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Evaluation of breast cancer and its relation with periodontal diseases: An original research

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***Abstract*---**Introduction: The aim of this case-control study was to evaluate the association between periodontitis and breast cancer in a sample of adult Brazilian women. Material and Methods: This was a hospital-based study, which included 67 cases and 134 controls (1:2). Women were selected consecutively between April, 2013 and June, 2015 among those attending the Department of Gynecology at the University Hospital of Santa Maria. Cases were selected among women

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diagnosed with breast cancer (ICD-10 C50), and controls were matched for age (T2 years), and smoking status (never, former and current smoker). Conditional logistic regression was used to model the association between periodontitis and breast cancer with and without adjustment for potential confounders. Four case definitions for periodontitis were used. Results: Cases had significantly greater clinical attachment loss than controls (*P*=.04). After adjusting for important covariates, women diagnosed with periodontitis had two to three times higher odds of breast cancer than women without periodontitis depending on the case definition of periodontitis (*P*<.05). Conclusions: A significant association was observed between periodontitis and breast cancer.

***Keywords*---**Breast Cancer, Observational Study, Periodontal Diseases, Periodontitis.

Introduction

Breast cancer is an important public health problem. Global estimates indicate that it is the second most common cancer in the world, and the most frequent cancer among women, with more than 1.5 million new cases diagnosed yearly.[1] The incidence rate among women is on the rise, and this is due to an earlier age of menarche, later age of first pregnancy, fewer pregnancies, shorter periods of breastfeeding and later menopause.[2] Other known risk factors for breast cancer are also increasing, including obesity, alcohol use and lack of physical activity.[3] Recent studies have investigated a possible association between periodontitis and breast cancer. Using data derived from the NHANES I Epidemiology Follow-up Study, Hujoel et al.[4] found no association between breast cancer and gingivitis, periodontitis or tooth loss.

Similarly, Mai et al.[5] using data from the buffalo osteoporosis and periodontal disease study observed no association between periodontal pathogens and breast cancer among postmenopausal women. By contrast, two prospective studies[6,7] have between observed associations periodontal disease and breast cancer. Eder et al.[6] reported a significant association between periodontal disease/tooth loss and breast cancer. Freudenheim et al.[7] observed a higher risk of breast cancer among study participants who self-reported having periodontal disease using data from 73 737 postmenopausal women followed up for 6.7 years. These conflicting findings might be explained, at least in part, by differences in study design, adjustment for confounders, periodontal assessment, and sample size, that is a small number of breast cancer cases.

Several hypotheses have been proposed to explain a possible association between periodontitis and cancer, but the underlying biological mechanisms remain unclear. The most frequently advocated biological plausibility is that persistent periodontal infection and inflammation induce a systemic chronic inflammatory state, which could act in a protumour fashion at distant sites.[8-10] Nevertheless, it is important to acknowledge that cancer, including breast cancer and periodontitis have common risk factors, which could also help explain this

association. Irrespective of the nature of this relationship—causal or co-occurrence—a confirmed association between these diseases would help inform health promotion initiatives for women at higher risk of breast cancer or already diagnosed with the disease.

There is limited and inconsistent evidence on the association between periodontitis and breast cancer. The aim of this case-control study was to evaluate that possible association in a sample of adult Brazilian women. Our hypothesis was that women diagnosed with periodontitis would have a significantly higher odds of having breast cancer than periodontally healthy controls.

Materials and Methods

This study used a hospital-based matched case-control design. Controls were selected from women without a previous diagnosis of breast cancer or any other cancer affecting the genitourinary tract who were receiving regular gynaecological care, including diagnosis of genitourinary infections and prevention of cervical and breast cancer (Papanicolau test and breast cancer screening), at the gynaecology and menopause clinic. Cases and controls were matched by age (T2 years) and smoking status. A sample size of 201 women (67 cases and 134 controls) was estimated to be necessary to observe a significant association between periodontitis and breast cancer. Full-mouth periodontal clinical examination was carried out at six sites per tooth (mesiobuccal, buccal, distobuccal, mesiolingual, lingual and distal-lingual), excluding third molars. The Plaque Index (PlI),[15] Gingival Index,[16] periodontal probing depth (PPD), bleeding on probing (BOP) and clinical attachment level (CAL) were recorded. $P<0.05$ was considered as significant.

Results

A total of 67 cases and 134 controls completed the study. Breast cancer diagnosis was as follows: 62 cases of invasive ductal carcinoma, two invasive lobular carcinoma, one invasive ductal carcinoma with apocrine differentiation, one adenoid cystic carcinoma and one liposarcoma. Perfect matching for smoking status was achieved, and the mean age difference between cases and controls was 0.4 years. No statistically significant differences were observed between cases and controls for sociodemographic characteristics. Statistically significant differences between cases and controls were observed for parity, age at first birth, breastfeeding time and hormone replacement therapy.

No significant differences in tooth loss were observed between cases and controls. Whereas cases consistently had worse periodontal parameters than controls, statistically significant differences were observed only for plaque index and CAL.
In the unadjusted analysis, periodontitis was significantly associated with breast cancer for three of four case definitions ($P<.05$); a nonsignificant association was observed when the CDC-AAP criteria for severe periodontitis were used ($P=.06$).
Table 1

In the multivariable analysis, periodontitis was significantly associated with breast cancer irrespective of the case definition; women diagnosed with periodontitis having between two and three times higher odds of having breast cancer than women with- out periodontitis after adjusting for important covariates. Separate analyses including only never-smokers and nondrinkers confirmed these findings.

Table 1
Association between periodontitis and breast cancer. Crude and adjusted conditional logistic regression (n=201)

	No of controls with and without periodontitis	No of cases with and without periodontitis	Crude[a]			Full-model[b]			Reduced model[c]		
			OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Model 1-Generalized severe periodontitis	21/113	19/48	2.02	1.02-4.01	.04	2.72	1.18-6.27	.02	2.61	1.16-5.84	.02
Model 2-CDC-AAP severe periodontitis	27/107	22/45	1.84	0.97-3.47	.06	2.10	1.00-4.43	.05	2.11	1.02-4.37	.04
Model 3-Mean CAL in mm (log)	NA	NA	1.93	1.02-3.67	.04	3.63	1.52-8.70	.004	3.44	1.50-7.92	.004
Model 4-Percentage of sites with CAL ≥5 mm (10% increments)	NA	NA	1.16	1.01-1.34	.03	1.28	1.08-1.52	.005	1.27	1.08-1.5	.005

Discussion

This case-control study evaluated the association between periodontitis and breast cancer in a sample of adult Brazilian women. Women diagnosed with periodontitis had two to three times higher odds of breast cancer than women without periodontitis after adjusting for important covariates. An association between periodontitis and breast cancer has been reported previously in two longitudinal studies. So€der et al.[6] using data from 1676 individuals followed up for 18 years, observed a 2.3 (95% CI 1.07-5.21) higher odds of breast cancer among those women with periodontal disease and loss of mandibular molars. Freudenhaim et al.[7] used data from 73 737 post- menopausal women participating in the Women's Health Initiative Observational Study. After a mean follow-up of 6.7 years, women who self-reported periodontal disease had a 14% (95% CI=1.05-1.77) higher risk of breast cancer than those without self-reported periodontal disease. However, it is important to acknowledge that self-reporting may lead to misclassification of exposure to periodontitis, which would affect the strength of this association. In contrast, Hujoel et al.[4] analysed data of 11 328 individuals followed up between 11 and 21 years during the NHANES I follow- up study, and observed that individuals with periodontitis had a higher odds of death due to cancer. Recently, Mai et al.[5,21] evaluated data of 1337 postmenopausal women participating in the Osteo- Perio Study (mean follow-up: 12.2 years). No associations were observed between radiographic alveolar bone loss or presence of periodontal pathogens and total or site-specific incidence of cancer including breast cancer. Contradictory findings among studies may be explained, at least in part, by differences in methodology, time of follow-up, and sample size. In contrast to the present study, which used a full-mouth six sites

per tooth periodontal assessment, other studies have used partial recording,[4,6] radiographic assess- ments[5] or self-reported periodontal disease.[7] Additionally, some studies[4,6] had a limited number of breast cancer cases, which may have affected the study power.

The true biological mechanisms underlying a possible association between periodontitis and cancer have yet to be established. Periodontitis is an inflammatory disease caused by an oral biofilm with local and systemic effects.[20,21] Increasing evidence supports the impact that periodontitis has on systemic inflammation, and that oral pathogens can colonize distant sites.[23] The strengths of this study include a comparable source of cases and controls, a moderate sample size of breast cancer cases, appropriate diagnosis of breast cancer and periodontitis, and appropriate adjustment for possible confounders.

Case-control studies are a very efficient study design for the investigation of diseases with low prevalence in that thousands of women would have to be screened in order to identify 67 cases of breast cancer. Periodontal diagnosis was based on a full- mouth, six sites per tooth clinical examination performed by calibrated periodontists. Additionally, established case definitions based on CAL or CAL in combination with PPD were used in the analysis. Two strategies were used to minimize bias and confounding. First, cases and controls were matched by age and smoking status. Secondly, data regarding several risk factors and potential confounders were collected and entered in the multivariable model to estimate adjusted ORs.

The weaknesses of this study are related to limitations associated with the study design, including differential recall bias between cases and controls, representativeness of our sample, and lack of distinction between prevalent and incident cases. Case-control studies do not allow for the establishment of causality as the temporal relationship between the exposure and outcome is hard to determine. Similarly, reverse causality cannot be ruled out as breast cancer or its treatment may have had a negative impact on periodontal health.[21] Thus, prospective studies are necessary to confirm our findings. For this study, cases and controls were selected from the same hospital population, which greatly improves logistics but may have introduced bias. To minimize the risk of selection bias, controls were selected independently of the exposure, and important confounders were taken into consideration through matching or statistical analysis. No significant differences were observed for educational level and household income between cases and controls, and the prevalence of periodontitis among controls is within range for this population, which seems to indicate that the risk of bias has been reduced. The inclusion of prevalent cases allowed women with varying length of time since breast cancer diagnosis to participate. It also only allowed for the assessment of the participants' periodontal status at the time of enrolment in the study, which prevents a determination on whether periodontitis preceded breast cancer onset. Nevertheless, stratified analysis according to the median time since diagnosis (33 months) yielded similar OR estimates for all periodontitis case definitions. In regard to the present OR estimates, it is important to acknowledge that the lower bound of the confidence intervals was very close to one for two of four multivariable estimates, and that

the confidence intervals for all estimates were some- what wide indicating uncertainty in our findings.

Self-reported alcohol use was not statistically significant in the univariable models (*P*=.85) and it was not considered a confounder in the multivariable analyses. Furthermore, exploratory analyses excluding women who self-reported alcohol use did not reveal major changes in the estimates. Obesity was statistically significant associated with the outcome in the multi- variable analyses; thus, BMI was entered in all multivariable analyses so that adjusted OR estimates for periodontitis were calculated.

Conclusion

In conclusion, our findings indicate that women with periodontitis had higher odds of breast cancer than women without periodontitis. Collectively, evidence from this and other studies underscore the need for comprehensive risk assessment, diagnosis and care of women diagnosed with breast cancer or periodontitis. A common risk factor strategy could be used to inform public healthy policy- making to benefit oral and general health.

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