Periodontitis and Oral Cancer Risk

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KEYWORDS

• Oral cancer • Periodontitis • Microbiome

KEY POINTS

- Periodontitis is associated with a systemic chronic inflammatory state which may indirectly contribute to the risk of cancers, including those of the mouth.
- Given significant differences in the epidemiologic and clinical features of oral cancer and periodontitis, it is unlikely that periodontal disease directly impacts oral cancer risk.
- Proof of an association between a specific microbiome as a driver of oral cancer risk requires significantly more research.

INTRODUCTION

Does Epidemiologic and Etiologic Data Support an Association Between Periodontitis and Oral Cancer? Do Both Diseases Share Common Risk Factors?

A link between periodontitis and oral cancer risk has been the subject of interest for years. Originally triggered by the observation that poor oral hygiene was commonly seen in patients with oral cancer and then catalyzed by an implied role for the oral microbiome, periodontitis has even been proposed as a specific risk factor for oral cancers.[1] Alternatively, the relationship between the two diseases seems more likely to be attributable to periodontitis' contribution to a systemic chronic inflammatory state which may lower the threshold for the development of malignancies, including oral cancer.

The destruction of periodontal tissues, which characterizes clinical periodontitis, is a consequence of a local inflammatory response which is associated with microbial dysbiosis and an exaggerated host immune response. Bacterial biofilms trigger a cascade

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Abbreviations	
CRP	C-reactive protein
IL	interleukin
RCT	randomized controlled trial
TNF-α	tumor necrosis factor-alpha

of inflammatory events, leading to tissue breakdown and systemic immune activation.[2] In the United States, approximately 42.2% of adults aged 30 years or older exhibit some form of periodontal disease with 7.8% experiencing severe cases and 34.4% classified as mild or moderate.[3,4] In quantitative terms, around 16.4 million US adults are affected by severe periodontitis.

Whereas the number of US adults with significant periodontal disease is in the millions, new cases of oral and oropharyngeal cancers account for only 3% of new cancers or about 60,000 patients per year.[5] Of new cases, the majority impact the oropharynx, the remainder (~24,000) are localized to the oral cavity.[6] Oral cancer is driven by well-established risk factors. Tobacco use and alcohol consumption account for nearly 90% of cases, and these factors exhibit a synergistic effect, significantly increasing cancer risk when combined.[7] Unlike the majority of oropharyngeal cancers, oral cancer is rarely associated with human papillomavirus (HPV) infection—particularly high-risk types HPV-16 and HPV-18.[8,9] But like oral cancer, HPV-related oropharyngeal cancer risk is elevated with synergistic tobacco use.[10]

While epidemiologic studies have suggested an association between periodontitis and oral cancer, causation has not been established and would seem to be difficult to corroborate given the marked difference in the prevalence between the two conditions. Association refers to a statistical relationship between two variables, whereas causation implies a direct mechanistic link where one variable influences the other. A classic example of this distinction is the correlation observed between coffee consumption and reduced skin cancer risk—not because coffee prevents cancer, but because of confounding factors such as reduced sun exposure among individuals who consume more coffee indoors.[11] Similarly, although numerous studies report a link between periodontitis and oral cancer, this does not imply that periodontitis is a direct cause of malignancy. Rather, periodontitis and oral cancer share common risk factors such as poor oral hygiene, smoking, and alcohol use.[1,12] Contrastingly, some factors associated with the risk of periodontal disease, such as obesity, are noted to be linked to a *reduced* risk for non-HPV-related oral cancers.[13]

Other data contradict a relationship between periodontal disease and overall cancer mortality. Huang and colleagues used nHANES data to study this question.[14] nHANES data are unique in that it includes objective dental diagnoses based on clinical examination of participants. Huang and colleagues found that a diagnosis of periodontitis did not have a statistically significant relationship with cancer-related mortality. Contrastingly, they noted that edentulism was associated with cancer mortality. This observation is not dissimilar with other studies which refuted a causal association between periodontal disease and rheumatoid arthritis but confirmed a relationship between tooth loss and the systemic condition.[15]

If in fact local periodontal injury was directly associated with cancer risk, one would expect that tissues of the local periodontium would be at highest risk of tumor development, which is not the case. Gingival cancers are relatively rare.[14,16]

As noted above, the large disparity between the number of cases of significant periodontal disease (>15 million individuals in the United States) and the number of newly diagnosed cases of oral cavity cancer (OCC) dampens the hypothesis of a direct link

between periodontitis and the development of OCC.[17] From an epidemiologic perspective, the high prevalence of periodontitis in the general population, contrasted with the relatively low incidence of oral cancers, suggests that periodontitis alone is unlikely to be a primary cause of cancer.[3,18] A more plausible explanation might be that a chronic inflammatory state in a subpopulation of patients with periodontitis creates a microenvironment conducive to carcinogenesis thereby placing periodontitis in the category of a risk modifier.

Evidence that Chronic Systemic Inflammation is a Risk for Malignancy

Chronic inflammation is a well-established predisposing factor for cancer development.[1] Persistent inflammatory responses, such as those associated with periodontal disease, lead to the sustained production of pro-inflammatory cytokines, such as interleukin (IL)-6, tumor necrosis factor-alpha (TNF-α), and IL-1, as well as reactive oxygen and nitrogen species by immune cells. These agents cause DNA damage and promote genetic mutations, thereby facilitating oncogenic transformation. Simultaneously, chronic inflammation fosters a tumor-promoting microenvironment by enhancing angiogenesis, cellular proliferation, and tissue remodeling, while also suppressing antitumor immunity.[19] This "perfect storm" of cellular injury, repair, and immunosuppression creates conditions that favor both the initiation and progression of malignancies.[1,12]

Periodontitis as a Contributor to Systemic Inflammation

A substantial body of evidence links periodontitis with mechanisms leading to systemic inflammation as indicated by an increase in levels of peripheral blood cytokines and inflammatory biomarkers. Periodontitis is characterized by persistent inflammation involving both the innate and adaptive immune systems and chronic inflammation initiated in periodontal tissues is associated with the systemic release of pro-inflammatory cytokines, such as IL-6 and TNF-α.[2,20] These cytokines enter the bloodstream, contributing to a chronic inflammatory state that has been implicated in the pathogenesis and exacerbation of over 50 systemic conditions,[21] including cardiovascular diseases, diabetes mellitus, rheumatoid arthritis, and neurodegenerative disorders.[22–25]

Further support implicating periodontal disease as a contributor to a systemic inflammatory state are findings associated with C-reactive protein (CRP), a well-established biomarker of inflammation[26] as elevated levels of CRP has been observed in individuals with periodontitis. Lee and Mun[27] reported that periodontitis significantly raises high-sensitivity CRP levels, which are associated with an increased risk of systemic diseases such as diabetes and hypertension. It is worth noting, however, that increased CRP levels like other systemic inflammatory markers may also be attributable to synergistic causations (periodontal disease and obesity for example), rather than a single factor.

Nonetheless, indirect corroborating evidence is noted in reports which suggest that effective periodontal treatment, including scaling and root planing or surgical interventions, can significantly reduce systemic inflammatory markers, including CRP, thereby mitigating chronic inflammation.[27]

Contradicting a hypothesis that a systemic inflammatory state elicited by periodontitis enhances tumor development is the recent study by Xiong and colleagues.[28] Using genomic analyses of publicly available databases, they studied whether there existed an association between periodontitis and the risk of 20 types of cancer. Their findings that periodontitis was associated with a risk of oropharyngeal cancer, but not

other oral cancer or 19 other common cancers or subtypes of head and neck cancer is demonstrative of the challenges of deriving a definitive conclusion.[28]

A Role of the Microbiome in Cancer Risk and Progression

A role for the microbiome as an integral part of overall health has been enthusiastically embraced. However, as suggested by Walker and Hoyles[29] many diseases are attributable to a "pathobiome" might be overstated and while alterations in the microbiome (dysbiosis) may be associated with diseases, the specificity of organisms is variable and, not infrequently, confounding factors are ignored.[29]

Certain microbial species have been identified as carcinogenic, while others appear to exhibit protective effects.[30] The gut microbiome, in particular, has been extensively studied due to its systemic influence on immune responses, metabolism, and carcinogenesis.[31] There are specific cancer types in which unique bacteria are not only strongly associated with a disease, but also are likely causative.

Microbiome and gastric and lung cancer

Gastric cancer is a well-established example of microbiome-related carcinogenesis. *Helicobacter pylori*, a bacterium classified as a Group 1 carcinogen by the International Agency for Research on Cancer, is a recognized risk factor for gastric cancer. Infection with *H pylori* role in carcinogenesis is well defined: infection induces chronic gastritis, leading to sustained inflammation, epithelial damage, metaplasia, dysplasia, and ultimately adenocarcinoma. Additionally, a shift in the gastric microbial community—with increased abundances of *Fusobacterium* and *Streptococcus*—may exacerbate carcinogenesis by modulating the immune microenvironment and affecting responses to chemotherapy and targeted therapies.[32,33] Importantly, effective antibiotic elimination of *H pylori* effectively reduces gastric cancer risk.[34] A landmark randomized controlled trial (RCT) conducted in a high-risk population in China demonstrated that *H pylori* eradication significantly decreased the incidence of gastric cancer over long-term follow-up.[35] Similarly, a meta-analysis of several RCTs found that antibiotic therapy led to a reduction in gastric cancer risk, particularly in individuals without pre-existing precancerous lesions.[36]

More similar to the role which periodontal pathogens play in the development of oral cancers is the observation that certain bacteria seem to be associated with lung cancer risk and progression. The lung, once considered a sterile environment, hosts a distinct microbiome that influences pulmonary health and disease. Similarly to the association between periodontitis and oral cancer, the pulmonary dysbiotic microbiome is associated with chronic inflammation.[37] However, there are also data to indicate that certain local bacteria such as *Mycobacterium tuberculosis* and chlamydia are themselves locally carcinogenic. As may be the case with other cancer-related conditions, the finding that microbial dysbiosis characterized by a reduction in taxonomic diversity within the lung tumor microenvironment is associated with cancer development could simply be recolonization of an altered tissue involvement driven by the unique characteristics which differentiate normal tissue from tumor.[38,39]

Does the Same Microbiome Which is Associated with Periodontal Disease also Play a Role in Oral Cancer Risk?

The oral microbiome is critical to understanding the pathogenesis of periodontitis and its systemic implications (**Fig. 1**). Periodontitis is associated with a dysbiotic shift in the oral microbiome, where pathogenic species outnumber commensal bacteria. Anaerobic Gram-negative bacteria such as *Porphyromonas gingivalis, Tannerella forsythia*, and *Treponema denticola* dominate the periodontal environment, forming biofilms that

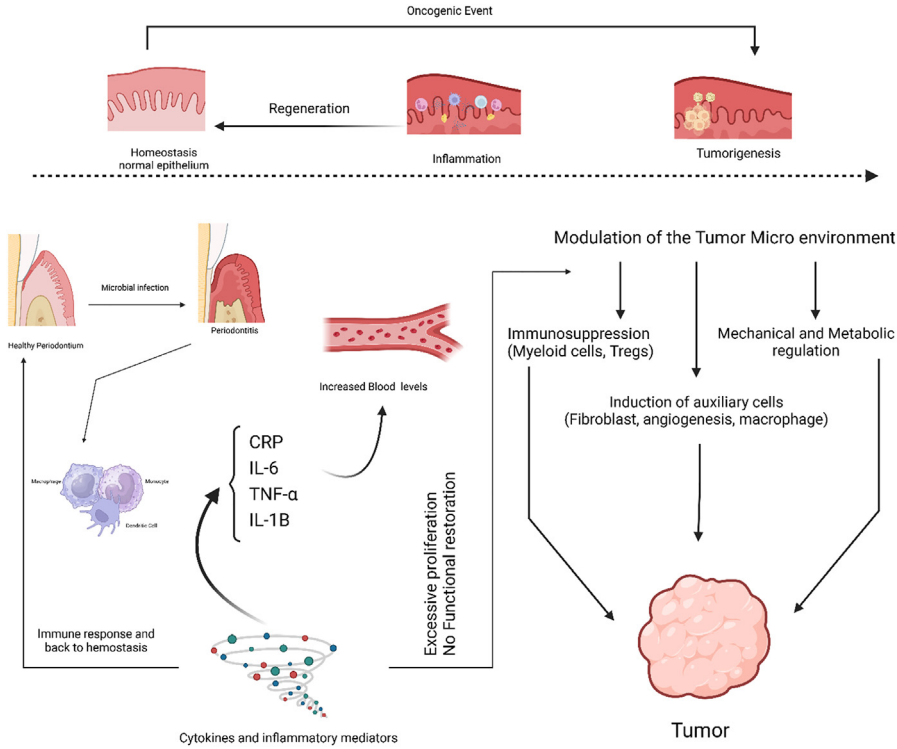

Fig. 1. As evidenced by increases in peripheral blood levels of inflammatory biomarkers such as pro-inflammatory cytokines and CRP, periodontitis contributes to a systemic chronic inflammatory state that is associated with an increased risk of range of diseases including cancer. Data also suggest that these same changes impact the tumor microenvironment through cytokine signaling, immune suppression, and metabolic regulation. (*Created in* BioRender. Mehrnia, N. (2025) https://BioRender.com/g64b287.)[48,49]

trigger robust immune-inflammatory responses and subsequent tissue destruction (**Table 1**). This microbial imbalance not only contributes to local periodontal damage but also promotes systemic inflammation.[20,40]

Research has demonstrated that effective periodontal therapy can lead to a partial or significant "reset" of the oral microbiome, shifting it toward a healthier composition. A longitudinal study assessing microbial changes following nonsurgical periodontal therapy found that therapeutic interventions not only reduce pathogenic bacterial load but also allow for the re-establishment of health-associated microbial communities. However, the degree of microbiome restoration varies among individuals and depends on factors such as treatment adherence, immune response, and host–microbiome interactions.[41]

Alterations in the oral microbiome may mediate the link between periodontitis and oral cancer. Recent studies have demonstrated that bacterial species commonly associated with periodontal disease including *Fusobacterium nucleatum* and *Porphyromonas gingivalis* are elevated in patients who later develop head and neck squamous cell carcinoma.[42,43] However, it is unclear whether these bacteria modulate immune responses, enhance epithelial cell invasiveness, and induce genomic instability, and thereby contributing to tumor progression. Confounding any argument suggesting that the finding of specific bacteria in the tumor or the tumor microenvironment might

Table 1
Specific bacteria reported to be associated with periodontitis and oral cancer an oral leukoplakia (considered to be a pre-malignant condition)

Microorganism	Associated with Periodontitis[42]	Associated with Oral Cancer/Oral Potentially Malignant Disorders[42,45]	Associated with Oral Leukoplakia[44]
Treponema denticola	*	*	
Porphyromonas gingivalis	*	*	
Tannerella forsythia	*	*	
Fusobacterium nucleatum	*	*	*
Prevotella intermedia	*	*	
Prevotella nigrescens	*	*	
Eubacterium nodatum	*	*	
Campylobacter showae	*	*	*
Campylobacter gracilis	*	*	*
Streptococcus sanguinis		*	
Leptotrichia species		*	*
Neisseria meningitidis			*
Rothia mucilaginosa			*
Alloprevotella spp.			*
Candida spp.			*
Prevotella salivae		*	
Capnocytophaga leadbetteri		*	
Campylobacter concisus		*	*
Prevotella shahii		*	

* = organisms identified
It is important to note the variability with which certain species are associated with common conditions that impact the mouth. The timing at which sampling is a critical variable as the tumor microenvironment may preferentially attract or support conditions for some species and not others.

affect tumor behavior is the question of whether tumor-specific changes such as hypoxia preferentially attract certain species.[6,38]

Additionally, the finding that periodontitis results from a complex, polymicrobial dysbiosis rather than a single pathogen. Although the “red complex” bacteria are frequently associated with periodontitis, their roles as primary drivers versus secondary colonizers remain a subject of ongoing debate.[44] Recent metagenomic studies further suggest that specific microbial community structures, rather than individual bacteria, may be key contributors to carcinogenesis.[43,45]

CLINICS CARE POINTS

- While periodontitis is not a primary cause of oral cancer, it may contribute to a systemic chronic inflammatory state which might increase the risk of malignancies including oral cancer.
- The role of the oral microbiome as a modifier of risk and progression of oral cancer is under investigation.

DISCLOSURE

SS is an employee of Biomodels, LLC and Primary Endpoint Solutions, LLC. Both companies assist industry, government and academics to study and enable drugs, biologicals and devices to treat patients for a variety of indications including supportive cancer care.

SUMMARY

The process by which oral carcinogenesis is initiated, and progresses is complex, but the fact that it represents the cumulative effect of multiple factors seems clear. How periodontitis fits into this spectrum is still not defined, although it seems unlikely that periodontitis or its associated microbiome are themselves directly causative. Rather, current data would suggest an indirect role for periodontitis with respect to oral and oropharyngeal cancer risk and progression in which its contribution to a chronic inflammatory state characterized by the persistent release of proinflammatory cytokines contribute to oxidative stress and DNA damage, potentially favoring carcinogenic processes.[46,47] It is also impossible to ignore the possibility that the periodontal health status of an individual is a surrogate for general health as those factors which contribute to good general health, environment, lifestyle, and access to care are also determinants of oral health.

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