HHS Public Access

Author manuscript

J Natl Cancer Cent. Author manuscript; available in PMC 2022 February 14.

Published in final edited form as:

J Natl Cancer Cent. 2021 June ; 1(2): 39–43. doi:10.1016/j.jncc.2021.01.002.

A long-term follow-up analysis of associations between tooth loss and multiple cancers in the Linxian General Population Cohort

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Abstract

Poor oral health, indicated by tooth loss and periodontal disease, may be an important risk factor for various cancers. Prior studies have found inconsistent associations between tooth loss and several cancer types. Here, we examined the relationship between tooth loss and incident cases of multiple cancers in the Linxian General Population Nutrition Intervention Trial cohort. In this large prospective cohort of over 29,000 participants, there were 3101, 1701, 626, 327, 348, and 179 incident esophageal, gastric cardia, gastric noncardia, liver, lung, and colorectal cancer cases, respectively, over 30 years of follow-up. Adjusted Cox proportional hazards regression models with time-varying covariates were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between tooth loss and cancer outcomes during three time intervals: ≤ 5 years (early), > 5 and ≤ 10 years (mid), > 10 years (late). Tooth loss was assessed as quartiles of the number of lost teeth in excess of the loess smoothed, age-specific median number of teeth lost. For esophageal cancer, the increase in risk associated with the highest quartile of tooth loss was 25% (95% CI: 1.02, 1.52) in the mid time interval, but the association weakened thereafter. For gastric cardia cancer, the increase in risk associated with the highest quartile of tooth loss was 1.34 in both the early (95% CI: 1.06, 1.71) and mid time intervals (95% CI: 1.02, 1.76), with no significant associations in the late interval. Gastric noncardia cancer was only associated with the second quartile of tooth loss in the late time interval (HR = 1.54; 95% CI: 1.16, 2.04). All associations between tooth loss and liver, lung, and colorectal cancers were null. Tooth loss was associated with risk of esophageal and gastric cancers in this updated analysis from the cohort.

Keywords

Oral health; tooth loss; cancer

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Introduction

Periodontal disease results from a bacterial infection in the oral cavity and often leads to tooth loss [1]. Since oral bacteria, including pathogens, are constantly swallowed with saliva, it is possible that some bacteria may influence systemic effects such as chronic inflammation, which often plays a role in carcinogenesis [2]. Indeed, there is increasing evidence from observational studies showing a link between poor oral health and cancer risk. Tooth loss has been associated with several cancers, including cancers of the esophagus [3], stomach [4], lung [5], and liver [6,7], in a number of studies. In addition, oral hygiene practices such as tooth brushing have been found to have a protective effect against some cancers, particularly those of the upper gastrointestinal (UGI) series (i.e., esophagus and stomach) [8–12]. However, there have also been some inconsistent findings in prior studies, and it is unclear if poor oral health is an important risk factor for specific cancer types more than others [13,14]. Additional evidence, particularly from prospective studies, are needed to verify the relationship between poor oral health and cancer risk.

Here, we update [7,15–17] and expand our analyses of tooth loss and incident cancer in the Linxian General Population Nutrition Intervention Trial (NIT) cohort after 30 years of follow-up. We report the associations between tooth loss and cancers of the esophagus, gastric cardia, gastric noncardia, liver, lung, and colorectum. Findings from this large, long-term prospective study will help elucidate the effects of poor oral health on cancer risk.

Methods

Study population and data collection

As described in detail previously, the General Population NIT cohort consisted of 29,584 individuals ages 40 to 69 years in Linxian, China, who participated in a randomized, placebo-controlled trial investigating the effects of multi-vitamin/mineral supplements on esophageal and gastric cancer incidence and mortality [18]. The intervention was initiated in March 1986 and ended in May 1991, after which participants continue to be followed. Participants were asked about their age, sex, height, weight, education, alcohol consumption, and cigarette smoking status at baseline. As part of the baseline interview, participants also received an oral exam and were asked if they had lost any permanent teeth. The remaining number of teeth were counted by interviewers for those who reported missing teeth. Cancer incidence was ascertained on a monthly basis at local hospitals and reviewed with the local cancer registry. Diagnoses were confirmed by a panel of experts from China and the United States. Gastric cardia and noncardia cancers were defined as adenocarcinomas occurring in the proximal 3 cm of the stomach and below the proximal 3 cm of the stomach, respectively.

Statistical analysis

After removing 69 subjects missing the number of lost teeth and 157 subjects missing other covariates, a total of 29,358 participants remained in the present analysis. To account for the strong correlation between age and tooth loss, a loess model was used to derive age-specific predicted numbers of teeth lost [16], and the loess smoothing parameter was selected based on the bias-corrected Akaike information criterion. Excess numbers of teeth

lost were calculated for each participant by taking the difference between the actual and loess predicted number of lost teeth. A categorical variable for tooth loss was created based on quartiles of the calculated excess numbers of lost teeth.

Cox proportional hazards regression models were used to estimate the hazard ratio (HR) and 95% confidence intervals (CIs) for the association between tooth loss and the following six outcomes: incidence of esophageal, gastric cardia, gastric noncardia, liver, lung, and colorectal cancers. The entry time was defined as the age at which participants began the trial, and follow-up was ended at the diagnosis of each of the six cancers, or the date of the last follow-up through March 31, 2016, whichever came first. During this period, a total of 395 subjects (1.35%) were lost to follow-up. Cox models were adjusted for the following covariates: age, age squared, sex, smoking (smoker or nonsmoker), alcohol use (yes or no), education (no formal school, 1–5 years of education, primary school, middle school and higher, or other), and body mass index (BMI).

Given that we are using 30-years of follow-up time and that tooth loss likely progressed in most individuals after the baseline assessment, we carefully evaluated the proportional hazards assumption using Schoenfeld residuals. Nonproportional hazards were observed for associations between tooth loss and several cancer outcomes, specifically cancers of the esophagus, gastric cardia, gastric noncardia, and liver (Table S1). Since plots of Schoenfeld residuals showed a non-constant effect of tooth loss over time for these cancers (Figure S1), time-varying covariates were created to look at the effects of tooth loss during the following time intervals: ≤ 5 years (early), > 5 and ≤ 10 years (mid), > 10 years (late) [19]. Although the Schoenfeld residuals test still failed for liver cancer even with the use of time-varying covariates, the proportional hazards assumption was fulfilled with all other cancers with the inclusion of time-varying covariates. Results of the association between tooth loss and liver cancer should be interpreted with caution. The R programming environment (version 3.6.2) was used for all statistical analyses.

Results

Table 1 describes the baseline characteristics of participants by quartiles of tooth loss. Most subjects did not smoke (70.0%), did not consume alcohol (76.5%), and received little to no formal schooling (71.3%). Women had more missing teeth [mean = 10.3, standard deviation (SD) = 10.3] than men (mean = 8.54, SD = 9.88; $P < 0.0001$). During the 30-year follow-up period, there were 3101, 1701, 626, 327, 348, and 179 incident esophageal, gastric cardia, gastric noncardia, liver, lung, and colorectal cancer cases, respectively. Essentially all esophageal cancers in this region are squamous cell carcinomas and all gastric cancers are adenocarcinomas [20]. We cannot report the distribution of histologic types for liver or lung cancers, but the liver cancers were all primary tumors.

For esophageal cancer, multivariate models showed that the highest quartile of tooth loss was associated with a 1.25 times (95% CI: 1.02, 1.52; $P = 0.0314$) increased risk compared to subjects in the lowest quartile of tooth loss in the mid time interval (> 5 and ≤ 10 years of follow-up), but this effect attenuated in the late time interval (HR = 1.07; 95% CI: 0.925, 1.23; $P = 0.382$), after 10 years of follow-up (Table 2). For gastric cardia cancer, the highest

quartile of tooth loss (vs lowest quartile) was associated with a HR of 1.34 (95% CI: 1.06, 1.71; $P = 0.0161$) in the early time interval (≤ 5 years of follow-up), and this effect continued in the mid time interval (HR = 1.34; 95% CI: 1.02, 1.76; $P = 0.0326$; Table 2). In the mid time interval, the third quartile (vs lowest quartile) was also associated with an increased risk of gastric cardia cancer with a HR of 1.41 (95% CI: 1.05, 1.88; $P = 0.0211$). In the late time interval, the second quartile of tooth loss (vs lowest quartile) was marginally associated with gastric cardia cancer (HR = 1.20; 95% CI: 1.00, 1.44; $P = 0.0498$), but none of the other quartiles showed a significant association. For gastric noncardia cancer, the second quartile of tooth loss (vs lowest quartile) was associated with a HR of 1.54 (95% CI: 1.16, 2.04; $P = 0.00314$) in the late time interval, but all other associations were null (Table 2). Associations between tooth loss and liver, lung, and colorectal cancers were null (Table 2).

We also explored associations between tooth loss and cancer stratified by sex, smoking status, education, and BMI. However, we found no systematic differences by these strata, and testing for statistical interactions had low power to detect differences given the complexity of the time-varying models (data not shown). For example, the HR for the highest quartile of tooth loss was 1.25 for esophageal cancer in the mid time interval (Table 2), but when stratifying on smoking status the HR was 1.20 and 1.28 in nonsmokers and smokers, respectively.

Discussion

In this large, prospective cohort with 30 years of follow-up, age-specific excess tooth loss was associated with an increased risk of esophageal, gastric cardia, and gastric noncardia cancers, but the effect varied over time. Excess tooth loss was associated with an increased risk of esophageal cancer between 5 and 10 years of follow-up, but the effect attenuated thereafter. The adverse effect of tooth loss on gastric cardia cancer risk was mostly apparent in the first 10 years of follow-up and weakened after 10 years. There were no associations between tooth loss and cancers of the liver, lung, and colorectum.

Our results concur with prior studies reporting an increase in the risk of UGI cancers associated with tooth loss [4,5,8,17,21,22]. The association between tooth loss and UGI cancer risk in the General Population NIT cohort has previously been reported after 5.25 years of follow-up [15]. In this earlier study, tooth loss categorized as median splits was associated with a HR of 1.3 (95% CI: 1.1, 1.6) for esophageal cancer and 1.3 (95% CI: 1.0, 1.6) for gastric cardia cancer. These results are similar to the effects observed for these cancers in the time interval between 5 to 10 years of follow-up in our updated analysis, which included an additional 25 years of follow-up. It is possible that because tooth loss was only assessed at baseline, the effects of tooth loss on UGI cancer risk may have attenuated over time, and thus resulted in the disappearance of effects after 10 years of follow-up in our study. This lack of updated exposure information is one of our study's limitations. This previous study also found an association between tooth loss (categorized as median splits) and gastric noncardia cancer (HR = 1.8; 95% CI: 1.1, 3.0) [15], but we did not see a similar effect within 10 years of follow-up in our analysis. In a Finnish cohort, tooth loss was also associated with a 65% higher risk of gastric noncardia cancer when comparing edentulous subjects with those missing fewer than 10 teeth, but there was no association between tooth

loss and cancers of the esophagus and gastric cardia in this population [21]. It is unclear why we did not see a strong association between tooth loss and gastric noncardia cancer, but we note gastric cardia cancers in Eastern and Western populations have many distinct risk factors including opposing effects of infection with *Helicobacter pylori*, which increase the risk of cardia cancer in Asian studies and reduced the risk of cardia cancer in studies of Westerners [23].

The relationship between tooth loss and other cancers, including those of the liver, lung, and colorectum remain unclear [13,14]. Although the association between tooth loss and lung cancer has been evaluated in several prior studies, this relationship may be obscured by the strong effect of smoking [5,24]. In our study, we did not find an association between tooth loss and lung cancer, and this is unlikely to be confounded by smoking since most subjects were never smokers. While we did not find a significant association between tooth loss and liver or colorectal cancers, other studies have found mixed results for these cancers [5,6,24,25].

The major strengths of this study include the large sample size, prospective design, and the minimal loss to follow-up. In addition, tooth loss was assessed by trained interviewers and was not based on self-report. However, as mentioned earlier, tooth loss was assessed only at baseline, and the number of missing teeth was not updated during follow-up. Another limitation of this study is that we did not have information about the dental hygiene practices (e.g., tooth brushing) of the participants or the reasons for tooth loss. We cannot rule out the possibility that tooth loss may have been caused by reasons other than poor oral health, such as trauma or accidents and lack access to dental services to care for tooth decay or periodontal disease. We also cannot rule out confounding by other lifestyle factors that we did not account for (e.g., diet, physical activity), as well as confounding by genetic factors.

Conclusion

In conclusion, we found that tooth loss significantly increased the risk of esophageal and gastric cardia cancers, with a time-varying effect. Although previous studies have found an association between tooth loss and gastric noncardia cancer, we did not see a similar effect. The relationship between tooth loss and cancers of the liver, lung, and colorectum were null but need to be verified with future studies. Further research is warranted to better understand the link between tooth loss and cancer risk, as this may point to the protective effects of oral hygiene practices and prophylactic dental treatments that may lead to a decrease in the burden of some of these cancers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This study was supported by the Intramural Research Program of the National Cancer Institute, NIH.

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Table 1.

Baseline characteristics of participants in the General Population Study, overall and by quartiles of excess tooth loss.

			Quartiles of excess tooth loss[1]			
		Overall[2]	Q1[3]	Q2[3]	Q3[3]	Q4[3]
		29358	7562 (25.8)	8422 (28.7)	6300 (21.5)	7074 (24.1)
Age, years, mean (SD)		51.9 (8.88)	56.5 (6.37)	46.9 (7.93)	49.1 (8.60)	55.6 (8.43)
Sex, *n* (%)	Female	16277 (55.4)	3325 (20.4)	4537 (27.9)	3890 (23.9)	4525 (27.8)
	Male	13081 (44.6)	4237 (32.4)	3885 (29.7)	2410 (18.4)	2549 (19.5)
Smoking, *n* (%)	Nonsmoker	20546 (70.0)	4839 (23.6)	5884 (28.6)	4614 (22.5)	5209 (25.4)
	Smoker	8812 (30.0)	2723 (30.9)	2538 (28.8)	1686 (19.1)	1865 (21.2)
Alcohol use, *n* (%)	No	22468 (76.5)	5705 (25.4)	6166 (27.4)	4801 (21.4)	5796 (25.8)
	Yes	6890 (23.5)	1857 (27.0)	2256 (32.7)	1499 (21.8)	1278 (18.5)
Education, *n* (%)	No school	11776 (40.1)	3335 (28.3)	2300 (19.5)	2319 (19.7)	3822 (32.5)
	1–5 years	9147 (31.2)	2593 (28.3)	2666 (29.1)	1976 (21.6)	1912 (20.9)
	Primary school	3147 (10.7)	527 (16.7)	1354 (43.0)	816 (25.9)	450 (14.3)
	Middle school+	2695 (9.18)	338 (12.5)	1458 (54.1)	662 (24.6)	237 (8.79)
	Other	2593 (8.83)	769 (29.7)	644 (24.8)	527 (20.3)	653 (25.2)
BMI, mean (SD)		21.9 (2.49)	22.1 (2.55)	22.1 (2.46)	22.0 (2.45)	21.6 (2.48)
Number of missing teeth, mean (SD)		9.52 (10.2)	2.84 (3.45)	3.35 (4.34)	9.12 (5.37)	24.4 (7.46)

1. Excess tooth loss is defined as the number of lost teeth in excess of the loess smoothed, age-specific median number of teeth lost.

2. Percentages are column-wise.

3. Percentages are row-wise.

Table 2.

Associations between quartiles of excess tooth loss and esophageal, gastric cardia, gastric noncardia, liver, lung, and colorectal cancers at different time intervals of follow-up: ≤ 5 years (early), > 5 and ≤ 10 years (mid), > 10 years (late). All models were adjusted for age, age squared, sex, smoking status, alcohol use, education, and body mass index.

	Time interval	Excess tooth loss	Adjusted HR	95% CI	p-value
Esophagus	Early	Q1	Reference		
		Q2	0.775	(0.623, 0.964)	0.0221
		Q3	0.992	(0.801, 1.23)	0.938
		Q4	1.08	(0.896, 1.31)	0.415
	Mid	Q1	Reference		
		Q2	1.07	(0.869, 1.33)	0.506
		Q3	1.19	(0.954, 1.48)	0.123
		Q4	1.25	(1.02, 1.52)	0.0314
	Late	Q1	Reference		
		Q2	1.08	(0.946, 1.24)	0.244
		Q3	1.11	(0.960, 1.28)	0.160
		Q4	1.07	(0.925, 1.23)	0.382
Gastric cardia	Early	Q1	Reference		
		Q2	0.903	(0.684, 1.19)	0.474
		Q3	0.914	(0.679, 1.23)	0.553
		Q4	1.34	(1.06, 1.71)	0.0161
	Mid	Q1	Reference		
		Q2	1.05	(0.782, 1.40)	0.761
		Q3	1.41	(1.05, 1.88)	0.0211
		Q4	1.34	(1.02, 1.76)	0.0326
	Late	Q1	Reference		
		Q2	1.20	(1.00, 1.44)	0.0498
		Q3	1.19	(0.978, 1.44)	0.0824
		Q4	0.940	(0.765, 1.15)	0.555
Gastric noncardia	Early	Q1	Reference		
		Q2	0.920	(0.582, 1.46)	0.723
		Q3	0.751	(0.446, 1.26)	0.282
		Q4	1.13	(0.759, 1.69)	0.540
	Mid	Q1	Reference		
		Q2	0.889	(0.530, 1.49)	0.654
		Q3	1.20	(0.720, 1.99)	0.489
		Q4	1.04	(0.646, 1.66)	0.882
	Late	Q1	Reference		
		Q2	1.54	(1.16, 2.04)	0.00314
		Q3	0.978	(0.700, 1.37)	0.899
		Q4	1.16	(0.851, 1.59)	0.345

	Time interval	Excess tooth loss	Adjusted HR	95% CI	p-value
Liver	Early	Q1	Reference		
		Q2	0.550	(0.215, 1.41)	0.213
		Q3	1.04	(0.461, 2.34)	0.925
		Q4	0.774	(0.354, 1.69)	0.522
	Mid	Q1	Reference		
		Q2	1.22	(0.642, 2.32)	0.543
		Q3	0.632	(0.267, 1.50)	0.297
		Q4	1.30	(0.700, 2.40)	0.410
	Late	Q1	Reference		
		Q2	1.19	(0.812, 1.74)	0.373
		Q3	1.27	(0.853, 1.90)	0.237
		Q4	1.18	(0.794, 1.76)	0.408
Lung	Early	Q1	Reference		
		Q2	1.01	(0.500, 2.04)	0.982
		Q3	0.654	(0.273, 1.56)	0.339
		Q4	0.819	(0.396, 1.69)	0.589
	Mid	Q1	Reference		
		Q2	0.620	(0.275, 1.39)	0.247
		Q3	0.944	(0.433, 2.06)	0.884
		Q4	1.35	(0.701, 2.60)	0.369
	Late	Q1	Reference		
		Q2	1.14	(0.799, 1.64)	0.462
		Q3	1.14	(0.781, 1.67)	0.493
		Q4	0.875	(0.578, 1.32)	0.525
Colorectum	Early	Q1	Reference		
		Q2	0.560	(0.102, 3.09)	0.506
		Q3	1.77	(0.471, 6.65)	0.398
		Q4	2.79	(0.871, 8.92)	0.0841
	Mid	Q1	Reference		
		Q2	0.476	(0.178, 1.27)	0.139
		Q3	0.415	(0.134, 1.29)	0.128
		Q4	0.867	(0.378, 1.99)	0.736
	Late	Q1	Reference		
		Q2	1.05	(0.630, 1.74)	0.858
		Q3	1.10	(0.652, 1.87)	0.712
		Q4	0.804	(0.456, 1.42)	0.451