Poor Oral Health and Esophageal Cancer Risk: A Nationwide Cohort Study

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ABSTRACT

Background: Previous research indicates that poor dental health increases risks for certain types of cancers, including esophageal cancer. This study aimed to investigate the association with esophageal cancer using Swedish Dental Health Register.

Methods: This is a prospective cohort study. The exposures were dental diagnoses classified into healthy, caries, root canal infection, mild inflammation, and periodontitis, as well as number of remaining teeth, at baseline and during multiple visits. The outcome was the incidence of esophageal cancer, which was further divided into esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC). Cox proportional hazards models were used to estimate hazard ratios (HR) and its corresponding confidence intervals (CI).

Results: A total of 5,042,303 individuals were included in the study and 1,259 EAC and 758 ESCC cases were identified. Root canal infection at baseline was associated with 41% higher risk for EAC (HR, 1.41; 95% CI, 1.10–1.82), whereas periodontitis at baseline was linked to 32% and 45% higher risks for respective histopathological subtypes (HR for EAC, 1.32; 95% CI, 1.13–1.53; HR for ESCC, 1.45; 95% CI, 1.20–1.75). Fewer remaining teeth at baseline also increased the risks for both histopathological types of esophageal cancer, with a dose–response effect ($P_{trend} < 0.01$). Cox regression analyses with time-varying exposures corroborated the above-mentioned results.

Conclusions: Impaired dental health before cancer diagnosis is associated with excess risks for both histopathological subtypes of esophageal cancer.

Impact: Our study provided corroborating evidence for the association between poor oral health and esophageal cancer risk.

Introduction

Esophageal cancer is the seventh most common cancer worldwide. There have been extensive epidemiological studies addressing etiological factors for esophageal cancer, with well-established distinct risk factor profiles regarding lifestyle, diet, and genetics, as well as disease characteristics between western and eastern populations and between countries with different development levels (1). Despite of the improvement in the early detection and treatment techniques, the 5-year survival rate of esophageal cancer remains lower than 25% (2), causing 544,000 cancer-specific deaths annually (3). Therefore, efforts are still needed for better understanding of the oncogenic mechanisms of the disease and to further build up an effective population-based prevention strategy.

A growing number of studies have shown that poor oral health is a risk factor for a range of cancers, including esophageal cancer, because of its systematic detrimental effect on overall health (4–9). The majorities of the studies were performed in Asian countries with high esophageal cancer burden like China and Japan (10–12), India (13), and Iran (14), with only two studies from Nordic countries (15, 16), and most of the studies were case–control studies with inconsistent effect sizes and various proxies were used to examine oral health, and the confidence intervals (CI) were wide due to the small number of cancer cases. Besides, esophageal cancer is more prevalent in Eastern Asia, whereas less prevalent in Europe, especially for the subtype of esophageal squamous cell carcinoma (ESCC; ref. 17). This leads to a lack of research on the association between oral health and ESCC in European countries.

Traditionally, questionnaires have been the most commonly used proxies of oral health (10, 11, 15, 18). Among them, number of tooth loss, age at the loss of first tooth during adulthood and tooth cleaning habit are common dental health parameters. Although a link between poor oral health and esophageal cancer was suggested, results from previous studies suffered from a lack of consistency and robustness. Moreover, very few of them studied the diagnosis of periodontal diseases with the risk for esophageal cancer.

Therefore, the objective of this study was to investigate the association between oral diseases grouped by dental inflammation level, tooth loss, and the risks for esophageal cancer, overall and by histopathological subtype, using data from a nationwide dental register.

Materials and Methods

Study participants

The data of this study were obtained from the nation-wide population-based Swedish Dental Health Register (DHR) and the detailed description of the data is available elsewhere (19). The register was launched in 2008, with continuously updated individual dental health care reimbursement data of the adult population (23 years and older). The data are collected electronically by the Swedish Insurance Agency

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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when the state reimbursement is issued to the patients treated by dental health care providers. Until the time of this study, there were 5,893,325 people listed in the register with 15,854,827 records. Specifically, the register includes information of patient demographical data, date of clinical visit, remaining number of teeth, and diagnoses connected with treatments and dental procedures. With the unique personal registration number assigned to each resident in Sweden, the DHR was further linked to multiple registers, including Total Population Register, Cancer Register, Cause of Death Register, National Patient Register, and the Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA), enabling accurate identification of outcomes and necessary covariates. The study was performed in accordance with CIOMS and was approved by the Ethics Review Board in Stockholm (approval no. 2021–02491). Because this is a strictly register-based study, individual informed consent was not required.

Identification of exposure

Dental health was defined by the recorded diagnoses associated with treatments at each visit. The dental health conditions were categorized on the basis of the codes in the Dental Care Benefits Scheme into healthy (without diagnosis of diseases of interest), caries, root canal infection, mild inflammation [mucositis (implants), pericoronitis, gingivitis, stomatitis and other unspecific inflammation conditions] and periodontitis (periodontitis and periimplantitis; diagnostic codes are shown in Supplementary Table S1). The first date of a patient appearing in the register was considered as the entry date, and the most severe diagnosis in the three months following the entry date was considered as the baseline dental health condition. The remaining number of teeth at baseline was also retrieved from the DHR. If remaining number of teeth was not recorded on the same day of the diagnosis, then the tooth number with the date that is closest to dental care date within half year before or five years after the diagnosis was used (Supplementary Fig. S1).

Identification of outcome

The outcome of incident esophageal cancer was identified using the seventh version of the International Classification of Diseases (ICD) from the Swedish Cancer Register (ICD-7: 150), which was established in 1958, with >98% nationwide completeness (20). Stratified analysis was further performed by histopathological subtype, that is, esophageal adenocarcinoma (EAC) and ESCC. The histopathology coding (pathoanatomic diagnosis) "096" was used to identify EAC, and "146" for ESCC. Patients with esophageal cancer were excluded from the study if they were diagnosed before their first visit to the dental care clinics.

Covariates

Factors associated with the occurrence of esophageal cancer and oral health are considered as covariates in the research models (21–24). Potential covariates were collected from the DHR and by cross-linkage to various national registers, including age and sex at time of clinic visit from DHR, and highest educational level (low: <9 years, middle: 10–12 years, high: ≥13 years), disposable family income (low, middle, high, categorized by tertile ranking) obtained from LISA (25). Tobacco abuse (yes or no) information was identified by the diagnosis of chronic obstructive pulmonary disease as a proxy of tobacco abusing. Likewise, heavy alcohol use (yes or no) was identified by the diagnoses of alcohol-related disorders, and obesity status (yes or no) was identified by the diagnoses of obesity-related diseases. Specially, because gastroesophageal reflux disease (GERD) is associated with tooth erosion and dental structure disruption, as well as a confirmed risk factor for EAC, it is also controlled for in the models for EAC (26, 27). Disease history of the above-mentioned diseases was identified using ICD codes from the Swedish National Patient Register. The ICD codes used for the identification of the diseases are shown in detail in Supplementary Table S2.

Statistical analysis

Baseline characteristics of participants were presented by stratification of dental inflammation status (healthy, caries, root canal infection, mild inflammation, and periodontitis) and remaining number of teeth (1–14, 15–20, 21–24, 25–27, and 28–32). Each participant was followed from the date of first record and was censored at the time of diagnosis of incident esophageal cancer, death, emigration out of Sweden, or end of follow-up (December 31, 2016), whichever happened first.

Age-standardized incidence rates were calculated for total esophageal cancer and by histopathological subtype, stratified by dental inflammation and remaining number of teeth, separately. Specifically, incidence rates of the outcomes were standardized to the distribution of person-years experienced by all participants in 5-year age intervals. Hazard ratios (HR) with corresponding 95% CIs were estimated to measure the association between dental inflammation level, number of teeth, and esophageal cancer risk, with healthy dental condition and 28+ remaining teeth group as the reference group, respectively. Moreover, dental inflammation and the number of teeth were simultaneously adjusted in the Cox models for the consideration of mutual confounding effects. Schoenfeld residuals were used to test the proportional hazards assumption for each variable and no violation was observed. Because the participants of the study had a wide range of age at entry (range of age at baseline, 19–106), attained age was used as the time scale for the Cox regression models. The simple model adjusted for baseline age and sex as covariates and the fully adjusted model further included all the covariates mentioned before, including education level, family income level, smoking-related diseases, alcohol-related diseases, and obesity. When analyzing EAC, history of GERD was further adjusted. The test for trend was performed by the orthogonal polynomial contrasts.

The interaction between dental inflammation and remaining teeth was examined by calculating the HRs in groups with different remaining number of teeth in people without and with dental inflammation (mild inflammation or periodontitis), separately. People without dental inflammatory conditions and having 28+ teeth were considered as the overall reference group. In the Cox model, the interaction terms of dental inflammation and remaining teeth were introduced in addition to the two exposures of interest. Log likelihood ratio test between models with and without interaction terms was performed to check whether the effect of remaining teeth number varies depending on the inflammation status. Similarly, we also checked whether the HRs associated with remaining teeth number differed by periodontitis status.

We further used the time-dependent Cox regression model to assess the effect of dental inflammation and the number of teeth in a time-varying manner. Specifically, the most severe record each year was considered as the representative record for that year. This is because when the inflammation has progressed to periodontitis the tissue damage is thereafter non-reversible with chronical destruction of supporting tissues (28). Thus, records with less severe inflammation were disregarded, as compared with the previous records.

The study reported two-sided P values with $P < 0.05$ as statistical significance level. All the analyses were performed in SAS 9.4 (SAS Institute).

Data availability

The data are not publicly available due to their containing information that could compromise the privacy of research participants, but are available from the corresponding authors upon reasonable request.

Results

In total, there were 5,042,303 subjects recruited into the study, with a median follow-up time of 6.4 years. Baseline characteristics of participants, stratified by oral health condition and remaining number of teeth, are summarized in **Table 1**. In brief, people with healthy dental condition or without tooth loss tended to be younger and to have higher education level and family income and were less likely to have smoking-related or alcohol-related disorders, to be obese and have a history of GERD.

HRs with the corresponding 95% CIs for total esophageal cancer and subtypes of EAC and ESCC according to baseline dental inflammation status are shown in **Table 2**. After adjusting for all potential confounders, periodontitis was associated with a 36% increased risk for overall esophageal cancer (HR, 1.36; 95% CI, 1.22–1.53). In the subanalyses by histopathology subtypes of esophageal cancer, people diagnosed with root canal infection and periodontitis presented an increased risk for EAC (HR of root canal infection, 1.41; 95% CI, 1.10–1.82; HR of periodontitis, 1.32; 95% CI, 1.13–1.53), whereas only periodontitis showed a 45% higher risk for ESCC (HR 1.45, 95% CI, 1.20–1.75).

The association between number of teeth and the risks of esophageal cancer and its histopathological subtypes are shown in **Table 3**. Individuals with lower number of teeth tended to have a higher risk for esophageal cancer, after controlling for all the potential confounders, compared with individuals with more than 28 teeth at baseline (25–27 teeth group, HR, 1.52; 95% CI, 1.33–1.73; 21–24 teeth group, HR, 1.91; 95% CI, 1.66–2.21; 15–20 teeth group, HR, 1.89; 95% CI, 1.61–2.23; 1–14 teeth group, HR, 2.17; 95% CI, 1.82–2.58; P_{trend} across all groups <0.01). The same risk patterns were also observed when histopathological subtypes of EAC and ESCC were considered as outcomes.

The HRs for the subjects with combinations of categorized remaining number of teeth and dental inflammation status (yes or no) are shown in **Fig. 1**. There was no statistically significant interaction effect between dental inflammation status and remaining teeth observed in total esophageal or any histopathological type. Similarly, no interaction effect between periodontitis and remaining teeth was detected (Supplementary Fig. S2).

The results of considering multiple visits during follow-up of dental inflammation using the time-dependent Cox regression model are summarized in **Table 4**. Mild dental inflammation and periodontitis were associated with an increased risk for overall esophageal cancer (HR of mild dental inflammation, 1.24; 95% CI, 1.04–1.47; HR of periodontitis, 1.48; 95% CI, 1.27–1.73). For patients of EAC, root canal infection, mild dental inflammation, and periodontitis all showed elevated risks (HR for root canal infection, 1.47; 95% CI, 1.08–2.00; HR for mild dental inflammation, 1.39; 95% CI, 1.11–1.74; HR for periodontitis, 1.47; 95% CI, 1.20–1.81). Whereas in the ESCC group, only periodontitis showed an increased risk for the occurrence of ESCC (HR, 1.51; 95% CI, 1.17–1.94; **Table 4**).

Likewise, when the grouped remaining teeth was investigated using the time-dependent Cox regression model, less remaining teeth was associated with a higher HR for esophageal cancer, with a statistically

Table 1. Baseline characteristics by dental health status and remaining number of teeth in the cohort identified from the Swedish Dental Health Register, 2009–2016.

Dental health status[a]	Healthy	Caries	Root canal infection	Mild inflammation	Periodontitis
Total (*N*, %)	2,414,936 (47.9)	847,074 (16.8)	203,384 (4.0)	963,421 (19.1)	613,482 (12.2)
Follow-up years (mean ± SD)	6.5 ± 1.9	6.5 ± 1.8	6.2 ± 2.1	6.4 ± 2.0	6.6 ± 1.9
Age at baseline (mean ± SD)	46.5 ± 18.9	47.7 ± 18.3	50.6 ± 16.5	48.3 ± 18.0	57.9 ± 15.5
Male (*N*, %)	1,110,501 (46.0)	425,794 (50.3)	109,531 (53.9)	481,085 (49.9)	316,199 (51.5)
Education (≥13 years, *N*, %)	798,662 (33.1)	258,088 (30.5)	48,381 (23.8)	336,467 (34.9)	157,813 (25.7)
Missing (*N*, %)	47,006 (1.9)	16,530 (2.0)	4,794 (2.4)	21,431 (2.2)	21,845 (3.6)
Family income (High, *N*, %)	932,009 (38.6)	283,205 (33.4)	58,249 (28.6)	372,778 (38.7)	207,666 (33.9)
Smoking-related diseases (*N*, %)	29,503 (1.2)	11,540 (1.4)	4,010 (2.0)	11,205 (1.2)	14,562 (2.4)
Alcohol-related disorders (*N*, %)	47,062 (1.9)	20,956 (2.5)	9,868 (4.9)	19,586 (2.0)	20,356 (3.3)
Obesity (*N*, %)	26,974 (1.1)	14,647 (1.7)	5,901 (2.9)	11,542 (1.2)	9,367 (1.5)
GERD (*N*, %)[b]	72,609 (3.0)	28,687 (3.4)	8,484 (4.2)	28,905 (3.0)	24,320 (4.0)
Remaining number of teeth	**28+**	**25–27**	**21–24**	**15–20**	**1–14**
Total (*N*, %)	3,169,727 (62.9)	950,783 (18.9)	478,088 (9.5)	256,840 (5.1)	186,858 (3.7)
Follow-up years (mean ± SD)	6.3 ± 2.0	6.8 ± 1.6	6.8 ± 1.7	6.5 ± 2.0	6.0 ± 2.2
Age at baseline (mean ± SD)	40.9 ± 15.1	55.2 ± 15.9	64.0 ± 15.3	72.1 ± 11.0	73.5 ± 12.3
Male (*N*, %)	1,610,443 (50.8)	427,758 (45.0)	207,099 (43.3)	112,294 (43.7)	85,514 (45.8)
Education (≥13 years, *N*, %)	1,179,770 (37.2)	276,801 (29.1)	94,058 (19.7)	30,815 (12.0)	17,966 (9.6)
Missing (*N*, %)	43,314 (1.4)	32,446 (3.4)	19,890 (4.2)	9,812 (3.8)	6,144 (3.3)
Family income (High, *N*, %)	1,229,313 (38.8)	361,573 (38.0)	156,051 (32.6)	66,519 (25.9)	40,451 (21.6)
Smoking-related diseases (*N*, %)	21,081 (0.7)	13,225 (1.4)	12,607 (2.6)	11,789 (4.6)	12,118 (6.5)
Alcohol-related disorders (*N*, %)	67,972 (2.1)	21,077 (2.2)	12,412 (2.6)	8,283 (3.2)	8,084 (4.3)
Obesity (*N*, %)	38,826 (1.2)	13,611 (1.4)	7,870 (1.6)	4,649 (1.8)	3,475 (1.9)
GERD (*N*, %)[b]	67,141 (2.1)	38,692 (4.1)	26,625 (5.6)	17,463 (6.8)	13,084 (7.0)

[a]Dental health status was defined by the diagnosis at baseline: Healthy, caries, root canal infection, mild inflammation (stomatitis, mucositis (implants), pericoronitis, gingivitis, other unspecific inflammation conditions), and periodontitis (periodontitis and periimplantitis).
[b]GERD, Gastroesophageal reflux disease.

Table 2. Hazard ratios (HR) for esophageal cancer and its histopathological subtypes according to dental health conditions in a cohort identified from the Swedish Dental Health Register, 2009–2016[a].

Characteristics[b]	Cases (*N*)	Person-years* 100,000	IR (per 100,000 person-years)[c]	Age, sex-adjusted HR (95% CI)[d]	Multivariable-adjusted HR (95% CI)[e]
Total esophageal cancer					
Healthy	837	156.2	5.9	Ref	Ref
Caries	313	55.2	6.3	0.98 (0.86–1.12)	0.96 (0.84–1.09)
Root canal infection	101	12.6	7.7	1.25 (1.02–1.54)	1.19 (0.96–1.47)
Mild inflammation	368	61.6	6.0	1.05 (0.93–1.19)	1.06 (0.93–1.20)
Periodontitis	502	40.4	8.4	1.41 (1.26–1.57)	1.36 (1.22–1.53)
Adenocarcinoma[f]					
Healthy	489	156.2	3.5	Ref	Ref
Caries	201	55.2	4.0	1.06 (0.90–1.24)	1.01 (0.86–1.20)
Root canal infection	70	12.6	5.3	1.45 (1.12–1.86)	1.41 (1.10–1.82)
Mild inflammation	222	61.6	3.6	1.07 (0.92–1.26)	1.09 (0.93–1.28)
Periodontitis	277	40.4	4.7	1.30 (1.12–1.51)	1.32 (1.13–1.53)
Squamous cell carcinoma[g]					
Healthy	306	156.2	2.2	Ref	Ref
Caries	100	55.2	2.0	0.88 (0.70–1.10)	0.88 (0.70–1.11)
Root canal infection	28	12.6	2.2	0.99 (0.68–1.47)	0.86 (0.57–1.29)
Mild inflammation	125	61.6	2.0	0.99 (0.80–1.22)	1.00 (0.80–1.24)
Periodontitis	199	40.4	3.2	1.57 (1.31–1.88)	1.45 (1.20–1.75)

[a]HR , Hazard ratio; CI, confidence interval.
[b]Dental health characteristics were defined by the diagnosis at baseline: Healthy, caries, root canal infection, mild inflammation (stomatitis, mucositis (implants), pericoronitis, gingivitis, other unspecific inflammation conditions), and periodontitis (periodontitis and periimplantitis).
[c]IR, incidence rate (per 100,000 person-years), standardized to age distribution of person-years experienced by all participants using 5-year age categories.
[d]Time-constant Cox regression models using attained age as time scale, further adjusted for age at baseline, sex, and number of remaining teeth at baseline.
[e]Time-constant Cox regression models using attained age as time scale, further adjusted for age at baseline, sex, number of remaining teeth at baseline, education level, family income level, smoking-related diseases, alcohol-related diseases, and obesity. In the subanalysis of esophageal adenocarcinoma, the model was further adjusted for gastroesophageal reflux disease history.
[f]Histopathological subtype of esophageal adenocarcinoma was identified by the patho-anatomic diagnosis code "096."
[g]Histopathological subtype of esophageal squamous cell carcinoma was identified by the pathoanatomic diagnosis code "146."

significant monotonic trends (all the $P_{trend} < 0.01$), overall or regardless of the histopathological subtypes (**Table 5**).

In the sensitivity analyses, excluding the first year of follow-up did not substantially alter the results (Supplementary Tables S3–S6).

Discussion

To the best of our knowledge, this is the largest population-based prospective study addressing the association between various dental inflammatory conditions and the risk for esophageal cancer, with precise diagnoses for dental diseases and definite histopathological information of esophageal cancer, from one of the most well-developed welfare societies. The results showed that periodontitis is associated with a higher risk for total esophageal cancer and both histological subtypes of EAC and ESCC, and root canal infection is related only with an excess risk of EAC. And fewer teeth is a persistent risk factor for esophageal cancer and its subtypes, after adjusting for multiple potential confounders.

Periodontitis has been linked with the risks of multiple cancers previously (4, 6), whereas its association with esophageal cancer was less studied, and the results from few previous studies were inconsistent. A cohort study in the U.S. males with 131 incident esophageal cancer cases, also reported an elevated point estimate of HR for people with periodontal disease, after adjusting for detailed smoking history and BMI in the models. Yet the results were not statistically significant and histopathology information was unavailable in the study. On the other hand, moderate but statistically significant increases in HRs were observed for lung cancer, pancreatic cancer, and kidney cancer (29). Another population-based study with more than 8,000 esophageal cancer cases in Sweden also reported an association between overall oral diseases diagnosed in Patient Register and EAC (OR, 1.6; 95% CI, 1.0–2.4), after adjusting for limited covariates of smoking or alcohol consumption, gastroesophageal reflux, obesity, and ulcer disease (15). A prospective study combining 98,459 people from the Nurses' Health Study and 49,685 people from the Health Professionals Follow-up Study with a total of 199 EAC cases also reported a positive association between a history of periodontal disease and EAC (HR, 1.43; 95% CI, 1.05–1.96; ref. 30).

The mechanism for the link between periodontitis and esophageal cancer risk has not been fully revealed. One possible explanation might be systematic detrimental effects, like imbalanced nutrition linked with dental pain and tooth loss. Another possible explanation is the alteration in the bacterial composition that colonizes the gastrointestinal tract, which may be associated with the change in the oral microenvironment and complex immune responses. Moreover, potential microbial targets have been suggested for other digestive tract cancers (31–33). For esophageal cancer, the appearance of *Campylobacter* that replaces the normal microbiota, might promote the progression of esophageal cancer (34). The domination of this bacterium in the gastrointestinal tract could lead to the production of carcinogenic cytokines like IL18 by the epithelial cells. And IL18 is a potential tumorous biomarker that has been shown to stimulate inappropriate immune responses and apoptosis of immunological cells, and improve tumor cell proliferation, invasion, and metastasis in previous studies (35, 36). A recent study has reported that the interplay between *Campylobacter spp.* infection and poor oral health

Table 3. Hazard ratios (HR) for esophageal cancer and its histopathological subtypes according to number of teeth in a cohort identified from the Swedish Dental Health Register, 2009–2016[a].

Grouped remaining teeth number	Cases (*N*)	Person-years* 100,000	IR (per 100,000 person-years)[b]	Age, sex adjusted model, HR (95% CI)[c]	Multivariate-adjusted model, HR (95% CI)[d]
Total esophageal cancer					
28+	517	200.8	4.6	Ref	Ref
25–27	492	65.0	5.3	1.53 (1.35–1.74)	1.52 (1.33–1.73)
21–24	485	32.3	7.8	2.08 (1.81–2.39)	1.91 (1.66–2.21)
15–20	333	16.6	9.8	2.11 (1.80–2.47)	1.89 (1.61–2.23)
1–14	294	11.3	12.8	2.54 (2.16–3.00)	2.17 (1.82–2.58)
P_{trend}				<0.01	<0.01
Adenocarcinoma[e]					
28+	309	200.8	2.6	Ref	Ref
25–27	302	65.0	3.3	1.60 (1.35–1.89)	1.59 (1.34–1.88)
21–24	272	32.3	4.4	2.00 (1.67–2.40)	1.79 (1.48–2.16)
15–20	202	16.6	5.5	2.21 (1.80–2.71)	1.94 (1.57–2.39)
1–14	174	11.3	7.9	2.59 (2.09–3.20)	2.24 (1.79–2.79)
P_{trend}				<0.01	<0.01
Squamous cell carcinoma[f]					
28+	175	200.8	1.7	Ref	Ref
25–27	175	65.0	1.9	1.58 (1.27–1.97)	1.53 (1.22–1.92)
21–24	187	32.3	3.0	2.31 (1.83–2.91)	2.15 (1.69–2.74)
15–20	113	16.6	3.9	2.04 (1.56–2.67)	1.85 (1.40–2.44)
1–14	108	11.3	4.6	2.69 (2.04–3.56)	2.15 (1.61–2.89)
P_{trend}				<0.01	0.042

[a]HR, Hazard ratio; CI, confidence interval.
[b]IR, incidence rate (per 100,000 person-years), standardized to age distribution of person-years experienced by all participants using 5-year age categories.
[c]Time-constant Cox regression models using attained age as time scale, further adjusted for age at baseline, sex, and dental health conditions at baseline.
[d]Time-constant Cox regression models using attained age as time scale, further adjusted for age at baseline, sex, dental health conditions at baseline, education level, family income level, smoking-related diseases, alcohol-related diseases, and obesity. In the subanalysis of esophageal adenocarcinoma, gastroesophageal reflux disease was further adjusted in the model.
[e]Histopathological subtype of esophageal adenocarcinoma was identified by the pathoanatomic diagnosis code "096."
[f]Histopathological subtype of esophageal squamous cell carcinoma was identified by the pathoanatomic diagnosis code "146."

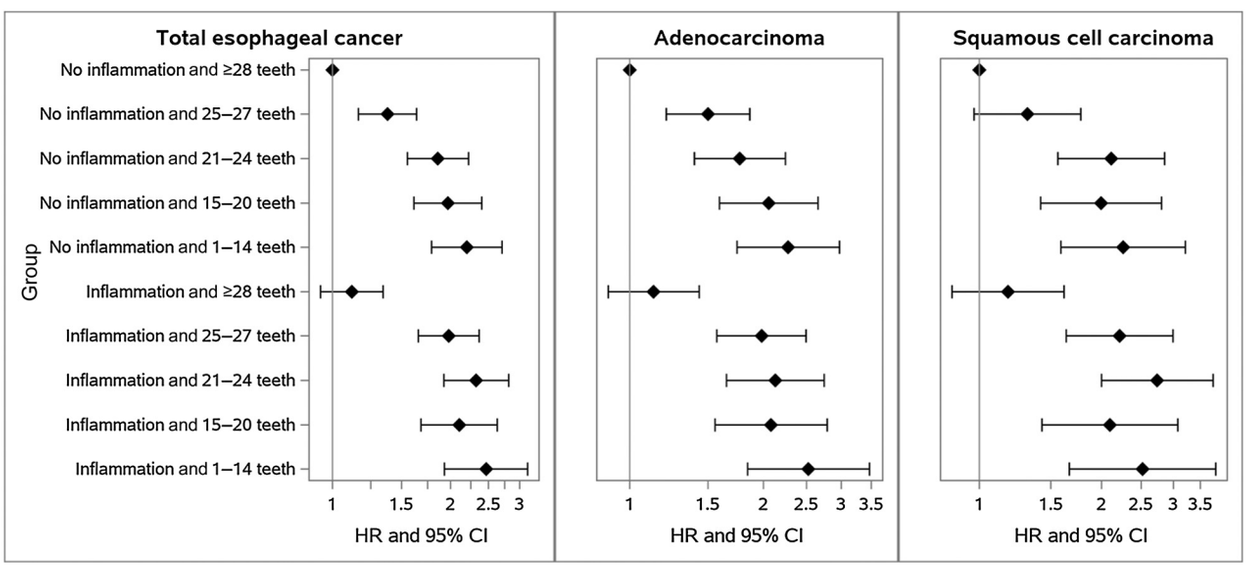

Figure 1.
Interaction between dental inflammation status and category of remaining teeth. Multivariable-adjusted hazard ratios (HR) for esophageal cancer, total and by histopathological subtypes, in relation to a combination of dental inflammatory conditions and number of remaining teeth, in a cohort identified from the Swedish Dental Health Register, 2009–2016. *P* values for interaction between inflammation status and category of remaining teeth were 0.217, 0.683, and 0.309 for total esophageal cancer, esophageal adenocarcinoma, and squamous cell carcinoma, respectively.

Table 4. Hazard ratios (HR) for esophageal cancer and its histopathological subtypes according to time-varying dental health conditions in a cohort identified from the Swedish Dental Health Register, 2009–2016[a].

Characteristics[b]	Age, sex-adjusted HR (95% CI)[c]	Multivariable-adjusted HR (95% CI)[d]
Total esophageal cancer		
Healthy	Ref	Ref
Caries	1.03 (0.85–1.26)	1.05 (0.86–1.29)
Root canal infection	1.24 (0.97–1.59)	1.23 (0.96–1.57)
Mild inflammation	1.20 (1.02–1.43)	1.24 (1.04–1.47)
Periodontitis	1.48 (1.27–1.72)	1.48 (1.27–1.73)
Adenocarcinoma[e]		
Healthy	Ref	Ref
Caries	0.99 (0.75–1.29)	0.99 (0.75–1.31)
Root canal infection	1.47 (1.08–2.00)	1.47 (1.08–2.00)
Mild inflammation	1.34 (1.08–1.67)	1.39 (1.11–1.74)
Periodontitis	1.43 (1.17–1.75)	1.47 (1.20–1.81)
Squamous cell carcinoma[f]		
Healthy	Ref	Ref
Caries	1.13 (0.82–1.55)	1.17 (0.85–1.61)
Root canal infection	1.05 (0.68–1.61)	1.00 (0.64–1.55)
Mild inflammation	0.98 (0.73–1.30)	1.01 (0.75–1.35)
Periodontitis	1.55 (1.21–1.98)	1.51 (1.17–1.94)

[a]HR, Hazard ratio; CI, confidence interval.
[b]Dental health characteristics were defined by the diagnosis along the whole follow-up time: Healthy, caries, root canal infection, mild inflammation [stomatitis, mucositis (implants), pericoronitis, gingivitis, other unspecific inflammation conditions], and periodontitis (periodontitis and periimplantitis).
[c]Time-dependent Cox regression models using attained age as time scale, further adjusted for age and sex at baseline, and number of remaining teeth along the whole follow-up time.
[d]Time-dependent Cox regression models using attained age as time scale, further adjusted for age, sex, education level, family income level, smoking-related diseases, alcohol-related diseases, and obesity at baseline and number of remaining teeth along the whole follow-up time. In the subanalysis of esophageal adenocarcinoma, gastroesophageal reflux disease was further adjusted in the model.
[e]Histopathological subtype of esophageal adenocarcinoma was identified by the pathoanatomic diagnosis code "096."
[f]Histopathological subtype of esophageal squamous cell carcinoma was identified by the pathoanatomic diagnosis code "146."

Table 5. Hazard ratios for esophageal cancer and its histopathological subtypes according to time-varying number of teeth in a cohort identified from the Swedish Dental Health Register, 2009–2016[a].

Grouped remaining tooth number	Age, sex-adjusted HR (95% CI)[b]	Multivariable-adjusted HR (95% CI)[c]
Total esophageal cancer		
28+	Ref	Ref
25–27	1.41 (1.19–1.67)	1.39 (1.17–1.65)
21–24	1.73 (1.44–2.08)	1.64 (1.36–1.98)
15–20	2.14 (1.75–2.61)	1.91 (1.56–2.34)
1–14	2.43 (1.99–2.98)	2.12 (1.72–2.61)
P_{trend}	<0.01	<0.01
Adenocarcinoma[d]		
28+	Ref	Ref
25–27	1.45 (1.16–1.81)	1.45 (1.15–1.82)
21–24	1.75 (1.37–2.24)	1.61 (1.25–2.07)
15–20	2.37 (1.83–3.08)	2.09 (1.60–2.74)
1–14	2.64 (2.02–3.45)	2.34 (1.77–3.08)
P_{trend}	<0.01	<0.01
Squamous cell carcinoma[e]		
28+	Ref	Ref
25–27	1.34 (1.02–1.77)	1.31 (0.99–1.74)
21–24	1.68 (1.25–2.27)	1.67 (1.23–2.26)
15–20	1.82 (1.31–2.54)	1.64 (1.17–2.30)
1–14	2.24 (1.60–3.12)	1.87 (1.33–2.63)
P_{trend}	<0.01	0.019

[a]HR, Hazard ratio; CI, confidence interval.
[b]Time-dependent Cox regression models using attained age as time scale, further adjusted for age and sex at baseline, and dental health conditions along the whole follow-up time.
[c]Time-dependent Cox regression models using attained age as time scale, further adjusted for age, sex, education level, family income level, smoking-related diseases, alcohol-related diseases, and obesity at baseline, and dental health conditions along the whole follow-up time. In the subanalysis of esophageal adenocarcinoma, gastroesophageal reflux disease was further adjusted in the model.
[d]Histopathological subtype of esophageal adenocarcinoma was identified by the pathoanatomic diagnosis code "096."
[e]Histopathological subtype of esophageal squamous cell carcinoma was identified by the pathoanatomic diagnosis code "146."

condition could markedly elevate the risk for esophageal cancer in a Thailand population, but a more detailed mechanism for this interaction is yet to be revealed (37). Another study showed the abundance of periodontal pathogenic bacteria like *Tannerella forsythia* and *Porphyromonas gingivalis* is associated with a higher risk for EAC and ESCC, respectively (38). Moreover, higher prevalence of bacteria in the dental plaque and saliva in patients with esophageal cancer also suggested a role of microbiome in the link between oral health and esophageal cancer (39). But any causative relationship can be hardly drawn from these case–control studies.

Our result that a lower number of teeth is associated with an elevated risk for esophageal cancer is in line with the results of several previous case–control studies performed in China, the US, Finland, and Latin American countries (10, 11, 14, 29). And we further confirmed the dose–response effect between the number of teeth and esophageal cancer risk, which holds for both histological subtypes. However, tooth loss is not only a marker for periodontal diseases, but also for overall health condition, socioeconomic status, and dental care accessibility, thus we can hardly conclude a causal relationship between the number of teeth and esophageal cancer risk from these studies because of the concern of residual confounding. But because an elevated cancer risk for loss of teeth is consistently observed in studies from different populations, it is unlikely that this association can be totally explained by the confounding effects.

The present study has several strengths. First, the study design is prospective cohort study, with linkages to various national mandatory registers, which ensures the completeness of identification of incident cases and accuracy of the information of potential confounding factors, and could possibly avoid recall bias and uncertainty of temporal relationship between exposures and outcomes. Second, the complete information of histopathological subtypes enabled us to study the influences on EAC and ESCC separately, and the large sample size also allowed us to further explore the interaction between dental inflammation and remaining teeth number. Third, previous studies were mostly performed in high risk regions like eastern Asia, mainly with the histopathological subtype of ESCC, and very few studies were from Europe in which EAC is more common than ESCC. As the risk factors for esophageal cancer are differently distributed in

western and eastern populations, this study contributes to add up evidence from the north European population, as well as confirmed the association between periodontitis and EAC.

However, several limitations for this study should also be noted. First, smoking and alcohol are well acknowledged risk factors for ESCC (40), and obesity and gastroesophageal reflux are most important risk factors for EAC (41). Although we included diagnoses of indication diseases into the models, this only accounted for severe smokers and alcohol users, but not moderate and light users. Similarly, we could identify only subjects with obesity and gastroesophageal reflux leading to hospitalization or specialist visit. Thus residual confounding effect may still exist for the results of this study. Second, because the people included in this dataset were passively collected when they requested a reimbursement during their visit in dental clinics, people in the register may have different characteristics compared with people not included in the register. But the DHR has been shown to have a good coverage in the population, so we do not that consider people included in this study were substantially different from those who were not included (19). Third, dental health status is associated with the social economic status and dental care policy. So it should be cautious when applying the conclusion of this study to populations with different societal structure and dental care policies.

In conclusion, this population-based prospective study showed periodontitis is associated with an increased risk for esophageal cancer, regardless of histopathology subtypes, whereas root canal infection is only associated with a higher risk for EAC. And less remaining tooth number is a strong predictive factor for both subtypes of esophageal cancer. But further studies are still needed to understand the underlying mechanisms for these associations.

Authors' Disclosures

No disclosures were reported.

Disclaimer

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Authors' Contributions

J. Zhang: Formal analysis, investigation, visualization, methodology, writing–original draft, writing–review and editing. **R. Bellocco:** Supervision, methodology, writing–review and editing. **G. Sandborgh-Englund:** Investigation, writing–review and editing. **J. Yu:** Conceptualization, resources, methodology, writing–review and editing. **M. Sällberg Chen:** Investigation, writing–review and editing. **W. Ye:** Conceptualization, resources, supervision, funding acquisition, investigation, writing–review and editing.

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