Review Article

ANNALS OF DENTISTRY
UNIVERSITY OF MALAYA

www.adum.edu.my

Ann Dent UM 2022, 29: 13-20
Dol: 10.22452/adum.vol29no3

Presence of the Periodontal Bacterium *Porphyromonas gingivalis* in Patients with and without Cancer: A Meta-analysis

Alberto Rodriguez-Archilla[1*], Eugenia Encina-Palazzolo[1]

KEYWORDS

Microbiota, neoplasms, periodontal bacteria, *Porphyromonas gingivalis*

ABSTRACT

A high presence of periodontal pathogens such as *Porphyromonas gingivalis* (*P. gingivalis*) has been found in cancers at different body locations. The imbalance of the oral microbiome (dysbiosis) promotes the chronic inflammatory process that could contribute to carcinogenesis. To assess the *P. gingivalis* detection in cancer patients. A search for studies on *P. gingivalis* and neoplasms was conducted from 1974 to 2021 in the following databases: PubMed (MEDLINE), Cochrane Library, Web of Science (WoS), and Scopus. For dichotomous outcomes, the estimates of effects of an intervention were expressed as odds ratios (OR) using Mantel-Haenszel (M-H) method with 95% confidence intervals. Funnel plot and Egger's test for publication bias analysis were used. Also, Newcastle-Ottawa (NOS) studies methodological quality assessment scale was employed. Thirteen studies that involved 1732 cancer patients and 3298 controls without cancer were included in this meta-analysis. *P. gingivalis* detection was 1.81 times more likely in cancer patients ($p<0.01$) compared to controls. *P. gingivalis* detection was also more likely in patients with colorectal (OR: 2.00, $p=0.02$) or pancreatic (OR: 1.32, $p=0.02$) tumors. In contrast, oral, esophageal, lung, or breast cancers did not show a significant increase of *P. gingivalis* detection ($p>0.05$).

INTRODUCTION

The balance of the oral microbiome plays an essential role in maintaining the normal physiological environment. All commensal and opportunistic bacteria, fungi, and viruses live in symbiosis with each other and with the host system, ensuring protection against environmental and systemic exposures or stresses [1].

A huge number of microbes (bacteria, fungi, and viruses) may be found in the oral cavity. The mouth is considered one of the largest microbiological reservoirs in the human body. Some periodontal microorganisms, especially *Porphyromonas gingivalis* (*P. gingivalis*) and *Fusobacterium nucleatum (F. nucleatum)*, have emerged as focal participants in the association between microbial dysbiosis and cancer. These oral bacteria have relevant mobility and invasion capabilities and may spread to other cancer sites or unbalance the immune system to facilitate tumorigenesis. Similarly, a greater presence of periodontal pathogens has been shown in potentially malignant disorders and cancer [2].

P. gingivalis is a highly prevalent periodontopathogenic bacterium in chronic and aggressive periodontitis. However, it is rarely present in a healthy periodontium. *P. gingivalis* is one of the highly invasive intracellular pathogens in periodontitis patients. This bacterium commonly resides symbiotically with other periodontal bacteria such as *F. nucleatum* and *Streptococcus gordonii* [3].

A strong link has been found between periodontal bacteria, mainly *P. gingivalis* and *F. nucleatum*, and

[1]Department of Stomatology, Oral Medicine Unit, Faculty of Dentistry, University of Granada, Spain
*Correspondence: alberodr@ugr.es

the development of cancers such as colorectal or pancreatic. *P. gingivalis* infection induces the production of various inflammatory cytokines (IL-1, IL-6, IL-8, and TNF-alpha), favoring cell migration, inhibiting apoptosis by inactivating the p53 tumor suppressor gene, and increasing host cell mutations [4].

P. gingivalis may invade oral keratinocytes and interfere with cell signaling pathways, providing possible molecular mechanisms for its involvement in epithelial transformation into oral squamous cell carcinoma [1]. Several factors may initiate an imbalance of the microbiome (dysbiosis) characterized by loss of microbial diversity, loss of beneficial microbes, and expansion of pathogenic microbes. This dysbiosis results in the activation of host defense mechanisms with overexpression of inflammatory molecules and production of carcinogenic bacterial metabolites. These bacterial toxins can cause DNA damage, disrupting normal cell division and apoptosis [5]. This study aimed to assess the *P. gingivalis* detection in cancer patients.

MATERIALS AND METHODS

The search and selection of studies, data extraction, and evaluation were carried out by the two authors (ARA and EMEP) independently. Later, both authors decided jointly on the articles to be included in this study.

Search strategy and study selection criteria

Case-control studies on *P. gingivalis* and cancer were searched from 1974 to 2021 in the following databases: PubMed (MEDLINE), Cochrane Library, Web of Science (WoS), and Scopus. Search strategies were developed for each database with a combination of Medical Subjects Headings (MeSH) and free-text terms. The search terms were as follows: "porphyromonas gingivalis"[MeSH Terms] AND "neoplasms"[MeSH Terms] AND "case control studies"[MeSH Terms]; "porphyromonas gingivalis" AND "cancer" AND "case control"; TITLE-ABS-KEY ("porphyromonas gingivalis" AND "cancer" AND "case control"). The exclusion criteria were: a) articles without full-text availability, b) studies that did not consider subjects without cancer, c) studies with a score of fewer than 6 points on the Newcastle-Ottawa methodological quality assessment scale, and d) studies with non-usable data.

Data extraction

The characteristics of the selected studies included the first author, year of publication, study populations, methods of detecting *P. gingivalis*, Newcastle-Ottawa scale score, and the outcome variable (cancer risk on different body locations).

Assessment of methodological quality

The methodological quality of the studies considered in this manuscript was analyzed with the Newcastle-Ottawa methodological quality assessment scale composed of eight items that assess three dimensions (selection, comparability, exposure) [6]. According to the score obtained, the studies are classified as high quality (≥7 points), moderate quality (4-6 points), and low quality (1-3 points).

Statistical analysis

Data were processed with the RevMan 5.4 meta-analysis software (The Cochrane Collaboration, Oxford, UK). For dichotomous outcomes, the odds ratio (OR) with the Mantel-Haenszel Chi-square formula (M-H) and 95% confidence intervals (95% CI) were used. Heterogeneity was determined according to the Higgins statistic (I^2). A random-effects model was applied if the heterogeneity was high (I^2>50%). The minimum level of significance was set at p<0.05. Publication bias was estimated using the funnel plot and the Egger test, with a value of p<0.1 as statistically significant.

RESULTS

Study selection

In the initial search, 61 articles (15 in PubMed, 31 in WoS, and 15 in Scopus) were collected, 12 of them were duplicates. Of the 49 articles for eligibility, 36 articles were removed after applying the exclusion criteria. Finally, 13 studies were included in this meta-analysis (Figure 1).

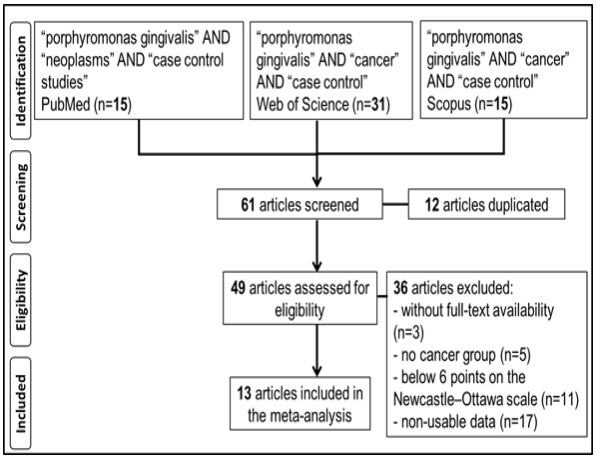

Figure 1 Study flow diagram

The main descriptive characteristics and the methodological quality analysis of the thirteen articles considered in the meta-analysis are shown

in Table 1 [7-19]. One of these studies analysed three cancer sites (colorectal, lung, breast) [10]. These studies involved 1732 cancer patients and 3298 controls without cancer. Considering the different locations of the tumor, four studies (30.8%) were performed in oral cancer patients, three studies (23.1%) in esophageal cancer patients, three (23.1%) in colorectal cancer patients, and another three (23.1%) in pancreatic cancer patients. Finally, a single study considered lung and breast cancer patients. The *P. gingivalis* detection methods used in the different studies included were: polymerase chain reaction (PCR) in 11 studies (84.6%), immunohistochemistry (IMH) in 3 studies (23.1%), microscopy indirect immunofluorescence (IIM) in one study, fluorescence in situ hybridization (FISH) in one study, and enzyme-linked immunosorbent assay (ELISA) in another study. According to the Newcastle-Ottawa (NOS) quality scale [6], two studies (15.4%) achieved 8 points, 7 studies (53.8%) had 7 points, and 4 studies (30.7%), 6 points.

Table 1 Description and methodological quality evaluation of the thirteen studies included in this meta-analysis

Study	Year	Country	Study population	Cancer location	Detection methods	NOS
Kang [7]	2009	South Korea	28 cancer (22M, 6F, ma=58.0y) 52 control (23M, 29F, ma=42.0y)	Oral cavity	PCR	7
Michaud [8]	2013	Europe*	405 cancer (196M, 209F, ma=57.8y) 416 control (199M, 217F, ma=57.8y)	Pancreas	ELISA	7
Gao [9]	2016	China	100 cancer (70M, 30F, na) 30 control (na, na, na)	Esophagus	PCR, IMH	6
Mai [10]	2016	USA	17 cancer (na, na, na) 1235 control (na, na, na)	Colorectal	IIM	6
Mai [10]	2016	USA	17 cancer (na, na, na) 1235 control (na, na, na)	Lung	IIM	6
Mai [10]	2016	USA	67 cancer (na, na, na) 1235 control (na, na, na)	Breast	IIM	6
Fan [11]	2017	USA	361 cancer (206M, 155F, ma=68.7y) 371 control (212M, 159F, ma=68.7y)	Pancreas	PCR	8
Peters [12]	2017	USA	106 cancer (85M, 21F, ma=67.3y) 210 control (168M, 42F, ma=67.4y)	Esophagus	PCR	8
Yuan [13]	2017	China	50 cancer (na, na, na) 30 control (na, na, na)	Esophagus	PCR, IMH	6
Chang [14]	2019	China	61 cancer (39M, 22F, ma=57.4y) 30 control (17M, 13F, ma=55.4y)	Oral cavity	PCR	7
Yang [15]	2019	USA	231 cancer (93M, 138F, na) 461 control (185M, 276F, na)	Colorectal	PCR	7
Zhang [16]	2020	China	50 cancer (32M, 18F, ma=61.0y) 50 control (na, na, na)	Oral cavity	PCR	7
Chen [17]	2021	China	95 cancer (65M, 30F, ma=55.8y) 39 control (21M, 18F, ma=52.6y)	Oral cavity	PCR	7
Wang [18]	2021	China	22 cancer (na, na, na) 20 control (na, na, na)	Colorectal	PCR, IMH, FISH	6
Petrick [19]	2022	USA	122 cancer (28M, 94F, ma=59.5y) 354 control (80M, 274F, ma=59.3y)	Pancreas	PCR	7

*****Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom; **USA:** United States of America; **cancer:** cancer patients**; control:** subjects without cancer; **M:** male; **F:** female; **ma:** mean age; **y:** years; **na:** non available data; **PCR:** Polymerase Chain Reaction; **ELISA:** Enzyme-Linked ImmunoSorbent Assay; **IMH:** Immunohistochemistry; **IIM:** Indirect immunofluorescence microscopy; **FISH:** Fluorescence in situ hybridization; **NOS:** Newcastle-Ottawa methodological quality scale.

Figure 2 presents the results on the detection of the periodontopathogen *P. gingivalis* in oral biofilms from patients with cancers in different locations (oral cavity, esophagus, colon, pancreas, lung, and breast) and controls without the disease.

Globally, cancer patients were 1.81 times more likely to be infected by *P. gingivalis* compared to subjects without cancer, observing a highly significant statistical association (OR=1.81; 95% CI: 1.25 to 2.62; p<0.01).

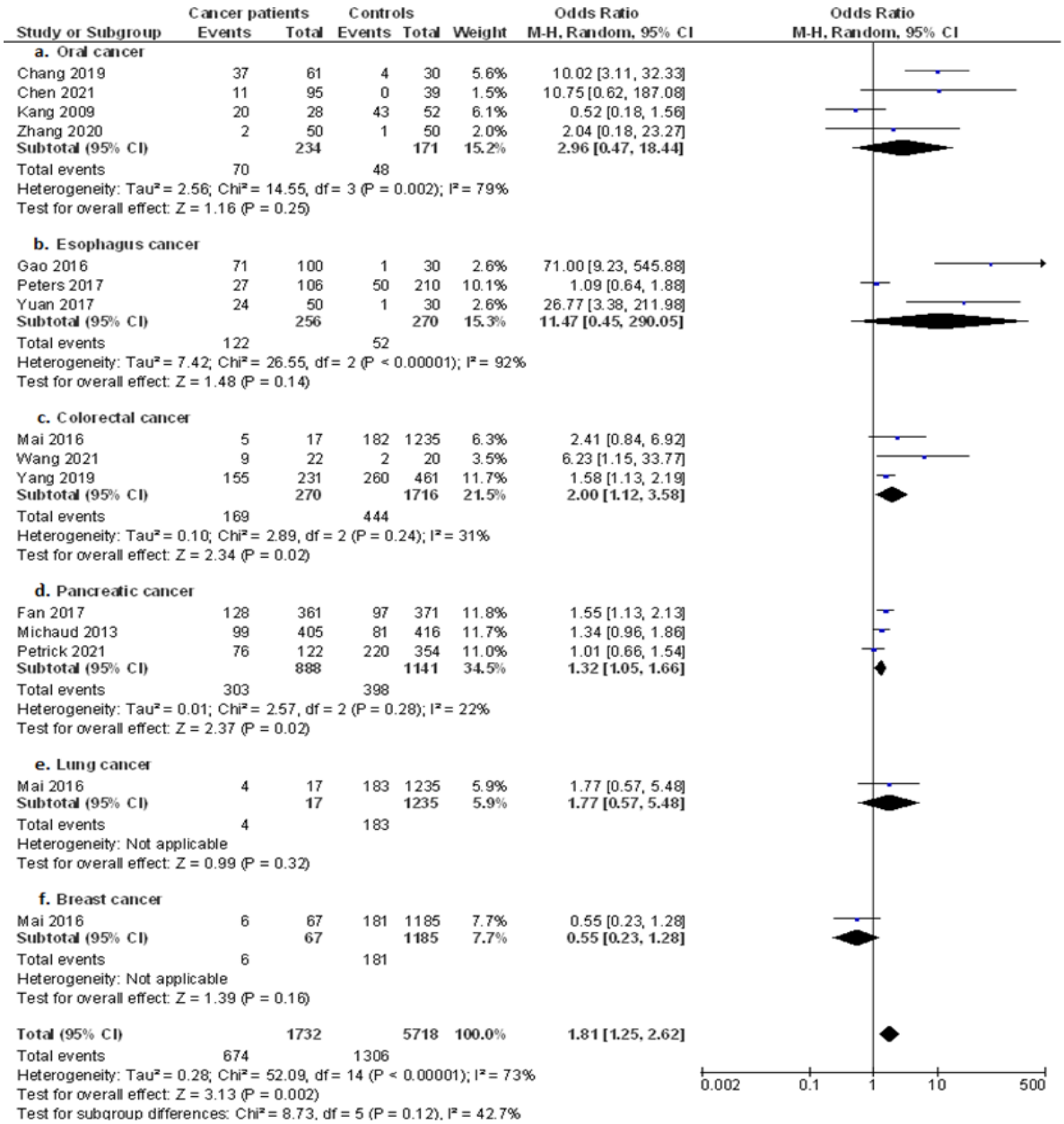

Figure 2 Data from studies and forest plot graphics for the detection of Porphyromonas gingivalis in oral biofilms from patients with different cancer locations ([a] oral, [b] esophagus, [c] colorectal, [d] pancreas, [e] lung, [f] breast) compared to controls without cancer. Events: number of cases with Porphyromonas gingivalis detection

Four studies [7,14,16,17] evaluated the detection of *P. gingivalis* in oral cancer patients and controls without the disease (Figure 2a), finding higher detection in oral squamous cell carcinoma patients, although with no statistically significant relationship (OR=2.96; 95% CI: 0.47 to 18.44; p=0.25). Three studies [9,12,13] analysed this microorganism in esophageal cancer (Figure 2b), and no relevant influence of *P. gingivalis* was found, with no statistically significant association (OR=11.47; 95% CI: 0.45 to 290.05; p=0.14). Other three studies [10,15,18] reviewed colorectal cancer (Figure 2c), finding that colorectal cancer patients were twice as likely to be infected with *P. gingivalis*. After the statistical analysis, statistically significant

differences were found (OR=2.00; 95% CI: 1.12 to 3.58; p=0.02).

As well, three studies [8,11,19] examined this periodontopathogen in pancreatic cancer patients and controls without the disease (Figure 2d). Patients with pancreatic cancers increased 1.32 times the risk of being infected by *P. gingivalis*, with a statistically significant relationship (OR=1.32; 95% CI: 1.05 to 1.66; p=0.02).

One study [10] verified the presence of this bacterium in patients with lung cancer (Figure 2e) or breast cancer (Figure 2f). In lung cancer patients there was a higher prevalence of *P. gingivalis* (OR=1.77; 95% CI: 0.57 to 5.48; p=0.32); while in breast cancer patients, this prevalence was lower (OR=0.55; 95% CI: 0.23 to 1.28; p=0.16). However, the results were not statistically significant.

Analysis of publication bias

The funnel plot of the meta-analysis did not show a uniform distribution on both sides, suggesting that there may be publication bias, as shown in Figure 3. Egger's test results (t=1.54, p=0.06) indicated evidence of some publication bias.

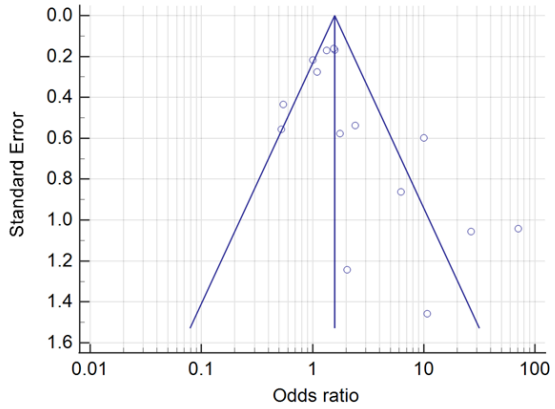

Figure 3 Funnel plot for the analysis of publication bias between *Porphyromonas gingivalis* detection and cancer risk.

DISCUSSION

Data from thirteen studies [7-19] on the possible relationship between *P. gingivalis* bacteria and cancers in different body locations have been included in the present meta-analysis. Overall, *P. gingivalis* detection was 1.81 times more likely in cancer patients than subjects without cancer, with a statistically significant association (p<0.01).

Regarding oral cancer, although a higher detection of the periodontopathogen was found in oral cancer patients compared to controls, no statistically significant relationship was observed (p=0.25). Of the four studies that evaluated the detection of this bacterium, three of them [14,16,17] agreed to indicate higher detection in patients with oral cancer, while one [7] found higher detection in controls. These variations in the concentrations of periodontal pathogens in oral cancer patients may be conditioned by a series of factors such as the patient's immune status or the effects derived from cancer treatment [7]. *P. gingivalis* can proliferate and survive in the cytoplasm of infected tumor cells, inhibiting apoptosis and, therefore, favoring the spread of cancer, affecting adjacent cells. The level of positivity for *P. gingivalis* is significantly higher in cancerous tissues than in tissues adjacent to tumor or in normal tissues. It seems that cells infected by *P. gingivalis* escape the host surveillance function, perpetuating the clonal expansion of these mutated cells, leading to cancer progression [14].

In the analysis of esophageal cancer, although the detection of *P. gingivalis* was higher in cancer patients, no significant influence of the detection of the bacteria on the esophageal cancer risk was found (p=0.14). All three studies [9,12,13] that examined this bacterium confirmed these higher detection rates in esophageal cancer patients. Although it is possible that *P. gingivalis* infection initiates or is a transforming factor of esophageal epithelial cells, the possibility that neoplastic tissues represent a suitable microenvironment for the proliferation of *P. gingivalis* cannot be excluded. However, the evidence to support the positive association between *P. gingivalis* infection and esophageal cancer progression is scarce, and this bacterium has not yet been confirmed as a possible new etiologic agent or cofactor of esophageal cancer [9].

P. gingivalis detection was two-folds more probably in colorectal cancer patients with statistically significant differences (p=0.02). The three studies [10,15,18] that evaluated the detection of the periodontopathogen confirmed this higher detection in colorectal cancer. The periodontopathogenic bacterium *F. nucleatum* and, to a lesser extent, *P. gingivalis*, can activate the Myc oncogene and cyclin D1, increasing the inflammatory response that stimulates the growth of neoplastic cells in colorectal cancer [10]. This fact is also revealed by other studies carried out in patients with colorectal cancer in which *P. gingivalis* in cooperation with other oral pathogens, may colonize and persist in the intestinal microbiota, forming an inflammatory microenvironment, which can promote the development of this type of cancer [15]. Pancreatic

cancer was also evaluated in this study, showing that pancreatic cancer patients increased 1.32 times the risk of being infected by *P. gingivalis*, with a statistically significant relationship (p=0.02). All studies [8,11,19] agreed with this finding.

The possible association between *P. gingivalis* infection and pancreatic cancer is not yet well established. Two mechanisms could explain this link. 1) Direct migration, whereby *P. gingivalis* and other oral bacteria move to the pancreas through ingestion or circulation following toothbrushing. 2) Systemic inflammation induced by *P. gingivalis* increases the levels of the proinflammatory cytokines and promotes the development of pancreatic cancer [19]. The presence of periodontal pathogens such as *P. gingivalis* and *Aggregatibacter actinomycetemcomitans* in the pancreas is associated with an increased risk of pancreatic carcinoma. *P. gingivalis* can alter the antitumor response of the host, favoring cell invasion and the interruption of signaling pathways through the degradation of cytokines and receptors [11].

There is a scarce of studies looking at the role of *P. gingivalis* on cancers in other body locations such as the lung or breast. Aspiration and ingestion of *P. gingivalis* could lead to colonization of other extraoral tissues such as the lungs. The migration of periodontal pathogens to these new sites may promote carcinogenic events. A chronic oral bacterial infection could initiate a signaling cascade of both immune cells and epithelial cells leading to systemic inflammatory processes that favor carcinogenesis. Similarly, *P. gingivalis* has been related to breast cancer due to microbial dysbiosis. Additionally, oral bacteria can facilitate the formation of important carcinogens including nitrosamines and acetaldehyde. The interrelationship between the periodontal pathogens and cancer risk could further be attributed to other risk factors such as lifestyle, genetic variation, and age-related changes in immune function [10].

This study has some limitations. First, the number of included studies is relatively small. Second, the results of this meta-analysis should be interpreted with caution due to the high heterogeneity found in some comparisons, which required the application of the random-effects model. Third, the results could be conditioned by the geographical differences of the study populations. Fourth, in some studies, the *P. gingivalis* count could not be adequately quantified and the possible influence of high bacteria counts on periodontal variables and/or tumor behavior could not either be considered. Another limitation of this study is publication bias in which studies that give positive results are more frequently submitted for publication and are more likely to be published.

Periodontal bacteria can lead to tooth loss in severe periodontitis. Moreover, they induce systemic inflammation related to several systemic disorders, such as cardiovascular diseases, diabetes mellitus, pulmonary diseases, rheumatoid arthritis, and malignancies. Periodontal bacteria infection, particularly by *P. gingivalis* and *F. nucleatum*, has been used as a marker to assess the prognosis of cancer patients [20].

New studies are needed in cancer patients to analyze the role of this periodontal bacterium and assess the molecular biomarkers that mediate the inflammatory response induced by *P. gingivalis*, conditioning the tumor progression and behavior.

CONCLUSIONS

In this meta-analysis, cancer patients were 1.81 times more likely to detect *P. gingivalis* ($p < 0.01$) compared to controls. *P. gingivalis* presence were also more likely in patients with colorectal (OR: 2.00, p=0.02) or pancreatic (OR: 1.32, p=0.02) tumors. In contrast, oral, esophageal, lung, or breast cancers did not show a significant increase of *P. gingivalis* presence ($p>0.05$).

ACKNOWLEDGEMENT

None.

DECLARATION OF INTEREST

None declared.

REFERENCES

1. Sun J, Tang Q, Yu S, Xie M, Xie Y, Chen G, et al. Role of the oral microbiota in cancer evolution and progression. Cancer Med. 2020;9(17):6306-6321.

2. Rajapriya P, Saravanan P, Burnice NK, Priyanka KC, Shalini S, Ramakrishnan R. Recent Advances in Salivary Proteomics, Genomics and Transcriptomics: A Reliable Tool in Periodontal diagnosis – A Review. Ann Dent UM. 2014;21(2):8-16.
3. Fujiwara N, Kitamura N, Yoshida K, Yamamoto T, Ozaki K, Kudo Y. Involvement of Fusobacterium Species in Oral Cancer Progression: A Literature Review Including Other Types of Cancer. Int J Mol Sci. 2020;21(17):6207.
4. Healy CM, Moran GP. The microbiome and oral cancer: More questions than answers. Oral Oncol. 2019;89:30-33.
5. Kakabadze MZ, Paresishvili T, Karalashvili L, Chakhunashvili D, Kakabadze Z. Oral microbiota and oral cancer: Review. Oncol Rev. 2020;14(2):476.
6. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Internet]. Ottawa (Canada): The Ottawa Hospital. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
7. Kang M-S, Oh J-S, Kim H-J, Kim H-N, Lee I-K, Choi H-R, et al. Prevalence of oral microbes in the saliva of oncological patients. J Bact Virol. 2009;39(4):277-285.
8. Michaud DS, Izard J, Wilhelm-Benartzi CS, You DH, Grote VA, Tjønneland A, et al. Plasma antibodies to oral bacteria and risk of pancreatic cancer in a large European prospective cohort study. Gut. 2013;62(12):1764-70.
9. Gao S, Li S, Ma Z, Liang S, Shan T, Zhang M, 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.
10. Mai X, Genco RJ, LaMonte MJ, Hovey KM, Freudenheim JL, Andrews CA, et al. Periodontal Pathogens and Risk of Incident Cancer in Postmenopausal Females: The Buffalo OsteoPerio Study. J Periodontol. 2016;87(3):257-67.
11. Fan X, Alekseyenko AV, Wu J, Peters BA, Jacobs EJ, Gapstur SM, et al. Human oral microbiome and prospective risk for pancreatic cancer: a population-based nested case-control study. Gut. 2017;67(1):120-127.
12. Peters BA, Wu J, Pei Z, Yang L, Purdue MP, Freedman ND, et al. Oral Microbiome Composition Reflects Prospective Risk for Esophageal Cancers. Cancer Res. 2017;77(23):6777-6787.
13. Yuan X, Liu Y, Kong J, Gu B, Qi Y, Wang X, et al. Different frequencies of Porphyromonas gingivalis infection in cancers of the upper digestive tract. Cancer Lett. 2017;404:1-7.
14. Chang C, Geng F, Shi X, Li Y, Zhang X, Zhao X, Pan Y. The prevalence rate of periodontal pathogens and its association with oral squamous cell carcinoma. Appl Microbiol Biotechnol. 2019;103(3):1393-1404.
15. Yang Y, Cai Q, Shu XO, Steinwandel MD, Blot WJ, Zheng W, et al. Prospective study of oral microbiome and colorectal cancer risk in low-income and African American populations. Int J Cancer. 2019;144(10):2381-2389.
16. Zhang L, Liu Y, Zheng HJ, Zhang CP. The Oral Microbiota May Have Influence on Oral Cancer. Front Cell Infect Microbiol. 2020;9:476.
17. Chen Q, Shao Z, Liu K, Zhou X, Wang L, Jiang E, et al. Salivary Porphyromonas gingivalis predicts outcome in oral squamous cell carcinomas: a cohort study. BMC Oral Health. 2021;21(1):228.
18. Wang X, Jia Y, Wen L, Mu W, Wu X, Liu T, et al. Porphyromonas gingivalis Promotes Colorectal Carcinoma by Activating the Hematopoietic NLRP3 Inflammasome. Cancer Res. 2021;81(10):2745-2759.
19. Petrick JL, Wilkinson JE, Michaud DS, Cai Q, Gerlovin H, Signorello LB, et al. The oral microbiome in relation to pancreatic cancer risk in African Americans. Br J Cancer. 2022;126(2):287-296.
20. 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 (Baltimore). 2020;99(15):e19698.

Editorial History

Date of Submission: 28 Dec 2021
Review & Revision: 11 Jan – 16 Mar 2022
Accepted: 21 Mar 2022
Published: 20 April 2022