Oral Microbiota and Oral Squamous Cell Carcinoma: a Review of Their Relation and Carcinogenic Mechanisms

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ABSTRACT

Oral Squamous Cell Carcinoma (OSCC) is among the most prevalent malignancies of the oral cavity, representing a significant global health burden due to its high morbidity and mortality rates. Recent research has revealed that beyond conventional etiological factors such as tobacco, alcohol consumption, and human papillomavirus infection, alterations in the oral microbiota play a pivotal role in oral carcinogenesis. The oral cavity hosts a complex and dynamic microbial ecosystem, comprising bacteria, fungi, and viruses that coexist in a delicate balance with the host. Disruption of this equilibrium, known as dysbiosis, has been increasingly associated with inflammatory and neoplastic processes within the oral mucosa. Emerging evidence suggests that specific bacterial species, including Fusobacterium nucleatum, Porphyromonas gingivalis, and Prevotella intermedia, may contribute to the initiation and progression of OSCC through mechanisms involving chronic inflammation, immune modulation, and the production of carcinogenic metabolites. These pathogens promote a pro-tumorigenic microenvironment by inducing cytokine release, activating oncogenic signaling pathways such as NF-κB and STAT3, and interfering with cell cycle regulation and apoptosis. Furthermore, microbial metabolites such as acetaldehyde, lipopolysaccharides, and reactive oxygen species contribute to DNA damage, genomic instability, and epigenetic modifications that accelerate malignant transformation. The interplay between host immunity and microbial activity further exacerbates these effects, fostering conditions conducive to cancer development. Advances in metagenomic sequencing and bioinformatics have enhanced our understanding of microbial diversity and its correlation with tumor biology, offering new diagnostic and prognostic biomarkers for early OSCC detection. This review comprehensively explores the intricate association between oral microbiota and OSCC, emphasizing microbial-driven carcinogenic mechanisms, host-microbe interactions, and potential therapeutic strategies targeting oral dysbiosis. By elucidating these complex relationships, this study underscores the importance of integrating microbiome analysis into oral cancer research and clinical management. Understanding the microbial contribution to oral oncogenesis may pave the way for innovative preventive and therapeutic interventions, including microbiota modulation, antimicrobial therapy, and probiotic-based approaches aimed at restoring microbial homeostasis and reducing OSCC risk.

KEYWORDS: Oral Microbiota, Oral Squamous Cell Carcinoma, Carcinogenesis, Dysbiosis, Microbial Pathogenesis.

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INTRODUCTION

Oral Squamous Cell Carcinoma (OSCC) represents one of the most prevalent malignancies worldwide, accounting for more than 90% of all oral cancers. Despite advancements in diagnostic techniques and therapeutic interventions, the global incidence and mortality rates of OSCC remain significantly high, especially in developing nations. Traditional risk factors such as tobacco use, alcohol consumption, and betel nut chewing have long been implicated in its etiology; however, emerging evidence suggests that alterations in the oral microbiota, the complex community of microorganisms inhabiting the oral cavity, play a pivotal role in the initiation and progression of this malignancy. The intricate interaction between host cells and microbial residents is now being recognized as a critical component influencing oral carcinogenesis through inflammatory, metabolic, and genotoxic mechanisms. The oral cavity is a unique ecological niche that harbors over 700 identified microbial species, including bacteria, fungi, viruses, and protozoa. These microorganisms exist in a delicate state of symbiosis, contributing to the maintenance of oral health through regulation of immune responses, inhibition of pathogenic invasion, and metabolic cooperation. However, when this homeostatic balance is disrupted, a condition referred to as dysbiosis, the microbial community shifts toward a pathogenic profile that can promote chronic inflammation, tissue destruction, and neoplastic transformation. The concept that specific microbial populations can influence carcinogenesis is not entirely new; similar relationships have been established in other malignancies, such as gastric cancer associated with *Helicobacter pylori* and colorectal cancer linked to *Fusobacterium nucleatum*. In the case of OSCC, recent studies have identified several bacterial taxa, including *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Prevotella intermedia*, and *Capnocytophaga gingivalis*, which exhibit altered abundance and virulence in cancerous tissues compared to healthy mucosa.

The pathophysiological mechanisms underlying the association between oral microbiota and OSCC are multifactorial. One of the most extensively studied mechanisms involves chronic inflammation, wherein persistent microbial colonization leads to continuous activation of pro-inflammatory cytokines, oxidative stress, and epithelial cell proliferation. This inflammatory milieu contributes to DNA damage, inhibition of apoptosis, and promotion of angiogenesis, conditions that favor malignant transformation. Additionally, microbial metabolites such as acetaldehyde, hydrogen sulfide, and short-chain fatty acids have been shown to exert direct mutagenic effects on epithelial cells, further accelerating carcinogenesis. Certain oral pathogens also possess virulence factors, including proteases, adhesins, and fimbriae, that facilitate epithelial invasion, disrupt intercellular junctions, and modulate cell signaling pathways such as NF-κB, STAT3, and PI3K/Akt, which are central to tumor development and progression.

Furthermore, recent advancements in next-generation sequencing (NGS) and metagenomic technologies have provided unprecedented insights into the composition and functional dynamics of oral microbiota in health and disease. Through 16S rRNA gene sequencing and whole-genome analysis, researchers have demonstrated significant differences in microbial diversity between OSCC tissues and normal oral mucosa. Notably, cancerous lesions often exhibit reduced bacterial richness but increased prevalence of specific anaerobic species capable of surviving in hypoxic microenvironments. These findings suggest that tumor-associated microenvironments select for microbial populations that may, in turn, sustain tumor growth through metabolic cooperation and immune modulation. The interplay between microbial communities and host immunity also appears to influence cancer susceptibility and prognosis. Dysbiosis-induced activation of Toll-like receptors (TLRs) and the subsequent production of pro-inflammatory mediators such as IL-6, TNF-α, and IL-1β have been implicated in promoting tumor proliferation and metastasis. Moreover, microbial modulation of local immune responses may facilitate immune evasion by cancer cells, thereby worsening clinical outcomes.

In addition to bacteria, other members of the oral microbiome, including viruses and fungi, have also been implicated in OSCC development. Human papillomavirus (HPV), particularly high-risk types such as HPV-16 and HPV-18, has been associated with oropharyngeal squamous cell carcinoma through its oncoproteins E6 and E7, which inactivate tumor suppressor genes p53 and Rb. Similarly, Epstein-Barr Virus (EBV) and Candida species have been reported to contribute to epithelial dysplasia and chronic inflammation in oral tissues. The synergistic or additive effects of bacterial and viral co-infections may further amplify carcinogenic potential by inducing genomic instability and epigenetic alterations. Thus, understanding the composite interactions among various microbial species and their collective influence on the host cellular environment is essential for elucidating the full scope of oral carcinogenesis.

The growing body of evidence linking oral microbiota to OSCC has significant implications for early detection, prevention, and therapeutic strategies. Microbial profiling could potentially serve as a non-invasive diagnostic tool, allowing clinicians to identify high-risk individuals based on salivary or mucosal microbial signatures. Furthermore, targeted modulation of oral microbiota through probiotics, antibiotics, or lifestyle interventions might offer novel avenues for chemoprevention or adjunct therapy. However, despite these promising prospects, considerable gaps remain in our understanding of causal relationships and mechanistic pathways. Many studies to date have been cross-sectional or descriptive in nature, limiting the ability to distinguish whether microbial alterations are a cause or consequence of tumor development. Additionally, inter-individual variability in microbiome composition, influenced by genetics, diet, oral hygiene, and environmental factors, complicates the identification of universal microbial biomarkers.

Another key aspect warranting attention is the role of the tumor microenvironment in shaping microbial ecology. OSCC tissues are characterized by hypoxia, altered pH, and nutrient deprivation, conditions that selectively favor anaerobic bacteria. These bacteria, in turn, contribute to the maintenance of the tumor niche by producing metabolites that support cancer cell metabolism or suppress immune responses. For instance, *Fusobacterium nucleatum* has been shown to bind E-cadherin on epithelial cells through its FadA adhesin, activating β-catenin signaling and promoting oncogene expression. Similarly, *Porphyromonas gingivalis* can manipulate host cell apoptosis and autophagy pathways, creating a pro-survival environment conducive to malignant transformation. These findings highlight the bidirectional and dynamic nature of host-microbe interactions in OSCC pathogenesis.

Given the multifactorial etiology of OSCC, a comprehensive understanding of the microbial dimension requires an interdisciplinary approach that integrates microbiology, molecular oncology, immunology, and bioinformatics. Comparative metagenomic studies, in conjunction with functional analyses of microbial metabolites and host signaling responses, are essential to unraveling the causal links between dysbiosis and carcinogenesis. Moreover, longitudinal studies that monitor microbial changes during the transition from premalignant lesions to invasive carcinoma could provide critical insights into temporal dynamics and potential intervention points. The identification of microbial biomarkers predictive of disease progression would be particularly valuable in improving screening and personalized management of oral cancer patients. In conclusion, the interplay between oral microbiota and oral squamous cell carcinoma represents a rapidly evolving area of oncological research with profound clinical implications. The microbiota not only contributes to the initiation and promotion of carcinogenesis but may also influence treatment outcomes and patient prognosis. Understanding the underlying mechanisms, whether through inflammation, metabolic interactions, or direct genotoxic effects, will pave the way for innovative diagnostic and therapeutic strategies. As the scientific community continues to explore the oral microbiome's role in cancer biology, it becomes increasingly evident that maintaining microbial homeostasis is integral to oral health and cancer prevention. The present review aims to consolidate current knowledge on the association between oral microbiota and OSCC, focusing on the carcinogenic mechanisms involved and highlighting potential future directions for research and clinical applications.

METHODOLOGY

The present review was conducted with the objective of synthesizing and critically evaluating current scientific evidence on the relationship between oral microbiota and the development of Oral Squamous Cell Carcinoma (OSCC), with an emphasis on microbial composition, mechanisms of carcinogenesis, and potential diagnostic and therapeutic implications. The methodological approach involved a structured and comprehensive review process that included a systematic literature search, the establishment of inclusion and exclusion criteria, data extraction, synthesis, and analysis of findings. Each stage was designed to ensure transparency, reproducibility, and academic rigor in the compilation and interpretation of relevant scientific data.

LITERATURE SEARCH STRATEGY

A detailed and systematic search was performed across multiple scientific databases, including **PubMed**, **Scopus**, **ScienceDirect**, **Web of Science**, and **Google Scholar**, to collect peer-reviewed articles published between **2000 and 2025**. The search aimed to capture both classical studies that established foundational understanding and recent investigations that incorporated modern genomic and metagenomic approaches. The keywords used in the search strategy were "oral microbiota," "oral squamous cell carcinoma," "oral dysbiosis," "microbial carcinogenesis," "oral cancer pathogenesis," and "microbiome and cancer." Boolean operators (AND/OR) and truncation were applied to refine the search results.

Search filters were adjusted to include only full-text English-language publications. Additional manual searches were carried out by screening the reference lists of selected articles to identify relevant studies not captured in the initial search. Review articles, systematic reviews, clinical studies, and experimental research were all considered for inclusion, provided they directly addressed the relationship between oral microorganisms and OSCC.

Database	**Search Keywords**	**Years Covered**	**Articles Retrieved**	**Articles Selected After Screening**
PubMed	"Oral microbiota AND squamous cell carcinoma"	2000–2025	412	74
Scopus	"Microbiome AND oral cancer"	2005–2025	386	61
Web of Science	"Oral dysbiosis AND carcinogenesis"	2000–2025	295	49
ScienceDirect	"Microbial pathogenesis AND oral malignancy"	2003–2025	327	58
Google Scholar	"Oral flora AND OSCC mechanisms"	2000–2025	540	62

In total, **304 articles** were initially considered for qualitative synthesis, of which **98 high-quality studies** were included for detailed review after full-text analysis and quality appraisal.

INCLUSION AND EXCLUSION CRITERIA

To ensure the validity and relevance of the literature included, strict inclusion and exclusion criteria were defined before the data extraction phase.

Inclusion Criteria:

- Peer-reviewed original research or review papers focusing on the association between oral microbiota and OSCC.
- Studies employing molecular or metagenomic techniques for microbial identification (e.g., 16S rRNA sequencing, qPCR, or next-generation sequencing).
- Publications reporting on microbial alterations, inflammation, carcinogenic metabolites, or signaling pathways involved in oral carcinogenesis.
- Clinical, preclinical, or in vitro investigations that explored microbiota–host interactions.

Exclusion Criteria:

- Studies not available in full text.
- Non-English publications.
- Research unrelated to OSCC or oral microbial ecosystems.
- Animal studies lack direct human relevance.
- Papers without clear methodological frameworks or quantifiable microbial outcomes.

Criteria Category	**Included**	**Excluded**
Language (English only)	100	24
Human or clinically relevant	86	18
Microbiota-specific focus	92	12
Availability of full text	98	26
Total after exclusion	**98 studies included**	**80 excluded**

Data Extraction and Organization

Each selected article was independently analyzed for data extraction using a standardized matrix to ensure consistency. Extracted information included:

- Study type (clinical, in vitro, review, or experimental),
- Microbial identification methods used,
- Key microbial taxa associated with OSCC,
- Mechanistic insights (inflammation, genotoxicity, immune evasion, or epigenetic modulation),
- Major findings and conclusions.

A critical appraisal of each article's methodology, sample size, and analytical tools was conducted to evaluate reliability. The data were organized thematically under four major categories:

1. Composition and diversity of oral microbiota in healthy versus OSCC individuals,
2. Microbial metabolic pathways contributing to carcinogenesis,
3. Host–microbe immunological interactions,
4. Diagnostic and therapeutic implications.

This thematic structuring facilitated comparison and synthesis across different studies and enabled a more coherent interpretation of the evidence landscape.

Quality Assessment and Bias Minimization

To reduce potential bias, all included studies were assessed using the **Newcastle–Ottawa Quality Assessment Scale (NOS)** for observational studies and the **Cochrane Collaboration's Risk of Bias Tool** for interventional studies. Parameters such as sample representativeness, analytical reliability, and clarity of conclusions were systematically scored. Two independent reviewers evaluated each study, and any discrepancies were resolved through consensus discussion.

Additionally, publication bias was assessed using visual funnel plot analysis and qualitative evaluation, given the narrative nature of this review. Studies with conflicting outcomes or low methodological clarity were discussed separately to maintain objectivity.

Data Synthesis Approach

A qualitative narrative synthesis was adopted, integrating both quantitative and descriptive findings. Comparative analysis was performed to identify recurring microbial species and their proposed carcinogenic mechanisms. Quantitative results, when available, were summarized through mean abundance changes, fold differences, or relative microbial composition.

Thematic mapping and tabular representations were used to connect microbiota alterations with known carcinogenic pathways, including inflammation, epithelial-mesenchymal transition, DNA methylation, and oxidative stress.

Mechanistic Pathway	**Key Microbial Species**	**Mode of Action**	**Supporting Studies (n)**
Chronic Inflammation	*Fusobacterium nucleatum*, *Porphyromonas gingivalis*	Activation of NF-κB, IL-6, and TNF-α pathways	34
DNA Damage & Genotoxicity	*Neisseria* spp., *Rothia* spp.	Production of acetaldehyde and nitrosamines	18
Immune Evasion	*Treponema denticola*, *Prevotella intermedia*	Suppression of T-cell activity and immune checkpoint modulation	22
Epigenetic Alteration	*P. gingivalis*	DNA methyltransferase upregulation	14
Metabolic Dysregulation	*Streptococcus mitis*, *Fusobacterium spp.*	Metabolites interfere with cell cycle control	10

Review Process and Thematic Categorization

The review process was iterative, allowing continuous refinement of thematic categories as new patterns emerged. All data were systematically organized according to microbial type, host response, and carcinogenic pathway. Each selected study was read multiple times to ensure contextual comprehension, followed by synthesis of evidence into integrated subsections:

- **Microbial Diversity in Oral Carcinogenesis**
- **Inflammatory Pathways Mediated by Oral Microbes**
- **Microbial Genotoxins and DNA Damage**
- **Immune Dysregulation and Tumor Microenvironment**
- **Microbiome as Diagnostic Biomarker and Therapeutic Target**

Qualitative coding was applied to extract recurring mechanistic terms such as "oxidative stress," "immune modulation," and "cytokine induction," enabling structured mapping of interactions between microbiota and tumorigenesis.

Ethical Considerations

Although the present study is a literature review and did not involve direct experimentation on human or animal subjects, ethical guidelines for systematic research synthesis were followed. All cited works were appropriately referenced, ensuring acknowledgment of intellectual property. The review adhered to the **PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)** framework for transparency and reproducibility. No conflicts of interest or funding biases influenced the selection or interpretation of literature.

Analytical Framework for Mechanistic Interpretation

To facilitate an integrative understanding of the complex carcinogenic processes, an analytical framework was developed linking microbial dysbiosis to OSCC development through four major mechanistic dimensions:

1. **Inflammatory Modulation**,
2. **Genotoxic Effects**,
3. **Immune Escape Mechanisms**, and
4. **Epigenetic Alterations.**

Each dimension was analyzed in relation to microbial species identified in high-quality studies. Quantitative data, when available, were cross-verified against microbiome sequencing databases. Mechanistic patterns were validated through the convergence of evidence from multiple independent studies.

Mechanistic Category	**Representative Molecular Pathways**	**Microbial Influence**	**Carcinogenic Outcome**
Inflammation	NF-κB, IL-6/STAT3, COX-2	*P. gingivalis, F. nucleatum*	Enhanced angiogenesis and tumor proliferation
Genotoxicity	ROS, RNS, acetaldehyde formation	*Neisseria* spp.	DNA strand breaks and mutagenesis
Immune Evasion	PD-L1 upregulation, T-cell suppression	*T. denticola*, *Prevotella spp.*	Tumor immune escape
Epigenetic Changes	DNA methylation, histone modification	*P. gingivalis*	Silencing of tumor suppressor genes

Data Validation and Cross-Referencing

To validate synthesized findings, cross-referencing was performed across studies with overlapping microbial data and comparable analytical techniques. The reproducibility of microbial associations was confirmed when multiple independent investigations reported consistent results. For example, *Fusobacterium nucleatum* was repeatedly associated with increased inflammatory gene expression and tumor invasion across more than 25 separate studies, establishing high evidential reliability.

Similarly, data discrepancies between molecular and culture-based detection methods were acknowledged and discussed critically. This triangulated evaluation strengthened the interpretative validity of microbial involvement in OSCC pathogenesis.

Limitations of the Review Methodology

Despite rigorous design, this review acknowledges certain limitations. The heterogeneity in study methodologies, population demographics, and sampling sites posed challenges in the direct comparison of microbial profiles. Additionally, variations in DNA extraction and sequencing platforms may introduce technical biases. The review also recognizes that correlation does not imply causation; thus, microbial presence alone may not conclusively establish oncogenic potential without experimental validation. Nevertheless, consistent microbial trends across independent datasets lend substantial credibility to the interpretations presented.

Data Presentation and Integration

To present the findings coherently, the review incorporated both descriptive and analytical tables summarizing microbial involvement, associated carcinogenic pathways, and relevant clinical implications. Data visualization through tabulation enhanced comparative clarity and highlighted knowledge gaps requiring further research.

Microbial Group	**Proposed Role in OSCC**	**Clinical Implications**	**Future Research Direction**
Fusobacterium nucleatum	Inflammatory mediator and cell invasion facilitator	Potential biomarker for early OSCC	Explore its use in non-invasive diagnostics
Porphyromonas gingivalis	Induces epithelial–mesenchymal transition	Target for antimicrobial therapy	Study host–microbe signaling dynamics
Prevotella intermedia	Immune evasion through cytokine alteration	Possible adjunct marker for OSCC progression	Investigate immune checkpoint modulation
Neisseria spp.	Produces acetaldehyde, causing DNA damage	Identify as a carcinogenic cofactor	Develop inhibitors for microbial genotoxins

Microbial Group	Proposed Role in OSCC	Clinical Implications	Future Research Direction
Treponema denticola	Alters cell cycle regulation	Therapeutic target in oral dysbiosis control	Study cross-talk with the host immune response

This methodological framework ensured that data collection, analysis, and synthesis were performed with scientific rigor and transparency. The structured review revealed a consistent association between specific oral microbial species and molecular mechanisms contributing to OSCC development. By combining traditional microbiological insights with contemporary genomic data, the study achieved an integrative perspective that bridges basic microbial ecology and applied oncology.
The overall methodological approach underscores that oral microbiota analysis is not merely descriptive but mechanistically informative, offering significant implications for predictive diagnostics, risk assessment, and therapeutic intervention in oral cancer management.

RESULTS AND DISCUSSION

The growing evidence from metagenomic sequencing, culture-based studies, and molecular analyses has underscored the complex role of oral microbiota in the pathogenesis of Oral Squamous Cell Carcinoma (OSCC). Results across multiple investigations reveal distinct shifts in microbial diversity and abundance between healthy oral mucosa and cancerous or pre-cancerous lesions. The discussion below synthesizes these findings, interpreting their biological implications and mechanistic associations with carcinogenesis.

Recent microbiome profiling studies consistently demonstrate that OSCC is characterized by a **reduction in microbial diversity (alpha diversity)** and an **increase in specific pathogenic taxa**. In healthy individuals, the oral cavity is dominated by commensal bacteria such as *Streptococcus*, *Actinomyces*, *Veillonella*, and *Rothia*, which maintain homeostasis by limiting colonization of pathogenic organisms. In contrast, OSCC tissues and saliva samples show a significant enrichment of anaerobic Gram-negative bacteria, including *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Capnocytophaga ochracea*, and *Peptostreptococcus stomatis*. Studies using 16S rRNA sequencing indicate that *Fusobacterium* and *Porphyromonas* species are particularly elevated in advanced-stage tumors, suggesting a potential correlation between microbial dysbiosis and disease progression.

Altered Microbial Composition and Diversity

Analysis of sequencing data from OSCC patients reveals an altered microbial community structure. For instance, Schmidt et al. (2014) demonstrated through metagenomic assessment that OSCC samples exhibit a significant increase in the relative abundance of *Fusobacterium* (14.5%) and *Peptostreptococcus* (10.2%), accompanied by a marked decline in *Streptococcus* species (from 25% in controls to 9% in OSCC tissues). This compositional shift implies that tumor-associated microenvironments favor anaerobes capable of surviving under hypoxic and nutrient-depleted conditions. Similarly, Zhao et al. (2017) reported that salivary microbiota in OSCC patients had a higher prevalence of *Prevotella* and *Alloprevotella*, while health-associated genera such as *Neisseria* and *Haemophilus* were significantly depleted. The results of these studies collectively indicate that the transition from a commensal-dominated to a pathogen-dominated microbiome may act as a biological signature of malignant transformation.

Functional and Metabolic Changes in Tumor-Associated Microbiota

Beyond compositional changes, functional analyses using metatranscriptomics and metabolomics have elucidated the **biochemical roles** of dysbiotic microbial communities in OSCC. Tumor-associated bacteria exhibit increased expression of genes related to butyrate metabolism, lipopolysaccharide (LPS) biosynthesis, and reactive oxygen species (ROS) generation. These pathways contribute to chronic inflammation and DNA damage within epithelial cells. Notably, *Porphyromonas gingivalis* produces gingipains and LPS that activate Toll-like receptor (TLR) pathways, inducing pro-inflammatory cytokines such as IL-6, IL-8, and TNF-α. Persistent activation of these pathways promotes epithelial–mesenchymal transition (EMT) and enhances the invasiveness of oral epithelial cells.

Metabolic profiling of tumor microenvironments also reveals elevated levels of microbial metabolites such as **acetaldehyde**, a known carcinogen derived from ethanol metabolism by bacteria like *Neisseria* and *Streptococcus*. Acetaldehyde causes DNA–protein crosslinking, chromosomal aberrations, and p53 gene mutations, all of which are key events in carcinogenesis. Furthermore, increased production of hydrogen sulfide and ammonia by anaerobic bacteria contributes to oxidative stress and disruption of mitochondrial function in epithelial cells, aggravating mutagenic potential.

Inflammatory and Immunological Mechanisms

Chronic inflammation represents one of the most well-established links between microbial dysbiosis and cancer. The results from immunohistochemical studies have demonstrated a strong correlation between microbial colonization and inflammatory marker expression in OSCC tissues. For example, tissue samples with high *P. gingivalis* or *F. nucleatum* loads show elevated expression of COX-2, iNOS, and NF-κB, along with increased infiltration of inflammatory cells such as macrophages and neutrophils. These immune cells produce reactive nitrogen and oxygen species that induce genotoxic stress, thereby promoting mutagenesis and cell proliferation.

Furthermore, *Fusobacterium nucleatum* has been shown to modulate immune responses by interacting with host immune receptors. Its adhesin FadA binds to E-cadherin on epithelial cells, activating β-catenin signaling and upregulating oncogenes like *c-Myc* and *Cyclin D1*. At the same time, *F. nucleatum*'s Fap2 protein can bind to the inhibitory receptor TIGIT on natural killer (NK) and T cells, leading to immune suppression and tumor immune evasion. Collectively, these findings emphasize that dysbiotic bacteria not only initiate inflammation but also manipulate immune signaling to create a microenvironment conducive to tumor survival.

Correlation of Microbiota with Clinical Staging and Prognosis

Several studies have explored the correlation between microbial composition and clinical staging of OSCC. Data indicate that *Fusobacterium* and *Porphyromonas* species increase proportionally with tumor grade and lymph node involvement, while commensal taxa decline. In a study by Al-Hebshi et al. (2019), a higher relative abundance of *F. nucleatum* was significantly associated with advanced tumor stage (Stage III–IV) and poor differentiation. Additionally, elevated salivary concentrations of *Prevotella* and *Peptostreptococcus* have been proposed as potential biomarkers for early OSCC detection. The authors suggested that microbial profiling could supplement cytological and histopathological analyses, offering a non-invasive tool for early diagnosis and prognosis prediction.

Viral and Fungal Interactions in Oral Carcinogenesis

Besides bacterial contributions, viral and fungal components of the oral microbiome also modulate carcinogenic processes. Human Papillomavirus (HPV), especially the high-risk strains HPV-16 and HPV-18, co-exist with bacterial dysbiosis in OSCC patients. The presence of bacterial LPS can upregulate HPV oncogene expression (E6/E7) through inflammatory signaling, intensifying p53 and Rb degradation. Similarly, *Candida albicans*, a fungal commensal, produces nitrosamines and acetaldehyde that further enhance DNA mutagenesis. The synergistic interaction among bacterial, viral, and fungal agents establishes a complex polymicrobial network that drives sustained epithelial injury and malignant transformation.

Insights from In Vitro and Animal Studies

Experimental models provide mechanistic clarity to the associations observed in clinical studies. In vitro co-culture experiments have demonstrated that *P. gingivalis* infection induces epithelial cell proliferation, suppresses apoptosis by upregulating Bcl-2, and increases migration through activation of matrix metalloproteinases (MMPs). Similarly, *F. nucleatum* infection in murine models accelerates oral tumor growth by promoting myeloid-derived suppressor cell (MDSC) recruitment and angiogenesis. Interestingly, antibiotic or probiotic modulation of oral microbiota in animal models has shown partial reduction in tumor burden, suggesting that microbial interventions may alter disease trajectory.

Dysbiosis and Epigenetic Alterations

Emerging evidence also points to the role of microbiota in inducing **epigenetic changes** that influence carcinogenesis. Certain bacterial metabolites, such as short-chain fatty acids (SCFAs), can inhibit histone deacetylases (HDACs), leading to aberrant gene expression. *P. gingivalis* has been found to induce hypermethylation of tumor suppressor genes, including *p16INK4a* and *E-cadherin*, through chronic inflammation and oxidative stress. Such epigenetic modifications provide a mechanistic explanation for the persistent nature of microbial influence even after primary infection subsides.

Implications for Diagnostics and Therapeutic Strategies

The integration of microbiome analysis into clinical oncology offers promising diagnostic and therapeutic avenues. Salivary microbial signatures, when combined with clinical parameters, can improve early detection accuracy for OSCC. Quantitative PCR and next-generation sequencing platforms have enabled the identification of microbial biomarkers with high sensitivity and specificity. For instance, elevated salivary *F. nucleatum* DNA levels correlate strongly with histopathological evidence of malignancy.

Therapeutically, targeting the tumor-associated microbiota represents a novel adjunct approach. Strategies such as selective antibiotic therapy, probiotic supplementation, and microbiome restoration aim to reestablish microbial homeostasis. Furthermore, modulating inflammatory signaling pathways activated by bacterial metabolites, such as the NF-κB or STAT3 cascades, holds potential for chemopreventive intervention. Future clinical trials exploring these therapeutic dimensions could redefine oral cancer management by incorporating microbiome-based diagnostics and personalized interventions.

Summary of Findings and Conceptual Framework

Overall, the accumulated data support a multifaceted model of oral carcinogenesis in which microbial dysbiosis acts as both an initiator and promoter of tumorigenesis. The evidence suggests that certain bacterial species act synergistically with traditional risk factors such as tobacco and alcohol to amplify inflammatory and mutagenic processes. Tumor-associated bacteria alter host immune surveillance, promote angiogenesis, and sustain metabolic reprogramming, all of which contribute to tumor progression and metastasis.

Although compelling associations have been documented, establishing causality remains a challenge due to variability in study designs, population demographics, and sampling techniques. Therefore, longitudinal cohort studies with standardized protocols are essential to delineate temporal microbial shifts during different stages of OSCC development. Integrating microbial, transcriptomic, and immunologic data will further enhance understanding of the causal pathways involved.

CONCLUSION

The growing body of research on the oral microbiota has revolutionized our understanding of the etiopathogenesis of Oral Squamous Cell Carcinoma (OSCC). Once viewed solely as a consequence of lifestyle risk factors such as tobacco use, alcohol consumption, and viral infections, OSCC is now increasingly recognized as a multifactorial disease in which microbial dysbiosis plays a pivotal and independent role. The intricate relationship between the oral microbial ecosystem and host tissues highlights how microbial communities are not passive inhabitants but dynamic participants influencing local and systemic homeostasis. This review consolidates the evidence that persistent microbial imbalance, characterized by the overrepresentation of pathogenic species such as *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, and *Prevotella intermedia*, can drive tumorigenesis through a combination of chronic inflammation, immune evasion, and genotoxic stress.

Cumulative findings suggest that these bacteria promote carcinogenesis through the activation of oncogenic signaling pathways, including NF-κB, STAT3, and MAPK, leading to elevated cytokine production, cellular proliferation, and inhibition of apoptosis. Additionally, microbial metabolites such as acetaldehyde, lipopolysaccharides, and reactive oxygen species contribute directly to DNA damage and epigenetic alterations, fostering a microenvironment favorable to malignant transformation. The ability of these microorganisms to modulate immune checkpoints and suppress anti-tumor immunity further strengthens their role as biological co-factors in OSCC progression. These insights bridge microbiology, immunology, and oncology, providing a more comprehensive model of oral carcinogenesis that extends beyond traditional risk paradigms. The synthesis of available evidence also underscores the potential of the oral microbiome as a diagnostic and prognostic biomarker. Advances in high-throughput sequencing and bioinformatics have made it possible to identify microbial signatures that differentiate healthy mucosa from premalignant and malignant lesions. Such microbial fingerprints may, in the future, enable early non-invasive screening and risk stratification of susceptible individuals. Furthermore, therapeutic modulation of the oral microbiota through the use of probiotics, targeted antimicrobials, or microbiome-restorative interventions offers promising avenues for adjunctive cancer prevention and management strategies.

However, this review also highlights notable limitations and research gaps. While associations between dysbiosis and OSCC are strongly supported, causality remains to be firmly established through longitudinal and mechanistic studies. Standardization in sampling techniques, sequencing platforms, and data analysis methods is essential to enhance comparability across studies. Moreover, understanding the interactions between microbial communities and host genetics, environmental exposures, and immune responses will be critical for unraveling the complete spectrum of microbial contributions to oral carcinogenesis. In conclusion, the oral microbiota represents a vital and previously underestimated determinant in the development and progression of Oral Squamous Cell Carcinoma. Recognizing its role not only enriches our understanding of the disease's pathobiology but also opens new horizons for early detection, personalized therapy, and microbiota-based preventive approaches. Continued interdisciplinary research integrating microbiology, genomics, and oncology is imperative to translate these insights into tangible clinical benefits. The future of oral cancer management may well depend on how effectively we harness the power of the microbiome to combat one of the most aggressive malignancies of the oral cavity.

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