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A link between severe periodontal disease and cancer risk: A review

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Abstract

Periodontal disease is a destructive disease which affects the supporting structures of the teeth .It is mainly caused by gram negative and gram positive microorganisms. Apart from this various systemic causes have also been identified. Recently a link has been associated between cancer and periodontal disease. Various studies have shown an associations between periodontal disease or tooth loss and risk of oral, upper gastrointestinal, lung and pancreatic cancer. This review gives us an insight on the possible linkage between them and the various types of cancer which acts as an risk factor for the periodontal disease.

Keywords: Cancer Periodontal Disease, Oral Cancer, Microorganisms.

Introduction

Periodontitis is a chronic, mixed infection of gram negative bacteria such as Porphyromonas gingivalis, Prevotella intermedia, Bacteroides forsythus, Actinobacillus actinomycetemconmitans, and gram positive organisms, such as Peptostreptococcus micros and Streptococcus intermedius. It results in inflammation of the supporting structures of the tooth, which leads to progressive attachment and bone loss, characterized by pocket formation and recession and also cause epithelial proliferation and migration, which results in the chronic release of inflammatory cytokines, prostaglandins, growth factors and enzymes. [1]

Periodontal disease has been linked to various systemic conditions like cardiovascular disease, diabetes, pulmonary diseases and low-birth weight complications in pregnancy .[2] More recently ,a link has been established between periodontal diseases and cancer. The scientific rationale behind the proposed association is that inflammation is a major factor in both periodontal disease and cancer .[1,3-4] Several studies have reported an associations between

periodontal disease or tooth loss and risk of oral, upper gastrointestinal, lung and pancreatic cancer. This article reviews the literature on the possible link between periodontal disease and various types of cancer.

Bacteria and Viruses in Periodontitis

Apart from the gram negative and gram positive bacteria's which have been identified to play an etiologic role in the development of periodontal disease (such as Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans, forsythensis, and Treponema denticola) ,many other pathogens have also been identified in periodontal lesions ,including human cytomegalovirus (HCMV) and the carcinogenic Epstein-Barr virus (EBV).[5,6] Human papilloma viruses (HPVs) are small DNA viruses have been also identified in periodontal pocket and gingival sulcus . [7] Certain bacteria's such as Helicobacter pylori , Chlamydia pneumonia and Streptoccocus bovus have also been identified. Streptococcus bovis infection is associated with colon cancer, Salmonella Typhi is associated with gall bladder cancer and hepatobiliary carcinoma . [8]

There are various studies which show the presence of bacteria and viruses in periodontal diseases .One such study was conducted by Hormia et al., in 2005, where gingival biopsies from 38 patients, which were clinically diagnosed as periodontal disease were taken. The study concluded that high-risk Human Papilloma virus was detected in 26% of the biopsies .[9] Another study stated that the reservoir for HPV's in oral mucosa may be periodontal pocket . In 2009 Sahin et al did a study in which whole saliva was collected from 14 periodontitis patients, 15 gingivitis patients, and 13 complete denture wearers**.** These subjects were systemically healthy. Salivary cytomegalovirus was detected in 50% of the periodontitis patients, but not in any gingivitis or denture wearers. The salivary EBV(Epstein-Barr virus) was seen in 79% of the periodontitis patients and a small percentage in gingivitis patients and denture wearers. It was concluded that HCMV (human cytomegalovirus) and EBV(Epstein-Barr virus) were commonly present in the saliva of periodontitis patients . [10]

These viruses may act as risk factor for the development of various cancers like Epstein Barr virus which is believed to be associated with Burkitt lymphoma, Hodgkin Lymphoma, nasopharyngeal carcinoma, and stomach cancer. Human Herpes 8 is associated with Kaposi sarcoma , Hepatitis B virus has its involvement in liver cancer and human T-lymphocytic virus with adult T-cell leukaemia**.** The virus associated with cancer of the salivary gland and prostate is cytomegalovirus. The human papilloma virus is linked with cancer of the cervix, vulva, penis, and anus .[11] Pradeep et al in 2006, did a research on the microorganism H. pylori (Helicobacter pylori) .The purpose of the research was to determine whether dental plaque, poor oral hygiene, and periodontal disease were risk factors for Helicobacter pylori (H. Pylori) infection. The result was that there was no significant association of periodontal disease and poor oral hygiene with H. Pylori infection. There was higher prevalence of the microorganism in the dental plaque of patients with gastric H. pylori infection than in the controls, but both the cases and control group had a high positive urease test for H. pylori infection in the plaque (89 and 71%, respectively). H.pylori in dental plaque are seldom eliminated by the H. pylori eradication therapy, and these may act as a source for future

reinfection. It is usually present in patients with gastric ulcers and chronic gastritis. It is also believed to be linked with the development of duodenal ulcer and stomach cancer. It is believed that Helicobacter pylori infection is linked with gastric cancer and Chlamydia pneumonia infection with lung cancer development .[12]

Association between Periodontal Disease and Cancer

The various cancer that are associated with the periodontal diseases are :Oral cancer ,Esophageal cancer, Hematological cancer ,Breast cancer ,Upper gastro-intestinal cancer, Lung cancer, Pancreatic cancer.

There are various mechanisms which shows a possible linkage between periodontal diseases and cancer. Chronic infections such as periodontitis can play a direct or indirect role in carcinogenesis .[1]

A. Direct Toxic Effect Of Microorganisms:

Microorganisms and their products such as endotoxins, enzymes, and metabolic by products, that are toxic to the surrounding cells, may directly induce mutations in the tumour-suppressor genes and proto-oncogenes or alter the signalling pathways that may affect cell proliferation and/or survival of the epithelial cells .[1]

Chronic infections with bacteria, such as S. Typhi, can also cause tumour development. Many bacterial toxins may interfere with the cellular signalling molecules in a manner that is characteristic of tumour promoters (Pasteurella multocida toxins act as mitogens). This leads to activation of COX2 (Cyclooxygenase-2) , which is involved in several stages of tumour development, inhibiting apoptosis**.** These toxins could play an important role in the causation of cancer and its progression . [13] There are various factors that can lead viral infection to the development of cancer .These factors include the host's genetic makeup, mutation occurrence, exposure to cancer causing agents, and immune impairment. Many viruses such as human cytomegalovirus (HCMV) and Epstein Bar virus (EBV) which belong to the family of herpes viridae may also mediate oncogenic growth**.** human cytomegalovirus (HCMV) is the most common life-threatening infection in Human immunodeficiency virus(HIV) patients and Epstein Bar virus (EBV) is the causative agent of oncogenic growth. The main source of its transmissions is saliva and it resides in marginal and apical periodontitis. Viruses initiates the development of cancer by suppression of the immune system of the host or by alteration of the host's gene .[14]

There are two possible mechanisms by which the viruses can cause tumour .They are either by direct oncogenic viral mechanism or by indirect viral oncogenecity .

A direct oncogenic viral mechanism involves either insertion of additional viral oncogenic genes into the host cell or it enhances the already existing oncogenic genes (proto-oncogenes) in the genome. Here the virus infects a cell and express its own genes. The growth potential of that cell is enhanced by the gene products**.** If a growth enhancing change occurs in the same cell, it may grow into a cancer .[11] Direct tumour viruses should have at least one copy of the virus in every tumour cell, expressing at least one protein or RNA that is causing the cell to become cancerous. Indirect viral oncogenicity involves chronic nonspecific inflammation occurring over decades of infection, as in the case for human cytomegalovirus (HCMV) induced liver cancer .[15] Here the cofactor for the tumour is the virus which is not actually present in the tumour cells**.** It allows

viruses such as the EBV and Kaposi's sarcoma-associated herpes virus to act opportunistically and cause uncontrolled cell growth in the absence of normal immune control mechanisms (e.g., the HIV affected) .[11]

The Epstein Bar virus (EBV) may mediate oncogenic growth because of its close relationship with certain tumours arising in the lymphoid tissue, such as, Burkitt lymphoma, Hodgkin disease, and those from the epithelial tissue, such as, nasopharyngeal carcinoma. The reservoir for herpes virus is salivary gland tissue and ductal epithelial cells which is believed to cause Kaposi sarcoma. Presence of the herpes virus is usually seen in aggressive periodontitis .[16]

B. Indirect effect through inflammation:

Microorganisms and their products activate host cells such as neutrophils, macrophages, monocytes, lymphocytes, fibroblasts, and epithelial cells to generate reactive oxygen species (ROS) and nitrogen species, reactive lipids and metabolites, and matrix metalloproteases, which can induce DNA damage in epithelial cells and produce cytokines, chemokine's, growth factors, and other signals that produce an environment for cell survival, proliferation, migration, and angiogenesis, and also help in inhibition of apoptosis .[1]

Myeloperoxidase and superoxide dismutase helps to regulate inflammation that are found to be elevated in periodontitis, and polymorphisms of these genes have been associated with elevated pancreatic cancer risk .[17] This dual condition result of genetic polymorphisms has been suggested for gastric cancer and periodontitis.[4] Many cancers are linked to local chronic inflammation, including inflammatory bowel disease and colon cancer, Hepatitis C inflammation and liver carcinoma, and H. pylori-associated ulcers and gastric cancer.[18-20] Also of interest is the relationship between the pro-inflammatory expression of the receptor for advanced glycation end products (RAGE) and oesophageal, gastric, colon, biliary, pancreatic, and prostate cancers.[21] RAGE(receptor for advanced glycation end products) has been shown to play a role in the inflammatory processes of oral infections including periodontal disease .[22]

There are other plausible theories which links the association between periodontal disease and oral neoplasm and which may be explained by: 1) broken mucosal barrier in the presence of periodontal disease and consequent enhanced penetration of carcinogens such as tobacco and alcohol. 2. Increased cellularity in blood vessels and connective tissue in chronic inflammation. Association between chronic inflammation and cancer is coupled with the development of chronic diffuse epithelial hyperplasia which is regarded as a common precursor to intraepithelial neoplasia . [23] Immunosuppression as a common mechanism leading both to periodontal disease and oral cancer. For example, major concentrations of defensins (which have antibacterial, antiviral, and antitumor activities and are likely to play an important role in killing periodontal pathogens) found in neutrophils and epithelia suggest potential implications for critical immune surveillance within periodontal attachment .[24,25] Bacterial overgrowth in patients with poor oral hygiene may lead to an increased rate of metabolites with possible carcinogenic potential. For example, higher microbial production of carcinogenic acetaldehyde from ethanol has been shown in patients with poor oral hygiene. [26]

Oral Cancer

Oral cancer globally is one of the 10 commonest cancers .[27] Several studies have found an association between oral cancer and periodontal diseases . Most found a significant increase in risk of oral cancer with patients with increased tooth loss or other parameters of periodontal disease even after adjustment for tobacco and alcohol. There are two most informative studies of these , one was given by Tezal et al as the objective measures of periodontal disease were used in these as opposed to tooth loss as a measurement tool. [4,28] The first study reported a 5.23-fold increase in risk of tongue cancer with each millimetre of bone loss in periodontal disease patients in a study of men with tongue cancer in Buffalo, New York, and in fact found no association with other parameters of dental disease such as caries or significant prior dental work tool .[1] In an earlier cohort study of a NHANES III data, Tezal et al. found that in patients with greater than 1.5 mm clinical attachment loss there was an increased incidence of oral tumours or precancerous oral lesions .[28] The other study was done by Michaud et al which was a large cohort study that used a specific periodontal disease indicator and was in fact the only study not finding a significant association .[3] There are eleven other studies which found a significant increase in risk of oral cancer and periodontal disease and one found no association . There by indicating that in the case of oral cancer, a valid association is likely present for both tooth loss and periodontal disease.

Oesophageal Cancer

Several studies have found a link between oesophageal cancer and periodontal disease [3-4,29] In one of the study done by Hiraki et al. reported a significant association with oesophageal cancer similar to their previously mentioned work with head and neck cancer .[30]

In a recent study by Abnet et al. in Iran found that increasing numbers of teeth lost had a direct relationship on the risk of oesophageal squamous cell carcinoma noting that edentulous subjects had twice the risk as compared to subjects who lost fewer than 13 teeth .[4] Guha et al. showed that missing between 6 and 15 teeth doubled the risk of oesophageal cancer when compared with subjects missing less than 5 in two concurrent studies in Europe and Latin America .[29] Michaud et al., used a specific measure of periodontal disease rather than missing teeth, and their large scale cohort study failed to find an association with oesophageal cancer either with patient self-reported periodontal disease verified by radiographic bone loss or with missing teeth .[3]

In 2016, Shegan Gao et al proposed for the first time that Porphyromonas gingivalis ,the bacterium behind gum disease could be a risk factor for oesophageal cancer. They found levels of P.gingivalis to be significantly higher in the cancerous tissue of oesophageal squamous cell carcinoma(ESCC) patients than in surrounding tissue or tissue of normal controls. They concluded that P. gingivalis infection could be a biomarker for oesophageal squamous cell carcinoma(ESCC) as there these findings demonstrated that P. gingivalis infected the epithelium of the oesophagus of ESCC patients thereby establishing an association between infection with P. gingivalis and the progression of ESCC. So this indicates that eradication of P.Gingivalis (Oral pathogen) could potentially contribute to a reduction in the overall ESCC burden .(79)

Therefore an association may be present for an increased risk of oesophageal cancer for patients with an overall poor oral condition and increased numbers of missing teeth, the evidence does not yet support a specific association to periodontal disease indicators.

Upper GI and Gastric Cancer

The second leading cause of cancer death worldwide is the Gastric cancer. The risk factors for gastric cancer includes age, gender, diets poor in fruits and vegetables , diets with excessive salt and nitrates, Helicobacter pylori infection and smoking . People with this type of cancer usually have poor prognosis. Poor oral health has been seen with increased risk of cancer at several sites .[31-33] An association between oral hygiene and/or tooth loss and gastric cancer has also been reported in retrospective studies conducted in Japan .[34,35]

Abnet et al. found a significantly elevated risk between tooth loss and oesophageal squamous, gastric cardia adenocarcinoma, cell carcinoma and gastric non-cardia adenocarcinoma. The strongest association was noted between gastric non-cardia adenocarcinoma and tooth loss in a study originating in China .[4]

However, in a study done in Finland, by Abnet et al. found a significant association between tooth loss and gastric non-cardia adenocarcinoma but not with oesophageal squamous cell carcinoma or gastric cardia adenocarcinoma .[36]

Of the studies, there were two large cohort studies that evaluated the relationship between specific periodontal indicators and stomach cancer .[32,37]

Michaud et al in 1986-2004, conducted a study which consisted of 106 cases of stomach cancer out of 48,328 cohort in United States. The criteria of the study was patient reported history of periodontal disease and loss of teeth. The result of the study reported no significant association between stomach cancers and history of periodontal disease or with tooth loss .[3]

Hujoel et al. in the NHANES I Epidemiologic Follow-up Study found no significant association between stomach cancer and periodontitis as defined by clinical examination but had a small number of cases within their cohort . [37]

In review of gastric cancer and periodontal disease or tooth loss studies, four studies found an increased risk of cancer and three did not .

Several different hypotheses could explain the tooth loss and cancer association. The first hypothesis proposes tooth loss as a specific risk factor , in itself for upper gastrointestinal cancers. The second potential mechanism proposes tooth loss could be associated with a dietary pattern that increases the risk of gastric cancer. Polymorphisms in certain genes that mediate inflammatory responses affect the severity of periodontal disease [38] and also modify the risk of gastric cancer .[39] Poor oral hygiene has been linked to increased internal production of nitrosamines [40] , some of which are gastrointestinal organ-specific carcinogens. Poor oral hygiene and the attendant greater tooth loss might cause greater endogenous nitrosamine production and therefore greater risk of gastric cancer. Oral bacteria can produce upper gastrointestinal tract carcinogens such as aldehydes and nitrosamines. In a study conducted by Nair et al concluded that individuals with poor oral hygiene had 8 fold increase in the potential to form nitrosamines in the oral cavity .This is thought to occur because the bacteria associated with caries and periodontal disease such as streptococcus mutants are efficient reducers of nitrate to nitrite which is necessary for in-vivo formation of nitrosamines.

As the studies specifically measuring parameters of periodontal disease did not show an association, the evidence as of yet does not support a link from gastric or upper GI cancer with periodontal disease.

Lung Cancer

It has been found that periodontal disease shared numerous genetic factors with cancers.[41] Hujoel and colleagues performed a prospective cohort study to investigate the association of periodontal disease and fatal cancers (as ascertained from death certificates) and lung cancer demonstrated the strongest correlation .[37] Cigarette smoking is a common risk factor of periodontal disease and lung cancer.[42]

A case-control study by Hiraki *et al.* found a significant association of lung cancer and teeth loss after adjusting for smoking and alcohol.[30] Individuals with periodontal disease are more susceptible to respiratory diseases e.g. chronic obstructive pulmonary disease (COPD).[44-45] Specific oral bacteria have been suggested to be involved in carcinogenesis and their role in the pathogenesis of lung cancer.[46]

Scannapieco and Mylotte have proposed four mechanisms to explain the role of oral bacterial in lung cancer[47]: (1) aspiration of oral pathogens (such as *Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans*) into the lungs, leading to bronchitis and other respiratory infections; (2) periodontal disease -associated enzymes in saliva may modify mucosal surfaces to promote adhesion and colonization of respiratory pathogens; (3) periodontal disease -associated enzymes in saliva may destroy salivary pellicles on pathogenic bacteria, thereby hindering their clearance from the mucosal surface; (4) Cytokines originating from periodontal tissues may alter respiratory epithelium and promote pathogenic infections.

However, despite this proposed mechanism of infection development, inflammation remains a critical component of cancer progression .[18]

Periodontal disease itself is a chronic inflammatory disease and the close anatomical proximity between the oral cavity and the lungs may well be another potential mechanism behind the association of periodontal disease and lung cancer.

Pancreatic Cancer

Although pancreatic cancer (exocrine adenocarcinoma) is relatively uncommon cancer, it is a major cause of cancer mortality. It ranks eighth in the world, according to the International Agency for Research on Cancer, and fifth in the United States .[48]

The oral cavity acts as a link between the external environment and the gastrointestinal tract, and also facilitates food ingestion and digestion. Gastrointestinal flora and nutritional status can be potentially affected by the oral hygiene and tooth loss and thus they have implications for the development of chronic diseases.[49] Several studies suggested that dental plaque is a reservoir for Helicobacter pylori [50-56], and one large study (n = 4500) that used data from the United States National Health and Nutrition Examination Survey showed that periodontal disease, specifically periodontal pocket depth, was associated with seroprevalence of H.Pylori [57] Furthermore, gastric carriage of H. Pylori is a known risk factor for gastric cancer [58] with the cytotoxin associated gene–A-positive (CagA+) strain having a greater propensity for inflammation, ulceration, and malignancy . [58] Recently, a positive association for H. pylori and CagA+ strain carriage and pancreatic cancer was reported .[59] In addition, chronic

pancreatitis has been associated with extremely high risks of pancreatic cancer [60] , suggesting that inflammation may be involved in the initiation and/or promotion of pancreatic cancer. The inflammatory pathway genes myeloperoxidase (MPO), and superoxide dismutase (SOD2) are involved with regulation of inflammation through reactions with hydrogen peroxide (H2O2). The MPO enzyme is expressed abundantly in neutrophils, in which its antimicrobial function converts hydrogen peroxide (H2O2) to the bactericidal and DNA-damaging hypochlorous acid. Conversely, superoxide dismutase (SOD2) protects cells from reactive oxygen species (ROS) by converting superoxide radicals, which are produced by mitochondrial activity, into hydrogen peroxide (H2O2) and oxygen .[62] A single thymine (T) to cytosine (C) base change in the mitochondrial targeting sequence (MTS) of the superoxide dismutase (SOD2) gene results in a valine (Val) to alanine (Ala) amino acid change in the MTS .[63] It has been demonstrated that Val-containing genotypes carry an increased risk of breast cancer, prostate cancer, lung cancer, and bladder cancer. [64-67]

There are several mechanisms besides H. pylori carriage that may potentially explain the increased risk associated with tooth loss and pancreatic cancer. Tooth loss that occurs through poor dental hygiene may be a marker for more deleterious gastrointestinal flora and, consequently, greater endogenous nitrosation .[40] Nitrosamines induce pancreatic cancer in animals and are considered potential human pancreatic carcinogens Exogenous exposure to nitrate and nitrite comes from food and water. It has been estimated that 45%–75% of nitrosamine formation comes from endogenous formation by gastrointestinal and salivary bacteria converting nitrate to nitrite and nitrosamines [68-71] , with the rest coming from macrophage response and immunostimulation via intermediate production of nitric oxide .[72] There have also been several association studies linking sporadic pancreatic cancer risk with tooth loss and periodontitis, a condition that is characterized by chronic, low-level inflammation . [37,3,59] This association remained significant even after accounting for cigarette smoking. [3]

During periodontitis, MPO and SOD2 are elevated in the gingival crevicular fluid .[73,74] The MPO G/G genotype also has a reported association with an increased risk of coronary artery disease .[75] These associations raise the possibility that inflammatory processes may be important etiologically in pancreatic cancer, as reported in several other conditions.[76-78] Hujoel et al. found a significant association between pancreatic cancer and periodontitis measured by examination but again had a relatively small number of cases within their cohort .[37] A significant association was found between pancreatic cancer and tooth loss by a Finnish study.[59] Hiraki et al., however, found no association between pancreatic cancer and tooth loss.[30] The evidence favouring an association specifically with periodontal disease appears promising for pancreatic cancer when the two studies by Michaud et al., and Hujoel et al., are taken into account. [3, 37]

Prostate Cancer

There are several studies have shown a relationship between prostate cancer and tooth loss or periodontal disease . There are two studies which used tooth loss as an indicator actually found an inverse relationship. .Hiraki et al. found that subjects with greater tooth loss actually demonstrated a decreased risk of prostate cancers.[30] The study conducted by

Michaud et al. And Hujoel et al. were the only study which used direct assessment of periodontal state and established a slight positive association between prostate cancer and periodontal disease; however, they had a low sample size (20 cases of patients with prostate cancer).[3,37] It appears that as of yet a strong association cannot be made at this time between periodontal disease and prostate cancer.

Hematologic cancer

Hematologic cancers in association with periodontal disease have had limited study .[3,30]

Michaud et al. looked at hematologic malignancy for an association with history of periodontal disease with verified radiographic bone loss and reported an increase with non-Hodgkin lymphoma (NHL), leukaemia, and myelomas but only non-Hodgkin lymphoma (NHL) yielded a significant relationship.[3] They also evaluated loss of teeth in relationship to hematologic malignancies and found no significant increase in risk. [3]

Hiraki et al. could not demonstrate an association between lymphomas in general and tooth loss.[30] As of yet, there has been insufficient study to conclude if a relationship exists, but as the Michaud study was a cohort study with quite large numbers and found a relationship with non-Hodgkin lymphoma (NHL) after separating out periodontal patients from general tooth loss, the suggestion of a link is an interesting course for future study.

Breast Cancer

Breast cancer was investigated in two studies ,one conducted by Hujoel which showed a significant association between breast cancer risk and periodontal disease by examination [37] but in a study done by Hiraki found no association between breast cancer risk and tooth loss.[30] The Hiraki et al. study was not specific for periodontal indicators but did have a much higher numbers of breast cancer patients, whereas Hujoel et al. used a specific measure of periodontal disease but had rather low numbers. This may reflect a difference between the tooth loss group and true periodontal disease groups; however, the data seems insufficient to draw a strong conclusion .

Other Cancers

Hiraki et al. also investigated liver, ovary, uterus, bladder, thyroid, and colon cancer in their study and found no significant associations for these cancers and missing teeth.[30]

Michaud et al. also studied several other cancers in relationship to a history of periodontal disease and missing teeth and found rectal, bladder, and brain with no significant association found. They also found kidney cancer to have a significant association with history of periodontal disease, and noted an inverse relationship between melanoma and tooth loss.[3]

Hujoel et al. also looked at colon cancer and periodontitis by examination and found no significant association.[37]

Conclusion

In summary the literature shows the strongest evidence of association to periodontal disease is with oral cancer . There is also suggestive positive evidence for pancreatic cancer as well as overall cancer rates. Mixed results appear to be present for esophageal, gastric, lung, prostate, breast, hematologic and other cancers in regards to a link specifically to periodontal disease.

References

1. Tezal M, Sullivan MA, Reid ME, Marshall JR, Hyland A, Loree T et al. Chronic periodontitis and the risk of tongue cancer. Arch Otolaryngol Head Neck Surg 2007; 133:450-4.

2. Pihlstrom BL, Michalowicz BS, Johnson NW (2005) periodontal diseases. Lancet 366:1809–1820.
3. Michaud DS, Liu Y, Meyer M, Giovannucci E, Joshipura K. Periodontal disease, tooth loss, and cancer risk in male health professionals: a prospective cohort study. The Lancet Oncology 2008;9:550–8.
4. Abnet CC, Kamangar F, Dawsey SM, Stolzenberg-Solomon RZ, Albanes D, Pietinen P, et al. Tooth loss is associated with increased risk of gastric non-cardia adenocarcinoma in a cohort of Finnish smokers. Scandinavian Journal of Gastroenterology 2005;40:681–7.
5. Slots J, Saygun I, Sabeti M, Kubar A (2006) Epstein-Barr virus in oral diseases. J Periodontal Res 41:235–244
6. Saygun I, Kubar A, Ozdemir A, Slots J (2005) Periodontitis lesions are a source of salivary cytomegalovirus and Epstein-Barr virus. J Periodontal Res 40:187–191.
7. Manjunath MD ,Anna S, Dinesh G(2015),Periodontal Pocket as a potential reservoir of high risk human papilloma virus: A pilot study, Indian society of periodontology,
8. Mager DL. Bacteria and cancer: Cause, coincidence or cure? A review. J Transl Med 2006;4:14.
9. Hormia M, Willberg J, Ruokonen H, Syrjanen S. Marginal Periodontium as a potential reservoir of human papillomavirus in oral mucosa. J Periodontol 2005;76:358-63.
10. Sahin S, Saygun I. Periodontitis lesions are the main source of salivary cytomegalovirus. Oral Microbiol Immunol 2009;24:340-2.
11. Crawford DH. An introduction to virus and cancer. Microbiol Today 2005;32:110-12.
12. Anand PS, Nandakumar K, Shenoy KT. Are dental plaque, poor oral hygiene and periodontal disease associated with *Helicobacter pylori* infection? J Periodontol 2006;77:692-8.
13. Lax AJ, Thomas W. How Bacteria could cause cancer: One step at a time. Trends Microbiol 2002;10:293-9.
14. K. S. Rajesh, Deepak T, Shashikanth H, M. S. Arun Kumar. Poor periodontal health: A cancer risk?;JISP 2017;17:708-10.
15. Parsonnet J. Microbes and malignancy: Infection as a cause of human cancers. Oxford: Oxford University Press; 1999.
16. Pow EH, Mcmillan AS, Leung WK, Kwong DL, Wong MC. Oral health condition in southern Chinese after Radiotherapy for nasopharyngeal Carcinoma: Extent and nature of the problem. Oral Dis 2003;9:196-202.
17. Wheatley-Price P, Asomaning K, Reid A, Zhai R, Su L, Zhou W, *et al*. Myeloperoxidase and superoxide dismutase polymorphisms are associated with an increased risk of developing pancreatic adenocarcinoma. *Cancer* 2008;112:1037–42.
18. Coussens LM, Werb Z. Inflammation and cancer. *Nature* 2002;420:860–7.
19. Mantovani A, Allavena Sica A, Balkwill F. Cancer-related inflammation. *Nature* 2008;454:436–44.
20. Karin M, Lawrence T, Nizet V. Innate immunity gone awry: linking microbial infections to chronic inflammation and cancer. *Cell* 2006;124:823–35.
21. Tateno T, Ueno S, Hiwatashi K, Matsumoto M, Okumura H, Setoyama . Expression of receptor for advanced glycation end products

(RAGE) is related to prognosis for patients with esophageal squamous cell carcinoma. Annals of Surgical Oncology 2009;16:440–6.

22. Lalla E, Lamster IB, Stern DM, Schmidt AM .advanced glycation end products, inflammation, and accelerated periodontal disease in diabetes: mechanisms and insights into therapeutic modalities. Annals of Periodontology/The American Academy of Periodontology 2001;6:113–8.
23. Ord RA, Blanchaert RH. Epidemiology of oral cancer. In: Oral Cancer. Carol Stream, Illinois: Quintessence; 2000: 3-11.
24. Zhang I, Yu W, He T. Contribution of Human alpha-defensin 1, 2 and 3 to the anti-HIV activity of CD8 antiviral factor. Science 2002;298:995-1000.
25. Biragyn A, Ruffini PA, Leifer CA. Toll-like receptor 4- dependent activation of dendiritic cells by beta-defensin 2. Science 2002;298:1025-1029.
26. Homann N, Tillonen J, Rintamaki H, Salaspura M, Lindqvist C, Meurman JH. Poor dental status increases acetaldehyde production from ethanol in saliva: A possible link to increased oral cancer risk among heavy drinkers. Oral Oncol 2001;37:153-158.
27. Moore S, Johnson N, Pierce A, Wilson D. The epidemiology of mouth cancer: a review of global incidence. Oral Dis 2000; 6:65 −/74.
28. Tezal M, Grossi SG, Genco RJ. Is periodontitis associated with oral neoplasms? Journal of Periodontology 2005;76:406– 10.
29. Guha N, Boffetta P, Filho VW, Neto JE, Shangina O, Zaridze D, et al. Oral health and risk of squamous cell carcinoma of the head and neck and esophagus: results of two multicentric case–control studies. American Journal of Epidemiology 2007;166:1159–73.
30. Hiraki A, Matsuo K, Suzuki T, Kawase T, Tajima K. Teeth loss and risk of cancer at 14 common sites in Japanese. Cancer Epidemiology Biomarkers & Prevention A Publication of the American Association for Cancer Research cosponsored by the American Society of Preventive Oncology 2008;17:1222–7
31. Bundgaard T, Wildt J, Frydenberg M, Elbrond O, Nielsen JE. Case-control study of squamous cell cancer of the oral cavity in Denmark. Cancer Causes Control 1995;6:57/67.
32. Zheng TZ, Boyle P, Hu HF, Duan J, Jian PJ, Ma DQ, et al. Dentition, oral hygiene, and risk of oral cancer: a casecontrol study in Beijing, People's Republic of China. Cancer Causes Control 1990;1:235/41.
33. Zheng W, Blot WJ, Shu XO, Diamond EL, Gao YT, Ji BT, et al. Risk factors for oral and pharyngeal cancer in Shanghai, with emphasis on diet. Cancer Epidemiol Biomarkers Prev 1992;1:441/8.
34. Watabe K, Nishi M, Miyake H, Hirata K. Lifestyle and gastric cancer: a case-control study. Oncol Rep 1998;5: 1191/4.
35. Demirer T, Icli F, Uzunalimoglu O, Kucuk O. Diet and stomach cancer incidence. A case-control study in Turkey. Cancer 1990;65:2344/8.
36. Abnet CC, Qiao YL, Mark SD, Dong ZW, Taylor PR, Dawsey SM. Prospective study of tooth loss and incident esophageal and gastric cancers in China. Cancer Causes & Control 2001;12:847–54.
37. Hujoel PP, Drangsholt M, Spiekerman C, Weiss NS. An exploration of the periodontitis-cancer association. Annals of Epidemiology 2003;13:312
38. Cullinan MP, Westerman B, Hamlet SM, Palmer JE, Faddy MJ, Lang NP, et al. A longitudinal study of interleukin-1 gene polymorphisms and periodontal

disease in a general adult population. J Clin Periodontol 2001;28:1137/44.

39. El Omar EM, Carrington M, Chow WH, McColl KE, Bream JH, Young HA, et al. Interleukin-1 polymorphisms associated with increased risk of gastric cancer. Nature 2000;404:398/402.
40. Nair J, Havovi S, Chakradeo P, Jakhi SA, Bhide SV. Effect of oral hygiene on nitrosamine formation in the mouth. In: Nitroso compounds: biological mechanisms, exposure and cancer etiology. Lyon: International Agency for Research on Cancer; 1992.
41. Zeng XT, Deng AP, Li C, Xia LY, Niu YM, Leng WD. Periodontal disease and risk of head and neck cancer: a meta-analysis of observational studies. PLoS One 2013;8:e79017
42. Gelskey SC. Cigarette smoking and periodontitis: methodology to assess the strength of evidence in support of a causal association. Community Dent Oral Epidemiol 1999;27:16-24.
43. Meyer MS, Joshipura K, Giovannucci E, Michaud DS. A review of the relationship between tooth loss, periodontal disease, and cancer. Cancer Causes Control 2008;19:895-907.
44. Zeng XT, Tu ML, Liu DY, Zheng D, Zhang J, Leng W. Periodontal disease and risk of chronic obstructive pulmonary disease: a meta-analysis of observational studies. PLoS One 2012;7:e46508.
45. Azarpazhooh A, Leake JL. Systematic review of the association between respiratory diseases and oral health. J Periodontol 2006;77:1465-1482.
46. Meurman JH, Uittamo J. Oral micro-organisms in the etiology of cancer. Acta Odontol Scand 2008;66:321-326.
47. Scannapieco FA, Mylotte JM. Relationships between periodontal disease and bacterial pneumonia. J Periodontol 1996;67:1114-1122.
48. Anderson KE, Potter JD, Mack TM. Pancreatic cancer. In: Schottenfeld D, Fraumeni JF, eds. Cancer epidemiology and prevention. New York: Oxford University Press, 1996:725–71.
49. Marshall JR, Graham S, Haughey BP, et al. Smoking, alcohol, dentition and diet in the epidemiology of oral cancer. Eur J Cancer B Oral Oncol 1992;28B:9–15.
50. Song Q, Lange T, Spahr A, Adler G, Bode G. Characteristic distribution pattern of Helicobacter pylori in dental plaque and saliva detected with nested PCR. J Med Microbiol 2000;49:349–53.
51. Higazy E, Al Saeedi F, Loutfi I. et al. The impact of brushing teeth on carbon-urea breath test results. J Nucl Med Technol 2000;28:162–4.
52. Peach HG, Pearce DC, Farish SJ. Helicobacter pylori infection in an Australian regional city: prevalence and risk factors. Med J Aust 1997;167:310–3.
53. Avcu N, Avcu F, Beyan C, et al. The relationship between gastric-oral Helicobacter pylori and oral hygiene in patients with vitamin B12- deficiency anemia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;92:166–9.
54. Ozdemir A, Mas MR, Sahin S, Saglamkaya U, Ateskan U. Detection of Helicobacter pylori colonization in dental plaques and tongue scrapings of patients with chronic gastritis. Quintessence Int 2001; 32:131–4.
55. Karczewska E, Konturek JE, Konturek PC, et al. Oral cavity as a potential source of gastric reinfection by Helicobacter pylori. Dig Dis Sci 2002;47:978–86.
56. Kim N, Lim SH, Lee KH, et al. Helicobacter pylori in dental plaque and saliva. Korean J Intern Med 2000;15:187–94.
57. Dye BA, Kruszon-Moran D, McQuillan G. Helicobacter pylori infection and pathological

peridontal conditions among adults in the United States. Am J Epidemiol 2000;151:S15 .

58. Forman D. Helicobacter pylori infection and cancer. Br Med Bull 1998;54:71–8.
59. Stolzenberg-Solomon RZ, Blaser MJ, Limburg PJ, et al. Helicobacter pylori seropositivity as a risk factor for pancreatic cancer. J Natl Cancer Inst 2001;93:937–41.
60. Lowenfels AB , Maisonneuve P , Lankisch PG . Chronic pancreatitis and other risk factors for pancreatic cancer . Gastroenterol Clin North Am 1999 ; 28 : 673 – 85, x .
61. Cascorbi I, Henning S, Brockmoller J, et al. Substantially reduced risk of cancer of the aerodigestive tract in subjects with variant 2463A of the myeloperoxidase gene. Cancer Res. 2000;60:644–649.
62. Robinson BH. The role of manganese superoxide dismutase in health and disease. J Inherit Metab Dis. 1998;21:598–603.
63. Mitrunen K, Sillanpaa P, Kataja V, et al. Association between manganese superoxide dismutase (MnSOD) gene polymorphism and breast cancer risk. Carcinogenesis. 2001; 22:827–829.
64. Li H, Kantoff PW, Giovannucci E, et al. Manganese superoxide dismutase polymorphism, prediagnostic antioxidant status, and risk of clinical significant prostate cancer. Cancer Res. 2005;65:2498–2504.
65. Bergman M, Ahnstrom M, Palmeback Wegman P, Wingren S. Polymorphism in the manganese superoxide dismutase (MnSOD) gene and risk of breast cancer in young women. J Cancer Res Clin Oncol. 2005;131:439–444.
66. Wang LI, Miller DP, Sai Y, et al. Manganese superoxide dismutase alanine-to-valine polymorphism at codon 16 and lung cancer risk. J Natl Cancer Inst. 2001;93:1818–1821.
67. Hung RJ, Boffetta P, Brennan P, et al. Genetic polymorphisms of MPO, COMT, MnSOD, NQO1, interactions with environmental exposures and bladder cancer risk. Carcinogenesis. 2004;25:973–978.
68. Ziebarth D, Spiegelhalder B, Bartsch H. N-nitrosation of medicinal drugs catalysed by bacteria from human saliva and gastrointestinal tract, including Helicobacter pylori. Carcinogenesis 1997;18:383–9.
69. Crespi M, Ohshima H, Ramazzotti V, et al. Intragastric nitrosation and precancerous lesions of the gastrointestinal tract: testing of an etiological hypothesis. IARC Sci Publ 1987;84:511–7.
70. Thompson M. Aetiological factors in gastrointestinal carcinogenesis. Scand J Gastroenterol Suppl 1984;104:77–89.
71. Ruddell WS, Bone ES, Hill MJ, Blendis LM, Walters CL. Gastricjuice nitrite. A risk factor for cancer in the hypochlorhydric stomach? Lancet 1976;2:1037–9.
72. Tannenbaum SR, Wishnok JS, Leaf CD. Inhibition of nitrosamine formation by ascorbic acid. Am J Clin Nutr 1991;53(suppl): 247S–50S.
73. Kaner D, Bernimoulin JP, Kleber BM, Heizmann WR, Friedmann A. Gingival crevicular fluid levels of calprotectin and myeloperoxidase during therapy for generalized aggressive periodontitis. J Periodontal Res. 2006;41:132–139.
74. Akalin FA, Toklu E, Renda N. Analysis of superoxide dismutase activity levels in gingiva and gingival crevicular fluid in patients with chronic periodontitis and periodontally healthy controls. J Clin Periodontol. 2005;32:238–243.
75. Nikpoor B, Turecki G, Fournier C, Theroux P, Rouleau GA. A functional myeloperoxidase polymorphic variant is associated with coronary artery

disease in French-Canadians. Am Heart J. 2001;142:336–339.

76. Coleman WB. Mechanisms of human hepatocarcinogenesis. Curr Mol Med. 2003;3:573–588.
77. Dusheiko GM. Hepatocellular carcinoma associated with chronic viral hepatitis. Aetiology, diagnosis and treatment. Br Med Bull. 1990;46:492–511.
78. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut. 2001;48: 526–535.
79. Shegan Gao, Shuoguo Li, Zhikun Ma, Shuo Liang, Tanyou Shan, Mengxi Zhang, Xiaojuan Zhu, Pengfei Zhang, Gang Liu, Fuyou Zhou, Xiang Yuan, Ruinuo Jia, Jan Potempa, David A. Scott, Richard J. Lamont, Huizhi Wang, and Xiaoshan Feng . Presence of *Porphyromonas gingivalis* in esophagus and its association with the clinicopathological characteristics and survival in patients with esophageal cancer. Infect Agent Cancer. 2016; 11: 3.