Published in final edited form as:
Cancer Causes Control. 2008 November ; 19(9): 895–907. doi:10.1007/s10552-008-9163-4.

A Review of the Relationship between Tooth Loss, Periodontal Disease, and Cancer

Mara S. Meyer[1], **Kaumudi Joshipura**[1,2,3], **Edward Giovannucci**[1,4,5], and **Dominique S. Michaud**[1,6]

[1] Department of Epidemiology, Harvard School of Public Health, Boston, MA

[2] School of Dentistry, Medical Sciences Campus, University of Puerto Rico, San Jan, Puerto Rico

[3] Department of Oral Health Policy and Epidemiology, Harvard School of Dental Medicine, Boston, MA

[4] Department of Nutrition, Harvard School of Public Health, Boston, MA

[5] Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

[6] Department of Epidemiology and Public Health, Imperial College, London, UK

Abstract

Recent studies have investigated the association between periodontal disease, tooth loss, and several systemic diseases including cancer, cardiovascular disease, and preterm birth. 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 percent.

The relationship between oral health and cancer has been examined for a number of specific cancer sites. Several studies have reported associations between periodontal disease or tooth loss and risk of oral, upper gastrointestinal, lung, and pancreatic cancer in different populations. In a number of studies, these associations persisted after adjustment for major risk factors, including cigarette smoking and socioeconomic status. This review provides a summary of these findings, discusses possible biological mechanisms involved, and raises methodological issues related to studying these relationships.

Keywords

Periodontal Diseases; Tooth Loss; Cancer

Introduction

Periodontal disease, a chronic, destructive condition affecting a large portion of the adult population of the United States, is one of the major causes of tooth loss in adults.[1] 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

Corresponding Author: Mara S. Meyer, ScM, Department of Epidemiology, Harvard School of Public Health, Kresge Building, 677 Huntington Ave. Boston, MA 02115, USA, Email: mameyer@hsph.harvard.edu.

the teeth.[2,3] The National Health and Nutrition Examination Survey (NHANES) 1999–2000 estimates that the prevalence of periodontitis among adults in the USA is 4.2%, which was an appreciable decline from the 7.3% reported during NHANES III, using data collected between 1988 and 1994.[4] 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.[4] Elderly Mexican-American adults in the USA currently experience the highest prevalence of periodontitis, with 18.1% of people aged 60 years or older suffering from the disease. In that same age group, 15.6% of non-Hispanic black adults, and 8.2% of non-Hispanic white adults had periodontitis. Younger adults are diagnosed less frequently with periodontal disease, with prevalence estimates of 1.1% for non-Hispanic whites, 1.3% for Mexican-Americans, and 2.1% for non-Hispanic blacks aged 18–34 years. For adults aged 35–59 years, 4.2% of non-Hispanic whites, 6.8% of Mexican-Americans, and 9.6% of non-Hispanic blacks had periodontitis.[4] Worldwide prevalence of the disease varies by race and geographic area, with older populations typically experiencing higher rates of periodontitis.[1,2] Estimates of the global prevalence of severe periodontal disease generally range from 10 to 15 percent, although up to 90% may be affected by some form of milder periodontal disease, including gingivitis.[2,5] In addition to age and race, other known risk factors for periodontal disease include gender,[2] body mass index (BMI),[6] tobacco, diabetes, and nutrition.[5] The impact of diabetes mellitus on periodontal disease has been shown to be independent of other major risk factors.[1] Populations with low socioeconomic status and those with limited access to dental care may also be at an increased risk for the disease.[1] Furthermore, limited research on the genetic component of adult periodontitis suggests that approximately one-half of cases may be heritable.[7]

The bacteria identified to most likely play an etiologic role in the development of periodontal disease include *Porphyromonas gingivalis*, *Actinobacillus actinomycetemcomitans*, *Tannerella forsythensis*, and *Treponema denticola*.[5,8] However, many other pathogens have been identified in periodontal lesions, including human cytomegalovirus and the carcinogenic Epstein-Barr virus.[9,10] Interestingly, many of these bacteria are also present at low levels in the dental plaque of healthy people.[11] Periodontal disease progression is signaled by a shift in the bacterial makeup of the dental biofilm from largely aerobic Gram-positive bacteria to a pathogenic infectious state dominated by anaerobic Gram-negative organisms.[11] 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.[12,13] Thus the onset of periodontal disease is not marked by the establishment of a novel infectious strain, but rather by a shift in the dominant strains composing the dental plaque biofilm. The exact mechanisms leading to the high proportion of invasive, destructive bacterial strains, and thus inflammation and disease progression, are unclear. It is thought that a local infection such as that occurring in periodontal disease may contribute to the establishment of a systemic inflammatory condition in genetically susceptible individuals known as “hyperinflammatory phenotype,” potentially involving increased production of inflammatory mediators and a breakdown of pathways responsible for immune resolution.[11,14] Recent research suggests that the ongoing inflammatory response instigated by periodontal pathogens leads to an increase in numerous markers of systemic inflammation including C-reactive protein, IL-1β, IL-6, TNF-α, and Matrix Metalloprotenases.[11,15–17]

Recent epidemiologic research has linked periodontal pathogens to several systemic diseases, including cardiovascular disease, diabetes mellitus, and preterm birth, possibly mediated through markers of systemic infection and inflammation.[11,18–20] Associations with osteoporosis, respiratory disease, and systemic infections have also been observed.[10,13,20, 21] In addition, the results of several 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.[3,22–27] In light of recent

findings between periodontal disease, oral health, and carcinogenesis, a review of the current literature in this area is presented. This review includes only studies that directly assessed and quantitatively measured tooth loss or periodontal disease as a potential risk factor for carcinogenesis in humans, and that included some assessment of potential confounding factors. Studies using only less specific and indirect measures of gum disease such as oral hygiene, frequency of tooth brushing, or denture use, or studies with insufficient quantitative data on associations with tooth loss were not included in this review. Articles were identified through searches of PubMed MEDLINE through September 2007, using the following search terms: “periodontitis,” “tooth loss,” “periodontal disease,” “gum disease,” “oral health,” and “oral hygiene” in combination with “cancer,” as well as specific cancers, and by scanning the reference lists of retrieved articles. A summary of these studies is presented in Table 1.

Review of Epidemiologic Literature

Measuring Periodontal Disease

Studies investigating the association between periodontal disease and cancer have used a variety of measures to define periodontal disease and the manner in which disease progression is ascertained. There is no standardized definition or clinical criteria for periodontal disease used consistently in periodontal epidemiologic research, making comparisons of studies examining the association between periodontal disease and cancer difficult.[2] Various methods of assessing periodontal status include self-reported or medical history of periodontal disease; measuring several sites on each tooth to assess pocket depth and attachment loss; and measuring alveolar bone height with radiographs. Since periodontitis is a primary cause of tooth loss in adults, the number of lost adult teeth has also been used as a marker of periodontal disease in epidemiologic literature.[3,28] However, population and age at which tooth loss occurs influences whether or not the tooth loss was caused by periodontal disease. Tooth loss at an older age is more likely to be caused by chronic periodontal disease, while teeth lost at younger ages may most likely be the result of dental caries.[1] It is estimated that between 30 and 35% of all tooth extractions are due to periodontitis, while approximately one-half are the result of dental caries.[1] Since the association between tooth extraction and dental caries has been shown to considerably vary with age,[29] assessing the presence of periodontal disease by extent of tooth loss alone may be inadequate to examine the link between periodontal disease and cancer; studies in this area may, however, provide some insights into the overall role of oral health in relation to malignant neoplasms. If clinical exams are not feasible, or are not carried out in a standardized manner, measures such as reported history of periodontal disease, self-reported tooth loss due to periodontal disease, or bitewing radiographs may provide a better assessment of the presence of periodontal disease.

Oral Cancer

Measures of oral hygiene have been considered as potential risk factors for oral cancer for many decades.[30–32] However, the results have been inconsistent.[27] The main risk factors for the development of oral cancer are tobacco and alcohol consumption, both of which are associated with dental hygiene and therefore likely to be confounders of an association with tooth loss.[27,33] In addition, some studies have noted that infection with high-risk strains of Human Papillomavirus (HPV) is an independent risk factor for development of oral cancer, particularly in the tonsils, oropharynx, and oral cavity.[34,35] The following section will review six recent case-control studies on the possible link between tooth loss, periodontal disease, and oral cancer. All articles quantified the extent of tooth loss, and also included assessment of important confounders such as tobacco and alcohol use, whereas some prior studies not reviewed here used more general evaluations of dentition.

A case-control study of dentition and risk of oral cancer was conducted in Beijing, China between 1989 and 1990.[31] The 404 matched cases and hospital-based controls completed a standardized questionnaire and underwent an oral examination, which included recording the number of missing teeth and presence of gingivitis or periodontal disease.[31] Multivariate analyses were stratified by gender; for men, a 2–3 fold increase in risk of oral cancer was observed for any tooth loss with and without tooth replacement, and a 5–8 fold increase in risk for the same comparison in women (see Table 1). A multiplicative interaction was observed between lost teeth, tobacco smoking, and alcohol drinking; when compared to participants who had not lost teeth, and did not smoke or drink alcohol, participants who responded positively to all three risk factors had more than 15 times the risk of oral cancer (OR: 15.5, 95% CI: 7.2, 33.7).[31] This OR was markedly attenuated when inadequate dentition was removed from the regression model, comparing participants who smoked and drank to those who did not (OR: 4.1, 95% CI: 1.6, 10.4). In this study, inadequate dentition was identified as an independent risk factor for oral cancer, and the authors hypothesized that chronic trauma and irritation of the oral mucosa may play a role in carcinogenesis.

Marshall, et al. examined the connection between tobacco, alcohol, dentition, and dietary factors in a case-control study of oral cancer conducted in Western New York State between 1975 and 1983.[33] One control was matched to each of 290 cases of oral cancer, with all information collected by interview. The authors found a significant 2.7-fold increase in risk of oral cancer for participants who lost 11 or more teeth, compared to those who lost none, after adjustment for alcohol and smoking (see Table 1).[33] Persons who smoked cigarettes, drank alcohol, and had lost teeth without replacement were at increased risk for oral cancer (OR: 12.8, 95% CI: 4.9, 33.8) when compared to individuals who did not smoke or drink and had not lost any teeth; these latter findings are consistent with the results from the Chinese case-control study.[33]

The risk of intra-oral squamous cell carcinoma was examined in 161 cases and 400 matched controls from Denmark between 1986 and 1990.[36] All information was collected by questionnaires administered at baseline, including detailed information on a number of risk factors for oral cancer including tobacco, alcohol, dental status, and occupational exposures. A significant two-fold increase in cancer risk was observed for individuals with fewer than 15 teeth after adjustment for lifetime consumption of tobacco and alcohol (see Table 1). Similar findings were observed when a variety of potentially confounding factors were controlled for in the analysis.[36]

A more recent case-control study conducted in Cuba as part of an international study of oral cancer and HPV collected information on 200 cases of oral and oropharyngeal cancer and 200 hospital-based controls between 1996 and 1999.[37] Information on potential risk factors and confounders was collected via questionnaire. Indicators of oral status, such as number of missing teeth without replacement and general oral condition, were assessed by dental examinations conducted by dentists not blinded to case status. In this study, missing 16 or more teeth was associated with a significant 2.7-fold increase in oral cancer after multivariable adjustment, as compared to participants missing five or fewer teeth, while missing 6–15 teeth was associated with a non-significant 1.8-fold increase (see Table 1).[37]

A case-control study conducted in Italy from the same international study on oral cancer and HPV examined tooth loss, dental care, and general condition of the mouth as potential risk factors for oral cancer.[38] Information was collected on 132 cases and 148 hospital-based controls in the same manner as for the Cuban study. However, in this population, missing 16 or more teeth was not found to be significantly associated with an increased cancer risk in multivariate analyses, although there was a marginal 1.4-fold increase.

More recently, a population-based case-control study investigated the association between oral status and oral infections as risk factors for oral and oropharyngeal squamous cell carcinoma (OOSCC) in southern Sweden.[27] Between 2000 and 2004, 132 cases and 320 matched controls completed standardized interviews and comprehensive oral exams, including panoramic radiographs and a modified gingival bleeding index (GBI) to measure gum bleeding after gentle probing of the gingival crevice. The authors found that poor and average oral hygiene, as measured by visible plaque, were significant predictors of disease after adjustment for tobacco and alcohol, compared to good oral hygiene. Regular dental check-ups were associated with a significantly reduced risk of OOSCC (OR: 0.4, 95% CI: 0.2, 0.6), while individuals who had lost more than 20 teeth experienced a significant three-fold increase in risk of cancer in multivariate analyses. Panoramic radiographs revealed that participants with "a high degree of marginal bone loss," a marker of periodontal disease progression, experienced an elevated cancer risk in unadjusted analyses; the association was similar but the estimate not statistically significant after adjustment for confounders.[27]

In summary, five of the six case-control studies that have quantitatively examined the association between tooth loss and oral cancer have observed 2–3 fold significant increases in risk from tooth loss after controlling for smoking and alcohol use (Figure 1). Moreover, two of these studies reported interactions with smoking and alcohol, suggesting that tooth loss may be contributing to oral carcinogenesis through the promotion of initiated tumors or other complex interactive mechanisms. Since the magnitude of associations with known risk factors such as smoking, alcohol, and HPV may vary between sites in the oral cavity, the effects of periodontal disease on oral cancer may also differ by site.[39] Future studies should carry out their analyses according to oral cancer site, such as the pharynx, larynx, and oral cavity, to determine whether similar associations between cancers at these sites and tooth loss exist. To date, only six studies, all with a case-control design, have evaluated the association between tooth loss and oral cancer; no studies have examined oral cancer risk with a more precise measure of periodontal disease. Therefore, further research in this area is warranted to better understand the role of oral hygiene and oral cancer.

Upper Gastrointestinal and Gastric Cancer

The association between tooth loss or periodontal disease and upper gastrointestinal cancers, including cancers of the upper aerodigestive tract (UADT), esophagus, and stomach (cardiac and non-cardiac), has been assessed in a number of studies. To date, four studies have been conducted on this topic in various populations; two in Chinese populations,[24,25] one in a cohort of Finnish smokers,[40] and one in Japan.[41] These studies are summarized in Table 1 and discussed below. In addition, two earlier studies had also examined tooth loss and gastric cancer but these did not provide measures for the associations. In one study (published in 1976), early tooth loss was suggested to be a possible predictor of the disease in Germany,[42] and in a case-control study from Turkey, individuals with stomach cancer had significantly fewer teeth.[43]

In a case-control study from Hokkaido, Japan in the 1990s, consisting of 242 cases with gastric cancer and 484 matched controls, the loss of more than 10 teeth led to a two-fold increased odds of gastric cancer. The authors observed a significant dose-response relationship between the odds of developing gastric cancer and the number of teeth lost (p=0.0002).[41]

Two recent studies measured poor oral health and hygiene, as reflected by the degree of tooth loss, in Linxian, People's Republic of China.[24,25] The authors mentioned that many people in this region experience tooth loss early in life, as dental care is difficult to attain.[24] It should also be noted that this population experiences extraordinarily high rates of esophageal and gastric cardia cancer.[24] In 2001, Abnet, et al. investigated the relationship between tooth loss and development of incident esophageal and gastric cancers in a large cohort in the rural

Linxian region of China. Tooth loss was measured at baseline examinations in 1985, and further classified according to the number of teeth lost and age at first tooth loss. Results showed a median of 6 teeth lost among the 74% of participants who reported missing teeth, with the median age at first permanent tooth loss being 39 years. In multivariate adjusted analyses, statistically significant associations were detected for tooth loss and the risk of esophageal squamous cell carcinoma, gastric cardia adenocarcinoma, and gastric non-cardia adenocarcinoma; the strongest association was observed for non-cardia adenocarcinoma (see Table 1). The greatest risk associated with tooth loss for all studied cancers, and gastric non-cardia adenocarcinoma in particular (RR: 3.3, 95% CI: 0.85–12.4), was observed among participants less than 50 years old.[24]

In 2005, Abnet, et al. further explored the association between tooth loss and total mortality, upper GI cancer deaths, other cancer deaths, and deaths from heart disease and stroke in this cohort of nearly 29,000 individuals over a more extended follow-up period (15 years).[25] The authors found a significant relationship between tooth loss and risk of dying from upper GI cancer, with age as an effect modifier; the greatest increase in risk was observed among participants less than 50 years old (RR: 1.25, 95% CI: 1.06, 1.48).[25] In addition, a difference in the effect of tooth loss on upper GI cancer mortality was noted between smokers and non-smokers; the risk of upper GI cancer associated with increased tooth loss among male never-smokers was actually higher than that observed in male ever-smokers (see Table 1). In this population, esophageal, gastric cardia and non-cardia cancers were responsible for 51%, 23% and 10% of total cancer deaths, respectively.

A third study by Abnet, et al. examined tooth loss and gastric non-cardia adenocarcinoma in a cohort of Finnish male smokers participating in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC).[40] This study assessed potential confounding of previously reported associations between tooth loss and gastric non-cardia cancer by testing for infection with carcinogenic *Helicobacter pylori* in a subset of 249 cases and 246 controls. Dental history, including number of missing permanent teeth, was self-reported through questionnaires administered at baseline.[40] A significant two-fold increase in the risk of gastric non-cardia adenocarcinoma was reported for edentulous individuals, compared to individuals who lost 10 or fewer teeth after adjusting for age and education. Further adjustment for dietary factors, smoking, and *H. pylori* seropositivity did not impact the estimates (see Table 1).

To date, six studies have examined the relation between tooth loss and upper gastrointestinal cancers; three of which were cohort studies (Figure 2). The strongest associations were reported for non-cardia gastric cancer; elevated risks were observed in two different populations, and after controlling for *H.pylori* in one study. As *H.pylori* is only associated with non-cardia gastric cancer, the observed increase in risk with tooth loss suggests that certain oral bacteria could play a role in this subtype of cancer through similar inflammatory mechanisms. However, more studies, with accurate assessment of periodontal disease and tight control for smoking and *H.pylori* infection, are needed to confirm these preliminary findings.

Lung Cancer

Several studies have investigated the relationship between periodontal disease and lung cancer. In the population-based NHANES I Epidemiologic Follow-up Study, encompassing 11,328 adults, periodontal structure was assessed by dentists and trained recorders using the Russell Index, a summary measure for periodontitis, during baseline examinations between 1971 and 1975.[23] Periodontitis was defined as having a periodontal pocket with attachment loss. Follow-up through 1992 identified 191 fatal cases of cancer of the lung and bronchus.[23] Hujoel, et al. found periodontitis was significantly associated with total cancer deaths, as well as lung cancer specifically. A more detailed analysis of the association with lung cancer found a statistically significant 73% increase in the risk of dying from lung cancer for individuals

with periodontitis after adjustment for age, gender, socioeconomic status, smoking habits, vitamin A and C consumption, and alcohol intake. However, this association no longer remained significant when the adjusted analysis was restricted to never-smokers.[23] When restricted to smokers, the adjusted hazard ratio was higher by approximately two-fold (see Table 1).

The association between periodontal pathogens and lung cancer is controversial, especially given the well-established and strong association between cigarette smoking and the risk of lung cancer. In a recent study conducted in Scotland, no association was observed between tooth loss, both with and without adjustment for baseline smoking status, and lung cancer.[44]

Only two studies, both cohort studies, have examined tooth loss or periodontal disease with risk of lung cancer. Based on these two studies alone, it does not appear as though tooth loss or periodontal disease is associated with lung cancer as most of the excess risk is likely due to confounding by smoking.

Pancreatic Cancer

A positive association between tooth loss and pancreatic cancer was reported in a study of the ATBC cohort of male smokers in Finland.[22] Incident cases of pancreatic cancer were recorded between 1985 and 1997 among an eligible cohort of 29,104 men. A trend of increasing cancer risk with number of lost teeth was observed in this study. However, only the hazard ratio for edentulous individuals remained significant after multivariate adjustment, compared to individuals missing 0–10 teeth (see Table 1).[22]

In addition to an increased risk of lung cancer, Hujoel, et al. observed an increased risk for pancreatic cancer in individuals with periodontitis in the NHANES I population.[23] Positive associations were suggested for individuals with periodontitis, gingivitis, and edentulism with pancreatic cancer, but these relationships were attenuated after adjustment for a limited number of potential confounding factors. No adjustment was made for smoking status in this analysis.

A recently published prospective study of 48,375 male health professionals found a 64% increase in the risk of pancreatic cancer for those reporting a history of periodontal disease at baseline (see Table 1).[3] The association between periodontal disease and pancreatic cancer was stronger among those who were never-smokers, minimizing the possibility of residual confounding by smoking. Number of teeth at baseline was not related to risk of pancreatic cancer; however, measuring tooth loss only over the past 4 years was a statistically significant predictor of pancreatic cancer risk after adjustment for baseline periodontal disease.[3] When both periodontal disease and tooth loss over the past 4 years were assessed jointly, risk of pancreatic cancer increased greatly, with a risk ratio of 2.71 (95% CI: 1.70, 4.32) compared to individuals with neither periodontal disease nor recent tooth loss. These results suggest that recent tooth loss may be a marker for severity of periodontal disease.

To date, three cohort studies, two of which had direct data on periodontal disease,[3,23] suggest that periodontal disease may play a role in the development of pancreatic cancer, independent of other known risk factors such as smoking. More work is needed to confirm these findings and explore potential biological mechanisms.

Total Cancer

Only three studies have examined the relationship between periodontal disease and total cancer mortality, with limited findings.[23,28,44] In the NHANES I Study, baseline periodontitis, gingivitis, and edentulism were associated with increased risk of fatal cancer but the analyses were not adjusted for smoking and therefore difficult to interpret.

Cabrera, et al. examined the relation between tooth loss and cancer mortality in a prospective cohort of 1462 women in western Sweden over a 24 year follow-up period.[28] There was no significant association between tooth loss and all site cancer morbidity or mortality in this study (see Table 1).[28] It should be noted that no association was reported between tooth loss and C-reactive protein in this study.

Similarly, no association was observed between cancer and tooth loss using data from the Glasgow Alumni Cohort, a cohort of 12,223 university students recruited between 1948 and 1968, and followed up for more than 50 years. Oral health was measured by number of lost teeth at baseline, likely before smoking could have greatly impacted oral health.[44] There was no association found between number of teeth lost in young adulthood and cancer mortality (see Table 1). Since the study population was quite young at baseline, it is possible that reported tooth loss may be due primarily to caries and not periodontal disease in these individuals.

Discussion

Potential Confounding of the Association between Tooth Loss, Periodontal Disease and Cancer

It has been suggested that any observed association between tooth loss, periodontal disease and cancer may be due largely to residual confounding by unmeasured smoking or socioeconomic factors.[23,28,45] Smoking has been identified as a major modifiable risk factor for developing periodontal disease, and may be responsible for a large proportion of adult cases in the US, particularly among current smokers.[46,47] Smoking is also associated with increased risk of tooth loss, which may confound the interpretation of the tooth loss-cancer association.[47] The relative risk of destructive periodontal disease for a smoker is estimated to be 5 to 6-fold higher than that of a non-smoker, and may vary based on the definition of disease. This estimate increases for heavy smokers, with a 10- to 15-fold increase in risk of periodontal disease compared to non-smokers.[47] As it is estimated that smoking increases the risk of lung cancer by 20-fold compared to never-smokers,[48] residual confounding could explain the small excess risk observed with periodontal disease. In an analysis of data from the NHANES I Study, the observed increase in lung cancer among individuals with baseline periodontitis did not persist when the analysis was restricted to never-smokers.[23] Additionally, Tu, et al. considered a lung cancer-tooth loss association as evidence of residual confounding due to smoking.[44] It has been suggested that studies on periodontal disease and systemic diseases should be restricted to never-smokers in order to reduce the influence from smoking.[49] However, the concern of residual confounding by smoking may not apply to all cancers. For example, the increase in risk of gastric cancer associated with smoking is much lower than for lung cancer, with the 2004 US Surgeon General's Report providing a relative risk of 1.6 for all stomach cancers.[50] Therefore, a two-fold increase in risk observed between periodontal disease and gastric cancer is unlikely to be explained by smoking alone.

Similarly, for pancreatic cancer, smoking is associated with a two-fold increase in risk and therefore, residual confounding by smoking is unlikely to explain the increase in risk for periodontal disease reported by Michaud et al.[51] Moreover, the association between these conditions was stronger among never-smokers in the Health Professionals Follow-Up Study (RR 2.09 in non-smokers versus 1.63 overall). A stronger association among male never-smokers (RR 1.59 versus RR 1.35 overall) was also reported by Abnet, et al. for tooth loss and upper gastrointestinal cancer.[25]

Other possibilities for confounding exist. Tooth loss resulting from advanced periodontal disease may be related to changes in diet, such as reduced intake of fruits and vegetables.[52] For some cancers, such as oral cancer and gastric cancer, where fruit, vegetable, and vitamin C intake is thought to decrease the risk of cancer, not controlling for diet could result in

confounding. A prospective assessment of diet in the years preceding a diagnosis of periodontal disease may help to determine the direction of the association. In addition, diabetes is another known risk factor for periodontitis and tooth loss that could, to some degree and for certain cancers,[53–55] result in confounding if not adjusted for in the analysis.

Possible Explanations and Biological Mechanisms

In numerous observational studies, tooth loss or periodontal disease have been identified as potential risk factors for cancer at different sites. Several hypotheses have been proposed to explain the observed relationships between periodontal disease and cancer, including chronic systemic 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 more important role.

The relationship between inflammation and cancer has been well documented in the recent literature, although the original hypotheses linking the two appeared more than a century ago.[56–58] Periodontitis is a chronic inflammatory disease attacking the supporting tissues around the teeth, resulting in constant low-grade systemic inflammation with elevated levels of circulating inflammatory markers.[11] Identified inflammatory markers produced in the immune response to periodontal disease include pro-inflammatory plasma cytokines, peripheral white blood cells, prostanoids, proteases including matrix metalloproteinases, and acute-phase proteins.[8,11,56,59] It is also possible 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.[56] Periodontal bacteria may also play a more direct role through local inflammatory responses and carcinogenic transformations.

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 may be a marker of a type of immune function that has implications for tumor growth and progression.

Increased production of carcinogenic nitrosamines is another plausible mechanism which may explain the reported observations. The formation of endogenous nitrosamines in the oral cavity by nitrate-reducing bacteria is promoted by poor oral hygiene and periodontal disease, as well as by tobacco use and certain dietary factors.[60–62] Tooth loss resulting from poor oral hygiene may also contribute to greater nitrosamine production.[40]

Conclusion

To date, only a limited number of studies have reported associations between periodontal disease or tooth loss and cancer risk, and most have focused on oral and upper gastrointestinal tract cancers. Although these studies have been conducted in different populations and have used different measures of periodontal status, associations with oral, gastric and pancreatic cancers tend to persist despite tight control for smoking. The risk of oral cancer is approximately twofold higher in individuals with extensive tooth loss, an estimate that appears to be dose-dependent. A weaker association may exist for tooth loss and gastric cancer, although it may be stronger specifically for non-cardia gastric cancer. Three cohort studies suggest that tooth loss and periodontal disease may be related to the risk of pancreatic cancer. Studies on lung cancer and total cancer suggest an increased risk from periodontal disease, although the associations are weaker, and more likely influenced by smoking and other non-causal factors.

Analyses with adjustment for smoking exposure, including some restricted to non-smokers, have found significant positive associations with different cancer sites. This suggests that although residual confounding by smoking may still be present, it is unlikely to account for all of the observations with tooth loss and periodontal disease. In addition, populations with largely homogenous socioeconomic status such as the Health Professionals Follow-Up Study and the cohort of farmers from rural Linxian, China have reported positive findings, suggesting that socioeconomic factors are not likely to account entirely for the reported relationships.

This review has outlined recent epidemiologic research pointing to a possible role for tooth loss and periodontal disease in carcinogenesis, independent of other known risk factors. Future research is warranted to confirm present findings using more specific measures of periodontal status, and to explore this postulated association among never smokers. If additional epidemiologic data confirm the role of periodontal disease in cancer etiology, further studies will be needed to elucidate the biological mechanisms involved.

Acknowledgments

This work was supported by grant T32 CA 09001 from the National Institutes of Health.

References

1. Papapanou PN. Periodontal diseases: epidemiology. Ann Periodontol 1996;1:1–36. [PubMed: 9118256]
2. Irfan UM, Dawson DV, Bissada NF. Epidemiology of periodontal disease: a review and clinical perspectives. J Int Acad Periodontol 2001;3:14–21. [PubMed: 12666973]
3. Michaud DS, Joshipura K, Giovannucci E, Fuchs CS. A prospective study of periodontal disease and pancreatic cancer in US male health professionals. J Natl Cancer Inst 2007;99:171–175. [PubMed: 17228001]
4. 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;84:924–930. [PubMed: 16183792]
5. Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. Lancet 2005;366:1809–1820. [PubMed: 16298220]
6. Genco RJ, Grossi SG, Ho A, Nishimura F, Murayama Y. A proposed model linking inflammation to obesity, diabetes, and periodontal infections. J Periodontol 2005;76:2075–2084. [PubMed: 16277579]
7. Michalowicz BS, Diehl SR, Gunsolley JC, et al. Evidence of a substantial genetic basis for risk of adult periodontitis. J Periodontol 2000;71:1699–1707. [PubMed: 11128917]
8. Oringer RJ. Modulation of the host response in periodontal therapy. J Periodontol 2002;73 :460–470. [PubMed: 11990448]
9. Slots J, Saygun I, Sabeti M, Kubar A. Epstein-Barr virus in oral diseases. J Periodontal Res 2006;41:235–244. [PubMed: 16827715]
10. Saygun I, Kubar A, Ozdemir A, Slots J. Periodontitis lesions are a source of salivary cytomegalovirus and Epstein-Barr virus. J Periodontal Res 2005;40:187–191. [PubMed: 15733155]
11. Moutsopoulos NM, Madianos PN. Low-grade inflammation in chronic infectious diseases: paradigm of periodontal infections. Ann N Y Acad Sci 2006;1088:251–264. [PubMed: 17192571]
12. Gibson FC, Yumoto H, Takahashi Y, Chou HH, Genco CA. Innate immune signaling and Porphyromonas gingivalis-accelerated atherosclerosis. J Dent Res 2006;85:106–121. [PubMed: 16434728]
13. Wactawski-Wende J. Periodontal diseases and osteoporosis: association and mechanisms. Ann Periodontol 2001;6:197–208. [PubMed: 11887465]
14. Taylor JJ, Preshaw PM, Donaldson PT. Cytokine gene polymorphism and immunoregulation in periodontal disease. Periodontol 2004;35:158–182.
15. Salvi GE, Brown CE, Fujihashi K, et al. Inflammatory mediators of the terminal dentition in adult and early onset periodontitis. J Periodontal Res 1998;33:212–225. [PubMed: 9689617]

16. Joshipura KJ, Wand HC, Merchant AT, Rimm EB. Periodontal disease and biomarkers related to cardiovascular disease. J Dent Res 2004;83:151–155. [PubMed: 14742654]
17. Emingil G, Tervahartiala T, Mantyla P, Maatta M, Sorsa T, Atilla G. Gingival crevicular fluid matrix metalloproteinase (MMP)-7, extracellular MMP inducer, and tissue inhibitor of MMP-1 levels in periodontal disease. J Periodontol 2006;77:2040–2050. [PubMed: 17209789]
18. Haraszthy VI, Zambon JJ, Trevisan M, Zeid M, Genco RJ. Identification of periodontal pathogens in atheromatous plaques. J Periodontol 2000;71:1554–1560. [PubMed: 11063387]
19. Southerland JH, Taylor GW, Moss K, Beck JD, Offenbacher S. Commonality in chronic inflammatory diseases: periodontitis, diabetes, and coronary artery disease. Periodontol 2006;40:130–143.
20. Teng YT, Taylor GW, Scannapieco F, et al. Periodontal health and systemic disorders. J Can Dent Assoc 2002;68:188–192. [PubMed: 11911816]
21. Scannapieco FA, Ho AW. Potential associations between chronic respiratory disease and periodontal disease: analysis of National Health and Nutrition Examination Survey III. J Periodontol 2001;72:50–56. [PubMed: 11210073]
22. Stolzenberg-Solomon RZ, Dodd KW, Blaser MJ, Virtamo J, Taylor PR, Albanes D. Tooth loss, pancreatic cancer, and Helicobacter pylori. Am J Clin Nutr 2003;78:176–181. [PubMed: 12816788]
23. Hujoel PP, Drangsholt M, Spiekerman C, Weiss NS. An exploration of the periodontitis-cancer association. Ann Epidemiol 2003;13:312–316. [PubMed: 12821269]
24. 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;12:847–854. [PubMed: 11714113]
25. Abnet CC, Qiao YL, Dawsey SM, Dong ZW, Taylor PR, Mark SD. Tooth loss is associated with increased risk of total death and death from upper gastrointestinal cancer, heart disease, and stroke in a Chinese population-based cohort. Int J Epidemiol 2005;34:467–474. [PubMed: 15659476]
26. Velly AM, Franco EL, Schlecht N, et al. Relationship between dental factors and risk of upper aerodigestive tract cancer. Oral Oncol 1998;34:284–291. [PubMed: 9813724]
27. Rosenquist K, Wennerberg J, Schildt EB, Bladstrom A, Goran Hansson B, Andersson G. Oral status, oral infections and some lifestyle factors as risk factors for oral and oropharyngeal squamous cell carcinoma. A population-based case-control study in southern Sweden. Acta Otolaryngol 2005;125:1327–1336. [PubMed: 16303683]
28. Cabrera C, Hakeberg M, Ahlqwist M, et al. Can the relation between tooth loss and chronic disease be explained by socio-economic status? A 24-year follow-up from the population study of women in Gothenburg, Sweden. Eur J Epidemiol 2005;20:229–236. [PubMed: 15921040]
29. McCaul LK, Jenkins WM, Kay EJ. The reasons for extraction of permanent teeth in Scotland: a 15-year follow-up study. Br Dent J 2001;190:658–662. [PubMed: 11453155]
30. Martin HE, Pflueger OH. Cancer of the cheek (buccal mucosa). Arch Surg 1935;30:731–747.
31. Zheng TZ, Boyle P, Hu HF, et al. Dentition, oral hygiene, and risk of oral cancer: a case-control study in Beijing, People's Republic of China. Cancer Causes Control 1990;1:235–241. [PubMed: 2102296]
32. Graham S, Dayal H, Rohrer T, et al. Dentition, diet, tobacco, and alcohol in the epidemiology of oral cancer. J Natl Cancer Inst 1977;59:1611–1618. [PubMed: 926184]
33. 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. [PubMed: 1422474]
34. Ringstrom E, Peters E, Hasegawa M, Posner M, Liu M, Kelsey KT. Human papillomavirus type 16 and squamous cell carcinoma of the head and neck. Clin Cancer Res 2002;8:3187–3192. [PubMed: 12374687]
35. Hansson BG, Rosenquist K, Antonsson A, et al. Strong association between infection with human papillomavirus and oral and oropharyngeal squamous cell carcinoma: a population-based case-control study in southern Sweden. Acta Otolaryngol 2005;125:1337–1344. [PubMed: 16303684]
36. 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. [PubMed: 7718736]
37. Garrote LF, Herrero R, Reyes RM, et al. Risk factors for cancer of the oral cavity and oro-pharynx in Cuba. Br J Cancer 2001;85:46–54. [PubMed: 11437401]

38. Talamini R, Vaccarella S, Barbone F, et al. Oral hygiene, dentition, sexual habits and risk of oral cancer. Br J Cancer 2000;83:1238–1242. [PubMed: 11027440]
39. Furniss CS, McClean MD, Smith JF, et al. Human papillomavirus 16 and head and neck squamous cell carcinoma. Int J Cancer 2007;120:2386–2392. [PubMed: 17315185]
40. 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;40:681–687. [PubMed: 16036528]
41. Watabe K, Nishi M, Miyake H, Hirata K. Lifestyle and gastric cancer: a case-control study. Oncol Rep 1998;5:1191–1194. [PubMed: 9683833]
42. Wolff G, Lauter J. [On epidemiology of gastric cancer (author's transl)]. Arch Geschwulstforsch 1976;46:1–14. [PubMed: 962497]
43. Demirer T, Icli F, Uzunalimoglu O, Kucuk O. Diet and stomach cancer incidence. A case-control study in Turkey. Cancer 1990;65:2344–2348. [PubMed: 2346918]
44. Tu YK, Galobardes B, Smith GD, McCarron P, Jeffreys M, Gilthorpe MS. Associations between tooth loss and mortality patterns in the Glasgow Alumni Cohort. Heart 2007;93:1098–1103. [PubMed: 17164486]
45. Joshipura KJ, Ritchie C. Can the relation between tooth loss and chronic disease be explained by socio-economic status? Eur J Epidemiol 2005;20:203–204. [PubMed: 15921035]
46. Tomar SL, Asma S. Smoking-attributable periodontitis in the United States: findings from NHANES III. National Health and Nutrition Examination Survey. J Periodontol 2000;71:743–751. [PubMed: 10872955]
47. Bergstrom J. Tobacco smoking and chronic destructive periodontal disease. Odontology 2004;92:1–8. [PubMed: 15490298]
48. Alberg AJ, Samet JM. Epidemiology of lung cancer. Chest 2003;123:21S–49S. [PubMed: 12527563]
49. Hujoel PP, Drangsholt M, Spiekerman C, DeRouen TA. Periodontitis-systemic disease associations in the presence of smoking--causal or coincidental? Periodontol 2002;30:51–60.
50. Department of Health and Human Services. The Health Consequences of Smoking: A Report of the Surgeon General. Atlanta, GA: Dept. of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2004.
51. Michaud DS. Epidemiology of pancreatic cancer. Minerva Chir 2004;59:99–111. [PubMed: 15238885]
52. Hung HC, Colditz G, Joshipura KJ. The association between tooth loss and the self-reported intake of selected CVD-related nutrients and foods among US women. Community Dent Oral Epidemiol 2005;33:167–173. [PubMed: 15853839]
53. Kuriki K, Hirose K, Tajima K. Diabetes and cancer risk for all and specific sites among Japanese men and women. Eur J Cancer Prev 2007;16:83–89. [PubMed: 17220709]
54. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose level and cancer risk in Korean men and women. Jama 2005;293:194–202. [PubMed: 15644546]
55. Inoue M, Iwasaki M, Otani T, Sasazuki S, Noda M, Tsugane S. Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. Arch Intern Med 2006;166:1871–1877. [PubMed: 17000944]
56. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420:860–867. [PubMed: 12490959]
57. van Kempen LC, de Visser KE, Coussens LM. Inflammation, proteases and cancer. Eur J Cancer 2006;42:728–734. [PubMed: 16524717]
58. Karin M, Lawrence T, Nizet V. Innate immunity gone awry: linking microbial infections to chronic inflammation and cancer. Cell 2006;124:823–835. [PubMed: 16497591]
59. Loos BG. Systemic markers of inflammation in periodontitis. J Periodontol 2005;76:2106–2115. [PubMed: 16277583]
60. Nair J, Ohshima H, Nair UJ, Bartsch H. Endogenous formation of nitrosamines and oxidative DNA-damaging agents in tobacco users. Crit Rev Toxicol 1996;26:149–161. [PubMed: 8688158]

61. Shapiro KB, Hotchkiss JH, Roe DA. Quantitative relationship between oral nitrate-reducing activity and the endogenous formation of N-nitrosoamino acids in humans. Food Chem Toxicol 1991;29:751–755. [PubMed: 1761254]

62. Risch HA. Etiology of pancreatic cancer, with a hypothesis concerning the role of N-nitroso compounds and excess gastric acidity. J Natl Cancer Inst 2003;95:948–960. [PubMed: 12837831]

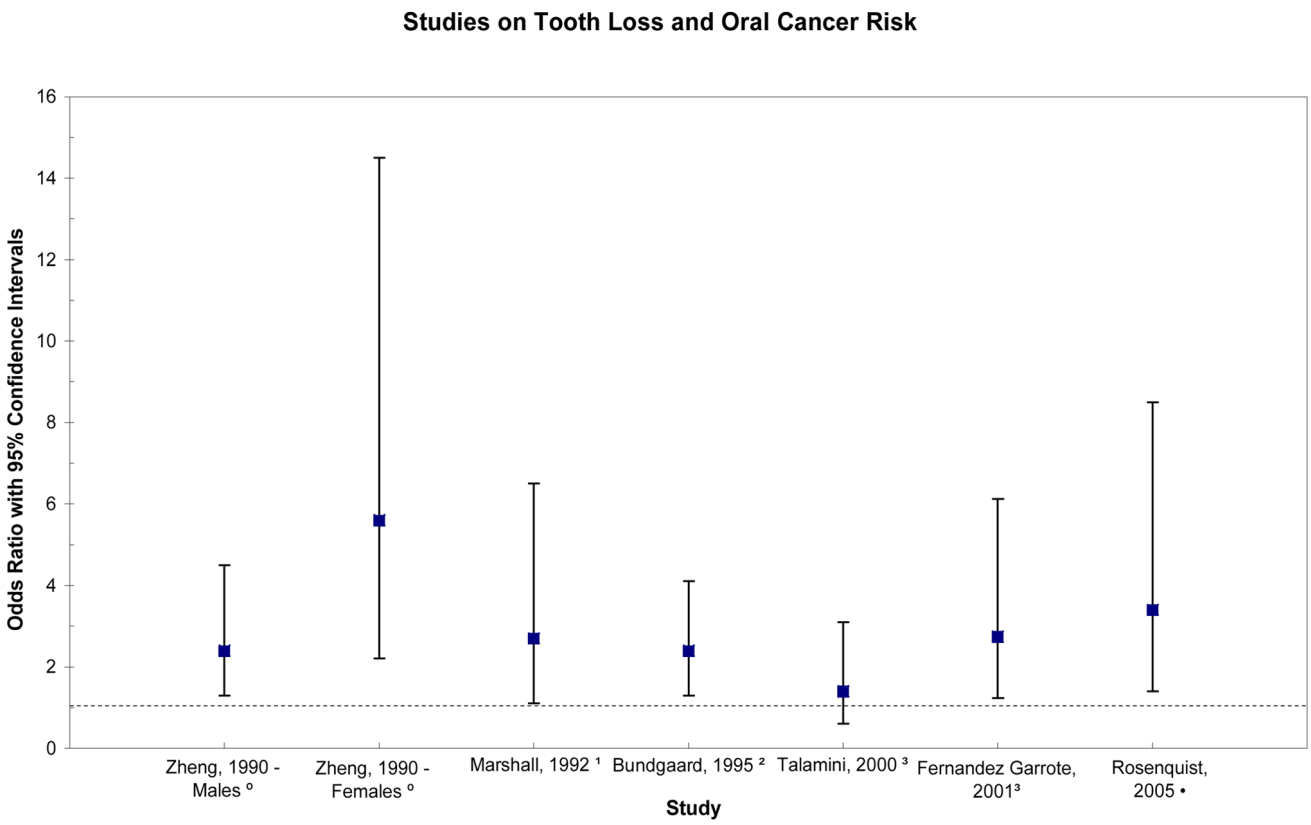

Figure 1.

All estimates are from case-control studies and adjusted for multiple factors including age, gender, tobacco, and alcohol. º tooth lost with replacement; [1] ≥ 11 teeth lost; [2] ≥ 28 teeth lost; [3] ≥ 16 teeth lost;• >20 teeth lost.

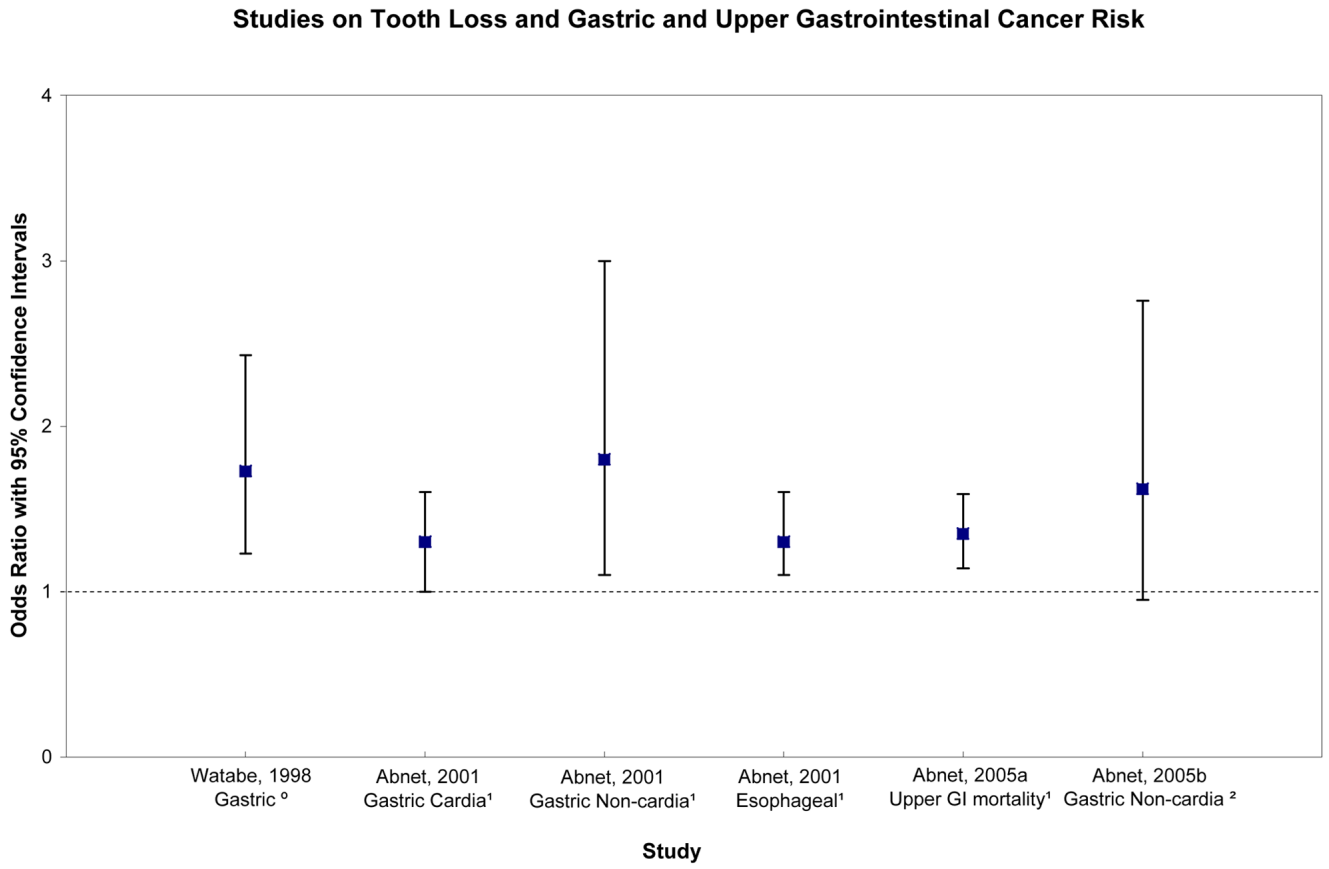

Figure 2.

All estimates are adjusted for multiple factors including age. [o] ≥ 10 teeth lost, case-control study; [1] Median number of teeth lost, cohort study; [2] 11–31 teeth lost, cohort study.

Table 1

Summary of reviewed articles

Cancer Site	Author	Study Design	Population	Oral Health Status	Risk Estimate (95% CI)	Adjusted Factors
Oral	Zheng, et al. 1990 (31)	Case-control	404 case/control pairs; Beijing, People's Republic of China Baseline age range: 18–80	Missing teeth	Males: OR: 2.4 (1.3, 4.5) tooth loss with replacement; 3.7 (2.2, 6.4) without replacement	Age, gender, tobacco (pack-years), alcohol, education (years)
					Females: OR: 5.6 (2.2, 14.5) tooth loss with replacement; 8.3 (3.5, 19.6) without replacement	
	Marshall, et al. 1992 (33)	Case-control	290 case/control pairs; Western New York, USA Baseline age range: ≤50–≥76	Missing teeth	OR: 2.7 (1.1, 6.5) ≥11 teeth lost without replacement	Age, gender, neighborhood, smoking (pack-years), alcohol
	Bundgaard, et al. 1995 (36)	Case-control	161 cases, 400 controls; Denmark Baseline age range: ≤45–>75	Missing teeth	OR: 1.9 (1.1, 3.4) 5–14 teeth remaining	Age, gender, tobacco (lifetime consumption), alcohol
					OR: 2.4 (1.3, 4.1) 0–4 teeth remaining	
	Talamini, et al. 2000 (38)	Case-control	132 cases, 148 controls; Italy Baseline age range: 27–86	Missing teeth	OR: 1.4 (0.6, 3.1) ≥16 teeth lost	Age, gender, fruit and vegetable intake, smoking and drinking habits
					OR: 4.5 (1.8, 10.9) poor oral condition	
	Fernandez Garrote, et al. 2001 (37)	Case-control	200 case/control pairs; Cuba Baseline age range: 25–91	Missing teeth	OR: 2.74 (1.23, 6.12) ≥16 teeth lost	Age, gender, area of residence, education (years), smoking and drinking habits
					OR: 1.82 (0.76, 4.35) 6–15 teeth lost	
					OR: 2.55 (1.24, 5.24) poor oral condition	
Oral	Rosenquist, et al. 2005 (27)	Case-control	132 cases, 320 controls; Southern Sweden Baseline age range: 33–89	Missing teeth, Panoramic radiograph	OR: 5.3 (2.5, 11.3) poor visible plaque score	Age, gender, county, tobacco (lifetime consumption), alcohol
					OR: 3.4 (1.4, 8.5) >20 teeth lost	Unadjusted only *

Cancer Site	Author	Study Design	Population	Oral Health Status	Risk Estimate (95% CI)	Adjusted Factors
					OR: 3.0 (1.0, 8.7) high degree of marginal bone loss	
Upper Gastrointestinal and Gastric	Watabe, et al. 1998 (41)	Case-control	242 cases, 484 controls; Japan Baseline age range: 40–79	Missing teeth	OR: 1.73 (1.23, 2.43) Gastric cancer,, ≥10 teeth lost	Age, gender, residential area
	Abnet, et al. 2001 (24)	Cohort	28868 person cohort; Linxian, People's Republic of China 620 esophagus cases 431 gastric cardia cases 102 gastric non-cardia cases Baseline age range: 40–69	Missing teeth	RR: 1.3 (1.1, 1.6) Esophagus, median split model	Age, gender, tobacco (never vs. ever used regularly for ≥6 months), alcohol
					RR: 1.3 (1.0, 1.6) Gastric cardia, median split model RR: 1.8 (1.1, 3.0) Gastric non-cardia, median split model	
	Abnet, et al. 2005a (25)	Cohort	28790 person cohort; Linxian, People's Republic of China 2625 upper GI deaths Baseline age range: 40–69	Missing teeth	RR: 1.35 (1.14, 1.59) Upper GI cancer mortality	Age, gender, tobacco (never vs. ever used regularly for 6 months), interaction for tooth loss and age
					RR: 1.24 (0.98, 1.58) Females RR: 1.59 (1.03, 2.45) Male never smokers RR: 1.39 (1.06, 1.83) Male ever smokers	
Upper Gastrointestinal and Gastric	Abnet, et al. 2005b (40)	Cohort	29124 male smokers; Finland 179 gastric non-cardia cases 66 esophageal/ gastric cardia cases 49 esophageal cases Baseline age range: 50–69	Missing teeth	HR: 1.46 (0.97, 2.21) Gastric non-cardia, 11–31 teeth lost	Age, education

Cancer Site	Author	Study Design	Population	Oral Health Status	Risk Estimate (95% CI)	Adjusted Factors
					HR: 1.65 (1.09, 2.49) Gastric non-cardia, edentulous HR: 0.86 (0.46, 1.60) Esophageal./gastric cardia, 11–31 teeth lost HR: 0.93 (0.50, 1.75) Esophageal/gastric cardia, edentulous HR: 0.92 (0.46, 1.83) Esophageal, 11–31 teeth lost HR: 0.73 (0.35, 1.55) Esophageal, edentulous	
		Nested case-control	63 gastric non-cardia cases		OR: 1.62 (0.95, 2.76) Gastric non-cardia, 11–31 teeth lost	Age, education, *H. pylori* infection
			75 gastric non-cardia cases		OR: 2.09 (1.22, 3.60) Gastric non-cardia, edentulous	
Lung	Hujoel, et al. 2003 (23)	Cohort	11328 person cohort; USA 191 lung and bronchus cancer deaths Baseline age range: 25–74	Baseline dental examination	HR: 1.73 (1.01, 2.97) Periodontitis	Age, gender, poverty index, education, race, smoking (duration, packs per day, cigar smoking [yes/no], passive smoke [yes/no]), alcohol, vitamin A and vitamin C consumption
					HR: 0.58 (0.12, 2.78) Periodontitis, never-smokers HR: 1.94 (1.14, 3.30) Periodontitis, smokers	
	Tu, et al. 2007 (44)	Cohort	12223 person cohort; Glasgow, Scotland Lung cancer cases unspecified Baseline age range: ≤30 years	Missing teeth	HR: 1.36 (0.71, 2.61) ≥9 teeth lost	Baseline smoking status
Pancreatic	Stolzenberg-Solomon, et al. 2003 (22)	Cohort	29104 men; Finland 174 cancer cases Baseline age range: 50–69	Missing teeth	HR: 1.23 (0.82, 1.85) 11–31 teeth lost	Age, smoking (years), education, urban living, height
					HR: 1.63 (1.09, 2.46) Edentulous	

Cancer Site	Author	Study Design	Population	Oral Health Status	Risk Estimate (95% CI)	Adjusted Factors
	Hujoel, et al. 2003 (23)	Cohort	11328 person cohort; USA 12 pancreatic cancer deaths Baseline age range: 25–74	Periodontitis	OR: 1.77 (0.85, 3.67)	Age, gender
	Michaud, et al. 2007 (3)	Cohort	48375 men; USA 216 cancer cases Baseline age range: 40–75	Missing teeth, periodontal disease history	RR: 1.64 (1.19, 2.26) History of periodontal disease	Age, smoking history (pack-years, time since quit), profession, race, geographic location, physical activity, diabetes, BMI, height, cholecystectomy, NSAID use, multivitamin use, baseline teeth number, dietary factors, total calories
					RR: 2.09 (1.18, 3.71) History of periodontal disease among never smokers	Age, profession, race, geographic location, physical activity, diabetes, BMI, height, cholecystectomy, NSAID use, multivitamin use
					RR: 1.63 (1.12, 2.37) History of periodontal disease among ever smokers	
Total cancer	Hujoel, et al. 2003 (23)	Cohort	11328 person cohort; USA 884 cancer deaths Baseline age range: 25–74	Baseline dental examination	OR: 1.55 (1.25, 1.92) Periodontitis	Age, gender
					OR: 1.43 (1.16, 1.76) Edentulism	
	Cabrera, et al. 2005 (28)	Cohort	1462 women; Gothenburg, Sweden 68 cancer deaths Baseline age range: 38–60	Missing teeth	RR: 1.16 (0.90, 1.49) Cancer mortality, >10 teeth lost	Age, smoking, age at first birth, parity, husband's occupational category
					RR: 1.08 (0.92, 1.28) Cancer morbidity, >10 teeth lost	
	Tu, et al. 2007 (44)	Cohort	12223 person cohort; Glasgow, Scotland 549 cancer deaths Baseline age range: ≤30 years	Missing teeth	HR: 1.00 (0.98, 1.02) Cancer mortality, missing teeth as continuous variable	Age, year of birth, gender, smoking (categorical), BMI, systolic blood pressure, father's socioeconomic status

Cancer Site	Author	Study Design	Population	Oral Health Status	Risk Estimate (95% CI)	Adjusted Factors

* Adjusted estimate not given in text