

# Oral microbe, periodontitis and oral cancer: Unraveling the complex connection

Nazia Khan<sup>1</sup>, Krishan kant<sup>2</sup>, Richa Verma<sup>3</sup>, Sameep Garg<sup>4</sup>, Preeti Kale<sup>5</sup>

<sup>1</sup>Assistant Professor (Clinical Microbiology), Basic Medical Science, College of Medicine Majmaah University, Al-Majmaah, Riyadh, Saudi Arabia

<sup>2</sup>Consultant Periodontist, Rohatak, Haryana, India

<sup>3</sup>Consultant Periodontist, Verma Dental Clinic, Circular Road Rewari-123401, Haryana, India

<sup>4</sup>Professor, Department of Pathology, Kiran Medical College, Olpad, Surat, Gujarat, India

<sup>5</sup>Department of Periodontology, Rural Dental College and Hospital, Loni, 413736, Ahmednagar, Maharashtra, India

ABSTRACT

Periodontitis and oral cancer are significant health concerns with considerable impacts on global populations. Despite their apparent dissimilarity, emerging evidence suggests a possible association between these two conditions. This review article aims to explore the complex connection between periodontitis and oral cancer, delving into potential shared risk factors, underlying biological mechanisms, and the latest research findings. Chronic inflammation, a hallmark feature of periodontitis, is increasingly recognized as a key player in cancer development. Shared risk factors, such as smoking and poor oral hygiene, are associated with both periodontitis and oral cancer. This review aims to contribute to the development of preventive strategies and therapeutic approaches for both conditions. Ultimately, enhancing oral health outcomes and strengthening cancer prevention efforts requires a multifaceted approach, addressing both periodontitis and oral cancer as intertwined components of oral health management.

**Key words:** periodontitis, oral cancer, inflammation, chronic inflammation

## INTRODUCTION

The human oral cavity harbors a diverse ecosystem of microorganisms, collectively known as the oral microbiome. This complex microbial community plays a crucial role in maintaining oral health, aiding in digestion, and contributing to the body's immune system. However, an imbalance in this delicate ecosystem can lead to various oral diseases, including periodontitis and oral cancer [1].

Periodontitis is a chronic inflammatory condition that affects the supporting structures of the teeth, including the gums, periodontal ligament, and alveolar bone. It is primarily caused by the accumulation of plaque and tartar on the teeth, resulting in the colonization of harmful bacteria that trigger an immune response, leading to tissue damage and bone loss. While periodontitis is a well-known oral health concern, recent research has revealed intriguing connections between oral microbiota, chronic inflammation, and the development of oral cancer [2].

Oral cancer encompasses a group of malignant tumors that can arise in different parts of the oral cavity, including the lips, tongue, cheeks, and throat. It is a significant global health issue with substantial morbidity and mortality rates. The primary risk factors for oral cancer have traditionally been linked to tobacco use, alcohol consumption, and viral infections, such as Human Papillomavirus (HPV). However, emerging evidence suggests that the oral microbiome's composition and dysbiosis may also contribute to the initiation and progression of oral cancer. Understanding the intricate relationship between oral microorganisms, periodontitis, and oral cancer is of paramount importance for improving oral healthcare and developing targeted prevention and treatment strategies. This comprehensive review aims to unravel the complex connection between oral microbes, periodontitis, and oral cancer, shedding light on the potential mechanisms that link these conditions and exploring the implications for clinical practice [3].

Throughout this review, we will delve into the current state of knowledge regarding the oral microbiome's role in maintaining oral health and the factors that lead to its dysregulation. Furthermore, we will examine the mechanisms through which periodontitis-associated bacteria may promote the development of oral cancer and how chronic inflammation may contribute to this process. We will also explore the potential impact of lifestyle factors and host immune responses in modulating this intricate

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### Address for correspondence:

Sameep Garg, Professor, Department of Pathology, Kiran Medical College, Olpad, Surat, Gujarat - 394540, India  
Email id: drsameepgarg2@gmail.com

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relationship [4].

By shedding light on the interplay between oral microorganisms, periodontitis, and oral cancer, this review aims to contribute to the growing body of research in the field of oral health and potentially pave the way for novel therapeutic approaches and preventive measures to combat these interconnected oral diseases. Ultimately, a deeper understanding of these complex interactions could lead to improved oral health outcomes and a reduced burden of oral cancer worldwide [5].

## Pathogenesis of complex connection between periodontitis and oral cancer

The pathogenesis of the complex connection between periodontitis and oral cancer involves a combination of biological, inflammatory, and immunological processes [6]. While the exact mechanisms are not fully understood, several key factors have been identified in the interplay between these two conditions:

### Chronic inflammation

Periodontitis is characterized by chronic inflammation resulting from the immune system's response to bacterial plaque on teeth and gums. The persistent release of pro-inflammatory molecules, such as cytokines and chemokines, creates an inflammatory microenvironment in the oral cavity. Chronic inflammation is a known risk factor for cancer development as it can cause damage to DNA, promote cell proliferation, and hinder apoptosis (programmed cell death), all of which are factors that can contribute to the initiation and progression of cancer [7].

### Immune dysfunction

In periodontitis, the immune response is often compromised, leading to impaired immune surveillance and clearance of abnormal cells. This may allow potentially cancerous cells to escape detection and elimination by the immune system, facilitating the development of oral cancer [8].

### Microbial interactions

The oral microbiota plays a significant role in the pathogenesis of both periodontitis and oral cancer. Periodontitis is characterized by a dysbiotic shift in the oral microbiome, leading to an imbalance in the bacterial community. Some pathogenic bacteria have been implicated in cancer development due to their ability to produce carcinogenic byproducts, activate oncogenic pathways, and modulate the immune response [9].

### Periodontitis-associated bacteria and oral cancer

Periodontitis-associated bacteria have been implicated in the development and progression of oral cancer. Several studies have revealed a potential link between chronic periodontal inflammation and an increased risk of oral cancer, suggesting that the oral microbiome plays a role beyond its conventional association with oral health. The mouth is a dynamic environment where microorganisms form biofilms on tooth surfaces and oral mucosa. In the presence of poor oral hygiene and other risk factors, the balance of these microbial communities can be disrupted, leading to dysbiosis and an overgrowth of potentially harmful bacteria [10]. Some of the key periodontitis-associated bacteria

that have been linked to oral cancer include:

- *Porphyromonas gingivalis*: This bacterium is one of the main culprits in periodontal disease and has been detected in oral cancer tissues. *P. gingivalis* produces various virulence factors that promote chronic inflammation and tissue destruction. It can also manipulate host immune responses and cellular signaling pathways, potentially contributing to cancer development [11].
- *Fusobacterium nucleatum*: Another prevalent bacterium in periodontal infections, *F. nucleatum*, has been found in oral cancer tissues as well. It is known to facilitate the adherence of other bacteria to host cells, promoting the formation of bacterial communities within biofilms. This bacterium's presence in oral cancer lesions suggests its potential role in disease progression [12].

The mechanisms through which these periodontitis-associated bacteria may contribute to oral cancer are still under investigation. One key aspect is the chronic inflammation triggered by the immune response to the bacterial infection. Prolonged inflammation can create a microenvironment conducive to cancer development, promoting genetic mutations, angiogenesis (formation of new blood vessels to support tumor growth), and immune system evasion [13].

Additionally, some studies have suggested that specific bacterial products and toxins produced by periodontitis-associated bacteria might directly promote oncogenic processes in oral cells. For example, *P. gingivalis* secretes a protease called gingipain, which can manipulate host cell signaling and promote cell proliferation, migration, and invasion. These effects could enhance the transformation of normal cells into cancerous ones [14].

It is essential to note that while the association between periodontitis-associated bacteria and oral cancer is becoming evident, the exact mechanisms and causal relationships are still being explored. Other factors, such as lifestyle choices (e.g., tobacco and alcohol use) and genetic predisposition, also play crucial roles in oral cancer development. Nevertheless, understanding the influence of the oral microbiome, particularly periodontitis-associated bacteria, in oral cancer may open new avenues for preventive and therapeutic strategies targeting these bacterial communities to reduce the risk of oral cancer and improve oral health outcomes [15].

### Shared risk factors

Periodontitis and oral cancer share common risk factors, such as smoking, poor oral hygiene, and certain dietary habits. These risk factors can independently contribute to the development of both conditions. For instance, smoking can promote inflammation, hinder immune function, and increase the risk of genetic mutations, all of which may promote cancer development [16].

### Epigenetic changes

Epigenetic modifications, such as DNA methylation and histone modifications, play a role in the regulation of gene expression. Studies have shown that chronic inflammation and microbial infections in the oral cavity can lead to epigenetic changes that influence the development of cancer [17].

## Angiogenesis and tissue remodeling

Chronic inflammation in periodontitis can lead to increased angiogenesis (the formation of new blood vessels) and tissue remodeling. These processes are also essential for cancer growth and metastasis. It is important to note that the relationship between periodontitis and oral cancer is likely multifactorial and complex, involving interactions between host factors, microbial factors, and environmental exposures. Understanding the pathogenesis of the complex connection between periodontitis and oral cancer is crucial for developing targeted preventive and therapeutic strategies. This includes promoting good oral hygiene practices, managing risk factors, and potentially exploring novel approaches to modulate the oral microbiome and immune response to reduce the risk of both periodontitis and oral cancer [18].

## Targeted preventive and therapeutic strategies to modulate the oral microbiome and immune response to reduce the risk of both periodontitis and oral cancer

Approaches that have shown promise in research and clinical practice:

**Improved oral hygiene practices:** Encouraging and educating individuals on proper oral hygiene practices, such as regular brushing, flossing, and dental check-ups, can help maintain a healthy oral microbiome and reduce the risk of periodontitis and oral cancer [19].

**Antibiotics and antimicrobial agents:** In cases of severe periodontitis or when specific pathogenic bacteria are identified, targeted antibiotics or antimicrobial agents may be prescribed to control the oral microbial imbalance and reduce inflammation [20].

**Probiotics and prebiotics:** Probiotics are beneficial live microorganisms that can promote a healthy oral microbiome. Incorporating probiotics into oral care products or dietary supplements may help maintain microbial balance. Prebiotics, which are non-digestible food components that promote the growth of beneficial bacteria, can also be considered [21].

**Anti-inflammatory therapies:** Targeting inflammation with anti-inflammatory drugs or local applications of anti-inflammatory agents can help reduce the chronic inflammatory response associated with periodontitis and its potential impact on oral cancer development.

**Immunomodulatory agents:** Modulating the immune response using immunomodulatory agents may help enhance the immune surveillance and clearance of abnormal cells, reducing the risk of oral cancer [22].

**Topical immunotherapy:** In cases of oral precancerous lesions or early-stage oral cancer, topical immunotherapy may be considered to stimulate the immune system to target and destroy precancerous or cancerous cells [23].

**Gene therapy:** Gene therapy approaches may hold potential for targeting specific genes involved in inflammation, cancer development, or immune regulation to prevent or treat periodontitis and oral cancer.

**Lifestyle modifications:** Encouraging lifestyle modifications, such

as smoking cessation and adopting a healthy diet, can significantly reduce the risk of both periodontitis and oral cancer.

**Oral microbiome restoration:** Research into oral microbiome transplantation or restoration is ongoing, aiming to re-establish a healthy microbial balance in individuals with dysbiotic oral microbiota [24].

**Precision medicine approaches:** Tailoring treatment plans based on an individual's genetic and immune profile may offer more effective and personalized strategies for preventing and managing periodontitis and oral cancer [25]. It is essential to note that while these strategies hold promise, further research is needed to establish their efficacy and safety. Additionally, preventive and therapeutic interventions should be integrated into a comprehensive oral health care plan that includes regular dental check-ups, early detection, and management of oral diseases. A multi-pronged approach that targets the oral microbiome and immune response can play a significant role in reducing the risk of both periodontitis and oral cancer. Implementing these strategies may contribute to improved oral health and overall well-being for individuals at risk of developing these conditions [26].

## Future directions to reduce the risk of both periodontitis and oral cancer

Future directions to reduce the risk of both periodontitis and oral cancer involve advancing research, technology, and public health initiatives to promote preventive measures and early detection [27]. Here are some key future directions:

### Advancements in precision medicine

Utilizing genetic profiling and biomarker analysis to identify individuals at higher risk of developing periodontitis and oral cancer can enable personalized preventive strategies. Precision medicine approaches can help tailor interventions based on an individual's unique genetic makeup and immune response [28].

**Oral microbiome research:** Further research into the oral microbiome's role in periodontitis and oral cancer can lead to innovative therapeutic approaches, such as targeted probiotics, prebiotics, and microbiome transplantation, to restore and maintain a healthy oral microbial balance [29].

**Immunotherapies for oral cancer:** Advancements in cancer immunotherapies, including checkpoint inhibitors and adoptive T-cell therapies, hold promise for improving the treatment outcomes of oral cancer. Combining these therapies with other treatments may enhance the immune response against cancer cells [30].

**Development of novel biomarkers:** Identifying specific biomarkers for periodontitis and oral cancer can aid in early detection, risk assessment, and monitoring disease progression. These biomarkers can be used in saliva or blood tests for non-invasive and cost-effective screening [31].

**Health education and awareness campaigns:** Continued efforts to raise awareness about the importance of oral health, risk factors, and early signs of periodontitis and oral cancer can encourage individuals to seek timely dental care and adopt preventive measures.

**Integration of dentistry and oncology:** Enhancing collaboration between dental professionals and oncologists can lead to a comprehensive approach in managing oral health during cancer treatment and improving overall patient outcomes.

**Use of Artificial Intelligence (AI):** AI-powered tools can analyze

large datasets to identify patterns and risk factors associated with periodontitis and oral cancer. AI can assist in predicting disease progression and personalizing treatment plans [31]. Translational research: Bridging the gap between basic research and clinical applications is essential to ensure that promising findings from laboratories can be translated into effective preventive and therapeutic strategies for patients [32].

Long-term cohort studies: Conducting long-term cohort studies can provide valuable insights into the development and progression of both periodontitis and oral cancer, as well as the efficacy of preventive interventions over time [33-34]. Telehealth and remote monitoring: Implementing telehealth and remote monitoring technologies can improve access to oral health care, especially for individuals in remote areas or underserved communities. Regular remote monitoring can help detect early signs of both periodontitis and oral cancer [35].

By focusing on these future directions, healthcare professionals, researchers, policymakers, and public health authorities can work together to develop comprehensive strategies to reduce the risk of

both periodontitis and oral cancer. Emphasizing prevention, early detection, and personalized care will be essential in promoting oral health and enhancing overall well-being in the population [35].

## CONCLUSION

In conclusion, the role of periodontitis in oral cancer remains a complex and evolving area of research. While there is evidence suggesting an association between these two conditions, the exact mechanisms underlying their connection are not fully understood. Nonetheless, several key factors have been identified that shed light on the potential interplay between periodontitis and oral cancer. Further research, including longitudinal studies and translational investigations, is needed to unravel the intricate mechanisms and establish causality definitively. Healthcare professionals and researchers must continue to collaborate and innovate, striving to improve preventive strategies and therapeutic interventions to benefit individuals at risk of developing periodontitis and oral cancer.

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