Revista Eletrônica
Acervo Saúde
Electronic Journal Collection Health ISSN 2178-2091

Association between periodontal disease and breast cancer: systematic review and meta-analysis

Associação entre doença periodontal e câncer de mama: revisão sistemática e metanálise

Asociación entre enfermedad periodontal y cáncer de mama: revisión sistemática y metanálisis

William Eduardo Pirola[1,2], Eliane Marçon Barroso[3], Ricardo Ribeiro Gama[1,4], Martins Fideles dos Santos Neto[1], Valiana Alves Teodoro[5], Fabíola Cristina Brandini da Silva Tozzo[1], René Aloísio da Costa Vieira[1,6].

ABSTRACT

Objective: To evaluate the possible association between periodontal disease and breast cancer in women. **Methods:** This is a systematic literature review combined with a meta-analysis. Five databases were searched, relevant published studies were retrieved and selected. The articles were evaluated and subsequently synthesized using the PRISMA methodology. Odds Ratios (OR) with 95% confidence intervals (CI) were calculated to evaluate the association between PD and the risk of breast cancer. The articles selected for meta-analysis were separated into two groups, as follows: (a) studies that did not present a clinical dental examination; (b) studies that presented a clinical dental examination. **Results:** In studies that did not include a clinical dental examination, it was found that women without periodontal disease had a 0.85-fold reduced risk of developing breast cancer, while studies that included a clinical dental assessment suggested that women without PD have a 0.50-fold reduced risk of developing breast cancer. **Final considerations:** Studies that clinically evaluated PD through dental parameters showed a greater decrease in the number of patients with breast cancer and periodontal disease.

Keywords: Breast Cancer, Periodontal Disease, Epidemiology.

RESUMO

Objetivo: Avaliar a possível associação entre a doença periodontal e o câncer de mama em mulheres. **Métodos:** Esta é uma revisão sistemática da literatura combinada com uma meta-análise. Cinco bases de dados foram pesquisadas, estudos relevantes publicados foram recuperados e selecionados. Os artigos foram avaliados e posteriormente sintetizados utilizando a metodologia PRISMA. Foram calculados *Odds Ratios*

[1] Programa de Pós-Graduação, Hospital de Câncer de Barretos – Fundação Pio XII, Barretos - SP.
[2] Departamento de Odontologia, Centro Universitário de Goiatuba, Goiatuba - GO.
[3] Departamento de Odontologia, Centro Universitário da Fundação Educacional de Barretos, Barretos – SP.
[4] Departamento de Cabeça e Pescoço, Hospital de Câncer de Barretos – Fundação Pio XII, Barretos - SP.
[5] Departamento de Epidemiologia e Bioestatística, Hospital de Câncer de Barretos – Fundação Pio XII, Barretos - SP.
[6] Programa de Pós-Graduação em Ginecologia, Obstetrícia e Mastologia, UNESP, Botucatu – SP.

SUBMETIDO EM: 11/2023 | ACEITO EM: 12/2023 | PUBLICADO EM: 2/2024

(OR) com intervalos de confiança (IC) de 95% para avaliar a associação entre DP e o risco de câncer de mama. Os artigos selecionados para metanálise foram separados em dois grupos, sendo: (a) estudos que não apresentaram exame clínico odontológico; (b) estudos que apresentaram exame clínico odontológico **Resultados:** Nos estudos que não incluíram exame clínico odontológico avaliou-se que mulheres sem doença periodontal têm um risco reduzido em 0,85 vezes de desenvolver câncer de mama, enquanto, estudos que incluíram avaliação odontológica clínica sugeriram que mulheres sem PD têm um risco reduzido em 0,50 vezes de desenvolver câncer de mama. **Considerações finais:** Estudos que avaliaram clinicamente a DP por meio de parâmetros odontológicos mostraram maior diminuição no número de pacientes com câncer de mama e doença periodontal

Palavras-chave: Câncer de Mama, Doença Periodontal, Epidemiologia.

RESUMEN

Objetivo: Evaluar la posible asociación entre enfermedad periodontal y cáncer de mama en mujeres. **Métodos:** Se trata de una revisión sistemática de la literatura combinada con un metanálisis. Se realizaron búsquedas en cinco bases de datos, se recuperaron y seleccionaron estudios publicados relevantes. Los estudios fueron evaluados y posteriormente sintetizados mediante la metodología PRISMA. Se calcularon los odds ratios con intervalos de confianza (IC) del 95% para evaluar la asociación entre la EP y el riesgo de cáncer de mama. Los estudios seleccionados para el metanálisis se separaron en dos grupos, de la siguiente manera: (a) estudios que no presentaron un examen clínico odontológico; (b) estudios que presentaron un examen clínico dental. **Resultados:** En los estudios que no incluyeron un examen clínico dental, se encontró que las mujeres sin enfermedad periodontal tenían un riesgo 0,85 veces menor de desarrollar cáncer de mama, mientras que los estudios que incluyeron un examen clínico dental La evaluación sugirió que las mujeres sin EP tienen un riesgo 0,50 veces menor de desarrollar cáncer de mama. **Consideraciones finales:** Estudios que evaluaron clínicamente la EP a través de parámetros dentales mostraron una mayor disminución en el número de pacientes con cáncer de mama y enfermedad periodontal.

Palabras clave: Cáncer de mama, Enfermedad periodontal, Epidemiología.

INTRODUCTION

Breast cancer is the most prevalent cancer among women worldwide, accounting for approximately 11.6% of cancers when non-melanoma skin cancers are excluded (BRAY F, et al., 2018). In Brazil, 28% of cancer cases in women are breast cancer, and 66,000 new cases are estimated per year until 2022 (INCA, 2019).

When studying the increased incidence of breast cancer, we must also evaluate the continuous increase in the number of women exposed to risk factors already established in the literature, such as obesity, alcohol consumption, inactivity and hormone replacement therapy (HOWELL A, et al., 2014), the decreased number of pregnancies, the decreased breastfeeding duration, and exposure to estrogen throughout reproductive life, characterized mainly by early menarche and late menopause (COLLABORATIVE GROUP ON HORMONAL FACTORS IN BREAST, 2002).

In addition to environmental risk factors, some patients may also have genetic risk factors, including hereditary risk factors such as alterations in the BRCA1 and BRCA2 genes, in addition to alterations in other genes, such as PALB2, ATM, BRIP1, CHEK and BARD1, to a lesser extent (JIAN W, et al., 2017). Nevertheless, more than half of diagnosed women do not have any of the known risk factors described in the literature (WANG A, et al., 2017).

It is important to know risk factors associated with breast cancer. Identifying these factors it is possible to perform primary prevention of cancer. Previous studies observed a modest association with Periodontal Disease (PD) and breast cancer, but multiple factors may be involved, and we do not now if this risk is real, or if PD is a confounding factor (SHAO J, et al., 2018; SHI T, et al., 2018). Periodontal disease (PD) is

characterized by chronic inflammation of the protective and supporting tooth tissues. Periodontal disease begins with gingivitis, a localized inflammation in the gums, which may progress to loss of bone structure and periodontal ligaments and the development of periodontal pockets (KINANE DF, et al., 2017; TAZAWA PS, et al., 2011).

PD is slow and progressive, and once it is established in the oral cavity, it becomes active through the presence of substrate, microorganisms and their products However, despite the association of periodontal disease with inflammatory processes in the body, it is still necessary to determine whether inflammation related to tumor factors is also associated with PD (SAHINGUR SE e YEUDALL WA, 2015; GAO S, et al., 2016). Several cancers have an associated inflammatory process (MACCIO A e MADEDDU C, 2013).

The literature describes an association between PD and cardiovascular disease, ischemic stroke and peripheral vascular disease, among others (GONZALEZ N, et al., 2017; LEIRA Y, et al., 2017; WANG H, et al., 2019). There is also a potential association between PD and several types of cancer, including digestive, pancreatic, prostate, breast, uterine, lung, esophagus/oropharynx and non-Hodgkin lymphoma, but there is a lack of standardization in the evaluation of periodontal disease, requiring further studies on the subject (CORBELLA S, et al., 2018).

Multiple criteria was used to evaluate PD, and multiple factors are used for variables adjusts, making necessary review the studies reporting PD and breast cancer. Based on this condition we performed a systematic review and meta-analysis, evaluating the quality of the studies, the criteria used to consider PD and variables used to adjust, with the objective to evaluate this potential association.

METHODS

The present study is a systematic literature review combined with a meta-analysis of data to determine whether PD is a possible risk factor for the development of breast cancer. To guide the elaboration of the questions related to this literature review, the PICO method was used, where P = breast cancer; I = periodontal disease; C = comparison between groups, in any study type; and O = the risk of developing breast cancer.

A comprehensive search of the literature was performed by 2 researchers independently (WEP and MFdSN) to identify all studies published until May 2023 in 5 databases: PubMed, Lilacs, Embase, Cochrane Library and Web of Science. This study is registered with PROSPERO CRD42023388722. The titles and abstracts of the collected articles were evaluated according to the inclusion criteria, which were studies conducted with humans, cohort studies, case-control studies, literature reviews, and studies with evaluations related to the presence of periodontal disease and breast cancer. Articles classified as letters to the editor and meeting and congress abstracts were excluded. The articles were evaluated individually. The PRISMA (Preferred Reporting Items for Systematic Review And Meta-Analyses) method was used to synthesize the articles (MOHER D, et al., 2009) as described in **Figure 1**.

After the articles were selected, data were systematically selected for the meta-analysis and were evaluated according to the quality of the studies. In studies with lack of data, the authors were contacted and the data were included in the analyses (JIA M, et al., 2020).

To assess the risk of bias, the Methodological Index for Nonrandomized Studies (MINORS) was used. This index is a scale composed of 12 items with a maximum score of 16 points for non-comparative studies and 24 points for comparative studies. The index classifies studies according to their scores as poor (≤ 5), reliable (6-10) or good (≥11) (SLIM K, et al., 2003).

A description of the studies according to MINORS is presented in **Table 1**. The investigations were categorized into two distinct groups: (a) investigations involving odontological evaluation executed by a qualified dental practitioner; and (b) investigations reliant upon data sourced from medical archives, self-reported information, or data derived from diagnostic imaging procedures.

Statistical analysis

The potential association between periodontal disease and breast cancer was evaluated using the combined odds ratio (OR) presented in the studies, with the corresponding 95% confidence interval (CI).

The OR parameters were recalculated after studies that did not present all data regarding the total patient sample, number of women with periodontal disease and number of women with breast cancer and periodontal disease were excluded. Comprehensive Meta-Analysis software version 2 was used to perform the meta-analysis.

RESULTS

According to the search strategy, 745 articles were selected, and another 2 articles that were not identified in the initial strategy were added. After the identification of duplicate articles, 127 studies were excluded. The titles and abstracts were read, and studies were subsequently excluded.

Thus, 28 studies were selected for full reading and qualitative evaluation. Of the 28 previously selected articles, 13 were excluded, of which 5 did not meet the inclusion criteria, 3 were systematic reviews, 3 were letters to the editor, 1 was in Chinese, and 1 was not available in full.

Of the 15 articles selected for qualitative evaluation, 3 that did not have enough data to calculate OR and thus were excluded. Therefore, 11 studies presented complete data for the meta-analysis (**Figure 1**), and 233,215 women were evaluated.

Table 2 and **Table 3** summarize the main findings. Of the 15 studies, all performed adjustments with a median of 3 variables, a range from 2 to 13 variables, and a mean of 5.13 variables; the main adjusted variables were age, sex and smoking.

Table 1 - Evaluation of methodological quality of studies by the MINORS instrument

	A	B	C	D	E	F	G	H	I	J	K	L	Score
Studies	**Non-comparative studies**												
Hujoel PP, et al. (2003)	2	1	2	1	0	2	0	0	#	#	#	#	8
Arora M, et al. (2010)	2	2	2	2	1	2	0	0	#	#	#	#	11
Söder B, et al. (2011)	1	1	1	1	1	2	2	0	#	#	#	#	9
Virtanen E, et al. (2014)	2	2	1	1	1	2	2	1	#	#	#	#	12
Mai X, et al. (2015)	2	2	2	2	1	1	2	0	#	#	#	#	12
Freudenheim JL, et al. (2016)	2	2	2	2	2	1	1	1	#	#	#	#	13
Nwizu NN, et al. (2017)	2	2	2	2	2	2	2	1	#	#	#	#	15
Michaud DS, et al. (2018)	2	2	2	1	2	2	1	1	#	#	#	#	13
Comparative studies													
Chung SD, et al. (2016)	2	2	2	2	2	2	2	2	2	2	2	2	24
Sfreddo CS, et al. (2017)	2	2	2	2	2	2	2	1	2	2	2	2	23
Jia M, et al. (2020)	2	2	2	2	2	2	2	2	2	2	2	2	24
Vieira RAC, et al. (2023)	2	2	2	2	2	2	2	2	2	2	2	2	24

Note: MINORS criteria.
- 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate)
- A: a clearly stated aim; B: inclusion of consecutive patients; C: prospective collection of data; D: endpoints appropriate to the aim of the study; E: unbiased assessment; F: follow-up period appropriate to the aim of the study; G: loss to follow up less than 5%; H: prospective calculation of the study size; I: an adequate control group; J: contemporary groups; K: baseline equivalence of groups; L: adequate statistical analyses.
The index classifies studies according to their scores as poor (≤ 5), reliable (6-10) or good (≥11).
Source: Pirola WE, et al., 2024.

Table 2 - Summary of the results evaluated in meta-analysis.

Studies	Control		Cases - Periodontal disease	
	Patients	Breast Cancer	Patients	Breast Cancer
Hujoel PP, et al. (2003)	6,862	79	1,006	19
Arora M, et al. (2010)	8,433	531	451	27
Söder B, et al. (2011)	1,676	24	286	5
Anwar A, et al. (2013)	200	-	200	-
Virtanen E, et al. (2014)	838	46	125	19
Mai X, et al. (2015)	1,337	89	1,022	70
Chung SD, et al. (2016)	20,206	367	-	203
Freudenheim JL, et al. (2016)	73,737	2,124	19,262	1,508
Dizdar O, et al. (2017)	151	-	-	5
Nwizu NN, et al. (2017)	65,869	2,416	17,103	714
Sfreddo CS, et al. (2017)	201	67	40	21
Michaud DS, et al. (2018)	4,088	202	2,850	104
Güven DC, et al. (2018)	3,048	67	-	-
Jia M, et al. (2020)	49,968	3,339	10,830	772
Vieira RAC, et al. (2023)	128	64	86	52
Total**	233,215	8,981	53,061	3,311

Note: * Studies used only in literature review. **Sum excluded studies that were not analyzed in the meta-analysis. **Source:** Pirola WE, et al., 2024.

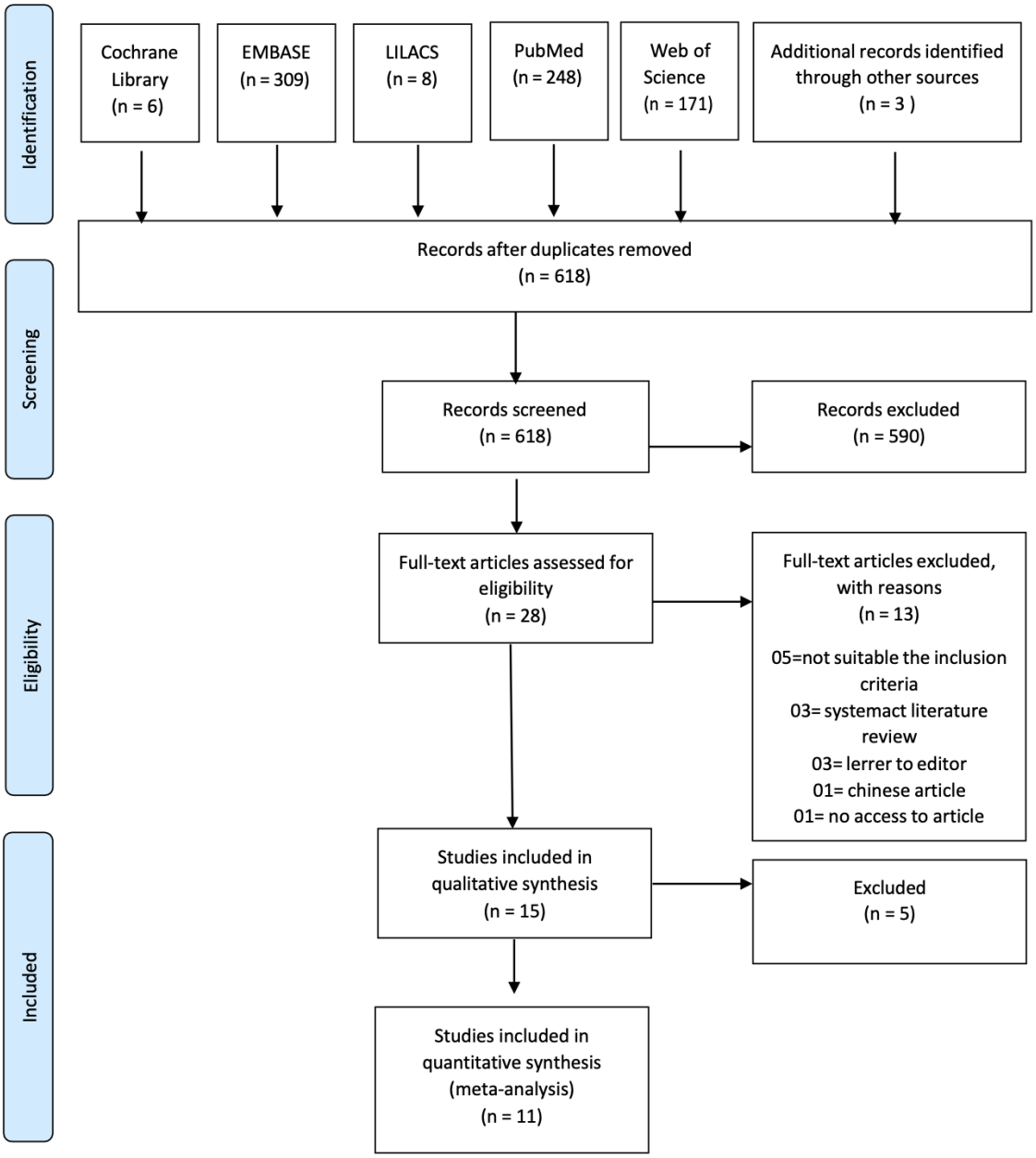
Table 3 – Studies evaluating the association of breast cancer and periodontal disease – Main characteristics.

Authors	Design	Country	Control	Periodontal Ascertainment
Hujoel PP, et al. (2003)	Prospective cohort	USA	No PD	Clinical diagnosis. Index not described
Arora M, et al. (2010)	Prospective cohort	Swedish	No PD	Self-report
Söder B, et al. (2011)	Prospective cohort	Finnish and Swedish	No PD	Group A – (n = 1597): number of remaining teeth excluding third molars; gingival index; dental plaque index Group B – (n = 1676): Not have a clinical examination
Anwar A, et al. (2013)	Case-control	Pakistani	No PD	(CPITN) Community Periodontal Index of Treatment Needs
Virtanen E, et al. (2014)	Prospective cohort	Sweden	No PD	Clinical diagnosis
Mai X, et al. (2015)	Prospective cohort	USA	No PD	Medical records - Bone loss and periodontal disease
Chung SD, et al. (2016)	Retrospect cohort	Chine	No PD	Clinical diagnosis
Freudenheim JL, et al. (2016)	Prospective cohort	USA	No PD	Self-report
Dizdar O, et al. (2017)	Retrospect cohort	Turkey	No control, use national cancer registry data	Medical records
Nwizu NN, et al. (2017)	Prospective cohort	USA	No PD	Medical records ; Self-report
Sfreddo CS, et al. (2017)	Case-control	Brazil	No PD	Clinical diagnosis; (CDC) Centers for Disease Control and Prevention; and (AAP) American Academy of Periodontology
Michaud DS, et al. (2018)	Prospective cohort	USA	No PD	Self-report ; Clinical diagnosis (CDC-AAP)
Güven DC, et al. (2018)	Prospective cohort	Turkey	No PD	Clinical diagnosis
Jia M, et al. (2020)	Prospective cohort	USA	Patients who had a sister diagnosed with breast cancer	Self-report
Vieira RAC, et al. (2023)	Case-control	Brazil	No PD	Clinical diagnosis

Note: *PD= Periodontal Disease. CP= Chronic periodontitis. RR= Risk Ratio. VA= Variables of adjustment. *Association between. **Source:** Pirola WE, et al., 2024.

The included studies were published between 2003 and 2023. In terms of study designs, 11 were prospective cohort studies, for group with methodology that includes clinical dental examination, 5 studies were included (HUJOEL PP, et al., 2003; VIRTANEN E, et al., 2014), 25, 47. Among the studies that performed clinical examinations, not all described the proposed method clearly.

Figure 1 - Study selection process.

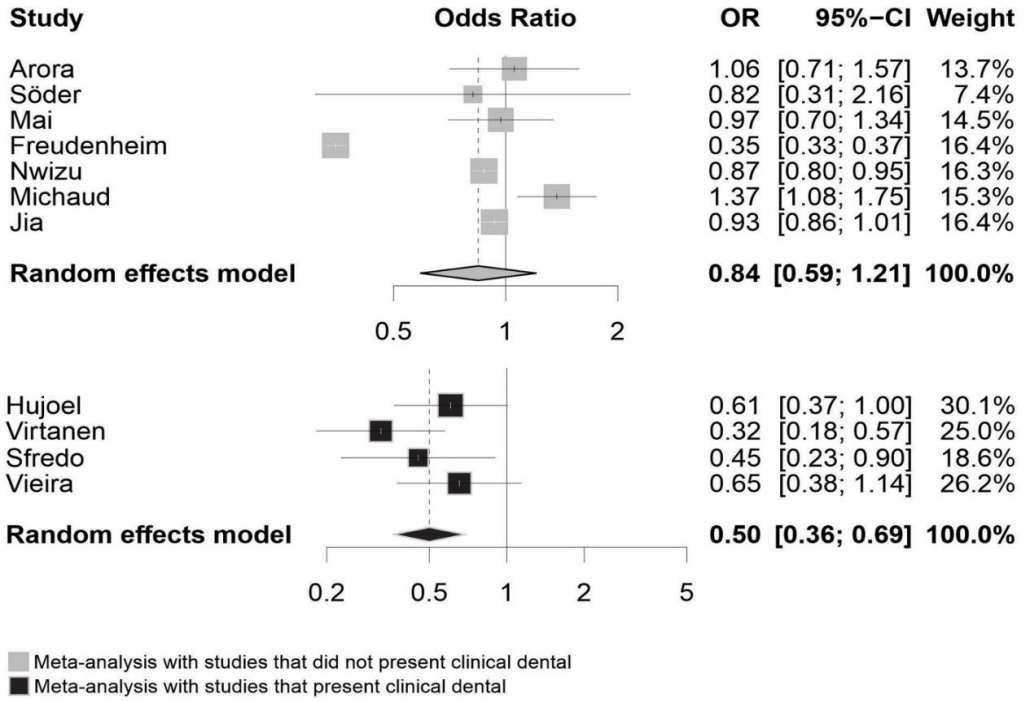


Source: Pirola WE, et al., 2024.

The periodontal evaluations of patients were not uniform among the studies, and 3 studies collected data only through patient self-reports (ARORA M, et al., 2010; FREUDENHEIM JL, et al., 2016; JIA M, et al., 2020). Two others combined self-reporting with data from medical records (NWIZU NN, et al., 2017) or clinical examinations (MICHAUD DS, et al., 2018). The method used to classify PD was described in 6 studies, which presented differences. Söder B, et al. (2011), evaluated the gingival index and plaque index in 1 group, whereas Anwar A, et al. (2013) used the Community Periodontal Index for Treatment Needs (CPITN), and Mai X, et al. (2015), classified patients according to bone loss assessed by radiographic examinations.

In case-control studies Sfreddo C, et al. (2017), and Michaud DS, et al. (2018), used 2 parameters: those of the Centers for Disease Control and Prevention (CDC) and American Academy of Periodontology (AAP). In a recent Brazilian study, researchers used classification of periodontal disease according to the AAP (VIEIRA RAC, et al., 2023).

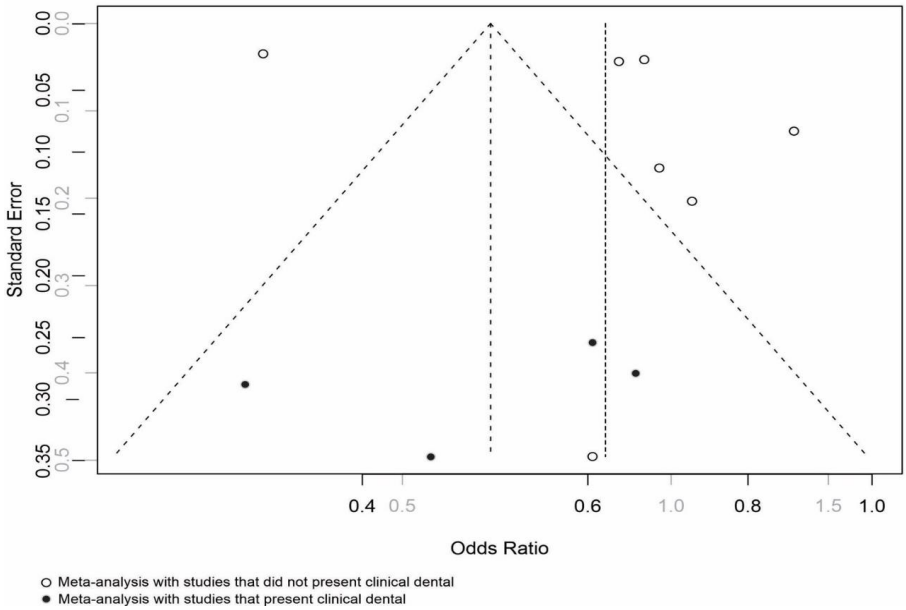
Figure 2 - Overall result of meta-analysis. OR and CI.



Source: Pirola WE, et al., 2024.

The data from the meta-analysis with seven studies that did not present clinical dental examination suggested that women without PD have a 0.85-fold decreased risk of developing breast cancer compared to women with PD (OR = 0.84, 95% CI = 0.59 – 1.21; I^2 = 99%, p<0.35; **Figure 2**).

Figure 3 - Funnel plot for publication bias.



Source: Pirola WE, et al., 2024.

Data from four studies that presented clinical dental evaluation, suggested that women without PD have a 0.50-fold decreased risk of developing breast cancer compared to women with PD (OR = 0.50, 95% CI = 0.36 – 0.69, I^2 = 20%, p<0.01; **Figure 2**). Visual inspection of the funnel plot shows the degree of publication bias (**Figure 3**).

Based on the quality of the studies described in **Table 1** using MINORS, 2 studies presented a comparative methodology (JIA M, et al., 2020; SFREDDO CS, et al., 2017). The other studies did not present a comparative methodology and had a mean score of 11.623 (ARORA M, et al., 2010; FREUDENHEIM JL, et al., 2016; HUJOEL PP, et al., 2003; MAI X, et al., 2015; MICHAUD DS, et al., 2018; NWIZU NN, et al., 2017; SODER B, et al., 2011; VIRTANEN E, et al., 2014). There was not any study classified as having poor quality.

DISCUSSION

When PD is independently evaluated, it is characterized by chronic inflammation associated with infection, which causes destruction of the supporting bone of the tooth and, in more severe cases, can lead to tooth loss (SODER B, et al., 2011).

Inflammatory processes have a causative microorganism, and PD in particular is associated with a number of bacteria's (TIETZE K, et al., 2006). Although PD is a local inflammatory disease, studies have indicated that patients with active PD have systemically elevated inflammatory marker levels (AMABILE N, et al., 2008).

PD has been shown to be a broad term that may be subjectively or objectively assessed and can range from self-assessed issues to tooth loss (CORBELLA S, et al., 2018; MICHAUD DS, et al., 2017). The prevalence of PD increases is greater with increased age, lower income (SEERIG LM, et al., 2015) and smoking, and many confounding factors have been observed. This lack of standardization may lead to potential differences among studies and results, a factor that should be considered when evaluating study results.

Several other benign diseases are associated with PD, including atherosclerosis, adverse pregnancy outcomes, rheumatoid arthritis, pneumonia (HAN YW, et al., 2014), Alzheimer's disease (DOMINY SS, et al., 2019), osteoporosis, systemic infections and inflammation (SHAO J, et al., 2018), cardiovascular disease, ischemic stroke and peripheral vascular disease, among others (GONZALEZ-NAVARRO B, et al., 2017; LEIRA Y, et al., 2017; WANG H, et al., 2019), in many of these pathologies, age and smoking are confounding factors. Cancer has been shown to be associated with PD; however, the present review included studies in which several adjustment factors were used, the main ones being sex, age, race and smoking or alcohol use (CORBELLA S, et al., 2018).

The differences in the number and the presence of adjustment variables were remarkable; they ranged from the absence of adjustments to the use of 14 adjustment variables, the main ones being age, sex, smoking, education, race/ethnicity, alcohol, diabetes, geographic location, employment, hypertension, visits to the dentist, occupational risk, marital status, tooth loss and consumption of vegetables (MAISONNEUVE P, et al., 2017; WANG H, et al., 2020; YAO QW, et al., 2014; YE L, et al., 2016; YIN XH, et al., 2016; ZENG XT, et al., 2013; ZENG XT, et al., 2016), furthermore, different adjustments were observed depending on the study and tumor type, and different adjustments were used for similar tumor types. The type of adjustment can influence the results, a factor that should be noted when evaluating a study.

PD has been associated with several cancer sites, and the main associated cancer types are lung, oral, head and neck, gastric, pancreatic and breast cancer. No association has been observed with bladder cancer (NWIZU; WACTAWSKI-WENDE; GENCO, 2020; XIE; JIN; LENG; WANG *et al.*, 2018) . However, no studies have evaluated a potential relationship between PD and thyroid, kidney or brain cancer, tumors in which potential external factors may be minimized.

Regarding breast cancer, a number of factors are already well-established as associated with risk. Such factors include obesity, especially in the climacteric period; exposure to ionizing radiation; increased life expectancy, as breast cancer is more common in women over 40 years of age; exposure to estrogen throughout reproductive life, characterized mainly by early menarche and late menopause (WANG H, et al.,

2019); shorter breastfeeding duration (HOWELL A, et al., 2014); smoking (BOYLE P e BOFFETTA P, 2009) and drinking (LUO J, et al., 2011), and the use of oral contraceptives and hormone replacement therapy during menopause (DALL GV e BRITT KL, 2017). PD is another factor, but we must take into account that both PD and breast cancer are complex and multifactorial, making it essential to remove or calibrate the maximum number of confounding factors; studies must be evaluated carefully, and adjustments and associated risk factors must be considered.

Three meta-analyses in the literature have evaluated the association of PD/tooth loss with breast cancer. Michaud DS, et al. (2017), evaluated 5 studies and observed a possible association between PD and/or tooth loss with tumor development (relative risk [RR] = 1.33, 95% CI: 1.19-1.49, I2 = 0.0%) (MICHAUD DS, et al., 2017), but of these studies, only 2 indicated an association between PD and breast cancer cancer (FREUDENHEIM JL, et al., 2016).

Shi T, et al. (2018), evaluated 8 studies and observed a modest association (RR = 1.18, 95% CI: 1.11–1.26, I2 = 17.6%). Different adjustments were performed in each study; the main adjustment factors were age, body mass index, sex, education, income, socioeconomic status, employment, smoking and diabetes (CHUNG SD, et al., 2016; SHI T, et al., 2018), and each study adjusted for at least 1 variable; however, that review also included 2 studies that did not present enough data to allow OR calculations to be performed (CHUNG SD, et al., 2016; DIZDAR O, et al., 2017).

Shao J, et al. (2018), evaluated 11 studies and observed an association (RR = 1.22, 95% CI: 1.06-1.90, I2 = 51.40%) (SHAO J; , et al., 2018), however, that meta-analysis also included 2 studies without sufficient data to allow OR to be calculated (CHUNG SD, et al., 2016; DIZDAR O, et al., 2017), a study involving data from cancer survivors (HAN, 2018) and a study that evaluated the mortality of patients with cancer associated with PD (HEIKKILA P, et al., 2003).

Two years have passed since the last review; because the lack of standardization in periodontal examinations and the use of self-reported data are biases that should be considered when evaluating the results, the performance of a new evaluation using more rigid criteria is justified.

The present systematic review included 15 studies, 11 of which were included in the meta-analysis and most of which presented data that supported the association between breast cancer and PD. Nevertheless, the investigations exhibit considerable methodological heterogeneity. Consequently, our proposed methodology entails segregating the outcomes into two distinct categories: one comprising exclusively of studies involving clinical dental assessments and the other encompassing alternative research methodologies. Among the studies that present clinical dental assessment methodology, it was possible to observe that patients without active periodontal disease had a lower risk of developing breast cancer.

Among the studies that showed a possible positive association, Hujoel PP, et al. (2003), performed a clinical examination but did not report which indices were measured during data collection; the authors showed this association when classifying PD, gingival disease and edentulism, and the cohort groups were classified according to age and sex.

Two studies evaluated a potential association with genetic causes. In a study of 15,333 participants, potential genetic causes were adjusted for twinship, and the authors noted several factors that could impact the results, such as age, education, employment, number of siblings, smoking, partner smoking, drinking, diabetes and body mass index (ARORA M, et al., 2010).

In the second study, 49,968 participants with a prior diagnosis of breast cancer were evaluated and paired with their siblings, and no association was observed between PD and breast cancer cancer (JIA M, et al., 2020). However, in both sibling studies, data regarding PD were self-reported, which may represent another source of bias.

Therefore, a meta-analysis was necessary to examine the results of studies that performed evaluations related to such risk factors. In our study, grouping articles that clinically evaluated patients, a mean 0.5-fold decrease in the development of breast cancer was identified in women without PD, compared to women with

active PD. We must consider 5 studies (ARORA M, et al., 2010; HUJOEL PP, et al., 2003; MAI X, et al., 2015; MICHAUD DS, et al., 2018; JIA M, et al., 2020) that did not come to the conclusion of a relationship between breast cancer and PD. Mai X et al. (2005), conducted a prospective cohort study that evaluated data from medical records; no evaluations were performed directly on patients. Michaud DS, et al. (2018), used clinical data and self-reported information.

When we evaluated the studies that performed clinical evaluations of patients (HUJOEL PP , et al., 2003; SFREDDO CS, et al., 2017; SODER B, et al., 2011; VIRTANEN E, et al., 2014), we determined that all of them found a positive association between PD and breast cancer. However, only 2 studies described the method used for periodontal evaluation (SFREDDO CS, et al., 2017; SODER B, et al., 2011).

Limitations related to the criteria for defining PD and the variables used for adjustment may have influenced the results, as demonstrated by the funnel plot visual scale, which indicates that heterogeneity and bias were present among the selected studies. This indicates the need for further prospective studies with well-defined criteria for PD and to control for potential confounding factors to determine the real impact of the association between PD and breast cancer.

FINAL CONSIDERATIONS

A meta-analysis of current studies showed an association between PD and breast cancer. Studies that evaluated PD clinically through dental parameters showed a greater decrease in the number of patients with breast cancer and periodontal disease, compared to studies that obtained results from evaluating PD using other methods. As the quality of the studies was heterogeneous, more studies with improved methods are needed to better quantify this risk.

REFERENCES

1. AMABILE N, et al. Severity of periodontal disease correlates to inflammatory systemic status and independently predicts the presence and angiographic extent of stable coronary artery disease. J Intern Med, 2008; 6: 644-652.
2. ANWAR A, et al. The linkage of gum disease with oncogenesis of breast tumor in Pakistani women - A new prospective. Pakistan Journal of Medical and Health Sciences, 2013; 7(4): 945-947.
3. ARORA M, et al. An exploration of shared genetic risk factors between periodontal disease and cancers: a prospective co-twin study. Am J Epidemiol, 2010; 171(2): 253-259.
4. BOYLE P and BOFFETTA P. Alcohol consumption and breast cancer risk. Breast Cancer Res, 2009; 11(3): S3.
5. BRAY F, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin, 2018; 68(6): 394-424.
6. CHUNG SD, et al. A population-based study on the associations between chronic periodontitis and the risk of cancer. Int J Clin Oncol, 2016; 21(2): 219-223.
7. COLLABORATIVE GROUP ON HORMONAL FACTORS IN BREAST CANCER. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. Lancet, 2002; 360(9328): 187-195.
8. CORBELLA S, et al. Is periodontitis a risk indicator for cancer? A meta-analysis. PLoS One, 2018; 13(4): e0195683.
9. DALL GV and BRITT KL, Estrogen Effects on the Mammary Gland in Early and Late Life and Breast Cancer Risk. Front Oncol, 2017; 7: 110.
10. DIZDAR O, et al. Increased cancer risk in patients with periodontitis. Mol Cancer, 2017; 33(12): 2195-2200.
11. DOMINY SS, et al. Porphyromonas gingivalis in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors. Sci Adv, 2019; 5(1): eaau3333.

12. FREUDENHEIM JL, et al. Periodontal Disease and Breast Cancer: Prospective Cohort Study of Postmenopausal Women. Cancer Epidemiol Biomarkers Prev, 2016; 25(1): 43-50.
13. GAO S, 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.
14. GONZALEZ-NAVARRO B, et al. Relationship between cardiovascular disease and dental pathology. Systematic review. Med Clin (Barc), 2017; 149(5): 211-216.
15. GUVEN DC, et al. Evaluation of cancer risk in patients with periodontal diseases. Journal of Clinical Oncology, 2018; 36(15): Conference Abstract.
16. HAN YW, et al. Periodontal disease, atherosclerosis, adverse pregnancy outcomes, and head-and-neck cancer. Adv Dent Res, 2014; 26(1): 47-55.
17. HEIKKILA P, et al. Inhibition of matrix metalloproteinase-14 in osteosarcoma cells by clodronate. Journal of Surgical Research, 2003; 111(1): 45-52.
18. HOWELL A, et al. Risk determination and prevention of breast cancer. Breast Cancer Res, 2014; 16(5): 446.
19. HUJOEL PP, et al. An exploration of the periodontitis-cancer association. Ann Epidemiol, 2003; 13(5): 312-316.
20. INSTITUTO NACIONAL DO CÂNCER (INCA). Estimativa 2020 - Incidência de Câncer no Brasil. 2019. Disponível em: https://www.inca.gov.br/sites/ufu.sti.inca.local/files//media/document//estimativa-2020-incidencia-de-cancer-no-brasil.pdf. Acessado em: 25 de outubro de 2023.
21. JIA M, et al. The association between periodontal disease and breast cancer in a prospective cohort study. Cancer Prev Res (Phila), 2020 13(12):1007-1016.
22. JIAN W, et al. Clinical and genetic characterization of hereditary breast cancer in a Chinese population. Hereditary Cancer in Clinical Practice, 2017; 15(19): 1-9.
23. KINANE DF, et al. Periodontal diseases. Nat Rev Dis Primers, 2017; 22(3): 17038.
24. LEIRA Y, et al. Association between periodontitis and ischemic stroke: a systematic review and meta-analysis. Eur J Epidemiol, 2017; 32(1): 43-53.
25. LUO J, et al. Association of active and passive smoking with risk of breast cancer among postmenopausal women: a prospective cohort study. BMJ, 2011; 342: d1016.
26. MACCIO A and MADEDDU C. The role of interleukin-6 in the evolution of ovarian cancer: clinical and prognostic implications--a review. J Mol Med (Berl), 2013; 91(12): 1355-1368.
27. MAI X, et al. Periodontal disease severity and cancer risk in postmenopausal women: the Buffalo OsteoPerio Study. Cancer causes and Control, 2015; 27(2): 217-228.
28. MAISONNEUVE P, et al. Periodontal disease, edentulism, and pancreatic cancer: a meta-analysis. Ann Oncol, 2017; 28(5): 985-995.
29. MICHAUD DS, et al. Periodontal Disease, Tooth Loss, and Cancer Risk. Epid Rev, 2017; 39(1): 49-58.
30. MICHAUD DS, et al. Periodontal Disease Assessed Using Clinical Dental Measurements and Cancer Risk in the ARIC Study. J Natl Cancer Inst, 2018; 110(8): 843-854.
31. MOHER D, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol, 2009; 62(10): 1006-1012.
32. NWIZU NN, et al. Periodontal disease and cancer: Epidemiologic studies and possible mechanisms. Periodontol 2000, 2020; 83(1): 213-233.
33. NWIZU NN, et al. Periodontal Disease and Incident Cancer Risk among Postmenopausal Women: Results from the Women's Health Initiative Observational Cohort. Cancer Epidemiol Biomarkers Prev, 2017; 26(8): 1255-1265.
34. SAHINGUR SE and YEUDALL WA. Chemokine function in periodontal disease and oral cavity cancer. Front Immunol, 2015; 6: 214.
35. SEERIG LM, et al. Tooth loss in adults and income: Systematic review and meta-analysis. J Dent, 2015; 43(9): 1051-1059.
36. SFREDDO CS, et al. Periodontitis and breast cancer: A case-control study. Community Dent Oral Epidemiol, 2017; 45(6): 545-551.

37. SHAO J, et al. Periodontal disease and breast cancer: A meta-analysis of 1,73,162 participants. Frontiers in Oncology, 2018; 8:601.
38. SHI T, et al. Periodontal disease and susceptibility to breast cancer: A meta-analysis of observational studies. J Clin Periodontol, 2018; 45(9): 1025-1033.
39. SLIM K, et al. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg, 2003; 73(9): 712-716.
40. SODER BPeriodontal disease may associate with breast cancer. Breast Cancer Res Treat, 2011; 127(2): 497-502.
41. TAZAWA PS, et al. Obesidade, um possível indicador de risco para a doença periodontal? [Obesity, a possible risk indicator for periodontal disease?]. Archives of Oral Research, 2011; 7(3): 311-320.
42. TIETZE K, et al. Differences in innate immune responses upon stimulation with gram-positive and gram-negative bacteria. J Periodontal Res, 2006; 41(5): 447-454.
43. VIEIRA RAdC, et al. Periodontal disease as a risk factor for breast cancer: A case-control study based on a comprehensive clinical periodontal evaluation Mastology 33, Supplement 1, 2023; BBCS Brazlian Breast Cancer Symposium 2023: in Press.
44. VIRTANEN E, et al. History of Dental Infections Associates with Cancer in Periodontally Healthy Subjects: A 24-Year Follow-Up Study from Sweden. Journal of Cancer, 2014; 5(2): 79-85.
45. WANG H, et al. Breast tissue, oral and urinary microbiomes in breast cancer. Oncotarget, 2017; 8(50): 88122-88138.
46. WANG J, et al. The risk of periodontitis for peripheral vascular disease: a systematic review. Rev Cardiovasc Med, 2019; 20(2): 81-89.
47. WANG J, et al. Relationship between periodontal disease and lung cancer: A systematic review and meta-analysis. J Periodontal Res, 2020; 55(5):581-593.
48. XIE WZ, et al. Periodontal Disease and Risk of Bladder Cancer: A Meta-Analysis of 298476 Participants. Front Physiol, 2018; 9: 979.
49. YAO QW, et al. Association of periodontal disease with oral cancer: a meta-analysis. Tumour Biol, 2014; 35(7): 7073-7077.
50. YE L, et al. Correlation between periodontal disease and oral cancer risk: A meta-analysis. J Cancer Res Ther, 2016; 12(Supplement): C237-C240.
51. YIN XH, et al. Association between Tooth Loss and Gastric Cancer: A Meta-Analysis of Observational Studies. PLoS One, 2016; 11(3): e0149653.
52. ZENG XT, et al. Periodontal disease and risk of head and neck cancer: a meta-analysis of observational studies. PLoS One, 2013; 8(10): e79017.
53. ZENG XT, et al. Periodontal Disease and Incident Lung Cancer Risk: A Meta-Analysis of Cohort Studies. J Periodontol, 2016; 87(10): 1158-1164.