Original Article

Association between the frequency of tooth brushing and esophageal carcinoma risk: an update systematic review and meta-analysis

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Background: Lower frequency of tooth brushing was thought to be associated with esophageal carcinoma (EC). However, some researchers suggested that this association did not exist or had not yet reached statistical significance. The purpose of this study was to calculate a more precise estimation of the relationship between the frequency of tooth brushing and the risk of EC by combining the results between different studies using the meta-analysis.

Methods: We searched the PubMed, Embase, Web of Science, and Scopus electronic databases up to July 2021. According to PECO approach (Population, Exposure, Comparator and Outcomes), we assessed the association between tooth brushing frequency and EC risk which reported the adjusted risk ratios (adjRR), hazard ratios (adjHR), or odds ratios (adjOR) with 95% confidence interval (CI). The random effects model was used to quantitatively evaluate the combined results. Two researchers independently evaluated the risk bias of the included studies using the Newcastle-Ottawa Scale (NOS). The robustness of results was evaluated by subgroup analysis, sensitivity analysis, and publication bias.

Results: In total, we identified 13 articles with 14 case-control studies which included 16,773 participants and 5,673 patients. Pooled results showed the lowest frequency of brushing was significantly associated with an increased risk of EC in comparison to the highest (adjOR: 2.00, 95% CI: 1.61–2.48). There was moderate heterogeneity among included studies (P=0.001, I^2=61.4%). The original studies included in this meta-analysis were all case-control studies. Study quality was all moderate or above based on NOS score ranges of 6 stars or more.

Conclusions: Available evidence suggests a low frequency of tooth brushing may be an important risk factor for EC. However, higher quality studies should continue to be conducted to investigate the optimal threshold of brushing frequency for the prevention of EC.

Keywords: Tooth brushing; esophageal carcinoma (EC); esophageal squamous cell carcinoma (ESCC); meta-analysis

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Introduction

Esophageal carcinoma (EC) comprises two major histological subtypes: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) (1). According to global cancer statistics, EC ranks seventh in prevalence among all worldwide cancers, and as the disease is frequently diagnosed at an advanced stage, the five-year survival rate is about 20% or less (2). Although diagnosis and treatment technologies of EC have been improving, the survival and prognosis of patients remains a serious problem (3,4). Studies have shown that there are significant geographical differences in the incidence of EC, suggesting that it is strongly influenced by environmental factors and lifestyle habits. Smoking, alcohol, and *Helicobacter pylori* infection are all considered to be important risk factors for EC (5,6).

Recently, the role of oral health as an important factor in the pathogenesis of EC is attracting increasing attention. Epidemiological studies have shown poor oral hygiene caused by tooth loss or ulcers is a risk factor for oral cancer, esophageal cancer, and other upper gastrointestinal malignancies (7,8). Tooth brushing is the most convenient and routine way to maintain oral hygiene, and some studies have suggested brushing may have a protective effect against EC (9,10). However, some studies have supported that frequency of tooth brushing is not associated with EC or that the association has not reached statistical significance (11,12). Most studies have investigated toothbrushing frequency by using several questions. Within response categories, the grouping settings for brushing frequency can vary considerably and may be underestimated. Meta-analysis was widely used to address controversies in a particular research topic. By combining results in different studies, it could provide more precise estimates (13,14).

A previous meta-analysis by Chen *et al.* [2015] assessed the relationship of tooth brushing frequency with EC risk. However, they included only eight case-control studies published from 1992 to 2014 (15), and the validity and robustness of the results were limited due to a high risk of bias. As the number of investigations with various design, origins, and samples has increased since that study, adding additional studies will improve the accuracy and robustness of the effect size in a meta-analysis and potentially clarify the results.

Considering the addition of new studies after 2014 and the inadequacy of the previous meta-analysis, it is necessary to conduct a meta-analysis of current literature to synthesize the available evidence. We aimed to update available epidemiological evidence and determine the association between tooth brushing frequency and the risk of EC. We present the following article in accordance with the MOOSE reporting checklist (16) (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-214/rc).

Methods

The research question was formulated a priori as: "*What is the relationship between the frequency of tooth brushing and the risk of esophageal carcinoma in the general population*?" We hypothesized that lower brushing frequency is associated with EC risk.

Search strategy

The relevant literature was searched in the PubMed, Embase, Web of science, and Scopus electronic databases up to July 25, 2021. We searched for all observational studies including cohort, case-control, and cross-sectional studies that examined the association between the frequency of tooth brushing and the risk of EC. We used different combinations of the keywords "toothbrushing", "oral hygiene", "dental health", "esophageal carcinoma", "esophageal", and "upper gastrointestinal tract carcinoma". The MeSH terms and free words were combined to acquire better retrieval result in PubMed, and we manually checked the reference lists of retrieved articles for inclusion in the meta-analysis. The detailed search strategy can be found in Table S1.

Study selection

The following inclusion criteria were applied, which generally met the PECO approach: (I) Population: general population. (II) Exposure: frequency of tooth brushing per day or per week. (III) Comparator: risk estimates for the lowest frequency of tooth brushing. (IV) Outcome: any type or epoch of EC reporting the adjusted risk ratio (adjRR), hazard ratio (adjHR), or odds ratio (adjOR) with 95% confidence interval (CI) of EC associated with the frequency of tooth brushing or provided sufficient date to calculate them. (V) Animal studies, clinical trials, letters, reviews, and commentaries were excluded. Two reviewers (LZ and JW) independently screened and assessed the eligible studies, and disagreements were resolved through consultation with a third author (LW). The EndNote X9 software (Clarivate

Analytics, US) was used to perform the screening and de-duplication of the literature.

Data extraction and quality assessment

Two investigators (LZ and JW) independently completed the data extraction, which was confirmed by another researcher (WY). The following characteristics were extracted for each eligible article: first author, publication year, study design, location, sex, age, type of EC, number of participants and cases, adjusted risk estimates with 95% CI, and adjusted factors. Differences in data extraction were resolved by consensus.

The Newcastle-Ottawa Scale (NOS) was used to evaluate the qualities of cohort, case control, and cross-sectional studies (17). The scale assesses three items: selection, exposure/outcome, and comparability, and the quality of each study is categorized as poor (0–3 stars), fair (4–6 stars), and good (≥7 stars). According to the NOS scale, a higher quality represents a study with a lower risk of bias. We set the risk of bias for the studies to be classified as low ('good' quality), medium ('fair' quality), and high ('poor' quality), respectively (18). The risk of bias for selected articles was evaluated independently by two reviewers (LZ and JW). Discrepancies were resolved through discussion.

Statistical analysis

Data analyses were conducted with STATA15.0 (College Station, TX, USA) and all tests were two-sided with a significance level of 0.05. We calculated the combined adjusted risk between the frequency of tooth brushing and the risk of EC using a random effects model and showed the adjusted risk and 95% CI for each study using forest plots. We used adjOR (95% CI) for cross-sectional and case-control studies and adjRR (95% CI) for cohort studies as risk estimates.

Heterogeneity among studies was assessed by the *Q* statistic with reporting the I^2 index. According to the estimated I^2 values, 25%, 50%, and 75% indicated low, moderate, and high degrees of heterogeneity (19).

Subgroup and sensitivity analyses

Subgroup analyses were stratified by study location, publication year, case type, family history of EC, controlling for drinking, and controlling for smoking to determine the possible influence of factors. Moreover, sensitivity analysis was performed to explore the key study which had a substantial impact on the overall risk estimates.

Publication bias

Potential publication bias was assessed by funnel plot, Egger's regression test, and Begger's funnel plot (20,21). In addition, we used the Duval and Tweedie's nonparametric trim-and-fill to adjust potential publication bias (22).

Results

Literature search

Figure 1 displays the literature retrieval selection process. Initially, based on the retrieval strategy, a total of 2,353 published articles were identified, including 64 from PubMed, 101 from Embase, 2,032 from Web of Science, and 156 from Scopus. After excluding duplicates (n=223), the remaining 2,130 articles were subjected to a titles and abstracts check, resulting in the exclusion of 2,087 which did not meet the inclusion criteria. Eventually, we conducted a full-text review of the remaining citations (n=43) and finally 13 articles with 14 studies were included in the meta-analysis.

Characteristics of the included studies

The main characteristics of the 13 eligible articles with 14 studies are described in the *Table 1*. Eligible studies were published from 1992 to 2020 (9-12,23-31), and six were published after 2014 (9,10,25-28). A total of 16,773 participants and 5,673 patients were included and were composed of ten case-control studies that reported the association between tooth brushing and ESCC risk and three reporting the association between tooth brushing and EC (ESCC and other types of EC) risk. The study in 1992 (11) conducted two separate case-controls and reported on the risk of EC in two populations in different areas. All were case-control studies and deemed as moderate to high quality with a rank of 6–8 stars according to NOS (the mean NOS score was 7.28). Of the 13 included studies (9-12,23-31), one study scored <7 with moderate risk of bias (11) and all other studies scored ≥7 with low risk of bias (9,10,12,23-31).

Association between tooth brushing and the risk of EC

Figure 2 shows the pooled adjOR for the risk of EC in relation to the frequency of tooth brushing. Compared

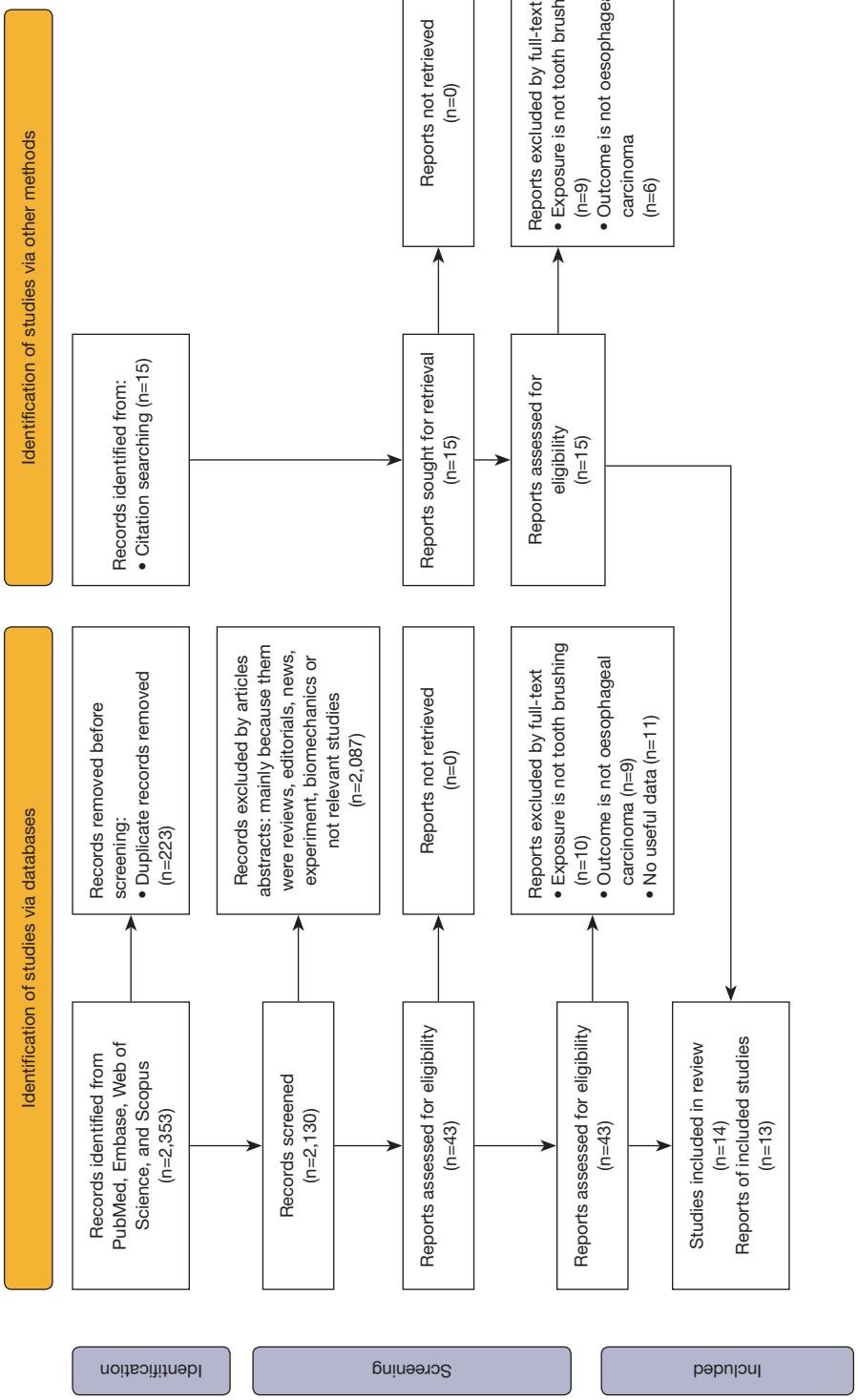

Figure 1 Flow diagram of identification of relevant observational studies. Note: 7 studies with 6 reports included in previous meta-analysis (up to Aug 1st, 2014) by Chen et al. [2015] (15) were also included in this meta-analysis (up to July 25, 2021).

Table 1 Main characteristics of the included studies involving toothbrushing and the risk of esophageal carcinoma

First author [publication year], region	Study design	Sex, age	Participants	Cases	Definition and grouping of exposure	Definition of outcome	Adjustment factors	Lowest *vs.* highest, OR [95% CI]	Study quality
Wang Y I (11) [1992], Asia	Case-control	M&F, ≥30	413	210	Self-reported brushing frequency: 0; ≥1/day	Ascertained from hospital registries (X-ray)	Age, sex and occupation	0 *vs.* ≥1, 0.91 [0.56, 1.43]	6
Wang Y II (11) [1992], Asia	Case-control	M&F, >30	305	116	Self-reported brushing frequency: 0; ≥1/day	Ascertained from hospital registries (pathologic examination)	Age, sex and occupation	0 *vs.* ≥1, 5 [2, 10]	6
Guha N (12) [2007], South America	Case-control	M&F, >0	454	95	Self-reported brushing frequency: 0; <1; 1; ≥2/day	Ascertained from hospital registries (histologically or cytologically confirmed diagnosis of squamous cell carcinoma)	Age, sex, country/center, education, tobacco pack-years, cumulative alcohol consumption	<1 *vs.* ≥2, 0.39 [0.11, 1.31]	8
Sato F (23) [2011], Asia	Case-control	M&F, ≥20	1,617	387	Self-reported brushing frequency: 1; ≥2/day	Ascertained from study visits and review of hospital discharge lists and medical charts	Age, sex, amount of smoking and alcohol consumption, intake of vegetables, fruits, BMI, occupation, and number of remaining teeth	1 *vs.* 2, 0.67 [0.12, 3.88]	7
Dar N (24) [2013], Asia	Case-control	M&F, >18	2,338	702	Self-reported brushing frequency: 0; <1; ≥1/day	Ascertained from hospital registries and completed questionnaires	Age, ethnicity, residence, education, wealth score, fruit and vegetable intake, smoking, gutka chewing, alcohol consumption and cumulative use of hookah, cigarette	0 *vs.* ≥1, 2.27 [1.29, 4]	7
Menya D (25) [2019], Africa	Case-control	M&F, ≥18	870	430	Self-reported brushing frequency: 0; ≥1/day	Ascertained from hospital registries morphological examination and pathologic examination	Age, sex, ethnicity, alcohol+tobacco, alcohol intensity, very hot/hot/warm beverage drinking, family history of esophageal cancer, education, brushing frequency, brush type, Sum of number of Decayed, Missing, Filled Teeth, dental fluorosis	0 *vs.* ≥1, 2.5 [1, 6]	8
Chen X (26) [2017], Asia	Case-control	M&F, ≥40	1,377	613	Self-reported brushing frequency: ≤1; ≥2 /day	Ascertained from study visits, the local Cancer Registry and review of hospital discharge lists and medical charts	Age, sex, education, marital status, tobacco smoking, alcohol drinking, tea drinking, family history of esophageal cancer, daily consumption of pickled vegetables, daily consumption of fresh fruits, and wealth score.	≤1 *vs.* ≥2, 1.81 [1.37, 2.38]	8
Mmbaga B (10) [2020], Africa	Case-control	M&F, ≥18	623	310	Self-reported brushing frequency: 0; ≥1 /day	Ascertained from hospital registries	Age, sex, education, region/district and ethnicity, alcohol, tobacco	0 *vs.* ≥1, 2.77 [1.20, 6.43]	8

Table 1 *(continued)*

Table 1 *(continued)*

First author [publication year], region	Study design	Sex, age	Participants	Cases	Definition and grouping of exposure	Definition of outcome	Adjustment factors	Lowest *vs.* highest, OR [95% CI]	Study quality
Chen T (27) [2015], Asia	Case-control	M&F, ≥45	1,391	619	Self-reported brushing frequency: <2; ≥2/day	Ascertained from hospital registries	Age, sex, family size	<2 *vs.* ≥2, 1.91 [1.49, 2.44]	7
Chen X (28) [2015], Asia	Case-control	M&F	571	171	Self-reported brushing frequency: <2; ≥2/day	Ascertained from study visits and hospital registries	Age, sex, education, smoking, alcohol drinking, family history of esophageal cancer	<2 *vs.* ≥2, 3.18 [1.52, 6.67]	7
Abnet C (29) [2008], Asia	Case-control	M&F, ≥18	843	283	Self-reported brushing frequency:0; <1; ≥1 /day	Ascertained from hospital registries and Primary Health Care System	Age, sex, place of residence, ethnicity, alcohol drinking, use of tobacco, opium, or both, education in three categories, number of appliances, and fruit and vegetable intake	0 *vs.* ≥1, 2.37 [1.42, 3.97]	8
Ahrens W (30) [2014], Europe	Case-control	M&F	1,966	234	Self-reported brushing frequency:0; ≥1/day	Ascertained from study visits and hospital registries	Age, sex, study center; smoking status, cumulative tobacco consumption, alcohol drinking duration, education, consumption of fruits and vegetables	0 *vs.* ≥1, 1.56 [1.08, 2.25]	7
Ekheden I (9) [2020], Asia	Case-control	M&F, ≥40	3,188	1,210	Self-reported brushing frequency: ≤1; ≥2/day	Ascertained from local hospitals and the local cancer registry	Age, sex, duration, marital status, occupation, family wealth score, body mass index 10 years before, tea drinking, history of esophageal cancer among first-degree relatives, smoking, alcohol consumption	≤1 *vs.* ≥2, 2.14 [1.72, 2.65]	7
Nasrollahzadeh D (31) [2012], Asia	Case-control	M&F	817	293	Self-reported brushing frequency:0; ≥1 /day	Ascertained from study visits, family health census and hospital registries	Age, sex, residence area, ethnicity, alcohol consumption, tobacco or opium use, education and vegetable/fruit consumption	0 *vs.* ≥1, 4.12 [2.05, 8.28]	8

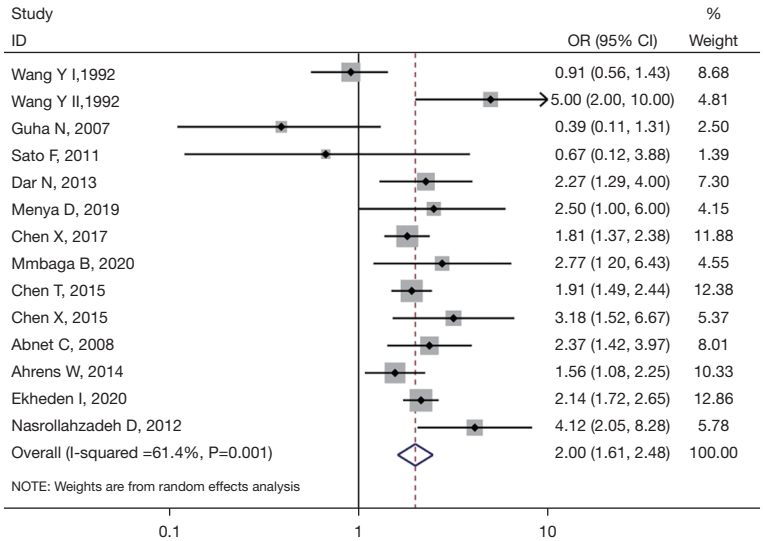

Figure 2 Forest plot of association between tooth brushing and the risk of esophageal carcinoma.

with the highest frequency of tooth brushing, participants in the lowest category had an increased risk for EC (pooled adjOR, 2.00; 95% CI, 1.61–2.48), and there was moderate heterogeneity across studies using random-effects models (I^2=61.4%; P=0.001).

Results of subgroup and sensitivity analyses

Subgroup analyses were established by study location, published years, the type of outcomes, controlling for smoking, and controlling for alcohol drinking to assess whether specific study characteristics influenced the overall risk estimates (*Table 2*). In general, the results were similar across the subgroups and showed brushing teeth once a day or not was positively associated with EC risk. After sensitivity analysis, the pooled estimates changed range between 1.91 (95% CI, 1.55–2.34) and 2.13 (95% CI, 1.76–2.58) without any material influence (*Figure 3*).

Results of publication bias

While funnel plot asymmetry indicated evidence of publication bias (*Figure 4*), Egger's test presented no publication bias in this meta-analysis (P=0.87). In addition, we used trim-and-fill analysis further confirming the stability of our study results and found that one missing study would make the funnel plot symmetric (*Figure 5*).

Discussion

In this meta-analysis, lower frequencies of brushing were closely associated with the risk of EC. The results demonstrated a one-fold increase in the risk of EC among the lowest category of brushing frequency compared with the highest group. We further obtained consistent results in subgroup analysis which showed the risk of ESCC in the lowest frequency of tooth brushing was 2.14-fold higher than in the highest. This suggests an increased frequency of brushing may be a protective factor for EC, especially ESCC. However, it is necessary to set the outcome variable as a specific type of EC to improve the accuracy and stability of the results.

Smoking and alcohol consumption are recognized risk factors for EC (32,33), so we further confirmed the impact of controlling or not controlling for these factors on the results of this study. We detected a significant heterogeneity in the groups not controlling for smoking or alcohol drinking, indicating that controlling for these confounding factors may be an effective way to control heterogeneity. However, further well-designed epidemiological studies are necessary to collect more comprehensive data on the demographics of patients.

It is well known that literature searches cannot be updated as new articles are published. Chen *et al.* [2015] conducted a meta-analysis consisting of six articles with

Table 2 Subgroups of the included studies

Subgroup	Number of studies	Risk estimated per 10 dB (95% CI)	P for heterogeneity	I^2 (%)
State				
Asia	10	2.10 (1.66–2.66)	0003	63.4
Europe	1	1.56 (1.08–2.25)	–	–
South America	1	0.39 (0.11–1.35)	–	–
Africa	2	2.64 (1.43–4.87)	0.870	0.0
Publication year				
≤2014	8	1.80 (1.13–2.87)	0.000	76.0
>2014	6	2.04 (1.78–2.33)	0.659	0.0
Case type				
Esophageal carcinoma	4	1.60 (0.80–3.19)	0.003	78.3
Esophageal squamous cell carcinoma	10	2.14 (1.78–2.57)	0.109	37.5
Family history of esophageal carcinoma				
Yes	4	2.07 (1.76–2.43)	0.483	0.0
No	10	1.91 (1.36–2.66)	0.000	70.3
Controlling for alcohol drinking				
Yes	11	2.07 (1.61–2.57)	0.058	43.9
No	3	1.92 (0.93–3.97)	0.001	86.2
Controlling for smoking				
Yes	11	2.07 (1.61–2.57)	0.058	43.9
No	3	1.92 (0.93–3.97)	0.001	86.2

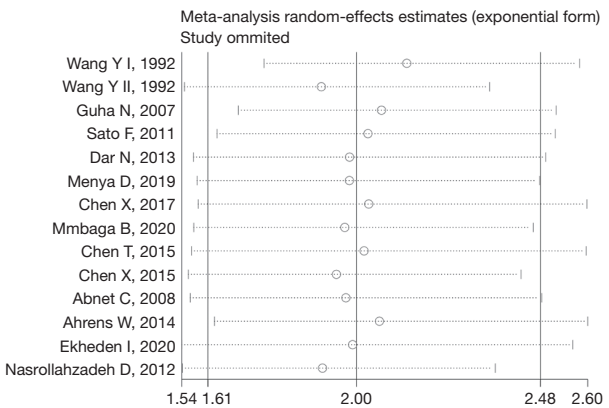

Figure 3 Sensitivity analysis plot to evaluate the effect of each study on the overall estimate.

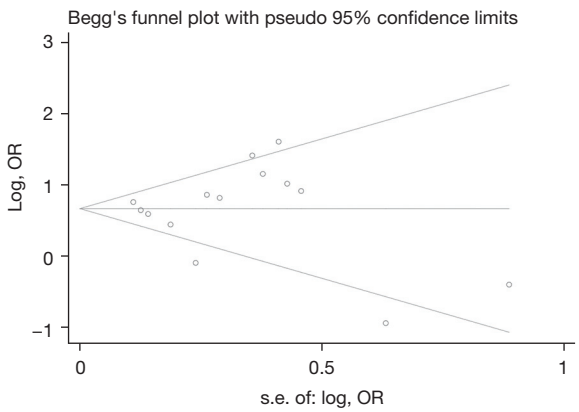

Figure 4 Funnel plot with 95% confidence interval.

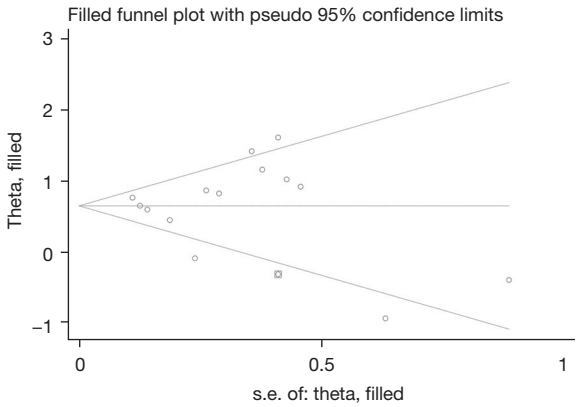

Figure 5 Filled funnel plot of odds ratio from studies investigating the association between tooth brushing and the risk of esophageal carcinoma.

significant heterogeneity among the included studies (15). However, due to developments in the field, new evidence has recently been published with various study origins and sample sizes (9,10), and our study further summarized and updated the relationship between the frequency of toothbrushing and risk of EC.

The physiological mechanisms between tooth brushing and EC risk are complex. The main function of brushing is to remove oral microorganisms and dental plaque and prevent periodontitis (34). An increased frequency of tooth brushing could reduce the amount of plaque and microorganisms and further prevent periodontitis or gingivitis (35). In addition, poor oral health produces acetaldehyde, which is known to be an EC carcinogen (36). At the same time, tooth brushing can directly clean the nitrosamine in tobacco, ethanol, and acetaldehyde in alcohol and other carcinogenic high-risk substances (32,33). Previous evidence revealed oral microorganisms play an important role in the occurrence and progression of esophageal cancer, and *Tannerella forsythia* and *porphyromonas gingivalis* are associated with EC by facilitating carcinogenesis via activation of toll-like receptors (37). In addition, dental plaque is an oral microbial community that exists on the surface of teeth and can cause periodontitis or systemic inflammation (34). Previous study showed that a lower frequency of tooth brushing is strongly associated with periodontitis (8). Importantly, periodontitis is a risk factor for EC, and periodontal disease increases the risk of EC by inducing a systemic immune response through inflammation (38). Finally, inflammation disrupts normal cell growth control, leading to cytopathic changes or increasing the production of carcinogenic nitrosamines (39).

One strength of this study is that to the best of our knowledge, it included the largest number of EC cases to date, including nearly three times that of a previous meta-analysis. In addition, in the subgroup analyses, we not only considered study location, publication year, and type of outcomes, but also analyzed second-order confounding factors such as smoking and alcohol consumption. Finally, heterogeneity detection and sensitivity analysis showed our results were robust and reliable.

There are also some limitations to this study. First, the included studies were case-control studies, and although such studies are of high quality, there are limitations in the interpretation of causality. Second, brushing frequency was self-reported, and the accuracy and reliability of this information cannot be assessed. Third, only articles published in English were retrieved, but sensitivity analysis and publication bias testing showed that the results of this study were robust.

Conclusions

This systematic review and meta-analysis assessed the association between the frequency of tooth brushing and risk of EC, and the overall results revealed lower frequencies of tooth brushing may be a significant risk factor. Future, prospective cohort studies with lager samples should be conducted to prove this causal link and to explore dose-response relationship between the two.

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Footnote

Reporting Checklist: The authors have completed the MOOSE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-214/rc

Conflicts of Interest: All authors have completed the ICMJE

uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-214/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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