



ORAL MICROBIOTA AND HEAD AND NECK CANCER: CARCINOGENIC MECHANISMS AND BIOMARKERS

Microbiota Oral e Câncer de Cabeça e Pescoço: Mecanismos Carcinogênicos e Biomarcadores

Microbiota Oral y Cáncer de Cabeza y Cuello: Mecanismos Carcinogénicos y Biomarcadores

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ABSTRACT

Cancer remains a significant global health problem, and the role of microorganisms in carcinogenesis has been increasingly investigated. The oral microbiota, due to its anatomical proximity and potential for translocation, emerges as a factor of interest in head and neck oncogenesis. This narrative review aims to synthesize and discuss, based on the provided literature, the associations between the oral microbiota and head and neck cancer, with emphasis on proposed carcinogenic mechanisms and biomarker potential. This is a narrative literature review constructed from the critical analysis and qualitative synthesis of seven original and review scientific articles provided as the exclusive data source. The findings indicate a consistent association of oral squamous cell carcinoma with bacteria such as *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Streptococcus mutans*, and other *Streptococcus* species, in addition to Epstein–Barr virus, human herpesvirus 8, herpes simplex virus type 1, human papillomavirus, and the yeast *Candida albicans*. In nasopharyngeal carcinoma, Epstein–Barr virus and the translocation of oral bacteria such as *Fusobacterium nucleatum* and *Prevotella*



intermedia into tumor tissue stand out. Identified carcinogenic mechanisms include: production of oncogenic metabolites (such as kynurenic acid by *S. mutans*), activation of the aryl hydrocarbon receptor, CD8⁺ T lymphocyte exhaustion, immunosuppressive reprogramming of the tumor microenvironment, induction of cancer stem cells, stress-induced dysbiosis, and bacterial translocation to extraoral sites. The oral microbiota plays a multifactorial role in head and neck carcinogenesis, acting through direct mechanisms (tumor colonization, production of oncometabolites) and indirect mechanisms (immune modulation, interaction with oncogenic viruses). The identification of specific microorganisms and their metabolites in the tumor microenvironment and saliva offers potential for the development of early diagnostic biomarkers and therapeutic targets.

Keywords: Oral microbiota; Head and neck cancer; Oral squamous cell carcinoma; Nasopharyngeal carcinoma; Carcinogenic mechanisms; Biomarkers.

RESUMO

O câncer permanece um problema de saúde global relevante, e o papel dos microrganismos na carcinogênese tem sido cada vez mais investigado. A microbiota oral, por sua proximidade anatômica e potencial para translocação, emerge como um fator de interesse na oncogênese de cabeça e pescoço. revisão narrativa tem por objetivo sintetizar e discutir, com base na literatura fornecida, as associações entre a microbiota oral e o câncer de cabeça e pescoço, com ênfase nos mecanismos carcinogênicos propostos e no potencial de biomarcadores. Trata-se de uma revisão narrativa da literatura, construída a partir da análise crítica e síntese qualitativa de sete artigos científicos originais e de revisão, fornecidos como fonte exclusiva de dados. Os estudos foram selecionados por abordarem a relação entre microrganismos orais (bactérias, vírus e fungos) e neoplasias malignas da cavidade oral, nasofaringe e cabeça e pescoço, bem como os mecanismos biológicos subjacentes. Os achados indicam associação consistente do carcinoma espinocelular oral com bactérias como *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Streptococcus mutans* e outras espécies de *Streptococcus*, além dos vírus Epstein-Barr, herpesvírus humano 8, herpes simples tipo 1 e papilomavírus humano, e da levedura *Candida albicans*. No carcinoma nasofaríngeo, destacam-se o vírus Epstein-Barr e a translocação de bactérias orais como *Fusobacterium nucleatum* e *Prevotella intermedia* para o tecido tumoral. Mecanismos carcinogênicos identificados incluem: produção de metabólitos oncogênicos (como o ácido quinurênico por *S. mutans*), ativação do receptor de aril hidrocarboneto, exaustão de linfócitos T CD8⁺, reprogramação imunossupressora do microambiente tumoral, indução de células-tronco cancerígenas, disbiose induzida por estresse crônico e translocação bacteriana para sítios extra-orais. A microbiota oral desempenha papel multifatorial na carcinogênese de cabeça e pescoço, atuando por meio de mecanismos diretos (colonização tumoral, produção de oncometabólitos) e indiretos (modulação imunológica, interação com vírus oncogênicos). A identificação de microrganismos específicos e de seus metabólitos no microambiente tumoral e na saliva oferece potencial para o desenvolvimento de biomarcadores de diagnóstico precoce e alvos terapêuticos.

Palavras-chave: Microbiota oral; Câncer de cabeça e pescoço; Carcinoma espinocelular oral; Carcinoma nasofaríngeo; Mecanismos de carcinogênese; Biomarcadores.



RESUMEN

El cáncer sigue siendo un problema de salud global relevante, y el papel de los microorganismos en la carcinogénesis ha sido cada vez más investigado. La microbiota oral, debido a su proximidad anatómica y su potencial de translocación, surge como un factor de interés en la oncogénesis de cabeza y cuello. Esta revisión narrativa tiene como objetivo sintetizar y discutir, con base en la literatura proporcionada, las asociaciones entre la microbiota oral y el cáncer de cabeza y cuello, con énfasis en los mecanismos carcinogénicos propuestos y el potencial como biomarcadores. Se trata de una revisión narrativa de la literatura construida a partir del análisis crítico y la síntesis cualitativa de siete artículos científicos originales y de revisión, proporcionados como fuente exclusiva de datos. Los estudios fueron seleccionados por abordar la relación entre microorganismos orales (bacterias, virus y hongos) y neoplasias malignas de la cavidad oral, nasofaringe y cabeza y cuello, así como los mecanismos biológicos subyacentes. Los hallazgos indican una asociación consistente del carcinoma escamocelular oral con bacterias como *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Streptococcus mutans* y otras especies de *Streptococcus*, además del virus de Epstein–Barr, herpesvirus humano 8, virus del herpes simple tipo 1, virus del papiloma humano y la levadura *Candida albicans*. En el carcinoma nasofaríngeo, destacan el virus de Epstein–Barr y la translocación de bacterias orales como *Fusobacterium nucleatum* y *Prevotella intermedia* hacia el tejido tumoral. Los mecanismos carcinogénicos identificados incluyen: producción de metabolitos oncogénicos (como el ácido quinurénico por *S. mutans*), activación del receptor de hidrocarburos de arilo, agotamiento de linfocitos T CD8+, reprogramación inmunosupresora del microambiente tumoral, inducción de células madre cancerosas, disbiosis inducida por estrés crónico y translocación bacteriana a sitios extraorales. La microbiota oral desempeña un papel multifactorial en la carcinogénesis de cabeza y cuello, actuando mediante mecanismos directos (colonización tumoral, producción de oncometabolitos) e indirectos (modulación inmunológica, interacción con virus oncogénicos). La identificación de microorganismos específicos y de sus metabolitos en el microambiente tumoral y en la saliva ofrece potencial para el desarrollo de biomarcadores de diagnóstico precoz y dianas terapéuticas.

Palabras clave: Microbiota oral; Cáncer de cabeza y cuello; Carcinoma escamocelular oral; Carcinoma nasofaríngeo; Mecanismos de carcinogénesis; Biomarcadores.

1. INTRODUCTION

Cancer constitutes one of the most serious public health problems on a global scale, demanding decades of research to elucidate its etiopathogenic mechanisms. In recent years, the scientific community has devoted increasing attention to the role played by microorganisms in the development and progression of malignant neoplasms, expanding the spectrum of risk factors beyond traditional genotoxic agents and lifestyle habits [1]. The oral cavity, being a complex ecosystem permanently exposed to a diverse microbial community, emerges as an anatomical site of particular interest for understanding host-microbiota interactions in the context of carcinogenesis [1,2].



Oral squamous cell carcinoma constitutes the most prevalent malignant neoplasm among head and neck cancers, characterized by a highly inflammatory, immunosuppressive, and aggressive tumor microenvironment [5]. Despite therapeutic advances, the precise mechanisms triggering malignant transformation of oral epithelial cells remain largely unknown, justifying the search for new etiological paradigms [4]. In this scenario, the oral microbiota has been implicated not only in tumor genesis but also in progression [5].

Several studies have demonstrated significant associations between specific microorganisms and different types of cancer affecting the upper aerodigestive tract. Bacteria such as *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, classically recognized as periodontal pathogens, are frequently found in oral squamous cell carcinoma tissues, as are *Streptococcus* species and the yeast *Candida albicans* [1]. Additionally, oncogenic viruses, notably human papillomavirus, human herpesvirus 8, herpes simplex virus type 1, and Epstein-Barr virus, have been consistently associated with head and neck neoplasms. Periodontitis, a chronic inflammatory condition mediated by dysbiotic microbial communities, has been recognized not only as a consequence of microbial imbalance but also as a potentiating factor for systemic pathological states, including oral cancer [2].

Despite advances in knowledge, significant gaps remain regarding the molecular and cellular mechanisms by which the oral microbiota exerts its carcinogenic effects. Recent studies have revealed the importance of previously unidentified microorganisms in periodontal disease progression, as well as immunological, genetic, and environmental mechanisms still poorly explored [2]. Furthermore, the etiological heterogeneity observed in neoplasms such as nasopharyngeal carcinoma, which involves complex interactions between Epstein-Barr virus infection, dietary factors, and host genetic variability, suggests that the oral microbiome may act as a yet incompletely understood risk modifier [3]. The possibility of oral microorganism translocation to extraoral sites, such as the nasopharynx, and their influence on the local tumor microenvironment opens new perspectives for investigating microorganism-mediated carcinogenesis [7].

Given the above, this narrative review aims to synthesize and critically discuss, based on the provided literature, the evidence associating oral microbiota with the development and progression of head and neck malignant neoplasms, with special emphasis on elucidating the proposed carcinogenic mechanisms and the potential clinical translation of microbial biomarkers for early diagnosis and innovative therapeutic strategies



2. METHODOLOGY

2.1 Type of Study

This is a narrative literature review, designed with the purpose of critically and qualitatively synthesizing the available scientific knowledge on the relationship between oral microbiota and head and neck cancer. The choice of this design is justified by the heterogeneous and multifaceted nature of the primary studies, which include experimental investigations, case-control studies, and literature reviews, allowing for an integrative approach to the findings.

2.2 Data Sources and Search Strategy

The primary database for study selection was PubMed, as explicitly stated in one of the provided articles [1]. However, for the present review, the entire analytical corpus was constituted exclusively by the seven full articles and their respective abstracts, kindly provided by the requester. These articles were considered as the sole source of primary and secondary data, ensuring absolute fidelity to the original content.

2.3 Eligibility Criteria

All provided articles were included, regardless of publication year, provided they addressed, in their abstracts or full text, the theme of oral microbiota (bacteria, viruses, fungi) in association with head and neck malignant neoplasms, including oral squamous cell carcinoma, nasopharyngeal carcinoma, and head and neck squamous cell carcinoma. Original studies (experimental and observational) and review articles were considered. No exclusion criteria were applied, as all submitted material proved pertinent to the review scope.

2.4 Data Collection

Data extraction was performed through analytical and critical reading of each provided abstract. Pertinent information was organized into thematic categories, including: (1) types of microorganisms associated with each neoplasm; (2) proposed carcinogenic mechanisms; (3) modifying factors (stress, diet, immunity); (4) potential biomarkers; and (5) clinical and translational implications. Only information explicitly mentioned in the abstracts was considered for synthesis.



2.5 Data Analysis

Extracted data were subjected to qualitative content analysis, aiming to identify consensus, divergences, and gaps in the literature. The synthesis of findings was structured to allow comparison between different studies, identification of recurring patterns, and construction of a cohesive narrative faithfully reflecting the state of knowledge as presented in the abstracts. No statistical methods or quantitative analysis software were employed.

2.6 Ethical Aspects

As this is a narrative literature review using secondary data from the public domain and previously published, submission to a Research Ethics Committee was not required. The conduct of this study respected principles of scientific integrity, with due attribution of authorship and original sources for all presented information.

3. RESULTS AND DISCUSSION

Analysis of the provided abstracts reveals a robust and multifaceted body of evidence associating oral microbiota with carcinogenesis in head and neck sites. The following discussion is organized to sequentially explore specific microbial associations, underlying molecular and cellular mechanisms, modulating factors, and emerging clinical implications.

The association between oral microorganisms and oral squamous cell carcinoma is one of the most consistent findings in the analyzed literature. Stasiewicz and Karpiński [1] synthesize evidence implicating a wide range of agents, including bacteria such as *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, and various *Streptococcus* species, in addition to oncogenic viruses (human papillomavirus, human herpesvirus 8, herpes simplex virus type 1, and Epstein-Barr virus) and the fungus *Candida albicans*. This plurality of microorganisms suggests that oral carcinogenesis is not attributable to a single pathogen but rather to a dysbiotic microbial consortium whose composition and interactions may determine oncogenic risk. Saikia and colleagues [5] corroborate this view by highlighting the involvement of *Human papillomavirus*, *Porphyromonas gingivalis*, and *Fusobacterium nucleatum* in tumor initiation, progression, and maintenance of stemness, suggesting that these microorganisms act synergistically with cancer stem cells and their niche to promote tumorigenesis.



Regarding nasopharyngeal carcinoma, the literature points to a more complex etiology, in which Epstein-Barr virus plays a central role. Chang and collaborators [3] describe the fascinating epidemiology of this neoplasm, marked by restricted geographic distribution and association with Chinese-style salted fish, but also emphasize the profound impact of EBV genetic sequence variation and possible effects of oral health and the oral microbiome. Advancing in this direction, Liao and collaborators [7] provide innovative evidence of microbial translocation from the oral cavity to the nasopharynx in patients with nasopharyngeal carcinoma. The study demonstrated that thirteen bacterial species, classified as oral-translocated, are enriched in the tumor, with *Fusobacterium nucleatum* and *Prevotella intermedia* validated by culturomics. The presence of these bacteria within the tumor was confirmed by nasopharyngeal biopsy metatranscriptomes, where they demonstrated the ability to influence the local microenvironment and cytokine response, in addition to correlating significantly with EBV viral load in the nasopharynx.

Investigation of carcinogenic mechanisms mediated by oral microbiota reveals sophisticated and interconnected molecular pathways. Zhou *et al.* [4] identified a novel mechanism involving *Streptococcus mutans* in oral squamous cell carcinoma. Saliva from patients with the neoplasm, but not from healthy controls, promoted carcinogenesis in animal models, and metabolomic analysis revealed elevated levels of kynurenic acid in both saliva and tumor tissues. The authors demonstrated that *S. mutans* colonizes tumor tissues and, through its protein antigen c, mediates KYNA overproduction. This oncometabolite acts by remodeling the tumor microenvironment, preferentially expanding S100a8^{high} S100a9^{high} neutrophils that produce interleukin 1 β . IL-1 β , in turn, amplifies the neutrophil population and induces CD8⁺ T lymphocyte exhaustion, creating an immunosuppressive environment favoring tumor progression. Additionally, KYNA compromised the efficacy of therapeutic blockades against PD-L1 and IL-1 β , and aryl hydrocarbon receptor expression correlated with poorer patient survival.

Concurrently, Lou and collaborators [6] explored the impact of chronic restraint stress on oral microbiota modulation and promotion of head and neck squamous cell carcinoma. Mice subjected to stress developed higher tumor incidence and oral microbial dysbiosis, with enrichment of *Pseudomonas* and *Veillonella* and depletion of *Corynebacterium* and *Staphylococcus*. Transfer of microbiota from stressed animals to germ-free mice was sufficient to promote tumorigenesis, cause oral and gut barrier dysfunction, and induce a host metabolome shift with increased plasma kynurenine.



Mechanistically, under stress conditions, kynurenine activated aryl hydrocarbon receptor nuclear translocation in CD8⁺ T cells and promoted its deubiquitination, leading to cell exhaustion and facilitating tumorigenesis. Notably, this study converges with that of Zhou *et al.* [4] in identifying the KYNA/Kyn-AHR axis as a central pathway in microbe-mediated immunosuppression, albeit in different inducing contexts (chronic stress vs. *S. mutans* colonization).

The interrelationship between microbial dysbiosis, inflammation, and cancer is also explored by Sedghi and collaborators [2], who review periodontal disease progression as a vicious cycle involving dysbiotic microbial communities and aberrant immune responses. The authors highlight the reciprocal importance of periodontitis in potentiating systemic pathological states, including oral cancer, suggesting that chronic periodontal inflammation may create a microenvironment conducive to malignant transformation and tumor progression. This perspective is complemented by Saikia *et al.* (5), who propose that oral microbiota activates inflammatory pathways and stemness pathways associated with cancer stem cells, modulating the oral mucosal stem cell niche and cancer stem cell defense niche to induce tumor initiation and progression.

An emerging consensus among studies is the central role of the tumor microenvironment as a target of microbial modulation. Zhou *et al.* [4] demonstrate that *S. mutans* metabolically reprograms the tumor microenvironment, while Liao *et al.* [7] evidence that bacteria translocated to the nasopharynx influence the local microenvironment and immune response. Saikia *et al.* [5] postulate that interactions between microorganisms, cancer stem cells, and niche cells are determinants for tumor progression and stemness maintenance. Together, these findings indicate that oral microbiota acts not only as an inducer of cellular transformation but also as a persistent modulator of the tumor ecosystem, favoring immune evasion and therapeutic resistance.

Point divergences can be identified regarding the relative weight of different risk factors. Chang and collaborators [3] observe, in their case-control study in southern China, a diminished role of Chinese-style salted fish in nasopharyngeal carcinoma etiology, contrasting with the classic historical association, and point to the emergence of new factors, such as household air pollution and the oral microbiome. This evolution in risk profile suggests that NPC epidemiology is dynamic and possibly modified by environmental and lifestyle changes.

The clinical implications of these findings are promising and multifaceted. The identification of specific microorganisms associated with tumors, such as *S. mutans* in OSCC [4] and *F. nucleatum* in



NPC [7], opens perspectives for developing salivary or tissue biomarkers for early diagnosis and risk stratification. The correlation between bacterial load and EBV viral load in the nasopharynx [6] suggests that microbiota may serve as a modifiable cofactor in viral oncogenesis. Additionally, the elucidation of mechanisms such as oncometabolite production (KYNA/Kyn) and AHR activation [4,6] points to new therapeutic strategies, including microbiota modulation, inhibition of microbial metabolic pathways, and blockade of immunomodulatory receptors.

Limitations inherent to current knowledge must be acknowledged. Significant gaps remain regarding the precise mechanisms by which oral dysbiosis is initiated and maintained, interindividual heterogeneity in susceptibility to tumor colonization by oral bacteria, and the complex interaction between multiple microorganisms and the host immune system. The need for large pooled studies, with detailed exposure data collection, is emphasized by Chang *et al.* [3] as fundamental to unraveling the intricate network of environmental, genetic, and viral causes of nasopharyngeal carcinoma.

4. CONCLUSION

The present review, based exclusively on the provided abstracts, allows concluding that the oral microbiota plays an unequivocal and multifaceted role in head and neck carcinogenesis, acting through direct and indirect mechanisms that converge on promoting malignant transformation and tumor progression. Evidence demonstrates that bacteria such as *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, and *Streptococcus mutans*, viruses such as Epstein-Barr virus and human papillomavirus, and fungi such as *Candida albicans* are consistently associated with neoplasms, whether through tumor colonization, production of oncogenic metabolites, or modulation of host immune response.

The scientific and clinical relevance of these findings lies in broadening the etiological paradigm of head and neck cancers, which now incorporates microbial dysbiosis as a modifiable risk factor potentially targetable by preventive and therapeutic interventions. The identification of specific molecular pathways, such as kynurenic acid production by *Streptococcus mutans* and consequent CD8⁺ T lymphocyte exhaustion mediated by the aryl hydrocarbon receptor, offers promising targets for developing salivary and tissue biomarkers for early diagnosis, as well as for formulating innovative therapeutic strategies, including microbiota modulation and pharmacological blockade of oncometabolites and their receptors.



For future research, conducting large-scale longitudinal studies capable of establishing robust causal relationships between specific microbial exposures and neoplasm development is recommended, as well as investigating the potential of probiotic, prebiotic, or antimicrobial interventions in primary and secondary prevention of head and neck cancer. Additionally, the integration of multi-omic analyses (metagenomics, metabolomics, transcriptomics) in paired saliva, tumor, and blood samples may elucidate complex host-microorganism interactions and accelerate the clinical translation of this knowledge to precision oncology.



REFERENCES

1. Stasiewicz M, Karpiński TM. The oral microbiota and its role in carcinogenesis. **Semin Cancer Biol.** 2022;86(Pt 3):633-642. doi:10.1016/j.semcancer.2021.11.002
2. Sedghi LM, Bacino M, Kapila YL. Periodontal disease: the good, the bad, and the unknown. **Front Cell Infect Microbiol.** 2021;11:766944. doi:10.3389/fcimb.2021.766944
3. Chang ET, Ye W, Zeng YX, Adami HO. The evolving epidemiology of nasopharyngeal carcinoma. **Cancer Epidemiol Biomarkers Prev.** 2021;30(6):1035-1047. doi:10.1158/1055-9965.EPI-20-1702
4. Zhou J, Hu Z, Wang L, Hu Q, Chen Z, Lin T, *et al.* Tumor-colonized *Streptococcus mutans* metabolically reprograms tumor microenvironment and promotes oral squamous cell carcinoma. **Microbiome.** 2024;12(1):193. doi:10.1186/s40168-024-01907-9
5. Saikia PJ, Pathak L, Mitra S, Das B. The emerging role of oral microbiota in oral cancer initiation, progression and stemness. **Front Immunol.** 2023;14:1198269. doi:10.3389/fimmu.2023.1198269
6. Lou F, Yan L, Luo S, Dong Y, Xu J, Kang N, *et al.* Dysbiotic oral microbiota-derived kynurenine, induced by chronic restraint stress, promotes head and neck squamous cell carcinoma by enhancing CD8⁺ T cell exhaustion. **Gut.** 2025;74(6):935-947. doi:10.1136/gutjnl-2024-333479
7. Liao Y, Wu YX, Tang M, Chen YW, Xie JR, Du Y, *et al.* Microbes translocation from oral cavity to nasopharyngeal carcinoma in patients. **Nat Commun.** 2024;15(1):1645. doi:10.1038/s41467-024-45518-2