Assessment of the association between periodontal disease and total cancer incidence and mortality: a meta-analysis

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Background: Periodontal disease（PD）is a chronic inflammatory disease that leads to alveolar bone resorption and tooth loss. Many studies have reported the association between periodontal disease and various cancers including oral cancer, lung cancer, breast cancer and so on. However, there is still no specialized meta-analysis that assesses the association between periodontal disease and cancer incidence and mortality in-deepth. Thus, we conducted this meta-analysis. **Methods:** This meta-analysis was registered with PROSPERO: CRD42020183497. We searched five online databases for observational studies about the association between periodontal disease and breast, prostate, lung and bronchial, colorectal, and total cancers by July 2020. Then we evaluated quality of the included studies by the Newcastle-Ottawa scale. Risk ratios (HRs) and their 95% confidence intervals (CIs) were pooled to evaluate the strength of the association between periodontal disease and four cancers, total cancer incidence and mortality . In addition, we analyzed heterogeneity by subgroup analysis and sensitivity analysis. At last, we inspected publication bias by Begg’s and Egger’s tests. **Results:** None of the studies included in this meta-analysis were of poor quality. PD is not only related to breast cancer incidence (HR=1.26,95%CI:1.11-1.43, I^2=75.8%, P=0.000), but also connected with total cancer mortality (HR=1.40,95%CI:1.24-1.58, I^2=0.0%, P=0.718). Subgroup analyses showed that study population, study design, dental status, follow-up period, adjustment for smoking partially explained the heterogeneity between studies. The results of Begg's test and Egger's test were consistent and indicated that there is no publication bias in this study. **Conclusion:** In conclusion, this meta-analysis revealed a positive relationship between periodontal disease and breast cancer incidence and total cancer mortality. Further well-designed studies with specific inclusion and exclusion criteria are required to strengthen the conclusion of this meta-analysis. However, longer follow-up period, multi-center trials

and even multinational studies are required to corroborate the results.

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Abstract

Background: Periodontal disease（PD）is a chronic inflammatory disease that leads to alveolar bone resorption and tooth loss. Many studies have reported the association between periodontal disease and various cancers including oral cancer, lung cancer, breast cancer and so on. However, there is still no specialized meta-analysis that assesses the association between periodontal disease and cancer incidence and mortality in-deepth. Thus, we conducted this meta-analysis. **Methods:** This meta-analysis was registered with PROSPERO: CRD42020183497. We searched five online databases for observational studies about the association between periodontal disease and breast, prostate, lung and bronchial, colorectal, and total cancers by July 2020. Then we evaluated quality of the included studies by the Newcastle-Ottawa scale. Risk ratios (HRs) and their 95% confidence intervals (CIs) were pooled to evaluate the strength of the association between periodontal disease and four cancers, total cancer incidence and mortality . In addition, we analyzed heterogeneity by subgroup analysis and sensitivity analysis. At last, we inspected publication bias by Begg's and Egger's tests. **Results:** None of the studies which included in this meta-analysis were of poor quality. No article presented poor quality. PD is not only related to breast cancer incidence (HR=1.26,95%CI:1.11-1.43, I^2=75.8%, P=0.000), but also connected with total cancer mortality (HR=1.40,95%CI:1.24-1.58, I^2=0.0%, P=0.718). Subgroup analyses showed that study population, study design, dental status, follow-up period, adjustment for smoking partially explained the heterogeneity between studies. The results of Begg's test and Egger's test were consistent and indicated that there is no publication bias in this study. **Conclusion:** In conclusion, this meta-analysis revealed a positive relationship between periodontal disease and breast cancer incidence and total cancer mortality. Further well-designed studies with specific inclusion and exclusion criteria are required to strengthen the conclusion of this meta-analysis. However, longer follow-up period, multi-center trials and even multinational studies are required to corroborate the results.

Keywords: Periodontal disease, cancer, incidence, mortality, Meta-analysis

Introduction

Periodontal disease is a chronic inflammatory disease that eventually leads to tooth loss. The initial factor associated with periodontal disease is dental plaque, which attacks the first immune defense line of periodontal tissue, leading to inflammation and disease. Periodontitis has a range of clinical manifestations, including gingiva bleeding, periodontal pocket, alveolar bone resorption, and tooth loss. Periodontitis is the major cause of tooth loss in adults. According to a National Health and Nutrition Examination survey, approximately 42% of American adults aged 30 years or older have periodontitis, with 7.8% having severe periodontitis [1]. In Turkey, the proportion of individuals with more than 3 mm loss of attachment (LOA) ranged from 43% to 91% [2]. In the fourth national oral health survey, the prevalence of probe bleeding in the 35 to 44-year-old population was 87.4% [3]. There is a verified association between periodontal disease and a variety of diseases, such as rheumatoid arthritis [4], diabetes [5], cardiovascular

disease [6], chronic obstructive pulmonary disease [7], depression [8], and Alzheimer's disease [9].

Periodontitis is not only related to the abovementioned diseases but also to cancers. In recent years, an increasing number of studies have revealed the relationship between periodontal disease and various cancers, particularly head and neck [10], esophageal [11], and pancreatic [12] cancers. Subsequently, researchers conducted meta-analyses of previous studies in order to reach a more accurate and objective conclusion. For example, Yao Q et al. reviewed five reliable studies, obtained data through the random effect model, and finally concluded that patients with periodontitis are prone to oral cancer [13]. Six years later, Gopinath D et al. analyzed nine studies and confirmed a significant correlation between periodontitis and head and neck cancer [14].

Cancer is not only difficult to overcome but also a heavy economic burden. In China [15], lung cancer remains the most common cancer and accounts for nearly 30% of cancer deaths. In 2015, the five cancers with the highest incidence included lung, stomach, colorectum, liver, and breast, accounting for nearly 60% of all diagnosed cancers. Every year, the American Cancer Society estimates the number of new cancer cases and cancer-related deaths in the population. According to recent data collected in 2019, prostate and lung & bronchial cancers are the two most common cancers in men, while, breast, lung, uterine corpus and colorectal cancers are the four most common cancers in women. The largest number of deaths result from lung, prostate, and colorectal cancers in men and lung, breast, and colorectal cancers in women [16].

In this context, we aimed to assess the correlations, in terms of incidence and mortality, between periodontal disease and cancers, including breast, prostate, lung and bronchial, colorectal, and total cancers, as well as the strength of these correlations. Furthermore, we aimed to preliminarily explore the factors that influence these correlations.

Materials and methods

Methodology

This meta-analysis was reported according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines. The protocol was registered in PROSPERO (http://www.crd.york.ac.uk/PROSPERO) before the research was begun (CRD 42020183497).

Criteria for the inclusion of studies

The following criteria were applied: (1) studies published in English or Chinese;(2) studies on human subjects;(3) observational studies (including cohort and case-control studies)with a prospective or retrospective design; (4) studies with periodontal disease as the exposure and ,the incidence of or mortality associated with breast or prostate cancer , lung& bronchial or colorectal cancer, or total cancers as the outcome; and (5) studies providing relative risks (RRs), hazard ratios (HRs), or odds ratios (ORs) and corresponding 95% confidence intervals (CIs).

Literature search and selection

Databases: PubMed, Embase, Web of Science, China National Knowledge Infrastructure [CNKI] and Wanfang.

Search terms: (<Neoplasm= OR <Carcinoma= OR <cancer= OR <tumor= OR <tumour=) and (<periodontal diseases= OR <gum disease= OR <periodontitis= OR <gingivitis= OR <periodontal= OR <periodontium= OR <periodontal attachment loss= OR <periodontal pocket= OR <alveolar bone loss= OR <tooth mobility=).

Time: by to July 2020.

First, two authors (Kaili Wang and Zheng Zhang) independently retrieved studies from the databases using specific search terms. Subsequently, a hand search was performed by reading abstracts and key words, and studies that were eligible for the inclusion criteria were selected . Lastly, a consensus regarding the final studies to be included was reached via a discussion or by consulting a third author (Zuomin Wang).

Data extraction

Kaili Wang sorted out the information for the subsequent classification of the included studies: first author, publication date, country/region, study design type, numbers of samples, age range of the study population, diagnostic criteria for periodontal disease and cancer, cancer type and outcomes, follow-up period, whether adjustments were performed for smoking, adjusted variables, and multiple adjusted HRs and corresponding 95% CIs. Next, Zheng Zhang checked the information and supplemented it if necessary.

Quality assessment

We evaluated the quality of the included studies using the Newcastle-Ottawa scale. This evaluation system includes three aspects: selection, comparability and exposure. In the selection part, we evaluated the following four aspects: whether the exposed cohort could basically represent the average of the community population, whether the non-exposed cohort was from the same source as the exposure cohort, whether the selection of the exposed cohort was reliable based on records, and whether no outcome events occurred in the study subjects before the study began. In the comparability part, we assessed whether the exposed and non-exposed cohorts were matched in terms of age and other confounding factors. In the exposure part, we assessed the following three aspects: whether there were reliable data or records, such as examination or medical records, for the evaluation of outcome events; whether the follow-up period was equal to or longer than 5 years; and the completeness of follow-up through factors, such as the loss to follow-up rate.

Based on the scores, the studies were defined as follows: ＜ 4 points, low quality; 4-6 points, moderate quality; and 7-9 points, high quality.

Classification of studies

First, the included studies were classified according to the study scope: breast, prostate, lung & bronchial, colon & Rectum, and total cancers. Next, according to the specific content and purpose of the studies, we divided them based on two aspects: cancer occurrence and cancer mortality. Of course, som studies involved both incidence and mortality.

Statistical analysis

We used the HR with the 95% CI to assess the association between periodontal disease and the risk of cancer incidence and mortality. The data extracted from the studies were analyzed using STATA software (version 12.0, Stata Corp, College Station, TX, USA). Heterogeneity was tested through the Q test(statistical significance was set at $P < 0.1$) and I^2 test($I^2 \geq 50\%$ indicated significant heterogeneity) and was represented using a forest plot.

Subgroup analyses were conducted to explore the factors influencing heterogeneity. Subgroup analyses were stratified by study population, study design, dental status, follow-up period, and whether or not smoking was adjusted for. A sensitivity analysis was performed to test the stability of the results.

Begg's and Egger's tests were used for assessing publication bias. Begg's test, also known as the rank correlation test, tests the correlation between effects and sample size. Egger's test, also known as the linear regression method, establishes a regression equation based on the standard normal deviate and precision of each included study. The larger the intercept of the regression line, the higher the bias. A P-value of ＞ 0.05 was considered to indicate no publication bias..

Results

Search and selection results

The process of study selection is shown in Fig. 1. First, 3324 records were collected from PubMed, 5681 from Embase, 5435 from Web of Science, 1095 from Wanfang, and 1576 from CNKI. Subsequently, 9860 publications remained after the duplicates were removed, of which 72 were deemed eligible based on their abstracts and key words. Finally, 27 publications were included in the meta-analysis after 45 studies were excluded for several reasons. Duplicates were removed for the following reasons: review/commentary/letter(n=13), repeat publication(n=7), no available data(n=22), and no full text(n=3).

Characteristics of the included studies Table 1 describes the studies included in the review. The articles were published between 2003 and 2020. Twelve studies were conducted in North America and six in China. Six studies were retrospective, and the others were prospective. Periodontal disease was diagnosed through a dental examination in 18 studies

[17,20,22,23,24,26,28,29,30,33,34,35,36,38,39,40,41,43], among which the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) was used in five studies [22,24,34,36,41], and the definition criteria of periodontal pocket and attachment loss were used in 13 studies [17,20,23,26,28,29,30,33,35,38,39,40,43]. The diagnosis was self-reported by patients based on questionnaires and tooth loss history in the remaining nine studies [18,19,21,25,27,31,32,37,42], among which dentists validated the diagnosis in three studies [27,31,37]. Six studies analyzed periodontal disease and cancer mortality [17,20,21,35,40,43], and 22 studies analyzed periodontal disease and cancer incidence [18,19,22-34,36-42]. Cancer diagnosis was based on ICD-9/10-CM in 15 studies [17,19-22,24,30-36,41-42], medical records and histological examination in 11 studies [18,23,25-28,37-40,43], and patient self-report in 1 study [29]. All the participants were aged above 18 years, and the follow-up period was more than 10 years in 15 studies [17,18,19,20,22,26,27,28,30,31,34,35,38,41,43] and less than 10 years in 12 studies [21,23,24,25,29,32,33,36,37,39,40,42]. Most studies collected information on whether the participants smoked, including how often and how much they smoked and the pack-years. Regarding smoking, eight studies [22,24,28,34,35,36,39,41] did not perform adjustments for smoking; however, the remaining studies included smokers and took smoking into account when calculating the HRs.

Quality assessment

Table S1 shows the quality assessment of the included studies. Twenty-four studies scored seven or more stars, indicating that 88.9% of the studies were of good quality.

Association between periodontitis and cancer incidence

The relationship between periodontal disease and cancer incidence is shown in Figure 2. The pooled estimate based on 11 studies revealed a modest association between periodontal disease and breast cancer incidence (HR=1.26, 95% CI:1.11-1.43), with greater heterogeneity (I2 =75.8%, PQ = 0.000). Similarly, we found a modest association between periodontal disease and prostate (HR=1.26, 95% CI:1.03-1.54, I2 =72.9%, PQ = 0.001), lung & bronchus (HR=1.30, 95% CI:1.13-1.50, I2 =63.7%, PQ = 0.000), colon & rectum (HR=1.18, 95% CI:1.03-1.36, I2 =79.0%, PQ = 0.000), and total (HR=1.14, 95% CI:1.08-1.20, I2 =67.4%, PQ = 0.000)cancer incidence.

Next, we explored the source of heterogeneity through subgroup analyses with $I^2 > 50\%$ and $P < 0.1$.

Sensitivity analyses of the association between periodontitis and cancer incidence

As shown in Figure 3, the pooled HRs were the same, and the 95%CI overlapped with the previous effect size. This means that our results are very reliable.

Subgroup analyses of the association between periodontitis and cancer incidence

The subgroup analysis results are presented in Table 2.

The following were the observations regarding the 11 studies that were conducted on periodontal disease and breast cancer incidence. Four studies were from North America and showed an HR of 1.12 (I^2 = 0%, 95% CI:1.05-1.19, P = 0.001). Two studies were retrospective and showed an HR of 1.52 (I^2 = 0%, 95% CI:1.17-1.98, P = 0.002). The pooled HR in four studies in which the periodontal disease diagnosis was self-reported was 1.15 (I^2 = 0%, 95% CI:1.09-1.22, P = 0.001). Six studies with follow-up periods of more than 10 years showed an HR of 1.11(I^2 = 14.4%, 95% CI:1.03-1.19, P = 0.005). The pooled HR in seven studies in which smoking was adjusted for was 1.13 (I^2 = 7.7%, 95% CI:1.07-1.21, P = 0.001). The CIs were all on the right side. The results of the subgroup analyses were consistent with those of the full dataset analysis. We can state with certainty that periodontal disease increases the risk of breast cancer incidence.
The following were the observations in the seven studies on periodontal disease and prostate cancer incidence. Three studies were from North America and showed an HR of 1.03 (I^2 = 36.9%, 95% CI:0.89-1.18, P = 0.728). Six studies with follow-up periods of more than 10 years showed an HR of 1.16 (I^2 = 60.8%, 95% CI:0.97-1.38, P = 0.100).We found that periodontal disease increased the risk of prostate cancer incidence under certain conditions in the European people, dental examination diagnosis of periodontal disease, follow-up period of less than 10 years. However, the association was not affected by smoking.
Among the 14 studies on periodontal disease and lung and bronchial cancer incidence, eight studies were from North America and showed an HR of 1.34 (I^2 = 46.9, 95% CI:1.24-1.46, P = 0.001), and eight studies in which periodontal disease was diagnosed through dental examination showed an HR of 1.33 (I^2 = 75.7, 95% CI:0.94-1.88, P = 0.000). Similar to prostrate cancer, we found that periodontal disease increased the risk of lung & bronchus cancer incidence under certain conditions in the North American population, self-reported diagnosis of periodontal disease , follow-up period of more than 10 years, and adjustments for smoking, but the association was not affected by study design type.
Among the 13 studies on periodontal disease and colorectal cancer incidence, seven studies were from North America and showed an HR of 1.08 (I^2 = 18.2, 95% CI:0.98-1.19, P = 0.134), and five studies in which periodontal disease was diagnosed by dental examination showed an HR of 1.17 (I^2 = 26.4, 95% CI:0.92-1.48, P = 0.203). We found that periodontal disease increased the risk of colorectal cancer incidence under certain conditions in retrospective study, self-reported diagnosis of periodontal disease , follow-up period of less than 10 years, adjustments for smoking, but the association was not affected by study design type.

Among the 12 studies on periodontal disease and total cancers incidence, three studies were from Asia and showed an HR of 1.09 (I^2 = 92.6, 95% CI:0.94-1.27, P = 0.243), and eight studies with

adjustments for smoking showed an HR of 1.13 (I^2 = 0, 95%CI :1.09-1.17, P = 0.001). We concluded that periodontal disease increased the risk of total cancer incidence under certain conditions in the North American and European population, prospective study design, but the association was not affected by the diagnostic method for periodontal disease, follow-up period, adjustment for smoking.

Association between periodontitis and cancer mortality

We also analyzed the relationship between periodontal disease and cancer mortality (Figure 4). A relationship between periodontal disease and total cancer mortality was observed in four studies, and the HR ranged from 1.24 to 1.58; the pooled HR was 1.40, with no heterogeneity (I^2 = 0, P = 0.718), indicating that the result is reliable. Although the results of current meta-analysis suggest that periodontal disease may increase the risk of breast(HR=1.25,95%CI: 0.83, 1.88, I2 = 0.0%, PQ = 0.809), prostate(HR=1.78, 95%CI:0.92, 3.46, I2 = 0.0%, PQ = 0.962), lung & bronchus(HR=1.48,95%CI: 0.93, 2.35, I2 = 50.8%, PQ = 0.154), colon & rectum(HR=1.66,95%CI: 0.44, 6.27, I2 = 76.7%, PQ = 0.083) cancer mortality, the overall estimate was not significant because of high levels of uncertainty or moderate heterogeneity . However, we did not perform a subgroup analysis because there were only two studies.

Publication bias in meta-analysis

Finally, we performed Begg's and Egger's tests to evaluate publication bias. The results of the two tests are shown in Table 3. We conducted Begg's test in the case of missing items; the P values of the test results after a continuity correction based on Kendall's score in the remaining studies ranged from 0.133-1.000. All the P values were greater than 0.05, indicating that there was no publication bias. We also conducted Egger's test in the case of missing items, the P values of the results of assessing whether the intercept of the remaining items was ranged from 0.147-0.860. All the P values were greater than 0.05, indicating no publication bias. The results of Begg's and Egger's tests were consistent, indicating that there is no publication bias in this meta-analysis.

Discussion

So far, there are a few relevant meta-analyses assessing the association between periodontal disease and breast [44], prostate [45], lung [46], and colorectal [47] cancers. Additionally, there are meta-analyses that have revealed that infections caused by periodontal pathogens increase the risk of total cancers incidence [48] and mortality [49]. However, no one study has described the correlation between periodontal disease and multiple types of cancer in terms of incidence and mortality comprehensively and in detail. Although our results are mostly consistent with those of the previous meta-analyses, our analysis is the most comprehensive because it includes new

studies and the latest results, and we reviewed nearly 20 years of reliable research. The sensitivity analysis further proved the accuracy of our results. The subgroup analysis helped us in better analyze the sources of heterogeneity.

On reviewing the 27 studies included in this meta-analysis, we preliminarily found that compared with healthy individuals, patients with periodontal disease were 1.14 times more susceptible to breast cancer, 1.26 times more susceptible to prostate cancers, 1.3 times more susceptible to lung and bronchial cancers, and 1.18 times more susceptible to colorectal cancer. Through a meta-analysis of eight studies, Tingting Shi [44] found that periodontal disease increased the susceptibility to breast cancer (risk ratio [RR] = 1.19, 95% CI:1.11-1.26, I^2 = 17.6%, P = 0.30). This result is consistent with ours. Yali Wei [45] analyzed seven studies, and the results showed that periodontal disease was significantly associated with prostate cancer (RR = 1.17, 95% CI:1.07-1.27, I^2 = 5.8%, P = 0.001); however, the results of the subgroup analysis showed that some of the 95% CIs fell on both sides. After 18 years of follow-up, Michaud [50] concluded that periodontal disease did not increase the risk of developing colorectal cancer (HR = 1.06, 95% CI:0.91-1.24). Based on a analysis of three cohort studies, Ren[51] also came to a conclusion that there is no relationship between oral health and colorectal cancer. By contrast, one study reported that women with moderate or severe periodontal disease were at a higher risk of colorectal cancer; there were no adjustments for smoking status, body mass index, or alcohol consumption [31]. Another study [52] found that periodontitis increased the risk of colorectal cancer among male patients, former or current smokers, and patients with an alcohol intake above the moderate level. Similarly, the association between periodontal disease and lung cancer is very controversial. Jiahe Wang[46]analyzed six high-quality studies and found that periodontal disease greatly increased the risk of lung cancer (HR = 1.40, 95% CI:1.25-1.58, I^2 = 8.7%). Two studies[18,50] also obtained the same result after adjustments for smoking-related variables, but they obtained the opposite result when they analyzed patients who never smoked cigarettes, but were pipe or cigar smokers. Xiao Li [53] found that periodontal bacterial infection increased the incidence of total cancer(OR = 1.25, 95%CI:1.03-1.52, I^2 = 71%, P = 0.02), but the results of the subgroup analysis showed that some of the 95% CIs fell on both sides.

This meta-analysis also concluded that there is a clear correlation between periodontal disease and total cancer mortality. Patients with periodontal disease have a 1.4 times higher risk of dying from total cancer than those without periodontal disease. Romandini [54] reviewed 57 studies and concluded that periodontal disease increased the risk of all-cause mortality, including cancer mortality(RR = 1.38, 95% CI:1.24-1.53, I^2 = 29.8%, P < 0.001), which is consistent with our result.

We found that the correlation between periodontal disease and breast cancer incidence was maintained after the subgroup analysis. While performing the meta-analysis, we found greater

heterogeneity in the included studies; subsequently, we performed a subgroup analysis of factors, such as study population, study design, dental status, follow-up period, and adjustments for smoking, which might affect heterogeneity. First, we found that, compared with studies from countries in Europe and Asia, those from North America were less heterogeneous. Second, prospective studies were more heterogeneous. In fact, the two study designs have their own advantages and disadvantages . It is recommended to adopt a prospective follow-up study design if the purpose of a study is to evaluate the effect of a certain treatment method. It is recommended to choose a retrospective follow-up study design if the purpose of a study is to explore and explain a certain phenomenon [55].The advantage of the prospective design is the accuracy of data including exposures, confounding factors, and endpoints, but these studies require a lot of time and financial resources. The merit of retrospective studies is the time saved by the direct use of existing data, but these studies are susceptible to selection bias. The limitation of retrospective studies is that it is not possible to establish causal effects. The results may be influenced by confounding factors expect to the exposure factors, which are often not accurately measured or may even be unknown [56]. Third, the heterogeneity of the studies, which was observed over a period of 10 years, was relatively low, indicating that the results obtained from the studies with long follow-up periods are relatively accurate and consistent. In the subgroup analysis, six studies with follow-up periods of over 10 years demonstrated a 1.11-fold increase in breast cancer risk, with low heterogeneity (I^2 = 14.4%). Among the eight studies included in Tingting's meta-analysis [44], five studies had a follow-up period of more than 10 years and revealed a 1.38-fold increase in breast cancer risk through a subgroup analysis with minimal heterogeneity (I^2 = 7.0%). Fourth, among the studies we included, the diagnosis of periodontal disease was self-reported in nine. In many of the previous studies, the diagnosis of periodontal disease was based on self-reported patient data or administrative data. Although this approach may sound unreliable, it can save time. In addition, the manpower and financial resources required for a periodontal examination can be saved. Moreover, self-reported diagnosis of periodontal disease has been proven to be acceptable, with a diagnostic OR of 1.4 (95% CI:0.9-2.2) for the question on bleeding gums and of 11.7 (95% CI:4.1-33.4) for the question on tooth mobility, it was also found to be suitable in large-scale epidemiological studies [57].

Smoking is a risk factor of many diseases. A previous study has confirmed that smoking is an independent risk factor for periodontal and respiratory diseases, including lung cancer(OR=2.12, 95% CI:1.32-3.42) [58]. Therefore, smoking should be excluded as an confounding factor in an analysis of the association between periodontal disease and lung cancer. Of the 27 studies included in this meta-analysis, adjustments for smoking were performed in 18 studies, and 10 of the 14 studies on periodontitis and lung cancer involved adjustments for smoking. The probability of the development of lung and bronchial cancer in patients with

periodontal disease was 1.35 times higher than that in individuals with healthy periodontal tissues, but the statistical heterogeneity was great. In Michaud's [48] review, based on five studies after adjustments for smoking, positive association was found between periodontal disease and lung cancer, with a pooled RR of 1.33 (95% CI:1.19-1.49,I^2 = 0%, P = 0.58), this is consistent with our conclusion, and the values are close to ours. In a prospective study by Tai [41], smoking was not excluded as a disincentive, therefore, the polled HR (HR = 1.9, 95% CI:1.08-3.35, P = 0.0267) was significantly higher than ours.

There are several limitations in this meta-analysis. First, although most confounding factors were adjusted for in the included studies, few studies adjusted for other oral health problems and stress, which may have affected the results of these studies. Second, genetic factors play a very important role in the occurrence of cancer. While diagnosing the patient's condition, few researchers noted whether there was a family history of cancer, therefore, this important influencing factor was most likely ignored in the data analysis, which would also affect the final results.

Conclusions

This meta-analysis revealed that periodontal disease is significantly associated with the risk of the incidence of breast cancer and that periodontal disease may increase the risk of total cancer mortality. Our results prompt the general public to pay attention to periodontal health and to receive periodontal treatment in a regular and timely manner. In conclusion, our results suggest that patients with periodontal disease should pay special attention to breast cancer screening during regular general health examinations. Apart from breast ultrasound, a mammography examination conducted once every 1-2 years would be helpful for the early detection and early treatment of breast cancer. Of course, attention should also be paid to other related cancers, such as lung, colorectal, and prostate cancers. However, well-designed studies, populations from diverse geographic regions, and adjustments for exact confounding factors are needed to confirm our findings and to further explore the relationship between periodontal disease and cancers incidence and mortality.

Competing Interest statement:

The authors declare that they have no competing interests.

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Figure 1

Flow chart from identification of eligible studies to final inclusion

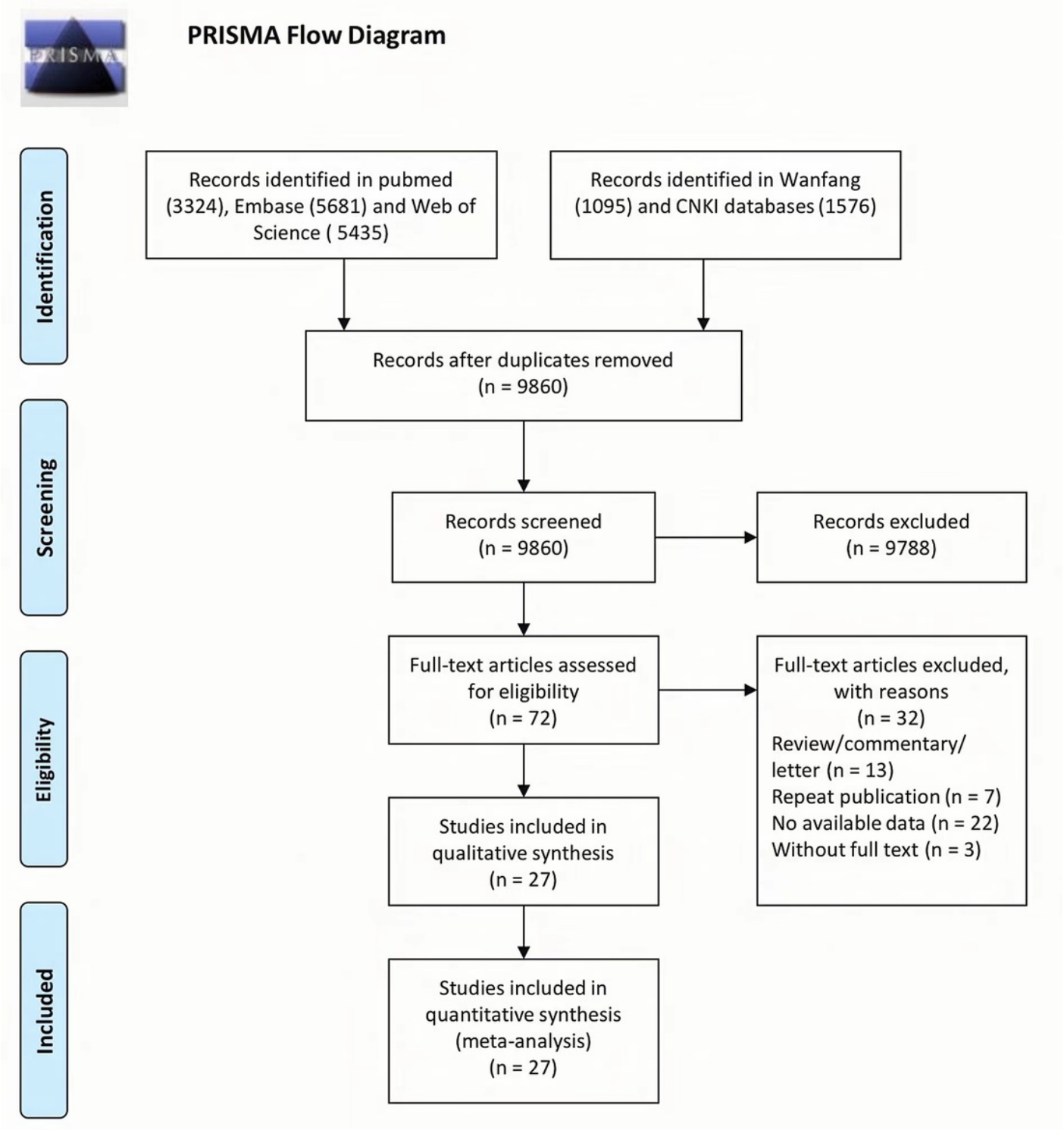

Figure 2

Forest plots of the association between periodontitis and cancer incidence

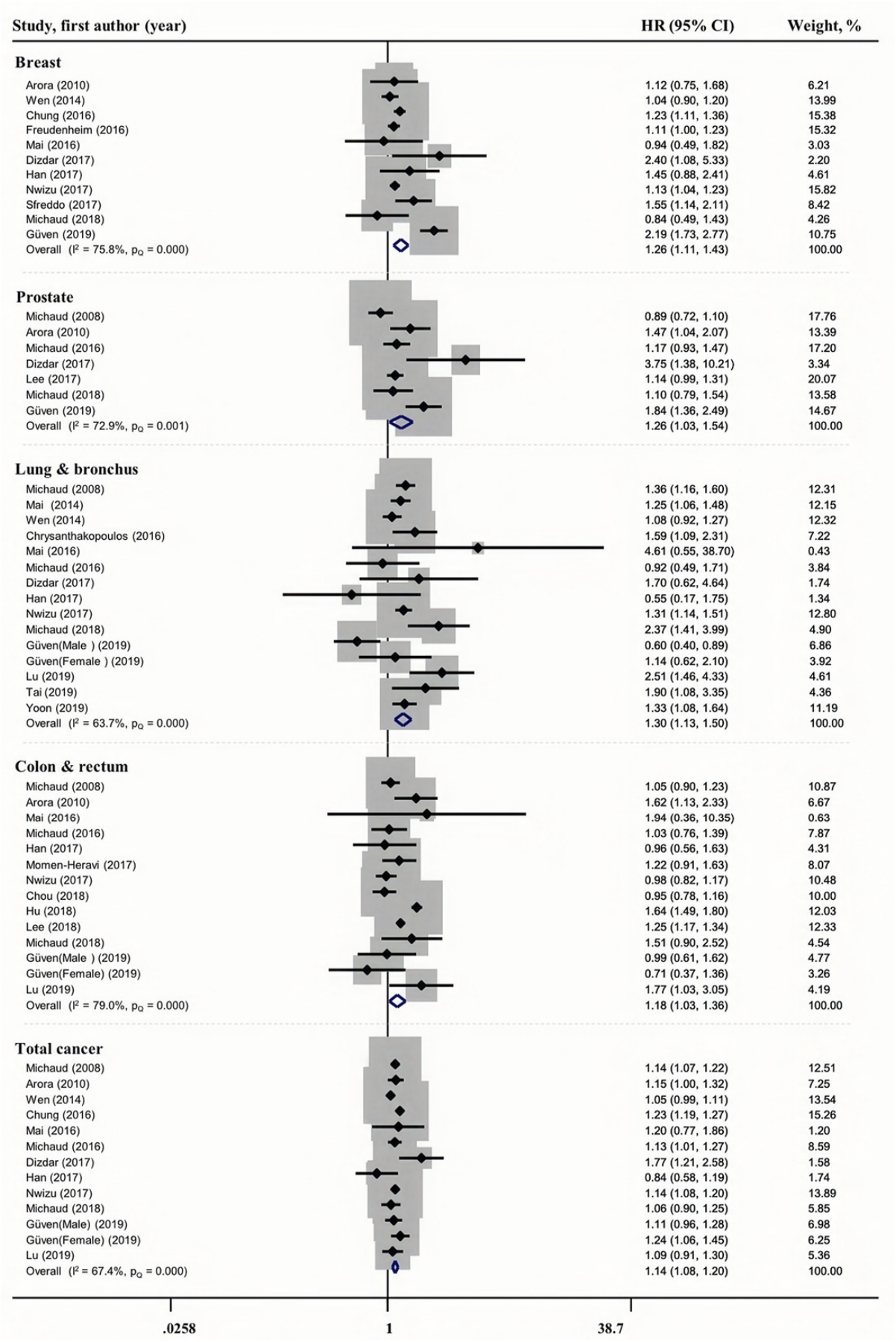
Study, first author (year)
HR (95% CI)
Weight, %
Breast
Arora (2010) 1.12 (0.75, 1.68) 6.21
Wen (2014) 1.04 (0.90, 1.20) 13.99
Chung (2016) 1.23 (1.11, 1.36) 15.38
Freudenheim (2016) 1.11 (1.00, 1.23) 15.32
Mai (2016) 0.94 (0.49, 1.82) 3.03
Dizdar (2017) 2.40 (1.08, 5.33) 2.20
Han (2017) 1.45 (0.88, 2.41) 4.61
Nwizu (2017) 1.13 (1.04, 1.23) 15.82
Sfreddo (2017) 1.55 (1.14, 2.11) 8.42
Michaud (2018) 0.84 (0.49, 1.43) 4.26
Güven (2019) 2.19 (1.73, 2.77) 10.75
Overall (I^2 = 75.8%, p_Q = 0.000) 1.26 (1.11, 1.43) 100.00
Prostate
Michaud (2008) 0.89 (0.72, 1.10) 17.76
Arora (2010) 1.47 (1.04, 2.07) 13.39
Michaud (2016) 1.17 (0.93, 1.47) 17.20
Dizdar (2017) 3.75 (1.38, 10.21) 3.34
Lee (2017) 1.14 (0.99, 1.31) 20.07
Michaud (2018) 1.10 (0.79, 1.54) 13.58
Güven (2019) 1.84 (1.36, 2.49) 14.67
Overall (I^2 = 72.9%, p_Q = 0.001) 1.26 (1.03, 1.54) 100.00
Lung & bronchus
Michaud (2008) 1.36 (1.16, 1.60) 12.31
Mai (2014) 1.25 (1.06, 1.48) 12.15
Wen (2014) 1.08 (0.92, 1.27) 12.32
Chrysanthakopoulos (2016) 1.59 (1.09, 2.31) 7.22
Mai (2016) 4.61 (0.55, 38.70) 0.43
Michaud (2016) 0.92 (0.49, 1.71) 3.84
Dizdar (2017) 1.70 (0.62, 4.64) 1.74
Han (2017) 0.55 (0.17, 1.75) 1.34
Nwizu (2017) 1.31 (1.14, 1.51) 12.80
Michaud (2018) 2.37 (1.41, 3.99) 4.90
Güven(Male) (2019) 0.60 (0.40, 0.89) 6.86
Güven(Female) (2019) 1.14 (0.62, 2.10) 3.92
Lu (2019) 2.51 (1.46, 4.33) 4.61
Tai (2019) 1.90 (1.08, 3.35) 4.36
Yoon (2019) 1.33 (1.08, 1.64) 11.19
Overall (I^2 = 63.7%, p_Q = 0.000) 1.30 (1.13, 1.50) 100.00
Colon & rectum
Michaud (2008) 1.05 (0.90, 1.23) 10.87
Arora (2010) 1.62 (1.13, 2.33) 6.67
Mai (2016) 1.94 (0.36, 10.35) 0.63
Michaud (2016) 1.03 (0.76, 1.39) 7.87
Han (2017) 0.96 (0.56, 1.63) 4.31
Momen-Heravi (2017) 1.22 (0.91, 1.63) 8.07
Nwizu (2017) 0.98 (0.82, 1.17) 10.48
Chou (2018) 0.95 (0.78, 1.16) 10.00
Hu (2018) 1.64 (1.49, 1.80) 12.03
Lee (2018) 1.25 (1.17, 1.34) 12.33
Michaud (2018) 1.51 (0.90, 2.52) 4.54
Güven(Male) (2019) 0.99 (0.61, 1.62) 4.77
Güven(Female) (2019) 0.71 (0.37, 1.36) 3.26
Lu (2019) 1.77 (1.03, 3.05) 4.19
Overall (I^2 = 79.0%, p_Q = 0.000) 1.18 (1.03, 1.36) 100.00
Total cancer
Michaud (2008) 1.14 (1.07, 1.22) 12.51
Arora (2010) 1.15 (1.00, 1.32) 7.25
Wen (2014) 1.05 (0.99, 1.11) 13.54
Chung (2016) 1.23 (1.19, 1.27) 15.26
Mai (2016) 1.20 (0.77, 1.86) 1.20
Michaud (2016) 1.13 (1.01, 1.27) 8.59
Dizdar (2017) 1.77 (1.21, 2.58) 1.58
Han (2017) 0.84 (0.58, 1.19) 1.74
Nwizu (2017) 1.14 (1.08, 1.20) 13.89
Michaud (2018) 1.06 (0.90, 1.25) 5.85
Güven(Male) (2019) 1.11 (0.96, 1.28) 6.98
Güven(Female) (2019) 1.24 (1.06, 1.45) 6.25
Lu (2019) 1.09 (0.91, 1.30) 5.36
Overall (I^2 = 67.4%, p_Q = 0.000) 1.14 (1.08, 1.20) 100.00
.0258
1
38.7

Figure 3

Sensitivity analyses of the association between periodontitis and cancer incidence

Study omitted	HR	LCI	UCI	HR(95%CI)
Breast				
Arora (2010)	1.27	1.11	1.45	
Wen (2014)	1.30	1.13	1.49	
Chung (2016)	1.27	1.08	1.48	
Freudenheim (2016)	1.29	1.11	1.50	
Mai (2016)	1.27	1.11	1.44	
Dizdar (2017)	1.24	1.09	1.40	
Han (2017)	1.25	1.09	1.42	
Nwizu (2017)	1.29	1.10	1.51	
Sfreddo (2017)	1.23	1.08	1.40	
Michaud (2018)	1.28	1.12	1.46	
Güven (2019)	1.15	1.07	1.24	
Prostate				
Michaud (2008)	1.35	1.10	1.65	
Arora (2010)	1.23	0.99	1.53	
Michaud (2016)	1.30	1.01	1.66	
Dizdar (2017)	1.21	1.00	1.45	
Lee (2017)	1.32	1.00	1.73	
Michaud (2018)	1.30	1.03	1.63	
Güven (2019)	1.16	0.97	1.38	
Lung & bronchus				
Michaud (2008)	1.30	1.10	1.53	
Mai (2014)	1.31	1.11	1.54	
Wen (2014)	1.33	1.14	1.56	
Chrysanthakopoulos (2016)	1.28	1.10	1.48	
Mai (2016)	1.29	1.12	1.49	
Michaud (2016)	1.32	1.14	1.52	
Dizdar (2017)	1.29	1.12	1.49	
Han (2017)	1.31	1.14	1.51	
Nwizu (2017)	1.30	1.10	1.54	
Michaud (2018)	1.26	1.10	1.44	
Güven (Male) (2019)	1.35	1.20	1.52	
Güven (Female) (2019)	1.31	1.13	1.51	
Lu (2019)	1.26	1.10	1.44	
Tai (2019)	1.28	1.11	1.47	
Yoon (2019)	1.30	1.11	1.52	
Colon & rectum				
Michaud (2008)	1.20	1.04	1.39	
Arora (2010)	1.16	1.00	1.33	
Mai (2016)	1.18	1.03	1.35	
Michaud (2016)	1.20	1.04	1.38	
Han (2017)	1.20	1.04	1.37	
Momen-Heravi (2017)	1.18	1.02	1.36	
Nwizu (2017)	1.21	1.05	1.39	
Chou (2018)	1.21	1.06	1.40	
Hu (2018)	1.12	1.02	1.25	
Lee (2018)	1.17	0.98	1.40	
Michaud (2018)	1.17	1.02	1.35	
Güven (Male) (2019)	1.19	1.04	1.37	
Güven (Female) (2019)	1.20	1.05	1.38	
Lu (2019)	1.16	1.01	1.34	
Total cancer				
Michaud (2008)	1.14	1.08	1.21	
Arora (2010)	1.14	1.08	1.20	
Wen (2014)	1.16	1.18	1.21	
Chung (2016)	1.12	1.07	1.17	
Mai (2016)	1.14	1.08	1.20	
Michaud (2016)	1.14	1.08	1.20	
Dizdar (2017)	1.13	1.08	1.19	
Han (2017)	1.15	1.09	1.20	
Nwizu (2017)	1.14	1.07	1.21	
Michaud (2018)	1.14	1.09	1.20	
Güven (Male) (2019)	1.14	1.08	1.20	
Güven (Female) (2019)	1.13	1.07	1.19	
Lu (2019)	1.14	1.08	1.20	

Figure 4

Forest plots of the association between periodontitis and cancer mortality

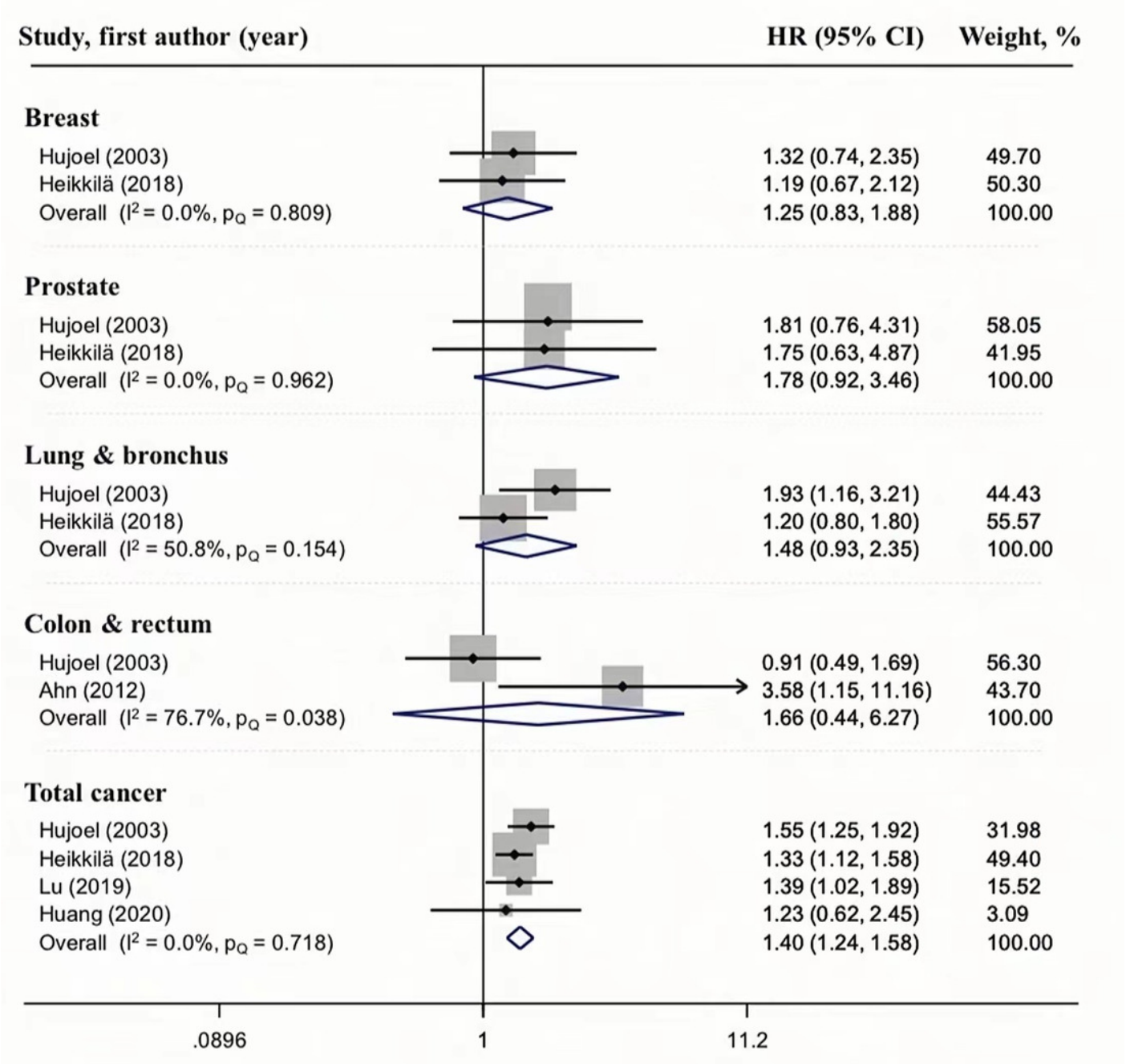

Table 1(on next page)

Table 1. Characteristics of eligible studies included in this meta-analysis.

Table 1. Characteristics of eligible studies included in this meta-analysis.

Author (Year)	Location	Study design	Participants number	Age (years)	Dental status	Outcomes	Cancer type	Assessment method	Follow-up (year)	Adjusted variables
Hujoel et al 2003	USA	Prospective study	11328	25-74	Dental examination	Cancer mortality	breast, prostate, lung & bronchus, colon & rectum, total cancer	ICD-9	18	age, gender, education, socioeconomic level, race, smoking, alcohol consumption, vitamin consumption, et al
Michaud et al 2008	USA	Prospective study	48375	40-75	Self-reported	Cancer incidence	prostate, lung & bronchus, colon & rectum, total cancer	Medical records or histological examination	17.7	age, race, smoking, alcohol consumption, vitamin consumption, body mass index, diabetes, physical activity, et al
Arora et al 2010	Swedish	Prospective study	15333	38-77	Self-reported	Cancer incidence	breast, prostate, colon & rectum, total cancer	ICD	27	age, gender, education, smoking, alcohol consumption, body mass index, diabetes, et al
Ahn et al 2012	USA	Prospective study	12605	≥17	Dental examination	Cancer mortality	colon & rectum	ICD-10	12	age, gender, education, race, smoking, body mass index, et al
Mai et al	USA	Prospective	77485	50-79	Self-reported	Cancer	lung & bronchus	ICD-O-2	6.8	age, education, race, smoking, alcohol

2014		study				mortality			consumption, body mass index, physical activity, et al
Wen et al 2014	China	Prospective study	1 million	⩾20	Dental examination	Cancer incidence	breast, lung & bronchus, total cancer	ICD-9	14	age, gender, et al
Chrysanthakopoulos et al 2016	Greek	Retrospective study	200	≥48	Dental examination	Cancer incidence	lung & bronchus	Medical records or histological examination	2	age, gender, education, socioeconomic level, smoking, et al
Chung et al 2016	China	Prospective study	40140	≥40	Dental examination	Cancer incidence	breast, total cancer	ICD-9	5	socioeconomic level, diabetes, et al
Freudenheim et al 2016	USA	Prospective study	73737	50-79	Self-reported	Cancer incidence	breast	Medical records or histological examination	6.7	age, education, race, smoking, alcohol consumption, body mass index, physical activity, et al
Mai et al 2016	China	Prospective study	1337	53-85	Dental examination	Cancer incidence	breast, lung & bronchus, colon & rectum, total cancer	Medical records or histological examination	12.2	age, smoking, et al

Michaud et al 2016	USA	Prospective study	19933	40-75	Self-reported	Cancer incidence	prostate, lung & bronchus, colon & rectum, total cancer	Medical records or histological examination	26	age, race, smoking, alcohol consumption, body mass index, diabetes, physical activity, et al
Dizdar et al 2017	Turkey	Prospective study	280	≥35	Dental examination	Cancer incidence	breast, prostate, lung & bronchus, total cancer	Medical records or histological examination	12	age, gender, et al
Han et al 2017	Korea	Retrospective study	22948	≥19	Dental examination	Cancer incidence	breast, lung & bronchus, colon & rectum, total cancer	self-reported	2	education, socioeconomic level, smoking, alcohol consumption, et al
Lee et al 2017	Korea	Prospective study	934	≥40	Dental examination	Cancer incidence	prostate, colon & rectum	ICD-10	12	age, gender, socioeconomic level, smoking, alcohol consumption, diabetes, physical activity, et al
Momen-Heravi et al 2017	USA	Prospective study	121700	30-55	Self-reported	Cancer incidence	colon & rectum	ICD-9	19	age, race, smoking, alcohol consumption, vitamin consumption, body mass index, diabetes, et al

Nwizu1 et al 2017	USA	Prospective study	65869	54-86	Self-reported	Cancer incidence	breast, lung & bronchus, colon & rectum, total cancer	ICD or Medical records	8.32	age, smoking, body mass index, et al
Sfreddo et al 2017	Brazil	Retrospective study	201	≥18	Dental examination	Cancer incidence	breast	ICD-10 or Medical records	2.2	age, smoking, body mass index, et al
Chou et al 2018	China	Retrospective study	67672	≥18	Dental examination	Cancer incidence	colon & rectum	ICD-9	10	age, gender, education, socioeconomic level, diabetes, et al
Heikkilä et al 2018	Finland	Prospective study	68273	≥29	Dental examination	Cancer mortality	breast, prostate, lung & bronchus, total cancer	ICD-10	10.1	age, gender, socioeconomic level, diabetes, et al
Hu et al 2018	China	Prospective study	212974	≥18	Dental examination	Cancer incidence	colon & rectum	ICD-9	3	age, gender, et al
Lee et al 2018	Korea	Retrospective study	42871	30-45	Self-reported	Cancer incidence	colon & rectum	Medical records or histological examination	3	age,sex,BMI, DM , HbA1c , HTN, LDL ,waist,alcohol intake,smoking status and pack-years.

Michaud et al 2018	USA	Prospective study	7466	44-66	Dental examination	Cancer incidence	breast, prostate, lung & bronchus, colon & rectum, total cancer	Medical records or histological examination	14.7	age, field center, education level, smoking status, smoking duration, drinking status, body mass index, and diabetes status
Güven et al 2019	Turkey	Prospective study	5199	≥50	Dental examination	Cancer incidence	lung & bronchus, colon & rectum, total cancer	Medical records or histological examination	7.2	age, gender, et al
Lu et al 2019	USA	Prospective study	15,792	44-66	Dental examination	Cancer incidence and mortality	lung & bronchus, colon & rectum, total cancer	Medical records or histological examination	4	age, education, race, smoking, alcohol consumption, diabetes, et al
Tai et al 2019	China	Prospective study	714246	No metion	Dental examination	Cancer incidence	lung & bronchus	ICD-9	≥10	no
Yoon et al 2019	USA	Retrospective study	84797	40-79	Self-reported	Cancer incidence	lung & bronchus	ICD-10	8	education, socioeconomic level, smoking, alcohol consumption, body mass index, et al

Huang et al 2020	USA	Prospective study	6034	≥40	Dental examination	Cancer mortality	total cancer	Medical records or histological examination	21.3	age, gender, education, socioeconomic level, race, smoking, body mass index, diabetes, et al

ICD: International Classification of Diseases

Table 2(on next page)

Table 2. Subgroup analyses of the association between periodontitis and cancer incidence.

Table 2. Subgroup analyses of the association between periodontitis and cancer incidence.

Subgroups	No. of studies	Meta-analysis			Heterogeneity	
		HR	95%CI	*P*-value	I^2(%)	*P*-value
Breast Cancer						
Study population						
North America	4	1.12	1.05-1.19	0.001	0.0	0.694
Asia	3	1.16	1.00-1.35	0.044	53.1	0.119
Europe	3	1.76	1.06-2.91	0.029	75.8	0.016
South America	1	1.55	1.14-2.11	0.006	-	-
Study design						
Prospective study	9	1.22	1.07-1.40	0.004	78.7	0.000
Retrospective study	2	1.52	1.17-1.98	0.002	0.0	0.832
Dental status						
Self-reported	4	1.15	1.09-1.22	<0.001	0.0	0.502
Dental examination	7	1.38	1.00-1.90	0.051	83.1	0.000
Follow-up (years)						
≥10	6	1.11	1.03-1.19	0.005	14.4	0.322
<10	5	1.43	1.15-1.78	0.001	86.3	0.000
Adjust for smoking						
Yes	7	1.13	1.07-1.21	<0.001	7.7	0.369
No	4	1.47	1.07-2.01	0.016	90.3	0.000
Prostate cancer						

Study population						
North America	3	1.03	0.89-1.18	0.728	36.9	0.205
Asia	1	1.14	0.99-1.31	0.065	-	-
Europe	3	1.73	1.39-2.16	<0.001	39.8	0.190
Study design						
Prospective study	7	1.26	1.03-1.54		72.9	0.001
Dental status						
Self-reported	3	1.12	0.86-1.47	0.395	70.6	0.034
Dental examination	4	1.44	1.02-2.02	0.036	77.1	0.004
Follow-up (years)						
≥10	6	1.16	0.97-1.38	0.100	60.8	0.026
<10	1	1.84	1.36-2.49	<0.001	-	-
Adjust for smoking						
Yes	5	1.11	1.01-1.22	0.035	43.7	0.130
No	2	1.95	1.46-2.61	<0.001	43.8	0.182

lung & bronchus cancer

Study population						
North America	8	1.34	1.24-1.46	<0.001	46.9	0.068
Asia	3	1.18	0.72-1.93	0.502	59.8	0.083
Europe	3	1.11	0.64-1.95	0.709	77.6	0.004
Study design						
Prospective study	11	1.30	1.10-1.53	0.002	68.5	<0.001

Retrospective study	3	1.36	1.14-1.63	0.001	34.4	0.218
Dental status						
Self-reported	6	1.31	1.21-1.42	<0.001	0.0	0.635
Dental examination	8	1.33	0.94-1.88	0	75.7	<0.001
Follow-up (years)						
≥10	9	1.28	1.18-1.38	<0.001	46.5	0.060
<10	5	1.20	0.81-1.77	0.368	78.8	<0.001
Adjust for smoking						
Yes	10	1.35	1.25-1.46	<0.001	44.6	0.062
No	4	1.10	0.76-1.59	0.618	69.3	0.011

Colorectal Cancer

Study population						
North America	7	1.08	0.98-1.19	0.134	18.2	0.291
Asia	4	1.22	0.97-1.55	0.089	91.4	<0.001
Europe	2	1.10	0.68-1.78	0.686	64.9	0.058
Study design						
Prospective study	11	1.19	0.99-1.43	0.063	81.8	<0.001
Retrospective study	2	1.24	1.16-1.33	<0.001	0.0	0.327
Dental status						
Self-reported	8	1.19	1.02-1.39	0.030	87.2	<0.001
Dental examination	5	1.17	0.92-1.48	0.203	26.4	0.236
Follow-up (years)						

≥10	9	1.21	0.99-1.48	0.065	85.4	<0.001
<10	4	1.24	1.16-1.33	<0.001	35.9	0.182
Adjust for smoking						
Yes	10	1.20	1.13-1.26	<0.001	45.2	0.058
No	3	1.08	0.71-1.63	0.718	90.3	<0.001
Total cancer						
Study population						
North America	6	1.13	1.09-1.18	<0.001	0.0	0.965
Asia	3	1.09	0.94-1.27	0.243	92.6	<0.001
Europe	3	1.18	1.09-1.28	<0.001	47.1	0.129
Study design						
Prospective study	11	1.15	1.09-1.20	<0.001	67.1	<0.001
Retrospective study	1	0.84	0.58-1.19	0.324	-	-
Dental status						
Self-reported	5	1.17	1.12-1.22	<0.001	57.1	0.054
Dental examination	7	1.08	1.03-1.13	0.001	46.1	0.072
Follow-up (years)						
≥10	8	1.11	1.08-1.15	<0.001	42.1	0.097
<10	4	1.22	1.18-1.25	<0.001	49.0	0.097
Adjust for smoking						
Yes	8	1.13	1.09-1.17	<0.001	0.0	0.803
No	4	1.18	1.06-1.32	0.002	86.2	<0.001

CI, confidence interval, HR, hazard ratio.

Table 3(on next page)

Table 3. Publication bias in meta-analysis.

Table 3. Publication bias in meta-analysis.

Publicaton bias (*P*-value)	Cancer incidence		Cancer mortality	
	Begg's test	Egger's test	Begg's test	Egger's test
Breast Cancer	0.640	0.328	1.00	-
Prostate cancer	0.133	0.147	1.00	-
lung & bronchus cancer	0.767	0.574	1.00	-
Colorectal Cancer	0.584	0.357	1.00	-
Total cancer	0.855	0.387	1.00	0.860