

The Possible Link between Periodontitis and Orodigestive Cancer: An Overview

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Abstract

Increasing evidences are found in the literature lately regarding the association between periodontitis and orodigestive tract cancers. Periodontopathic bacteria resulting in periodontal disease, acts as a risk factor for the initiation and development of carcinoma. They have been shown to act through various mechanisms including inhibition of apoptosis, activation of cellular proliferation, and others. This review is an attempt to find the possible connecting mechanism between the aforesaid.

Keywords: *Fusobacterium nucleatum*, orodigestive cancer, periodontitis, *Porphyromonas gingivalis*, *Treponema denticola*

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INTRODUCTION

Periodontitis is considered as one of the major causes of tooth loss in adults. It is a chronic inflammatory condition which is characterized by irreversible destruction of the tooth supporting structures and is mainly associated with Gram-negative anaerobic bacteria.^[1]

The periodontopathic organisms initiate the inflammatory response in the adjacent tissues which result in continuous release of bacterial and inflammatory markers into the saliva and blood. These further travel to the distant sites and adversely affect the systemic health.^[2] Recently, there has been intense research regarding potential associations between periodontal disease and various chronic systemic diseases and conditions including orodigestive cancers.^[3]

Orodigestive cancers are defined as cancers in the oral cavity and pharynx, esophagus, stomach, pancreas, liver, and colon, rectum, or anus. Oral cancers along with stomach, pancreatic, esophageal, and oropharyngeal cancers constitute an important global public health problem as they occupy the fourth, fifth, sixth, and eighth position, respectively, among the most common cancers in the world. In a prospective cohort study, a significant association was reported by Michaud *et al.* between cancers of orodigestive tract and oral health status.^[4]

This review is an attempt to throw some light on the current literature available on this relationship.

ORAL MICROBIAL DYSBIOSIS AND ORO-DIGESTIVE CANCER

Several distinct niches (including hard palate, soft palate, lateral and dorsal surfaces of the tongue and tooth surfaces above and below the gingival margin) present in the oral cavity displaying site specificity and distinct bacterial profile, provide unique conditions and nutrients for populating the microbes.^[5] The microbes which are predominantly anaerobic bacteria can induce carcinogenesis by following possible mechanisms [Figure 1].

Inhibition of apoptosis

According to Binder Gallimidi *et al.*,^[6] chronic coinfection with *Porphyromonas gingivalis* and *Fusobacterium nucleatum* activates IL-6/STAT 3 axis leading to progression of chemically induced oral cancer in a murine model. Groeger *et al.*^[7] suggested that *P. gingivalis* by secreting nucleoside diphosphate

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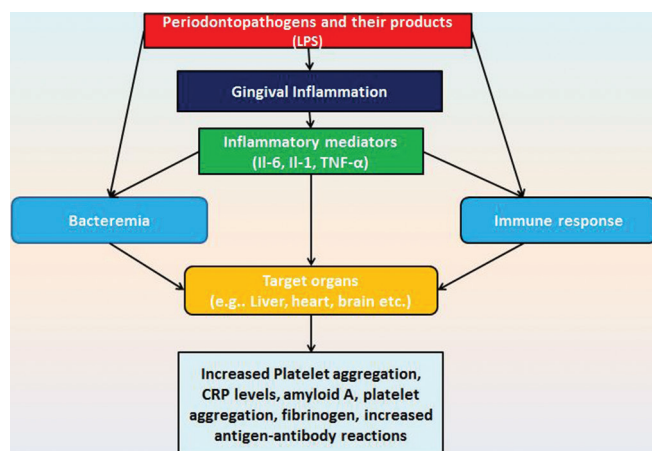


Figure 1: Possible effects of periodontopathogens and their products on major human organs

kinase might interfere with anticancer immune response and inhibits Adenosine Triphosphate (ATP)-dependent apoptosis of the cancer cells.

Activation of cell proliferation

Chang *et al.* in his recent literature concluded that *F. nucleatum* and *P. gingivalis* together promote cellular proliferation via upregulation of cyclins (A, D, E), activation of cyclin-dependent kinases (C, D, K), and diminishing the level of p53 tumor suppressor. *P. gingivalis* also leads to a phenotype which is proliferative in nature through activation of beta-catenin through gingipain-dependent proteolytic process.^[8]

Promotion of cellular migration and invasion

Repeated infection of gingival epithelial cells by *F. nucleatum* and *P. gingivalis* may lead to enhancement of cellular invasion and migration via upregulation of expression for proMMP-9 (*P. gingivalis*) and proMMP-13 (*F. nucleatum*).^[9]

Induction of inflammation

Chronic inflammation triggers the release of reactive oxygen species, reactive nitrogen intermediates, and cytokines which results in the induction of mutations, genomic instability and epigenetic alterations. These further support the pro-malignant process, resulting in sustained tumor promoting environment.^[10]

Production of carcinogens

Certain bacterial and fungal species including *Candida* possess the enzyme alcohol dehydrogenase responsible for the production of Acetaldehyde. Acetaldehyde along with hydroxyl ethyl radicals and hydroxyl radicals cause sister chromatid exchanges, point mutations, DNA adducts, and hyperproliferation of epithelial cells, thus leading to induction of carcinogenesis.^[11]

EVIDENCE FOR ASSOCIATION

Heikkilä *et al.*^[12] studied 68,273 adults-based cohort with 10 years' follow-up to check for the involvement of periodontitis as a risk factor for cancer mortality. They reported

a total of 797 cancer deaths in that time period and observed that stronger associations exist between periodontitis and risk for carcinoma with an increase in overall (relative risk [RR] 1.33, 95% confidence interval [CI] 1.10–1.58) and pancreatic cancer (RR 2.32, 95% CI 1.31–3.98) mortality.

Abnet *et al.*,^[13] in their prospective study in a 28,868-person cohort (followed for 5.25 years), to determine the association between tooth loss and the risk of developing esophageal squamous cell carcinoma, gastric cardia adenocarcinoma, or gastric noncardia adenocarcinoma found that tooth loss was associated with a significantly elevated risk of developing esophageal cancer (RR 1.3 [1.01–1.6], CI 95%), gastric cardia (RR 1.3 [1.0–1.6]), and gastric noncardia (RR 1.8 [1.1–3.0]) cancers. They further hypothesized that these may be related to alterations in oral bacterial flora and subsequent increases in the *in vivo* production of carcinogens (e.g., nitrosamines).

Velly *et al.*^[14] examined the relationship between dental health variables and risk of upper aerodigestive tract cancers in a case-control study on 717 cases (cancers of mouth, pharynx, and larynx) in Southern Brazilian population. Tobacco and alcohol consumption, diet, and sociodemographic variables were taken into consideration. It was concluded that poor oral hygiene resulting from infrequent daily tooth brushing was associated with increased risk of cancer of the tongue (odds ratio [OR] = 2.1, 95% CI 1.0–4.3) and of other parts of the mouth (OR = 2.4, 95% CI 1.0–5.4) and that these associations are unlikely to be due to insufficient control of confounding.

Abnet *et al.*^[15] in their case-control study stated that a simple intervention of teaching routine oral hygiene practices led to lower risk of esophageal squamous cell carcinoma in people living in the high-risk areas of Iran, matched for age, sex, and neighborhood. They found that individuals with esophageal cancer had significantly more decayed, missing or filled teeth index (DMFT) when compared to the controls. Thus, suggesting the association between two markers of poor oral hygiene (i.e. larger number of DMFT and lack of poor oral hygiene) and risk of esophageal carcinoma.

Stolzenberg-Solomon *et al.*^[16] investigated the relation between dentition history and pancreatic cancer and the association between dentition history and *Helicobacter pylori* seropositivity, in a cross-sectional prospective study with a sample of 475 individuals without cancer from Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort. It was observed that tooth loss was positively associated with pancreatic cancer but was not significantly associated with *H. pylori* seropositivity.

Michaud *et al.*^[17] conducted a 16-year prospective study on 216 patients diagnosed with pancreatic cancer of a 51,529 cohort of age group 40 and 75 years. They found that individuals with history of periodontal disease had a 64% increased risk of pancreatic cancer than with no history of it.

A case-control study with 404 matched cases and controls was conducted in Beijing for assessing the relation between

dentition and risk of oral cancer. The oral examination included recording of missing teeth and presence of gingivitis or periodontal disease. Analyses were stratified by gender, for males, a two-to three-fold increase in the risk of oral cancer was observed for any tooth loss, with or without tooth replacement, and a five-to eight-fold increase of risk was found for females.^[18]

Tezal *et al.*,^[19] in their study, conducted to assess the effect of chronic periodontitis on head and neck squamous cell carcinoma found that each millimeter of alveolar bone loss was associated with more than a four-fold increased risk of carcinoma and the strength of association was found to be the greatest in the oral cavity. They concluded that patients with periodontitis were more likely to have poorly differentiated oral squamous cell carcinoma than those without periodontitis. Thus, this can be suggested that chronic periodontitis is an independent risk factor for carcinoma; however, smoking modifies the association.

In another study, Tezal *et al.*^[20] found that each millimeter of alveolar bone loss was associated with a 5.23-fold increase in the risk of tongue cancer (OR, 5.23; 95% CI, 2.64–10.35). Thus, suggesting an association between chronic periodontitis and the risk of tongue cancer in men, independent of smoking status, age, race, ethnicity, and number of teeth.

Arora *et al.*^[21] in their study explored the shared genetic risk factors between periodontal disease and cancer. They analyzed the association between baseline periodontal disease through questionnaires and tooth mobility whereas, the cancer incidents were identified by linkage with National Registries between 1963 and 2004, in 15,333 Swedish twins. The authors observed that both the conditions exhibited common risk factors which was associated with increased risk of colorectal, pancreatic, and prostate cancers. In the cotwin analysis, dizygotic twins with baseline periodontal disease showed 50% increase in the total cancer risk suggesting that shared genetic factors may partially explain the associations between both.

Divaris *et al.*^[22] conducted a population-based, case-control study regarding the incident of squamous cell carcinoma of the head and neck. Oral health was assessed using questionnaire consisting of data on tooth loss and mobility, mouthwash use, and frequency of dental visits. The data obtained from this study showed that tooth mobility was moderately associated with an increased carcinoma risk and routine dental visits were associated with 30% risk reduction. However, the association did not persist among “never-smokers.”

In another study by Grant *et al.*,^[23] he reported that low Vitamin D status contributes to the link between periodontal disease and breast cancer.

CONCLUSION

There has been an increasing appreciation of a direct relationship between oral inflammation and cancer. This relationship exists even after confounding factors, for example,

smoking, body mass index, and socioeconomic status have been accounted for. It is compelling to propose that there may be a direct relationship between *P. gingivalis* and orodigestive cancers, where the contribution to carcinogenesis may be due to secondary intrusion of the oral microorganism outside of its primary location (oral cavity), yet still within anatomically continuous regions. More molecular epidemiological and mechanistic studies with larger cohorts and better controls will be important to answer these emerging questions.

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Conflicts of interest

There are no conflicts of interest.

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