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Systematic Review

Risk of breast cancer in people with periodontal disease: a systematic review and meta-analysis

Riesgo de cáncer de mama en personas con enfermedad periodontal: una revisión sistemática y metaanálisis

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ABSTRACT

Introduction: Periodontal disease (PD) has been associated with the incidence of chronic systemic diseases, including breast cancer (BC). However, studies on their association have shown inconsistent results.

Objective: To evaluate the risk of BC in people with PD.

Methods: A systematic review and meta-analysis following the PRISMA 2020 guidelines in Scopus, PubMed, ScienceDirect, EBSCO, Wiley Online Library, and Google Scholar was performed. Any observational study evaluating BC risk in people with and without PD was included. Study quality assessment was conducted using the Newcastle-Ottawa Scale. Fixed- or random-effects model meta-analyses were used and the results were reported as relative risks (RR) and 95% confidence intervals (CI). All statistical analyses were performed using Stata version 17.0 software.

Results: Fifteen observational studies involving 816,219 female participants were included. There was a 22% increased risk of BC in people with PD (RR = 1.22; 95% CI = 1.10-1.35; p = 0.0001; I^2 = 89.80%). Subgroup analysis showed consistent and significant results when stratified by sample size and follow-up period. This meta-analysis was robust based on sensitivity analysis; however, it should be interpreted with caution due to its high heterogeneity.

Conclusions: The risk of BC is increased in people with PD. Future studies are needed to evaluate the effect of periodontal treatment on reducing the risk of BC.

Keywords: breast cancer; meta-analysis; oral health; periodontal disease; periodontitis.

RESUMEN

Introducción: La enfermedad periodontal (PD) se ha asociado con la incidencia de enfermedades sistémicas crónicas, incluido el cáncer de mama (BC). Sin embargo, los estudios sobre su asociación han mostrado resultados inconsistentes.

Objetivo: Evaluar el riesgo de BC en personas con PD.

Métodos: Se realizó una revisión sistemática y metaanálisis siguiendo las pautas PRISMA 2020 en Scopus, PubMed, ScienceDirect, EBSCO, Wiley Online Library y Google Scholar. Se incluyó

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cualquier estudio observacional que evaluara el riesgo de BC en personas con y sin PD. La evaluación de la calidad del estudio se realizó utilizando la escala Newcastle-Ottawa. Se utilizaron metaanálisis de modelos de efectos fijos o aleatorios y los resultados se informaron como riesgos relativos (RR) e intervalos de confianza del 95 % (CI). Todos los análisis estadísticos se realizaron utilizando el software Stata versión 17.0.

Resultados: Se incluyeron quince estudios observacionales que involucraron a 816.219 participantes femeninas. Se observó un aumento del 22 % en el riesgo de BC en personas con PD (RR= 1,22; 95 % CI= 1,10-1,35; *p*= 0,0001; I^2= 89,80 %). El análisis de subgrupos mostró resultados consistentes y significativos cuando se estratificó por tamaño de muestra y período de seguimiento. Este metaanálisis fue sólido según el análisis de sensibilidad; sin embargo, debe interpretarse con cautela debido a su alta heterogeneidad.

Conclusiones: El riesgo de BC aumenta en personas con PD. Se necesitan futuros estudios para evaluar el efecto del tratamiento periodontal en la reducción del riesgo de BC.

Palabras clave: cáncer de mama; enfermedad periodontal; metaanálisis; periodontitis; salud bucal.

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INTRODUCTION

Periodontal disease (PD) is a chronic inflammatory disease of the tooth supporting tissue or periodontium, causing tissue damage and contributing to systemic chronic inflammation.[1] Accumulation of periodontal pathogenic bacteria and biofilm on teeth is considered to be the main factor in the occurrence of PD.[2] Currently, PD remains recognized as a global public health issue that needs to be addressed, with 1.1 billion cases and 91 million new cases of PD identified in 2019.[3] In addition to having a negative impact on oral health, PD also contributes to an increased risk of various chronic systemic conditions, including diabetes,[4] cardiovascular disease,[5]


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metabolic syndrome,[6] rheumatoid arthritis,[7] adverse pregnancy outcomes,[8,9] respiratory diseases,[10] chronic kidney disease,[11] cognitive impairment,[12] male reproductive health problems,[13,14] and various types of intraoral and extraoral cancer.[15]

Breast cancer (BC) is one of the most common types of deadly cancer in women, becoming a complex global health problem. Based on global epidemiological data in 185 countries obtained from GLOBOCAN, as many as 2.1 million cases and more than 600 thousand deaths due to BC were identified in 2018,[16] and increased to 2.26 million cases in 2020, making BC the most frequently diagnosed cancer globally among other cancers.[17] Various risk factors for BC include female gender, age, family history, BRCA gene mutations, pregnancy, menstrual periods and menopause.[18] In addition, alcohol consumption, smoking, lifestyle, diet, consumption of certain medications, and obesity are modifiable risk factors that contribute to the occurrence of BC.[19]

Mechanistic evidence between PD and the risk of various cancers has been observed, including the development of BC.[20] Oral pathogens are considered to be factors that have strong potential to enter the bloodstream and spread to other organs.[21] Periodontal pathogens have been shown to induce carcinogenesis through the interaction of integrin and Toll-like receptor 4 (TLR4)/MyD88 signaling pathways, further contributing to BC cell metastasis.[22] In addition, chronic inflammation caused by PD triggers systemic inflammation. Inflammatory mediators produced by periodontal pathogens are suggested to be associated with oncogene activation, cell cycle inhibition, cell proliferation, mutagenesis, DNA damage, angiogenesis, and metastasis.[23]

Studies investigating the relationship between PD and the risk of BC incidence have been conducted. However, their results have shown inconsistent results, with some studies showing a significant association;[24,25,26] however, other studies revealing no increased risk of BC in people with PD.[27,28,29] Therefore, this study aims to identify the pooled risk of BC in people with PD using meta-analysis.


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METHODS

Protocol and focused question

This study is a systematic review and meta-analysis followed the PRISMA 2020 guidelines.[30] The research question of this study was "What is the risk of BC in people with PD?". The population, exposure, comparison, outcome, and study (PECOS) framework was used to address the research questions, with P: any population; E: PD; C: population without PD or healthy controls; O: risk of BC; and S: cohort, case-control, or cross-sectional studies.

Search strategy

A systematic and comprehensive literature search in Scopus, PubMed, ScienceDirect, EBSCO, Wiley Online Library, and Google Scholar from inception to December 2024 was performed. The following are the terms used in literature searches: periodontal OR periodontal disease OR periodontitis OR oral health AND breast OR breast cancer OR breast neoplasm OR cancer.

Eligibility criteria

Articles were included if they: 1) were cohort, case-control, or cross-sectional studies, 2) observed the risk of BC in people with PD, 3) used study subjects from a population diagnosed with PD and control subjects from a population without PD, 4) reported risk relative (RR), odds ratio (OR), or hazard ratio (HR) along with 95% confidence interval (CI), and 5) were full-text and peer-reviewed. In contrast, all review articles, commentaries, letters to editors, short communications, case reports, and case series were excluded from this study. Authors strictly addressed studies that have the potential for data or sample duplication using the same dataset, if any, where studies that involve more samples or use a longer time span and/or studies that use more rigorous and comprehensive research methods were selected. This was a concern to reduce selection bias and increase the validity of meta-analysis results. Finally, other restraints were not applied in the study selection, including publication year and language restrictions. Therefore, all observational articles published until December 2024 were considered for inclusion.


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Quality assessment

Newcastle-Ottawa Scale (NOS) was employed for the quality assessment of included studies.[31] The NOS has three components: selection, comparability, and results, with overall score ranges from 0 to 9. Study quality was assessed as high if the overall score was ≥7, moderate if the overall score was 4-6, and poor if the overall score was ≤3. Study quality was assessed by two reviewers (F.M.R. and A.S.) and validated by a senior researcher (A.I.). Any discrepancies during the assessment of study quality were addressed through in-depth discussion between authors and careful decision making.

Data extraction

Independently, two authors (F.M.R. and A.S.) performed data extraction from included studies using table containing reference, country, study design, sample size, age, PD assessment, BC assessment, adjustments for confounding factors, and estimates (RR, OR, or HR) with 95% CI. All data were processed quantitatively and qualitatively to draw definite conclusions.

Statistical analysis

Risk of BC in people with PD was measured using meta-analysis and presented as adjusted RR and 95% CI, with a *p*-value considered statistically significant being <0.05. Estimates in the form of OR or HR were considered as RR when performing a pooled analysis. Heterogeneity test (I^2) was performed to evaluate data variation between included studies, where low heterogeneity was stated if I^2 was ≤50% or p ≥0.1 and high heterogeneity if I^2 was >50% or p <0.1. Referring to the results of the heterogeneity test, a fixed-effects model meta-analysis was selected if the heterogeneity was low, whereas a random-effects model was used otherwise. Subgroup analysis was also performed to evaluate the significance and consistency of the meta-analysis results stratified by country, study design, sample size, follow-up period, periodontal assessment, and BC assessment. Sensitivity analysis was conducted to evaluate the robustness of the meta-analysis results, using the leave-one-out method by omitting one study at a time and recalculating the pooled RR and its 95% CI.[32]

Initially, a funnel plot was used to identify possible publication bias, in accordance with the consensus that a funnel plot can be used if the number of included studies is more than 10 studies.[33] In addition, publication bias was also assessed using the Egger regression test[34] and the Begg and

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Mazumdar nonparametric rank correlation test,[35] with a *p*-value of >0.05 considered no publication bias was observed. All statistical analyses were performed using Stata version 17.0 software.

RESULTS

Study selection

After removing duplicate articles, 1,137 potential articles were identified from the electronic database search. Initial screening of the records was then performed and 904 articles were excluded, leaving 233 papers. In the next selection stage, 197 articles were not retrieved based on the irrelevance of the title and abstract. The remaining 36 articles were subjected to a thorough eligibility assessment, excluding 22 reports for the following reasons: article not available (*n* = 2), unspecified data (*n* = 5), reviews articles (*n* = 6), issues in study methods (*n* = 4), ineligible comparison (*n* = 3), and articles using the same dataset (*n* = 2). A manual search through other sources was also conducted to minimize study selection bias, finding two studies, but one study had to be excluded because the article was not available. Finally, fifteen studies were included in this meta-analysis (Fig. 1).

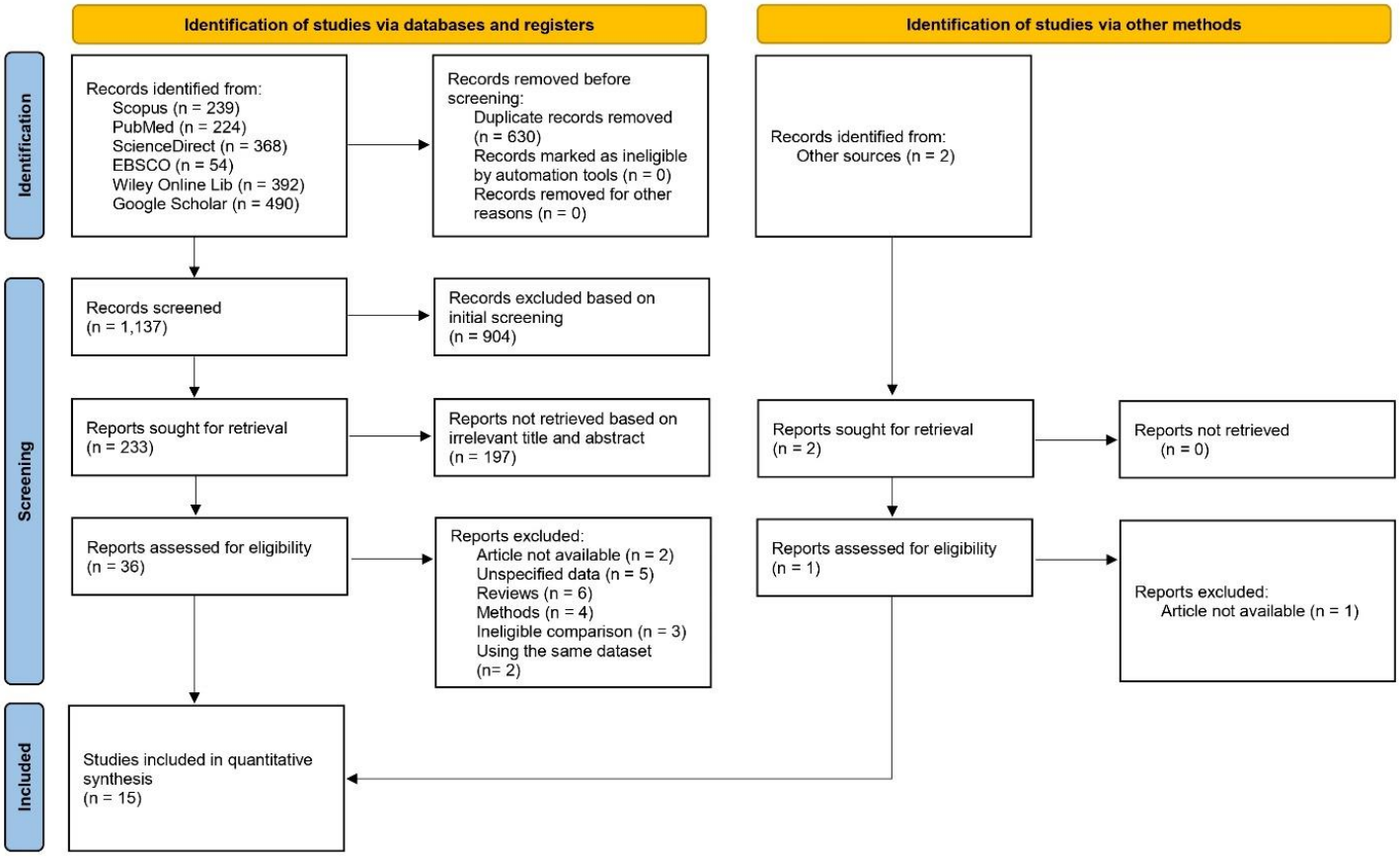

Fig. 1 – PRISMA flowchart.

Characteristics of included studies

This study included 15 observational studies involving 816,219 female participants aged 19 years or older. The included studies consisted of nine prospective cohort,[25,27,29,36,37,38,39,40,41] three retrospective cohort,[26,28,42] and three case-control studies.[24,43,44]

Studies using a cohort design, the follow-up period varied from 2 to 27 years. The participants involved came from the following regions: Asia including Taiwan[24,26,42] and South Korea;[38] Europe including Sweden,[36,41] Greece,[43] and Finland;[28] North America including the USA;[25,27,29,37,39,40] and South America including Brazil.[44]

In assessing PD, several methods/criteria were used: self-report,[27,29,36,37] ICD,[24,26,39,42] oral examination,[41,43] CPI score,[38] medical records,[28] radiographic alveolar crestal bone height,[40]

and CDC-AAP criteria.[25,44] Meanwhile, assessment for BC was carried out using the following methods/criteria: ICD,[24,26,28,29,36,37,39,41,42,44] medical records,[25,40,43] and self-report.[27,38] A table of characteristics of included studies is available in the supplementary file.

Quality assessment of included studies

Based on the results of the quality assessment of the included studies, six studies[26,27,28,29,42,44] obtained an overall score of 9, five studies[24,25,37,38,40] obtained an overall score of 8, and four studies[36,39,41,43] were assessed with an overall score of 7. Overall, the studies included were of high quality.

Risk of breast cancer in people with periodontal disease

The results of the random-effects model meta-analysis showed a statistically significant increase in the risk of BC of 22% in people with PD (RR = 1.22; 95% CI = 1.10-1.35; p = 0.0001). Interpretation of this meta-analysis should be done with caution because the heterogeneity test showed that the studies were heterogeneous (I^2 = 89.80%; p = 0.00) (Fig. 2).

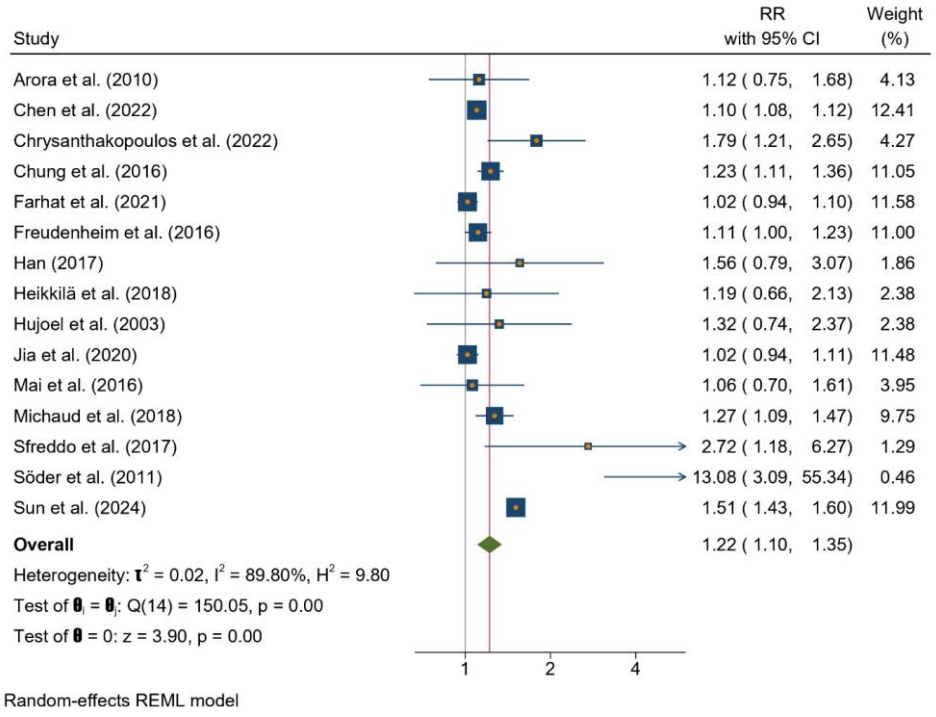

Fig. 2 – Forest plot of the risk of BC in people with PD.

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Subgroup analysis of the risk of breast cancer in people with periodontal disease

Given the diversity of characteristics of the included studies, authors subsequently performed subgroup analyses stratified by country, study design, sample size, follow-up period, PD assessment, and BC assessment, described in table 1.

Subgroup meta-analysis stratified by country found significant and consistent results in Asian (RR = 1.28; p = 0.005), North American (RR = 1.06; p = 0.01), and South American populations (RR = 2.72; p = 0.02), but not in European populations (RR = 1.93; p = 0.12).

Based on study design, the risk of BC in people with PD was consistent across prospective cohort (RR = 1.10; p = 0.02) and retrospective cohort study designs (RR = 1.36; p = 0.0008), but not across case-control studies (RR = 1.56; p = 0.08).

BC risk in the PD people also consistently increased based on sample size, both in studies with samples <10,000 (RR = 1.41; p = 0.0005) and ≥10,000 (RR = 1.16; p = 0.02), and based on follow-up period, both in studies with follow-up periods <10 years (RR = 1.12; p = 0.03) and ≥10 years (RR = 1.25; p = 0.006). When stratified by PD assessment, significant and consistent results were observed in studies with ICD (RR = 1.27; p = 0.005) and medical records (RR = 1.19; p = 0.006), while inconsistent results were found in self-report (RR = 1.04; p = 0.12), oral/radiographic examination (RR = 2.49; p = 0.18), CDC-AAP (RR = 1.66; p = 0.16), and CPI score (RR= 1.56; p = 0.20).

Meanwhile, based on the criteria for BC diagnosis, studies using ICD as BC assessment showed consistent results (RR = 1.27; p = 0.0004), but were not significant in studies using medical records (RR = 1.21; p = 0.08) and self-report (RR = 1.03; p = 0.52).

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Table 1 – Subgroup analysis of the risk of BC in people with PD

Subgroup	Studies (*n*)	Heterogeneity		Model	RR (95% CI)	*p*-value
		p	I^2 (%)			
Overall	15	0.00	89.80	Random	1.22 (1.10-1.35)	0.0001
Country						
Asia	4	0.00	95.84	Random	1.28 (1.08-1.53)	0.005
Europe	4	0.01	89.06	Random	1.93 (0.83-4.49)	0.12
North America	6	0.12	42.17	Fixed	1.06 (1.01-1.11)	0.01
South America	1	NA	NA	NA	2.72 (1.18-6.27)	0.02
Study design						
Prospective cohort	9	0.01	62.84	Random	1.10 (1.02-1.20)	0.02
Retrospective cohort	3	0.00	82.54	Random	1.36 (1.14-1.62)	0.0008
Case-control	3	0.01	80.42	Random	1.56 (0.96-2.53)	0.08
Sample size						
<10,000	8	0.02	58.96	Random	1.41 (1.16-1.70)	0.0005
≥10,000	7	0.00	94.90	Random	1.16 (1.03-1.30)	0.02
Follow-up period						
<10	4	0.03	65.52	Random	1.12 (1.01-1.25)	0.03
≥10	8	0.00	81.91	Random	1.25 (1.07-1.47)	0.006
Periodontal assessment						
ICD	4	0.00	95.65	Random	1.27 (1.07-1.51)	0.005
Self-report	4	0.55	0.00	Fixed	1.04 (0.99-1.09)	0.12
Oral/radiographic examination	3	0.00	94.06	Random	2.49 (0.66-9.44)	0.18
CDC-AAP	2	0.08	67.70	Random	1.66 (0.81-3.37)	0.16
CPI score	1	NA	NA	NA	1.56 (0.79-3.07)	0.20
Medical records	1	NA	NA	NA	1.19 (1.66-2.13)	0.006
Breast cancer assessment						
ICD	9	0.00	90.28	Random	1.27 (1.11-1.45)	0.0004
Medical records	4	0.01	78.26	Random	1.21 (0.98-1.50)	0.08
Self-report	2	0.22	32.69	Fixed	1.03 (0.95-1.11)	0.52

Sensitivity analysis

To determine the robustness of the results, sensitivity analysis was subsequently conducted by removing studies one by one and recalculating the remaining studies. The results showed stable

pooled RR, 95% CI, and *p*-value, no significant changes were observed, concluding that this meta-analysis is robust (Fig. 3).

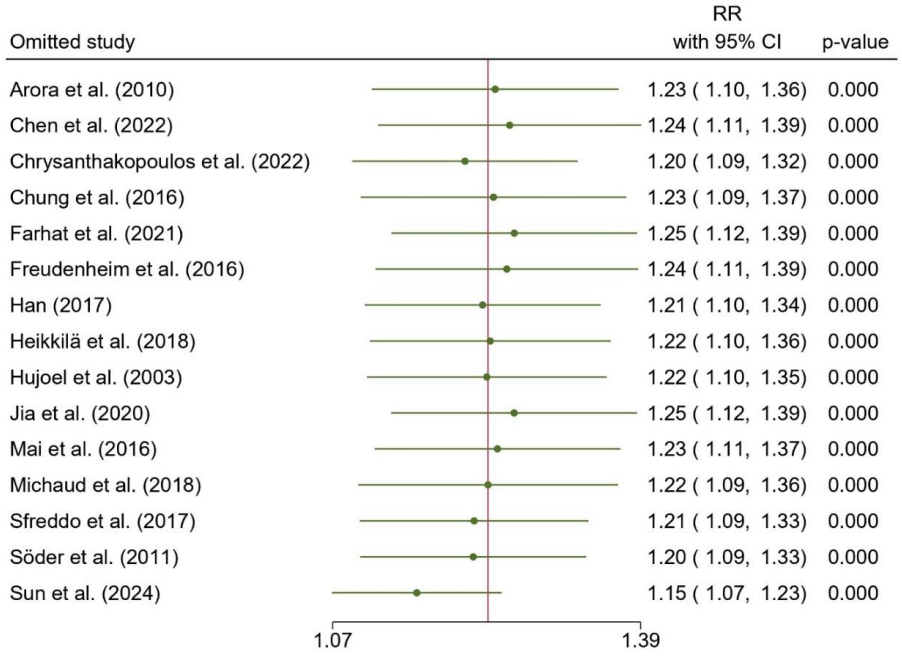

Fig. 3 – Leave-one-out analysis of sensitivity.

Publication bias

The results of the funnel plot revealed an asymmetric distribution of studies (Fig. 4). To confirm the funnel plot results, authors also conducted the Egger regression test ($p = 0.0055$) and the Begg and Mazumdar nonparametric rank correlation test ($p = 0.0478$). Based on these results, publication bias was observed.

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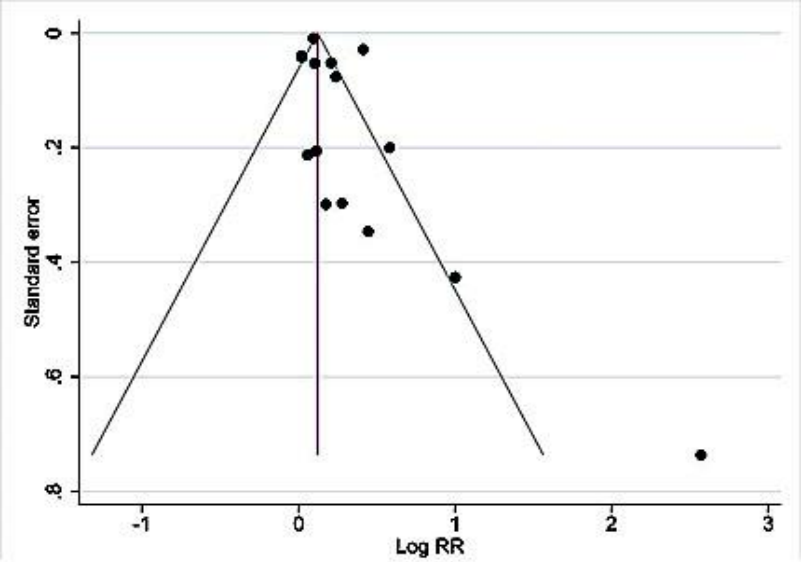

Fig. 4 – Funnel plot.

DISCUSSION

The results of this study revealed a significant increase in the risk of BC in people with PD by 22%. The subgroup analyses of this meta-analysis were also consistent when stratified by sample size and follow-up period, but inconsistent when stratified by country, study design, periodontal assessment, and BC assessment.

Nonetheless, this meta-analysis should be interpreted with caution, given that heterogeneity tests showed substantial variation between studies. These differences are believed to be caused by factors such as population characteristics, sample size, study design, and/or measurement methods used in each study. In addition, the high heterogeneity among studies is likely due to differences in the confounding factors adjusted for. The results of the publication bias analysis indicated publication bias, which may affect the interpretation of the results. However, sensitivity analysis showed that the meta-analysis results remained stable, indicating that the effect estimates were not dependent on a single study. In conclusion, this meta-analysis should be interpreted with caution despite their robustness.


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Previous meta-analyses by *Shao J* et al.[45] and *Shi T* et al.[46] both conducted in 2018 and involving approximately 180 thousand samples showed significant results. However, one of these meta-analyses included studies that were excluded in this meta-analysis on the grounds of ineligible comparison, where one study[47] did not use a control/comparison group in its research subjects. Furthermore, the two previous meta-analyses need to be updated to incorporate newer studies with larger study samples. Therefore, this meta-analysis is currently the latest and most comprehensive, involving larger study samples from additional studies.

Mechanisms of PD in increasing BC risk have been proposed. Strong suspicion arises from chronic periodontal inflammation that has systemic effects. Oral microbiota promote genomic instability, chronic inflammation, mutation accumulation, and cancer development through specific substances produced by them.[23] Furthermore, people with PD have increased levels of C-reactive protein (CRP) and the transcription factors, receptor activator of nuclear factor kappa B (RANK) and RANK ligand (RANKL).[22,48] Higher risk of systemic diseases has been linked to systemically raised CRP levels, including higher risk of BC.[49] Meanwhile, increased transcription factors RANK and RANKL are believed to induce the formation of pre-neoplastic and invasive tumors in the breast.[50]

Periodontal pathogens, such as *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, were reported to produce lipopolysaccharides (LPS) that contribute to chronic inflammation and potentially increase the risk of BC.[51] LPS from oral pathogens has been documented to increase inflammatory protein expression, nuclear factor kappa β (NF-κβ) activation, and anti-apoptotic BCL-2 and BCL-xL expression.[52] This may occur via immune receptors such as TLR4, which in turn serves to increase more inflammatory and cancer-related chemokines and cytokines.[53] In addition, *F. nucleatum* increases matrix metalloproteinase-9 (MMP-9), triggers inflammatory responses and facilitates a microenvironment that promotes carcinogenesis.[54] Furthermore, *P. gingivalis* have carcinogenic properties such as preventing cell apoptosis, growing and surviving in epithelial cells and spreading to other organs, inducing cellular proliferation, activating cyclooxygenase-2 (COX-2) gene expression, and increasing the production of tumor necrosis factor-α (TNF-α), interleukin (IL)-6, IL-8, and IL-1β.[55] In conclusion, systemic chronic


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inflammation and activation of various inflammatory biomarkers by periodontal pathogens and their toxins contribute to carcinogenesis, leading to increased risk of BC.

The findings of this meta-analysis suggest an increased risk of BC in individuals with PD, which provides a clinically important signal regarding a possible association between periodontal health and BC risk. However, the high heterogeneity among the studies analyzed suggests that these results should be interpreted with caution. Therefore, although the potential for PD as a risk factor for BC is noteworthy, the current evidence is insufficient to provide a basis for changes in policy or clinical guidelines. Nevertheless, it is important for healthcare professionals to begin to raise clinical awareness of this possible association. Given that PD is a chronic disease that can be modified through preventive and therapeutic interventions, evaluation of periodontal status can be considered as part of a comprehensive screening and holistic approach in early detection of BC risk, especially in women with additional risk factors.

The findings also provide a rational basis for collaboration between dentists and medical personnel in integrating aspects of oral health and systemic health. In the future, more rigorous longitudinal studies and intervention trials are needed to establish a causal relationship between these two conditions and to assess whether periodontal management can contribute to BC prevention efforts.

This study has several strengths. First, this meta-analysis is the most recent and comprehensive to date, with updated studies and involving a larger sample. Second, the literature search was conducted systematically and comprehensively from various electronic databases and manual searches with strict eligibility assessment, reducing study selection bias. Third, the quality assessment of the included studies showed high study quality. Fourth, the pooled estimation results have been adjusted for confounding factors; therefore, the results are not influenced by other factors. Fifth, the sensitivity analysis showed that the results of this meta-analysis were robust.

However, this meta-analysis also acknowledges several limitations. First, the included studies had high variation as indicated by high heterogeneity test results, making this meta-analysis must be interpreted with caution. Second, publication bias exists, indicated by the results of visual interpretation with funnel plot and confirmed by Egger's test and Begg and Mazumdar's test. Third, there is a controversy in establishing the diagnosis of PD, where several studies used appropriate

clinical criteria such as CDC-AAP, ICD, oral and radiographic examination, and CPI score, but several others used self-report methods. This is certainly a concern because it is prone to bias, where it is possible for periodontally healthy people to be included in the PD group, and vice versa. Therefore, the use of the latest criteria for establishing the diagnosis of PD is highly recommended for future research.[56]

In conclusion, this meta-analysis revealed a significantly increased risk of BC in people with PD. This is believed to be due to the periodontal inflammatory response and toxins from periodontal pathogens that cause systemic chronic inflammation and initiate BC-causing factors. This meta-analysis involved observational studies that could not evaluate causal relationships, so this study requires future studies with rigorous methods to analyze the causal relationship between PD and increased risk of BC. In addition, studies related to the provision of periodontal treatment interventions to reduce the risk of BC need to be conducted, considering that studies related to this are rarely conducted.

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Data availability

Supplementary file: Research results. Word 2016. Available from:
https://revmedmilitar.sld.cu/index.php/mil/libraryFiles/downloadPublic/62

Figure 1 – original resolution:
https://revmedmilitar.sld.cu/index.php/mil/libraryFiles/downloadPublic/63