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Tooth loss is associated with increased risk of esophageal cancer: evidence from a meta-analysis with dose-response analysis

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Epidemiological studies have revealed the association between tooth loss and the risk of esophageal cancer (EC); however, consistent results were not obtained from different single studies. Therefore, we conducted the present meta-analysis to evaluate the association between tooth loss and EC. We conducted electronic searches of PubMed until to February 10, 2015 to identify relevant observational studies that examined the association between tooth loss and the risk of EC. Study selection and data extraction from eligible studies were independently performed by two authors. The meta-analysis was conducted using Stata 12.0 software. Finally eight eligible publications with ten studies involving 3 cohort studies, 5 case-control studies, and 1 cross-sectional study were yielded. Meta-analysis identified tooth loss increased risk of EC 1.30 times (Relative risk $= 1.30$, 95% confidence interval $= 1.06$–1.60, $I^2 = 13.5\%$). Dose-response analysis showed linear relationship between tooth loss and risk of EC (RR $= 1.01$, 95%CI $= 1.00$–1.03; P for non-linearity test was 0.45). Subgroup analysis proved similar results and publication bias was not detected. In conclusion, tooth loss could be considered to be a significant and dependent risk factor for EC based on the current evidence.

Tooth loss is known to considerably influence food choice, diet, nutrition intake, and esthetics[1]. It has also has been considered to impact oral health-related quality of life[2], aggravate people with severe mental illnesses[3], and increase the risk of cardiovascular disease[4–6] as well as head and neck cancer (HNC)[7]. Zheng *et al.* (1990)[8] first reported that tooth loss is a strong risk factor for oral cancer, and this association was further confirmed by Zeng *et al.* (2013) using meta-analysis[7]. For head and neck is adjoined to esophagus; besides, tooth loss as well as HNC and esophageal cancer (EC) share common risk factors, including age, gender, diabetes, social and geographical disparities, smoking, and alcohol consumption[9–16]. Therefore, the real relationship between tooth loss and EC need to be elucidated.

Abnet *et al.* (2001) reported that tooth loss increased the risk of developing esophageal squamous cell carcinoma (ESCC) in China[17]. Following this, many relevant epidemiological studies have been published; however, these studies have provided inconsistent or even contradicting results. The present study aimed to systematically review existing literature and to analyze the relationship between the tooth loss and the risk of EC using a meta-analysis. We hypothesize that tooth loss is associated with an increased risk of EC.

Methods

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[18].

Eligibility criteria. Cohort, case-control, and cross-sectional studies that evaluated the association between tooth loss and EC while meeting the following criteria were considered eligible for inclusion: (1) full-text articles could be obtained; (2) clear diagnostic criteria for EC and definition of tooth loss were reported; and (3) either the adjusted and/or unadjusted hazard ratios (HRs), odds ratios (ORs), or relative risks (RRs) and their

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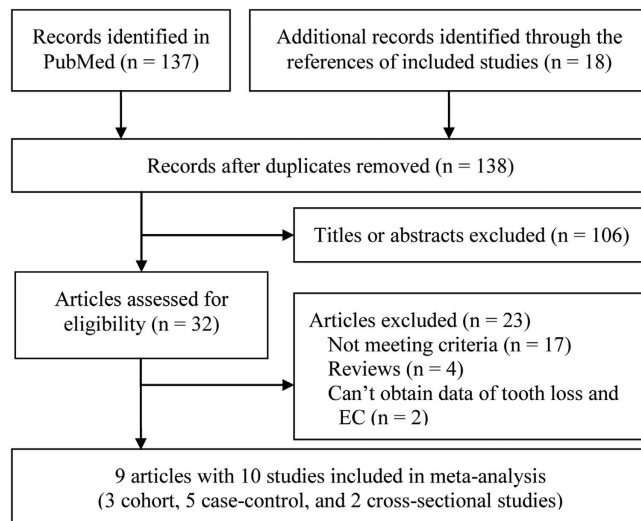
Figure 1. Flow chart from identification of eligible studies to final inclusion. EC, esophageal cancer.

corresponding 95% confidence intervals (CIs) or the numbers of events that could be used for their calculation were reported. When studies with overlapping data were eligible, we chose the one with the most comprehensive information. Two authors independently evaluated the eligibility of all the retrieved studies, and disagreements were resolved by discussion.

Search strategy. For identifying relevant studies, we conducted electronic searches of the PubMed database until February 10, 2015 using the search terms (esophageal OR oesophageal OR gullet) AND (dentition OR "tooth loss" OR edentulous OR "lost of tooth"). Reference lists of recent reviews and the selected papers and were manually screened to identify additional relevant studies and avoid erroneous exclusions. Only publications in English were included.

Data extraction. Two authors independently extracted the following information from each eligible study: last name of the first author; year of publication; study design; country of origin; sample size; age; pathological characteristics of EC; unadjusted or adjusted ORs, RRs, and HRs and relevant 95% CIs or standard errors (SEs); and the covariates for the adjusted point estimates.

Data analysis. Statistical analysis was performed using STATA 12.0 software. First, we transformed ORs, RRs, or HRs and their CIs to their natural logarithms and SEs. We directly considered HR as RR[7,19] and computed the combined RRs and 95% CIs from the estimates reported in each study[20,21]. Heterogeneity was quantified using I^2 values and chi-square test[22]; when both $I^2 \leq 50\%$ and $p > 1.0$ indicated no or acceptable heterogeneity[23], we used the fixed-effects model; otherwise, we used the random-effects model. In addition, we performed subgroup analyses on the basis of stratified ORs, RRs, and HRs, given that these pooled may result in the overestimation of OR variance[24]. We also conducted a dose-response meta-analysis using STATA 12.0 software with restricted cubic spline function by the method of Orini[25] for those studies reported sufficient data, including RRs, serving size, and the sample size in each categories. Furthermore, we performed subgroups analyses on the basis of the study design, and type of cancer, adjustment, and definition of reference group. Publication bias was assessed by visual inspection of the funnel plots[26].

Results
Study selection and characteristics. From the 155 records initially identified, 8 articles involving 3 cohort studies[17,27,28], 5 case-control studies[29–32], and 1 cross-sectional studies[33] were selected for the present meta-analysis. A detailed flow chart of the selection process is shown in Fig. 1.

Among the selected studies, the study of Guha et al.[31] involved 2 multicentric case-control studies from central Europe (including Romania, Poland, and Russia) and Latin America (including Cuba, Argentina, and Brazil), while the other 8 were single center studies. All the cases under study were confirmed to have EC through histological, pathological or cytological means, and 6 articles of 7 studies were ESCC[17,27,29,31–33]. All the studies clearly defined the reference group of on the basis of tooth loss, with the major characteristics presented in Table 1. All the studies reported adjusted point estimates and 95% CIs. The adjusted covariates are shown in Table 2.

Tooth loss and risk of EC. Among the eight included studies, two showed a significantly positive association between tooth loss and the risk of EC[29,30], while the other six were negative[17,27,28,31–33]. No substantial heterogeneity among these trials was observed ($I^2 = 13.5\%$, $p = 0.32$), and the overall result based on the fixed effect model showed that tooth loss increased risk of EC by 1.30 times (RR = 1.30, 95%CI = 1.06–1.60; Fig. 2).

References	Country	Study design	Sample sizes	Age (yrs)	Outcomes	Definition of reference group	Estimation (95%CI) (Highest vs. lowest)
Abnet 2001	China	Cohort	28868	57(12)*	ESCC	None lost tooth	0.90 (0.49–1.70)
Abnet 2005	Finland	Cohort	29124	57.2 ± 5.1#	ESCC	Lost ≤ 10 teeth	0.73 (0.35–1.55)
Dye 2007	China	CS	579	40–67	ESCC	Lost < 4 teeth	1.45 (0.76–2.76)
Guha 2007	Latin America	CC	173/1805	any age	ESCC	Lost ≤ 5 teeth	1.07 (0.41–2.77)
Guha 2007	Central Europe	CC	132/928	any age	ESCC	Lost ≤ 5 teeth	1.80 (1.80–4.07)
Michaud 2008	USA (White, Asian, Black)	Cohort	48375	40–75	EC	Lost ≤ 8 teeth	1.34 (0.78–2.30)
Abnet 2008	Iran	CC	283/560	65(56–73)/65(57–72)*	ESCC	Lost ≤ 12 teeth	1.79 (1.03–3.13)
Hiraki 2008	Japan	CC	354/708	20–79	EC	Lost ≤ 11 teeth	2.36 (1.17–4.75)
Dar 2013	India	CC	703/1664	61.6 ± 11.1/59.8 ± 11.1#	ESCC	None lost tooth	1.08 (0.68–1.69)

Table 1. Characteristics of included studies in the meta-analysis. CS, cross-sectional; CC, case-control; EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma;*, median (IQR);#, mean ± standard deviation.

References	Adjustment
Abnet 2001	age, gender, smoking, and alcohol
Abnet 2005	age and education
Dye 2007	age, gender, village, education, smoking
Guha 2007	age, gender, country/center, education, smoking, alcohol, and all other oral health variables
Abnet 2008	age, gender, place of residence, ethnicity, alcohol, smoking, opium, or both, education, number of appliances, and fruit and vegetable intake
Hiraki 2008	age, gender, tobacco, alcohol, vegetable and fruit intake, body mass index, and regular exercise
Michaud 2008	age, race, physical activity, history of diabetes, alcohol, body-mass index, geographical location, height, calcium intake, total calorific intake, red-meat intake, fruit and vegetable intake, vitamin D score, and smoking
Dar 2013	age, ethnicity, residence, education, wealth score, fruit and vegetable intake, bidi smoking, gutka chewing, alcohol consumption and cumulative use of hookah, cigarette, and nass

Table 2. Adjustments in studies included in the meta-analysis
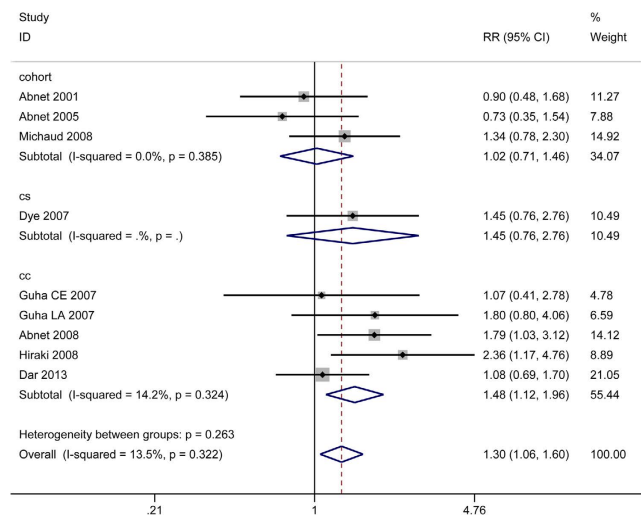

Figure 2. Forest plot of tooth loss and risk of esophageal cancer in overall population. Guha CE 2007, the study was conducted in Europe; Guha LA 2007, the study was conducted in Latin-America.

Five studies provided sufficient data of dose-response relationship. Our dose-repose meta-analysis showed an increased risk of EC corresponding to every 1 tooth loss increment (RR = 1.01, 95%CI = 1.00–1.03). No evidence of nonlinear relationship was detected (P = 0.45; Fig. 3).

Table 3 shows the results of subgroup analyses. The results of all subgroup analyses showed significantly increased risk in case-control studies and in adjustments for smoking and/or alcohol.

Publication bias. Visual inspection of the funnel plot did not identify any substantial asymmetry (Fig. 4), which indicated no publication bias existed.
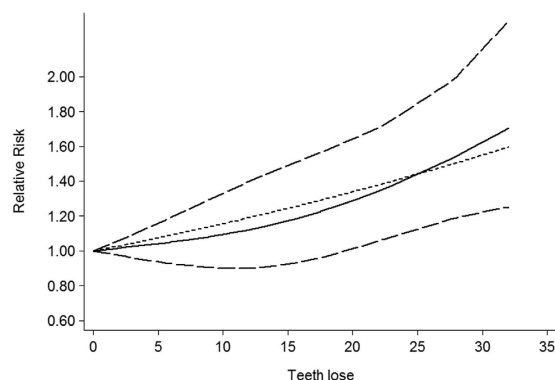
Figure 3. Dose-response analysis of every 1 tooth loss increment and risk of esophageal cancer. The black solid line and the black long dashed line represent the estimated RRs and corresponding 95% CIs for the non-linearity. The black short dashed line represents the estimated RRs for the linearity.

Subgroups	No. of studies	Heterogeneity		Effect model	Meta-analysis	
		I^2(%)	p^h		RR (95%CI)	p
Study design						
Cohort	3	0	0.39	Fixed	1.02 (0.71–1.46)	0.91
Case-control	5	14.2	0.32	Fixed	1.48 (1.12–1.96)	<0.01
Cross-sectional	1	NA	NA	NA	1.45 (0.76–2.76)	0.26
Outcomes						
ESCC	7	1.2	0.42	Fixed	1.21 (0.95–1.53)	0.13
Mixed	2	36.4	0.21	Fixed	1.66 (1.08–2.54)	0.02
Definition of reference group						
None lost tooth	2	0	0.64	Fixed	1.01 (0.70–1.46)	0.94
No. of lost tooth	7	6.4	0.38	Fixed	1.46 (1.14–1.89)	<0.01
Effect estimation						
Relative risk	1	NA	NA	NA	0.90 (0.48–1.68)	0.74
Hazard ratio	2	40.3	0.20	Fixed	1.09 (0.70–1.68)	0.71
Odds ratio	6	0	0.46	Fixed	1.47 (1.14–1.91)	<0.01
Adjustment						
Smoking	8	0	0.46	Fixed	1.37 (1.10–1.70)	<0.01
Smoking and alcohol	7	10.4	0.35	Fixed	1.36 (1.08–1.71)	0.01

Table 3. Results of subgroups analyses of pooled RRs and 95% CIs. No., number; ESCC, esophageal squamous cell carcinoma; RR, relative risk; CI, confidence interval.

Discussion

The present meta-analysis found evidence of an association between tooth loss and the risk of developing EC, with the loss of tooth significantly increasing the risk by 30%. And the relationship between tooth loss and the risk of developing EC is linearly dependent. Subgroup analyses revealed similar results of pooled estimations, and publication bias was not observed. In fact, this significant association could be explained. Periodontal disease is a chronic inflammatory disease, which contributing to constant low-grade systemic inflammation with elevated levels of circulating inflammatory markers[4,34] and is associated with HNC[35] and EC[36,37]. Periodontal disease is the major cause of tooth loss[38,39], and tooth loss is also a maker of systemic inflammation[40,41]. The link between inflammation and cancer has long been recognized[42–45], and it is likely that the progression of periodontal disease to tooth loss also represents a progression in the breakdown of normal cell-cycle control and potential carcinogenesis. In addition, the progression of tooth loss destroys the normal periodontal tissue, allowing oral microorganisms to accumulate deep into the oral tissue, thereby facilitating their growth. Oral microorganisms produce greater amounts of nitrosamine[46], which is significantly associated with the development of cancer[47,48]. It is not difficult to envisage that during normal physiological behavior such as swallowing and drinking, oral microorganisms as well as the produced nitrosamine are passed into the esophagus from the oral cavity along with food and drinks; therefore, an association between tooth loss and EC seems plausible.

Subgroup analyses provided varied results of cross-sectional study design, which could be partly due to the smaller number of included studies or the limitations of this design; however, the pooled results from case-control studies and cohort studies presented a significantly increased risk of EC associated with tooth loss (Table 3). On the other hand, according to the Hill's criteria, which are widely accepted for determining causality[49], our meta-analysis
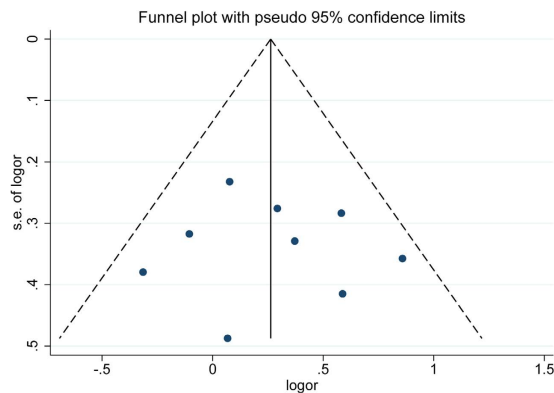
Figure 4. Funnel plot with pseudo-95% CIs of results of 5 studies based on the result of overall population.

indicates that tooth loss is a marker rather than a causal factor for EC. In our meta-analysis, all included studies did not show consistency in results, and pooled RRs only showed a weak association. In addition, only 3 cohort studies among the 10 included studies involved to temporality, although their pooled result showed a significant association. Furthermore, there is no evidence whether control of tooth loss can prevent EC up to now; therefore, the specificity of the association cannot be evaluated. Moreover, there is lack of experimental research. In summary, these factors suggest that that tooth loss is a marker rather than a causal factor for EC.

The heterogeneity was none to mild among the studies examining the association between tooth loss and the risk of EC[23]. This mild heterogeneity can be attributed to the differences in the characteristics of different populations, definitions of the reference and tooth loss group(s), and adjustment for confounding factors. Our subgroup analyses provide evidence that the study design, definition of the reference group, reported effect size, pathological type, and adjustment of origin was not the source of the heterogeneity (Table 3). Hence, the mild heterogeneity might be the inherent shortage of meta-analysis or due to the statistic heterogeneity.

Our meta-analysis also has some strengths and implications. To the best of our knowledge, this study is the first meta-analysis on this topic. We have searched relevant published studies via electronic and manual searching and collected all published studies that met the inclusion criteria; no publication bias has been detected. In addition, all included studies provided adjusted effect sizes. Nine studies have adjusted for smoking, while 7 have simultaneously adjusted for smoking and alcohol (Table 2). For smoking and alcohol are the well accepted risk factor of EC[9–16], we conducted subgroup analysis to investigate the smoking adjusted studies and both smoking and alcohol adjusted studies, the results were both significantly and similar. Thereby ensuring the accuracy of the results obtained and indicating that tooth loss is independent of the conventional risk factors for EC. Furthermore, accumulating evidence and the large sample size of included studies provide the statistical power to present precise and reliable risk estimates relative to a single study. The results of the included studies are not consistent, and subgroup analysis revealed that the sample size could influence the result. Moreover, we could not identify a causal relationship between tooth loss and the risk of EC; the actions, such as toothbrushing[32,50] are suggested to prevent tooth loss and this may decrease the risk of developing EC. Relevant animal studies and interventional studies are necessary to further explore the association between tooth loss and EC. Finally, people who cessation smoking, mild drinking, daily use of dental floss, and seeks periodontal therapy are all important ways of countering the increased risk of EC in these subjects.

Despite these strengths, several limitations should be acknowledged in our meta-analysis. First, the definition of the reference group and tooth loss used varied among studies. Nowadays, no international unification index for evaluating tooth loss in relevant studies is available, which could result in heterogeneity and increase the difficulty of performing meta-analysis, even resulting in failure to meet the criteria for meta-analysis. Second, substantial heterogeneity was observed among studies, although it was mild and very commonly found in meta-analysis of observational studies and is understandable, which cannot be ignored. We have investigated heterogeneity using subgroup analyses; however, the real source(s) of heterogeneity could not be identified. Third, subgroup analyses revealed that the results are significantly inconsistent with limited statistical power owing to a relatively small number of included studies. We used Hill's criteria to argue causality and have discussed how the results could be influenced by the sample size; greater numbers of relevant studies addressing this topic are required for enlarging the sample size. Furthermore, while almost all included studies have adjusted for smoking and alcohol consumption, other unmeasured factors, such as diabetes, gastroesophageal reflux, and socioeconomic factors may confound the interpretation of an association between tooth loss and EC and potentially introduce bias. Only a few included studies have adjusted for these factors (Table 2). Fourth, although no evidence of publication bias was observed, the statistical power of our study is limited by a relatively small number of included studies; thus, it is difficult to be certain that there is no publication bias. These limitations of the present meta-analysis may affect the accuracy of our results. Finally, for lacking of relevant assessment tool of cross-sectional study, we could not assess the risk of bias of included studies[51].

In summary, the present meta-analysis indicates that tooth loss is probably a significant and dependent risk factor for EC, suggesting that people who have lost teeth should pay attention to the symptoms and avoid other

classical risk factors for EC. Moreover, according to the Hill's criteria for causal inference, tooth loss is a marker rather than causality for EC.

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Q.L.C. and X.T.Z. designed this article. Z.X.L. and X.L.D. searched studies and collected data. J.Q. and W.D.L. analysed and explained the data. Q.L.C. and X.T.Z. drafted the manuscript. Z.X.L. and W.D.L. reviewed the manuscript. All authors read and approved the final manuscript.

Additional Information

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