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Review

# Role of oral microbiome on oral cancers, a review

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ABSTRACT

The oral cavity is inhibited by many of the bacterial species. Some of them have a key role in the development of oral disease. Interrelationships between oral microbiome and systemic conditions such as head-and-neck cancer have become increasingly appreciated in recent years. Emerging evidence also suggests a link between periodontal disease and oral cancer, and the explanation being that chronic inflammation could be a major factor in both diseases. Squamous cell carcinoma is that the most frequently occurring malignancy of the oral cavity and adjacent sites, representing over 90% of all cancers. The incidence of oral cancer is increasing, significantly among young people and women. Worldwide there are 350,000–400,000 new cases diagnosed every year. Bacteria, viruses, and fungi are strongly implicated as etiological factors in certain cancers. In this review we will discuss the association between the development of oral cancer in potentially malignant oral lesions with chronic periodontitis, chronic *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, candida, other microbes and described mechanisms which may be involved in these carcinoma.



**Contents**



## 1. Introduction

The oral microbiome plays an essential role within the maintenance of a normal oral physiological environment. They play a role in development of oral diseases, such as, periodontal disease and tooth loss [1,2]. Although little studied, the oral microbiome could also be important in cancer and other chronic diseases, through direct metabolism of chemical carcinogens and general inflammatory effects [3]. A role for bacterial infection in inflicting or promoting cancer is renowned with relevancy to the association of *Helicobacter pylori* with gastric cancer [4]. Other cancers, such as, colon, gallbladder, prostate and lung, have been associated with particular bacterial infections [5,6]. The oral cavity is home to a various microbial community of more than 700 microbial species as well as commensal and opportunistic bacterium, fungi and viruses. They are living in a symbiotic relationship with one another and the host immune system [7,8].

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Deregulated host immune responses ensuring from environmental and systemic exposures (e.g., obesity, smoking, diabetes, aging, stress), host genetic, and epigenetic defects. Dysbiotic oral microflora subvert the host defense mechanisms result in chronic periodontal disease [9,10]. It is reasonable to ask, therefore, if shifts within the composition of the normal oral cavity microbiome, comprised of more than 600 different bacterial species [11]. Also chronic bacterial infection might be promoters or causes of oral cancer. Indeed, changes within the microbial community are commonly related to dental diseases like periodontitis, that is possibly a polymicrobial disease characterized by outgrowth of certain pathologic organisms [12]. Chronic periodontal disease has been reported to be a risk factor for oral premalignant lesions and cancers [13]. Emerging evidence also suggests a link between periodontal disease and oral cancer. The explanation being that chronic inflammation could be a major factor in periodontitis and oral cancer [14,15]. The development and progression of periodontal disease could be a complex process initiated by a dysbiotic polymicrobial insult. This complex process involves multiple host cells of myeloid and non-myeloid origin such as neutrophil polymorphs (PMNs), oral keratinocytes, monocytes, macrophages, osteoblasts, osteoclasts and dendritic cells. These cells possess cytosolic, membrane-associated receptors, and secreted pattern recognition receptors (PRRs) as well as NOD-like receptors (Nucleotide-binding Oligomerization Domain, NLRs), toll-like receptors (TLRs), RIG-I-like receptors (RLR), and C- type lectin receptors. They may intract with periodontal microbial associated molecular patterns (MAMPs) [e.g., fimbriae, BspA (*Bacteroides* surface protein A), lipoproteins, lipopolysaccharide (LPS), nucleic acids] and damage/danger associated molecular patterns (DAMPs) (e.g., fibrinogen, heat-shock proteins, nucleic acids) [16]. Squamous cell carcinoma is that the most frequently occurring malignancy of the oral cavity and adjacent sites, representing over 90% of all cancers. Worldwide, 200,000 new cases of oral cavity and lip cancer are diagnosed every year, with around 98,000 deaths (http://globocan.iarc.fr/Pages/fact_sheets_population.aspx). The incidence of oral cancer is increasing, significantly among young people and women. Worldwide there are 350,000–400,000 new cases diagnosed every year [17,18]. The predominant risk factors for oral cavity cancer are tobacco and alcohol use. The carcinogens impact on the oral mucosa to form a field that's susceptible to undergo malignant transformation, so-called "field cancerization" [19]. The foremost risk factors, alcohol and tobacco use, cannot explain the changes in incidence, as a result of oral cancer also commonly occurs in patients while not a history of alcohol or tobacco exposure [20]. Recently, human papillomavirus (HPV) has been known as an etiologic agent for oropharyngeal cancer, however HPV infection isn't a major contributor to oral cancer, because the virus is rarely found in these cancers (2–4% of cases) [21]. The molecular pathogenesis of oral cavity cancer is, in several cases, the results of dysregulation of common signaling pathways that actively drive oncogenesis, on a background of tumor suppressor inactivation. The basis for this could be a mixture of somatic mutations, as represented recently [22], along with transcriptomic alterations and epigenetic. Inactivation of the P53 and CDKN2A tumor suppressors additionally happens with high frequency in oral cancer. Additionally to molecular dysregulation as a results of chemical carcinogens in alcohol and tobacco, infectious agents play a significantly role in development and progression of oral cancer. Though significantly less frequent than within the oropharynx, human papilloma viral related carcinogenesis contributes to a little proportion of oral cavity cancers [around 10%] [22].

## 2. Periodontitis

The oral cavity is liable to variety of bacterial infectious diseases, like periodontal disease. Periodontal disease is potential that oral bacterium might serve to initiate or promote tumor development, analogous to the association of gastric cancer with *Helicobacter pylori* infection. In fact, variety of periodontal bacteria such as *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Prevotella intermedia*, are related to oral squamous cell carcinoma (OSCC) [23,24]. Mager et al. suggested that high salivary counts of *Prevotella melaninogenica*, *Streptococcus mitis* and *Capnocytophaga gingivalis* could also be diagnostic indicators of OSCC [23]. These findings taken with those of associate earlier study indicate that the presence of an OSCC features a more powerful impact on the salivary microbiota than either periodontitis or smoking. Instead oral microbiome might have a direct or indirect role in oral carcinogenesis. Some oral microbiome biotypes might contribute more to carcinogenesis than others. Arguments for and against these prospects are going to be designed below:

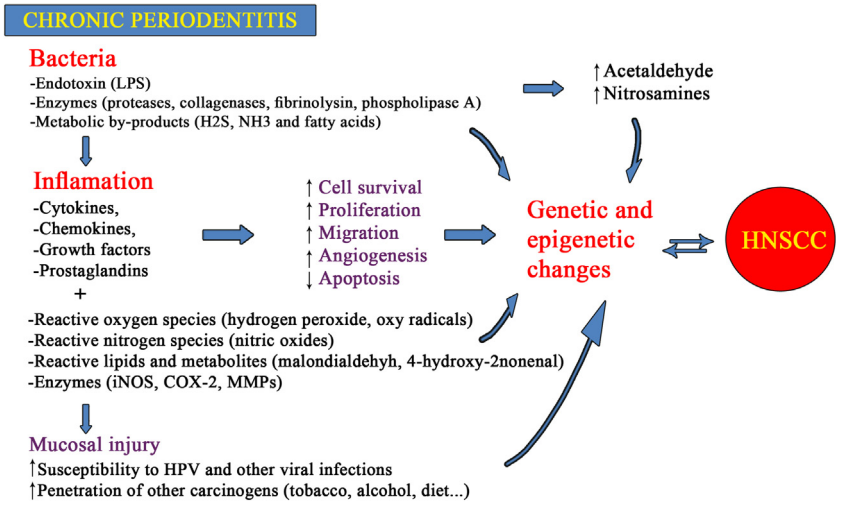


**Fig. 1.** A model for the role of chronic periodontal disease in head-and-neck cancer [30]. Enzymes, endotoxin and metabolic by-products of bacteria could be induced to secrete some inflammation substances from squamous cells, such as cytokines, which may act on the cells. Cytokines effect on cells may decrease apoptosis pathway and cell survival can be increased. This factors together multiple toxic components, which in turn may cause genetic and epigenetic changes and mucosal injury. Over time, all above-mentioned processes can cause head-and-neck squamous cell carcinoma.

- Colonization of the epithelium
- Ability to produce carcinogens and initiate carcinogenesis [Such a carcinogen (for example, nitrosamines [6]] will bind with DNA to form adducts with bases, phosphate residues, or hydrogen bonding sites that could cause miscoding or irregularities with DNA replication [25])
- Ability to promote carcinogenesis in initiated epitheliume by repeated administration of 4 nitroquinoline 1-oxide (4NQO) [26]
- Ability to metabolize procarcinogenesis (metabolize alcohol to toxic compounds such as acetaldehyde, hydroxyethyl radicals, ethoxy radicals, and hydroxyl radicals [27] and also metabolize tobacco smocking to acetaldehyde in oral cavity has a definite association with the development of OSCC [28]. Inhibits lipopolysaccharide-induced production of inflammatory cytokines by suppressing the activation of activator protein-1 in bronchial epithelial cells [29].
- Modify to microenviroment and chronic inflamation.

Recent studies showed that Periodontal disease is associated with cardiovascular disease (CVD) [30]. Through an experiment, periodontitis is associated with measures of endothelial dysfunction and atherosclerosis [30]. Periodontal pathogens induce anticardiolipin in periodontal disease patients by molecular mimicry of the serum protein β-2 glycoprotein I. These antibodies have biological and pathological activities according to those reported for different infection- induced antiphospholipid antibodies [30]. Chronic periodontal disease could also be severally related to head-and-neck squamous cell carcinoma (HNSCC). This taint could related to direct toxic effects of bacterium and their products, or through indirect effects of inflammation [30]. Within the oral cavity, periodontitis could be a chronic inflammatory disease related to Gram-negative anaerobic dental plaque bacteria that promote the continual release of bacteria and inflammatory cytokines into saliva [31]. A history of periodontal disease predicted poorly differentiated tumor status in patients with cancer of the oral cavity. A surprising finding was that the association between periodontal disease and HNSCC was weaker in current smokers compared with former and never- smokers. Supporting these results, different studies have also reported that the associations of oral health variables with pancreatic, upper gastrointestinal, esophageal, and head-and-neck cancers were weaker in smokers compared with non-smokers [32–34]. Different studies showed that smoking one cigarette every 2 h inhibited the LPS-induced production of inflammatory cytokines in bronchial epithelial cells [29]. Clinical signs of gingival inflammation also increase after smoking cessation [35]. It's so potential that whereas multiple toxic components can initiate carcinogenesis. Different components in tobacco might delay clinical manifestations (Fig. 1) [30].

## 3. Candida

There is less proof of associate etiological association between fungal infection and cancer. Several years Candida spp. are concerned in various epithelial cancers. Candidal infection does not seem to be a risk factor for cervical carcinoma or dysplastic cervical lesions [36]. Most interest in Candida and carcinogenesis are exponded to esophageal and oral carcinoma. There are variety of reports of esophageal or oral carcinoma developing in immune compromised patients with chronic mucocutaneous candidiasis and infrequently with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy [37,38]. Domingues-Ferreira et al. report [39] suggested that the participation of nitrosamine compounds produced by chronic Candida infections could be as a risk factor for esophageal cancer in a patient, who is infected autosomal-dominant chronic mucocutaneous candidiasis. Candida albicans is that most typical Candida species present in candidal leukoplakia and chronic hyper plastic candidiasis (CHC) [40,41]. McCullogh et al. [42] has also been observed that the extent of oral carriage of C. albicans is higher in patients presenting with OSCC or leukoplakia than in patients while not oral pathology.

## 4. *Prevotella gingivalis*

*Prevotella gingivalis* possesses multiple mechanisms for inhibition of programmed cell death or apoptosis in epithelial cells. Periodontal diseases are clearly multifactorial, perhaps beginning with the activation of the immune system at the cellular level by the LPS of a potential pathogen such as *P. gingivalis* or *F. nucleatum*. Simultaneously, genes are up-regulated to express tissue-active inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [43]. The events become cyclic, leading to periodontal attachment and tissue damage. Higher levels of IL-1β in periodontitis tissue [44] may play a pivotal role in the onset of chronic inflammatory periodontal disease and pathogenesis [45]. IL-1β is one of the factors known to secretion of proteinase and may be involved in bone resorption and the attachment loss which are characteristic property of periodontitis [46–48]. Tumor necrosis factor (TNF), play a role in host surveillance against neoplasms [49]. Macrophages are the most important source of TNF which are induced by Endotoxin. TNF alpha (TNF-α) was identified as a factor produced by leukocytes TNF-α play a role in the generation of free radicals, the pathophysiological changes during sepsis and also, septic shock [49].

Similar to IL-1, TNF-α induces fever by its ability to stimulate hypothalamic prostaglandin E2 synthesis directly [50]. The effects of these agents clearly are directly related to the oral disease activity observed clinically in immune-compromised patients and immunologically healthy. Activation and differentiation of human monocyte cell line (THP-1) by oral LPS in the presence of GM-CSF may suggest a role for human [43]. In the last few years, many studies have been showed the role of LPS of aerobic bacteria on monocyte or THP-1 cell activation. The composition of *P. gingivalis* LPS contains phosphorylated 2-keto-3-deoxyoctonate. It is not in the LPS of *Escherichia coli* [51].

Epithelial cell responses to *P. gingivalis* infection include each changes to apoptosis and cell division. In primary cultures of gingival epithelial cells, *P. gingivalis* is powefully antiapoptotic. Indeed, it will suppress with chemicals induced apoptosis [52]. *P. gingivalis* infection modulates several antiapoptotic pathways in addition to disseminating intercellularly through actin-based membrane protrusions and interfering with other cell-signalling pathways [52,53]. In the first pathway, *P. gingivalis* activates Jak1/Akt/Stat3 signaling. This signaling controls intrinsic mitochondrial apoptosis pathways [52,53]. At the mitochondrial membrane, the activity of pro-apoptotic Bad is inhibited. There for Bcl2 (anti-apoptotic); Bax (pro-apoptotic) ratio is enhanced, consequently curtailing the discharge of the apoptosis effector cytochrome c [54]. In the second pathway, *P. gingivalis* is an intracellular bacterium and successful colonizer of oral tissues. It can inhibit gingival epithelial cell apoptosis induced by ATP ligation of P2X7 receptors [55]. The purinergic receptor P2X7 is involved in cell death and apoptosis, inhibition of intracellular infection and secretion of inflammatory cytokines [55]. The role of the P2X7 receptor in bacterial infection has been primarily established in macrophages. A *P. gingivalis* homologue of nucleoside diphosphate kinase (NDK). It is an ATP-consuming enzyme. NDK is secreted extracellularly and is required for maximal suppression of apoptosis [55]. An NDK-deficient mutant was unable to prevent ATP induced host-cell death nor plasma membrane permeabilization in the epithelial cells. NDK promotes survival of host cells by hydrolysing extracellular ATP and preventing apoptosis-mediated

through P2X7 [55]. *P. gingivalis* impact on purinergic receptor $P2X_7$ by ATP-dependent apoptosis [55]. Another role of *P. gingivalis* is decreasing ATP sctivation of $P2X_7$ receptors on dendritic cells, which can impede activation of the NLRP3/ASC/caspase-1 inflammasome. In turn, it will cut back secretion of IL-1β and following that IFNγ-producing tumor–antigen-specific $CD8^+$ T cells [56]. Another pathway, *P. gingivalis* by utilization of cyclin/CDK (cyclin-dependent kinase) activity and reducing the extent of p53 tumor suppressor will accelerate progression through the S-phase of the cell cycle [57]. Groeger et al. showed that *P. gingivalis* induce the expression of the B7-H1 and B7-DC receptors in each OSCC cells and primary gingival epithelial cells [58]. B7-H1 expression promotes the event of regulatory T cells (Treg) that suppress effector T cells. So B7-H1 expression might contribute to immune evasion by oral cancers. *P. gingivalis* infection activates the ERK1/2-Ets1, p38/HSP27, and PAR2/NF-KB pathways to induce promatrix metalloproteinase (proMMP-9) expression [59]. Gingipains, cysteine proteinases produced by *P. gingivalis*, play a twin role during this process. They each engage the PAR2 receptor and cleave the MMP-9 pro-enzyme into the mature active form. Extracellular matrix and MMP-9 degrades basement membrane that promotes carcinoma cell migration and invasion. So they allowing carcinoma cells to enter the lymphatic system and blood vessels for dissemination and metastatic growth at remote sites. During this manner, *P. gingivalis* might contribute to OSCC metastasis Fig. 2.

## 5. *Fusobacterium nucleatum*

Similar to *P. gingivalis* LPS effect on epithelial cell, *Fusobacterium nucleatum* LPS activated inflammatory cytokines such as TNF-α, IL-1β, and IL-6. This events become cyclic, leading to periodontal attachment and tissue damage [43]. *F. nucleatum* differs from the classical *E. coli* LPS. It contains a significant amount of small quantities of 2-keto-3-deoxyoctonate and heptose [60]. The role of the lipopolysaccharide (LPS) of this oral microorganism in cytokine-mediated destructive lesions of the gingiva, inflammatory and periodontium merits investigation [60]. *F. nucleatum* infection modulates several antiapoptotic pathways. *F. nucleatum* additionally activates p38, resulting in the secretion of MMP-9 and MMP-13 (collagenase 3). In other study, Fischman et al. demonstrated that *F. nucleatum* induced NF-κB signaling in tongue epithelium of mouse [61]. NF-κB signaling is known consequence of TLR activation [62]. Exposure of SCC cells of oral cavity to the periodontal pathogens affected at the induction of additional bioactive molecules, enzymes, and cytokines implicated in oral cavity SCC proliferation, survival and aggressiveness (such as TNFα, cyclin D1, heparanase, and MMP9). Kind of like MMP-9, MMP-13 plays a very important role in tumor invasion and metastasis. Recently, an additional direct relationship between *F. nucleatum* and CRC was incontestable whereby the fusobacterial adhesin FadA binds to E-cadherin on colon carcinoma cells and activates B-catenin signaling. This pathway results in enhanced transcriptional activity of Wnt, pro-inflammatory cytokines, oncogenes, and stimulation of CRC cell proliferation Fig. 3 [63].

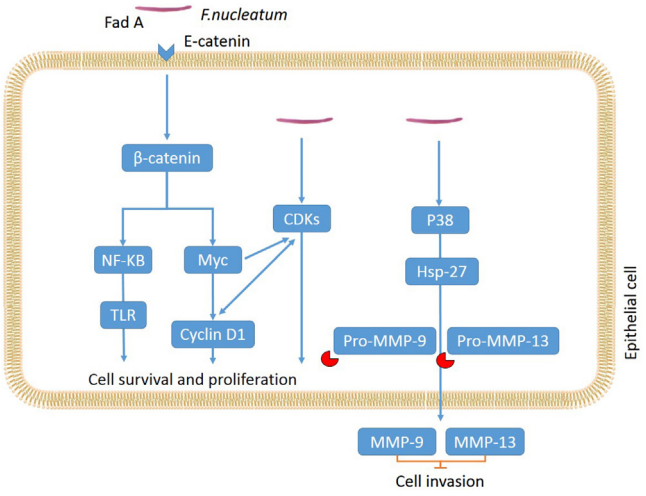


**Fig. 3.** *F. nucleatum* could produce an oncogenic phenotype of epithelial cell. FadA of *F. nucleatum* by activation E-catenin leads to activate β-catenin pathway, which cause cell survival. Intracelluar *F. nucleatun* by activation p38 leads to secrete MMP-9 and MMP13, which cause a crucial role in transformed squamous EP and cell invasion.

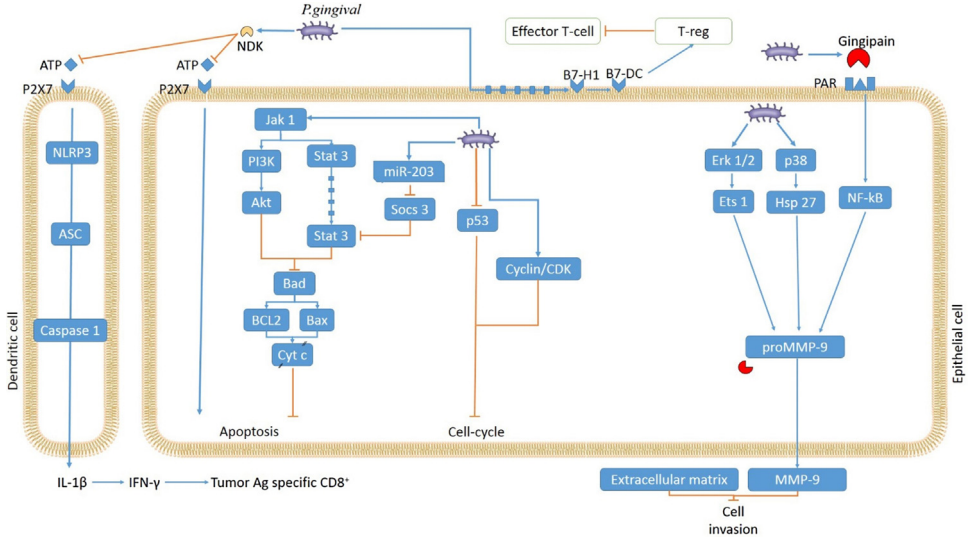


**Fig. 2.** *P. gingivalis* could produce an oncogenic phenotype of epithelial cell. *P. gingivalis* could cause apoptosis and cell-cycle changes by different way. Extracellular *P. gingivalis* release gingipain, which engage the PAR2 receptor, and activates PAR2 signaling pathway which together Erk1/2 and p38 signaling pathway activated by Intracellular *P. gingivalis* could cleave the MMP-9. Extracellular matrix and MMP-9 degrades basement membrane that promotes carcinoma cell migration and invasion. In other pathway, Intracellular *P. gingivalis* activates jak 1 and miR-203 signaling pathway could cause inhibited Bad which leading to apoptosis. Extracellular *P. gingivalis* secretes NDK. NDK by hydrolyzing extracellular ATP prevents apoptosis through P2X7 receptor in EP and activates caspase 1 through this receptor in DC which leading to produce Tumor AG specific $CD8^+$.

Jiyoung Ahn et al. study [64] showed that increasing risk for orodigestive cancer mortality in respect to increasing severity of periodontitis and repect to serum *P. gingivalis* immune gamma globin or IgG, a biomarker for exposure to the present periodontitis-related pathogen. The discovered associations remained statistically significant following control for smoking, age, sex, education, BMI and race/ethnicity [64]. Many different studies have related cancer risks to periodontitis and tooth loss, a generally accepted surrogate marker in adults for periodontal disease [65]. Loesche et al. studies [66] showed that Periodontitis is a chronic inflammatory disease associated with Gram-negative anaerobic bacteria in the dental biofilm. It leads to irreversible destruction of tissues supporting teeth, clinically detectable as periodontal pockets and alveolar bone loss. Champagne studies [67] showed that Periodontitis leads to a continuous release of bacterial and inflammatory markers into saliva and, to a lower degree, into blood. Moreover, Scannapieco et al. studies and different studies [68–71] showed that periodontic pathogens and inflammatory cytokines travel with saliva and blood from the affected tissues to distant sites and adversely affect general health. Based on the López et al. and D'Aiuto et al. studies [72,73], treatment of periodontal disease has been shown to prevent and reverse systemic adverse events. Previous studies from Tezel et al. suggested that chronic periodontitis could be related to tongue cancers [13], tumor human papillomavirus (HPV) status in base of tongue cancers [74] and oral premalignant lesions [75]. During this study HPV-16 and HPV-18 DNA were studied on paraffin-embedded tumor samples by polymerase chain reaction and HPV-16 (70%) were identified however none of the samples were identified for HPV-18 DNA [74]. Tezel et al. study [13] suggested that periodontal infection history is related to poorly differentiated tumors within the oral cavity. Factors that initiate periodontal infection are poorly understood. Smoking reduces gingivitis [76] however it is a powerful risk factor for periodontal infection [77]. Gingivitis is mostly related to Gram-positive facultative bacterium, whereas periodontitis with Gram-negative anaerobic bacterium [66]. Accumulating evidence supports a role of viruses within the initiation and progression of periodontal disease [78,79]. Tezel et al. study also suggested a synergy between oral HPV infection in base of tongue cancers and chronic periodontal disease [74]. The recent increase during a set of HNSCC has also been attributed to the enhanced rates of HPV infection. Epidemiologic studies have shown that nonsmokers are more likely than smokers to have HPV-related HNSCC [80]. It is reasonable to theorize that the increase in HPV-related HNSCC is additionally associated with the declining rates of smoking. The interactions between these risk factors could also be essential to understand carcinogenesis within the head and neck. This study suggests an association between chronic periodontal disease and poorly differentiated tumors within the oral cavity. Continuous stimulation of cellular proliferation by chronic inflammation could also be responsible for this histologic type [5]. Rapid cell division provides rise to replication errors and aberrant DNA repair. Many studies have established the rise in cytokine levels in patients with increasing grade of cervical intraepithelial pathological process and neoplasia [81]. Grading is subjective with high interobserver variability and that we only discovered this association within the oral cavity. Therefore, this association could also be due to probability and wishes additional exploration. Certain species, like *Porphyromonas gingivalis*, can disrupt this equilibrium, leading to a dysbiotic host microbiota interaction. Afterwards, different community constituents, like *Fusobacterium nucleatum*, can become opportunistically pathogenic, and therefore the combined impact of a dysbiotic microbic community beside a dysregulated immune response ultimately causes periodontitis [82]. May be the foremost probably carcinogenic link with oral bacterium is with oral squamous cell carcinoma (OSCC), one in all the foremost common cancers worldwide. OSCC surfaces have been reported to harbor considerably higher levels of Fusobacterium and Porphyromonas compared with contiguous healthy mucosa layer [24]. Moreover, immunohistochemistry assay with *P. gingivalis* antibodies disclosed higher levels of detection and intensity of staining in gingival carcinomas compared with healthy gingival tissue, though only a little range of cases were examined [83]. And additionally Several recent studies have shown a powerful association between colorectal cancer (CRC) and *F. nucleatum* [84,85]. Chronic or dysregulated inflammation has long been appreciated as contributive to tumor development, partly through modulation of the tumor microenvironment [86]. Both *F. nucleatum* and *P. gingivalis* establish chronic infections that involve intracellular persistence inside epithelial cells, will spread systemically and cause extra-oral infections, and have well-characterized immune disruptive properties [87]. *Fusobacterium nucleatum* is powerfully pro-inflammatory. McCoy et al. [84] demonstrated a positive correlation between *Fusobacterium spp.* and mRNA levels for several local cytokines in CRC cases. Finally, the implications of oral bacterium involvement in cancer are many. The detection of *F. nucleatum* or *P. gingivalis* in precancerous lesions might be used as a poor prognosis indicator.

## 6. Conclusion

Improved oral hygiene and treatment of periodontal disease could also be helpful in limiting the development or spread of cancer. Also, use of commensal bacterial strains of oral as probiotics could promote oral health and prevent oral cancer.

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## References

[1] D. Preza, I. Olsen, T. Willumsen, S.K. Boches, S.L. Cotton, B. Grinde, B.J. Paster, Microarray analysis of the microflora of root caries in elderly, Eur. J. Clin. Microbiol. Infect. Dis. 28 (5) (2009) 509–517.
[2] Y. Abiko, T. Sato, G. Mayanagi, N. Takahashi, Profiling of subgingival plaque biofilm microflora from periodontally healthy subjects and from subjects with periodontitis using quantitative real-time PCR, J. Periodontal Res. 45 (3) (2010) 389–395.
[3] J. Meurman, Oral microbiota and cancer, J. Oral Microbiol. 2 (2010).
[4] P. Correa, W. Haenszel, C. Cuello, S. Tannenbaum, M. Archer, A model for gastric cancer epidemiology, Lancet 306 (7924) (1975) 58–60.
[5] A.J. Lax, W. Thomas, How bacteria could cause cancer: one step at a time, Trends Microbiol. 10 (6) (2002) 293–299.
[6] S.J. Hooper, M.J. Wilson, S.J. Crean, Exploring the link between microorganisms and oral cancer: a systematic review of the literature, Head Neck 31 (9) (2009) 1228–1239.
[7] A.P.V. Colombo, S.K. Boches, S.L. Cotton, J.M. Goodson, R. Kent, A.D. Haffajee, S. S. Socransky, H. Hasturk, T.E. Van Dyke, F. Dewhirst, Comparisons of subgingival microbial profiles of refractory periodontitis, severe periodontitis, and periodontal health using the human oral microbe identification microarray, J. Periodontol. 80 (9) (2009) 1421–1432.
[8] A.E. Duran-Pinedo, T. Chen, R. Teles, J.R. Starr, X. Wang, K. Krishnan, J. Frias-Lopez, Community-wide transcriptome of the oral microbiome in subjects with and without periodontitis, ISME J. 8 (8) (2014) 1659–1672.
[9] P. Bullon, H.N. Newman, M. Battino, Obesity, diabetes mellitus, atherosclerosis and chronic periodontitis: a shared pathology via oxidative stress and mitochondrial dysfunction? Periodontology 2000 64 (1) (2014) 139–153.
[10] A. Johannsen, C. Susin, A. Gustafsson, Smoking and inflammation: evidence for a synergistic role in chronic disease, Periodontology 2000 64 (1) (2014) 111–126.
[11] F.E. Dewhirst, T. Chen, J. Izard, B.J. Paster, A.C. Tanner, W.-H. Yu, A. Lakshmanan, W.G. Wade, The human oral microbiome, J. Bacteriol. 192 (19) (2010) 5002–5017.
[12] H.F. Jenkinson, R.J. Lamont, Oral microbial communities in sickness and in health, Trends Microbiol. 13 (12) (2005) 589–595.

[13] M. Tezal, M.A. Sullivan, A. Hyland, J.R. Marshall, D. Stoler, M.E. Reid, T.R. Loree, N.R. Rigual, M. Merzianu, L. Hauck, Chronic periodontitis and the incidence of head and neck squamous cell carcinoma, Cancer Epidemiol. Biomark. Prev. 18 (9) (2009) 2406–2412.
[14] S.G. Fitzpatrick, J. Katz, The association between periodontal disease and cancer: a review of the literature, J. Dent. 38 (2) (2010) 83–95.
[15] Q.-W. Yao, D.-S. Zhou, H.-J. Peng, P. Ji, D.-S. Liu, Association of periodontal disease with oral cancer: a meta-analysis, Tumor Biol. 35 (7) (2014) 7073–7077.
[16] G. Hajishengallis, Immunomicrobial pathogenesis of periodontitis: keystones, pathobionts, and host response, Trends Immunol. 35 (1) (2014) 3–11.
[17] A. Jemal, F. Bray, M.M. Center, J. Ferlay, E. Ward, D. Forman, Global cancer statistics, CA Cancer J. Clin. 61 (2) (2011) 69–90.
[18] C.H. Shiboski, B.L. Schmidt, R.C. Jordan, Tongue and tonsil carcinoma, Cancer 103 (9) (2005) 1843–1849.
[19] S.E. Sahingur, W.A. Yeudall, Chemokine function in periodontal disease and oral cavity cancer, Front. Immunol. 6 (2015).
[20] B.L. Schmidt, E.J. Dierks, L. Homer, B. Potter, Tobacco smoking history and presentation of oral squamous cell carcinoma, J. Oral Maxillofac. Surg. 62 (9) (2004) 1055–1058.
[21] M.L. Gillison, Human papillomavirus-associated head and neck cancer is a distinct epidemiologic, clinical, and molecular entity, Seminars in Oncology, Elsevier, 2004, pp. 744–754.
[22] C.G.A. Network, Comprehensive genomic characterization of head and neck squamous cell carcinomas, Nature 517 (7536) (2015) 576–582.
[23] D. Mager, A. Haffajee, P. Devlin, C. Norris, M. Posner, J. Goodson, The salivary microbiota as a diagnostic indicator of oral cancer: a descriptive, non-randomized study of cancer-free and oral squamous cell carcinoma subjects, J. Transl. Med. 3 (1) (2005) 27.
[24] K. Nagy, I. Sonkodi, I. Szöke, E. Nagy, H. Newman, The microflora associated with human oral carcinomas, Oral Oncol. 34 (4) (1998) 304–308.
[25] R.P. Hill, I. Tannock, The Basic Science of Oncology, Pergamon Press, 1987.
[26] P. Dwivedi, S. Mallya, A. Dongari-Bagtzoglou, A novel immunocompetent murine model for Candida albicans-promoted oral epithelial dysplasia, Med. Mycol. 47 (2) (2009) 157–167.
[27] A. Garro, C. Lieber, Alcohol and cancer, Annu. Rev. Pharmacol. Toxicol. 30 (1) (1990) 219–249.
[28] B.J. Davidson, T. Hsu, S.P. Schantz, The genetics of tobacco-induced malignancy, Arch. Otolaryngol. Head Neck Surg. 119 (11) (1993) 1198–1205.
[29] M. Laan, S. Bozinovski, G.P. Anderson, Cigarette smoke inhibits lipopolysaccharide-induced production of inflammatory cytokines by suppressing the activation of activator protein-1 in bronchial epithelial cells, J. Immunol. 173 (6) (2004) 4164–4170.
[30] Y. Han, W. Houcken, B. Loos, H. Schenkein, M. Tezal, Periodontal disease, atherosclerosis, adverse pregnancy outcomes, and head-and-neck cancer, Adv. Dent. Res. 26 (1) (2014) 47–55.
[31] F. Scannapieco, P. Ng, K. Hovey, E. Hausmann, A. Hutson, J. Wactawski-Wende, Salivary biomarkers associated with alveolar bone loss, Ann. N. Y. Acad. Sci. 1098 (2007) 496.
[32] C.C. Abnet, Y.-L. Qiao, S.M. Dawsey, Z.-W. Dong, P.R. Taylor, S.D. Mark, Tooth loss is associated with increased risk of total death and death from upper gastrointestinal cancer, heart disease, and stroke in a Chinese population-based cohort, Int. J. Epidemiol. 34 (2) (2005) 467–474.
[33] D.S. Michaud, K. Joshipura, E. Giovannucci, C.S. Fuchs, A prospective study of periodontal disease and pancreatic cancer in US male health professionals, J. Natl. Cancer Inst. 99 (2) (2007) 171–175.
[34] A. Hiraki, K. Matsuo, T. Suzuki, T. Kawase, K. Tajima, Teeth loss and risk of cancer at 14 common sites in Japanese, Cancer Epidemiol. Biomark. Prev. 17 (5) (2008) 1222–1227.
[35] P. Nair, G. Sutherland, R. Palmer, R. Wilson, D. Scott, Gingival bleeding on probing increases after quitting smoking, J. Clin. Periodontol. 30 (5) (2003) 435–437.
[36] M. Engberts, C. Vermeulen, B. Verbruggen, M. Van Haaften, M. Boon, A. Heintz, Candida and squamous (pre) neoplasia of immigrants and Dutch women as established in population-based cervical screening, Int. J. Gynecol. Cancer 16 (4) (2006) 1596–1600.
[37] N. Firth, J. O'Grady, P. Reade, Oral squamous cell carcinoma in a young person with candidosis endocrinopathy syndrome: a case report, Int. J. Oral Maxillofac. Surg. 26 (1) (1997) 42–44.
[38] R. Teles, F. Teles, J. Frias-Lopez, B. Paster, A. Haffajee, Lessons learned and unlearned in periodontal microbiology, Periodontology 2000 62 (1) (2013) 95–162.
[39] M. Domingues-Ferreira, A.S. Grumach, A.J.D.S. Duarte, D. De Moraes-Vasconcelos, Esophageal cancer associated with chronic mucocutaneous candidiasis. Could chronic candidiasis lead to esophageal cancer? Med. Mycol. 47 (2) (2009) 201–205.
[40] A. Jepsen, J. Winther, Mycotic infection in oral leukoplakia, Acta Odontol. Scand. 23 (3) (1965) 239–256.
[41] I. Van der Waal, Potentially malignant disorders of the oral and oropharyngeal mucosa; terminology, classification and present concepts of management, Oral Oncol. 45 (4) (2009) 317–323.
[42] M. McCullough, M. Jaber, A. Barrett, L. Bain, P. Speight, S. Porter, Oral yeast carriage correlates with presence of oral epithelial dysplasia, Oral Oncol. 38 (4) (2002) 391–393.
[43] A. Baqui, T.F. Meiller, J.J. Chon, B.-F. Turng, W.A. Falkler, Granulocyte-macrophage colony-stimulating factor amplification of interleukin-1β and tumor necrosis factor alpha production in THP-1 human monocytic cells stimulated with lipopolysaccharide of oral microorganisms, Clin. Diagn. Lab. Immunol. 5 (3) (1998) 341–347.
[44] E. Gemmell, G. Seymour, Interleukin 1, interleukin 6 and transforming growth factor-β production by human gingival mononuclear cells following stimulation with Porphyromonas gingivalis and Fusobacterium nucleatum, J. Periodontal Res. 28 (2) (1993) 122–129.
[45] J. Hönig, C. Rordorf-Adam, C. Siegmund, W. Wiedemann, F. Erard, Increased interleukin-1 beta (IL-1β) concentration in gingival tissue from periodontitis patients, J. Periodontal Res. 24 (6) (1989) 362–367.
[46] M. Gowen, D.D. Wood, E.J. Ihrie, M.K. McGuire, R.G.G. Russell. An interleukin 1 like factor stimulates bone resorption in vitro 306 (5941), 1983, 378–380.
[47] E. Mochan, L. Armor, R. Sporer, Interleukin 1 stimulation of plasminogen activator production in cultured gingival fibroblasts, J. Periodontal Res. 23 (1) (1988) 28–32.
[48] K. Sato, Y. Fujii, K. Kasono, M. Saji, T. Tsushima, K. Shizume, Stimulation of prostaglandin E2 and bone resorption by recombinant human interleukin 1 alpha in fetal mouse bones, Biochem. Biophys. Res. Commun. 138 (2) (1986) 618–624.
[49] P. Brouckaert, C. Libert, B. Everaerdt, N. Takahashi, A. Cauwels, W. Fiers, Tumor necrosis factor, its receptors and the connection with interleukin 1 and interleukin 6, Immunobiology 187 (3) (1993) 317–329.
[50] C.A. Dinarello, J.G. Cannon, S.M. Wolff, H.A. Bernheim, B. Beutler, A. Cerami, I. Figari, M. Palladino, J. O'connor, Tumor necrosis factor (cachectin) is an endogenous pyrogen and induces production of interleukin 1, J. Exp. Med. 163 (6) (1986) 1433–1450.
[51] T. Fujiwara, T. Ogawa, S. Sobue, S. Hamada, Chemical, immunobiological and antigenic characterizations of lipopolysaccharides from Bacteroides gingivalis strains, Microbiology 136 (2) (1990) 319–326.
[52] S. Mao, Y. Park, Y. Hasegawa, G.D. Tribble, C.E. James, M. Handfield, M.F. Stavropoulos, Ö. Yilmaz, R.J. Lamont, Intrinsic apoptotic pathways of gingival epithelial cells modulated by Porphyromonas gingivalis, Cell. Microbiol. 9 (8) (2007) 1997–2007.
[53] Ö. Yilmaz, T. Jungas, P. Verbeke, D.M. Ojcius, Activation of the phosphatidylinositol 3-kinase/Akt pathway contributes to survival of primary epithelial cells infected with the periodontal pathogen Porphyromonas gingivalis, Infect. Immun. 72 (7) (2004) 3743–3751.
[54] L. Yao, C. Jermanus, B. Barbetta, C. Choi, P. Verbeke, D. Ojcius, Ö. Yilmaz, Porphyromonas gingivalis infection sequesters pro-apoptotic Bad through Akt in primary gingival epithelial cells, Mol. Oral Microbiol. 25 (2) (2010) 89–101.
[55] Ö. Yilmaz, L. Yao, K. Maeda, T.M. Rose, E.L. Lewis, M. Duman, R.J. Lamont, D.M. Ojcius, ATP scavenging by the intracellular pathogen Porphyromonas gingivalis inhibits P2X7-mediated host-cell apoptosis, Cell. Microbiol. 10 (4) (2008) 863–875.
[56] L. Aymeric, L. Apetoh, F. Ghiringhelli, A. Tesniere, I. Martins, G. Kroemer, M.J. Smyth, L. Zitvogel, Tumor cell death and ATP release prime dendritic cells and efficient anticancer immunity, Cancer Res. 70 (3) (2010) 855–858.
[57] M. Kuboniwa, Y. Hasegawa, S. Mao, S. Shizukuishi, A. Amano, R.J. Lamont, Ö. Yilmaz, P. gingivalis accelerates gingival epithelial cell progression through the cell cycle, Microbes Infect. 10 (2) (2008) 122–128.
[58] S. Groeger, E. Domann, J.R. Gonzales, T. Chakraborty, J. Meyle, B7-H1 and B7-DC receptors of oral squamous carcinoma cells are upregulated by Porphyromonas gingivalis, Immunobiology 216 (12) (2011) 1302–1310.
[59] H. Inaba, H. Sugita, M. Kuboniwa, S. Iwai, M. Hamada, T. Noda, I. Morisaki, R.J. Lamont, A. Amano, Porphyromonas gingivalis promotes invasion of oral squamous cell carcinoma through induction of proMMP9 and its activation, Cell. Microbiol. 16 (1) (2014) 131–145.
[60] S. Hamada, T. Koga, T. Nishihara, T. Fujiwara, N. Okahashi, Characterization and immunobiologic activities of lipopolysaccharides from periodontal bacteria, Adv. Dent. Res. 2 (2) (1988) 284–291.
[61] S. Fischman, B. Revach, R. Bulvik, A. Maliutina, A. Rubinstein, G. Nussbaum, M. Elkin, Periodontal pathogens Porphyromonas gingivalis and Fusobacterium nucleatum promote tumor progression in an oral-specific chemical carcinogenesis model, Oncotarget 6 (26) (2015) 22613–22623.
[62] S. Rakoff-Nahoum, R. Medzhitov, Toll-like receptors and cancer, Nat. Rev. Cancer 9 (1) (2009) 57–63.
[63] M.R. Rubinstein, X. Wang, W. Liu, Y. Hao, G. Cai, Y.W. Han, Fusobacterium nucleatum promotes colorectal carcinogenesis by modulating E-cadherin/β-catenin signaling via its FadA adhesin, Cell Host Microbe 14 (2) (2013) 195–206.
[64] J. Ahn, S. Segers, R.B. Hayes, Periodontal disease, Porphyromonas gingivalis serum antibody levels and orodigestive cancer mortality, Carcinogenesis (2012) bgs112.
[65] B.L. Pihlstrom, B.S. Michalowicz, N.W. Johnson, Periodontal diseases, Lancet 366 (9499) (2005) 1809–1820.
[66] W.J. Loesche, N.S. Grossman, Periodontal disease as a specific, albeit chronic, infection: diagnosis and treatment, Clin. Microbiol. Rev. 14 (4) (2001) 727–752.
[67] C.M. Champagne, W. Buchanan, M.S. Reddy, J.S. Preisser, J.D. Beck, S. Offenbacher, Potential for gingival crevice fluid measures as predictors of risk for periodontal diseases, Periodontology 2000 31 (1) (2003) 167–180.
[68] F.A. Scannapieco, B. Wang, H.J. Shiau, Oral bacteria and respiratory infection: effects on respiratory pathogen adhesion and epithelial cell proinflammatory cytokine production, Ann. Periodontol. 6 (1) (2001) 78–86.
[69] S. Paju, F. Scannapieco, Oral biofilms, periodontitis, and pulmonary infections, Oral Dis. 13 (6) (2007) 508–512.

[70] J. Brown, Oral biofilms, periodontitis and pulmonary infections, Oral Dis. 13 (6) (2007) 513–514.
[71] T.C. Nichols, T.H. Fischer, E.N. Deliargyris, A.S. Baldwin Jr., Role of nuclear factor-kappa B (NF-κB) in inflammation, periodontitis, and atherogenesis, Ann. Periodontol. 6 (1) (2001) 20–29.
[72] N.J. Lopez, I. Da Silva, J. Ipinza, J. Gutiérrez, Periodontal therapy reduces the rate of preterm low birth weight in women with pregnancy-associated gingivitis, J. Periodontol. 76 (11-s) (2005) 2144–2153.
[73] F. D'Aiuto, M. Parkar, G. Andreou, J. Suvan, P.M. Brett, D. Ready, M.S. Tonetti, Periodontitis and systemic inflammation: control of the local infection is associated with a reduction in serum inflammatory markers, J. Dent. Res. 83 (2) (2004) 156–160.
[74] M. Tezal, M.S. Nasca, D.L. Stoler, T. Melendy, A. Hyland, P.J. Smaldino, N.R. Rigual, T.R. Loree, Chronic periodontitis- human papillomavirus synergy in base of tongue cancers, Arch. Otolaryngol. Head Neck Surg. 135 (4) (2009) 391–396.
[75] M. Tezal, S.G. Grossi, R.J. Genco, Is periodontitis associated with oral neoplasms? J. Periodontol. 76 (3) (2005) 406–410.
[76] D. Scott, D. Singer, Suppression of overt gingival inflammation in tobacco smokers–clinical and mechanistic considerations, Int. J. Dent. Hyg. 2 (3) (2004) 104–110.
[77] F.O. Costa, C. Susin, J.R. Cortelli, I.A. Pordeus, Epidemiology of periodontal disease, Int. J. Dent. 2012 (2012).
[78] M. Hormia, J. Willberg, H. Ruokonen, S. Syrjänen, Marginal periodontium as a potential reservoir of human papillomavirus in oral mucosa, J. Periodontol. 76 (3) (2005) 358–363.
[79] I. Saygun, A. Kubar, A. Özdemir, J. Slots, Periodontitis lesions are a source of salivary cytomegalovirus and Epstein–Barr virus, J. Periodontal Res. 40 (2) (2005) 187–191.
[80] G. D'Souza, A.R. Kreimer, R. Viscidi, M. Pawlita, C. Fakhry, W.M. Koch, W.H. Westra, M.L. Gillison, Case–control study of human papillomavirus and oropharyngeal cancer, N. Engl. J. Med. 356 (19) (2007) 1944–1956.
[81] B. Goswami, M. Rajappa, M.A. Sharma, A. Sharma, Inflammation: its role and interplay in the development of cancer, with special focus on gynecological malignancies, Int. J. Gynecol. Cancer 18 (4) (2008) 591–599.
[82] G. Hajishengallis, R.J. Lamont, Beyond the red complex and into more complexity: the polymicrobial synergy and dysbiosis (PSD) model of periodontal disease etiology, Mol. Oral Microbiol. 27 (6) (2012) 409–419.
[83] J. Katz, M.D. Onate, K.M. Pauley, I. Bhattacharyya, S. Cha, Presence of Porphyromonas gingivalis in gingival squamous cell carcinoma, Int. J. Oral Sci. 3 (4) (2011) 209.
[84] A.N. McCoy, F. Araujo-Perez, A. Azcarate-Peril, J.J. Yeh, R.S. Sandler, T.O. Keku, Fusobacterium is associated with colorectal adenomas, PLoS One 8 (1) (2013) e53653.
[85] A.D. Kostic, D. Gevers, C.S. Pedamallu, M. Michaud, F. Duke, A.M. Earl, A.I. Ojesina, J. Jung, A.J. Bass, J. Tabernero, Genomic analysis identifies association of Fusobacterium with colorectal carcinoma, Genome Res. 22 (2) (2012) 292–298.
[86] S. Rakoff-Nahoum, Why cancer and inflammation, Yale J. Biol. Med. 79 (3–4) (2006) 123–130.
[87] Y. Han, X. Wang, Mobile microbiome oral bacteria in extra-oral infections and inflammation, J. Dent. Res. 92 (6) (2013) 485–491, doi:http://dx.doi.org/10.1177/0022034513487559.