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RISK OF GASTROINTESTINAL CANCER AND THE ORAL MICROBIOTA – REVIEW

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ABSTRACT

The oral microbiota, comprising over 700 bacterial species, plays a critical role not only in oral health but also in systemic diseases, including gastrointestinal (GI) cancers. Increasing evidence demonstrates that oral dysbiosis contributes to the initiation and progression of colorectal, gastric, esophageal, and pancreatic cancers through mechanisms involving chronic inflammation, immune modulation, carcinogenic metabolite production, and microbial translocation along the oral–gut axis. Key pathogens such as Fusobacterium nucleatum and Porphyromonas gingivalis have been detected within GI tumor tissues, where they influence tumor microenvironment remodeling, metastatic potential, and treatment resistance. Clinically, distinct oral microbial signatures offer promising non-invasive biomarkers for early cancer detection and prognosis. Preventive strategies targeting oral hygiene and periodontal health, alongside therapeutic approaches modulating the oral microbiome, hold substantial potential for reducing GI cancer risk. Understanding oral–GI microbial interactions through standardized and multi-omic methodologies will further advance precision oncology.

KEYWORDS: *Oral Microbiota, Gastrointestinal Cancer, Dysbiosis, Biomarkers, Fusobacterium Nucleatum*

INTRODUCTION

The oral cavity harbors the second largest and one of the most diverse microbiomes in the human body, comprising more than 700 identified bacterial species with higher alpha diversity than the gut microbiome. Although taxonomically and functionally distinct, the oral and gut microbiota remain closely connected through the oral–gut axis, allowing continuous microbial and immunological interactions that influence systemic health.[1] Growing evidence indicates that oral dysbiosis an imbalance in the oral microbial community plays a significant role in the development and progression of gastrointestinal (GI) cancers. Oral pathogens such as *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, and *Streptococcus* species have been detected not only in the oral cavity but also within tumor tissues of patients with esophageal, gastric, and colorectal cancers, suggesting a direct contribution to carcinogenesis.[2] These microorganisms may promote tumor initiation and progression through multiple mechanisms, including chronic inflammation, production of carcinogenic metabolites, immune modulation, disruption of host cell signaling pathways, and translocation to the GI tract where they alter gut microbial balance and mucosal immunity.[3]

Poor oral hygiene and increased periodontal pathogens are increasingly recognized as risk factors for GI precancerous lesions and malignancies, reinforcing the importance of the oral microbiome in systemic disease.[4] Consequently, managing oral health and modulating the oral microbiota through hygiene practices, dietary interventions, probiotics, or targeted antimicrobial strategies hold potential for reducing GI cancer risk. Moreover, emerging research highlights the promise of oral microbial signatures as non-invasive biomarkers for early cancer detection. Collectively, the evidence highlights the influential role of the oral microbiome in shaping GI cancer susceptibility and progression, positioning oral microbial monitoring and intervention as important components of future preventive and therapeutic strategies.[5]

Oral Microbiota: Composition and Functions

The oral microbiota comprises a complex community of commensal and pathogenic microorganisms that collectively maintain or disrupt oral and systemic health. The core oral microbiome includes beneficial commensal bacteria such as *Streptococcus oralis* and *Actinomyces* species, which support oral homeostasis by regulating immune responses and preserving mucosal integrity, while pathogenic organisms like *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* can initiate inflammation and contribute to periodontal disease.[6] The overall composition of this microbiota is shaped by several determinants, including dietary habits that influence nutrient availability, oral hygiene practices that regulate plaque formation, underlying periodontal inflammation that shifts the microbial balance toward pathogenic species, lifestyle factors such as tobacco and alcohol use that disturb microbial stability, and systemic conditions like diabetes or immunodeficiencies that alter immune–microbial interactions.[7] Oral bacteria can disseminate beyond the oral cavity through hematogenous routes, especially in the presence of periodontal inflammation that allows microbial entry into the bloodstream, or through direct swallowing, enabling translocation to the gastrointestinal tract where they can alter gut microbial balance. Additionally, oral microbes influence

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distant tissues via systemic immune modulation, contributing to inflammatory processes and altered host responses.[8]

Pathophysiological Pathways Linking Oral Microbiota to GI Cancer

Oral microbiota contribute to gastrointestinal carcinogenesis through multiple interconnected pathophysiological mechanisms involving inflammation, immune modulation, metabolic by-products, and epigenetic alterations. Microbial dysbiosis in the oral cavity triggers chronic inflammation by activating signaling pathways such as NF-κB, leading to increased production of pro-inflammatory cytokines including TNF-α and IL-6 that create a tumor-promoting microenvironment; pathogens like *Porphyromonas gingivalis* further enhance cancer invasiveness through the induction of matrix metalloproteinases and epithelial–mesenchymal transition. In addition to inflammatory effects, pathogenic oral bacteria promote immune evasion by inhibiting T-cell activity and expanding myeloid-derived suppressor cells, thereby weakening anti-tumor immunity and contributing to tumor progression and chemotherapy resistance.[9,10]

Metabolically, oral microbes generate carcinogenic substances such as acetaldehyde from alcohol metabolism, as well as nitrosamines and imbalanced short-chain fatty acids, which can damage DNA and cellular structures and foster tumor initiation. Moreover, certain oral pathogens drive epigenetic and genetic modifications, including DNA methylation that silences tumor suppressor genes and destabilizes genomic integrity, ultimately facilitating oncogenesis.[11]

Oral Microbiota and Specific Gastrointestinal Cancers

Colorectal Cancer (CRC)

Fusobacterium nucleatum (*F. nucleatum*) is one of the most thoroughly investigated oral bacteria implicated in colorectal cancer (CRC), recognized for its ability to ectopically colonize the gut and actively contribute to tumor initiation, progression, and treatment resistance.[13] While some oral bacteria such as *Campylobacter* species and *Stomatobaculum* have shown protective associations with CRC , *F. nucleatum* is consistently linked to pathogenic outcomes. It shapes the tumor microenvironment by activating the NF-κB pathway and upregulating chemokines like CCL20, which promote macrophage recruitment and polarization toward the tumor-supportive M2 phenotype, thereby facilitating immune evasion and cancer progression.[14]

Through its virulence adhesins, particularly FadA and Fap2, *F. nucleatum* directly interacts with CRC cells, driving pro-inflammatory and oncogenic signaling and enhancing cancer cell migration, invasion, and metastatic potential in experimental models.[15] Beyond tumor growth, *F. nucleatum* plays a significant role in chemoresistance by modulating autophagy pathways and suppressing chemotherapy-induced apoptosis, enabling tumor cells to withstand treatment. Its detectable presence in stool, saliva, or tumor tissue has positioned *F. nucleatum* as a promising microbial biomarker for early CRC detection, prognosis, and risk stratification. Overall, *F. nucleatum* functions as both a driver and indicator of colorectal cancer, influencing immune modulation, tumor microenvironment remodeling, metastatic behavior, and therapeutic response.[16]

Gastric Cancer and the Oral Microbiota

The oral microbiota plays a significant role in gastric cancer development through its interaction with *Helicobacter pylori* and its ability to modulate gastric inflammation and mucosal integrity. Oral pathogens such as *Porphyromonas gingivalis* and *Fusobacterium nucleatum* can translocate to the stomach, where they colonize the gastric mucosa and exacerbate *H. pylori*-driven inflammation, accelerating precancerous changes including chronic gastritis, atrophy, and intestinal metaplasia.[17] Evidence shows that *P. gingivalis* and *F. nucleatum* amplify *H. pylori* virulence by altering gastric microbial diversity, promoting epithelial barrier disruption, and triggering heightened pro-inflammatory responses, forming a synergistic "*H. pylori* initiation–non-*H. pylori* acceleration" pathway similar to mechanisms observed with *Streptococcus anginosus*.[18]

These oral anaerobes activate NF-κB signaling and elevate cytokines such as IL-6 and TNF-α, contributing to persistent inflammation and progression along the Correa cascade toward gastric dysplasia and carcinoma. In addition to these well-established pathogens, specific microbial risk profiles have been identified: *Veillonella rogosae* is associated with an increased odd of gastric cancer (OR = 1.14), likely through its nitrate-reducing capacity and pro-inflammatory potential, whereas *Haemophilus_D* demonstrates a protective effect (OR = 0.86), possibly by competing with pathogenic taxa or supporting mucosal homeostasis.[20]

Esophageal Cancer and the Oral Microbiota

The oral microbiota plays a central role in esophageal carcinogenesis, particularly through mechanisms driven by periodontal pathogens that promote chronic inflammation, mucosal injury, and immune dysregulation. Periodontal disease is strongly associated with increased esophageal cancer risk, with *Tannerella forsythia*—a major red-complex bacterium showing a notable link to esophageal adenocarcinoma (EAC). *T. forsythia* induces high levels of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α and activates NF-κB signaling, resulting in persistent mucosal inflammation and epithelial damage that facilitate tumor initiation.[19] Additional high-risk pathogens, including *Fusobacterium periodonticum* and *Fusobacterium massiliense*, are enriched in esophageal cancer tissues, with odds ratios of 1.36 and 1.31, respectively, and contribute to oncogenesis through epithelial barrier disruption, oxidative stress, and enhanced oncogenic signaling.[20]

Oral bacterial translocation also exacerbates gastroesophageal reflux disease (GERD), promoting chronic esophagitis and advancing the progression to Barrett's esophagus—a key precursor to EAC—via reactive oxygen species generation, DNA damage, and matrix metalloproteinase (MMP-2/9) overexpression that supports tissue remodeling and invasion.[21] Sustained colonization by anaerobic periodontal pathogens drives intraepithelial neoplasia and may contribute to both adenocarcinoma and squamous cell carcinoma development.[22]Conversely, certain commensal taxa such as *Streptococcus* and *Neisseria* appear protective, offering up to a 24% reduction

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in esophageal cancer risk, potentially through detoxification of tobacco-related carcinogens and maintenance of mucosal barrier stability. These microbial associations highlight the importance of the oral–esophageal microbial axis in disease progression and reinforce the role of oral hygiene and periodontal care as potential preventive strategies against esophageal cancer.[23]

Pancreatic Cancer and the Oral Microbiota

The oral microbiota has emerged as an important contributor to pancreatic cancer (PC) development, with strong associations observed between periodontal pathogens and increased PC risk. *Porphyromonas gingivalis* (*P. gingivalis*) and *Aggregatibacter actinomycetemcomitans* (*A. actinomycetemcomitans*) are among the most consistently linked bacteria, as evidenced by elevated antibody levels against these species in PC patients. *P. gingivalis*, a major keystone pathogen in periodontitis, can disseminate from the oral cavity to the pancreas, where it enriches the intratumoral microbiome and promotes tumor initiation and progression.[25] These pathogens contribute to carcinogenesis primarily through systemic inflammation, immune dysregulation, and remodeling of the tumor microenvironment. Chronic low-grade inflammation is driven by the formation of neutrophil extracellular traps (NETs), elevated neutrophil elastase, and increased pro-inflammatory cytokines, all of which foster a tumor-supportive microenvironment characterized by tumor-associated neutrophils. *P. gingivalis* can also persist intracellularly within pancreatic cancer cells, activating oncogenic pathways through LPS-mediated signaling, NF-κB activation, and enhanced survival under hypoxic conditions, while *A. actinomycetemcomitans* induces similar immune disturbances and promotes epithelial–mesenchymal transition.[26] Additionally, oral pathogens reshape the tumor microenvironment by recruiting immunosuppressive immune cells, increasing proliferative markers such as Ki67, and accelerating tumor growth, as demonstrated in oral-to-pancreas translocation models. These mechanisms highlight a direct pathophysiological link between periodontal disease and pancreatic cancer, suggesting that maintaining good oral hygiene and managing periodontal infections may reduce PC risk, while microbial biomarkers hold promise for improving early detection and prognosis.[27]

Clinical Implications of Oral Microbiota in Gastrointestinal Cancers

The oral microbiota has become a valuable clinical focus in gastrointestinal (GI) oncology due to its diagnostic, preventive, and therapeutic relevance. Distinct oral microbial signatures serve as effective non-invasive biomarkers for early detection and prognosis of colorectal and gastric cancers, with salivary profiles involving species such as *Campylobacter gracilis*, *Neisseria oralis*, and *Treponema medium* demonstrating strong discriminatory ability between cancer patients and healthy individuals.[28] Incorporating oral microbial risk scores alongside clinical factors further enhances prognostic accuracy in colorectal cancer, while the detection of pathogenic taxa such as *Fusobacterium* and *Porphyromonas gingivalis* within tumor tissues correlates with poor survival, reinforcing their prognostic value. From a preventive standpoint, maintaining oral hygiene and managing periodontal disease are essential to reducing oral dysbiosis and the associated GI cancer risk, supported by lifestyle practices such as smoking cessation, moderated alcohol consumption, and adherence to a healthy diet.[29] Therapeutically, modulation of the oral microbiome through probiotics, prebiotics, and targeted antimicrobial strategies offers promising avenues for restoring microbial balance and suppressing carcinogenic pathogens. Advancements in oral microbial DNA-based liquid biopsies further support precision oncology by enabling real-time monitoring of treatment response and disease progression.[30]

Conclusion

The growing evidence highlights the significant mechanistic and epidemiological role of the oral microbiota in the development and progression of gastrointestinal cancers. However, standardized methodologies and deeper strain-level analyses are essential to strengthen causal inferences and improve clinical applicability. Integrating multi-omics approaches including metagenomics, metabolomics, and proteomics will enable a more comprehensive understanding of oral–GI microbial interactions. Ultimately, early identification of dysbiosis and targeted microbial modulation hold strong promise for advancing prevention, early detection, and precision oncology in gastrointestinal malignancies.

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