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Tooth loss and cancer mortality in Cancer Prevention Study-I

By

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Degree to be awarded: Master of Public Health

Applied Epidemiology, Executive MPH

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Tooth Loss and Cancer Mortality in Cancer Prevention Study-I

By

Joan Kramer

M.D., St Louis University, 1991

B.S., Loyola Marymount University, 1987

Thesis Committee Chair: Veronika Fedirko, Ph.D.

An abstract of

a thesis submitted to the Faculty of the Rollins School of Public Health of Emory University

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2019

Abstract

Tooth Loss and Cancer Mortality in Cancer Prevention Study-I

By Joan Kramer, M.D.

Background: Oral health has been associated with cancer risk, but prospective data are limited, and residual confounding by smoking remains a concern.
Methods: Cox proportional hazard regression was used to estimate multivariable-adjusted hazard ratios (HRs) for tooth loss associated with death from specific cancer types among 879,595 Cancer Prevention Study I participants who provided information about tobacco use and tooth loss and were cancer free at baseline in 1959.
Results: During follow up through 1972, there were 29,711 cancer-related deaths, including 14,041 in never smokers. Loss of eight teeth was associated with a higher risk of dying from cancers of the head and neck (HR=1.13; 95% confidence interval (CI), 1.07-1.20), esophagus (HR=1.12; 95%CI, 1.04-1.22), stomach (HR=1.06; 95%CI, 1.02-1.10), liver (HR=1.16; 95%CI, 1.08-1.24), pancreas (HR=1.04; 95%CI, 1.01-1.08), lung (HR=1.12; 95% CI, 1.10-1.15), cervix (HR=1.10; 95%CI, 1.02-1.19), and bladder (HR=1.13; 95%CI, 1.07-1.20). Among nonsmokers, tooth loss was positively associated with death from cancer of the head and neck (per 8 teeth lost, HR=1.13; 95% CI, 0.99-1.28), esophageal cancer (per 8 teeth, HR=1.22; 95%CI, 1.04-1.43), liver cancer (HR=1.11; 95%CI, 1.00-1.22), and lung cancer (per 8 teeth, HR=1.06; 95%CI: 1.00-1.12).
Conclusions: Our results support an association, independent of smoking, between tooth loss and death from cancers of esophagus, head and neck, liver, and possibly lung. Increasing evidence that oral health affects cancer risk and mortality may indicate a possible role of dental care in the prevention of cancer.

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Chapter 1: Background and Introduction

Tooth loss, periodontitis, and oral health

Periodontitis is a chronic infectious disease leading to the loss of supporting tissues of the teeth [1] which can lead to tooth loss. [2-4]. The prevalence of periodontitis varies by age and country [5], and has been estimated at 35% to 50% in adults in the United States (US) [6, 7]. Risk factors for periodontitis include increasing age [6, 7], male sex [6, 7], tobacco smoking [8, 9], impaired glucose tolerance [10] and diabetes [11], and lower socioeconomic status [7]. Genetics may also play a role, with variants in the genes for the vitamin D receptor (VDR), Fc gamma receptor IIA (Fc-ɣRIIA), and Interleukin 10 (IL10) associated with the risk of periodontitis [12]. Smoking represents a major modifiable risk factor, with almost 75% of periodontitis in current smokers attributable to smoking [13]. In US adults, 42% of periodontitis cases are attributed to current smoking, and 11% of cases attributed to former smoking [13].

Risk of tooth loss is associated with a number of measures of oral health in multivariable models, including worsening severity of periodontal disease [14-19], previous tooth loss [14, 16], and the number of filled or decayed surfaces at baseline [14-16]. The relative contributions of dental caries and periodontal disease to tooth loss varies in studies [20-34] Although caries is more often cited as the most common cause of tooth loss, these conditions these can occur together [14, 22, 35] and both may contribute to loss of a tooth. Other factors that are associated with tooth loss in multivariable models include older age [16, 29, 36], tobacco smoking [3, 14, 17, 18, 19, increased body mass index {Bole, 2010 #267, 37] and obesity [38], and lower income [39], with an inverse association with increased education [14]. Diabetes increases the risk of tooth loss [40] overall, and specifically increases the risk of tooth loss due to periodontal reasons [3]. Dietary risk factors for tooth loss include alcohol consumption [41],

lower calcium intake [42], and higher sugar intake [43]. Many of the risk factors for tooth loss are also risk factors for periodontitis, and so their effects may be mediated by periodontal disease.

Tooth loss has been used as a surrogate for periodontal disease in studies [44], however because tooth loss has other causes, it is an imperfect marker of periodontal disease. Some authors maintain that it is better thought of as a marker for oral health. [14, 44]

Poor oral health, as measured by tooth loss and/or periodontal disease has been associated with chronic condition and diseases, such as hypertension [45], incident diabetes [46], stroke [47-50], cardiac disease [45, 50-52], and respiratory disease [51]. Periodontal disease could affect the risk of systemic diseases through exposure of distant organs and tissues to an altered oral microbiome through the transient bacteremia that is known to occur due to mastication and tooth cleaning. [53, 54] In addition, although the inflammation due to periodontal disease is most obvious in the mouth, it is accompanied by increased circulating levels of inflammatory markers [1, 36, 55], which could indicate systemic effects. These mechanisms could also plausibly contribute to an association between poor oral health and cancer.

Oral health and cancer

Total cancer

Associations between total cancer incidence or mortality and measures of oral health have been examined in three cohorts [56-59]. Periodontal disease was associated with total cancer risk in the Health Professionals Follow-up Study (HPFS; HR = 1.14; 95% CI, 1.07-1.22) [57]. In an updated analysis of the HPFS cohort limited to never-smokers, men reporting periodontitis at

baseline had a 13% increase in total cancer risk, with a 45% increase seen in men with more severe periodontitis (based on having both periodontitis and <17 remaining teeth) [59]. Similarly, in the Atherosclerosis Risk in Communities (ARIC) cohort, severe periodontitis was associated with an increased risk of total cancer (HR = 1.24; 95% CI, 1.07 to 1.44) [58]. Periodontal disease was also associated with cancer mortality in the National Health and Nutrition Examination Survey (OR = 1.55; 95% CI, 1.25-1.92) [56]. Periodontal disease was associated with total cancer risk in a retrospective cohort from Taiwan (HR=1.23; 95% CI, 1.20–1.27), however the analysis did not adjust by tobacco use [60]. In a cohort of Swedish twins, periodontal disease was associated with total cancer incidence in the overall cohort (HR=1.15; 95% CI, 1.01 -1.32). However, in the co-twin analysis, the association of periodontal disease and cancer risk was limited to dizygotic twins (HR=1.5; 95% CI, 1.04- 2.17), with no significant association seen in monozygotic twins (HR=1.07; 95% CI, 0.63- 1.81), suggesting that shared genetics could be, at least in part, responsible for the association. [61]

Head and neck cancers

Three previous case control studies have not found an association between tooth loss and head and neck cancers [62-64], however an association with oral cancer was seen in a number of case-control studies [65-69]. A linear dose-response meta-regression using estimates from 7 case-control studies found a 0.03 (95% CI, 0.01- 0.05) increase in the odds ratio for oral cancer with each additional tooth lost [44]. A cohort study, the Health Professionals Follow-up Study (HPFS), that examined the relationship between tooth loss and oral/oropharyngeal cancer did not find a significant association [57].

Results of studies of periodontal disease and head and neck cancer and oral cancer have been mixed. Periodontal disease has been associated with increased risk of oral cancer in case-control

studies from Brazil [70], Germany [71], and Japan [60], and with increased risk of head and neck cancer in a study from the Netherlands [72]. A prospective study used an insurance claims database in Taiwan to compare a cohort of patients with periodontitis to a cohort with gingivitis, and found a higher risk of incident oral cancer in the periodontitis cohort [73], however this analysis was not adjusted for smoking. Similar findings were seen when those without periodontal disease were used as the comparison group, but, again, the analysis was not adjusted for smoking/tobacco [60]. In the HPFS, periodontal disease was not associated with an increased risk of oral/oropharyngeal cancer [57] in the overall cohort, but in an updated analysis restricted to never-smokers, those with both periodontitis and <17 teeth had an increased risk of esophageal and head and neck cancers (composite outcome) [59].

Esophageal cancer

Several case-control studies have examined associations between poor oral health and esophageal cancer [62, 63, 74, 75], with most finding some evidence of increased risk. Loss of more than 6 teeth was associated with increased risk of esophageal SCC in case control study in China [74], however in case control studies in Europe and South America, while missing 6-15 teeth was associated with increased risk of esophageal cancer, missing more than 15 teeth was not [62]. In a Japanese case control study, having 8 or fewer teeth remaining was associated with an increased risk of esophageal cancer (for 1-8 teeth remaining, OR=1.93; 95% CI, 1.24-3.01, for no teeth remaining OR= 2.36; 95% CI, 1.17-4.75) [63]. A case control study in Iran, found that more decayed missing or filled teeth (composite) was associated with an increased risk of esophageal squamous cell carcinoma [75].

Results from prospective studies of oral health and esophageal cancer have been mixed. In a Swedish registry-based analysis, oral disease (including but not limited to periodontal disease)

was associated with increased risk of esophageal adenocarcinoma but not esophageal squamous cell carcinoma, however this study could only use indirect markers of smoking and alcohol use in the analysis [76]. Tooth loss was not associated with increased risk of esophageal cancer in the Alpha-Tocopherol, Beta-Carotene Cancer (ATBC) Prevention Study cohort which was limited to male smokers [77] or the HPFS [57]. The HPFS also examined the possible association between periodontal disease and esophageal cancer, and did not find an increased risk [57]. In a Chinese cohort, tooth loss was associated with increased risk of esophageal cancer (RR=1.3; 95% CI, 1.0-1.6) [78].

Lung cancer

Associations between oral health and risk of lung cancer have been examined in 7 cohort studies [56-58, 61, 79-81] and 2 case-control studies [60, 63]. Most of these studies reported positive associations, although no study has reported a clear association in never smokers. Loss of 8 or more teeth was associated with an increased risk of lung cancer in the HPFS (for 17-24 teeth remaining, HR=1.34; 95%CI, 1.10–1.63, for 0-16 teeth remaining HR=1.70; 95%CI, 1.37–2.11) [57]. Periodontal disease was also associated with an increased risk of lung cancer in the HPFS cohort (HR=1.36; 95%CI, 1.15–1.60) [57]. In the National Health and Nutrition Examination Survey (NHANES) I Epidemiologic Follow-up Study, periodontitis was associated with an increased risk of lung cancer (HR=1.73; 95%CI, 1.01-2.97), however there was no significant increase in the risk lung cancer associated with complete tooth loss [56]. In the Buffalo OsteoPerio Study cohort, which included only post-menopausal women, periodontal disease (based on alveolar crestal height) was associated with increased risk of lung cancer (per 1 mm loss of alveolar crestal height in worst site HR=1.34; 95 % CI, 1.08-1.66) [79]. In the Women's Health Initiative (WHI) observational cohort, which was also limited to post-menopausal

women, periodontal disease was associated with an increased risk of lung cancer (HR=1.24; 95 % CI, 1.07-1.45), however no increase in risk was seen when the analysis was limited to never smokers (HR=1.02; 95 % CI, 0.68-1.53) [80]. Within a Swedish twin cohort, periodontal disease was not associated with a significant increase in the risk of lung cancer (HR=1.41; 95% CI, 0.81-2.46) [61]. In the ARIC study cohort, both edentulous subjects and those with severe periodontitis had an increased risk of lung cancer [58]. Tooth loss was not associated with lung cancer mortality in the Glasgow alumni cohort [81]. In a case control of chronic periodontitis, no increased risk of respiratory cancer was seen in those with chronic periodontitis [60]. In a case-control study in Japan, those who were edentulous had increased risk of lung cancer (HR=1.54; 95%CI, 1.05-2.27) [63].

Pancreatic cancer

A total of 7 studies have examined associations between measures of oral health and pancreatic cancer [57, 61, 82-86]. Although periodontal disease was associated with pancreatic cancer risk in the HPFS (HR=1.54; 95% CI, 1.16–2.04), tooth loss was not [57]. Periodontal disease was also associated with pancreatic cancer in a cohort of Swedish twins (HR = 2.06; 95% CI, 1.14, 3.75) [61]. In an analysis using insurance claims data from Taiwan, periodontal disease was associated with increased risk of pancreatic cancer (HR=1.55; 95%CI, 1.02-2.33), however only surrogates for alcohol and smoking were available for the analysis [85]. In the Black Women's Health Study (BWHS), the incidence of pancreatic cancer was significantly associated with tooth loss (HR=1.94; 95% CI, 1.04–3.64), with evidence of increased risk with increased numbers of teeth lost (1 to 4 teeth lost, HR=1.72; 95% CI, 0.86–3.43; 5 or more teeth lost, HR=2.20; 95%CI, 1.11–4.33). In the BWHS analysis, tooth loss was significantly associated with pancreatic cancer incidence in non-smokers (includes never and former smokers; HR=2.42; 95% CI, 1.09–5.37), but

not in smokers (HR=1.31; 95%CI, 0.48–3.58). In addition, the incidence of pancreatic cancer was not significantly associated with periodontal disease in the BWHS (periodontal disease with tooth loss, HR=1.58; 95%CI, 0.70–3.57; periodontal disease without tooth loss, HR=1.77; 95%CI, 0.57–5.49). [86] Neither periodontal disease nor being edentulous was associated with a significant increased pancreatic cancer mortality in the NHANES I Epidemiologic Follow-up Study [56]. Edentulous patients had a higher risk of pancreatic cancer in the ATBC cohort [82]. In a Swedish registry study, tooth loss was not significantly associated with pancreatic risk [83]. A nested case control study among subjects from the Cancer Prevention Study II and the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, found that subjects that carried the oral pathogens *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitan* had higher risks of pancreatic cancer [84]. Tooth loss not associated with pancreatic cancer risk in a case control study in Japan [63].

Gastric cancer

A smaller number of studies [56, 57, 76-78, 87] have examined associations between oral health and risk of gastric cancer, providing some evidence for an association, particularly for non-cardia gastric cancer. In the ATBC cohort, edentulous subjects had an increased risk of gastric non-cardia cancer (HR=1.65; 95% CI, 1.09- 2.49), but no statistically significant associations were found between tooth loss and esophageal/gastric cardia adenocarcinoma [77]. Neither tooth loss nor periodontal disease associated with risk of gastric cancer in HPFS [57] or NHANES [56]. Tooth loss was associated with an increased risk of gastric cancer in a Dutch cohort (gastric cardia cancer, HR=1.3; 95%CI, 1.0-1.6; gastric non-cardia cancer, HR=1.8; 95%CI, 1.1-3.0) [78]. In a Swedish registry study, oral disease (including but not limited to periodontal disease) was not associated with gastric cancer [76]. Periodontal disease was not associated with gastric cancer in

a cohort of Swedish twins [61]. In a case-control study from Iran, an increased number of decayed, missing, and/or filled teeth was associated with an increased risk of gastric cancer [87]. Tooth loss not associated with gastric cancer risk in a case control study in Japan [63].

Colorectal cancer

Studies of oral health and risk of colorectal cancer have yielded mixed results. Neither tooth loss nor periodontal disease associated with risk of colorectal cancer in HPFS cohort [57], the ARIC cohort [58], or NHANES [56]. Periodontal disease was associated with an increased risk of colorectal cancer in a cohort of Swedish twins (HR = 1.62; 95% CI, 1.13- 2.33) [61] and with increased risk of colorectal mortality in the National Health and Nutrition Examination Survey (RR=3.58; 95% CI, 1.15-11.16) [88]. Tooth loss was not associated with colorectal cancer risk in the cohorts from the Southern Community Cohort Study, the Shanghai Men's Health Study (SMHS), or the Shanghai Women's Health Study (SWHS) [89]. However, tooth loss was associated with increased risk of colorectal cancer in the Nurses' Health Study cohort (for women with <17 teeth, HR=1.20; 95%CI, 1.04-1.39 as compared to those with 25-32 teeth) [90]. Tooth loss not associated with colon cancer risk in a case control study in Japan [63].

Liver cancer

The few studies that have examined the relationship between oral health and liver cancer [63, 91-93] have had mixed results. A case control study in Japan found an increased risk of liver cancer in those with 9-20 teeth remaining (HR=1.74; 95%CI, 1.04-2.89). However, a significant increased risk of liver cancer was not seen in those who had lost more teeth (1-8 teeth remaining: HR=1.64; 95% CI, 0.90-2.98; no teeth remaining: HR=1.35, 95% CI, 0.51-3.58), with no dose response relationship between number of teeth lost and liver cancer risk evident (p for trend 0.113). [63]

Tooth loss was associated with liver cancer in a cohort of male smokers (the ATBC study), however the HRs were similar for those who had lost 11-31 permanent teeth (HR=1.42; 95% CI, 1.01-1.98) and those who had lost all 32 teeth (HR=1.45; 95% CI, 1.00-2.10) [91].

No significant association of tooth loss with liver cancer was seen in a Chinese cohort (HR=1.27; 95%CI, 0.96- 1.67). However, a significant association of liver cancer with tooth loss was seen when the analysis was limited to women (HR=1.64; 95%CI, 1.04-2.59) [92].

Periodontitis was found to be associated with a higher stage of liver cancer [93].

Bladder cancer

The few studies to date examining the association of oral health and bladder cancer have not found an association [57, 61, 63]. Neither tooth loss nor periodontal disease was associated with bladder cancer incidence in the HPFS cohort [57]. Periodontal disease was not associated with bladder cancer in a cohort of Swedish twins [61]. In addition, tooth loss was not found to have a significant association with bladder cancer in a case control study in Japan [63].

Breast cancer

Most of the studies examining oral health and breast cancer have not found a significant association, however two studies did. Self-reported periodontal disease was associated with breast cancer risk in the WHI observational cohort (HR=1.11; 95% CI, 1.00–1.23) [94], however periodontal disease as determined by measurements of alveolar crestal height was not associated with risk of breast cancer in a similar population [79]. Periodontitis was associated with breast cancer risk in a retrospective Taiwanese cohort (HR=1.23; 95% CI, 1.11–1.36), however the analysis did not adjust for smoking [60]. In a cohort of Swedish twins, no

association between tooth loss and breast cancer was seen [61]. In addition, no association of periodontitis or loss of all teeth with breast cancer was seen in NHANES [56].

Uterus cancer

Uterine (corpus) cancer was associated with tooth loss in a cohort of Swedish twins (HR=2.20; 95%CI, 1.16- 4.18) [61]. However, periodontal disease was not associated with endometrial cancer in a cohort of post-menopausal women [79].

Prostate cancer

Tooth loss was associated with prostate cancer risk in a cohort of Swedish twins (HR=1.47; 95%CI, 1.04- 2.07) [61]. However, no association of periodontitis or the loss of all teeth with prostate cancer was seen in NHANES [56].

Summary

Confounding by smoking is an important potential limitation of nearly all previous studies of oral health and cancer risk, as smoking is strongly associated with both periodontitis [13] and tooth loss [3, 41, 95-98], as well as with many types of cancer [99].

To help clarify the association between oral health and cancer risk, I analyzed the association between tooth loss and cancer mortality in the Cancer Prevention Study I (CPS-I) cohort. This cohort included nearly one million participants, making this the largest study of oral health and cancer risk to date. In addition, over 400,000 participants indicated at study entry that they had never used tobacco, providing a large group in which the association between tooth loss and cancer mortality can be examined without confounding by smoking or other forms of tobacco use.

Chapter 2: Tooth Loss and Cancer Mortality in Cancer Prevention Study-I

Abstract

Background: Oral health has been associated with cancer risk, but prospective data are limited, and residual confounding by smoking remains a concern.

Methods: Cox proportional hazard regression was used to estimate multivariable-adjusted hazard ratios (HRs) for tooth loss associated with death from specific cancer types among 879,595 Cancer Prevention Study I participants who provided information about tobacco use and tooth loss and were cancer free at baseline in 1959.

Results: During follow up through 1972, there were 29,711 cancer-related deaths, including 14,041 in never smokers. Loss of eight teeth was associated with a higher risk of dying from cancers of the head and neck (HR=1.13; 95% confidence interval (CI), 1.07-1.20), esophagus (HR=1.12; 95%CI, 1.04-1.22), stomach (HR=1.06; 95%CI, 1.02-1.10), liver (HR=1.16; 95%CI, 1.08-1.24), pancreas (HR=1.04; 95%CI, 1.01-1.08), lung (HR=1.12; 95% CI, 1.10-1.15), cervix (HR=1.10; 95%CI, 1.02-1.19), and bladder (HR=1.13; 95%CI, 1.07-1.20). Among nonsmokers, tooth loss was positively associated with death from cancer of the head and neck (per 8 teeth lost, HR=1.13; 95% CI, 0.99-1.28), esophageal cancer (per 8 teeth, HR=1.22; 95%CI, 1.04-1.43), liver cancer (HR=1.11; 95%CI, 1.00-1.22), and lung cancer (per 8 teeth, HR=1.06; 95%CI: 1.00-1.12).

Conclusions: Our results support an association, independent of smoking, between tooth loss and death from cancers of esophagus, head and neck, liver, and possibly lung. Increasing evidence that oral health affects cancer risk and mortality may indicate a possible role of dental care in the prevention of cancer.

Introduction and background

Dental decay (caries) and periodontitis are the major causes of tooth loss in adults. [2-4]. Periodontitis is a chronic infectious disease in which a localized oral infection is met with an exaggerated host inflammatory response leading to the loss of supporting tissues of the teeth [1], which can lead to tooth loss. [2-4]. The prevalence of periodontitis varies by age and country [5], and has been estimated at 35% to 50% in adults in the United States (US) [6, 7]. Risk factors for periodontitis include increasing age [6, 7], male sex [6, 7], tobacco smoking [8, 9], and impaired glucose tolerance [10] and diabetes [11], and lower socioeconomic status [7]. Genetics may also play a role, with variants in the genes for the vitamin D receptor (VDR), Fc gamma receptor IIA (Fc-ɣRIIA), and Interleukin 10 (IL10) associated with the risk of periodontitis [12]. Smoking represents a major modifiable risk factor, with almost 75% of periodontitis in current smokers attributable to smoking [13]. In US adults, 42% of periodontitis cases are attributed to current smoking, and 11% of cases attributed to former smoking [13].

Risk of tooth loss is associated with a number of measures of oral health in multivariable models, including worsening severity of periodontal disease [14-19], previous tooth loss [14, 16], and the number of filled or decayed surfaces at baseline [14-16]. Other factors that have been associated with tooth loss include older age [14, 16, 29, 36], tobacco smoking [3, 14, 17-19], diabetes [3, 40] increased body mass index [19, 37, 38], and lower income [39], with an inverse association with increased education [14]. Dietary risk factors for tooth loss include alcohol consumption [41], lower calcium intake [42], and higher sugar intake [43]. Many of the risk factors for tooth loss are also risk factors for periodontitis, and so their effects may be mediated by periodontal disease.

Tooth loss has been used as a surrogate for periodontal disease in epidemiologic studies [44], however because tooth loss has other causes, it is an imperfect marker of periodontal disease. Some authors maintain that it is better thought of as a marker for oral health. [14, 44]

Poor oral health, as measured by tooth loss and/or periodontal disease has been associated with chronic conditions and diseases, such as hypertension [45], incident diabetes [46], stroke [47-50], cardiac disease [45, 50-52], and respiratory disease [51]. The mechanisms underlying the link between oral health and systemic disease can be traced to the altered oral microbiome seen in periodontal disease. Components of the microbiome (such as bacteria and their lipopolysaccharides -LPS) can enter the bloodstream during mastication and tooth cleaning, exposing distant organs and tissues. [53, 54] Additionally, the salivary microbiome, which is part of the oral microbiome, is constantly being swallowed, exposing the digestive tract to its contents.[100] *Porphyromonas gingivalis*, a bacterium in chronic periodontitis, produces LPS that bonds to Toll Like Receptor-4, which leads to production and secretion of pro-inflammatory cytokines.[101] Although the inflammation due to periodontal disease is most obvious in the mouth, it is accompanied by increased circulating (blood) levels of inflammatory markers [1, 36, 55], which could indicate systemic effects. In addition, oral bacteria generate substances that can affect health, such as nitric oxide, which influences blood pressure [102], and the carcinogen acetaldehyde [103]. These effects of the oral microbiome could plausibly contribute to the association between poor oral health and cancer.

A considerable number of epidemiologic studies, most published in the last 10 years, have reported positive associations between periodontal disease and/or tooth loss and either total cancer risk, or risk of individual types of cancer [44]. Such associations have most

consistently been observed for oral, lung, and pancreatic cancers, although data on other individual cancer sites from prospective studies is limited [44].

Smoking is strongly associated with periodontitis [13], tooth loss [3, 41, 95-98], and many types of cancer [99], making confounding by smoking an important consideration in the study of the association of oral health and cancer risk. Attempts to minimize this confounding by stratifying on smoking status in previous studies has been challenging due to lower numbers of cases in non-smokers. [56, 57, 80, 86]

To help clarify the association between oral health and cancer risk, we analyzed the association between tooth loss and mortality from cancer in the Cancer Prevention Study I (CPS-I) cohort. This cohort included nearly one million participants, making this the largest study of oral health and cancer risk to date. In addition, over 400,000 participants indicated at study entry that they had never used tobacco, providing a large group in which the association between tooth loss and cancer mortality can be examined without confounding by smoking or other forms of tobacco use.

Methods

Study population

Enrollment and data collection procedures for CPS-I were reported previously. Briefly, in 1959, 1,051,031 adults (456,487 men and 594,544 women) 30 years of age and older were enrolled by American Cancer Society volunteers who asked their friends and neighbors to complete a self-administered questionnaire that included information on demographic, medical,

and lifestyle factors. Participants were followed for mortality through the end of the study in 1972. [104, 105]

For this analysis, we excluded participants who self-reported any cancer other than non-melanoma skin cancer at enrollment (n = 7,167) and those with missing or incomplete data on tobacco use (n = 80,942).

Tooth loss

The initial questionnaire asked the participants the number of teeth they had lost and whether they had full or partial dentures. Based on the distribution of the stated number of teeth lost, a categorical variable for tooth loss was created to divide the cohort into approximate quartiles: 0-4 teeth lost, 5-15 teeth lost, 16-31 teeth lost, and all 32 teeth lost. For some participants who did not report number of teeth lost, answers regarding dentures were used to impute the number of teeth lost. Specifically, participants who did not report number of teeth lost but did report full dentures were assigned a value of 32 teeth lost. Similarly, participants who did not report number of teeth lost (n = 71,154, 8%) but reported partial dentures were assigned a value of 24 teeth lost, the mean value for teeth lost among those reporting losing 16-31 teeth (i.e. half or more, but not all, of their teeth lost). If answers to the tooth loss and denture questions conflicted, such as for someone with full dentures who reported loss of only two teeth, tooth loss was considered unclassifiable, and that subject was removed from the analytic cohort. A total of 17,494 participants were eliminated the analysis due to missing or unclassifiable data regarding tooth loss, resulting in an analytic cohort of 879,595 participants, 528,711 (60%) women and 350,884 (40%) men. For most analyses, tooth loss was modeled as a continuous variable using the numeric value for teeth lost divided by

eight, to give results per eight teeth lost (one quarter of the normal original number of permanent teeth).

Outcomes

The participants' vital status over the 12 years of the study was determined through personal inquiry by the volunteer that recruited them. In addition, vital status was determined by questionnaires sent in 1961, 1963, 1971, and 1975, as well as by checks of vital status data in selected states for all state residents. By December 1972, 18 % had died. Death certificates were obtained for 97% percent of deaths and coded to the International Classification of Diseases, Seventh Revision. [105] The 110,004 participants (12.5%) in the analytic cohort who were lost to follow-up were censored on their last contact date.

This analysis examined mortality from any cancer (n = 29,711) and specific cancer types with at least 250 deaths in the analytic cohort, which included deaths from cancers of the lung (n = 4899), colon and rectum (n = 4659), female breast (n = 2870), pancreas (n = 1924), stomach (n = 1481), prostate (n = 1479), ovary (n = 1247), brain (n = 892), bladder (n = 756), head and neck (n = 617), kidney (n = 606), liver (n = 470), gallbladder and bile duct (n = 453), cervix (n = 366), esophagus (n = 347), and uterus (n = 273), as well as leukemia (n = 1359), non-Hodgkin lymphoma (n = 943), multiple myeloma (n = 506), Hodgkin disease (n = 268), and melanoma (n = 272). Leukemia included all acute and chronic leukemia. Head and neck cancer included cancers of the lip, tongue, salivary gland, mouth, pharynx (including oropharynx, hypopharynx, nasopharynx), nasal cancer, and larynx. Cancer of the oral cavity and oropharynx included cancers of the lip, tongue, mouth, and oropharynx. The analysis of prostate cancer mortality was limited to males, while the analyses of breast, cervical, uterus, and ovarian cancers were limited to females.

Statistical analysis

We used Cox proportional hazards regression to estimate hazard ratios (HRs)and 95% confidence intervals (CIs) for cancer mortality. Participants contributed time at risk from enrollment until cancer death, death due to other causes, end of study in 1972, or date of last contact. The proportional hazards assumption was assessed using likelihood ratio tests by comparing multivariable-adjusted models with and without cross-product terms for follow-up time and tooth loss (continuous). Tooth loss fulfilled proportional hazard requirements for all cancer mortality outcomes except all/any cancer mortality, therefore analysis for that outcome will not be presented here.

Crude models were adjusted for age and sex using the stratified Cox proportional hazards regression, with single year age strata. Multivariable models were additionally adjusted for race, education, tobacco smoking (including cigarettes and cigars/pipes), smokeless tobacco use, body mass index (BMI), physical activity, vegetable intake, alcohol intake, history of diabetes, and doctor visit within year of enrollment. All covariates were based on status reported in the initial questionnaire in 1959, and, with the exception of smoking status (described below), using the categories shown in Table 1. Tooth loss was modeled as a continuous variable in both the crude and multivariable models (tables 2 and 3), with the multivariable models repeated after splitting follow up time into four year increments (table S3). For cancer sites for which mortality had a significant association with tooth loss, the multivariable model was repeated with tooth loss as a categorical variable (table S1).

Smoking status was categorized as current cigarette, current cigar/pipe, former cigarette, former cigar/pipe, or never smoker. The current cigarette category was then classified into 10 subcategories based on combinations of duration [<30 years (y), 30-39 y, 40 and more

years], and amount of cigarettes smoked [<1 pack per day (PPD), 1 PPD, >1 PPD], with a separate level for unknown amount or duration number of cigarette pack-years. Former cigarette smokers were classified into 13 subcategories based on combinations of amount of cigarettes smoked (<1 PPD, 1 PPD, >1 PPD, and unknown PPD) and time since quitting (<10 y, 10-19 y, and 20 y and higher), with separate level for unknown time since quitting. Cigar/pipe smoking was classified as current or former. Participants who had smoked both cigarettes and cigars or pipes were assigned to the highest risk category that was applicable to them (current cigarette smoker, then former cigarette smoker quit less than 10 years ago, then current cigar or pipe smoker, then former cigarette smoker, then former cigar or pipe smoker). Smokeless tobacco was treated as a separate covariate, and was classified as never, occasional, regular, and former. For analyses examining the association of tooth loss with cancer mortality stratified by cigarette smoking status, the cohort was divided into 3 sub-groups (never, current, and former cigarette smokers) after exclusion of ever users of cigars/pipes or smokeless tobacco. Models including only current smokers were still adjusted for combinations of duration and cigarettes per day as described above, with models including only former smokers adjusted for amount smoked and time since quit. Likelihood ratio tests were used to test for multiplicative interactions of current and former smoking status on the associations of tooth loss with risk of death from specific cancer types after excluding ever users of cigars/pipes and/or smokeless tobacco.

Interaction terms between the continuous variable for tooth loss and specific covariates (age at enrollment in years, sex, and education) were created and tested using the multivariable models. For those outcomes in which the interaction was significant by the Wald test, results were examined separately among participants stratified by that covariate.

Analyses were performed using SAS 9.4 (Cary, NC). Statistical tests were two-sided, and a P value of less than 0.05 was considered to be statistically significant.

Results

Baseline characteristics of the study participants adjusted by age are summarized in Table 1. Among all study participants, 187,816 (21%) were missing all teeth (edentulous), while 158,735 (18%) had lost 16 to 31 teeth. Participants with higher numbers of teeth lost tended to be older at enrollment. When adjusted for age, those with more lost teeth were less likely to drink alcohol, but more likely to be current smokers, have less education, and have higher body mass index (BMI).

In multivariable adjusted analyses, (Table 2), tooth loss (modeled as a continuous variable) was statistically significantly ($p<0.05$) associated with higher mortality from eight cancer sites, head/neck (HR= 1.13; 95%CI, 1.07-1.20), esophagus (HR=1.12; 95% CI, 1.04-1.22), stomach (HR= 1.06; 95% CI: 1.02-1.10), liver (HR=1.16; 95%CI: 1.08-1.24), pancreas (HR=1.04; 95% CI= 1.01-1.08), lung (HR=1.1; 95% CI, 1.10-1.15), cervix (HR= 1.10; 95% CI, 1.02-1.19), and bladder (HR=1.13; 95% CI, 1.07-1.20). Additionally, tooth loss was associated with mortality for cancer of the oral cavity and oropharynx (HR=1.22; 95% CI, 1.11-1.34), sites included in head/neck cancer. Repeating the multivariable analysis with tooth loss as a categorical variable (table S1) revealed increasing HRs with increasing numbers of teeth lost for most of these sites. However, for cervical cancer, mortality associated with tooth loss for those missing all teeth (HR=1.36; 95%CI, 0.98-1.88) was lower than for those missing 16 to 31 teeth (HR=1.58; 95%CI, 1.15-2.16).

Because residual confounding by smoking is less of a concern in self-reported never smokers than in former or current smokers, multivariable analyses were repeated separately in

never, former, and current smokers (see table 3). For 6 of the 8 cancers significantly associated with tooth loss in overall analyses (lung, stomach, liver, pancreas, cervix, and bladder), HR point estimates were smaller in never smokers than in current or former smokers. However, among never smokers, the HR point estimates associated with tooth loss was similar or higher than what was observed for current and former smokers for esophageal (never smokers: HR=1.23; 95% CI, 1.04-1.43; current smokers: HR=1.09; 95%CI, 0.98-1.21) and head/neck (never smokers: HR=1.13, 95% CI, 0.99-1.28; current smokers HR=1.11; 95%CI, 1.03-1.20) cancer mortality. Differences in the HRs between never smokers and current smokers (and between never smokers and former smokers) were not statistically significant for most of the cancer sites for which tooth loss was associated with cancer-related death, with the exception of lung and cervical cancer. For lung cancer mortality, the HRs were significantly different between never smokers (HR=1.06; 95%CI, 1.00-1.12), and both former (HR=1.15; 95% CI, 1.08-1.23) and current smokers (HR=1.13; 95%CI, 1.10-1.16). For cervical cancer mortality, the HR for current smokers (HR=1.24; 95%CI, 1.09-1.41) was significantly different from that in never smokers (HR=1.02; 95%CI, 0.92-1.12).

Because a significant interaction between tooth loss and age at enrollment was seen for bladder cancer mortality ($P_{\text{interaction by age}}$ =0.012), the multivariable analysis was repeated in strata defined by age at enrollment. For bladder cancer mortality, the HR with tooth loss was higher in people who were younger than age 60 at enrollment.

A significant interaction between tooth loss and education was found for liver, colon/rectum, leukemia, uterus, and cervix cancer mortality (all $P_{\text{interaction}} < 0.03$; Table S2). For those cancers, the multivariable analysis was repeated in strata defined as no college and at least some college education (Table S2). For all of these sites, the HR for mortality associated

with tooth loss was higher in the higher education group (those with at least some college). For cancers of the colon/rectum, uterus, and cervix, an association of tooth loss with mortality was observed only in the higher education group.

A significant interaction between tooth loss and sex was seen for pancreatic cancer mortality. In the sex-stratified analysis, tooth loss was associated with increased pancreatic cancer mortality in males (HR=1.09; 95% CI, 1.05-1.14), but not in females (HR= 0.98; 95% CI, 0.93-1.03; $P_{\text{interaction by sex}} = 0.006$).

We repeated the multivariable analyses restricting follow up to four-year intervals (table S3) in order to assess potential reverse causality, however no substantial evidence for this effect was seen.

Discussion

In this large, prospective study of tooth loss and cancer-related death, we found positive associations with tooth loss and risk of death from cancers of the head/neck, esophagus, stomach, liver, pancreas, lung, cervix, and bladder, with hazard ratios per 8 teeth lost ranging from 1.10 to 1.16 for most of these sites (head/neck, esophagus, liver, lung, cervix, and bladder). Findings from this study contribute to the growing body of evidence that oral health affects cancer risk.

Residual confounding by smoking is a particular concern, since these cancers are all smoking-related and statistical adjustment for smoking might only partly separate the risk of cancer-related death due to smoking from a possible risk due to tooth loss. However, confounding by smoking was minimized by assessing the association of tooth loss and cancer death in participants who reported never smoking in their initial questionnaire. For both

esophageal and head and neck cancer, the HRs for never smokers were at least as high as those for current smokers, arguing against confounding as the explanation for the positive association of mortality from these cancers with tooth loss.

Because previous studies have seen a more consistent association between oral cancer and tooth loss [65-69] than the broader category of head and neck cancer [62-64], we also examined the association of tooth loss with oral and oropharyngeal cancer mortality, finding a significant positive association. Our study provides further evidence of an association between oral health and oral cancer risk. Michaud used data from seven case-control studies for a dose response meta-regression analysis, finding that each lost tooth increased the odds of oral cancer by 0.03 (95%CI, 0.01-0.05). [44]. The relationship between tooth loss and periodontal disease with oral/oropharyngeal cancer was examined in the Health Professionals Follow-up Study (HPFS) cohort. Although no association with either tooth loss or periodontal disease was observed in the overall cohort [57], in an updated analysis restricted to never-smokers, those with both periodontitis and <17 teeth had an increased risk of esophageal and head and neck cancers (composite outcome) [59].

Although information regarding histology of the esophageal cancer in the CPS-1 cohort was not available, based on the epidemiology of esophageal cancer at the time [106], most of the cancers were likely to be squamous cell carcinomas. Other prospective studies have indicated that the association of tooth loss and esophageal cancer may not be consistent across histologic types. In the United States and most other Western countries, adenocarcinoma is now the predominant histologic type of esophageal cancer. [107] Although no association of tooth loss and esophageal cancer incidence was seen in more modern cohorts in the United States [57] and Finland [77], the esophageal cancers in those cohorts were likely to be predominantly

adenocarcinomas. However, squamous cell is the predominant histologic type of esophageal cancer in Asia [107], so the increased risk of esophageal cancer associated with tooth loss in a Chinese cohort [78], likely reflected an increased risk of squamous cell carcinomas, consistent with the findings in the CPS-1 cohort.

Our study found that tooth loss is positively associated with liver cancer mortality. Although the HR in never smokers was lower than in current smokers, the difference was not statistically significant. In addition, the HR from the crude model (which did not include tobacco use) was similar to the HR resulting from the multivariable adjusted model. These findings provide evidence that the association between liver cancer and tooth loss was not only due to residual confounding by smoking.

The liver is a common site of metastases and misclassification of liver cancer as an underlying cause of death in death certificates has been documented previously. [108] Based on a previous study examining the accuracy of death certificate diagnoses of liver cancer, we could expect approximately 20% of the CPS-I participants whose deaths were attributed to liver cancer did not have this cancer. Such misclassification would be expected to bias towards the null, so would not invalidate the association of tooth loss and liver cancer mortality demonstrated in our analysis.

Our study adds to the few previous studies that have examined the association of tooth loss and liver cancer [63, 91, 92], one of which found that tooth loss was associated with liver cancer incidence [91].

For lung cancer, although the HR in never smokers is smaller than those in former and current smokers, it approached statistical significance. Still, the statistically significant differences in the HRs by smoking status raises concern of residual confounding by smoking.

A number of prior studies have found an association between periodontal disease and lung cancer [56-58, 79]. However, an association of tooth loss and lung cancer has been inconsistent, with a significant association seen in the HPFS cohort [57], but not in the Glasgow alumni cohort [81]. In the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study, no significant association was seen between the loss of all teeth and lung cancer mortality. [56] In contrast, our study found an association between tooth loss and lung cancer mortality with the loss of five or more teeth.

The associations between tooth loss mortality from cancers of the stomach and pancreas were significant but modest.

Although, cervical cancer mortality was significantly associated with both continuous and categorical tooth loss in this analysis, the association of categorical tooth loss with cervical cancer mortality lacked a clear dose response. Additionally, the significant difference between current and never smokers provides evidence that the association between tooth loss and cervical cancer mortality in our analysis may be the result of residual confounding by tobacco exposure.

The association between tooth loss and cancer mortality was heterogeneous with respect to sex for pancreatic cancer, age for bladder cancer, and education for several cancer sites (liver, colon/rectum, uterus, and cervix). For pancreatic cancer, the association of tooth loss with mortality was seen in men, who are known to have an increased risk of pancreatic cancer [109]. For age and education, the association between tooth loss and cancer mortality was stronger in the group which would have been expected to have a lower risk of both cancer and tooth loss – younger age, higher education.

Strengths of this analysis include the large size of our cohort which was followed prospectively, detailed smoking histories obtained, and inclusion of both sexes. In addition, the large number of participants who did not use tobacco allowed us to examine the association of tooth loss and cancer mortality in never smokers, in order to minimize confounding by smoking.

Limitations of this analysis reliance on death certificates for the causes of death, which likely led to misclassification of the primary site of some cancers, particularly cancers of the brain, liver, and lung, as these are common secondary sites. The use of death certificates also meant that no information regarding histologic types of cancers could be collected, which would have been helpful for cancers of the lung, esophagus, and possibly stomach. In addition, all exposures were obtained by self-report at the time of enrollment, and subject to social desirability and other biases. In addition, no information on reason for tooth loss was available, nor were there direct assessments of periodontal disease.

Conclusions

Our results support a positive association between tooth loss and death from cancers of the head and neck, esophagus, stomach, liver, pancreas, lung, and bladder. For cancers of the head and neck, esophagus, liver, and lung the association between tooth loss and cancer death was observed in nonsmokers, indicating the association of tooth loss with cancer death was independent of smoking. Further research is needed to understand the mechanisms underlying these associations. These findings add to the evidence that oral health is important factor in systemic disease. Improving oral hygiene and treating periodontal disease has the potential to improve overall health and mortality.

Chapter 3: Public health implications

Previous studies have found that poor oral health (as evidenced by tooth loss and/or periodontal disease), is positively associated with a number of diseases, including hypertension [45], diabetes [46], stroke [47-50], dementia [110], cardiac disease [45, 50-52], and respiratory disease [51]. Some studies have also found a positive association with cancer [44]. The finding that tooth loss is associated with mortality from some cancers in the CPS-I cohort provides further evidence that oral health affects both cancer and general health.

Lack of access to dental care can be a barrier to good oral health [95]. Those who are uninsured are less likely to see the dentist, as are those of lower socioeconomic status and racial minorities [95]. A recent study found that only 37% of adults in the United States (US) saw a dentist within the previous year, with cost cited most often as the reason for not seeing the dentist [111]. Cost is likely in part due to lack of insurance coverage. In US, insurance coverage for dental care is less common than health care coverage [112], as Medicare does not cover dental care and neither do most health insurance plans [113]. In addition, although Medicaid does cover dental care, reimbursements are so low that many dentists do not accept new Medicaid patients [95]. Improving access to affordable dental care by expanding dental coverage has the potential to improve oral health as well as general health, including improving mortality from cancer, and possibly cancer prevention.

TABLES

Table 1. Age-standardized baseline characteristics (%) of participants in the Cancer Prevention Study I cohort by number of missing teeth, 1959-1972

Baseline characteristic	Teeth missing, N			
	0-4	5-15	16-31	32
	(n=291,040)	(n=242,004)	(n=158,735)	(n=187,816)
Age (years)*				
<55	78.5	66.2	45.2	35.1
55-<60	11.3	15.2	17.3	16.2
60-<65	5.8	9.5	14.7	15.5
65-<70	2.8	5.4	11.2	13.6
70-<75	1.1	2.5	6.5	9.6
75+	0.5	1.2	5	10
Women	60	59.3	61.7	57.4
Race**				
White	97.2	96.8	96.4	97.1
Black	1.8	2.2	2.4	1.7
Education**				
<High school	26.6	34.6	49	54.6
High school graduate	23.6	24.6	22.6	22
Some college	23.9	21.9	17.4	15.6
College graduate	25.3	18.4	10	7
Marital Status**				
Single	5.6	4.8	3.3	2.4
Married	85	85	84	85.3
Widowed	6.9	7.5	9.5	9.2
Divorced/Separated	1.7	1.9	2.2	2.1
Cigarette smoking				
Never	56.5	52.9	50.7	48.9
Current	31.4	35.3	39	40.5
Former	12.1	11.8	10.3	10.6
Cigar/Pipe smoking				
Never	96.2	95.9	95	93.6
Occasional	2.2	2.6	3.1	3.9
Regular	1.5	1.5	1.8	2.4
Former	0	0	0.1	0.1
Body mass index, (kg/m^2)				
<22.5	28.9	25.1	24.4	24.6
22.5 to <25	28	27	25.3	24.6
25 to <27.5	23	24.4	23.1	23.1
27.5 to <30	8.8	10.2	10.6	10.7
30+	5.7	7.6	9.1	9.5
Alcohol intake, drinks/day**				
None	62.9	65.1	69	71.9
>0 to <1	12.1	11.5	10.8	10.2
1	9.8	8.7	7	6.1
>1 to ≤2	8.3	7.5	6.1	5.2
>2 to ≤3	3.1	3.1	2.6	2.3
>3	3.4	3.7	3.9	3.6

Physical Activity**				
None	2.1	2	2.1	2.2
Slight	18.9	17.5	14.4	13.7
Moderate	68.2	68.5	67.9	67.2
Heavy	9.4	10.5	12.8	14.9
Vegetable intake, servings/week**				
0 to 7	15.2	17.9	23	24.9
8 to 10	23.1	25.1	25.3	25.9
11 to 13	29.6	28.5	25.3	24.3
14+	29.2	25.7	21.7	20.6
Smokeless tobacco use				
Never	96.2	95.9	95	93.6
Occasional	2.2	2.6	3.1	3.9
Regular	1.5	1.5	1.8	2.4
Former	0	0	0.1	0.1
Prevalent diabetes	1.4	1.7	2	2.7
Doctor visit within last year	47.6	44.1	41.3	41.1

* All variables except age standardized to the age distribution of the study population

** Percentages do not add up to 100% because of missing/unknown values.

Table 2. Crude and multivariable-adjusted hazard ratios for cancer mortality by tooth loss (per 8 teeth), Cancer Prevention Study I cohort*, 1959-1972

Cause of cancer death	Deaths/ person-years	Crude* HR (95% CI	Adjusted** HR (95% CI)
Head/neck	617/879,595	1.21 (1.15-1.28)	1.13 (1.07-1.20)
Oral+	239/879,595	1.30 (1.19-1.42)	1.22 (1.11-1.34)
Stomach	1,481/879,595	1.11 (1.08-1.16)	1.06 (1.02-1.10)
Colon/Rectum	4,659/879,595	1.01 (0.99-1.03)	1.01 (0.99-1.03)
Liver	470/879,595	1.19 (1.11-1.27)	1.16 (1.08-1.24)
Gallbladder/biliary	453/879,595	1.09 (1.02-1.17)	1.06 (0.99-1.14)
Pancreas	1,924/879,595	1.07 (1.04 -1.10)	1.04 (1.01-1.08)
Lung	4,899/879,595	1.25 (1.23-1.28)	1.12 (1.10-1.15)
Melanoma	272/879,595	1.02 (0.94 -1.11)	1.02 (0.93-1.12)
Breast‡	2,870/528,711	1.00 (0.98-1.03)	1.01 (0.98-1.04)
Cervix‡	366/528,711	1.17 (1.08-1.26)	1.10 (1.02-1.19)
Uterus‡	273/528,711	1.08 (0.99-1.17)	1.06 (0.97-1.16)
Ovary‡	1,247/528,711	0.95 (0.92 -0.99)	0.96 (0.92-1.01)
Prostate†	1,479/350,884	1.05 (1.01-1.09)	1.04 (1.00-1.08)
Kidney	606/879,595	1.03 (0.98-1.10)	1.01 (0.95-1.07)
Bladder	756/879,595	1.17 (1.11-1.23)	1.13 (1.07-1.20)
Brain	892/879,595	0.99 (0.94-1.03)	0.99 (0.94-1.04)
Hodgkin lymphoma	268/879,595	1.01 (0.93-1.11)	1.00 (0.91-1.10)
NHL	943/879,595	1.01 (0.96-1.06)	1.01 (0.96-1.06)
Myeloma	506/879,595	0.98 (0.92-1.04)	1.00 (0.94-1.07)
Leukemia**	1,359/879,595	1.00 (0.96-1.03)	0.99 (0.95-1.03)

*adjusted for age, sex

** adjusted for age, sex, race, education, tobacco use, body mass index, physical activity, vegetable intake, alcohol intake, history of diabetes, and doctor visit within 1 year of enrollment.

+oral cavity and oropharyngeal cancers are included in head/neck cancer

†males only

‡females only

.

Table 3. Multivariable-adjusted hazard ratios for cancer mortality by tooth loss (per 8 teeth) and smoking status, Cancer Prevention Study I cohort, 1959-1972

Cause of cancer death	NEVER SMOKERS		FORMER SMOKERS			CURRENT SMOKERS		
	Deaths/ person-years	HR (95% CI)	Deaths/ person-years	HR (95% CI)	*p*-value former vs never	Deaths/ person-years	HR (95% CI)	*p*-value current vs never
Head/neck	149/419,705	1.13 (0.99-1.28)	58/88,636	1.06 (0.88-1.28)	*0.90*	364/294,358	1.11 (1.03-1.20)	*0.47*
Oral	38/419,705	1.27 (0.98-1.66)	16/88,636	1.29 (0.89-1.87)	*0.71*	143/294,358	1.15 (1.02-1.30)	*0.20*
Stomach	742/419,705	1.02 (0.96-1.08)	184/88,636	1.05 (0.94-1.17)	*0.88*	416/294,358	1.10 (1.02-1.18)	*0.069*
Colon/Rectum	2,747/419,705	1.01 (0.98-1.04)	510/88,636	1.01 (0.94-1.08)	*0.30*	1,104/294,358	1.00 (0.96-1.04)	*0.72*
Liver	234/419,705	1.11 (1.00-1.22)	54/88,636	1.14 (0.93-1.39)	*0.98*	152/294,358	1.21 (1.08-1.36)	*0.83*
Gallbladder/biliary	283/419,705	1.03 (0.94-1.12)	46/88,636	1.25 (1.01-1.55)	*0.46*	97/294,358	1.06 (0.91-1.22)	*0.63*
Pancreas	884/419,705	1.03 (0.98-1.08)	212/88,636	1.07 (0.97-1.19)	*0.20*	697/294,358	1.04 (0.98-1.10)	*0.91*
Lung	719/419,705	1.06 (1.00-1.12)	502/88,636	1.15 (1.08-1.23)	*<0.001*	3,293/294,358	1.13 (1.10-1.16)	*0.046*
Melanoma	138/419,705	1.00 (0.88-1.13)	39/88,636	1.21 (0.96-1.52)	*0.75*	84/294,358	0.96 (0.81-1.13)	*0.53*
Breast‡	2028/354,691	1.00 (0.97-1.04)	164/29,795	1.07 (0.94-1.20)	*0.27*	678/294,358	1.03 (0.97-1.09)	*0.56*
Cervix‡	226/354,691	1.02 (0.92-1.12)	20/29,795	1.20 (0.85-1.68)	*0.14*	120/144,225	1.24 (1.09-1.41)	*0.024*
Uterus‡	212/354,691	1.06 (0.96-1.18)	9/29,795	1.24 (0.69-2.23)	*0.55*	52/144,225	1.01 (0.83-1.25)	*0.55*
Ovary‡	880/354,691	0.95 (0.91-1.00)	73/29,795	0.96 (0.79-1.17)	*0.40*	294/144,225	1.00 (0.91-1.09)	*0.53*
Prostate†	553/65,014	1.05 (0.99-1.12)	232/58,841	0.99 (0.90-1.09)	*0.051*	444/150,133	1.03 (0.96-1.10)	*0.43*
Kidney	255/419,705	0.97 (0.88-1.06)	89/88,636	0.96 (0.82-1.11)	*0.66*	209/294,358	1.08 (0.97-1.19)	*0.43*
Bladder	296/419,705	1.06 (0.97-1.15)	97/88,636	1.17 (1.01-1.36)	*0.082*	305/294,358	1.20 (1.10-1.30)	*0.051*
Brain	397/419,705	1.00 (0.93-1.08)	129/88,636	1.01 (0.88-1.15)	*0.38*	308/294,358	0.98 (0.90-1.07)	*0.82*
Hodgkin lymphoma	127/419,705	1.05 (0.92-1.19)	23/88,636	0.92 (0.67-1.25)	*0.58*	99/294,358	0.92(0.79-1.08)	*0.11*
NHL	527/419,705	0.95 (0.89-1.02)	94/88,636	1.13 (0.97-1.31)	*0.061*	265/294,358	1.05 (0.96-1.15)	*0.027*
Myeloma	280/419,705	1.03 (0.94-1.13)	59/88,636	0.80 (0.65-0.98)	*0.017*	130/294,358	1.03 (0.91-1.17)	*0.66*
Leukemia**	709/419,705	0.98 (0.93-1.04)	158/88,636	1.04 (0.92-1.17)	*0.31*	391/294,358	0.96 (0.89-1.03)	*0.74*

*adjusted for age, sex, race, education, body mass index, physical activity, vegetable intake, alcohol intake, history of diabetes, and doctor visit within 1 year of enrollment. For former smokers, also adjusted for amount smoked per day and time since quit. For current smokers, also adjusted for amount and duration of smoking

**Leukemia includes all chronic and acute leukemia

†males only

‡females only

Table S1. Multivariable-adjusted hazard ratios for cancer mortality by categories of tooth loss, Cancer Prevention Study I cohort, 1959-1972 *

Cause of cancer death	<5 teeth lost	5-15 teeth lost (95% CI)	16-31 teeth lost (95% CI)	all 32 teeth lost (95% CI)
Head/neck	1.0 (ref)	0.98 (0.76-1.26)	1.18 (0.91-1.54)	1.64 (1.29-2.10)
Oral/ oropharynx	1.0 (ref)	1.04 (0.68-1.58)	1.64 (1.07-2.49)	2.45 (1.65-3.63)
Stomach	1.0 (ref)	1.04 (0.88-1.23)	1.17 (0.99-1.39)	1.27 (1.08-1.50)
Liver	1.0 (ref)	1.23 (0.92-1.66)	1.46 (1.07-1.99)	1.81 (1.35-2.43)
Pancreas	1.0 (ref)	1.09 (0.95-1.25	1.10 (0.95-1.28)	1.19 (1.03-1.37)
Lung	1.0 (ref)	1.13 (1.04-1.24)	1.37 (1.25-1.50)	1.55 (1.42-1.70)
Cervix	1.0 (ref)	1.01 (0.74-1.38)	1.48 (1.08-2.04)	1.32 (0.95-1.83)
Bladder	1.0 (ref)	1.28 (0.99-1.65)	1.46 (1.13-1.89)	1.71 (1.34-2.12)

*for cancer sites in which tooth loss as a continuous variable had a significant effect

Table S2: Multivariable-adjusted hazard ratios per 8 teeth lost for cancer mortality by education level categorized as no college or at least some college for cancer sites for which a statistically significant interaction was detected, Cancer Prevention Study I cohort, 1959-1972.

Cause of cancer death	No college HR (95% CI)	At least some college HR (95% CI)	*P* for interaction
liver	1.10 (1.02-1.20)	1.24 (1.10-1.40)	*0.041*
colon/rectum	0.99 (0.96-1.02)	1.05 (1.01-1.09)	*0.003*
leukemia	0.96 (0.92-1.01)	1.04 (0.97-1.11)	*0.009*
uterus	0.99 (0.88-1.10)	1.18 (1.02-1.38)	*0.026*
cervix	1.05 (0.96-1.15)	1.26 (1.08-1.47)	*0.025*

Table S3
Multivariable adjusted hazard ratios per 8 teeth lost for cancer mortality at different follow up times, Cancer Prevention Study I cohort, 1959-1972

Cause of cancer death	**<4 years**		**4≤, >8 years**		**8 + years**		
	cases/ person-years	**HR* (95% CI)**	**cases /person-years**	**HR* (95% CI)**	**cases/ person-years**	**HR*(95% CI)**	***p*-value¥**
Head/neck	125 / 3,419,941	1.14 (0.99-1.30)	203 / 3,104,111	1.14 (1.03-1.27)	289 / 3,355,480	1.13 (1.03-1.23)	*0.51*
Esophagus	63 / 3,419,941	1.03 (0.85-1.25)	115 / 3,104,111	1.13 (0.99-1.30)	169 / 3,355,480	1.15 (1.03-1.29)	*0.11*
Stomach	434 / 3,419,941	1.05 (0.97-1.12)	477 / 3,104,111	1.07 (1.00-1.15)	570 / 3,355,480	1.06 (0.99-1.12)	*0.37*
Colon/rectum	988 / 3,419,941	1.03 (0.99-1.08)	1,582 / 3,104,111	1.00 (0.97-1.04)	2,089 / 3,355,480	1.00 (0.97-1.03)	*0.42*
Liver	119 / 3,419,941	1.29 (1.12-1.49)	167 / 3,104,111	1.11 (0.99-1.25)	184 / 3,355,480	1.13 (1.01-1.26)	*0.43*
Gallbladder/ Biliary	129 / 3,419,941	1.10 (0.96-1.26)	126 / 3,104,111	1.06 (0.93-1.21)	198 / 3,355,480	1.04 (0.94-1.15)	*0.29*
Pancreas	492 / 3,419,941	1.04 (0.97-1.11)	595 / 3,104,111	1.04 (0.98-1.10)	837 / 3,355,480	1.05 (1.00-1.10)	*0.74*
Lung	1,025 / 3,419,941	1.14 (1.09-1.19)	1,595 / 3,104,111	1.11 (1.07-1.15)	2,279 / 3,355,480	1.12 (1.09-1.16)	*0.77*
Melanoma	66 / 3,419,941	1.08 (0.90-1.31)	95 / 3,104,111	0.96 (0.82-1.12)	111 / 3,355,480	1.04 (0.91-1.20)	*0.78*
Breast‡	453 / 2,066,482	1.04 (0.97-1.11)	969 / 1,899,823	1.00 (0.95-1.05)	1,448 / 2,090,471	1.01 (0.97-1.05)	*0.097*
Cervix‡	97 / 2,066,482	1.16 (1.00-1.36)	150 / 1,899,823	1.07 (0.95-1.21)	119 / 2,090,471	1.08 (0.95-1.24)	*0.38*
Uterus‡	59 / 2,066,482	1.10 (0.91-1.34)	82 / 1,899,823	1.03 (0.88-1.21)	132 / 2,090,471	1.06 (0.93-1.21)	*0.87*
Ovary‡	305 / 2,066,482	1.04 (0.95-1.13)	423 / 1,899,823	0.92 (0.85-0.99)	519 / 2,090,471	0.96 (0.90-1.03)	*0.48*
Prostate†	247/ 1,353,459	1.08 (0.98-1.20)	480/ 1,204.288	1.03 (0.96-1.10)	752/ 1,265,008	1.04 (0.99-1.09)	*0.21*
Kidney	137 / 3,419,941	0.97 (0.86-1.10)	190 / 3,104,111	1.03 (0.93-1.14)	279 / 3,355,480	1.01 (0.92-1.10)	*0.16*
Bladder	148 / 3,419,941	1.34 (1.17-1.55)	230 / 3,104,111	1.15 (1.04-1.27)	378 / 3,355,480	1.07 (0.99-1.15)	*0.05*
Brain	269 / 3,419,941	0.95 (0.87-1.04)	289 / 3,104,111	1.05 (0.96-1.14)	334 / 3,355,480	0.96 (0.89-1.05)	*0.87*

Hodgkin Lymphoma	71 / 3,419,941	0.91 (0.76-1.08)	100 / 3,104,111	1.01 (0.87-1.17)	97 / 3,355,480	1.06 (0.92-1.23)	*0.21*
NHL	214 / 3,419,941	0.99 (0.89-1.10)	318 / 3,104,111	1.03 (0.95-1.12)	411 / 3,355,480	0.99 (0.93-1.07)	*0.49*
Myeloma	99 / 3,419,941	0.98 (0.85-1.14)	169 / 3,104,111	1.04 (0.92-1.16)	238 / 3,355,480	0.98 (0.89-1.08)	*0.49*
Leukemia	347 / 3,419,941	0.95 (0.87-1.02)	436 / 3,104,111	1.04 (0.97-1.12)	576 / 3,355,480	0.97 (0.91-1.03)	*0.62*

*HR per 8 teeth lost, adjusted for age, sex, race, education, tobacco use, body mass index, physical activity, vegetable intake, alcohol intake, history of diabetes, and doctor visit within 1 year of enrollment.
¥P-value for interaction between tooth loss (continuous) and time (continuous)
† males only
‡females only

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