Tooth Loss and Risk of Head and Neck Cancer: A Meta-Analysis

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Abstract

Background: Observational studies suggest an association between tooth loss and risk of head and neck cancer. However, whether tooth loss is an independent risk factor for head and neck cancer still remains controversial. The aim of this study is to assess the association between tooth loss and head and neck cancer risk.

Methods: Eligible studies were searched in PubMed and Embase databases from their inception to March 2013. A random-effects model or fixed-effects model was used to calculate the overall combined risk estimates.

Results: Eight case-control studies and one cross-sectional study involving 5,204 patients and 5,518 controls were included in the meta-analysis. The overall combined odds ratio for tooth loss and head and neck cancer was 2.00 (95% confidence interval, 1.28–3.14). Similar results yielded both in the moderate and severe tooth loss group. Sensitivity analysis based on various exclusion criteria maintained this significance with respect to head and neck cancer individually. Little evidence of publication bias was observed.

Conclusion: This meta-analysis suggests that tooth loss is associated with increased risk of head and neck cancer. This increase is probably independent of conventional head and neck cancer risk factors.

Background

Head and neck cancer includes cancer of oral cavity, pharynx, and larynx. It is estimated that one out of 99 people born in the United States today will experience head and neck cancer during their lifetime [1]. It has been recognized as a significant component of the global burden of cancer [2,3,4]. Any possible risk factors to increase head and neck cancer should be explored thoroughly. Tobacco use and alcohol consumption have been well established as the predominant etiologic factors for head and neck cancer, with their population-attributable risk for head and neck cancer in the United States by 74% [5]. Other risk factors such as periodontal disease [6], Human papillomavirus (HPV) infections [7], oral hygiene and dental status [8,9], have also been implicated in the etiology of head and neck cancer.

Periodontal disease is a chronic, destructive disease that affects approximately 35% dentate adults 30 to 90 years old in the United States [10] and up to 90% of the worldwide population [11]. Periodontal disease is believed to be one of the major causes of tooth loss in adults [12]. Nowadays, multiple epidemiologic studies investigating the association between tooth loss and risk of head and neck cancer. The following search terms were used: periodontal disease, periodontitis, tooth loss, and head and neck cancer, filtered by Human, without language restrictions. Reference lists of reviews or studies identified in the literature search were hand searched for additional studies. If duplicated data were presented in several studies, only the most recent, largest or most complete study was included. Studies meeting the following criteria were included: (i) investigating the association between tooth loss and risk of head and neck cancer. The following search terms were used: periodontal disease, periodontitis, tooth loss, and head and neck cancer, filtered by Human, without language restrictions. Reference lists of reviews or studies identified in the literature search were hand searched for additional studies. If duplicated data were presented in several studies, only the most recent, largest or most complete study was included. Studies meeting the following criteria were included: (i) evaluating the association between tooth loss and head and neck cancer; (ii) with ≤5 lost teeth as the referent category; and (iii) providing the adjusted odds ratios (ORs) with the corresponding...
### Table 1. Characteristics of studies included in this meta-analysis.

| Study                | Location      | Study design | Group | No. of subjects | Age, Median (Range), yrs | Assessment of tooth loss | Cancer site                  | Source of controls | Adjustment for covariates                                                                 |
|----------------------|---------------|--------------|-------|-----------------|--------------------------|--------------------------|------------------------------|---------------------|----------------------------------------------------------------------------------------|
| Talamini et al 2000  | Italy         | Case-control | case  | 132             | 60 (27–86)               | Self-reported            | Oral cavity, oropharynx, unspecified cancer | Hospital            | Age, gender, fruit and vegetable intake, and smoking and drinking habits                 |
| control              |               |              |       | 148             | 60 (30–83)               |                          |                             |                     |                                                                                        |
| Fernandez Garrote et al 2001 | Cuba | Case-control | case  | 200             | 64 (28–91)               | Inspected by dentist     | Oral cavity, oropharynx, and both site cancer | Hospital            | Age, gender, area of residence, education, smoking and drinking habits                   |
| control              |               |              |       | 200             | 62 (25–88)               |                          |                             |                     |                                                                                        |
| Balaram et al 2002   | India         | Case-control | case  | 591             | NA (18–87)               | Inspected by interviewer | Oral cavity               | Hospital            | Age, center, education and (men only) smoking and drinking habits                        |
| control              |               |              |       | 582             | NA (18–80)               |                          |                             |                     |                                                                                        |
| Lissowska et al 2003 | Poland        | Case-control | case  | 122             | NA (23–80)               | Inspected by dentist     | Oral cavity, oropharynx, unspecified cancer | Hospital            | Age, gender, residence, smoking and drinking habits                                      |
| control              |               |              |       | 124             | NA (NA)                  |                          |                             |                     |                                                                                        |
| Rosenquist et al 2005 | Sweden   | Case-control | case  | 132             | NA (33–87)               | Inspected by dentist     | Oral cavity, oropharynx, unspecified cancer | Population | NA                                                                                     |
| control              |               |              |       | 320             | NA (NA)                  |                          |                             |                     |                                                                                        |
| Guha et al 2007      | Central Europe| Case-control | case  | 712             | NA (NA)                  | Inspected by dentist or interviewer | Oral cavity, pharynx, larynx | Hospital and Population | Age, gender, country, education, tobacco pack-years, cumulative alcohol consumption, and all other oral health variables |
| control              |               |              |       | 928             | NA (NA)                  |                          |                             |                     |                                                                                        |
| Guha et al 2007      | Latin America | Case-control | case  | 1,976           | NA (NA)                  | Inspected by dentist or interviewer | Oral cavity, pharynx, larynx | Population | Age, gender, country, education, tobacco pack-years, cumulative alcohol consumption, and all other oral health variables |
| control              |               |              |       | 1,805           | NA (NA)                  |                          |                             |                     |                                                                                        |
| de Rezende et al 2008 | Brazil  | cross-sectional | case  | 50              | NA (NA)                  | Inspected by dentist     | Oral cavity, oropharynx   | Population | NA                                                                                     |
| control              |               |              |       | 50              | NA (NA)                  |                          |                             |                     |                                                                                        |
95% CI or raw data to calculate the crude ORs and 95% confidence intervals (CIs).

Data extraction and outcome measure

Two reviewers (XYH and WJG) independently extracted data about the characteristics of selected studies using a standardized data extraction form. Data were recorded as follows: first author, year of publication, location, number of subjects (cases/controls), patient characteristics, assessment of tooth loss, cancer site, statistical adjustment for confounding factors, source of controls, study design, and outcome data. Disagreements were resolved by discussion and consensus with a third author (RSW).

Statistical analyses

OR with 95% CI was used as a common measure of the association between tooth loss and risk of head and neck cancer across studies. For purposes of the present analysis, tooth loss was coded as a three-level indicator variable, with ≤5 lost teeth as the referent category, 6–15 lost teeth as the moderate tooth loss group, and >15 lost teeth as the severe tooth loss group, respectively. Statistical heterogeneity was evaluated using the Cochran Q test (significance level at <0.10). The I² statistic [28], which was a quantitative measure of inconsistency across studies, was also calculated. The random-effects model (DerSimonian and Laird method [29]) was taking into account when heterogeneity was observed among studies. Otherwise, a fixed-effects model (Mantel–Haenszel method [30]) was applied. In the presence of heterogeneity, sensitivity analyses based on assessment of tooth loss, adjustment for covariates, and sample size were conducted to identify potential sources. We also assessed the influence of individual studies on the combined risk estimate by sequentially excluding one study in each turn to test the stability of the main results.

Potential publication bias was assessed both by visually inspecting of the Begg funnel plot and statistically via Begg and Egger's unweighted regression tests [31,32]. A P value less than 0.05 was judged as statistically significant, except where otherwise specified. Statistical analyses were carried out with STATA version 11.0 (Stata Corporation, College Station, Texas, USA). All the P values were two-sided.

Results

Identification of eligible studies

The search strategy identified 3,569 potential studies from PubMed and Embase databases. Of these, the majority were excluded after reviewing titles and abstracts, mainly because they were reviews, letter, comment, or not relevant to our analysis, leaving 18 for full-text review. In the review, 9 articles were excluded for the reasons as follows: three articles with unavailable data for analysis [16,17,20], and six articles not with ≤5 lost teeth as the referent category [6,13,14,15,18,19]. One study [25] was conducted in Central Europe and Latin America, respectively. We considered it as two case-control studies. Finally, nine studies [8,21,22,23,24,25,26,27] were included in our meta-analysis. A detailed flowchart of the selection process was shown in Diagram S1.

Study characteristics

The characteristics of all included studies were presented in Table 1. Theses studies were published between 2000 and 2010. Sample size ranged from 50 to 1,976 (total 10,722). Eight were case-control studies and one was a cross-sectional prospective study. Among these studies, all reported tooth loss events, eight...
reported moderate tooth loss events, and eight reported severe tooth loss events.

The assessment of tooth loss was from a variety of sources, including self-reported, and inspected by dentist or interviewer. The anatomical sites of head and neck cancer were various across studies, including oral cavity, pharynx, larynx, and unspecified cancer site. Three studies reported an association between tooth loss and three sites of head and neck cancer (oral cavity, pharynx, and larynx). Two studies did not adjust for confounder factors, whereas others controlled a group of conventional risk factors for head and neck cancer, including age, gender, smoking, and drinking.

Tooth loss and risk of head and neck cancer

A total of 10,722 participations were included in the nine studies exploring the association between tooth loss and risk of head and neck cancer (5,204 assigned to case group and 5,518 assigned to control group). Overall, tooth loss experienced a significant elevated risk for developing head and neck cancer (>5 vs. ≤5: OR 2.00, 95%CI 1.28–3.14; \(P=0.002\)). Substantial heterogeneity was observed \((I^2 = 82.9\%); \(P=0.000\)) (Figure 1). Subsequently, sensitivity analyses were conducted to explore the potential source of heterogeneity and to examine the effect of various exclusion criteria on the combined risk estimates. Similar results were observed in these analyses, with substantial evidence of heterogeneity (data were shown in Table 2).

The severity of tooth loss and risk of head and neck cancer

Furthermore, we conducted meta-analyses based on the grade to explore the effect of the severity of tooth loss on head and neck cancer, and the results were relatively consistent. A significantly increased risk of head and neck cancer was found in both the moderate tooth loss group (6–15 vs. ≤5: OR 1.18, 95%CI 1.02–1.38; \(P=0.032\)) and severe tooth loss group (>15 vs. ≤5: OR 1.54, 95%CI 1.08–2.21; \(P=0.018\)) (Figure 2). Substantial evidence of heterogeneity was only observed in the severe tooth loss group \((I^2 = 73.0\%); \text{heterogeneity} \(P=0.001\)), rather than in the moderate tooth loss group \((I^2 = 16.8\%); \text{heterogeneity} \(P=0.297\)). To test the robustness of our findings, sensitivity analyses were performed. Sensitivity analyses yielded similar results, with substantial evidence of heterogeneity (data were presented in Table 2).

Tooth loss and anatomical sites of head and neck cancer

When studies were divided by anatomical sites of head and neck cancer, there was significant increase in larynx cancer (6–15 vs. ≤5: OR 1.45, 95%CI 1.14–1.85; \(P=0.009\); \(I^2 = 21.0\%); heterogeneity \(P=0.282\)). However, no association was observed in tooth

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**Table 1. Forest plot showing the association of tooth loss with the risk of head and neck cancer.** (Balaram et al. 2002 had separate adjusted OR in male and female population.)

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| Study                     | ID | OR (95% CI)     | Weight |
|---------------------------|----|----------------|--------|
| Takemoto et al 2000       |    | 1.04 (0.81, 2.55) | 9.60   |
| Fernández-Garre et al 2001|    | 2.03 (1.18, 3.79)  | 9.56   |
| Balaram et al 2002        |    | 3.39 (2.06, 5.57)  | 11.22  |
| Balaram et al 2002        |    | 7.61 (3.89, 14.84) | 9.89   |
| Lisowski et al 2003       |    | 9.44 (7.16, 25.29) | 7.16   |
| Rosenquist et al 2005     |    | 1.58 (1.06, 2.41)  | 11.49  |
| Guha et al 2007           |    | 0.84 (0.50, 1.42)  | 16.82  |
| Guha et al 2007           |    | 1.30 (0.82, 2.05)  | 11.23  |
| de Heus et al 2008        |    | 1.14 (0.92, 1.40)  | 7.18   |
| Divets et al 2010         |    | 1.14 (0.92, 1.40)  | 11.23  |
| Overall (L-squared – 82.9\%, \(P=0.000\)) |    | 2.10 (1.29, 3.14)  | 100.00 |

**NOTE:** Weights are from random effects analysis
loss with oral cavity (6–15 vs. ≤5: OR 0.92, 95%CI 0.72–1.18; P = 0.531; I\(^2\) = 0.0%; heterogeneity P = 0.282) or pharynx cancer (6–15 vs. ≤5: OR 1.25, 95%CI 0.94–1.65; P = 0.128; I\(^2\) = 24.1%; heterogeneity P = 0.268).

Publication bias
Both Begg’s (rank correlation test) and Egger’s funnel plot asymmetry test (regression method) in the meta-analysis indicated that there was no significant publication bias (>5 vs. ≤5: Begg’s test, P = 0.371; Egger’s test, P = 0.309; Figure 4).

Discussion
The overall estimates of the present meta-analysis provided evidence that tooth loss was significantly associated with increased risk of head and neck cancer. In addition, the moderate tooth loss and the severe tooth loss experienced a significantly increased risk of head and neck cancer by 18% and 54%, respectively. Furthermore, the moderate tooth loss was associated with a 45% increase in the risk of larynx cancer. The combined estimates were robust across sensitivity analyses and had no observed publication bias.

Several plausible mechanisms may explain why a significant increased association of tooth loss with head and neck cancer was observed in the present analysis. The link between inflammation

| Studies, N | Cases, N | Control, N | OR, 95%CI | P-value | P of heterogeneity | I\(^2\) (%) |
|-----------|---------|-----------|-----------|---------|-------------------|-----------|
| >5 vs. ≤5 |         |           |           |         |                   |           |
| Total     | 9       | 5,204     | 5,518     | 2.00 (1.28–3.14) | 0.002 | 0.000 | 82.9 |
| Assessment of tooth loss | | | | | | |
| Inspected by dentist or interviewer | 7 | 3,783 | 4,009 | 2.31 (1.35–3.97) | 0.002 | 0.000 | 84.8 |
| Self-reported | 2 | 1,421 | 1,509 | 1.17 (0.79–1.72) | 0.430 | 0.846 | 0.0 |
| Adjustment for covariates | | | | | | |
| Yes | 7 | 5,022 | 5,148 | 2.21 (1.26–3.87) | 0.006 | 0.000 | 86.3 |
| NA | 2 | 182 | 370 | 1.52 (1.04–2.23) | 0.030 | 0.539 | 0.0 |
| Sample size | | | | | | |
| Large | 8 | 5,154 | 5,468 | 2.11 (1.31–3.38) | 0.002 | 0.000 | 84.5 |
| Small | 1 | 50 | 50 | 1.14 (0.42–3.10) | NA | NA | NA |
| 6–15 vs. ≤5 | | | | | | |
| Total | 8 | 4,613 | 4,936 | 1.18 (1.02–1.38) | 0.032 | 0.297 | 16.8 |
| Assessment of tooth loss | | | | | | |
| Inspected by dentist or interviewer | 6 | 3,192 | 3,427 | 1.24 (1.03–1.50) | 0.023 | 0.179 | 34.3 |
| Self-reported | 2 | 1,421 | 1,509 | 1.07 (0.82–1.40) | 0.603 | 0.950 | 0.0 |
| Adjustment for covariates | | | | | | |
| Yes | 6 | 4,431 | 4,566 | 1.21 (1.02–1.42) | 0.024 | 0.162 | 36.7 |
| NA | 2 | 182 | 370 | 1.01 (0.63–1.62) | 0.969 | 0.859 | 0.0 |
| Sample size | | | | | | |
| Large | 7 | 4,563 | 4,886 | 1.19 (1.01–1.38) | 0.032 | 0.210 | 28.6 |
| Small | 1 | 50 | 50 | 1.11 (0.35–3.51) | NA | NA | NA |
| >15 vs. ≤5 | | | | | | |
| Total | 8 | 4,613 | 4,936 | 1.54 (1.08–2.21) | 0.018 | 0.001 | 73.0 |
| Assessment of tooth loss | | | | | | |
| Inspected by dentist or interviewer | 6 | 3,192 | 3,427 | 1.77 (1.02–3.06) | 0.042 | 0.000 | 80.1 |
| Self-reported | 2 | 1,421 | 1,509 | 1.22 (0.96–1.56) | 0.100 | 0.739 | 0.0 |
| Adjustment for covariates | | | | | | |
| Yes | 6 | 4,431 | 4,566 | 1.39 (0.96–1.56) | 0.084 | 0.004 | 71.5 |
| NA | 2 | 182 | 370 | 2.34 (1.47–3.73) | 0.000 | 0.148 | 52.3 |
| Sample size | | | | | | |
| Large | 7 | 4,563 | 4,886 | 1.59 (1.08–3.33) | 0.018 | 0.000 | 76.8 |
| Small | 1 | 50 | 50 | 1.16 (0.40–3.32) | NA | NA | NA |

OR, odds ratio; CI, confidence interval; NA, not available; Large, cases ≥100; Small, cases <100.
and cancer has long been recognized [33, 34, 35]. Periodontitis, a chronic inflammatory disease, contribute to constant low-grade systemic inflammation with elevated levels of circulating inflammatory markers [36]. Identified inflammatory markers, including pro-inflammatory plasma cytokines, peripheral white blood cells, prostanoids, proteases including matrix metalloproteinases, and acute-phase proteins [36, 37, 38], produced in the immune response to periodontal disease. Chronic inflammation induced by periodontal pathogens may also result in the breakdown of normal cell growth control and potential carcinogenesis [33]. Alternatively, immune system in an individual with chronic periodontal disease may be deficient at clearing infection, and subsequently deficient at surveillance for tumor growth. Therefore, periodontitis are considered as a marker of a type of immune function that has potential influences on tumor growth and progression. Another plausible mechanism by which may explain the reported observations is increased production of carcinogenic nitrosamines. The formation of endogenous carcinogenic nitrosamines in the oral cavity is elevated by poor oral hygiene, periodontal disease, tobacco smoking, and certain dietary factors [39, 40]. Oral microbiota also result in greater nitrosamine production [41]. Therefore, drawing a link between tooth loss and head and neck cancer seems plausible. Other mechanisms by which consumptions of alcohol might be risky of head and neck cancer are the acetaldehyde production from alcohol by oral microbiota.

A cohort study on overall cancer risk and tooth loss by Tu et al. suggested that as tooth loss increases, periodontal disease may decrease (as edentulous patients no longer have active periodontal disease) [42]. It was in agreement with another observational study where they found that if the missing teeth were more than 15 the association with esophageal cancer disappeared [25]. That might be a limiting factor in establishing a solid link between tooth loss and head and neck cancer risk. Interestingly, overall risk estimates of the moderate and severe tooth loss did not change such an association of tooth loss with increased head and neck cancer risk (although the strength of the association was slightly attenuated), suggesting that tooth loss is probably an independent risk factor of head and neck cancer. Moreover, sensitivity analyses based other various exclusion criteria did not materially alter the overall estimates, which added robustness to our main finding.

An interesting clue on the topic may be useful for future research. Three case-control studies included in our meta-analysis were conducted to assess the association of tooth loss with the anatomical sites of head and neck cancer. Only two studies consistently suggest that tooth loss significantly increase the risk of larynx cancer rather than oral cavity and pharynx cancer. Thus, a new question arise, does tooth loss really increase the risk of different anatomical sites of head and neck cancer? However, overall risk estimates show that only the moderate tooth loss was associated with a 45% increase in the risk of larynx cancer. The results should be interpreted with caution. There might be several factors ascribing to these contradicting findings. Small numbers of
Figure 3. Forest plot showing the association of severe tooth loss with the risk of head and neck cancer.
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Figure 4. Funnel plots of tooth loss for assessment of publication bias.
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Author Contributions

Conceived and designed the experiments: RSW BW. Performed the experiments: XYH. Analyzed the data: WJG. Contributed reagents/materials/analysis tools: ZH. Wrote the paper: XYH.
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