Systematic Review and Meta-Analysis

Medicine®

OPEN

The effect of periodontal bacteria infection on incidence and prognosis of cancer

A systematic review and meta-analysis

Li Xiao, BS[a], Qianyu Zhang, BS[a], Yanshuang Peng, BS[a], Daqing Wang, MD, PhD[b,*], Ying Liu, MD, PhD[a,*]

Abstract

Background: Periodontal bacteria is the major pathogens in the oral cavity and the main cause of adult chronic periodontitis, but their association with incidence and prognosis in cancer is controversial. The aim of this study was to evaluate the effect of periodontal bacteria infection on incidence and prognosis of cancer.

Methods: A systematic literature search of PubMed, Embase, Web of Science, and Cochrane Library databases was performed to obtain 39 studies comprising 7184 participants. The incidence of cancer was evaluated as odd ratios (OR) with a 95% confidence interval (95% CI) using Review Manager 5.2 software. Overall survival, cancer-specific survival and disease-free survival, which were measured as hazard ratios (HR) with a 95% CI using Review Manager 5.2 software.

Results: Our results indicated that periodontal bacteria infection increased the incidence of cancer (OR = 1.25; 95%CI: 1.03–1.52) and was associated with poor overall survival (HR = 1.75; 95% CI: 1.40–2.20), disease-free survival (HR = 2.18; 95%CI: 1.24–3.84) and cancer-specific survival (HR = 1.85, 95%CI: 1.44–2.39). Subgroup analysis indicted that the risk of cancer was associated with *Porphyromonas gingivalis* (*Pg*) infection (OR = 2.16; 95%CI: 1.34–3.47) and *Prevotella intermedia* (*Pi*) infection (OR = 1.28; 95%CI: 1.01–1.63) but not *Tannerella forsythia* (*Tf*) (OR = 1.06; 95%CI: 0.8–1.41), *Treponema denticola* (*Td*) (OR = 1.30; 95%CI: 0.99–1.72), *Aggregatibacter actinomycetemcomitans* (*Aa*) (OR = 1.00; 95%CI: 0.48–2.08) and *Fusobacterium nucleatum* (*Fn*) (OR = 0.61; 95% CI: 0.32–1.16).

Conclusion: This meta-analysis revealed periodontal bacteria infection increased the incidence of cancer and predicted poor prognosis of cancer.

Abbreviations: Aa = *Aggregatibacter actinomycetemcomitans*, CI = 95% confidence interval 95%, CSS = cancer-specific survival, DFS = disease-free survival, Fn = *Fusobacterium nucleatum*, HR = hazard ratios, OR = odd ratios, OS = overall survival, Pg = *Porphyromonas gingivalis*, Pi = *Prevotella intermedia*, Td = *Treponema denticola*, Tf = *Tannerella forsythia*.

Keywords: meta-analysis, neoplasms, periodontal bacteria, prognosis

1. Introduction

Cancer is the second leading cause of death globally and is estimated to account for 9.6 million death in 2018, according to new data from the world health organization.[1] Epidemiological studies established several well-defined risk factors for cancer, including age, heredity, diet, tobacco use, chronic viral infections, and inflammation. However, the viewpoint that bacterial infections cause cancer has been ignored. Until 1994, *Helicobacter pylori*, which is defined as a class I carcinogen, was associated with the development of cancer in humans.[2] Since

Editor: Jianxun Ding.

All data analyzed during this study are included in this published article.

This work was supported by the Special Fund for Municipal and University Cooperative Scientific Research (no.: 18SXHZ0270), the Scientific Research Project of Guangdong Provincial Key Oral Medicine Laboratory (no.: KF2016120103) and the Doctor of North Sichuan Medical College Fund (no.: CBY13-QD-07. The funding bodies had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

The authors have no conflicts of interests to disclose.

Supplemental Digital Content is available for this article.

[a] Department of Stomatology North Sichuan Medical College, [b] Department of Ophthalmology North Sichuan Medical College, Affiliated Hospital of North Sichuan Medical College, Nanchong, China.

[*] Correspondence: Ying Liu, Department of Stomatology North Sichuan Medical College, Affiliated Hospital of North Sichuan Medical College, Nanchong, China (e-mail: liuying08_nsmz@163.com); Daqing Wang, Department of Ophthalmology North Sichuan Medical College, Affiliated Hospital of North Sichuan Medical College, Nanchong, China (e-mail: Wdq11@sina.com).

How to cite this article: Xiao L, Zhang Q, Peng Y, Wang D, Liu Y. The effect of periodontal bacteria infection on incidence and prognosis of cancer: A systematic review and meta-analysis. Medicine 2020;99:15(e19698).

Received: 2 December 2019 / Received in final form: 27 February 2020 / Accepted: 28 February 2020

http://dx.doi.org/10.1097/MD.0000000000019698

then there has been a growing number of evidence supporting an association between cancer and bacterial infection,[3–7] including those in the oral cavity.[8–10] Periodontal disease is one of the most common inflammatory diseases in adults.[11] Periodontal bacteria, one of the most important causes of periodontal disease, which can lead to tooth loss and systemic inflammation, are associated with many systemic disorders such as cardiovascular diseases, diabetes, pulmonary diseases and rheumatoid arthritis.[12] Recently, mounting evidence suggests a causal relationship between periodontal bacteria infections and the development of malignancies.[10,13,14] Several periodontal bacteria have been reported to be related with development of cancer, such as Pg and Fn. Furthermore, periodontal bacteria infection has been used as marker to evaluate the prognosis of cancer patients.[15–17] However, owing to difference in study method, sample size, study population and research region, the effect of periodontal bacteria infections on incidence and prognosis of cancer are unclear.

In this study, we performed a systematic review of the available literature on this topic in PubMed, Embase, Web of Science, and the Cochrane Library. Then, we conducted a meta-analysis to determine the incidence and prognosis of periodontal bacteria in cancer, for purpose of addressing controversy.

2. Methods

2.1. Literature search

Articles relevant with the subject were retrieved from PubMed, Embase, Web of Science, and Cochrane Library databases on June 10, 2019. The search strategy was listed as follows: ((((cancer [Title/Abstract]) OR tumor [Title/Abstract]) OR malignancy [Title/Abstract]) OR carcinoma [Title/Abstract]) OR neoplasm [Title/Abstract]) AND (((((*Porphyromonas gingivalis* [Title/Abstract]) OR *Fusobacterium nucleatum* [Title/Abstract]) OR *Tannerella forsythia* [Title/Abstract]) OR *Treponema denticola* [Title/Abstract]) OR *Aggregatibacter actinomycetemcomitans* [Title/Abstract]) OR *Prevotella intermedia* [Title/Abstract]). Two reviewers (L.X. and Q.Y.Z.) inspected all candidate articles independently. Discrepancies were resolved by discussion with the senior authors (DQW and YL).

2.2. Inclusion and exclusion criteria

The inclusion criteria were:

(1) the diagnosis of cancer was confirmed by pathological examination;
(2) Study designs must be prospective or retrospective cohort study. Studies must compare patients with periodontal bacteria infected and periodontal bacteria uninfected;
(3) Studies must analyze the cancer incidence, OS, DFS, and CSS in cancer patients;
(4) Articles were published as original research.

The exclusion criteria were:

(1) reviews, meeting abstracts, letters;
(2) animal model studies.

2.3. Data extraction and quality assessment

Two reviewers (LX and QYZ) independently extracted following data and information from final studies: author, year of publication, types of periodontal bacteria, study country, sample size, survival data, and the tumor location. The enrolled literatures were then qualified by PRISMA checklists (Supplementary Table 1: https://enlol.cn/Supplementary%20Materials/Supplementary%20Table%201.docx). Disagreements were resolved by discussion. Two authors (YSP and LX) assessed the final studies, scored them using the modified Newcastle–Ottawa Scale (NOS) and the scoring system was based on three categories: selection, comparability, and outcome.[18] The full score was 8 points, and a high-quality study in our analysis was defined as a study with ≥7 points. Consensus was reached by discussion with senior reviewers (YL and DQW).

2.4. Statistical analysis

Review Manager 5.2 (RevMan 5.2) (Cochrane Collaboration, Denmark) was used to conduct all statistical analyses. Standard Cochran Q test and I^2 statistics were used to identify heterogeneity between the included studies. A value of I^2 statistics >50% and P value < .1 indicated significant heterogeneity, therefore a random effects model was used to calculate the pooled OR, HR, and 95% CI in such cases. Otherwise, a fixed effects model was applied. We used the mean sample size as the boundary between studies with large and small sample sizes. Publication bias was detected with the Begg and Egger regression intercept test by using STATA 12. A 2-tailed P value < .05 was considered statistically significant.

3. Results

3.1. Study characteristics

The process used to select the studies included in this article is summarized in Figure 1. From an initial 1194 potentially relevant articles, the duplicate studies were removed and we screened titles and abstracts of articles. Finally, a total of 18 articles including 39 studies and 7264 participants were enrolled in the meta-analysis. The detailed characteristics of the selected studies are presented in Table 1. The selected articles were published from 2013 to 2018, and all articles were evaluated by the NOS (Supplementary Table 2: https://enlol.cn/Supplementary%20Materials/Supplementary%20Table%202.docx). There were 9, 8, 4, and 3 articles related with incidence,[19–27] OS,[15,16,26–31] DFS,[17,30,32,33] and, CSS,[15,29,32] respectively. Sixteen studies were conducted in Asia, 19 in North America and 3 in Europe. Among the 38 included studies, 10 studies involved patients with *Pg* infection, 15 with *Fn* infection, 5 with *Tf* infection, 3 with *Aa* infection, 3 with *Td* in infection and 2 with *Pi* infection. The sample sizes of the included studies ranged from 80 to 1069. According to the mean of all samples, 12 studies were considered to have a large sample size (n > 467), while 11 had a small sample size (n ≤ 467).

3.2. Periodontal bacteria and incidence of cancer

Twenty-three studies with 10,736 patients reported the relationship between periodontal bacteria and incidence of cancer (Fig. 2). Periodontal bacteria infection increased the incidence of cancer as much as 1.25 times compared with those no infecting with periodontal bacteria (OR = 1.25, 95%CI: 1.03–1.52, P = .02) although with heterogeneity (I^2 = 71%, P_h < .00001). The subgroup studies consisted of different periodontal bacteria,

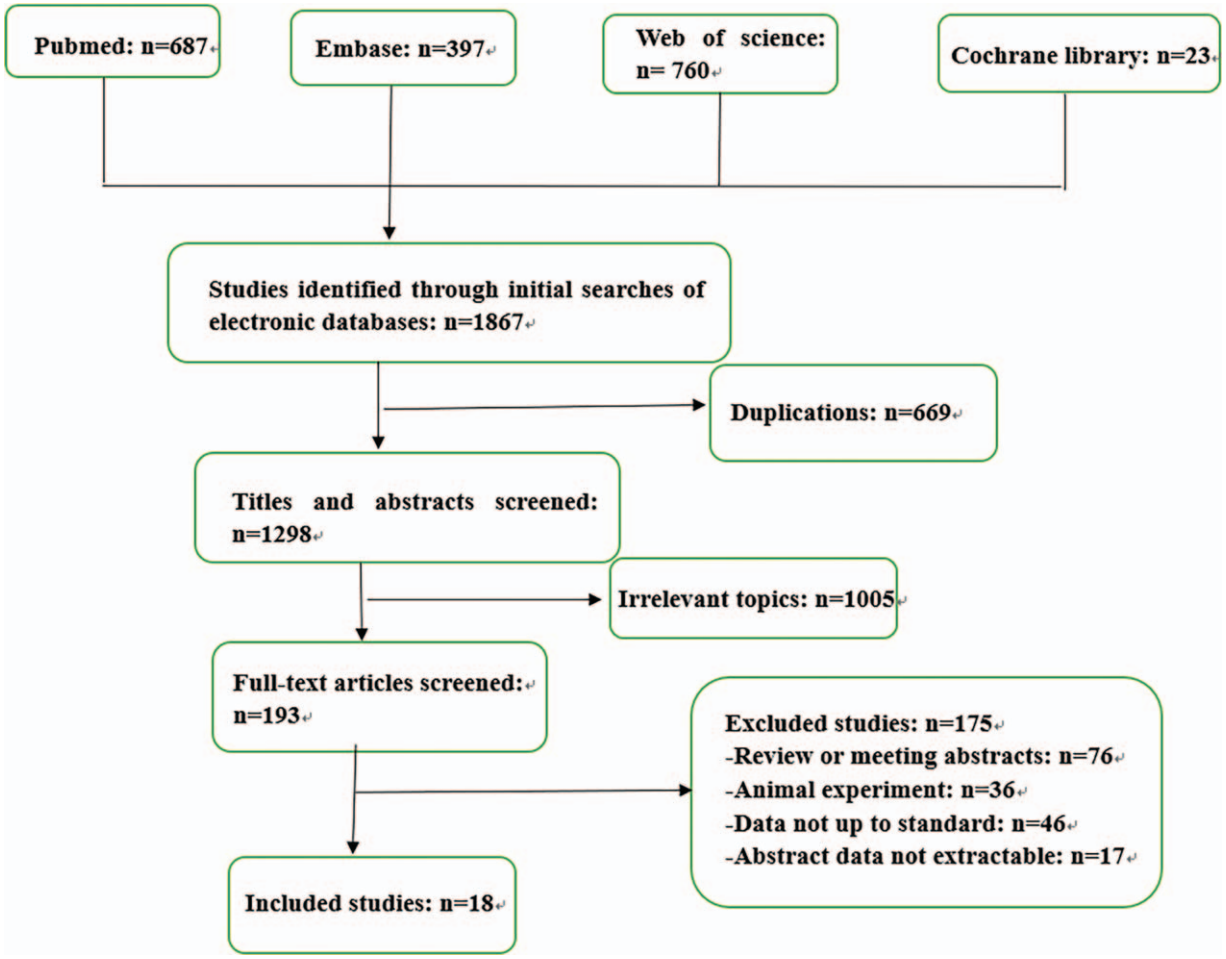


Figure 1. Flow chart of literature search and screening process.

Table 1

Characteristics of included studies.

Author year	Target bacterium	Country	Ethnicity	Type of cancer	Sample size (cases/controls)	Samples	Detection method	Outcome	Study design	NOS score
Peters et al[19]	*Pg/Tf/Td*	USA	North America	EAC/ESCC	316 (106/210)	mouthwash	16sRNA gene sequencing	Incidence	P	7
Fan et al[20]	*Pg/Aa/Tf/Pi*	USA	North America	PC	732 (361/371)	mouthwash	16sRNA gene sequencing	Incidence	P	7
Michaud et al[21]	*Pg/Aa/Tf*	EPIC	Europe	PC	821 (405/416)	blood	immunoblot array	Incidence	P	7
Sun et al[22]	*Pg/Tf/Td/Aa*	USA	North America	PLGC	105 (35/70)	saliva	qPCR	Incidence	R	6
Yang et al[23]	*Pg/Tf/Td/Pi/Fn*	USA	North America	CRC	692 (231/461)	mouth rinse	16sRNA gene sequencing	Incidence	P	6
Chang et al[24]	*Pg*	China	Asia	OSCC	91 (61/30)	tissue	qPCR	Incidence	R	5
Yuan et al[25]	*Pg*	China	Asia	EC	80 (50/30)	tissue	qPCR	Incidence	R	6
Gao et al[26]	*Pg*	China	Asia	ESCC	130 (100/30)	tissue	qPCR	Incidence /OS	P	6
Yamaoka et al[27]	*Fn*	Japan	Asia	CRC	172 (100/72)	tissue	droplet digital PCR	Incidence /OS	P	7
Gao et al[16]	*Pg*	China	Asia	ESCC	216	serum	Elisa	OS	P	4
Wei et al[28]	*Fn*	China	Asia	CRC	180	tissue	16sRNA gene sequencing	OS	P	6
Yamamura et al[29]	*Fn*	Japan	Asia	EC	325	tissue	qPCR	CSS/OS	P	6
Lee et al[30]	*Fn*	South Korea	Asia	CRC	246	tissue	qPCR	DFS/OS	P	6
Liu et al[31]	*Fn*	USA	North America	CRC	951	tissue	qPCR	OS	P	7
Yan et al[32]	*Fn*	China	Asian	CRC	280	tissue	qPCR	CSS/DFS	P	6
Mima et al[15]	*Fn*	USA	North America	CRC	1069	tissue	qPCR	CSS/OS	p	7
Oh et al[33]	*Fn*	South Korea	Asia	CRC	593	tissue	qPCR	DFS	P	6
Yu et al[17]	*Fn*	China	Asia	CRC	Cohort1:92 Cohort2: 173	tissue	qPCR	DFS	P	6

Aa = *Aggregatibacter actinomycetemcomitans*, CRC = colorectal cancer, CSS = cancer specific survival, DFS = disease free survival, EAC = esophageal adenocarcinoma, EC = esophageal cancer, EPIC = European Prospective Investigation into Cancer and Nutrition study, within 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom), ESCC = esophageal squamous cell carcinoma, Fn = *Fusobacterium nucleatum*, NOS = Newcastle–Ottawa Quality Assessment Scale, OS = overall survival, P = prospective Cohort, PC = pancreatic cancer, Pg = *Porphyromonas gingivalis*, Pi = *Prevotella intermedia*, PLGC = precancerous lesions of gastric cancer, R = retrospective Cohort, Td = *Treponema denticola*, Tf = *Tannerella forsythia*.

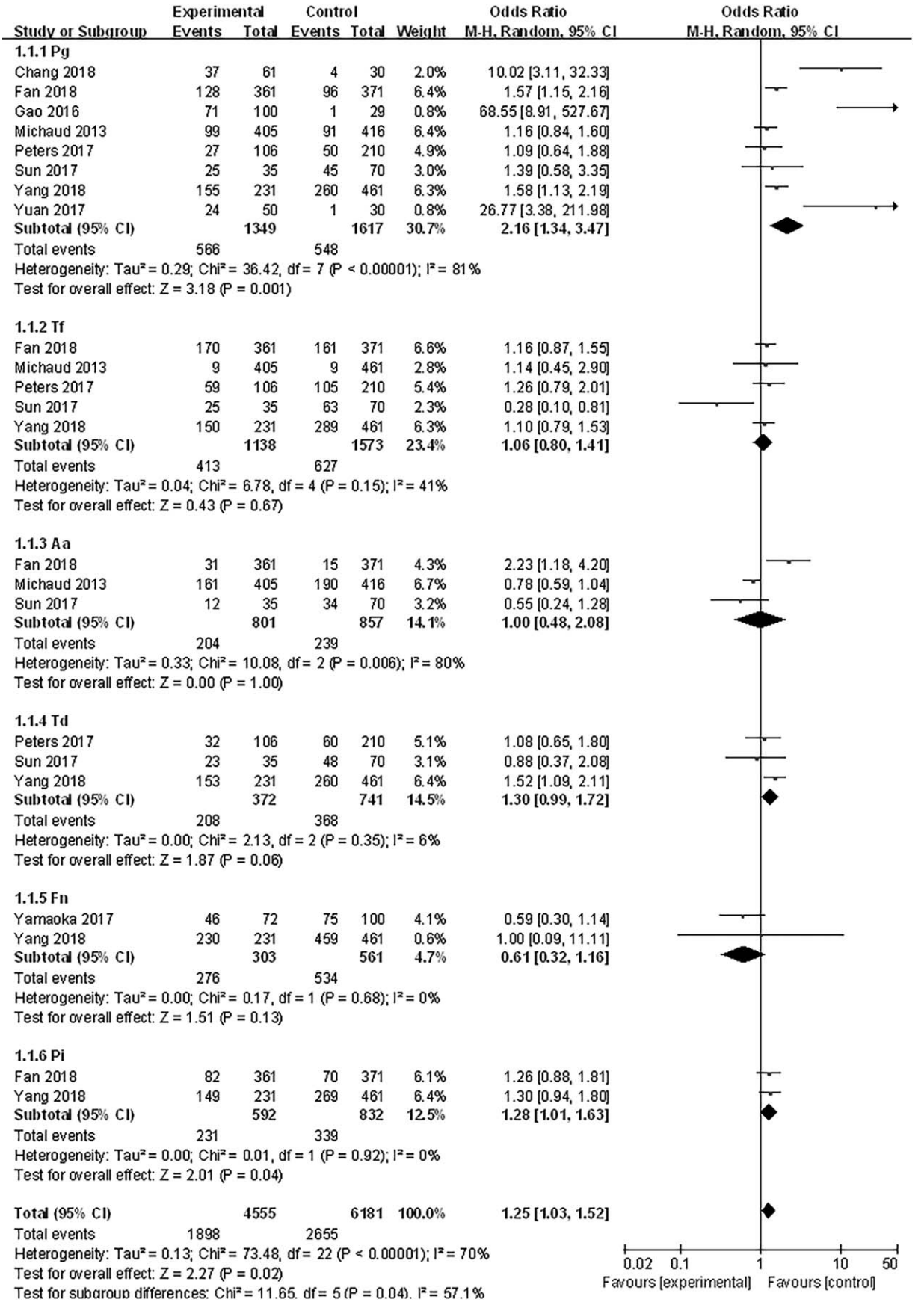


Figure 2. Forest plot of the association between periodontal bacteria infection and incidence of cancer.

Table 2

Subgroup analysis results for periodontal bacteria on incidence of cancer.

	Study no.	Sample size	OR (95%CI)	*P* value	Heterogeneity	
					I^2	*P* value
overall	23	10656	1.22 (1.01, 1.47)	.02	70%	<.00001
periodontal bacteria						
Pg	8	299	1.86 (1.20, 2.88)	.005	79%	<.0001
Tf	5	2711	1.06 (0.80, 1.41)	.67	41%	.15
Aa	3	1658	1.00 (0.48, 2.08)	1.00	80%	.006
Td	3	1113	1.30 (0.99, 1.72)	.06	6%	.35
Fn	2	864	0.61 (0.32, 1.16)	.13	0%	.68
Pi	2	1424	1.28 (1.01, 1.63)	.04	0%	.92
Ethnicity						
Asia	4	392	2.59 (1.65, 4.05)	<.0001	94%	<.00001
Caucasian	19	10219	1.19 (1.03, 1.36)	.02	44%	.02
Tumor location						
OSCC	1	91	10.02 (3.11, 32.33)	.0001	–	–
EC	5	1077	1.73 (0.80, 3.73)	.17	82%	.0007
PC	7	5391	1.21 (0.96, 1.53)	.1	61%	.02
PLGC	4	420	0.69 (0.37, 1.29)	.24	48%	.12
CRC	6	3632	1.26 (1.00, 1.57)	.05	42%	.12
Sample size						
Large	12	8851	1.26 (1.08, 1.46)	.003	46%	.04
Small	11	1760	1.24 (0.73, 2.12)	.42	80%	<.00001

Aa = *Aggregatibacter actinomycetemcomitans*, CRC = colorectal cancer, EAC = esophageal adenocarcinoma, EC = esophageal cancer, ESCC = esophageal squamous cell carcinoma, Fn = *Fusobacterium nucleatum*, PC = pancreatic cancer, Pg = *Porphyromonas gingivalis*, Pi = *Prevotella intermedia*, PLGC = precancerous lesions of gastric cancer, Td = *Treponema denticola*, Tf = *Tannerella forsythia*.

ethnicity of participants, tumor location, and sample size (Table 2). In our subgroup analysis, individuals whose infected with *Pg* were at 2.16 times greater risk of developing cancer than those no infecting with *Pg* (OR = 2.16, 95%CI: 1.34–3.47; $P = .001$; $I^2 = 79\%$, $P_h < .0001$). Individuals with *Pi* infection exhibit increased incidence of cancer (OR = 1.28; 95%CI: 1.01–1.63; $P = .04$). However, there was no significant relation between the infection of *Tf* (OR = 1.06, 95%CI: 0.8–1.41, $P = .67$; $I^2 = 41\%$, $P_h = .15$), *Aa* (OR = 1.00, 95%CI: 0.48–2.08, $P = 1.00$; $I^2 = 80\%$, $P_h = .006$), *Td* (OR = 1.30, 95%CI: 0.99–1.72, $P = .06$; $I^2 = 6\%$, $P_h = .35$), *Fn* (OR = 0.61; 95%CI: 0.32–1.16; $P = .13$; $I^2 = 0\%$, $P_h = .68$) and incidence of cancer. There was association in Asia (OR = 2.59, 95%CI:1.65–4.05, $P < .0001$; $I^2 = 94\%$, $P_h < .00001$) and Caucasian (OR = 1.19, 95%CI:1.03–1.36, $P = .02$; $I^2 = 44\%$, $P_h = .02$) between periodontal bacteria infection and incidence of cancer. In the subgroup analysis of tumor location, incidence of cancer was associated with periodontal bacteria infection in OSCC (OR = 10.02, 95%CI:3.11–32.33, $P < .0001$) but not EC (OR = 1.73, 95%CI:0.80–3.73, $P = .17$; $I^2 = 82\%$, $P_h = .0007$), PC (OR = 1.21, 95%CI:0.96–1.53, $P = .1$; $I^2 = 61\%$, $P_h = .02$), PLGC (OR = 0.69, 95%CI:0.37–1.29, $P = .24$; $I^2 = 48\%$, $P_h = .12$) and CRC (OR = 1.26, 95%CI:1.00–1.57, $P = .05$; $I^2 = 42\%$, $P_h = .12$). According to the subgroup analysis of the sample size, periodontal bacteria infection were related to incidence of cancer in large sample size (OR = 1.26, 95%CI:1.08–1.46, $P = .003$; $I^2 = 46\%$, $P_h = .04$), but not in small sample size (OR = 1.24, 95% CI:0.73–2.12, $P = .42$; $I^2 = 42\%$, $P_h < .00001$).

3.3. Periodontal bacteria and OS in cancer

Figure 3A indicates the OS of cancer patients evaluated in 8 studies with 3289 patients. The HR for OS in cancer patients infecting with periodontal bacteria compared with those no infecting with periodontal bacteria was 1.75 times (95% CI: 1.40–2.20, $P < .00001$). The result revealed periodontal bacteria infection was related to poor OS in cancer. There was little heterogeneity between studies ($I^2 = 0\%$, $P_h = .79$). The subgroup analysis involved in different periodontal bacteria (Mainly *Pg* and *Fn*), ethnicity of participants, tumor location and sample size (Table 3). In the subgroup, both of *Pg* and *Fn* infection was correlated with poor OS in cancer (*Pg*: HR = 4.04, 95% CI: 1.54–10.63, $P = .05$; *Fn*: HR = 1.67, 95% CI: 1.32–2.11, $P < .0001$). There was little heterogeneity between studies (*Pg*: $I^2 = 0\%$, $P_h = .64$; *Fn*: $I^2 = 0\%$, $P_h = .99$). Periodontal bacteria infection was correlated with poor OS of cancer patients in Asia (HR = 1.90, 95%CI:1.43–2.53, $P < .0001$; $I^2 = 0\%$, $P_h = .70$) and Caucasian (HR = 1.53, 95%CI:1.05–2.23, $P = .03$; $I^2 = 0\%$, $P_h = .77$). In the subgroup of tumor location, there were consistent findings in EC (HR = 2.13, 95%CI:1.36–3.35, $P = .0010$; $I^2 = 15\%$, $P_h = .31$) and CRC (HR = 1.64, 95%CI:1.26–2.13, $P = .0002$; $I^2 = 0\%$, $P_h = .97$). According to the subgroup analysis of sample size, periodontal bacteria infection exhibited a trend of correlation with poor OS in large (HR = 1.53, 95% CI:1.05–2.23, $P = .03$; $I^2 = 0\%$, $P_h = .77$) and small sample size (HR = 1.90, 95%CI:1.43–2.53, $P < .0001$; $I^2 = 0\%$, $P_h = .70$).

3.4. Periodontal bacteria and DFS in cancer

Figure 3B shows the results of DFS of cancer patients in 5 studies with 1384 patients. The HR for DFS in cancer patients infecting with periodontal bacteria compared with those not periodontal bacteria was 2.18 times (95% CI: 1.24–3.84, $P = .007$). The result revealed there was significant association between periodontal bacteria infection and poor DFS in cancer. Interstudy heterogeneity was noted ($I^2 = 81\%$, $P_h = .0003$). The subgroup studies involved in types of periodontal bacteria, ethnicity of participants, tumor location, and sample size (Table 3).

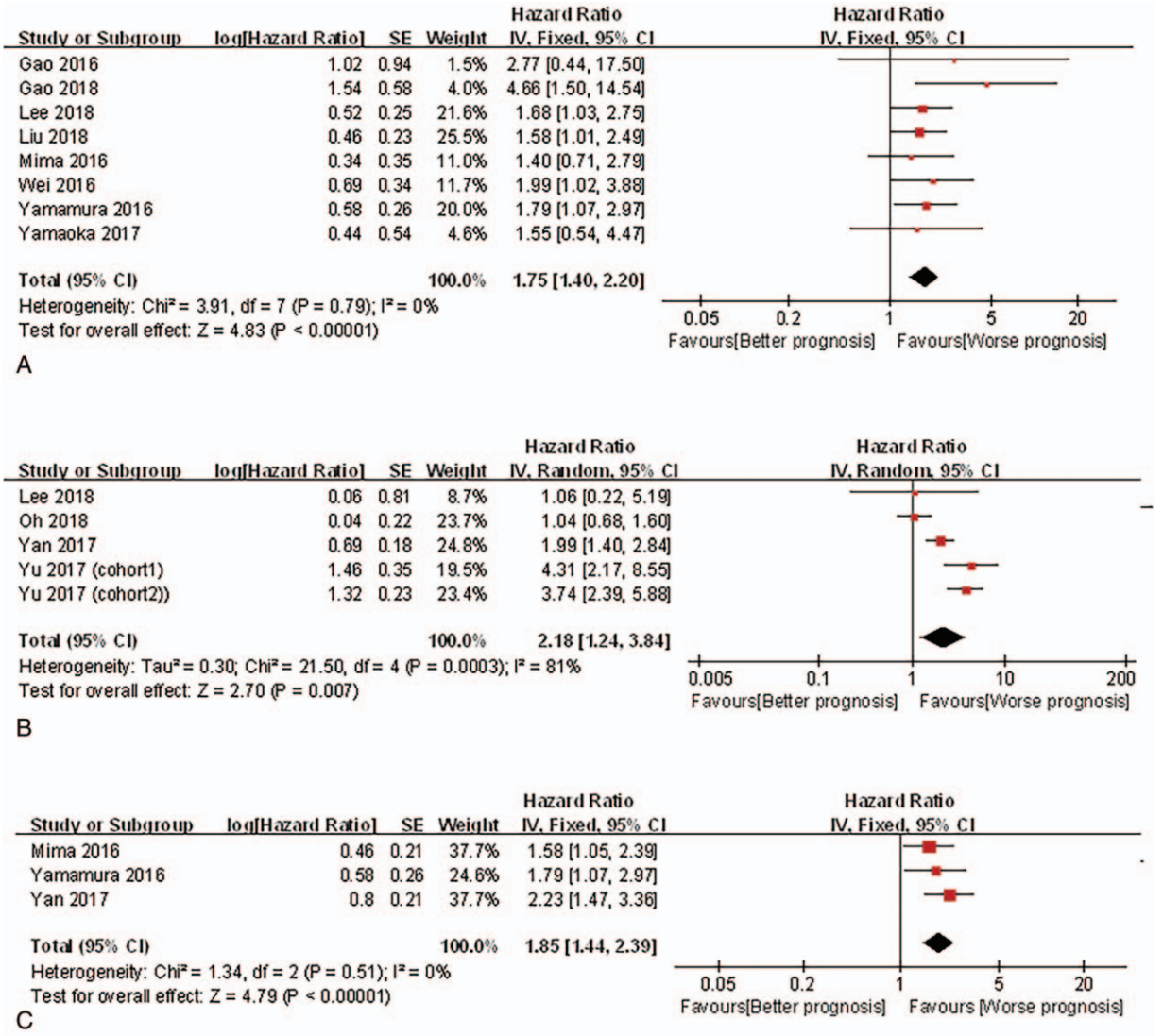


Figure 3. A. Forest plot of the association between periodontal bacteria infection and overall survival in patients with cancer. B. Forest plot of the association between periodontal bacteria infection and DFS and in patients with cancer. C. Forest plot of the association between periodontal bacteria infection and CSS in patients with cancer.

3.5. Periodontal bacteria and CSS in cancer

The association of periodontal bacteria infection and DFS in cancer was supplied by 3 studies with 1674 patients (Fig. 3C). Data analysis showed that the periodontal bacteria infection was related to poor CSS (HR = 1.85, 95% CI: 1.44–2.39, $P < .00001$) without obvious heterogeneity ($I^2 = 0\%$, $P_h = .51$).

3.6. Heterogeneity and sensitivity analysis

There was evidence of significant heterogeneity in incidence of cancer ($I^2 = 71\%$, $P_h < .00001$) and DFS ($I^2 = 81\%$, $P_h = .0003$) but not OS ($I^2 = 0\%$, $P_h = .79$) and CSS ($I^2 = 0\%$, $P_h = .51$). Subgroup analyses detecting potential sources of heterogeneity indicated that different periodontal bacteria, ethnicity of participants, tumor location, and sample size were not significantly correlated with the heterogeneity in this meta-analysis. We found that Gao 2016 study was the source of heterogeneity in the meta-analysis for incidence of cancer and Oh 2018 for DFS. After removing Gao 2016 and Oh 2018, the heterogeneity among the studies decreased slightly for incidence of cancer ($I^2 = 64\%$, $P_h < .0001$), but decreased significantly for DFS ($I^2 = 62\%$, $P_h = .05$), and the result for incidence of cancer (OR = 1.21, 95%CI: 1.02–1.44, $P = .03$) (Supplementary Fig. 1, http://links.lww.com/MD/E32) and DFS (HR = 2.79, 95%CI: 1.72–4.54, $P < .0001$) (Supplementary Fig. 2, http://links.lww.com/MD/E33) followed the same trends as those in the previous analysis.[34–36] We also performed a sensitivity analysis through removing low-quality studies (NOS < 7). The result for incidence of cancer (OR = 1.29, 95%CI: 1.08–1.53, $P = .005$) (Supplementary Fig. 3, http://links.lww.com/MD/E34), OS (OR = 1.67, 95% CI: 1.28–2.18, $P = .0002$) (Supplementary Fig. 4, http://links.lww.com/MD/E35), DFS (HR = 2.34, 95%CI: 1.28–4.28, $P = .006$) (Supplementary Fig. 5, http://links.lww.com/MD/E36) followed the same trends as those in the previous analysis.

Table 3

Subgroup analysis results for Pg and Fn infection on the prognostic effects of cancer.

	Variable	Study no.	Sample size	HR (95%CI)	*P* value	Heterogeneity	
						I^2	*P* value
OS	Overall	8	3289	1.75 (1.40, 2.20)	<.00001	0%	.79
periodontal bacteria							
	Pg	2	346	4.04 (1.54, 10.63)	.005	0%	.64
	Fn	6	2943	1.67 (1.32, 2.11)	<.0001	0%	.99
Ethnicity							
	Asia	6	1269	1.90 (1.43, 2.53)	<.0001	0%	.70
	Caucasian	2	2020	1.53 (1.05, 2.23)	.03	0%	.77
Tumor location							
	EC	3	671	2.13 (1.36, 3.35)	.0010	15%	.31
	CRC	5	2618	1.64 (1.26, 2.13)	.0002	0%	.97
Sample size							
	Large	2	2020	1.53 (1.05, 2.23)	.03	0%	.77
	Small	6	1269	1.90 (1.43, 2.53)	<.0001	0%	.70
DFS	Overall	5	1384	2.18 (1.24, 3.84)	.007	81%	.0003
periodontal bacteria							
	Fn	5	1384	2.18 (1.24, 3.84)	.007	81%	.0003
	Ethnicity						
	Asia	5	1384	2.18 (1.24, 3.84)	.007	81%	.0003
Tumor location							
	CRC	5	1384	2.18 (1.24, 3.84)	.007	81%	.0003
Sample size							
	Large	2	873	1.46 (0.77, 2.76)	.25	81%	.02
	Small	3	511	3.64 (2.53, 5.62)	<.00001	22%	.28
CSS	Overall	3	1674	1.85 (1.44, 2.39)	<.00001	0%	.51

CRC = colorectal cancer, CSS = cancer specific survival, DFS = disease free survival, EC = esophageal cancer, Fn = *Fusobacterium nucleatum*, OS = overall survival, Pg = *Porphyromonas gingivalis*.

3.7. Publication bias

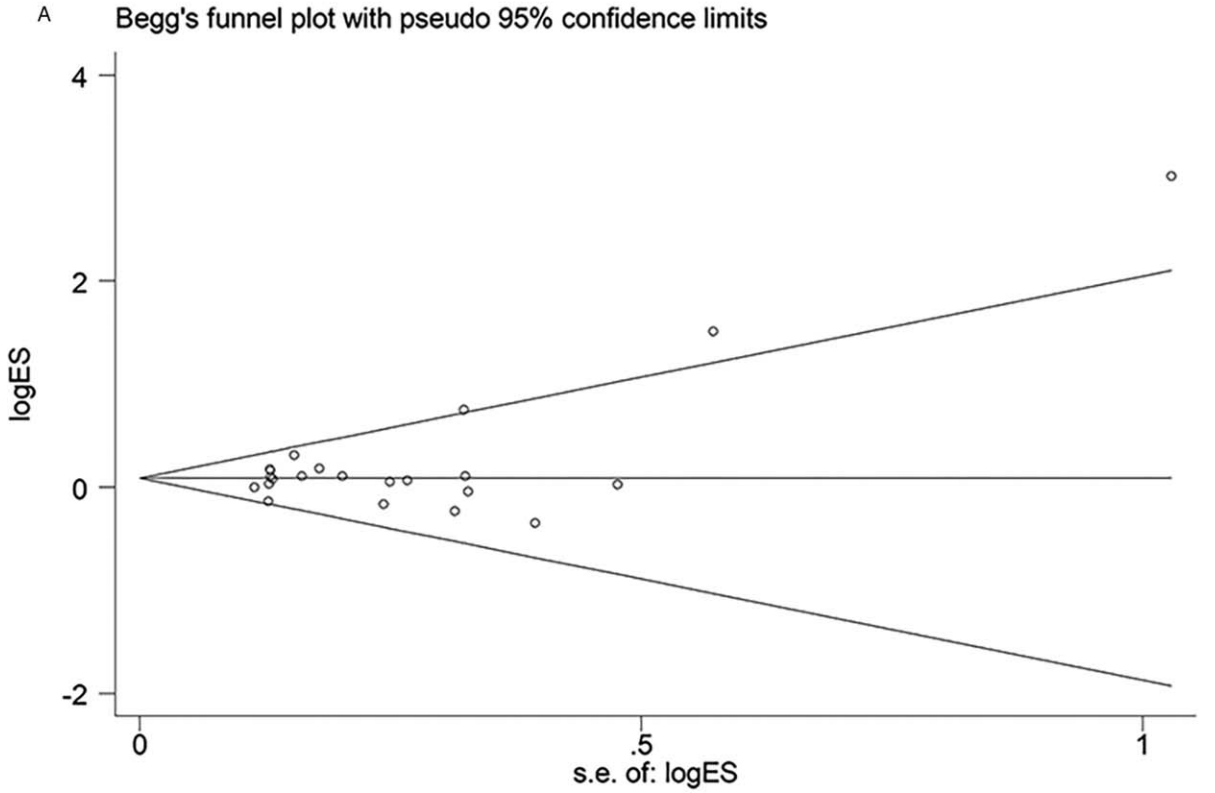
The results of the risk of bias assessment are shown in Figure 4A, B. Egger and Begg tests indicated the potential publication bias for incidence (0.092) and prognosis (including OS, DFS, and CSS: 0.624) of cancer. There was no significant publication bias in these studies.

4. Discussion

There is increasing evidence that bacteria play an important role in tumorigenesis by activating chronic inflammation.[37] Chronic inflammation and infections are increasingly identified as an important epidemiologic and environmental factor in cancer development. There is considerable evidence that proves the interrelationship between bacterial infections and carcinogenesis, such as *Helicobacter Pylori* for gastric cancer[38] and *Fn* for CRC.[39] The relationship between periodontal bacteria and inflammation has attracted the attention from researchers due to the potential influence of periodontitis on initiation and/or progression of several systemic diseases, including cancer.[12] Therefore, many recent studies explore the interrelationship between periodontal bacteria, inflammation, and cancer.[40–42] However, no consensus has been reached on the effects of periodontal bacteria on incidence and prognosis of cancer.

In this meta-analysis, 38 studies including 7184 patients were involved, and we summarized the associations between 6 periodontal bacteria and incidence and prognosis of cancer. The infection of 6 periodontal bacteria was found to increase incidence of cancer and the risk of cancer as much as 1.25 times compared with uninfected patients. Further, the infection of 6 periodontal bacteria was a considerable prognostic factor for poor OS, DFS and CSS. However, in our subgroup analysis, infection of *Fn* had no significant effect on incidence of cancer. According to numerous current study reports, *Fn* was tightly related to the occurrence and development of gastrointestinal cancer.[43–45] Moreover, in our subgroup of OS, *Fn* was associated with poor OS in cancer patients. Because the sample sizes about incidence of cancer are relatively limited, our results require careful interpretation.

Subgroup analysis of cancer incidence showed that infection *Pg* increased risk of cancer as much as 2.16 times compared with uninfected patients. In line with our results, it has been reported that infection *Pg* was is a significant risk factor for various malignancies including orodigestive cancers, gastrointestinal cancer, and even prostate cancer.[6,46,47] Previous study showed that *Pg* can promote the development of orodigestive cancers by inducing epithelial-to-mesenchymal transition, activating metalloproteinase-9 and interleukin-8 and accelerating cell cycling and suppressing apoptosis.[47] In our results, there was no significant relationship between infection of *Tf, Aa, Td*, and *Fn* and incidence of cancer. Previous studies indicated that *Tf, Aa*, and *Td* had a positive effect on progression of cancer.[48–50] It is pity that the number of related studies are limited. A large number of studies focused on the relationship between *Pg* and *Fn* infection and incidence and prognosis of cancer, while less attention was paid to the remaining periodontal bacteria, including *Tf, Aa, Td,* and *Pi*. Therefore, the number of included studies about *Tf, Aa, Td,* and *Pi* are relatively small, which there were only 5 studies on *Tf*, 3 on *An*, 3 on *Td* and 2 on *Pi*. Numerous studies showed that 6 periodontal bacteria play an equally important role in the incidence and development of periodontitis and are associated with systemic diseases, but the detection rates may be different due to ethnic differences.[12,51,52] These results hinted that more



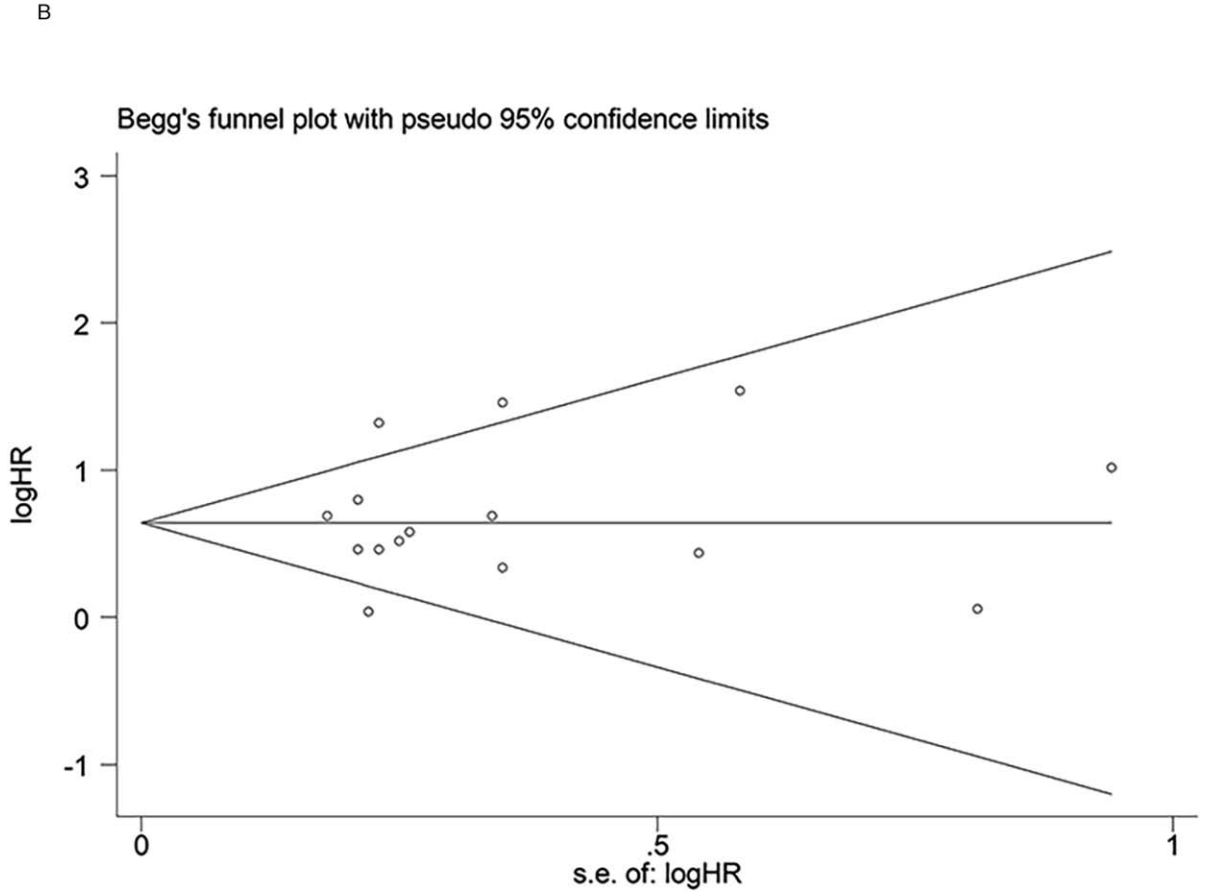


Figure 4. A. Begg funnel plot of publication bias test for incidence in cancer. B. Begg funnel plot of publication bias test for overall survival, disease-free survival, and cancer-specific survival in cancer.

studies are needed to determine whether the infection of these periodontal bacteria can influence the incidence of cancer.

Subgroup analysis of OS and DFS suggested that infection of *Pg* and *Fn* predicted a poor prognosis in cancer patients. Similarly, current study reported that both *Pg* and *Fn* had attributes consistent with a role in cancer development and progression.[9] Moreover, there is extensive evidence showing that *Pg* and *Fn* are abundant in tumors and activate transduction pathways, such as anti-apoptotic pathway and nuclear factor-κB, leading to poor prognosis of cancer.[53,54] In addition, the subgroup analysis of tumor location indicated that periodontal bacteria infection was correlated with a poor prognosis in patients with EC and CRC. Recently studies in animals and man have indicated that oral bacteria can influence the prognosis of patients with digestive system cancers including EC and CRC by perpetuating inflammation, regulating the immune system-microbe-tumor axis, affecting metabolism, and altering the tumor microenvironment.[55]

Although we have conducted a comprehensive search and systematic analysis of the relevant studies, inevitably, this meta-analysis has the following limitations. Firstly the number of included studies about *Aa, Td,* and *Pi* are relatively small. Secondly, the overall heterogeneity was high, so random effects models were required for the analysis. Thirdly, the study populations were all of Asian or Caucasian ethnicity, which may have caused a population selection bias. Last but not least, we did not take into account the effects of oral fungi on periodontal bacteria. The association between oral fungi, especially *Candida spp* and oral cancer and oral precancerous lesions was reported in previous studies.[56,57]*Candida spp* has been reported to interact with individual members of the oral bacterial microbiota, leading to either synergistic or antagonistic relationships.[58,59] As a result, oral fungi may also regulate tumors indirectly through the interaction with periodontal bacteria.

5. Conclusion

this meta-analysis suggested that different periodontal bacteria infection correlated with different incidence of cancer: *Pg* and *Pi* infection was associated with high incidence of cancer, while there is no obvious relationship between the *Tf, Aa, Td* and *Fn* infection and incidence of cancer. Furthermore, our study revealed that the infection of periodontal bacteria, mainly *Pg* and *Fn*, predicted poor OS, DFS, and CSS in cancer patients. Our meta-analysis hinted that improvement of oral hygiene and treatment of periodontal disease should also be taken into consideration in the prevention and treatment strategies for cancer.

Acknowledgments

We are grateful to all researchers of enrolled studies.

Author contributions

Two reviewers (L.X and Q.Y.Z) independently extracted data and information from final studies. Two authors (Y.S.P &L.X) assessed the final studies, scored them using the NOS and consensus was reached by discussion with senior reviewers (Y.L. and D.Q.W.).

References

[1] WHO. The International Agency for Research on Cancer. Available at: https://www.who.int/cancer/en/. Accessed December 5, 2018.
[2] Kim SS, Ruiz VE, Carroll JD, et al. Helicobacter pylori in the pathogenesis of gastric cancer and gastric lymphoma. Cancer Lett 2011;305:228–38.
[3] Long X, Wong CC, Tong L, et al. Peptostreptococcus anaerobius promotes colorectal carcinogenesis and modulates tumour immunity. Nature Microbiol 2019;4:2319–30.
[4] Xie FJ, Zhang YP, Zheng QQ, et al. Helicobacter pylori infection and esophageal cancer risk: an updated meta-analysis. World J Gastroenterol 2013;19:6098–107.
[5] Okushin K, Tsutsumi T, Ikeuchi K, et al. Helicobacter pylori infection and liver diseases: epidemiology and insights into pathogenesis. World J Gastroenterol 2018;24:3617–25.
[6] da Silva APB, Alluri LSC, Bissada NF, et al. Association between oral pathogens and prostate cancer: building the relationship. Am J Clin Exp Urol 2019;7:1–0.
[7] Memba R, Duggan SN, Ni Chonchubhair HM, et al. The potential role of gut microbiota in pancreatic disease: a systematic review. Pancreatology 2017;17:867–74.
[8] Wu-chao W, Yafei W, Lei Z. Research progress on the relationship between Porphyromonas gingivalis and oral squamous cell carcinoma. Hua Xi Kou Qiang Yi Xue Za Zhi = West China J Stomatol 2015;33:651–5.
[9] Whitmore SE, Lamont RJ. Oral bacteria and cancer. PLoS Pathog 2014;10:e1003933.
[10] Galvao-Moreira LV, da Cruz MC. Oral microbiome, periodontitis and risk of head and neck cancer. Oral Oncol 2016;53:17–9.
[11] Skaleric U, Kovac-Kavcic M. Some risk factors for the progression of periodontal disease. J Int Acad Periodontol 2000;2:19–23.
[12] Bui FQ, Almeida-da-Silva CLC, Huynh B, et al. Association between periodontal pathogens and systemic disease. Biomed J 2019;42:27–35.
[13] Karpinski TM. Role of oral microbiota in cancer development. Microorganisms 2019;7:e20.
[14] Komiya Y, Shimomura Y, Higurashi T, et al. Patients with colorectal cancer have identical strains of *Fusobacterium nucleatum* in their colorectal cancer and oral cavity. Gut 2019;68:1335–7.
[15] Mima K, Nishihara R, Qian ZR, et al. *Fusobacterium nucleatum* in colorectal carcinoma tissue and patient prognosis. Gut 2016;65:1973–80.
[16] Gao S, Li S, Ma Z, et al. Presence of *Porphyromonas gingivalis* in esophagus and its association with the clinicopathological characteristics and survival in patients with esophageal cancer. Infect Agent Cancer 2016;11:3.
[17] Yu T, Guo F, Yu Y, et al. *Fusobacterium nucleatum* promotes chemoresistance to colorectal cancer by modulating autophagy. Cell 2017;170:548–63. e516.
[18] Jia YQ, Yang B, Wen LL, et al. Prognostic value of immune checkpoint molecules in head and neck cancer: a meta-analysis. Aging 2019;11:501–22.
[19] Peters BA, Wu J, Pei Z, et al. Oral microbiome composition reflects prospective risk for esophageal cancers. Cancer Res 2017;77:6777–87.
[20] Fan X, Alekseyenko AV, Wu J, et al. Human oral microbiome and prospective risk for pancreatic cancer: a population-based nested case-control study. Gut 2018;67:120–7.
[21] Michaud DS, Izard J, Wilhelm-Benartzi CS, et al. Plasma antibodies to oral bacteria and risk of pancreatic cancer in a large European prospective cohort study. Gut 2013;62:1764–70.
[22] Sun J, Zhou M, Salazar CR, et al. Chronic periodontal disease, periodontal pathogen colonization, and increased risk of precancerous gastric lesions. J Periodontol 2017;88:1124–34.
[23] Yang Y, Cai Q, Shu XO, et al. Prospective study of oral microbiome and colorectal cancer risk in low-income and African American populations. Int J Cancer 2019;144:2381–9.
[24] Chang C, Geng F, Shi X, et al. The prevalence rate of periodontal pathogens and its association with oral squamous cell carcinoma. Appl Microbiol Biotechnol 2019;103:1393–404.
[25] Yuan X, Liu Y, Kong J, et al. Different frequencies of Porphyromonas gingivalis infection in cancers of the upper digestive tract. Cancer Lett 2017;404:1–7.
[26] Gao SG, Yang JQ, Ma ZK, et al. Preoperative serum immunoglobulin G and A antibodies to *Porphyromonas gingivalis* are potential serum

biomarkers for the diagnosis and prognosis of esophageal squamous cell carcinoma. BMC Cancer 2018;18:17.
[27] Yamaoka Y, Suehiro Y, Hashimoto S, et al. *Fusobacterium nucleatum* as a prognostic marker of colorectal cancer in a Japanese population. J Gastroenterol 2018;53:517–24.
[28] Wei Z, Cao S, Liu S, et al. Could gut microbiota serve as prognostic biomarker associated with colorectal cancer patients' survival? A pilot study on relevant mechanism. Oncotarget 2016;7:46158–72.
[29] Yamamura K, Baba Y, Nakagawa S, et al. Human microbiome *Fusobacterium nucleatum* in esophageal cancer tissue is associated with prognosis. Clin Cancer Res 2016;22:5574–81.
[30] Lee DW, Han SW, Kang JK, et al. Association between *Fusobacterium nucleatum*, pathway mutation, and patient prognosis in colorectal cancer. Ann Surg Oncol 2018;25:3389–95.
[31] Liu L, Tabung FK, Zhang X, et al. Diets that promote colon inflammation associate with risk of colorectal carcinomas that contain *Fusobacterium nucleatum*. Clin Gastroenterol Hepatol 2018;16:1622–31. e1623.
[32] Yan X, Liu L, Li H, et al. Clinical significance of *Fusobacterium nucleatum*, epithelial-mesenchymal transition, and cancer stem cell markers in stage III/IV colorectal cancer patients. Onco Targets Ther 2017;10:5031–46.
[33] Oh HJ, Kim JH, Bae JM, et al. Prognostic impact of *Fusobacterium nucleatum* depends on combined tumor location and microsatellite instability status in stage II/III colorectal cancers treated with adjuvant chemotherapy. J Pathol Transl Med 2019;53:40–9.
[34] He K, Hu H, Ye S, et al. The effect of metformin therapy on incidence and prognosis in prostate cancer: a systematic review and meta-analysis. Sci Rep 2019;9:2218.
[35] Chao X, Chen K, Zeng J, et al. Adjuvant radiotherapy and chemotherapy for patients with breast phyllodes tumors: a systematic review and meta-analysis. BMC Cancer 2019;19:372.
[36] Peng Y, Huang D, Qing X, et al. Investigation of MiR-92a as a prognostic indicator in cancer patients: a meta-analysis. J Cancer 2019;10:4430–41.
[37] Francescone R, Hou V, Grivennikov SI. Microbiome, inflammation, and cancer. Cancer journal (Sudbury, Mass) 2014;20:181–9.
[38] Wroblewski LE, Peek RMJr. Helicobacter pylori, cancer, and the gastric microbiota. Adv Exp Med Biol 2016;908:393–408.
[39] Shang FM, Liu HL. Fusobacterium nucleatum and colorectal cancer: a review. World J Gastrointest Oncol 2018;10:71–81.
[40] Hoare A, Soto C, Rojas-Celis V, et al. Chronic inflammation as a link between periodontitis and carcinogenesis. Mediators Inflamm 2019; 2019:1029857.
[41] Zambirinis CP, Pushalkar S, Saxena D, et al. Pancreatic cancer, inflammation, and microbiome. Cancer J (Sudbury, Mass) 2014;20:195–202.
[42] Shrihari TG, Vasudevan V, Manjunath V, et al. Potential co-relation between chronic periodontitis and cancer - an emerging concept. Gulf J Oncolog 2016;1:20–4.
[43] Proenca MA, Biselli JM, Succi M, et al. Relationship between Fusobacterium nucleatum, inflammatory mediators and microRNAs in colorectal carcinogenesis. World J Gastroenterol 2018;24:5351–65.
[44] Liu Y, Baba Y, Ishimoto T, et al. Progress in characterizing the linkage between Fusobacterium nucleatum and gastrointestinal cancer. J Gastroenterol 2019;54:33–41.
[45] Bullman S, Pedamallu CS, Sicinska E, et al. Analysis of Fusobacterium persistence and antibiotic response in colorectal cancer. Science (New York, NY) 2017;358:1443–8.
[46] Ahn J, Segers S, Hayes RB. Periodontal disease, *Porphyromonas gingivalis* serum antibody levels and orodigestive cancer mortality. Carcinogenesis 2012;33:1055–8.
[47] Olsen I, Yilmaz O. Possible role of *Porphyromonas gingivalis* in orodigestive cancers. J Oral Microbiol 2019;11:1563410.
[48] Malinowski B, Wesierska A, Zalewska K, et al. The role of *Tannerella forsythia* and *Porphyromonas gingivalis* in pathogenesis of esophageal cancer. Infect Agent Cancer 2019;14:3.
[49] Zhu B, Macleod LC, Newsome E, et al. *Aggregatibacter actinomycetemcomitans* mediates protection of *Porphyromonas gingivalis* from Streptococcus sanguinis hydrogen peroxide production in multi-species biofilms. Sci Rep 2019;9:4944.
[50] Nieminen MT, Listyarifah D, Hagstrom J, et al. *Treponema denticola* chymotrypsin-like proteinase may contribute to orodigestive carcinogenesis through immunomodulation. Br J Cancer 2018;118:428–34.
[51] Gatto MR, Montevecchi M, Paolucci M, et al. Prevalence of six periodontal pathogens in subgingival samples of Italian patients with chronic periodontitis. New Microbiol 2014;37:517–24.
[52] Montevecchi M, Angelini F, Checchi V, et al. Microbiological distribution of six periodontal pathogens between untreated Italian and Dutch periodontal patients. Oral Health Prev Dent 2016;14:329–37.
[53] Arjunan P, Meghil MM, Pi W, et al. Oral pathobiont activates anti-apoptotic pathway, promoting both immune suppression and oncogenic cell proliferation. Sci Rep 2018;8:16607.
[54] Yang Y, Weng W, Peng J, et al. Fusobacterium nucleatum increases proliferation of colorectal cancer cells and tumor development in mice by activating toll-like receptor 4 signaling to nuclear factor-kappaB, and up-regulating expression of microRNA-21. Gastroenterology 2017;152: 851–66. e824.
[55] Kudo Y, Tada H, Fujiwara N, et al. Oral environment and cancer. Genes Environ 2016;38:13.
[56] Gall F, Colella G, Di Onofrio V, et al. Candida spp. in oral cancer and oral precancerous lesions. New Microbiol 2013;36:283–8.
[57] Castillo GDV, Blanc SL, Sotomayor CE, et al. Study of virulence factor of Candida species in oral lesions and its association with potentially malignant and malignant lesions. Arch Oral Biol 2018;91:35–41.
[58] Rodrigues ME, Gomes F, Rodrigues CF. Candida spp./bacteria mixed biofilms. J Fungi (Basel, Switzerland) 2019;6:e5.
[59] Montelongo-Jauregui D, Lopez-Ribot JL. Candida interactions with the oral bacterial microbiota. J Fungi (Basel, Switzerland) 2018;4:e122.