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Predictive association between periodontitis and oral cancer

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Abstract

Periodontitis is a dysbiotic inflammatory disease which causes constant irritation at molecular tissue level. Periodontopathogens release substances which are toxic to local micro-environment nad may lead to genetic mutations and tumorogenesis. Evidence regarding role of Porphyromonas gingivalis in oral cancer initiation and progression through anti-apoptotic action and immunosuppression gives credence to association between oral cancer and periodontitis. This review attempts to highlight the recent evident in regards to periodontal microbiota and their role in cancer. The review also suggests areas of future research where an indirect association between periodontal disease and oral cancer may be explored.

Keywords: periodontal diseases, oral cancer, Porphyromonas gingivalis, inflammation, tobacco, nutrition.

Introduction

Periodontitis is a dysbiotic, inflammatory disease leading to a variety of oral and systemic complications. It is a biofilm associated chronic oral infection caused by predominantly gram-negative anaerobic bacteria. (1) According to World Health Organisation, severe periodontitis affects more than 10% of world population. (2)

Periodontititis is a chronic, irreversible, destructive condition leading to tooth loss in adults. It presents clinically as periodontal pockets, gingival recession and alveolar bone loss. Periodontitis starts as gingivitis, which is a reversible condition, but if unchecked, approximately 10–15% of cases progresses to chronic periodontitis.

Considerable evidence indicates that cancer may develop as a consequence of persistent inflammation and infection through the years. (3,4) Viral etiology had been mostly associated with carcinogenesis. However, the evidence

regarding connection between bacterial infections is also increasing like implication of Helicobacter pylori (gastric cancer), Chlamydia pneumonia (lung cancer), Streptococcus bovis (colon cancer), Salmonella typhii (gall bladder and hepato-billary carcinoma) in carcinogenesis.

Key pathogenic bacteria for periodontitis initiation and progression are Porphyromonas gingivalis, Tannerella forsythia (previously Bacteroides forsythus) and Treponema denticola. Recent evidence correlates periodontal disease with an increased cancer risk.(5,6) The studies have explored positive association between carcinoma and periodontal infection not only in oral cancers but also in upper gastrointestinal tract, lungs, colon and pancreas. Corbella et al in their metanalysis concluded that sparse scientific evidence exists with results of low statistical power and studies lacking in standardization and comparable methods to give credence to a possible association between periodontitis and cancer. (5) Further population-based studies are required to provide substantial evidence for a possible relationship.

This narrative review attempts to describe the available evidence and discuss the areas where future research might benefit in answering hitherto unexplained questions about oral carcinoma and potential role of inflammatory chronic periodontitis in its initiation or progression.

Role of Periodontal diseases in cancer development?

Periodontal disease is associated with chronic infection caused by dysbiotic bacteria, characterised by inflammation of the gums, and gradual destruction of periodontal tissues and tooth supporting alveolar bone in periods of exacerbation and remissions. (7) Exact mechanism through which periodontal disease may promote cancer development remains unclear. Oral pathogens may contribute to carcinogenesis at oral sites as well as extra-oral distant sites. Oral pathogens may be ingested through saliva into the gut, transferred through blood from inflamed periodontal disease sites into circulation, or aspired into the respiratory tract. These theories are similar to those implicated in periodontal disease association with systemic diseases like diabetes, cardio-vascular events, rheumatic disease, adverse pregnancy outcomes, and respiratory events. (8–10)

It is believed that increased bacterial load in systemic circulation is short-lived leading to transient bacteraemia, however, certain bacteria like Porphromonas gingivalis have inherent characterstics that protect them from natural phagocytosis by neutrophils.(11,12) A study by Tezal et al has found that each millimeter increase in alveolar bone loss caused by chronic periodontitis was associated with >4-fold increase in risk of head and neck cancers. The odds ratio for this association was calculated to be 4.36 (95% confidence interval: 3.16-6.01). (13)

Reasonability of association between periodontitis and oral cancer may be explained through-(14)

- Enhanced exposure of carcinogens like tobacco through broken mucosal barrier as a result of periodontal disease.
- Inflammation leads to diffused, chronic epithelial hyperplasia as a result of increased cellular content in microvasculature and in inflamed connective tissue. Epithelial hyperplasia is a common precursor for periodontitis and intraepithelial neoplasia.
- Suppression of antibacterial, antiviral, and antitumour defensins expressed on neutrophils, macrophages and gingival epithelial cells leading to compromise in critical immune surveillance within periodontal attachment apparatus.
- Isolation of viruses (human papilloma virus (HPV), herpes simplex virus-1, Candida albicans) from lesions of both oral cancer and periodontal disease.

- Poor oral hygiene may lead to accumulation of degradation products with possible carcinogenic potential like acetaldehyde from ethanol.

Periodontitis being chronic inflammatory process may exert both direct and indirect role in carcinogenesis.

1. Direct effect through microorganism

Microorganisms and their products such as endotoxins, enzymes, and metabolic by products are toxic to surrounding cells and may directly induce genetic changes in tumour suppressor genes/ proto- oncogenes.

Direct role of periodontal key Pathogens (P gingivalis)?

Main etiological factor for periodontal disease is dental plaque associated biofilm. Lipopolysaccharides, proteases, collagenases, fibrinolysin, phospholipase A, hydrogen sulfide, and fatty acids are certain metabolic products released from periodontopathogens that create toxic micro-environment which may alter signalling pathways related to epithelial-mesenchymal transition and change in cell proliferation and/ or survival of epithelial cell (Table 1).

Red complex bacteria Porphyromonas gingivalis, Tannerella forsythia and Treponema denticola are associated with severity of periodontitis. (15) Amongst these, P gingivalis fulfils all criteria of key pathogen hypothesis and is implicated in pathogenesis of chronic periodontitis. (16) The inflammatory and immune response to these key pathogens bring about a change in local sub-gingival environment, resulting in homeostatic imbalance, converting healthy symbiotic community into dysbiotic periodontal and systemic disease-causing trigger. (17)

In animal studies, P gingivalis has been found colonising distant tissues like coronary artery, liver, brain, etc, leading to activation of Toll like receptors and resulting in specific infections. (18) Molecular biology for increased P gingivalis pathogenicity are not completely understood including possible mechanism of P gingivalis associated periodontitis and its association with the head and neck cancer.

An inherent feature of P gingivalis is intra-cellular invasion and infection of mucosal surfaces and inhibition of host cell apoptosis. (19) This multi-step, regulated apoptotic pathway is disrupted through impingement of caspases, Nuclear factor kappa, and Bcl2 family of proteins. (20,21) Apoptosis regulates removal of old and damaged cells. It is part of host protective mechanism wherein infected cells are removed and healthy, normal epithelial cells are allowed to grow to maintain tissue integrity. (21) Disruption of apoptotic pathways may have detrimental effects on pathogen-host equilibrium. Role of P gingivalis on apoptosis is uncertain. P gingivalis produces butyric acid and proteases which may induce apoptosis in T and B lymphocytes, and fibroblasts respectively. (22,23) However, P gingivalis lipopolysaccharides inhibit apoptosis in polymorphonuclear leukocytes. (24) Various studies have proven survival of epithelial cells for upto 8 days after exposure with P gingivalis giving credence to its role in inducing an anti-apoptotic phenotype in epithelial cells. (25–28) Studies suggest that P gingivalis inhibit apoptosis in gingival epithelial cells through up-regulation of the anti-apoptotic molecule Bcl-2. (19) The prevention of apoptosis of invaded host cells may lead to their accumulation and may be a process in cancer initiation and progression.

Besides anti-apoptotic mechanisms, bacteria may induce carcinogenesis either through induction of chronic inflammation and continuous irritation of tissues. They may also cause interference, directly or indirectly, with eukaryotic cell cycle and signalling pathways. Another mechanism may be by affecting metabolism of potentially

carcinogenic substances (acetaldehyde) leading to mutations.

2. Indirect effect through inflammation

Chronic periodontitis is an inflammatory disease leading to clinical attachment loss and alveolar bone destruction. Bacterial ingression starts a cascade of events causing release of pro inflammatory cytokines like interleukin (IL)-1 or tumour necrosis factor (TNF) alpha. These cytokines trigger osteoclastic activity. The localised inflammation softens the cancellous bone and may serve as a potential route of invasion for progressing carcinoma. Oral squamous cell carcinoma (OSCC) of the mandible may invade through occlusal route, neural foramen, cortical defects in edentulous ridges, attached gingivae, extension of neck tumours through lower borders, and periodontal membranes. (29) Inflamed periodontal space will form a soft target for tumour invasion and progression.

Inflammation also exposes gingival epithelial cells to substances with carcinogenic potential. Sustained and persistent inflammation leads to development of a micro-environment infested with presence of variable inflammatory cellular components released by neutrophils, macrophages, lymphocytes and fibroblasts. They stimulate release of inflammatory cytokines and growth factors, chemotactic factors, and genotoxic substances like reactive oxygen species and nitrogen oxide which have a potential for inducing DNA methylation and destruction. (30) It therefore stands to reason that chronic inflammation provides intrinsic niche for oncogenesis and onco-progression.

3. Indirect effect through Tobacco use

Tobacco in any form, cigarettes, cigars, pipes, bidi, snuff, chewable or any other form is the single largest associated risk factor for OSCC. (31,32) More than 85% of head and neck cancers are linked to some form of tobacco use. (33) Prolonged tobacco use lead to epigenetic alterations in oral epithelial cells, inhibit at multiple levels host-systemic immune functions. More than sixty toxic metabolites and by-products from tobacco may invade tissues and cause oxidative stress which may lead to induction of OSCC. (34)

Similarly, smoking is also associated with increased risk of periodontal disease. (35) The relative risk for severe periodontal disease in a smoker is estimated to be 5 to 6-fold higher compared to a non-smoker. This risk increases for heavy smokers to about 10- to 15-fold compared to non-smokers. A synergistic effect may therefore link tobacco and periodontal disease with initiation and progression of oral cancer.

4. **Indirect effect through Diet and Nutrition**

Food plays an important role in boosting individual immunity. Vegetables and fruits provide diverse variety of nutrients and phytochemicals rich in carotenoids, vitamins (A, C, E), selenium, flavonoids, and other micro-nutrients with anti-tumorigenic effects. Few animal and human studies have focused on effect of vegetable rich diet or specific vegetables and reduced risk of cancer development. (36–38) Evidence suggests that consumption of non-starchy vegetables decreases the risk of oro-pharyngeal cancer. (39,40)

Chronic periodontal disease results in progressive attachment loss leading to increased tooth mobility and eventually tooth loss. This can inadvertently affect nutritional status and vegetable intake of an individual. In patients with co-morbidities, periodontitis may exert an indirect effect in cancer initiation. This is a research area that needs to be addressed in future studies.

5. Indirect effect through Obesity

Increase body weight, waist-hip ratio, and fat is associated with endocrine and metabolic syndromes like hyperinsulinemia, diabetes and high levels of bioavailable

estrogen. Evidence suggests increased insulin and estrogen accumulation in tissues stimulates mitogenesis and inhibits apoptosis. (41–43)This in turn leads to exponential cell proliferation.

Periodontal disease is an inflammatory disease and obesity stimulates inflammatory response and may lead to tumorigenesis. (44) Further research is required to explore this link further.

Periodontal management

Despite lack of substantial evidence, periodontal disease may be a probable cause of cancer initiation, progression and worsening prognosis. Management of periodontal disease at an early stage may prevent significant burden of systemic disease and reduce risk for premalignant lesions and malignant transformations. Suggestions for preventing periodontal disease and maintenance of oral health:

- Early diagnosis through regular half-yearly check ups
- Community surveillance
- Meticulous oral hygiene maintenance at home
- Proper and balanced dietary intake
- Regular physical activity and obesity control
- Stress management
- Counselling for smoking and habit breaking regimens
- Personalised supportive periodontal therapy and maintenance protocols

Conclusion

Current evidence gives a probable causality association between chronic periodontitis and cancer. If this association is proved through further research, it will add to the impact on understanding of cancer etiology and open further avenues for its prevention, early diagnosis and control measures. Confounders like smoking, alcohol use, nutritional state, and socio-economic status play a crucial role when describing association between cancer and periodontal disease. Till date, Porphyromonas gingivalis, key pathogen of periodontitis, and its virulence factors like GrOEL proteins, gingipains, proteases, etc. have shown to exert effect on epithelial cell lines linked to OSCC. Further, human studies are required to assess its role it carcinogenesis, and effectiveness of periodontal therapy in controlling disease.

To conclude, severe periodontitis is the sixth most prevalent disease afflicting mankind. Dysbiotic oral biofilm is the major etiologic agent in development of periodontal disease. The micro-organisms exert direct role in modifying local micro-environment and releasing tumorogenic stimuli. Besides, various indirect effects associated with inflammation and synergistic effects can also increase risk for genetic mutations and malignant transformations. Cancer is a slow, multilevel process involving micro-changes in local environment and signalling pathways. Periodontitis is also a slow inflammatory chronic disease causing persistent irritation to tissues and disrupting host immune responses. A predictive association between the two diseases stand to reason and should be explored further with robust study designs accounting for potential confounders.

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Table 1: Evidence related to direct effects of periodontopathogens on carcinogenesis.

Study	Model	Bacteria associated	Inference
Groeger et al, 2014 (45)	Oral squamous cell carcinoma cells (OSCC) SCC-25,BHY, and primary human gingival keratinocytes	P gingivalis	Induce expression of B7-H1 and B7-DC receptors in OSCC and human gingival keratinocytes facilitating immune evasion by oral cancers.
Katz et al, 2011(46)	Human	P gingivalis and Streptococcus gordonii	Potential association with gingival squamous cell carcinoma. Abundant presence of P gingivalis in malignant oral epithelium
Ahn et al, 2012(47)	Human survey	P gingivalis	Periodontitis (moderate or severe) relative risk (RR) for orodigestive cancer mortality: 2.28 (95% confidence interval:1.17-4.45); RR: 4.56 for periodontitis-associated mortality for colorectal and for pancreatic cancer Greater serum P gingivalis IgG
Inaba et al, 2014(48)	OSCC cell lines	P gingivalis	Activates ERK1/2-Ets1, p38/HSP27, and PAR2/NF-kB pathways to induce proMMP9 expression. This proenzyme is activated by gingipains to promote cellular invasion of OSCC cell lines.
Gallmidi et al, 2015 (49)	Murine	P gingivalis and F nucleatum	Chronic bacterial infection promotes OSCC with augmented signaling along the IL-6-STAT3 axis Direct interaction with oral epithelial cells through Toll-like receptors
Ha et al, 2015(50)	OSCC cell lines	Repeated infection of oral cancer cells by P gingivalis twice a week for 5 weeks	Morphological changes in host cancer cells and acquisition of an epithelial-to-mesenchymal transition (EMT).

			Long-term infection induced increased expression of CD44 and CD133 (cancer stem cell markers)
Lin et al, 2015 (51)	C26 carcinoma cell-carrying BALB/c mice and chick eggs and human endothelial progenitor cells	P gingivalis	P gingivalis GroEL protein may act as a potent virulence factor resulting in neovasculogenesis of tumor cells and accelerated tumor growth
Gao et al, 2016(52)	Human (Case- control)	P gingivalis • qRT-PCR for 16S rDNA • immunohistochemistry using antibodies targeting whole bacteria and gingipain Kgp	P gingivalis detected in: 61 % of esophageal cancerous tissues 12 % of adjacent tissues undetected in normal esophageal mucosa. Similar distribution of gingipain P gingivalis infection was positively associated with multiple clinicopathologic characteristics (differentiation, metastasis, and overall survival rate)
Ha et al, 2016 (53)	OSCC cell lines (SCC-25, OSC-20, SAS cells)	P gingivalis	Promotes invasive ability of OSC-20 and SAS cells via upregulation of MMP-1 and MMP-2 and increased secretion of IL-8
Mai et al, 2016 (54)	Human	Orange-complex Bacteria (Fusobacterium nucleatum, Prevotella intermedia, and Campylobacter rectus) Red-complex periodontal pathogens (Porphyromonas gingivalis and Tannerella forsythia)	No associations between the presence of individual subgingival pathogens and cancer risk. Borderline positive associations of orange-complex pathogens with total cancer and lung cancer risk.
Geng et al, 2017 (55)	human immortalized oral epithelial cells	Exposure to P gingivalis at a low multiplicity of infection for 5-23 weeks	Bioinformatics analyses and validation assays: tumor-related genes (NNMT, FLI1, GAS6, lncRNA CCAT1, PDCD1LG2, and

			CD274) are key regulators in tumor-like transformation in response to long-time exposure of P gingivalis.
Lee et al, 2017 (56)	primary oral epithelial cells	Long-term P gingivalis infection	Increased Matrix metalloproteinases 2, 7, and 9 Epithelial cells show initial molecular and cellular changes consistent with EMT with long-term infection by P gingivalis
Woo et al, 2017 (57)	mouse xenograft model oral squamous cell carcinoma cell lines	Sustained infection with P gingivalis	P gingivalis-infected cells showed higher resistance to Taxol through Notch1 activation and formed more metastatic foci in the lung than uninfected cells.
Abdulkareem et al, 2018 (58)	Cultures of OSCC cell line (H400)	Treated separately with F. nucleatum, or P. gingivalis or E. coli LPS for 8 days	EMT induced in OSCC cells in response to stimulation by periodontal pathogens
Cho et al, 2018(59)	YD10B oral cancer cells	P gingivalis	oral cancer cells become more aggressive when they are infected with P gingivalis
Wu et al, 2018 (60)	Mice	P gingivalis	P gingivalis promoted oral carcinogenesis and aggravated disturbance of fatty acid metabolism, indicating a close association among P gingivalis, lipid metabolic and oral carcinogenesis.
Chang et al, 2019 (61)	oral squamous cell carcinoma cell lines	Porphyromonas gingivalis, Fusobacterium nucleatum and Streptococcus sanguinis	P gingivalis and F nucleatum at higher levels in cancer tissue compared to normal tissues. P gingivalis: 60.7% of OSCC tissues 32.8% of paracancerous tissues 13.3% of normal tissues.
Geng et al, 2019(62)	immortalized oral epithelial	Persistently exposed to P gingivalis for 15 weeks	Identified IL6, STAT1, LYN, BDNF, C3, CD274, PDCD1LG2,

	cells		and CXCL10 as potential candidate genes for prevention and treatment of OSCC
Kageyama et al, 2019 (63)	Human (Case-control)	Salivary microbiota (diverse group through 16S ribosomal RNA gene sequencing)	salivary bacteria higher in tongue/pharyngeal/ esophageal cancer most abundant: P gingivalis Fusobacterium nucleatum, Streptococcus parasanguinis II, and Neisseria species: higher in tongue/pharyngeal cancers Neisseria species: gastric cancer Actinomyces odontolyticus: colorectal cancer
Park et al, 2019(64)	Human (case-control)	P gingivalis and F nucleatum	serum levels of P. gingivalis IgG and IL-6 were higher in OSCC patients than in non-OSCC controls High serum level of IL-6 was associated with a worse prognosis in OSCC patients
Wen et al (65)	Mouse	P gingivalis	Generates cancer-promoting microenvironment CXCL2, CCL2, interleukin (IL)-6, and IL-8 may be potential genes