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**Poor oral health was associated with higher risk of gastric cancer: Evidence from 1431677 participants**

Liu F *et al.* Poor oral health and GC

## **Abstract**

### **BACKGROUND**

In recent years, the association between oral health and the risk of gastric cancer (GC) has gradually attracted increased interest. However, in terms of GC incidence, the association between oral health and GC incidence remains controversial. Periodontitis is reported to increase the risk of GC. However, some studies have shown that periodontitis has no effect on the risk of GC. Therefore, the present study aimed to assess whether there is a relationship between oral health and the risk of GC.

### **AIM**

To assess whether there was a relationship between oral health and the risk of GC.

### **METHODS**

Five databases were searched to find eligible studies from inception to April 10, 2023. Newcastle-Ottawa Scale score was used to assess the quality of included studies. The quality of cohort studies and case-control studies were evaluated separately in this study. Incidence of GC were described by odds ratio (OR) and 95% confidence interval (CI). Funnel plot was used to represent the publication bias of included studies. We performed the data analysis by StataSE 16.

### **RESULTS**

A total of 1431677 patients from twelve included studies were enrolled for data analysis in this study. According to our analysis, we found that the poor oral health was associated with higher risk of GC (OR = 1.15, 95%CI: 1.02-1.29;  $I^2 = 59.47\%$ ,  $P = 0.00 < 0.01$ ). Moreover, after subgroup analysis, the outcomes showed that whether tooth loss (OR = 1.12, 95%CI: 0.94-1.29;  $I^2 = 6.01\%$ ,  $P > 0.01$ ), gingivitis (OR = 1.19, 95%CI: 0.71-1.67;  $I^2 = 0.00\%$ ,  $P > 0.01$ ), dentures (OR = 1.27, 95%CI: 0.63-1.19;  $I^2 = 68.79\%$ ,  $P > 0.01$ ), or tooth brushing (OR = 1.25, 95%CI: 0.78-1.71;  $I^2 = 88.87\%$ ,  $P > 0.01$ ) had no influence

on the risk of GC. However, patients with periodontitis (OR = 1.13, 95%CI: 1.04-1.23;  $I^2$  = 0.00%,  $P < 0.01$ ) had a higher risk of GC.

## CONCLUSION

Patients with poor oral health, especially periodontitis, had a higher risk of GC. Patients should be concerned about their oral health. Improving oral health might reduce the risk of GC.

**Key Words:** Oral health; Tooth loss; Periodontitis; Gastric cancer; Risk factor

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**Core Tip:** The aim of this current study was to assess whether there was a relationship between oral health and the risk of gastric cancer (GC). A total of 1431677 patients from twelve included studies were enrolled for data analysis in this study. This article summarised all the papers over the years on the relationship between oral health and the incidence of GC. After analysing them, the existing controversies were resolved to some extent. It was useful to guide clinical work.

## INTRODUCTION

Gastric cancer (GC) is one of the most common tumours worldwide and the forth leading cause of cancer death<sup>[1-3]</sup>. The incidence and mortality of GC continue to increase, and there are approximately 1 million new cases worldwide each year<sup>[3-5]</sup>. In China, more than 400000 new cases are diagnosed each year, accounting for 50% of new cases worldwide<sup>[6-8]</sup>. Prevention of GC has become a focal point because of these worrisome numbers. <sup>3</sup>Prevention of GC can be divided into primary prevention (reducing the incidence of GC) and secondary prevention (early detection and

treatment). Primary prevention includes smoking cessation, reducing salt intake, increasing fruit and vegetable intake, and other health behaviours, such as oral health behaviours<sup>[9]</sup>.

The oral cavity is the conduit between the external environment and the gastrointestinal tract and is involved in the intake and digestion of food. Oral hygiene plays an important role in human health. Measures of oral health included tooth loss, periodontitis, gingivitis, dentures, and tooth brushing. Poor oral health has been shown to be a risk factor for many diseases, including cardiovascular disease, atherosclerosis, oral cancer, kidney cancer, lung cancer, oesophageal cancer, and pancreatic cancer<sup>[10-18]</sup>.

In recent years, the association between oral health and the risk of GC has gradually attracted increased interest. However, in terms of GC incidence, the association between oral health and GC incidence remains controversial. Periodontitis is reported to increase the risk of GC<sup>[19]</sup>. However, some studies have shown that periodontitis has no effect on the risk of GC<sup>[20,21]</sup>. Therefore, the present study aimed to assess whether there is a relationship between oral health and the risk of GC.

## **MATERIALS AND METHODS**

### ***Methods***

Our study was produced in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement<sup>[22]</sup>.

### ***Search strategy***

The PubMed, Embase, Cochrane Library, Medline, and Ovid databases were searched from inception to April 10, 2023. The two keywords used were oral health and GC. For oral health, the search strategy was as follows: “dental” OR “oral” OR “oral health” OR “oral hygiene behaviour” OR “oral hygiene” OR “oral behaviour” OR “tooth loss” OR “tooth missing” OR “dental caries” OR “full teeth” OR “salivary flow” OR “probing depth” OR “periodontal disease” OR “periodontitis” OR “gingivitis” OR “dentures” OR “tooth brushing”. In terms of GC, “gastric cancer” OR “gastric carcinoma” OR

“gastric neoplasms” OR “stomach cancer” OR “stomach carcinoma” OR “stomach neoplasms” were searched. Then, we used “AND” to combine the two keywords. The language was limited to English.

### ***Inclusion and exclusion criteria***

The inclusion and exclusion criteria were established to find eligible studies. The inclusion criteria for patients were as follows: (1) Patients were reported to have oral health problems; and (2) The incidence of GC was reported. The exclusion criteria for patients were as follows: (1) Had case reports, comments, letters to the editor, or conference abstracts; (2) Had data repeated or overlapped; and (3) Incomplete information.

### ***Study selection***

The database search was independently conducted by two authors. The steps for screening eligible studies were as follows: (1) Excluded duplicate studies; (2) Scanned the titles and abstracts; and (3) Read the full text, including the reference. All disagreements were settled by group discussion.

### ***Data collection***

The baseline characteristics of the individuals included in the studies and the incidence of GC were collected for data analysis in the present study. The baseline information of the enrolled studies included author, publication year, publication country, study period, sample size, study type, follow-up period, diagnosis of GC, definition of oral health, and Newcastle-Ottawa scale (NOS) score.

### ***Quality assessment***

The quality of the included studies was evaluated by the NOS score<sup>[23]</sup>. According to the NOS score, we divided studies into high quality (9 points), median quality (7-8 points),

and low quality (< 7 points) groups. We evaluated the quality of the cohort studies and case–control studies separately in this study.

### ***Statistical analysis***

We defaulted the risk ratio (RR) and hazard ratio (HR) of GC reported in the included studies to be equivalent to the odds ratio (OR)<sup>[24]</sup>. The incidence of GC was described by the OR and 95% confidence interval (CI).  $I^2$  values and chi-square tests were used to assess the statistical heterogeneity<sup>[25,26]</sup>. The random effects DerSimonian-Laird model was used only. When a random effects model was used,  $P < 0.01$  was considered to indicate statistical significance. StataSE 16 was used for the data analysis.

## **RESULTS**

### ***Study selection***

A total of 13279 studies were identified from five databases (2652 in PubMed, 3982 in Embase, 1262 in the Cochrane Library, 2416 in Medline, 2967 in Ovid, and two from the citation searching) from inception to April 10, 2023. After duplicate removal, 5509 records remained. Three thousand forty-one unqualified studies were excluded according to the exclusion criteria. After excluding unqualified studies, 2168 studies were needed for eligibility, and six records were not retrieved. Finally, twelve eligible studies were included in this study<sup>[8,19-21,27-34]</sup> (Figure 1).

### ***Baseline characteristics of the included studies***

Twelve studies involving 1431677 patients were included in this study. The publication years ranged from 1998 to 2022. The published countries were mainly in China, Japan, United States, and Iran. The study period ranged from 1973 to 2011. There were nine cohort studies and three case-control studies. There were nine studies reporting tooth loss, three studies reporting periodontitis, two studies reporting gingivitis, three studies reporting dentures, and five studies reporting tooth brushing. More details of the

included studies' baseline characteristics, including the author, the number of patients, the follow-up period, the diagnosis of GC, and the NOS score, are shown in Table 1.

Tables 2 and 3 show the results of the quality assessment by the NOS score for cohort studies and case-control studies, respectively. For cohort studies, three studies were graded as high quality (nine points), five studies were graded as median quality (seven to eight points), and one study was graded as low quality (six points). For case-control studies, one study was graded as high quality (nine points), and two studies were graded as low quality (six points). The details of the quality assessment are shown in Tables 2 and 3.

### *The association between oral health and risk of GC*

Before the data analysis, we adjusted the RR or HR to the OR. The information on the participants' adjustment is shown in Table 4. According to the data analysis, poor oral health could increase the risk of GC (OR = 1.15, 95%CI: 1.02-1.29;  $I^2 = 59.47\%$ ,  $P = 0.00 < 0.01$ ) (Figure 2).

### *Subgroup analysis*

We classified oral health into five subgroups and analysed their respective effects on the risk of GC. We found that patients with periodontitis (OR = 1.13, 95%CI: 1.04-1.23;  $I^2 = 0.00\%$ ,  $P < 0.01$ ) had a greater risk of GC. However, tooth loss (OR = 1.12, 95%CI: 0.94-1.29;  $I^2 = 6.01\%$ ,  $P > 0.01$ ), gingivitis (OR = 1.19, 95%CI: 0.71-1.67;  $I^2 = 0.00\%$ ,  $P > 0.01$ ), dentures (OR = 1.27, 95%CI: 0.63-1.19,  $I^2 = 68.79\%$ ,  $P > 0.01$ ), and tooth brushing (OR = 1.25, 95%CI: 0.78-1.71,  $I^2 = 88.87\%$ ,  $P > 0.01$ ) had no effect on the risk of GC (Figure 3).

### *Publication bias*

According to the data analysis, the funnel plot was relatively symmetrical, indicating low publication bias (Figure 4).

### *Sensitivity analysis*



Each study was excluded each time the sensitivity was assessed. There were no significant differences in the results after each analysis was performed.

## **DISCUSSION**

A total of 1431808 patients were enrolled from twelve studies in the present study. After the data analysis, the outcomes showed that poor oral health was associated with a greater risk of GC. We classified oral health into five subgroups: Tooth loss, periodontitis, gingivitis, dentures, and tooth brushing. After subgroup analysis, the outcomes showed that patients with periodontitis had a greater risk of GC. However, tooth loss, gingivitis, dentures, and tooth brushing had no effect on the risk of GC.

In recent years, a growing number of researchers have focused on the relationship between oral health and cancer<sup>[27,28,35,36]</sup>. Periodontitis, a common disease that affects oral health, is a chronic inflammatory disease caused by bacteria that carry the risk of supporting tissue breakdown and tooth loss<sup>[37]</sup>. Moreover, periodontitis was reported to be a predictive factor for GC<sup>[19]</sup>. With the increase in the number of GC patients in China<sup>[6]</sup>, the association between oral health and the risk of GC needs more attention in the future.

However, previous studies on oral health and the incidence of GC have been controversial. Several studies reported that tooth loss was not a predictive factor for increased risk of GC<sup>[19,29,30,32]</sup>. In contrast, some studies have reported that tooth loss could increase the risk of GC<sup>[27,33]</sup>. Previous studies have shown that periodontitis increases the risk of GC<sup>[19]</sup>. However, Hujoel *et al*<sup>[20]</sup> and Michaud *et al*<sup>[29]</sup> showed that there was no association between periodontitis and the risk of GC. Therefore, it was necessary to explore the real association between oral health and the risk of GC.

In our study, we found that poor oral health, especially periodontitis, was associated with a greater risk of GC. However, the mechanism by which poor oral health increases the risk of GC is unclear. There are several hypotheses that might explain the association between oral health and the risk of GC. First, the oral cavity provides passage between the external environment and the gastrointestinal tract, which is

involved in the intake and digestion of food. Oral hygiene might affect the gastrointestinal flora and nutritional status, therefore resulting in the development of chronic diseases<sup>[19]</sup>. Second, periodontal disease and poor oral hygiene could lead to tooth loss<sup>[38]</sup>. However, in our study, we found that there was no significant difference between tooth loss and the risk of GC. Tooth loss is often accompanied by chronic infection and inflammation, such as periodontitis<sup>[39]</sup>. Moreover, tooth loss leads to a decrease in the ability to chew and might alter the patient's eating patterns<sup>[40-42]</sup>. These inflammatory conditions and changes in dietary habits associated with tooth loss might be the cause of the increased risk of GC. Third, patients with periodontal disease and poor oral hygiene had significantly greater levels of oral bacteria, while nitrosamine levels were significantly greater in the oral cavity due to the presence of nitrate-reducing bacteria; moreover, it is widely known that nitrites are recognized carcinogens<sup>[43]</sup>. Tooth brushing could also affect oral health; however, we did not find an association between tooth brushing and GC. Shakeri *et al*<sup>[31]</sup> discussed the relationship between toothbrushing frequency and GC incidence in their study. They found that those who never brushed their teeth had significantly greater rates of GC, while those who brushed their teeth every day or less than daily had no significant change in their rates of GC. In our study, we explored the effect of toothbrushing on the incidence of GC only. This might have contributed to our results.

To the best of our knowledge, the present study was the first to pool the risk of GC in patients who had oral health problems. Our study had a large sample size, and subgroup analysis was conducted. Moreover, the publication bias of the included studies was low. Thus, the outcomes were relatively reliable. This study has several limitations. In our study, there were more cohort studies and fewer case-control studies. Second, because of insufficient data, we lacked information on the effect of different numbers of missing teeth on the incidence of GC. Therefore, further case-control studies need to be performed in the future.

## CONCLUSION

In conclusion, patients with poor oral health, especially those with periodontitis, had a higher risk of GC. Thus, patients should be concerned about their oral health. Improving oral health might reduce the risk of GC.

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