Periodontal disease, tooth loss, and the risk of liver cancer: A systematic review

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Abstract

Background A number of epidemiological studies have suggested a positive association between periodontal diseases and oro-digestive cancers, including liver cancer. The present systematic review aimed to assess the potential association between periodontitis and/or tooth loss and the risk of liver cancer.

Methods A comprehensive search of PubMed, Scopus and Web of Science databases was conducted in August 2019. The inclusion criteria comprised all observational studies that assessed the relationship between periodontitis or tooth loss and liver cancer. Case reports, animal studies, experimental studies, and reviews were excluded. Due to great heterogeneity among the included studies, no meta-analysis was conducted.

Results Seven studies (five prospective cohorts, one cross-sectional, and one case-control) comprising 620,169 subjects (including 994 liver cancer cases) were included. The studies were conducted in the United States, Europe, and Asia. Four studies reported a positive association between periodontitis or tooth loss and the risk of liver cancer. One case-control study found some association between liver cancer and loss of 12-23 teeth, but such association was not replicated in patients with greater number of tooth loss. Contrarily, two studies failed to report any association between periodontitis and/or tooth loss and the risk of liver cancer.

Conclusion The available evidence suggests a possible link between tooth loss/periodontitis and the risk of liver cancer. However, the evidence is not conclusive enough, a fact that drives to conduct more, well-designed, prospective cohort studies to further explore the potential association between periodontitis and the risk of liver cancer.
BACKGROUND

Globally, liver cancer is the sixth most common cancer and the fourth leading cause of cancer mortality, accounting for an estimated 841,000 new cases and 782,000 deaths annually.[1] Among its well established risk factors are: hepatitis B virus, hepatitis C virus, heavy alcohol consumption, tobacco use, aflatoxin exposure, obesity, and diabetes mellitus.[1] These factors induce chronic liver inflammation, which may progress (if left untreated) to a more severe chronic form of hepatic inflammation (cirrhosis), and eventually liver cancer.[2] A number of recent studies have suggested periodontitis and/or tooth loss as a possible risk factor for orodigestive cancers including liver cancer. [3-6]

Periodontitis is a highly prevalent oral disease that results from a chronic, destructive, inflammation of the teeth-supporting tissues including gingiva, alveolar bone and periodontal ligament in response to the bacterial dental plaque.[7, 8] It is characterized by complex processes of immunological breakdown of the bone and soft tissues.[7] Unless properly treated, periodontitis can progress, leading ultimately to tooth loss.[7, 8] Indeed, tooth loss is considered as a marker of periodontal disease, [9] though teeth can be lost due to other reasons such as dental decay and trauma. Fundamentally, tooth loss is considered as a lifetime cumulative indicator of poor oral health. On a large scale, the current evidence suggests an association between periodontitis and several systemic diseases including cardiovascular diseases, [10] rheumatoid arthritis [11], pneumonia [12] and fatty liver disease. [13, 14] Of paramount importance in this context are the findings from epidemiologic studies, which suggested an association between periodontitis and/or tooth loss and the risk of cancers including lung cancer,
esophagus cancer, gastric cancer, colorectal cancer and pancreatic cancer. \[3, 15-21\]

The mechanism behind the claim connecting periodontitis and distant cancers might be related to the persistent periodontal infection, and the resultant inflammation that induce a state of systemic chronic inflammation, and eventually cancer. Surprisingly, periodontal pathogens, especially *porphyromonas gingivalis* and *fusobacterium nucleatum* have been isolated from some orodigestive cancer tissues, a matter that indicates potential roles for these pathogens in carcinogenesis and tumor proliferation at distant sites.\[22-24\]

In line with that, a number of epidemiological studies have evaluated the association between periodontitis/tooth loss and the risk of liver cancer; \[3-6, 25, 26\] the findings were inconsistent, however. Among these, one large scale-cohort study, comprising Finnish male smokers, has reported an association between tooth loss and the risk of liver cancer even after adjusting for the potential confounders.\[6\] Similar results were reported by another prospective-cohort study conducted among Chinese patients.\[5\] Additionally, a retrospective cross-sectional study in Japan has substantiated these findings.\[4\] Contrarily, however, one cohort study did not find a significant association between tooth loss and liver cancer among community-dwelling elderly in Japan.\[27\]Owing to the obvious controversy in the medical literature with this regard, the present systematic review sought to summarize the current available evidence regarding the potential association between periodontitis and/or tooth loss and the risk of liver cancer.

**METHODS**

**Focused question**
This systematic review adhered strictly to the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA).[28] The PECO research question was: Is periodontitis and/or tooth loss a risk factor for liver cancer?

Eligibility criteria

All observational studies (cross-sectional studies, case-control, and cohort studies) that assessed the relationship between periodontitis and/or tooth and the risk liver cancer in humans were considered eligible to be included in this systematic review. Case reports, animal studies, experimental studies, commentaries, review articles, and studies published in a language other than English were excluded.

Outcomes

liver cancer

Exposure

periodontal disease and/or tooth loss.

Literature search

An extensive literature search was conducted in PubMed/Medline, Scopus, and Web of Science (ISI) databases to identify all relevant articles published in English from date of Inception till and including July 2019. For this purpose, different combination the following keywords were used: (“tooth loss” OR “Edentulism” OR “periodontitis” OR “gingivitis” OR “periodontal disease” AND “liver cancer” OR “digestive cancer” OR “hepatocellular carcinoma” OR “hepatic cancer”). Titles and abstracts of the retrieved articles were screened for potential eligibility by two authors (MNA and SAA) independently, and irrelevant studies were excluded. Full-texts of the remaining potentially eligible articles were evaluated by the two authors independently for inclusion. Moreover, the reference lists of the included articles
were manually searched for additional studies.

Assessment of quality

Critical appraisal of the included studies was performed by two authors (SAA and AS) independently according to The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies [29]. The NOS is based on three major components: selection of the study groups (0–4 stars), comparability of cases and controls by controlling for relevant factors (0–2 stars), and exposure (0–3 stars).

Data extraction

The following data was extracted by two authors (MSA and WII) independent using a standard data collection form: authors and year of study; country; study design; number of patients; age and gender of patients; adjusted confounders; exposure parameters such as tooth loss or periodontal diseases; periodontal disease parameters such as clinical attachment loss, gingival bleeding, periodontal pocket, or bone loss; and not to mention the main outcomes.

Statistical analysis

Our aim was to carry out meta-analysis but owing to the substantial heterogeneity and inconsistency of data among the included studies, no statistical analysis was performed.

RESULTS

Search results

A total of 740 articles were retrieved, of which 275 were duplicates (Figure 1). The titles and abstracts of the remaining 465 articles were screened by two reviewers (MA and SA) independent for eligibility. Among these, 440 were irrelevant and were
thus excluded. The full text of the remaining 25 potentially relevant studies were obtained and assessed for inclusion. Out of these, 18 articles were excluded for various reasons (Supplementary Table 1). Eventually, 7 studies met the inclusion criteria and were further processed for data extraction [3-6, 25, 27, 30].

**General characteristics of the included studies**

Seven studies [3-6, 25, 27, 30] comprising 620,169 subjects (including 994 liver cancer cases) were included in this systematic review (Table 1). Five studies were prospective cohort [5, 6, 25, 27, 30], one case-control [3], and one retrospective cross-sectional [4]. Three studies were conducted in Japan [3, 4, 27], one in China [5], one in the UK [30], one in Finland [6] and one in the USA [25]. Number of participants ranged from 64 to 475,766 subjects. The age of participants ranged from 18 to 80 years old. All studies reported the gender of the subjects: one study included exclusively male subjects [6], one study included female subjects [25], and the remaining five studies included both genders [3-5, 27, 30] (Table 1).

**Tooth loss/periodontal parameters**

The exposure parameters were: number of missing teeth in four studies [3, 5, 6, 27], periodontitis in two studies [25, 30], and both periodontitis and number of missing teeth in one study [4]. Ascertainment of tooth loss/periodontal status varied greatly across studies; self-reported in four studies [3, 6, 25, 30]; and evaluated by dental examination in three studies [4, 5, 27] (Table 1).

**Main outcomes**

Four studies found a positive association between periodontitis/tooth loss and the risk of liver cancer.[4-6, 30] Three studies,[3, 25, 27] on contrary, failed to report any association between periodontitis and/or tooth loss and the risk of liver cancer (Table 2).
Yang et al., [6] assessed the association between tooth loss and liver cancer incidence on a cohort of 29,096 Finnish male smokers. A total of 213 liver cancers were recorded over the follow-up period of 17 years. The authors found a significant association between tooth loss and the incidence of liver cancer after adjusting for all confounding factors. Interestingly, the authors observed that the more the number of missing teeth, the higher the risk of liver cancer incidence. The authors concluded that periodontal infection might be a risk factor for liver cancer [6].

Jordaao et al,[30], in their large UK Biobank prospective-cohort study (n=475,766), investigated the epidemiological association between self-reported periodontitis (bleeding gum, painful gum, loose teeth) and the incidence of gastrointestinal cancers. Over the follow-up period, around 4069 gastrointestinal cancers were diagnosed. The authors found a statistically significant association between self-reported periodontitis and the increased risk of hepatobiliary cancers (hazard ratio 1.32, 95% confidence interval 0.95-1.80), with stronger association with hepatic cancers (HR: 1.75, 95% confidence interval 1.04-2.92). However, no association was observed for the risk of other gastrointestinal cancers namely esophageal, stomach, pancreatic, small intestine and colorectal cancers.

Thistle et al [5] in their large-scale prospective cohort study on 32,689 subjects (14,541 males, and 18,148 females) assessed the association between tooth loss and liver cancer incidence. Around 329 liver cancers were diagnosed over the 30 year-follow-up period. The results showed that subjects in the highest quartile of age-specific tooth loss had an increased risk of liver cancer incidence, with gender-based variable results: greater tooth loss was positively associated with an increased risk of liver cancer in women (HR = 1.64, 95%CI: 1.04, 2.59), but not in
men (HR = 1.08, 95%CI = 0.75, 1.57) [5].

A more recent cross-sectional study among Japanese cancer patients (n = 332), Sakai et al. [4] retrospectively assessed the relationship between dental diseases and the risk of digestive cancers including liver cancer. The authors found higher prevalence of missing teeth and periodontal diseases among patients with liver cancer as compared to healthy patients based on the Japanese 2016 national survey. The authors concluded that periodontal diseases and/or tooth loss might be risk factors for digestive cancers including liver cancer [4].

In a large-scale case-control study conducted on 5,240 Japanese cancer patients (of which 167 were liver cancers), and 10,480 age- and gender matched controls, the authors found some association between liver cancer and a loss of 12 to 23 teeth, but such an association was not replicated in patients with greater number of tooth loss [3].

Contrarily to the above findings, Ansai et al. [27] assessed the association between tooth loss and oro-digestive cancers among a cohort of 80-year old Japanese population. After a 12-year follow-up period, a total of 13 liver cancers were diagnosed. The authors did not find a significant association between periodontitis and incidence of liver cancer in this population [27]. Another large scale prospective cohort study by Nwizu et al, investigated the potential association between self-reported periodontitis and the incidence of different types of cancers including liver cancer among American women (n=65,869). During the mean follow-up period of 8.32 years a total of 7,149 cancers including 329 liver cancers were diagnosed. The authors observed a significant association between periodontitis and incidence of some types of cancers, but no association was observed between periodontitis and liver cancer [25].
**Quality of the included studies**

NOS-based results are presented in table 3. Overall, the quality of the included studies was good ranging from 7 to 9 stars.

**Discussion**

Periodontal diseases and/or tooth loss have been suggested as potential risk factors for distant cancers including oro-digestive cancers. [19, 31, 32] In this context, some epidemiological studies have explored the potential association between tooth loss and/or periodontal health status and the risk of liver cancer, and concluding conflicting results.[4-6, 25] Therefore, the present study sought to systematically review, summarize and appraise the available evidence regarding the potential association of periodontal diseases and/or tooth loss with the risk of liver cancer. Overall, the findings were inconsistent: four studies (three cohorts and one cross-sectional)[4-6, 30] supported the existence of a significant positive association between periodontal diseases and/or tooth loss and the risk of liver cancer; two cohorts studies failed to replicate such results; [25, 27] and one case-control study found some association between liver cancer and loss of 12 to 23 teeth, but no such an association was found in patients with greater number of tooth loss [3]. It is pertinent to mention that the two cohort studies that reported lack of association comprised very small sample sizes with a limited number of liver cancers, being 19 cases in one study [25] and only 13 cases in the other [27]. By contrast, among the four studies that reported positive associations, three were prospective cohorts studies [5, 6, 30] with very large sample sizes (n=32,689, n= 29,096, and 475,766, respectively) and relatively adequate number of liver cancer cases (n=329, n= 213,
By and large, the findings of this review are inconclusive and should be interpreted with caution in light of the heterogeneity and other limitations discussed in the subsequent sections.

Previous studies have linked periodontal disease/tooth loss with various cancers including gastric cancer, esophagus cancer, colorectal cancer, pancreatic cancer, oral cancer, and lung cancer. [3, 15-20] Tooth loss is a devastating end result of uncontrolled bacterial infections, mainly periodontitis.[7, 8] So far, the exact mechanism underlying the potential association between periodontal disease/tooth loss with distant cancers has not fully understood. A number of etiological pathways have been suggested, however. First, persistent periodontitis can induce systemic inflammation through activating inflammatory mediators such as histamine, prostaglandin, cytokines and proteinases.[33, 34] Owing to being elevated chronically, these mediators can lead eventually to tissue injuries with subsequent DNA breakdown with malrepair, and/or genetic mutations, which subsequently increase the risk of cancer development. The second possible mechanism is related to the direct role of oral pathogens [24, 35-37]. In fact, there is a growing body of evidence implicating oral microbiome in initiation and progression of oro-digestive cancers [31, 37]. Oral pathogens including periodontal pathogens are believed to contribute to carcinogenesis through producing carcinogenic metabolic byproducts, with subsequent oncogenic and antiapoptotic effects [22, 24, 35, 38]. More specifically, certain periodontal pathogens namely *p. gingivalis* and *Fusobacterium nucleatum* have been implicated in cancer progression and were isolated from various orodigestive cancers [22, 24, 38, 39].

In the same context, periodontal infection has been implicated in chronic liver
inflammation including cirrhosis and non-alcoholic fatty liver disease, both of which are well-known predisposing conditions of liver cancer [14, 40-42]. In line with that, a recent systematic review of clinical and microbial studies concluded a strong association between periodontal diseases and non-alcoholic fatty liver disease [13]. Additionally, numerous studies conducted on humans found a strong positive association between periodontal pathogens especially \textit{P. gingivalis} and non-alcoholic fatty liver disease [13, 43-45]. Further evidence comes from animal studies that confirmed that oral administration of \textit{P. gingivalis} caused impaired gut barrier function, increased serum endotoxin levels, and dissemination of enterobacteria to the liver, which could be hepatocarcinogenic. [46, 47] Although the findings of the present review are based on a limited number of published studies, they are supported by some other studies that showed higher mortality rates of oro-digestive cancers, including hepatic cancers, among patients with periodontitis [14, 23] and those who were seropositive to periodontal pathogens namely \textit{P. gingivalis} [23]. Furthermore, Hirarki et al. [3] found that liver cancer patients with chronic periodontitis revealed higher serum bilirubin levels and higher levels of reactive oxygen species than those with healthy periodontum. The authors also found a significant association between progression of liver cancer and severity of periodontitis [3]. In sum, the findings of the present review are consistent with the previous literature that suggested a potential association between tooth loss/periodontitis and other types oro-digestive cancers [17-19, 31]. It is well recognized that the level of evidence is dependent on many factors, one important of which is the quality of the included studies. For this purpose, we critically appraised the included studies using NOS, a widely used quality assessment tool for the observational studies. The results of the quality assessment
revealed some methodological flaws that might have caused some bias. Particularly important flaw is related to the methods of exposure ascertainment (tooth loss and periodontal disease); unfortunately, more than half of the included studies relied on self-reported data rather than on clinical examination. Self-reported data is potentially prone to recall errors, and thus might have biased the results. Irrespective of the reported association between tooth loss/periodontal disease and liver cancer as per the current systematic review, several limitations should be acknowledged. The first main limitation is related to the relatively limited number of the included studies as well as the small sample sizes of liver cancer cases in some of these studies. The second key limitation is related to the mixed study designs across the reviewed studies (5 cohort studies, one case control study and one retrospective cross-sectional study), and thus no robust conclusion can be drawn. The third key limitation is related to the substantial heterogeneity among the included studies with respect to the gender and age of the subjects, exposure parameters, methods of exposure measurements, ethnicity, and geographical differences. Such heterogeneity complicates performing statistical analysis to quantify the magnitude of the association. The fourth important drawback is that the exposures (tooth loss and/or periodontitis) were self-reported, rather than clinically ascertained, in most of the included studies, and thus is prone to recall bias. Finally, although most of the included studies adjusted for the effects of some confounders like gender, age, smoking and alcohol consumption, other important confounders (metabolic diseases, serum hepatitis B and C infection status, and socioeconomic status) were not controlled in most of the included studies and thus might have biased the results.

Nevertheless, despite the above mentioned methodological shortcomings, the
current review has some strengths worth mentioning. First, this is the first systematic review that summarized the current literature and provided an insight on the possible association between tooth loss/periodontal disease and the risk of liver cancer. Second, five out of the six included studies were prospective cohort studies with a relatively long follow-up period as well as large sample sizes in most of these studies. Third, the included studies were conducted on populations from three continents (Europe, North America, and Asia), suggesting that the results are generalizable.

CONCLUSIONS

In summary, within the limitations of the current review, we can conclude that there is some evidence that periodontitis/tooth loss may be associated with liver cancer. More well-designed, large-scale, prospective cohort studies with long follow-up periods and sound methodologies are required to further explore the potential association between tooth loss and the risk of liver cancer.

DECLARATIONS

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Authors’ contribution

SAA and ES participated in designing the study, interpretation of the data and drafting the manuscript. WII and MSA participated in extraction of the data and statistical analysis. AS and MNA participated in data collection and drafting the manuscript. All authors read and approved the final manuscript.

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**Availability of data and materials**

The datasets supporting the findings of this article are available from the corresponding author.

**Competing interests**

The authors declare that they have no competing interests.

**Consent for publication**

Not applicable.

**Ethics approval and consent to participate**

Not applicable.

**Abbreviations**

NOS: Newcastle-Ottawa Scale; PECO: (Population, Exposure, Comparison, Outcomes).

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Tables

Table 1: General characteristics of the included studies
| Author (country) | Study Design | No of Participants | Gender (age yrs) | Exposure parameters (measurements) |
|-----------------|--------------|-------------------|-----------------|-----------------------------------|
| Yang et al., 2017 (Finland) | Prospective Cohort | 29,096 (213 LC) | M: 100% F: 0.0 (50-69) | Tooth loss (Self-reported) |
| Thistle et al., 2018 (China) | Prospective Cohort | 32,689 (329 LC) | M: 14541 F: 18148 (40-69) | Tooth loss (Clinically) |
| Nwizu et al., 2017 (USA) | Prospective Cohort | 65,869 (19 LC) | F: 100% 54-86 (68.3) | Periodontitis (Self-reported) |
| Jordao et al. 2019 (UK) | Prospective Cohort | 475,766 (175 LC) | M: 187,546 F: 212,002 | Periodontitis (Self-reported) |
| Ansai et al. 2013 (Japan) | Prospective Cohort | 697 (13 LC) | M: 277 F: 420 80 ys | Tooth loss (Clinically) |
| Hiraki et al. 2008 (Japan) | Case-control study | 5,240 cancers 10,480 controls (167 LC) | M: 51.5 % F: 49.5% (18-79) | Tooth loss (Self-reported) |
| Sakai et al., 2019 (Japan) | Retrospective-cross-sectional | 332 digestive cancer patients (78 LC) | M: 217 F: 115 (19-80) | Tooth loss -Periodontitis (PD) (Clinically) |

LC: liver cancer; BMI: body mass index; PD: pocket depth; MHT: menopausal hormone therapy; HBV: Hepatitis B virus infected; HCV: Hepatitis C virus infected; NA: not available

Table 2: Summary of the main outcomes
Yang et al. 2017 | Tooth loss was significantly associated with liver cancer; having 11-31 permanent missing teeth was associated with a 42% higher risk of liver cancer (HR 1.42, 95% CI 1.01-1.98), and having all 32 teeth lost was associated with a 45% higher risk of liver cancer (HR 1.45, 95% CI 1.00-2.10), compared to having 0-10 teeth lost.

Thistle et al., 2018 | Overall, greater tooth loss was associated with an increased risk of liver cancer (HR = 1.27, 95%CI: 0.96, 1.67), with a great variation according to gender; Greater tooth loss was positively associated with an increased risk of liver cancer in women (HR = 1.64, 95%CI: 1.04, 2.59), but not in men (HR = 1.08, 95%CI = 0.75, 1.57)

Nwizu et al. 2017 | No significant association between periodontal disease and the risk of liver cancers HR 1.33 (95% CI: 0.77, 2.29).

Jordao et al. 2019 | Self-reported poor oral health was associated with a 75% increased risk of hepatocellular carcinoma (HR 1.75, 95% CI 1.04-2.92).

Ansai et al. 2013 | Subjects with tooth loss had no significant risk of liver cancer (HR: 1.07, 95% CI: 0.98-1.17)

Hiraki et al. 2008 | There was an insignificant increase in the risk of liver cancer in patients with 12-23 missing teeth (OR 1.35 (95% CI: 0.51-3.58), but no such association in patients with greater number of tooth loss.

Sakai et al., 2019 | Proportion of patients with remaining teeth less than 20 was higher in liver cancer patients than in controls (national survey)

**HR**: hazard risk; **OR**: odds ratio; **CI**: confidence interval

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**Table 3: NOS-based quality analysis of the included studies.**

| Study            | Selection | Comparability | Exposure | Outcome |
|------------------|-----------|---------------|----------|---------|
| Yang et al. 2017 | ***       | **            |          | ***     |
| Thistle et al. 2018 | ****     | **            |          | ***     |
| Nwizu et al. 2017 USA | ***  | **            |          | ***     |
| Ansai et al. 2013 | **       | **            |          | ***     |
| Hiraki et al. 2008 | ***     | **            | **       | ***     |
| Jordao et al. 2019 | ***     | **            |          | ***     |
| Sakai et al. 2019 | ***     | **            | ***      | ***     |
Flow-chart of methodology according to PRISMA guidelines