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CHRONIC PERIODONTITIS AND THE RISK OF HEAD AND NECK SQUAMOUS CELL CARCINOMA: FACTS AND FIGURES

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Substantial evidence supports an association between periodontal disease and several systemic diseases including cardiovascular diseases, diabetes mellitus, respiratory diseases, adverse pregnancy outcomes, osteoporosis etc. Periodontal disease, a chronic inflammatory condition, is highly prevalent in adult populations around the world, and may be preventable. Estimates of prevalence vary between races and geographic regions, with a marked increase in the occurrence of periodontal disease with advancing age. Worldwide estimates for the prevalence of severe periodontal disease generally range from 10 to 15%. The relationship between periodontal disease and cancer has been examined for a number of specific cancer sites. The grim statistics of head and neck cancer incidence and survival have remained essentially unchanged over the past 3 decades despite the prevention efforts against known risk factors of head and neck cancer, and advances in the diagnosis and treatment, arguing forcibly for new insights regarding the etiology as well as the strategies for prevention. Recent reports have linked periodontal disease with increased risk of squamous cell carcinoma of head and neck. This review provides current literature for a role of periodontal disease in carcinogenesis of head and neck region and discusses possible biological mechanisms involved.
***Key Words*: periodontal disease, head and neck cancer, risk factors.**

INTRODUCTION

Periodontitis, a chronic, destructive condition affecting a large portion of the adult population, is one of the major causes of tooth loss in adults. Periodontitis is characterized by a chronic infection 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 [1, 2]. In recent years, periodontal disease has been linked to many systemic conditions such as cardiovascular disease [3], low-birth weight complications in pregnancy [4], diabetes mellitus [5], pulmonary disease [6], possibly mediated through markers of systemic infection and inflammation [7]. Associations with osteoporosis [8], rheumatoid arthritis [9], renal diseases [10] and systemic infections have also been observed [11]. In addition, the results of recent epidemiologic studies have suggested a possible positive association between periodontal disease and cancer risk in different tissues, most notably in the mouth, upper gastrointestinal system, lung, and pancreas [12–15]. In light of recent findings between periodontal disease, oral health, and carcinogenesis, it seems surprising that population-based association studies between periodontitis and cancer of the head and neck are so scarcely published. This review will attempt to provide the current literature available in this area.

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Abbreviation used: EBV – Epstein – Barr virus; HPV – human papilloma virus; NHANES – The National Health and Nutrition Examination Survey; SCCHN – squamous cell carcinoma of the head and neck; WHO – World Health Organization.

PERIODONTAL DISEASES

Periodontal disease is characterized by a chronic oral bacterial infection which results in inflammation of the gums, leading to the gradual destruction of periodontal tissues and alveolar bone supporting the teeth [15]. However, recent evidence also suggests a significant role for viruses in the initiation and progression of periodontitis. Periodontal bacteria and viruses may act synergistically to cause periodontitis [16–18]. More interestingly, studies suggest that periodontal pockets act as reservoirs for human papilloma virus (HPV) [19], cytomegalovirus, and Epstein — Barr virus (EBV) [20], suspected agents associated with oral cancer. Although both are called periodontal disease, gingivitis and periodontitis are distinct diseases. Gingivitis is a non-destructive reversible inflammation of the gums strongly associated with poor oral hygiene. On the other hand, only a small subset of the population with poor oral hygiene develops destructive periodontitis, leading to epithelial migration and bone loss [2]. Periodontitis cases were defined as individuals who had at least three tooth sites with clinical attachment loss greater than or equal to 4 mm, and at least two sites with pocket depth greater than or equal to 3 mm [21]. Worldwide prevalence of the disease varies by race and geographic area, with older populations typically experiencing higher rates of periodontitis [22–24]. Estimates of the global prevalence of severe periodontal disease generally range from 10 to 15%, although up to 90% may be affected by some form of milder periodontal disease, including gingivitis [21].

It is a multifactorial disease modified by numerous risk factors such as smoking, social background, diabetes, genetic susceptibility, attitude towards health, and supragingival plaque control [25]. Such risk factors influence the susceptibility to extent, severity and course of the disease.

The bacteria identified to most likely play an etiologic role in the development of periodontal disease include *Porphyromonas gingivalis* (*P. gingivalis*). *Actinobacillus actinomycetemcomitans, Tannerella forsythensis, and Treponema denticola* [21, 26]. Periodontal disease progression is signaled by a shift in the bacterial makeup of the dental biofilm from largely aerobic Gram-positive bacteria to pathogenic infectious state dominated by anaerobic Gram-negative organisms [7]. The pathogenic organisms initiate an inflammatory response in nearby tissues, and begin to attack and destroy the alveolar bone and supporting tissues around the teeth [27, 28]. The periodontal pocket is composed of stratified squamous epithelium and is characterized by continuous epithelial proliferation, migration, rete-ridge formation, and ulcerations, providing ample opportunity for initial HPV infection and its persistence [19]. Periodontitis results in a continuous release of bacterial and inflammatory markers including C-reactive protein, IL-1β, IL-6, TNF-α, and matrix metalloproteinase into saliva and, to a lower degree, into blood [7, 29]. Furthermore, periodontal pathogens and inflammatory cytokines travel with saliva and blood from the affected tissues to distant sites and adversely affect systemic health [30, 31].

HEAD AND NECK SQUAMOUS CELL CARCINOMA

Squamous cell carcinoma of the head and neck (SCCHN) includes cancer of oral cavity, pharynx, and larynx and has been recognized as a significant component of the global burden of cancer [32–34]. These cancers are characterized by marked geographic, racial, and gender disparities [33, 35, 36]. Notably, oral cancer was recently included among the World Health Organization's (WHO) priorities for action [37, 38]. The grim statistics of oral cancer incidence and survival have remained essentially unchanged over the past 3 decades despite the accessibility of the oral cavity to direct examination, prevention efforts against known risk factors of oral cancer, and advances in treatment and diagnosis, arguing forcibly for new approaches. Morbidity and mortality from SCCHN also remain high. The cause of SCCHN is multifactorial [39]. Tobacco use and alcohol consumption have been well established as the predominant etiologic factors for SCCHN [40]. HPV and EBV infections have also been implicated in the etiology of SCCHN [41, 42]. These infections may have a substantial role among nonsmoker and non-drinker cases [43, 44]. Conversely, dietary factors, specifically fruit and vegetable intake and several micronutrients have been consistently associated with decreased SCCHN risk [45, 46].

Inflammation caused by infections has been suggested to be one of the most important preventable causes of cancers in general. It has been estimated that 15–20% of human tumors are driven by infection and inflammation [47]. The biological mechanism of the association between chronic infection/inflammation and cancer has been described extensively [48]. Periodontitis is a chronic inflammatory disease and several studies are known showing associations between periodontitis and cancer risk at different sites including the oral cavity [12, 49, 50]. In the US population study the National Health and Nutrition Examination Survey (NHANES)III, periodontal attachment loss was associated with the presence of oral tumors as well as with precancerous lesions [49, 51].

Possible biological mechanisms linking periodontal diseases with the risk of SCCHN

Numerous observational studies identified periodontal disease as potential risk factors for cancer at different sites (Table).

Table. Periodontal bacteria/virus and oral cancer

Bacteria/Virus	Possible Mechanism
Bacteria associated with periodontitis with possible mechanism of inducing the head and neck cancer	
P. gingivalis, A. actinomycetemcomitans	Induces an anti-apoptotic phenotype in epithelial cells by rendering the host cells resistant to cell death caused by potent pro-apoptotic agents
Human Papillomavirus	Inflammatory cytokines, including interleukin-1 (IL-1), IL-6, and tumor necrosis factor, modulate proliferation of HPV and expression of its oncogenes E6 and E7 in oral epithelial cells. E6 and E7 have ability to bind and inactivate the tumor suppressors' p53 and pRb, and these respective properties have been associated with carcinogenic potential
Exiguobacteriumoxidotolerans, Prevotellamelaninogenica, Staphylococcus aureus, Veillonellaparvula, Capnocytophagagingivalis, P. melaninogenica, Streptococcus mitis	Induce carcinogenesis either through induction of chronic inflammation or by interference, either directly or indirectly, with eukaryotic cell cycle and signaling pathways, or by metabolism of potentially carcinogenic substances like acetaldehyde causing mutagenesis
Bacteria associated with periodontitis with possible mechanism of inducing cancer at other sites in the body	
H. pylori	Cervical cancer
Streptococcus anginosus	Esophageal and pharyngeal cancers: Induce carcinogenesis either through induction of chronic inflammation or by interference, either directly or indirectly, with eukaryotic cell cycle and signaling pathways, or by metabolism of potentially carcinogenic substances like acetaldehyde causing mutagenesis
	Lung cancer, Kidney cancer, Blood malignancies: Pathogenic bacteria, and the toxins associated with them, alter the inflammation process and cause the liver to produce C-reactive proteins (CRP). CRP levels have inflammatory effects on arteries allowing these bacteria to attach themselves and form dangerous plaques inside the linings of these vessels

Several hypotheses have been proposed to explain the observed relationships between periodontal disease, precancer [52] and cancer of the head and neck region, including chronic inflammation and increased exposure to carcinogenic nitrosamines through smoking or diet, but no mechanisms are established.

Mechanisms of carcinogenesis could also differ by site. For example, bacteria may play a more direct role in carcinogenesis in the mouth or lung, whereas in more distant organs, systemic inflammation or nitrosamines may play a moreimportant role. The question of how infection and inflammation can influence carcinogenesis has interested scientists for over one and a half centuries, but only now are the general principles and the complexity of this association emerging [53]. Chronic infections, such as periodontitis, can play a direct or indirect role in carcinogenesis (Figure).

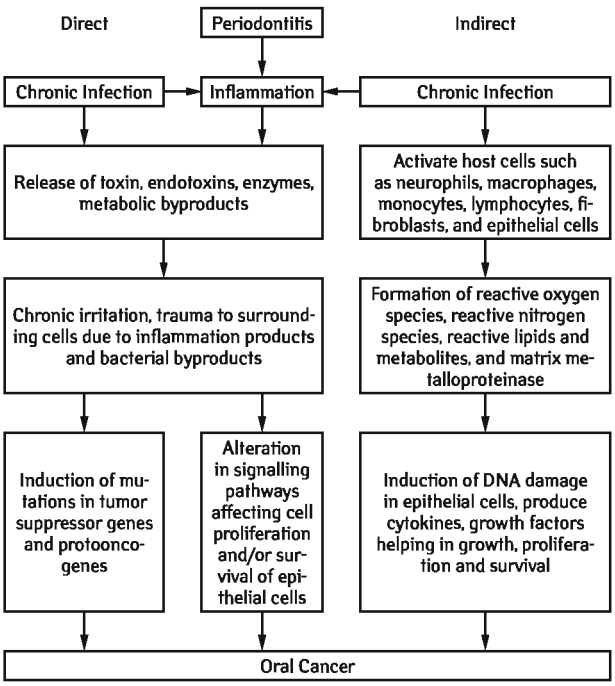

Figure. Possible mechanism suggesting the correlation between periodontitis and head and neck cancer development

Direct effect: There is sufficient evidence to suggest that epidemiological and etiological links between microbial infection in the oral cavity and oral cancer could exist [54]. A possible explanation could be the accumulation of carcinogenic metabolites produced by periodonto-pathogenic bacteria [55]. These microorganisms and their products such as endotoxins (lipopolysaccharides), enzymes (proteases, collagenases, fibrinolysin, and phospholipase A), and metabolic byproducts (hydrogen sulfide, ammonia, and fatty acids) are toxic to surrounding cells and may directly induce mutations in tumor suppressor genes and proto-oncogenes or alter signaling pathways that affect cell proliferation and/or survival of epithelial cells. Various investigators have proposed that oral ecological shifts accompanying periodontal disease are characterized by proliferation of ketone-producing and nitrate-reducing microorganisms. The latter may contribute to increases in carcinogen concentrations [56], which is consistent with evidence of oral metabolism of alcohol to acetaldehyde [57]. The formation of endogenous nitrosamines in the oral cavity by nitrate-reducing bacteria is promoted by poor oral hygiene and periodontal disease. Tooth loss resulting from poor oral hygiene may also contribute to greater nitrosamine production [58]. *P. gingivalis* is a common gram negative anaerobic oral bacteria strongly associated with periodontal disease which, in recently reported population-based cohort study, found to be associated with increased oro-digestive cancer mortality [59]. *P. gingivalis* is known for its capacity to penetrate and invade various epithelial cells. While inside the cell, the bacteria have been shown to affect cell cycle related molecules at different stages. Most importantly, *P. gingivalis* has been shown to prevent apoptosis of epithelial cells, an inherent protective mechanism of cells affected by cancerous processes [60, 61]. *P. gingivalis* can block the apoptotic pathway in gingival epithelial cells through manipulation of the JAK/Stat pathways that controls the intrinsic mitochondrial cell death pathways and prevent programmed host cell death [62]. *P. gingivalis* has also the ability to protect itself from both the humoral and cellular immune system, can suppress all three mechanisms of complement activation and is resistant to killing by oxidative stress [60]. In addition, *P. gingivalis* may inhibit host cell death by prolonging cell survival and increasing cell proliferation [63]. Cariogenic bacteria, *Streptococci*, *Lactobacilli*, and *Actinomyces* are associated with periodontal health [64]. Recent evidence indicates that *Streptococci* may contribute substantially to increased acetaldehyde concentration in the oral cavity [65]. From the literature, it may be concluded that there is a continuously increasing risk of cancer with increasing severity of periodontitis or gingivitis.

Indirect effect: The evidence supporting an association between chronic infections/inflammation and cancer has accumulated substantially [48, 66]. Periodontitis is a chronic inflammatory disease attacking the supporting tissues around the teeth, resulting in constant low-grade systemic inflammation with continuous release of bacterial and inflammatory markers into saliva and, to a lower degree, into blood [7, 67]. Chronic infection may stimulate the formation of epithelial-derived tumors through an indirect mechanism involving activation of surrounding inflammatory cells. Inflammation exposes epithelial cells to substances with mutagenic potential. Microorganisms and their products activate host cells [7, 68] such as neutrophils, macrophages, monocytes, lymphocytes, fibroblasts, and epithelial cells to (i) generate reactive oxygen species (hydrogen peroxide and oxy radicals), reactive nitrogen species (nitric oxides), reactive lipids and metabolites (malondialdehyde and 4-hydroxy-2-nonenal), and matrix metalloproteinases, which can induce DNA damage in epithelial cells and (ii) produce cytokines, chemokines, growth factors, and other signals that provide an environment for cell survival, proliferation, migration, angiogenesis, and inhibition of apoptosis. This environment may help epithelial cells to accumulate mutations and drive these mutant epithelial cells to proliferate, migrate, and give them a growth advantage. Thus, substantial evidence from previous studies suggests a possibility that the chronic inflammation induced by periodontal

pathogens serves to promote already initiated cells, leading to the breakdown of normal cell growth control, and potential carcinogenesis [67]. M. Tejal et al. [49] in their study suggested that there is positive correlation between history of chronic periodontitis and increased percentage of poorly differentiated tumors in the oral cavity. Continuous stimulation of cellular proliferation by chronic inflammation may be responsible for this histologic type [48].

Alternatively, chronic periodontal disease may indicate that an individual's immune system is deficient at clearing infection, and subsequently deficient at surveillance for tumor growth. It is possible that periodontitis can act as an indicator of altered immune function which can have possible repercussion in tumor growth and progression.

Prevention of periodontal disease

Regular checks ups along with improved self-performed oral hygiene, daily use of fluoridated dentifrice and regularly repeated professional tooth cleaning effectively prevented recurrence of dental disease. Following precaution steps can help in preventing the development of periodontal disease thereby may reduce the risk of cancer development: 1. Daily cleaning of teeth and oral hygiene maintenances, 2. adequate balanced health nutrition, 3. reduction in stress, 4. regular exercise.

CONCLUSION

The current literature provides a support for a possible modest association of periodontal disease with SCCHN. This evidence of a chronic periodontitis-SCCHN association has practical implications for prevention, early diagnosis, and treatment. Chronic periodontitis may represent a clinical high-risk profile for SCCHN. Although validation through further prospective studies is essential, prevention of periodontitis may decrease the incidence of SCCHN, whereas periodontal treatment, as an adjunct to conventional oncologic management, may improve the prognosis of this disease.

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