

# 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 populationbased association studies between periodontitis and cancer of the head and neck are so scarcely published.

\*Correspondence: E-mail: monal9817@gmail.com *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. This review will attempt to provide the current literature available in this area.

## 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].

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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-1 $\beta$ , IL-6, TNF- $\alpha$ , 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].

supragingival plaque control [25]. Such risk factors

influence the susceptibility to extent, severity and

# 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).

lable.	Periodontal	bacteria/virus	and oral	cance
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Table. Tenodontal bacteria/virus and oral cancer					
Bacteria/Virus	Possible Mechanism				
Bacteria associated with periodontitis with possible mechanism of induc-					
ing	<u>g the head and r</u>	leck cancer			
P. gingivalis, A. actino-	Induces an anti-apoptotic phenotype in epithelial				
mycetemcomitans	cells by render	ing the host cells resistant to cell			
	death caused b	y potent pro-apoptotic agents			
Human Papillomavirus	Inflammatory cy	tokines, including interleukin-1 (IL-			
	1), IL-6, and tu	mor necrosis factor, modulate pro-			
	liferation of HP	/ and expression of its oncogenes			
	E6 and E7 in or	al epithelial cells. E6 and E7 have			
	ability to bind a	and inactivate the tumor suppres-			
	sors' p53 and pl	Rb, and these respective properties			
	have been asso	ciated with carcinogenic potential			
Exiguobacteriumoxi-	Induce carcino	genesis either through induction			
dotolerans, Prevotella-	of chronic inflammation or by interference, either				
melaninogenica, Staph-	directly or indirectly, with eukaryotic cell cycle and				
ylococcus aureus, signaling pathways, or b		vays, or by metabolism of poten-			
Veillonellaparvula, Cap-	tially carcinogenic substances like acetaldehyde				
nocytophagagingiva-	causing mutagenesis				
lis, P. melaninogenica,	0 0				
Streptococcus mitis					
Bacteria associated with periodontitis with possible mechanism of induc-					
ing cancer at other sites in the body					
H. pylori	Cervical cancer				
Streptococcus angi-	Esophageal	Induce carcinogenesis either			
nosus	and pharynge-	through induction of chronic inflam-			
	al cancers	mation or by interference, either di-			
		rectly or indirectly, with eukaryotic			
		cell cycle and signaling pathways,			
		or by metabolism of potentially car-			
		cinogenic substances like acetalde-			
		hyde causing mutagenesis			
	Lung cancer	Pathogenic bacteria, and the toxins			
	Kidney cancer	associated with them, alter the in-			
	Blood malig-	flammation process and cause the			
	nancies	liver to produce C-reactive proteins			
		(CRP). CRP levels have inflammato-			
		ry 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.

#### REFERENCES

1. Loesche WJ, Grossman NS. Periodontal disease as a specific, albeit chronic, infection: diagnosis and treatment. ClinMicrobiol Rev 2001; 14: 727–2.

**2.** Burt B. Epidemiology of periodontal diseases. J Periodontol 2005; **76**: 1406–9.

**3.** Cronin A. Periodontal disease is a risk marker for coronary heart disease? Evid Based Dent 2009; **10**: 22.

**4.** Rakoto-Alson S, Tenenbaum H, Davideau JL. Periodontal diseases, preterm births, and low birth weight: findings from a homogeneous cohort of women in Madagascar. J Periodontol 2010; **81**: 205–3.

**5.** Taylor GW, Borgnakke WS. Periodontal disease: Associations with diabetes, glycemic control and complications. Oral Dis 2008; **14:** 191–3.

6. Awano S, Ansai T, Takata Y, *et al.* Oral health and mortality risk from pneumonia in the elderly. J Dent Res 2008; 87: 334–9.

7. Moutsopoulos NM, Madianos PN. Low-grade inflammation in chronic infectious diseases: paradigm of periodontal infections. Ann NY Acad Sci 2006; **1088**: 251–4.

**8.** Snophia S, Kumar TSS, Saraswathy PK, *et al.* Periodontitis and bone mineral density among pre and post-menopausal women: A comparative study. J Ind Soc Periodontol 2010; **14**: 30–4. **9.** Scardina GA, Messina P. Microvascular periodontal alterations: A possible relationship between periodontitis and rheumatoid arthritis. Clin Hemorheol Microcirc 2007; **37**: 229–5.

**10.** Ardalan MA, Ghabili K, Paurabbas R, *et al.* A causative link between periodontal disease and glomerulonephritis: a preliminary study. Ther Clin Risk Manag 2011; **7**: 93–8.

11. Teng YT, Taylor GW, Scannapieco F, *et al.* Periodontal health and systemic disorders. J Can Dent Assoc 2002; 68: 188–2.

**12.** Tezal M, Sullivan MA, Reid ME, *et al.* Chronic periodontitis and the risk of tongue cancer. Arch Otolaryngol Head Neck Surg. 2007; **133**: 450–4.

**13.** Eliot MN, Michaud DS, Langevin SM, *et al.* Periodontal disease and mouthwash use are risk factors for head and neck squamous cell carcinoma. Cancer Causes Control 2013; **24**: 1315–2.

**14.** Fitzpatrick SG, Katz J. The association between periodontal disease and cancer: a review of the literature. J Dent 2010; **38**: 83–5.

**15.** Michaud DS, Liu Y, Meyer M, *et al.* Periodontal disease, tooth loss, and cancer risk in male health professionals: a prospective cohort study. Lancet Oncol 2008; **9**: 550–8.

**16.** Chalabi M, Rezaie F, Moghim S, *et al.* Periodontopathic bacteria and herpes viruses in chronic periodontitis. Mol Oral Microbiol 2010; **25**: 236–40.

**17.** Kamma JJ, Contreras A, Slots J. Herpes viruses and periodontopathic bacteria in early-onset periodontitis. J Clin Periodontol 2001; **28**: 879–85.

**18.** Cappuyns I, Gugerli P, Mombelli A. Viruses in periodontal disease — a review. Oral Dis 2005; **11**: 219–9.

**19.** Hormia M, Willberg J, Ruokonen H, *et al.* Marginal periodontium as a potential reservoir of human papillomavirus in oral mucosa. J Periodontol 2005; **76**: 358–3.

**20.** Saygun I, Kubar A, Ozdemir A, *et al.* Periodontitis lesions are a source of salivary cytomegalovirus and Epstein — Barr virus. J Periodontal Res 2005; **40**: 187–1.

**21.** Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. Lancet 2005; **366**: 1809–0.

**22.** Tezal M, Sullivan MA, Hyland A, *et al.* Chronic periodontitis and the incidence of head and neck squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev 2009; **18**: 2406–12.

**23.** Krüger M, Hansen T, Kasaj A, *et al.* The Correlation between Chronic Periodontitis and Oral Cancer. Case Reports in Dentistry, vol. 2013, Article ID 262410, 8 pages, 2013.

**24.** Irfan UM, Dawson DV, Bissada NF. Epidemiology of periodontal disease: a review and clinical perspectives. J Int Acad Periodontol 2001; **3**: 14–1.

**25.** Borrell LN, Burt BA, Taylor GW. Prevalence and trends in periodontitis in the USA: from the NHANES III to the NHANES, 1988 to 2000. J Dent Res 2005; **84**: 924–0.

**26.** Oringer RJ. Modulation of the host response in periodontal therapy. J Periodontol 2002; **73**: 460–0.

**27.** Gibson FC, Yumoto H, Takahashi Y, *et al.* Innate immune signaling and Porphyromonas gingivalis-accelerated atherosclerosis. J Dent Res 2006; **85**: 106–1.

**28.** Wactawski-Wende J. Periodontal diseases and osteoporosis: association and mechanisms. Ann Periodontol 2001; **6**: 197–8.

**29.** Emingil G, Tervahartiala T, Mantyla P, *et al.* Gingival crevicular fluid matrix metalloproteinase (MMP)-7, extracellular MMP inducer, and tissue inhibitor of MMP-1 levels in periodontal disease. J Periodontol 2006; **77**: 2040.

**30.** Paju S, Scannapieco FA. Oral biofilms, periodontitis, and pulmonary infections. Oral Dis 2007; **13**: 508–2.

**31.** Mealey BL, Rose LF. Diabetes mellitus and inflammatory periodontal diseases. Curr Opin Endocrinol Diabetes Obes 2008; **15**: 135–1.

**32.** Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol 2009; **45**: 309–6.

**33.** Marur S, Forastiere AA. Head and neck cancer: changing epidemiology, diagnosis, and treatment. Mayo Clin Proc 2008; **83**: 489–1.

**34.** Parkin DM, Bray F, Ferlay J. *et al.* Global cancer statistics, 2002. CA Cancer J Clin 2005; **55**: 74–8.

**35.** Goodwin WJ, Thomas GR, Parker DF, *et al.* Unequal burden of head and neck cancer in the United States. Head Neck 2008; **30**: 358–1.

**36.** Morse DE, Kerr AR. Disparities in oral and pharyngeal cancer incidence, mortality and survival among black and white Americans. J Am Dent Assoc 2006; **137**: 203–2.

**37.** Petersen PE. Oral cancer prevention and control — the approach of the World Health Organization. Oral Oncol 2009; **45**: 454–60.

38. World Health Organization. World Health Assembly. Oral health: action plan for promotion and integrated disease prevention. WHA60.17. Geneva: WHO, 2007.

**39.** Dambi C, Voros-Bolog T, Czegledy A, *et al.* Risk group assessment of oral precancer attached to X-ray lung-screening examinations. Community Dent Oral Epidemol 2001; **29**: 9–13.

**40.** Blot WJ, McLaughlin JK, Winn DM, *et al.* Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Res 1988; **48**: 3282–7.

**41.** Gillison ML, Lowy DR. A causal role for human papillomavirus in head and neck cancer. Lancet 2004; **363**: 1488–9.

**42.** Kutok JL, Wang F. Spectrum of Epstein — Barr virus-associated diseases. Ann Rev Path 2006; **1**: 375–4.

**43.** Andrews E, Seaman WT, Webster-Cyriaque J. Oropharyngeal carcinoma in non-smokers and non-drinkers: a role for HPV. Oral Oncol 2009; **45**: 486–1.

**44.** Dahlstrom KR, Little JA, Zafereo ME, *et al.* Squamous cell carcinoma of the head and neck in never smoker-never drinkers: a descriptive epidemiologic study. Head Neck 2008; **30**: 75–4.

**45.** Lucenteforte E, Garavello W, Bosetti C, *et al.* Dietary factors and oral and pharyngeal cancer risk. Oral Oncol 2008; **45**: 461–7.

**46.** Subapriya R, Thangavelu A, Mathavan B, *et al.* Assessment of risk factors for oral squamous cell carcinoma in Chidambaram, Southern India: a case-control study. Eur J Cancer Prev 2007; **16**: 251–6.

**47.** Meurman JH. Infectious and dietary risk factors of oral cancer. Oral Oncol 2010; **46:** 411–3.

**48.** Mantovani A, Allavena P, Sica A, *et al.* Cancer-related inflammation. Nature 2008; **454**: 436–4.

**49.** Tezal M, Sullivan MA, Hyland A, *et al.* Chronic periodontitis and the incidence of head and neck squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev 2009; **18**: 2406–12.

**50.** Michaud DS, Joshipura K, Giovannucci E, *et al.* A prospective study of periodontal disease and pancreatic cancer in US male health professionals. J Natl Cancer Inst 2007; **99**: 171–5.

**51.** Tezal M, Grossi SG, Genco RJ. Is periodontitis associated with oral neoplasms? J Periodontol 2005; **76**: 406–10.

**52.** Meisel P, Holtfreter B, Biffar R, *et al.* Association of periodontitis with the risk of oral leukoplakia. Oral Oncol 2012; **48:** 85963.

**53.** Karin M, Lawrence T, Nizet V. Innate immunity gone awry: linking microbial infections to chronic inflammation and cancer. Cell 2006; **124**: 823–35.

**54.** Hooper SJ, Wilson MJ, Crean SJ. Exploring the link between microorganisms and oral cancer: a systematic review of the literature. Head Neck 2009; **31**: 1228–39.

**55.** Abnet CC, Kamangar F, Islami F, *et al.* Tooth loss and lack of regular oral hygiene are associated with higher risk of esophageal squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev 2008; **17**: 3062–8.

**56.** Guha N, Boffetta P, Wünsch Filho V, *et al.* Oral health and risk of squamous cell carcinoma of the head and neck and esophagus: results of two multicentric case-control studies. Am J Epidemiol 2007; **166**: 1159–73.

**57.** Lachenmeier DW, Gumbel-Mako S, Sohnius EM, *et al.* Salivary acetaldehyde increase due to alcohol-containing mouth wash use: a risk factor for oral cancer. Int J Cancer 2009; **125**: 730–5.

**58.** Abnet CC, Kamangar F, Dawsey SM, *et al.* Tooth loss is associated with increased risk of gastric non-cardia adenocarcinoma in a cohort of Finnish smokers. Scand J Gastroenterol 2005; **40**: 681–7.

**59.** Ahn J, Segers S, Hayes RB. Periodontal disease, *Porphyromonas gingivalis* serum antibody levels and orodigestive cancer mortality. Carcinogenesis 2012; **33**: 1055–8.

**60.** Hajishengallis G. *Porphyromonas gingivalis*-host interactions: open war or intelligent guerilla tactics? Microbes Infect 2009; **11**: 637–45.

**61.** Yilmaz O. The chronicles of *Porphyromonas gingivalis*: the microbium, the human oral epithelium and their interplay. Microbiol 2008; **154**: 2897–903.

**62.** Mao S, Park Y, Hasegawa Y, *et al.* Intrinsic apoptotic pathways of gingival epithelial cells modulated by *Porphyromonas gingivalis*. Cell Microbiol 2007; **9**: 1997–2007.

**63.** Kuboniwa M, Hasegawa Y, Mao S, *et al. P. gingivalis* accelerates gingival epithelial cell progression through the cell cycle. Microbes Infect 2008; **10**: 122–8.

**64.** Socransky SS, Haffajee AD. Periodontal microbial ecology. Periodontol 2000, 2005; **38**: 135–44.

**65.** Kurkivuori J, Salaspuro V, Kaihovaara P, *et al.* Acetaldehyde production from ethanol by oral streptococci. Oral Oncol 2007; **43:** 181–6.

66. van Kempen LC, de Visser KE, Coussens LM. Inflammation, proteases and cancer. Eur J Cancer 2006; 42: 728–34.

**67.** Champagne CME, Buchanan W, Reddy MS, *et al.* Potential for gingival crevice fluid measures as predictors of risk for periodontal disease. Periodontol 2000, 2003; **31**: 167–80.

**68.** Coussens LM, Werb Z. Inflammation and cancer. Nature 2002; **420**: 860–7.