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IMPACT OF ORAL MICROBIOME DYSBIOSIS ON THE RISK, PATHOGENESIS AND TREATMENT OF HEAD AND NECK CANCERS: A LITERATURE REVIEW

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ABSTRACT

Background: Head and neck squamous cell carcinoma (HNSCC) is the seventh most common malignancy worldwide and is associated with substantial morbidity and mortality. Although tobacco use, alcohol consumption, and human papillomavirus (HPV) infection remain the principal risk factors, growing evidence suggests that oral microbiome dysbiosis may contribute to tumor initiation, progression, and treatment response.
Aim: This review summarizes current evidence linking oral microbiome dysbiosis with HNSCC, evaluates proposed biological mechanisms, and highlights major gaps requiring future investigation.
Methods: A literature review was conducted by searching PubMed, Scopus, Web of Science, and Google Scholar for studies published through March 2026.
Summary: Prospective cohort studies and case-control analyses have reported enrichment of periodontal-associated pathogens, including Fusobacterium nucleatum, Porphyromonas gingivalis, and Treponema denticola, in tumor tissues and saliva of patients with HNSCC, alongside depletion of commensal genera such as Streptococcus, Rothia, and Actinomyces. These organisms may influence carcinogenesis through NF-κB activation, Wnt/β-catenin signaling, epithelial–mesenchymal transition, apoptosis resistance, and immune modulation. Cancer therapies, particularly radiotherapy and chemotherapy, profoundly alter oral microbial communities and may worsen oral mucositis, candidiasis, and dental complications. Microbiome-targeted strategies, including probiotics, represent promising adjunctive approaches, although robust clinical validation is still required.

KEYWORDS

Oral Microbiome, Dysbiosis, Head and Neck Cancer, Squamous Cell Carcinoma, Carcinogenesis

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1. Introduction

Head and neck cancers comprise a heterogeneous group of malignancies arising from the oral cavity, oropharynx, hypopharynx, larynx, nasopharynx, and related structures [1]. Approximately 90% are histologically classified as squamous cell carcinoma, making HNSCC the seventh most common cancer worldwide, with approximately 792,000 new cases and 424,000 deaths reported globally in 2021 [1,2]. The median age at diagnosis is approximately 60 years, though the incidence among younger adults has risen in recent decades, driven largely by HPV-associated oropharyngeal carcinoma [3,4].

Despite advances in multimodal treatment - including surgery, radiotherapy, systemic chemotherapy, and immune checkpoint inhibitors - survival outcomes for advanced-stage disease remain unsatisfactory. Approximately 60% of patients present with locoregionally advanced tumors, and five-year overall survival rates for this group range from 25% to 60%, depending on subsite and HPV status [3]. Treatment itself carries substantial functional consequences affecting speech, swallowing, and quality of life, and survivors of HNSCC have among the highest rates of psychological morbidity across cancer types [5].

The principal established risk factors include tobacco use, excessive alcohol consumption, and infection with oncogenic HPV strains, particularly HPV-16. In the United States and Europe, HPV now accounts for 60 - 70% of newly diagnosed oropharyngeal squamous cell carcinomas, and the incidence of HPV-positive disease has risen sharply since the early 2000s [3]. However, a growing proportion of oral squamous cell carcinoma cases arise in individuals without traditional exposures. Ganly et al. demonstrated that periodontal pathogens were enriched in HPV-negative, nonsmoking patients with oral cavity squamous cell carcinoma, suggesting that microbial factors may contribute to carcinogenesis independently of conventional risk factors [6].

The oral cavity harbors one of the most diverse microbial ecosystems in the human body. More than 700 bacterial species have been identified across distinct ecological niches - including the tongue dorsum,

buccal mucosa, supragingival and subgingival plaque, and tonsillar crypts - with additional contributions from fungi, viruses, and archaea [7,8,9].

Population-level data from the US National Health and Nutrition Examination Survey confirm that five dominant phyla (Firmicutes, Actinobacteria, Bacteroidetes, Proteobacteria, and Fusobacteria) and six core genera (Streptococcus, Rothia, Prevotella, Veillonella, Gemella, and Actinomyces) are near-universally present and account for approximately two-thirds of total bacterial abundance [10]. Under physiological conditions, this ecosystem supports colonization resistance against exogenous pathogens, modulates mucosal immune tolerance, contributes to nitrate metabolism and pH regulation, and maintains epithelial barrier integrity [11,12,13].

Disruption of this equilibrium - termed dysbiosis - may promote chronic inflammation, impaired epithelial integrity, altered host immunity, and accumulation of carcinogenic metabolites. Analogous microbe - cancer relationships were established for Helicobacter pylori in gastric cancer and Fusobacterium nucleatum in colorectal cancer [14,15].

Over the past decade, increasing attention has focused on whether oral microbiome alterations play a parallel role in HNSCC, and the field has progressed from small cross-sectional studies toward prospective cohort analyses, mechanistic models, and early interventional trials.

This review critically synthesizes current evidence on the relationship between oral microbiome dysbiosis and HNSCC, with emphasis on the strength and limitations of epidemiological associations, proposed biological mechanisms, treatment interactions, and emerging therapeutic strategies. Where prior reviews have focused primarily on taxonomic cataloguing, this review evaluates the quality of evidence supporting each claim, integrates the most recent prospective and interventional data, and identifies important gaps requiring future investigation [16,17,18].

2. Methods

A literature review was conducted using PubMed, Scopus, Web of Science, and Google Scholar for studies published through March 2026. Search terms included combinations of "oral microbiome," "oral microbiota," "dysbiosis," "head and neck cancer," "HNSCC," "oral squamous cell carcinoma," "Fusobacterium nucleatum," "Porphyromonas gingivalis," "oral mucositis," "probiotics," and "immunotherapy microbiome." Manual screening of reference lists from eligible articles was also performed.

Included publications comprised original human studies, prospective cohorts, case-control studies, randomized clinical trials, systematic reviews and meta-analyses, and mechanistic in vitro and in vivo studies with direct relevance to HNSCC or oral microbiome biology. Isolated case reports, conference abstracts without full-text publication, and studies without direct relevance to the review topic were excluded. Priority was given to higher-quality evidence, including multicenter cohorts, prospective studies, randomized trials, and peer-reviewed systematic reviews.

3. Oral Microbiome Under Physiological Conditions

The oral cavity represents one of the most complex microbial habitats in the human body, second only to the gastrointestinal tract in ecological diversity [19].

Oral microbial communities are distributed across highly specialized niches, each with distinct physicochemical conditions - oxygen tension, nutrient availability, salivary flow, and epithelial turnover - that select for characteristic microbial assemblages [7,8]. While the oral microbiome may exhibit topographical and inter-individual diversity, its core function remains identical - to support nutritional, physiological and immunological processes [7].

The dominant bacterial phyla in healthy adults include Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, Fusobacteria, and Spirochaetes. At the genus level, Streptococcus, Veillonella, Actinomyces, Rothia, Prevotella, Neisseria, Gemella, and Haemophilus constitute the core healthy oral microbiome [8,9]. These organisms are not passive bystanders; they perform several physiologically important functions. Oral commensal Streptococci, for example, serve as primary colonizers that modulate microbial succession through hydrogen peroxide production, bacteriocin secretion, and competitive metabolite scavenging, thereby antagonizing cariogenic and periodontal pathogens [11]. The oral microbiome also contributes to host metabolic and immunological homeostasis through nitrate metabolism and maintenance of epithelial integrity [20].

The oral microbiome is relatively stable in healthy adults but remains sensitive to modifying factors including age, smoking, alcohol use, oral hygiene practices, periodontal disease, salivary flow, antibiotic exposure, systemic disease, and diet [12,13]. When these regulatory mechanisms are disrupted, microbial communities may shift toward a dysbiotic, pro-inflammatory state that has been associated with both oral disease and, increasingly, carcinogenesis.

4. Microbiome Dysbiosis in Patients with HNSCC

A growing body of evidence demonstrates that patients with HNSCC harbor distinct oral microbial profiles compared with healthy controls [21].

Kwak et al. conducted a nested case-control study within three large epidemiological cohorts, using whole-genome shotgun sequencing to characterize the oral microbiome of 236 patients who subsequently developed HNSCC and 485 matched controls. With a mean lead time of 5.1 years before diagnosis, 13 bacterial species were differentially associated with HNSCC risk. A composite microbial risk score was significantly associated with subsequent HNSCC development. Notably, no fungal taxa were associated with HNSCC in this study, despite comprehensive internal transcribed spacer sequencing [19].

Similar findings were reported by Ganly et al., who demonstrated significant enrichment of periodontal pathogens in oral cavity squamous cell carcinoma tissues compared with healthy controls, independent of tobacco, alcohol exposure, and HPV status [6].

Across multiple case-control studies and systematic reviews, a consistent pattern has emerged: enrichment of anaerobic, periodontal-associated genera (*Fusobacterium, Porphyromonas, Peptostreptococcus, Prevotella, Capnocytophaga, Treponema*) and depletion of health-associated commensals (*Streptococcus, Rothia, Actinomyces, Haemophilus, Corynebacterium*) [17,18]. Ting et al. systematically reviewed 20 studies and found that while alpha-diversity comparisons were inconsistent, beta-diversity consistently differed between HNSCC and controls [18]. Ahmad et al. conducted a systematic review of 21 studies encompassing 1,023 HNSCC patients and 837 controls, confirming these taxonomic patterns [17]. Both the red and orange complexes of periodontal pathogens are moderately yet consistently associated with an increased risk of developing head and neck squamous cell carcinoma, suggesting that dysbiosis within the oral microbiome may precede the clinical manifestation of the malignancy [22].

An important but underexplored dimension is whether microbiome profiles differ by HPV status. HPV-positive and HPV-negative HNSCC are biologically distinct diseases with different immune microenvironments, mutational landscapes, and clinical behaviors. Kylmä et al. found that Treponema denticola chymotrypsin-like protease expression was particularly associated with HPV-negative oropharyngeal tumors and correlated with distinct toll-like receptor expression patterns [23]. Oliva et al. observed that baseline oral microbiome composition in HPV-positive oropharyngeal cancer varied by stage, with increased Fusobacterium nucleatum in stage III disease [24]. However, most published microbiome studies have not stratified by HPV status, representing a significant gap in the literature that limits clinical translation.

Substantial heterogeneity exists across published studies. Investigators have used different sampling approaches (saliva, oral swabs, tumor tissue biopsies), DNA extraction techniques, sequencing platforms, bioinformatic pipelines, and reference databases. This methodological variability partly explains inconsistencies in taxa-level findings and underscores the need for standardized protocols before microbiome signatures can be reliably used as biomarkers [17,18].

5. Key Pathogens and Their Oncogenic Mechanisms

Among the microorganisms inhabiting the oral cavity, several key pathogens stand out due to their particularly strong association with the initiation and progression of HNSCC. These primarily include the bacteria Fusobacterium nucleatum and Porphyromonas gingivalis as well as Treponema denticola and the fungus Candida albicans. Each of these microorganisms possesses unique virulence factors and utilizes distinct, yet often complementary, molecular pathways to promote carcinogenesis [25].

The strength of evidence varies considerably across organisms and mechanisms, ranging from well-supported in vitro and in vivo data to preliminary clinical associations.

5.1. *Fusobacterium nucleatum*

Fusobacterium nucleatum is an anaerobic Gram-negative pathobiont whose oncogenic potential is best established in colorectal cancer but increasingly implicated in HNSCC [26].

A comprehensive review in Nature Reviews Microbiology characterized *F. nucleatum* as a key player in both local and systemic diseases, with pathogenic roles mediated through virulence factors, chronic inflammation, immune evasion, and direct tumor cell interactions. In HNSCC specifically, the evidence base is growing but remains less mature than in colorectal cancer. The bacterial adhesin FadA binds E-cadherin and activates β-catenin signaling, promoting cellular proliferation - though this pathway has been primarily characterized in gastrointestinal models and requires further validation in oral epithelial systems [27]. The outer membrane protein Fap2 interacts with TIGIT receptors on NK cells and CEACAM1 receptors on T lymphocytes, potentially suppressing antitumor immunity [14]. *F. nucleatum* activates NF-κB pathway and

induces pro-inflammatory cytokines (such as IL-1β, IL-6, TNF-α) and chemokines like CXCL2, which may promote M2 macrophage polarization and a tumor-permissive microenvironment. A systematic review by El-Dwaikat et al. encompassing 63 studies confirmed alterations in epithelial - mesenchymal transition markers, inflammatory mediators, and DNA repair pathways following *F. nucleatum* infection in OSCC models [28].

A particularly noteworthy finding is that *F. nucleatum* may impair DNA mismatch repair in HNSCC. Hsueh et al. demonstrated that high Fusobacterium abundance correlated with deficient mismatch repair and microsatellite instability in HNSCC tissues, mediated through TLR4/MYD88/miR-205-5p signaling. If validated, this would represent a direct genotoxic contribution beyond inflammation alone [29]. Additionally, Khoshbayan et al. identified significant associations between *F. nucleatum* abundance and miR-21 expression in OSCC tissues, a relationship previously reported in colorectal cancer and now observed in oral malignancy [30].

It is important to note that the strength of evidence varies across these mechanisms: immune evasion via Fap2/TIGIT and NF-κB activation are supported by multiple in vitro and some in vivo studies; FadA/β-catenin activation is primarily extrapolated from colorectal models; and the mismatch repair findings derive from a single study requiring replication.

5.2. *Porphyromonas gingivalis*

Porphyromonas gingivalis is a keystone periodontal pathogen strongly linked with periodontitis and increasingly associated with oral carcinogenesis. Lamont et al. provided a comprehensive account of its oncogenic properties, noting that P. gingivalis is oncopathogenic in animal models and that infection correlates with poor prognosis in clinical studies [31].

Proposed mechanisms include activation of Toll-like receptors (TLR2/TLR4) promoting sustained inflammatory cytokine production; proteolytic tissue remodeling through gingipains that activate matrix metalloproteinases and degrade extracellular matrix; inhibition of mitochondrial apoptosis pathways and suppression of p53 signaling; and enhancement of epithelial - mesenchymal transition and angiogenesis [27,31,32]. Additionally, gingipains - proteases produced by P. gingivalis - convert inactive proMMP-9 into the mature, active form of matrix metalloproteinase (MMP), which has the capacity to degrade the basement membrane, thereby facilitating the invasion and dissemination of neoplastic cells [33]. Chang et al. demonstrated that P. gingivalis was detected in 60.7% of OSCC tissues compared with 13.3% of normal tissues, and its presence was positively associated with advanced clinical staging, poor tissue differentiation, and lymph node metastasis [34].

A critical insight from Lamont et al. is that the microbial community context matters: consortia of *P. gingivalis* and *F. nucleatum* are synergistically pathogenic in oral cancer models in vivo, while oral streptococci such as *Streptococcus gordonii* can antagonize protumorigenic phenotypes induced by *P. gingivalis.* This supports a polymicrobial synergy model in which functional properties of bacterial communities, rather than individual species, drive carcinogenesis [31].

Because periodontitis itself is associated with increased oral cancer risk, *P. gingivalis* may represent both a direct carcinogenic contributor and a marker of chronic inflammatory disease burden. A recent systematic review by Pigossi et al. integrating clinical, preclinical, and in vitro data confirmed the link between periodontitis and oral cancer, though the precise contribution of individual pathogens versus the inflammatory environment remains debated [35].

5.3. *Treponema denticola*

Treponema denticola is a motile anaerobic spirochete belonging to the periodontal "red complex." Its key virulence factor, dentilisin (Td-CTLP), is a chymotrypsin-like protease capable of activating matrix metalloproteinases (MMP-8 and MMP-9), degrading complement proteins (C1q), impairing tissue inhibitors of metalloproteinases (TIMP-1, TIMP-2), and promoting tissue invasion through TLR2/MyD88-dependent signaling [36,37].

Immunohistochemical studies have detected Td-CTLP in the majority of orodigestive tumor samples, including tongue and oropharyngeal squamous cell carcinoma [36,38]. Listyarifah et al. found Td-CTLP in 95% of early-stage mobile tongue squamous cell carcinomas, with high immunopositivity associated with greater invasion depth and early relapse in younger patients [38]. Kylmä et al. reported that Td-CTLP was highly expressed in oropharyngeal SCC and was particularly associated with HPV-negative tumors, with distinct TLR expression patterns compared with HPV-positive disease [23].

While these findings are suggestive, the evidence for *T. denticola* in HNSCC carcinogenesis remains primarily immunohistochemical and correlative. Functional studies demonstrating direct oncogenic effects of Td-CTLP on oral epithelial cells are limited, and prospective data linking *T. denticola* abundance to cancer risk are lacking.

5.4. *Candida albicans*

Although bacterial dysbiosis dominates the literature, fungal components of the oral microbiome may also be relevant. *Candida albicans* may contribute to carcinogenesis through production of acetaldehyde (a recognized carcinogen) from ethanol, secretion of candidalysin (a cytolytic peptide toxin that damages epithelial membranes and activates inflammatory signaling), and amplification of IL-17-mediated inflammatory responses [39]. Vadovics et al. demonstrated in vitro and in murine models that *C. albicans* enhanced OSCC progression through stimulation of proliferation, invasion, and metalloproteinase expression [40].

However, the prospective study by Kwak et al. found no fungal taxa associated with HNSCC risk despite comprehensive sequencing, and current human evidence remains substantially weaker than for bacterial taxa [19]. The role of *C. albicans* in HNSCC carcinogenesis should be considered hypothesis-generating rather than established.

6. The Oral-Gut Axis

The concept of the oral-gut axis describes bidirectional communication between oral and intestinal microbial ecosystems through microbial translocation, metabolite signaling, and immune modulation. Under physiological conditions, salivary defenses, gastric acidity, and intestinal barriers maintain ecological separation between these compartments. Wu et al. described that disruption of mucosal barriers and microbial translocation along the oral-gut axis may be promoted by smoking, alcohol exposure, systemic disease, and anticancer therapy [41].

The most direct HNSCC-relevant evidence comes from Oliva et al., who demonstrated that chemoradiotherapy in HPV-positive oropharyngeal cancer patients caused a shift toward gut-like microbiome composition in oropharyngeal samples, suggesting treatment-induced disruption of compartmental boundaries [24]. Experimentally, *P. gingivalis* has been shown to alter gut permeability and inflammatory signaling in animal models, and a recent review by Wu et al. detailed organ-specific oncogenic adaptations of *P. gingivalis* and *F. nucleatum* along the oral-gut axis [41].

Short-chain fatty acids (SCFAs) - acetate, propionate, and butyrate - produced primarily by gut bacterial fermentation of dietary fiber, have immunomodulatory effects including enhancement of epithelial barrier integrity, histone deacetylase inhibition, and metabolic support of cytotoxic T-cell function. Loss of SCFA-producing bacteria has been associated with impaired antitumor immunity across several cancer types [42,43]. The oral-gut axis is an area of high translational interest, but current evidence in HNSCC is largely inferential and requires direct investigation in HNSCC patient cohorts [44].

7. Impact of Oncological Treatment on the Oral Microbiome

The treatment of HNSCC is a complex therapeutic process encompassing surgical resection, radiotherapy, chemotherapy, and immunotherapy. The selection of a specific treatment regimen depends on numerous factors, including the location of the primary tumor, the clinical stage of the malignancy, the assessment of a multidisciplinary team, and the patient's own therapeutic goals [45]. Cancer treatment profoundly disrupts oral microbial homeostasis. Radiotherapy, chemotherapy, surgery, antibiotics, altered nutrition, xerostomia, and hospitalization all contribute to dysbiosis, which may worsen oral mucositis, opportunistic infection, dental caries, and quality of life [46,47].

7.1. Radiotherapy and Chemotherapy Induced Microbiome Changes

Head and neck radiotherapy commonly damages salivary glands, resulting in xerostomia, reduced buffering capacity, lower salivary antimicrobial activity, and acidification of the oral environment [48]. A systematic review by Kwiatkowski et al. encompassing 26 studies found that post-radiotherapy, there were significant increases in Candida species, Streptococcus mutans, and Lactobacillus, with dynamic fluctuations in other taxa and decreases in beneficial bacteria such as Neisseria [46]. Lim et al. demonstrated that chemoradiation caused specific depletion of genera regulating the enterosalivary nitrate-nitrite-nitric oxide pathway, with corresponding downregulation of nitric oxide-related metabolites [49].

Boksa et al. conducted a scoping review of 62 studies and found that across chemotherapy, radiation therapy, and stem cell transplantation, oral microbial communities showed decreased evenness dominated by a few species, with reductions in commensal taxa and increases in opportunistic organisms [47]. Müller et al. stated that elevated counts of Lactobacillus may persist for up to a year following the completion of treatment, sustaining an increased risk of dental caries [50]. Moore et al. demonstrated that nearly half of the patients developed new carious lesions within 6-12 months post-radiotherapy, and every 10 Gy increase in radiation dose was associated with a 26-32% increase in the risk of caries [51]. Given the clinical significance of

treatment-induced oral microbiome changes, it is essential that oncologists and dentists cooperate to provide comprehensive pre-radiotherapy dental evaluations, followed by rigorous dental surveillance that extends throughout and beyond the post-management period [52].

In patients receiving chemotherapy, health-associated commensal bacteria from the genera Streptococcus, Actinomyces, Gemella, Granulicatella, and Veillonella are depleted, while Gram-negative bacteria such as Fusobacterium nucleatum and Prevotella oris become enriched. This shift may contribute to aggravating mucosal damage, as the enriched F. nucleatum demonstrates pro-inflammatory and pro-apoptotic capacity in oral epithelial tissues [53]. Oral mucositis is now understood as a multifactorial process involving direct epithelial injury, oxidative stress, NF-κB activation, cytokine amplification, microbial colonization of ulcerated mucosa, and delayed healing [54]. Microorganisms may not initiate mucositis alone but can intensify inflammation and prolong tissue damage. Ue et al. demonstrated that increased Fusobacterium abundance was significantly associated with the severity of radiation-induced oral mucositis, with an occupancy rate exceeding 7% after radiotherapy showing a positive correlation with mucositis severity [55]. Torozan et al. found that baseline fungal families (Melampsoraceae and Herpotrichiellaceae) were more abundant in patients who later developed high-grade mucositis, suggesting potential predictive biomarkers [56].

These findings support the emerging concept that the oral microbiome is not merely a bystander in treatment toxicity but an active contributor to its severity and duration, with implications for microbiome-targeted supportive care strategies [54].

7.2. Oral Microbiome and Immunotherapy Response

Immune checkpoint inhibitors (ICIs), particularly anti-PD-1 agents pembrolizumab and nivolumab, are established treatments for recurrent/metastatic HNSCC. However, durable benefit is limited to a subset of patients, and predictive biomarkers beyond PD-L1 expression remain inadequate [3].

Across multiple cancer types, gut microbiome composition has emerged as a determinant of ICI efficacy. Favorable responses have been associated with enrichment of *Akkermansia muciniphila, Faecalibacterium, and Ruminococcaceae,* while antibiotic exposure has repeatedly correlated with poorer outcomes [42,57].

A systematic review and meta-analysis of over 41,000 patients found that antibiotic use around the time of ICI treatment was associated with significantly shorter overall survival and poorer progression-free survival [57]. However, confounding by the underlying conditions necessitating antibiotics cannot be excluded.

HNSCC-specific data are now emerging. Rühle et al. demonstrated that salivary *Lachnoanaerobaculum* abundance was associated with improved survival in HNSCC patients undergoing chemoradiotherapy, with corresponding increases in tumor-infiltrating lymphocytes [58]. While this study did not specifically evaluate ICI-treated patients, it provides the first direct evidence linking a specific oral taxon to treatment outcomes through a plausible immunological mechanism in HNSCC.

8. Discussion and Future Microbiome-Modulating Strategies

The distinct microbial signatures observed in HNSCC raise the possibility of non-invasive screening tools based on saliva or oral swabs. Sung et al. developed a machine-learning model using microbial taxa abundance that differentiated HNSCC patients from controls with an area under the curve of 0.902, identifying *Peptostreptococcus* and *Capnocytophaga* as candidate diagnostic biomarkers [59]. De Freitas Neiva Lessa et al. found that patients with higher initial abundances of Porphyromonas and Fusobacterium had poorer outcomes including recurrence, metastasis, and death, while disease-free patients had higher Streptococcus abundance [60].

Compelling prognostic data comes from Rühle et al., who analyzed saliva samples from 92 HNSCC patients undergoing chemoradiotherapy across two independent prospective cohorts. Higher salivary *Lachnoanaerobaculum spp*. abundance was independently associated with improved locoregional recurrence-free survival and overall survival in multivariable analysis. This association was accompanied by higher CD4+ and CD8+ tumor-infiltrating lymphocyte counts and was corroborated by data from The Cancer Microbiome Atlas showing that higher intratumoral *Lachnoanaerobaculum* levels were associated with improved overall survival. This represents one of the first studies linking a specific oral taxon to treatment outcomes through a plausible immunological mechanism [58].

However, clinical implementation remains limited by the absence of standardized sampling methods, small retrospective datasets, confounding from smoking and periodontitis, inconsistent sequencing pipelines, and lack of external validation. No oral microbiome assay has regulatory approval for HNSCC diagnosis or prognostication.

Several randomized studies suggest that probiotics may reduce treatment-related oral mucositis in head and neck cancer patients. Jiang et al. conducted a randomized, double-blind, placebo-controlled trial in 99 nasopharyngeal carcinoma patients undergoing chemoradiotherapy and found that a probiotic combination significantly reduced the severity of oral mucositis while decreasing the decline in CD3, CD4, and CD8 T cells [61]. Xia et al. confirmed these findings in a phase II trial using a modified probiotic cocktail, demonstrating reduced mucositis severity and restoration of gut microbial diversity [62]. More recently, Huang et al. reported that Streptococcus salivarius M18 supplementation significantly delayed mucositis onset and reduced severe mucositis duration in nasopharyngeal carcinoma patients receiving chemoradiotherapy [63]. Goh et al. found that Limosilactobacillus reuteri was safe and associated with reduced mucositis in patients receiving radiotherapy alone, though no significant benefit was observed in the concurrent chemoradiotherapy subgroup [64].

An umbrella meta-analysis by Yang et al. encompassing multiple interventional meta-analyses confirmed that probiotic supplementation significantly reduced oral mucositis, with multi-strain formulations showing greater efficacy than single-strain preparations [65]. Pereira Riveros et al. demonstrated that a probiotic combination significantly reduced total bacterial load and specifically Fusobacterium nucleatum abundance in post-radiotherapy head and neck cancer patients, while improving stimulated salivary flow [66].

However, routine clinical adoption requires caution due to strain-specific effects, heterogeneous trial quality, uncertain optimal dosing regimens, and safety concerns in immunocompromised patients.

9. Conclusions

Head and neck cancers represent a growing public health challenge on a global scale, and the rising incidence necessitates the intensification of efforts in both prophylaxis and therapeutic strategies [1]. Accumulating evidence links oral microbiome dysbiosis with HNSCC risk, progression, and treatment-related morbidity. Enrichment of periodontal pathogens such as Fusobacterium nucleatum and Porphyromonas gingivalis, together with loss of beneficial commensals, indicates a potential role in carcinogenesis through inflammatory, immune, and metabolic pathways [67].

Experimental data support mechanisms including NF-κB activation, apoptosis resistance, epithelial–mesenchymal transition, immune evasion, and impaired DNA repair [21]. The gut microbiota also plays a complex role in the biology of head and neck cancers, modulating the processes of initiation, progression, and response to oncological treatment by sustaining systemic inflammation and regulating the host's immune response [68].

Cancer therapy further disrupts oral microbial balance, with these changes associated with oral mucositis severity. Some taxa may also predict outcomes; higher Lachnoanaerobaculum abundance has been linked to better locoregional control and survival after chemoradiotherapy. [46]

Advancing our understanding of the interplay between key pathogens and the tumor microenvironment is uncovering novel therapeutic possibilities. Strategies designed to modulate the microbiome such as use of probiotics hold the potential to enhance the effectiveness of standard oncological treatments [17].

Future priorities include large multicenter prospective cohorts, standardized methods, functional multi-omics studies, HPV-stratified analyses, longitudinal studies from premalignant lesions to cancer, and randomized trials of microbiome-targeted therapies. With proper validation, microbiome-informed strategies may support prevention, early detection, supportive care, and personalized treatment of head and neck cancer [15].

Author's contributions:

Conceptualization: P.M., S.P., Z.S., E.D.W., M.S., J.S., W.N., D.M. and P.U.; literature search and data analysis: P.M., S.P., Z.S., E.D.W., M.S., J.S., W.N., D.M. and P.U.; writing—original draft preparation: P.M., S.P., Z.S., E.D.W., M.S., J.S., W.N., D.M. and P.U.; writing—review and editing: P.M., S.P., Z.S., E.D.W., M.S.; supervision: P.M., W.N. and D.M. All authors have read and agreed to the published version of the manuscript.

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