# Oral microbiome's role in tumor development, metastasis, and oral oncogenesis

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***Abstract-*** Cancer remains a serious worldwide health concern even after decades of research. The part that microorganisms play in the onset and spread of cancer has come under closer examination recently. This review's main objective is to highlight the important relationships between various cancers and the bacteria in the human mouth. Many oral bacteria (such as *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, and *Streptococcus* sp.), some viruses (such as human papillomavirus, Kaposi sarcoma Herpesvirus (KSHV), Human herpesvirus 1, and Epstein-Barr virus (EBV)), members have also been linked to lung, pancreatic, stomach, esophageal, and colon/rectum malignancies. Additionally, the current research describes several carcinogenic pathways that underlie the reported microbial links with cancer. In the oral cavity, there are about 700 different types of bacteria. Saliva and the various oral cavity habitats influence the population of the oral microbiome. The composition of the oral microbiome may change if certain risk factors for oral cancer such as alcohol, tobacco, and betel nuts are used. In oral cancer, commensal and pathogenic bacteria have played a major role. Bacterial products and their metabolic byproducts have the potential to permanently modify the host's epithelial cells' DNA, promoting their survival and/or proliferation. *Fusobacterium nucleatum* and *Porphyromonas gingivalis* alter the host cell's DNA, which supports the production of inflammatory cytokines, proliferation of cells, and the suppression of apoptosis, cellular invasion, and migration. In this review, we discuss how the microbiome functions as a predictive and early diagnostic biomarker for oral cancer and its involvement in the course of the disease.

***Index Terms***- Oral squamous cell carcinoma (OSCC), Head-and-neck squamous cell carcinoma (HNSCC), Oropharyngeal squamous cell carcinoma (OPSCC), *Porphyromonas gingivalis* (*P. gingivalis*).

## I. INTRODUCTION

Oral cancer often starts in the mucosal epithelial tissue, with squamous cell carcinoma (Skin cancer) being the most common variety (Caruntu and Caruntu, 2022). Oral squamous cell carcinoma (OSCC) and oropharyngeal squamous cell carcinoma (OPSCC) are the most frequent reasons for diagnosis for patients with head-and-neck squamous cell carcinoma (HNSCC) (Johnson *et al.*, 2020). Research indicates a significant association between malignancy and periodontal pathogens, particularly *Fusobacterium nucleatum*, *Treponema denticola*, and *Porphyromonas gingivalis* (Șurlin *et al.*, 2020). Candida is one of the fungi that is closely associated with oral cancer. Many studies have demonstrated that *human papillomavirus* (HPV), especially high-risk HPV16, is the risk factor for the development of oral squamous cell carcinoma (OSSCC). Oral cancer may be impacted by the interactions of microbial communities in addition to the function of a particular oral microbiome (Givony, 2020). The pathogenesis of periodontal disease involves Polymicrobial synergy and dysbacteriosis. Furthermore, the formation of periodontic biofilms resembles the cellular communities that cause cancer in humans. The processes by which a distinct oral microbiome may contribute to the oncogenesis of oral, tumor development and metastasis are discussed in this article (Li *et al.*, 2023)

## II. A huge Impact on Carcinogenesis: a cohort of Oral Microbiota

There are currently techniques available to assess and determine the level of infection. These developments have contributed to the growing body of evidence linking mouth bacteria to carcinogenesis (Kroemer *et al.*, 2015) A significant number of oral bacteria have been connected to the development of cancer. *F. nucleatum* and *Porphyromonas gingivalis* (*P. gingivalis*) are 2 of them that have been linked to the development of different types of cancer (Teles *et al.*, 2020). There has also been evidence linking certain other aerobic and anaerobic microorganisms to the development of cancer. It is commonly known that HPV plays a part in the development of oropharyngeal cancer. Oral fungal and parasite abnormalities may be linked to carcinogenesis, although there is insufficient evidence to support this theory (Sun *et al.*, 2020)

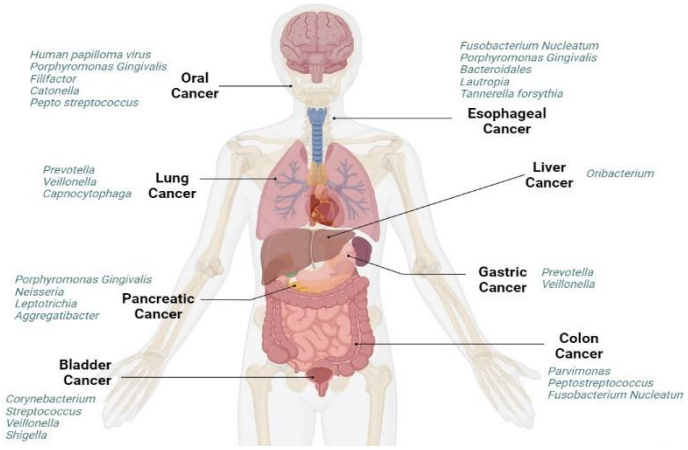


**Figure 1:** Oral microbiota distribution and related malignancy. The oral microbiota's dispersion throughout the human body and its impact on several cancer types are depicted in this picture. In addition to the mouth, the oral microbiota is also involved in the Cancer of the oral cavity, esophagus, colon, lung, liver, stomach, and cervix(Li *et al.*, 2023).

***Fusobacterium nucleatum***

A Gram-negative anaerobic bacillus, *Fusobacterium* is primarily found in the gastrointestinal system and mouth cavity. It is the oral cavity's natural resident (Teles *et al.*, 2020). However, *Fusobacterium* is believed to be the cause of human infectious agents(McIlvanna *et al.*, 2021) .*F. nucleatum* subspecies Polymorphum was most frequently found in oral cancer tissues in high abundance, based on a bioinformatic prediction study of sequencing data obtained during *in-situ* oral cancer (Sun *et al.*, 2020).

***Porphyromonas gingivalis***

A pathogenic, anaerobic, Gram-negative bacteria called *P. gingivalis* is responsible for the damaging effects of periodontitis *P. gingivalis* has lately been thought to have a possible impact on tumor growth because of its ability to disrupt host defense mechanisms and epithelial tissues (Wang and Ganly, 2014). *P. gingivalis*, a most frequent oral pathogen, was found at oral cancer locations based on rabbit *P. gingivalis* polyclonal antibodies staining immunohistochemically with strong favorable results. Given the continuous smooth passage nature of the or digestive tract, *P. gingivalis*, possessing far greater mobility and invasion potential than other oral bacteria, may be able to disseminate across the entire region and expedite the process of *in-situ* carcinogenesis (Nasiri et al.). Additionally, the colonization of *P. gingivalis* produced chemotherapeutic resistance, indicating that periodontitis acted as a barrier to the treatment of oral cancer (Wang and Ganly, 2014). Food and water movement can readily cause *P. gingivalis* to relocate from the mouth cavity to other or digestive tract regions(Sun *et al.*, 2020).

**Oral Bacteria with Carcinogenic Potential**

In a study by (Mager, 2006) 40 oral bacterial species were analyzed from individuals who had OSCC and from a control group who did not have the disease. Patients with OSCC had higher concentrations of three species in their saliva: *Streptococcus mitis*, *Prevotella melaninogenica*, and *Capnocytophaga gingivalis*(Li *et al.*, 2020) It was discovered that these three bacterial species could predict 80% of cancer cases, which led to their suggestion as diagnostic markers. The most commonly isolated bacteria *Streptococci* from oral cancer patients' cervical lymph nodes, include *S. constellatus*, *S. mitis*, *S. intermedius*, *S. oralis*, *S. sanguis*, and *S. salivarius*. *Peptostreptococcus* species dominated the anaerobic bacterial population (Yang *et al.*, 2021) After accounting for the aforementioned, the oral bacteria that are most frequently found in OSCCs are *Streptococcus* sp, *Peptostreptococcus* sp, *Prevotella* sp, *P. gingivalis*, and *C. gingivalis* (Li *et al.*, 2020)

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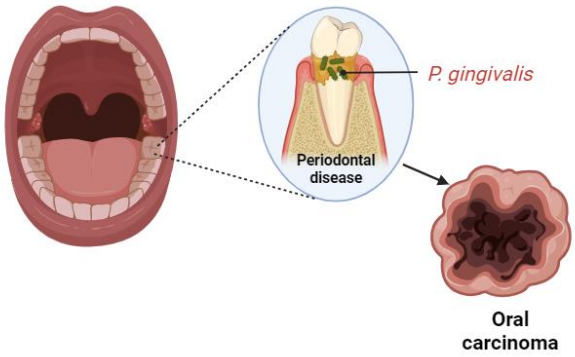


**Figure 2:** Oral microbiota associations with oral cancer (Stasiewicz and Karpiński, 2022).

In addition to being found in oral tumors, oral bacteria are also found in patients who have pancreatic and colorectal cancers. Particularly common in colorectal cancer cases are two species: *Porphyromonas gingivalis* and *Fusobacterium nucleatum* (Yang *et al.*, 2021). The *F. nucleatum*, in significant concentrations at the sites of colorectal cancer, has been linked to the location of the tumor (about 11% in the cecum and 2% in the rectum) and regional lymph node metastases (Bashir *et al.*, 2015). In addition to *P. gingivalis* and *F. nucleatum*, pancreatic cancers have also been linked to *Aggregatibacter actinomycetemcomitans*, *Neisseria elongata*, and *Streptococcus mitis* (Stasiewicz and Karpiński, 2022). Lung cancer patients have been observed to have higher concentrations of oral bacteria belonging to the genera *Veillonella* and *Capnocytophaga* (Karpiński, 2019).

**Mechanisms of Carcinogenic Action of Oral Bacteria**

There are three ways that the oral microbiota contributes to the development of cancer. The first is the ongoing inflammation that microbes cause (Tuominen and Rautava, 2021). As a result of this process, inflammatory mediators are produced, and these mediators can induce or promote oncogene activation, mutagenesis, angiogenesis, and cell proliferation (Stasiewicz and Karpiński, 2022). According to the 2nd mechanism, bacteria can change cytoskeletal reorganizations, cellular apoptosis suppression, NF-κB activation, and cell proliferation to affect the pathogenesis of malignancies(Biernat and Wróbel, 2021). About the third route, specific compounds generated by bacteria can induce cancer (Karpiński, 2019).

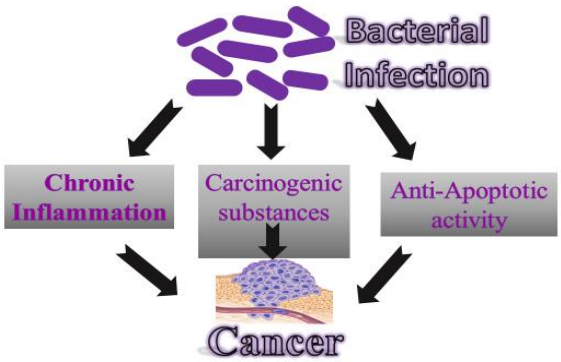


**Figure 3:** Role of oral bacteria in the etiology of cancer (Karpiński, 2019).

**Location and Ecology of the Oral Microbial Habitat**

All microbes and their genes within the human body are collectively called the "human microbiome". The genomes of microbes in the oral cavity (OC) are called the oral microbiome (Kumar *et al.*, 2020). In contrast to other host-derived biomarkers for oral tumors, the oral microbiome is thought to be the best biomarker (Burcher *et al.*, 2022). The nasopharyngeal and OC areas continue to provide the perfect conditions for the microbiota to flourish. Anaerobes have a specialized niche created by aerobic microorganisms (Sharma *et al.*, 2023). The OC is home to around 700 different types of microorganisms. To preserve equilibrium, mutualistic and pathogenic microorganisms coevolve. Saliva's pH range of 6.5 to 7.5 and OC's 37°C temperature offer bacterial organisms a stable environment (Tengku Ab Malek, 2023). Saliva keeps the bacteria hydrated and supplies them with nutrition. Together, anaerobic and aerobic bacteria create mouth biofilms that shield the organisms from environmental changes. Saliva and the several OC habitations (buccal mucosa, subgingival plaque, and supragingival,) influence the population of the oral microbiome (Giordano-Kelhoffer *et al.*, 2022).

The OC has a variety of microbial environments, including the tongue, periodontal pockets, and tooth surfaces. The tongue exhibits the greatest microbial diversity of all three habitats. The bacteria in saliva help other regions of the OC become colonized by bacteria.

Pathogenic microorganisms have a greater ability to cause oral disorders as environmental factors change (Zhang *et al.*, 2024). Saliva from oral cavity patients, the tongue, the hard and soft palates, the supragingival and subgingival surfaces of teeth, and the buccal mucosa may all be indicative of distinct biological habitats (Kashyap and Kullaa, 2024). Certain OC bacterial species exhibit distinct reactions to various biological surfaces, including the tongue, teeth, and mucosa. Through a "lock and key" mechanism, distinct bacterial species' adhesion molecules (adhesins) and receptors guarantee colonization on various oral surfaces. In the constantly shedding oral mucosa and nonshedding teeth surfaces, distinct ecosystems have been discovered. On the mucous membranes of the host, bacteria attach themselves to corresponding receptors. Oral soft tissues and saliva are colonized by *Streptococcus constellatus*, *S.mitis*, *S.salivarius*, *S. oralis*, *Streptococcus intermedius*, and *S. anginosus*, while teeth are preferred by *Streptococcus sanguis* (Senthil Kumar *et al.*, 2024).
Despite being a highly genetically diverse group, Streptococcus is a widely encountered genus in the human OC. *Actinobacillus actinomycetemcomitans*, *Prevotella intermedia*, *P gingivalis*, *Selenomonas* subspecies, *Veillonella atypica*, and *Capnocytophaga* have all been found in tongues (Khan *et al.*, 2023). While the oropharynx is home to *S.pyogenes*, *S.pneumoniae*, *H.* influenza, and *H.*parainfluenzae (Gönüllü *et al.*, 2020). Only in the OC are *Streptococcus faecalis*, *Eikenella corrodens*, *Enterobacteriaceae*, *Lactobacilli*, *Veillonella*, and *Treponema* detected; in the oropharynx, they are not (Chattopadhyay *et al.*, 2019).

**Oral Microbiome Colonization and Survival Inside Tissues**

The application of microbial carcinogenesis begins with the development of cancerous *in-situ* microbiomes and their persistence. Extended and continuous development by pathogenic microbiota permits additional carcinogenic effects to infect and colonize the skin's or mucosas basal epithelial cells, and to utilize the cells called epithelium' differentiation pathway to finish its lifecycle (Yang *et al.*, 2023). Consequently, HPV may persist in the vagina and oral cavity as a potential cause of cancer. Conventional wisdom maintains that the oral cavity is capable of fending off pathogen invasion, while other bodily regions, such as the genital system, may be excellent places for the virus to lie dormant (Cianciarullo *et al.*, 2024). Recent reports, however, have indicated that gingival tissue can also get infected by HPV. This may make sense considering that the oral cavity's defense system may be harmed by several high-risk factors, such as HIV infection, cigarette smoking, using tobacco-based products, and immunosuppression (Di Cosola *et al.*, 2021).

Furthermore, periodontitis destroys the integrity of the mucosal barrier. Additionally, it might make HPV more likely to remain in the oral cavity. The human papillomavirus (HPV) can only finish its life cycle in epithelial cells during their differentiation process because viral DNA replication can only take place in the basal layers of these cells which will eventually undergo maturity and senescence (Della Fera *et al.*, 2021). This form of contact provides the basis for *F. nucleatum* pathogenic potential to bind and/or enter several cell types, such as intestinal and oral epithelial cells.
The membrane protein Gal/GalNAc, which is overexpressed in colorectal cancer cells, can be recognized and bound by the protein Fap2 is primarily responsible for *F. nucleatum* localization to malignant tissues (Bashir *et al.*, 2015; Chen *et al.*, 2023). A distinct association between *F. nucleatum* and CRC cells is suggested by the Fap2-dependent-specific binding mechanism rather than by regular endocytosis. Moreover, *F. nucleatum* unique FadA adhesins may help attach to E-cadherin and activate the β-catenin signaling pathway, which will regulate the inflammatory and carcinogenic reactions (Groeger *et al.*, 2022). The location of *P. gingivalis* in the upper digestive tract and variations in its survival rate in an alkaline atmosphere with varying pH levels could account for some of the development of *P. gingivalis* in the upper gastrointestinal tract. This supports *P. gingivalis's* causal role in ESCC by elucidating the possibility of *P. gingivalis* colonization(Sun *et al.*, 2020).

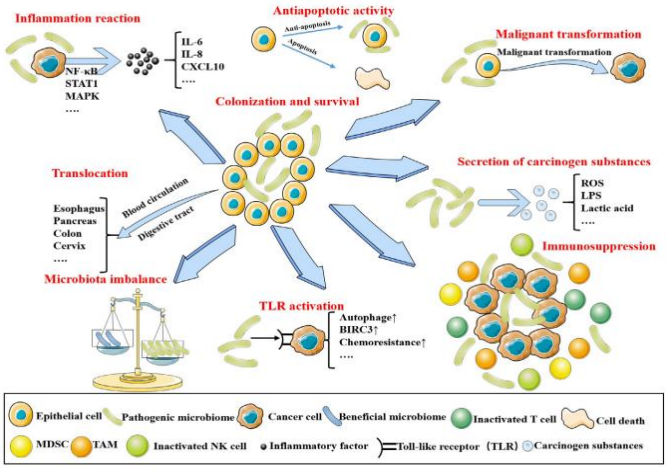


**Figure 4:** The processes involved in carcinogenesis are linked to microbiota. Seven prevalent and widely accepted mechanisms for carcinogenesis related to the microbiota are shown in the figure. Pathogenic microbiota may induce an imbalance in the microbiota, induce malignant transformation of epithelial cells, induce an inflammatory response, promote antiapoptotic activity, and secrete

substances known to cause cancer once they have successfully colonized and survived. In addition to *in-situ* colonization, oral microbiota may move through the bloodstream or digestive system and into other areas of the human body(Sun *et al.*, 2020).

**Promoting cell proliferation**

*P. gingivalis* may stimulate OSCC cell line growth through a variety of pathways, in accordance with numerous *in vitro* studies (Lan *et al.*, 2024). By regulating the expression of D1 cyclin, a critical regulator of the proliferation of cells, via the miRNA-21/PDCD4/AP-1 axis, *P. gingivalis* promoted the growth of OSCCs. Additionally, the bacteria may cause an increase in the expression of α-defensin, which functions as a ligand for the epidermal growth factor receptor and stimulates cell division (Hoppe et al., 2016). Furthermore, *P. gingivalis* has been shown in several studies to stimulate the growth of immortalized gingival epithelial cell lines that are not malignant. Long-term exposure to *P. gingivalis* causes morphological alteration of oral epithelial cells, according to *Geng et al. (2017).* The Synthesis-phase percentage of the cell cycle increased as a result of this, which improved the cells' capacity to proliferate. Without requiring Wnt, *P. gingivalis* can activate β-catenin by utilizing a proteolytic process that is dependent on gingipains to separate the β-catenin destruction complex (Ma *et al.*, 2024). Oral epithelial cell proliferation was enhanced by *P. gingivalis*-induced β-catenin activation (Zhou et al., 2015). If these pathways also apply to Oral cancer cells infected with *P. gingivalis*, more research is necessary to verify this (Li *et al.*, 2023).

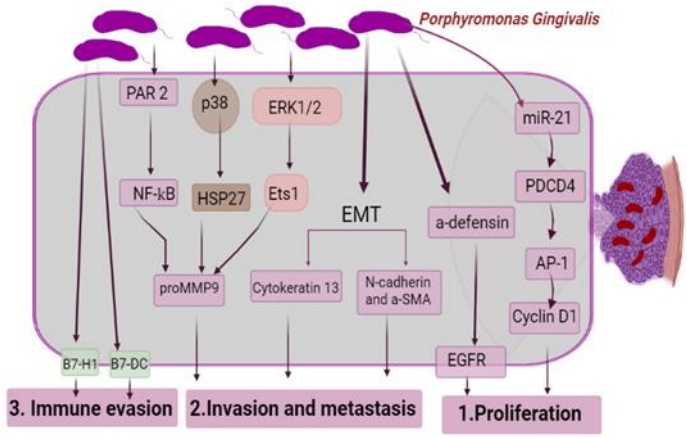


**Figure 5:** Potential roles for Porphyromonas gingivalis in the initiation and progression of oral squamous cell carcinoma.

**Promoting cell invasion and metastasis**

*P. gingivalis* facilitated by triggering the EMT (epithelial-mesenchymal transition) and upregulating matrix metalloproteinase (MMP) expression, oral cancer cells can invade and spread (Lamont *et al.*, 2022). OSCC cells underwent a mesenchymal-like phenotype (EMT) after being infected with *P. gingivalis* multiple times(Ma *et al.*, 2024). This EMT phenotype was characterized by an upregulation of mesenchymal markers (N-cadherin and α-SMA) and a decrease in epithelial markers (cytokeratin 13) (Ha et al., 2015). MMPs 9 have a key role in the degradation of extracellular matrix and basement membranes, which promote the invasion and metastasis of oral cancer cells. MMP1, MMP2, MMP9, and MMP10 were discovered to potentially be implicated (Mondal *et al.*, 2020). *P. gingivalis* activated the PAR2/NF-κB, p38/HSP27, ERK1/2-Ets1, and MMP9 precursor formation pathways (Yuan *et al.*, 2021). Afterward, gingipains increased OSCC cell invasion by activating the proenzyme to generate MMP9 (Li *et al.*, 2023).

**Regulating the tumor immune microenvironment**

Myeloid-derived suppressor cells (MDSCs) were found to be more invasive in clinical OSCC tissues when *P. gingivalis* was present compared to tumors lacking *P. gingivalis* (García-Arévalo *et al.*, 2024). This suggests a close connection between *P. gingivalis* infection and the tumor immune microenvironment (TIME). An *in vitro* investigation found that *P. gingivalis* infection enhanced OSCC cell lines' expression of B7-H1 and B7-DC receptors, which may limit T cell proliferation (Lafuente Ibáñez de Mendoza *et al.*, 2020). Furthermore, *P. gingivalis* may shield oral cancer cells from macrophage assaults, accelerating the growth of the tumor. In an *in vitro* experiment, macrophages and Cal-27 cells were cultured with living *P. gingivalis* for two hours (Tang *et al.*, 2022) used flow cytometry to demonstrate a decrease in the proportion of macrophages that phagocytized Cal-27 cells (Li *et al.*, 2023)

**Tumorigenesis-Associated Biological Behaviors of Oral Microbiota**

Despite a wealth of data supporting the association between mouth bacteria and cancer, nothing is understood about how oral microbiota may affect the carcinogenesis process (Irfan *et al.*, 2020). There are several significant microbial activities linked to cancer that may be seen before the direct oncogenic impact on carcinogenesis. Microbiota colonization, survival, and subsequent microbial dysbiosis are necessary conditions for oral *in-situ* carcinogenesis (Li *et al.*, 2022). Only then can a microbial carcinogenic impact be effectively induced. The process of systemic distal carcinogenesis is dependent on the microbiota's capacity to migrate from the oral cavity to other body parts (Sun *et al.*, 2020).

## III. CONCLUSION

Oral cavity microbiomes are crucial in the formation of colorectal, pancreatic, and oral malignancies. The most well-established is the cancer-causing effect of *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, two oral periopathogens. *Prevotella sp*, *Capnocytophaga gingivalis*, *Peptostreptococcus sp*, and *Streptococcus sp* appear to be additional factors crucial in carcinogenesis. Three mechanisms exist for bacteria to cause cancer in human cells: they can induce long-term inflammation, function as an antiapoptotic, or produce compounds that cause cancer. Nevertheless, more investigation is required to definitively identify particular oral bacteria as carcinogenic (Karpiński, 2019).

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