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*Original Article*

# Tooth loss and risk of oral squamous cell carcinoma in Chinese Han population

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**Abstract:** Objective: Association between tooth loss and oral cancer risk was investigated primary studies and meta-analyses, however, the results remain inconsistent. This study is to test the association between tooth loss and oral squamous cell carcinoma (OSCC) in Chinese Han population. Methods: Case-control study including histologically confirmed OSCC cases and healthy controls individually matched to the cases for age, sex, and district of residence between May 1, 2010, and Match 31, 2014. Univariate and multiple logistic regression models were used to calculate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) using the STATA 12.0 software. Results: Finally included 150 OSCC patients and 167 healthy controls. Cases had a significantly higher mean (SD) number of lost teeth than controls (10.03±6.62 vs. 8.69±5.20; P = 0.045). The results of univariate analysis and adjustment for smoking and alcohol showed a non-significant association between tooth loss and OSCC. After adjustment for age at diagnosis, gender, smoking, alcohol use, body mass index, and history of diabetes mellitus, those in the upper tertiles of lost tooth were significantly more likely to have OSCC (OR = 3.64, 95% CI = 1.15-11.53, P = 0.03; *P* for trend = 0.11) than in the lower tertiles. The unadjusted and adjusted results of per teeth also revealed non-significant association. Conclusions: Tooth loss may be not associated with risk of oral cancer in this case-control study. The relevant large-scale studies in Chinese are suggested to perform.

**Keywords:** Oral cancer, oral squamous cell carcinoma, tooth loss, case-controls study

## Introduction

Many published epidemiological studies have investigated an association between tooth loss and risk of orodigestive cancer, including the cancers in the oral cavity and pharynx, esophagus, stomach, pancreas, liver, and colon, rectum or anus [1-3]. However, evidence of a relationship between tooth and oral cancer is inconsistent. A case-control study of tooth loss and oral cancer risk was conducted in Beijing, People's Republic of China in 1990 by Zheng et al. indicated that tooth loss was significantly increased risk of oral cancer 5.98 times after adjusted age, gender, tobacco, alcohol, and education [4]. The another case-control study carried out in 1995 in Denmark also found tooth loss was significantly increased risk of oral squamous cell carcinoma (OSCC) after alcohol and smoking were adjusted [5]. However, three case-control studies from Italy [6], Sweden [7], and USA [8] found negative association between tooth loss and oral cancer. Interestingly, multicentric case-control studies in 2007 yielded an opposite direction of the trend between tooth loss and oral cancer in the Central Europe and the Latin America population [9]. In order to address the inconsistent results, two studies were conducted in 2013 [10, 11] using a meta-analytic approach [12]. Both of these two meta-analyses indicated that tooth loss is significantly associated with increased risk of head and neck cancer [10, 11]; however, they also suggested continued to perform relevant studies for further investigation, especially perform the dose-response analysis.

In the current study, we explore the associations between tooth loss and OSCC (including

**Table 1.** Characteristics of 150 cases and 167 healthy controls

| Characteristics | Cases (150) | Controls (167) | *P*-value[1] |
|---|---|---|---|
| Age at diagnosis, mean (SD), years | 59.35±13.64 | 58.83±13.57 | 0.74 |
| Gender (%) | | | 0.86 |
| Male | 111 (74.00) | 125 (74.85) | |
| Female | 39 (26.00) | 42 (25.15) | |
| Smoking status (%) | | | < 0.01 |
| Yes | 89 (59.33) | 20 (11.98) | |
| No | 61 (40.67) | 147 (88.02) | |
| Alcohol use (%) | | | 0.12 |
| Yes | 126 (84.00) | 150 (89.82) | |
| No | 24 (16.00) | 17 (10.18) | |
| Body mass index (%) | | | 0.01 |
| Normal | 81 (54.00) | 66 (39.52) | |
| Overweight | 64 (42.67) | 86 (51.50) | |
| Obese | 5 (3.33) | 15 (8.98) | |
| History of diabetes mellitus (%) | | | 0.22 |
| Yes | 6 (4.00) | 12 (7.19) | |
| No | 144 (96.00) | 155 (92.81) | |
| Number of lost teeth, mean (SD), No. | 10.03±6.62 | 8.69±5.20 | 0.045 |

[1]*P* values were derived from t tests for continuous variables and from $\chi^2$ tests for categorical variables comparing cases and controls.

oral cavity and or pharynx) in individuals from the Chinese Han population. We hypothesize that tooth loss may be associated with OSCC and the risk was increased gradually with the number of lost tooth increased. This study was reported according to the recommended STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) statement [13].

## Materials and methods

### *Study design and population*

This study used a case-control design. The participants were from the School & Hospital of Stomatology, Wuhan University, China. All patients seen between May 1, 2010, and May 1, 2015 were included; those who had a history of oral cancer, oral dysplasia, or immunodeficiency or were ≤ 18 years were excluded. This study was reviewed and approved by the institutional review boards of the Huizhou Municipal Stomatological Hospital.

All participants were selected from Han Chinese population and had signed the informed consent. The cases were newly diagnosed primary OSCC patients during the study period according to the International Classification of Diseases (ICD) for Oncology, 3rd Edition (Geneva, Switzerland: World Health Organization, 2000). The OSCC including following sites: tongue, buccal mucosa, gum, small area of the gum behind the wisdom teeth, floor of the mouth, lips, hard palate, soft palate, maxillary sinus, vestibule, oropharynx, and other parts of the mouth. The controls were the relatives or friends of OSCC patients, who visited or accompanied with the patient in hospital. The controls were all healthy or free of oral cancer.

### *Assessment of variables*

We used standard 32 teeth as reference and counted the existed number of teeth in the mouth, and then minus the number of existed teeth from 32 teeth, this was defined as number of lost teeth (or missing teeth). The number of teeth of every patient and control population was examined by the same author and examined two times; this duplicate measurement was made to provide intraexaminer reliability.

Information on the following variables was also obtained: age at diagnosis, gender, smoking status (no or yes), alcohol use (no or yes), tumor sites, body mass index (BMI; normal, overweight, or obese), and history of diabetes mellitus (no or yes).

### *Statistical analysis*

The means and corresponding standard deviations (SDs) were used to summarize the continuous variables, whereas percentages were used to summarize the binary variables. To investigate the association between tooth loss and oral cancer, the Pearson chi-square test or t-test was used to test the association, the crude odds ratios (ORs) with their 95% confidence intervals (CIs) were calculate. Considering the extraction of wisdom teeth and referred the previously studies [10, 14, 15], we used the lost of ≤ 5 teeth as reference group and catego-

**Table 2.** Association of oral squamous cell carcinoma with tooth loss

| No. of lost teeth | Cases | Controls | Unadjusted OR (95% CI); *P* | Adjusted OR[1] (95% CI); *P* | Adjusted OR[2] (95% CI); *P* |
|---|---|---|---|---|---|
| ≤ 5 | 44 | 48 | Ref [1.00] | Ref [1.00] | Ref [1.00] |
| 6-15 | 72 | 98 | 0.81 (0.48-1.33); 0.40 | 0.84 (0.49-1.45); 0.54 | 1.06 (0.53-2.13); 0.90 |
| ≥ 16 | 34 | 21 | 1.77 (0.89-3.49); 0.10 | 1.90 (0.92-3.89); 0.08 | 3.64 (1.15-11.53); 0.03 |
| *P* value for trend | | | 0.25 | 0.2 | 0.11 |
| Losing teeth, per tooth | 10.03±6.62[3] | 8.69±5.20[3] | 1.02 (0.99-1.05); 0.25 | 1.02 (0.99-1.06); 0.20 | 1.04 (0.99-1.10); 0.11 |

[1]Adjusted for smoking and alcohol use; [2]adjusted for age at diagnosis, gender, smoking, alcohol use, body mass index, and history of diabetes mellitus; [3]mean (SD).

rize exposure variables into 3 categories: ≤ 5 teeth, 6 to 15 teeth, ≥ 16 teeth. The trend with increase number of lost teeth was evaluated. A multiple logistic regression analysis was also performed to obtain adjusted ORs and their 95% CIs by considering the confounding risk factors of oral cancer. A two-side $P \leq 0.05$ was considered statistically significant. All analyses were carried out using the STATA 12.0 software.

## Results

A total of 317 participants with 150 OSCC patients and 167 healthy controls were finally included. The age of diagnosis (P = 0.74), gender (P = 0.86), alcohol use (P = 0.12), and history of diabetes mellitus (P = 0.22) were similar in the case and control group; however, the prevalence of smokers (P < 0.01) and overweight and obese participants (P = 0.01) were significantly higher among cases compared with controls. The mean number of lost tooth was higher among cases compared with controls (P = 0.045). **Table 1** presents the relevant characteristics of cases and controls.

In the unadjusted analysis, participants in the upper tertiles of lost tooth were more likely to have OSCC compared with lower tertiles, but the association is non-significant (OR = 1.77, 95% CI = 0.89-3.49, P = 0.10; P for trend = 0.25). After adjustment for smoking and alcohol use, the results were similar with unadjusted results (OR = 1.90, 95% CI = 0.92-3.89, P = 0.08; P for trend = 0.2). After adjustment for age at diagnosis, gender, smoking, alcohol use, body mass index, and history of diabetes mellitus, participants in the upper tertiles of lost tooth were significantly more likely to have OSCC (OR = 3.64, 95% CI = 1.15-11.53, P = 0.03; P for trend = 0.11). Tooth loss becomes significantly associated with OSCC (**Table 2**).

Number of missing teeth might be associated with increased risk of OSCC but was not significantly, either in the univariate analysis or the adjusted analyses (**Table 2**).

## Discussion

Our study found a non-significant association between tooth loss and risk of OSCC, after adjustment for smoking and alcohol use, the results remain keep non-significant; however, after adjustment for age at diagnosis, gender, smoking, alcohol use, body mass index, and history of diabetes mellitus, an inverse association was found in the group of 16 and more tooth loss (OR = 3.64, 95% CI = 1.15-11.53, P = 0.03). The trends for OSCC incidence risk and lost tooth of unadjusted and adjusted results were all non-significant. We also analyzed the association of per tooth but also revealed none significantly increased risk.

Our results are opposition to the meta-analysis [10, 11] and some previously studies [4, 5], whereas our results are in agreement with several other studies [6, 7, 14]. Periodontal diseases were associated with increased risk of oral cancer [16, 17]. As we know, periodontal disease is characterized by chronic bacterial infections and the major reason for tooth loss in adults [18, 19]. In the progress from periodontal disease to tooth loss, the oral bacteria in the mouth can erode the tissue and enter into the tissue. Specific oral bacteria have been suggested to be involved in carcinogenesis [20]; hence, this progress provides the chance to carcinogenesis. This might explain the reason why tooth loss increases the risk of oral cancer.

Why our study and some recently studies both indicated non-significant association? This might be explained by toothbrushing. Oral hygiene is also a risk factor of oral cancer [21, 22]. Toothbrushing is an effective approach to keep oral hygiene and decreased the risk of periodontal disease [23]. Recently meta-analysis also indicated that fewer toothbrushing is asso-

ciated with increased risk of oral cancer [24]. The participants of our study come from the Huizhou City, Guangdong Province. As we know, Guangdong is an economy-developed province and the front of the reform and opening to the outside of China. Hence, the economic status and awareness of the population is higher, this promote them routine keep effective toothbrushing and dental checks [25] in hospital. Of course, the oral bacteria can be controlled and the chance to carcinogenesis would be decreased. This can also explain why the first relevant study in Beijing in 1990 showed significant association between tooth loss and increased risk of oral cancer [4].

Considering the smoking and alcohol use are the classical risk factors of oral cancer [26], we collected the data of them and adjusted them but obtained non-significant association. The reason might also due to the effective oral cleaning of included participants. Diabetes mellitus is another risk factor of oral cancer and was assessed in a recently meta-analysis [27], then we also collected data of history of diabetes and adjusted it. After adjusting all variables, the upper tertiles of lost tooth were significantly. We think this phenomenon might be explained by age. Age is a factor of tooth loss and the elderly participants with less awareness to keep oral health; besides, the number of tooth loss is increased with age increased. Lost number of 16 and tooth of the OSCC patients and healthy controls are major elderly participants in our study, hence, we may understand why the upper tertiles of lost tooth were significantly associated with increased risk of OSCC after adjustment for age et al.

To our knowledge, his is the secondary study conducted to investigate the association between tooth loss and oral cancer in Chinese. The first one was performed by Zheng et al. in 1990 in Beijing [4]. Our study can provide current status of Chinese. However, the sample sizes of our study remain not enough which might bias the results. In addition, case-control study is a retrospective analysis and cannot judge the sequential relationship of tooth loss and incident of oral cancer. In our opinion, the genetic background of participants should be considered in further studies. Genetic factors are also play an important role in the development of oral cancer [28, 29]. Unfortunately we do not know to keep relevant tissues or blood of cases and controls and the genetic test cannot carry out in our study. Although we adjusted results for multiple potential confounding factors, existence of some unknown confounders in this population, such as genetic factor and habit to eat traditional Chinese medicine routinely, or residual confounding could not totally be excluded. Future studies assessing the potential effects of the oral bacteria and associated biological mechanism on OSCC remains necessary, especially using cohort design.

## Disclosure of conflict of interest

None.

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