most carcinogenic nitrosamines in tobacco: N′-nitrosonornicotine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), and its major metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL). They are generated during tobacco processing in all types of tobacco products, including smokeless tobacco, cigarettes, and cigars. Additionally, NNN undergoes metabolic activation via CYP2A6/CYP2A13, resulting in the formation of 5'-hydroxyNNN – a highly reactive intermediate capable of producing DNA adducts, leading to replication errors and irreversible mutations central to oral carcinogenesis [16].

Alcohol consumption and diet

Excessive alcohol consumption is another well-established major risk factor for oral cancer [4]. Dietary patterns, such as the intake of nitrosamine-rich foods and dietary deficiencies resulting from a lack of fruit and non-starchy vegetables, are also considered important risk factors for oral cancer [17]. These factors are associated with higher risk of oral cancer in both male and female populations, although epidemiological data indicate gender-specific trends – males seem to more frequently exhibit high alcohol intake combined with poor diet, whereas females show a higher prevalence of inadequate dietary patterns but generally lower alcohol consumption [18]. Furthermore, vitamin deficiencies, particularly vitamin D deficiency, have been associated with additional risk for oral cancer, emphasizing the importance of detecting and correcting hypovitaminosis in clinical practice [19].

Oral microbiome and dental hygiene

Oral microbiome dysbiosis is increasingly recognized as a significant risk factor for oral cancer and may be induced by smoking, aging, or poor oral hygiene. Age-related changes in salivary flow, denture use, and reduced mechanical cleaning create favorable conditions for overgrowth of pathogenic species. Recent integrative analyses revealed that dysbiotic bacterial communities in OSCC tissue correlate with host transcriptome and CpG-methylation changes, suggesting that microbial shifts may activate oncogenic pathways [20].

Periodontal pathogens, such as *Porphyromonas gingivalis*, *Fusobacterium* spp., *Prevotella* spp., *Peptostreptococcus* spp., and *Streptococcus* spp. have been strongly linked to oral cancer development. These pathogens may drive carcinogenesis through several mechanisms: chronic inflammation that promotes a tumor-supportive microenvironment, production of genotoxic metabolites such as nitrosamines and reactive oxygen/nitrogen species, impairment of epithelial barrier integrity, promotion of epithelial cell proliferation with reduced apoptosis, and enhancement of epithelial-mesenchymal transition (EMT). Such processes may facilitate precancerous changes, DNA damage, and epigenetic alterations, including onco-miRs dysregulation, which may significantly predispose to cancer development [21,22].

Therefore, both mechanistic and epidemiological studies demonstrate strong associations between periodontitis (PD) and oral cancer [23]. Moreover, PD may not only increase cancer risk but also influence its clinical progression and therapeutic outcomes [24]. However, managing PD and maintaining adequate oral hygiene may still pose a significant

challenge in the geriatric population due to factors such as reduced manual dexterity, diminished vision, or cognitive decline [25].

Human papillomavirus infection

Human papillomavirus (HPV) is one of the major viral etiologic agents involved in the development of oral and oropharyngeal cancers. HPV16, and to a lesser extent HPV18, are those most strongly associated with carcinogenesis in the head and neck region [26]. High-risk HPV infection is linked to sexual behaviors and may be influenced by cofactors such as immunosuppression, co-infection with other viruses, chronic inflammation, genetic susceptibility, poor oral hygiene, alcohol consumption, and smoking. Oral sexual behavior and multiple partners increase oncogenic HPV infection risk, particularly among males [27].

The oncogenic activity of HPV in the oral cavity is attributed to the expression of viral oncoproteins E6 and E7, which disrupt cell-cycle regulation and promote viral DNA replication in differentiated keratinocytes. In high-risk HPV isotypes, E6 promotes ubiquitin-dependent degradation of p53, while E7 is associated with the cullin-2 (CUL2) ubiquitin ligase complex, enhancing ubiquitination and subsequent inactivation of the retinoblastoma (pRb) tumor suppressor and functionally related cellular proteins [28].

However, the prognostic significance of HPV infection differs between oropharyngeal squamous cell carcinoma (OPSCC) and OSCC. OPSCC HPV-positive is generally linked to better treatment and survival outcomes [29]. In contrast, some evidence suggests that OSCC HPV-positive status may be associated with poorer prognosis compared to HPV-negative disease [30].

Chronic inflammation and obesity

Chronic inflammation is a key biological link between obesity, aging, and increased cancer susceptibility, including OSCC. Both excess adiposity and age-related immune dysfunction promote a pro-tumorigenic inflammatory milieu through mechanisms such as altered cytokine signaling, metabolic dysregulation, and weakened antitumor immune response [31].

Emerging evidence indicates that obesity-associated chronic inflammation enhances oral carcinogenesis in part through the expansion of myeloid-derived suppressor cells (MDSCs) in the local microenvironment. The mechanism underlying this phenomenon involves the

CCL9/CCR1 axis, while a high-fat diet augments the immunosuppressive capacity of MDSCs by promoting enhanced intracellular lipid accumulation [32]. Moreover, it was found that elevated expression of MDSC-associated markers, such as CD33, has been correlated with worse prognosis, while diminution of MDSCs significantly inhibited the development of OSCC, especially in cases where obesity coexisted with OSCC. This finding may define a new direction for research and the development of therapeutic strategies for patients affected by both conditions [32].

Oral cancer prevention strategies

Lifestyle choices

Lifestyle modifications remain a fundamental strategy in oral cancer prevention, particularly in older adults, who often present with cumulative carcinogen exposure, multiple comorbidities, and age-related impairment of immune surveillance.

One of the most impactful interventions is smoking cessation. At the individual level, eliminating tobacco use and limiting alcohol consumption have been estimated to be associated with the potential avoidance of up to three-quarters of oral cancer cases, while smoking cessation has been associated with an approximately 35% lower risk of developing oral cancer within 1-4 years, up to an 80% lower risk after 20 years, and over longer follow-up-risk estimates, this may approach those observed in individuals who never smoked [33].

Dietary habits may also play a significant protective role, as a diet rich in antioxidants and nutrients, such as carotenoids, flavonoids, vitamins A, C, or E, strengthens immune function and helps protect cells from damage. It was found that regular intake of fruits and non-starchy vegetables, around five servings per day, has been linked to a substantially lower risk of oral cancer development, with each additional portion being associated with an estimated 25% lower risk [34,35].

HPV vaccination represents another essential preventive tool. Although primarily recommended for preadolescents, catch-up vaccination in older adults may be considered based on individual risk factors and clinical assessment [36]. Additional strategies, such as maintaining proper oral hygiene and attending routine dental examinations, facilitate early detection of precancerous lesions and reduce the prevalence of infections and chronic inflammatory conditions that may potentiate oral carcinogenesis [36]. Moreover, regular

physical activity, through its systemic anti-inflammatory effects and positive impact on periodontal health, may further contribute to lowering oral cancer risk [37].

Altogether, these strategies provide a broad yet practical framework for reducing oral cancer incidence. Importantly, their benefits extend beyond the oral cavity, translating into broader improvements in systemic health and overall quality of life in the aging population.

Probiotics

Probiotics have recently gained attention as a potential adjunct in oral cancer prevention due to their ability to modulate the oral microbiome, regulate host immune responses, and attenuate chronic inflammation. However, the majority of available evidence remains preclinical.

Recent studies indicate that selected probiotic strains, especially *Lactobacillus*, *Bifidobacterium*, and *Streptococcus*, may be associated with reduced inflammation, regulation of the host's immune response, preservation of microbiome homeostasis, and inhibition of carcinogenic activity. Moreover, current research has demonstrated that strains such as *Lactobacillus acidophilus* can significantly inhibit proliferation of OSCC cell lines and induce apoptosis, suggesting potential therapeutic relevance [38]. Furthermore, emerging evidence also suggests that probiotics may constitute tumor markers, which provide valuable diagnostic information that requires further clinical validation. The concept of probiotic mapping for tumor biomarkers involves the identification and characterization of specific probiotic bacterial genes with antioxidant potential and possible therapeutic relevance in tumor suppression [39].

Chemoprevention

Chemoprevention of oral cancer is the use of natural or synthetic agents to inhibit, reverse, or delay the process of carcinogenesis. This may be implemented at different stages of disease development.

Although more than 500 chemopreventive agents have been identified, only a limited number have advanced to clinical trials [40]. One of the principal molecular targets is the epidermal growth factor receptor (EGFR). Its blockade using EGFR inhibitors has been shown to suppress cancer cell proliferation and clonal expansion in selected experimental and clinical settings. Other explored strategies for oral cancer include tyrosine kinase inhibitors, vitamin A analogues, COX-2 inhibitors, metformin, immunotherapy, and various herbal extracts. These

agents may interfere with multiple stages of carcinogenesis by inducing apoptosis *in vitro*, inhibiting proliferation, suppressing inflammation, or reducing angiogenesis. However, the toxicity of some chemopreventive agents has limited their clinical applicability, underscoring the need for further studies to clarify their therapeutic potential [41].

Oral cancer screening and early detection

Oral cancer screening and early detection continue to pose a major clinical challenge. Due to the lack of effective early screening techniques, oral cancer is most often diagnosed at advanced stages, which significantly limits treatment options. Many patients receive their diagnosis only after their quality of life has already declined because of symptoms such as dysphagia, speech difficulties, and pain during eating [4]. The five-year survival rate for stage I oral cavity cancer reaches approximately 80% but decreases to about 20% in stages III and IV [18]. In addition, treatment options in elderly patients are often limited by comorbidities, thus improving oral cancer diagnosis should be a priority.

Early detection is possible through the identification of precursor lesions, such as oral potentially malignant disorders (OPMDs), which are associated with an increased risk of malignant transformation [42]. Asymptomatic individuals can be screened for both oral cancer and OPMDs through systematic visual oral examination. Although targeted screening in high-risk groups is considered cost-effective, most national health organizations do not currently recommend population-wide screening due to insufficient evidence that it reduces oral cancer mortality [43].

Attempts to establish oral cancer screening programs have demonstrated low compliance rates in Sri Lanka, the United Kingdom, and Japan. In contrast, community-based (house-to-house) screening programs in India and Sri Lanka have achieved higher participation rates [43]. The screening method most commonly used in these programs and studies involved systematic visual inspection with palpation of the oral cavity to identify abnormalities suggestive of OPMDs or oral cancer. Additionally, examination of the cervical lymph nodes was often included. Unfortunately, testing for OPMDs and oral cancer using validated biomarkers has not yet been evaluated in primary care settings, and visual screening for OPMDs has been shown to be inefficient in the general population, likely because OPMDs do not precede as many oral cancers as initially assumed [43]. Fortunately, emerging research suggests new approaches, such as the use of circulating tumor DNA (ctDNA) for earlier detection of OSCC. ctDNA is released into the bloodstream through apoptotic and necrotic processes in the

tumor and may be detectable even in patients with minimal residual disease. It also holds potential as a prognostic marker and for optimizing treatment strategies [44]. Additionally, OSCC-associated markers have been identified in saliva, including specific upregulated mRNAs confirmed in multicenter cohorts, as well as inflammatory markers such as IL-8 [45].

Potential biomarkers

Accurate and early diagnosis of oral cancer may be potentially facilitated by certain molecular biomarkers detectable in minimally invasive samples, such as plasma, saliva, serum, oral rinse, blood, or tissue biopsies. Among nucleic acid-based candidates, circulating HPV-related markers, including cfHPV DNA, HPV16, and ctHPV DNA for high-risk genotypes 16, 18, 31, 33, and 35, show elevated levels in OSCC compared with healthy controls and may support early detection or risk stratification [46,47]. Genetic alterations frequently observed in OSCC, such as mutations in *TP53*, *CDKN2A*, *PIK3CA*, *FAT1*, and *NOTCH1*, also hold potential as relevant biomarkers [48].

Epigenetic changes have likewise emerged as informative indicators of malignant transformation. Differential methylation of specific CpG sites, including cg01009664 within the *TRH* gene, has been demonstrated as a promising diagnostic tool, with a reported sensitivity of 82.61% and specificity of 92.59%, underscoring the potential relevance of methylation-based assays in OSCC screening. The cited values were obtained in a cohort study analyzing oral rinse samples from 54 healthy controls, 42 patients with oral cancer, and 24 patients with oropharyngeal cancer [49]. Before this method can be applied in routine clinical practice, further studies are needed to expand our understanding of TRH gene methylation in cancer cells.

Circulating tumor cells (CTCs) may constitute another valuable class of biomarkers. Their number correlates with OSCC stage, showing a consistent increase from stage I to stage IV. A threshold exceeding 20 CTCs has been associated with a higher likelihood of regional lymph node involvement, reflecting their potential to mirror advancement of the disease. Reported diagnostic performance of CTCs-based detection, reaching a sensitivity of 94% and specificity of 98%, highlights its potential clinical utility. A prospective, single-center study included 152 treatment-naïve patients aged 15 to 80 years with OSCC [50].

Overall, molecular biomarkers represent a rapidly evolving field with substantial promise for improving early detection, prognostication, and potentially personalized

management of OSCC. Further research and validation in large, well-designed cohorts are essential before these markers can be integrated into routine clinical practice.

Conclusions

Aging profoundly modifies the biology of the oral cavity, promoting genomic instability, chronic inflammation, and impaired immune surveillance, which together increase susceptibility to oral cancer. These age-related vulnerabilities interact with cumulative exposures – tobacco use, alcohol, dietary deficiencies, microbiome dysbiosis, and systemic comorbidities in elderly – resulting in a disproportionately high disease burden in older adults. Lifestyle-focused prevention, including smoking cessation, alcohol reduction, dietary improvement, oral hygiene, and regular dental examinations, remains the most effective approach for reducing risk. Complementary strategies such as HPV vaccination and targeted nutritional correction may provide additional benefit in selected populations.

Although population-level screening is not yet feasible, emerging molecular biomarkers, including ctDNA, epigenetic signatures, and CTCs, offer promising avenues for earlier detection and improved risk stratification. Continued research focusing on the interplay between aging biology and environmental lifestyle-related factors is crucial for developing more effective prevention and early-detection strategies in the aging population.

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