

# Effect Modification by Age and Comorbidities on the Association Between Periodontitis and Female Breast Cancer: A Population-based Case-control Study

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## Research article

**Keywords:** breast cancer, periodontitis

**Posted Date:** March 17th, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-310502/v1>

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# Abstract

**Background:** The association between periodontitis and female breast cancer is not clear. The purpose of this study is to assess that periodontitis was associated with the risk of female breast cancer.

**Methods:** Using claims data taken from the 1997–2013 Taiwanese National Health Insurance Research Database (NHIRD), we identified 60,756 newly-diagnosed female breast cancer patients during the period 2003–2013 from all beneficiaries. We then randomly selected 243,024 women without breast cancer matching (1:4) for age and the year of the index date during 1997–2013 from a one million representative population acting as the control group. A conditional logistic regression analysis was used to examine the association between periodontitis and the risk of breast cancer, shown as an odds ratio (OR) with a 95% confidence interval (CI) after adjustments for the Charlson Comorbidity Index (CCI), geographic region and level of urbanization.

**Results:** The mean  $\pm$  standard deviation age was  $53 \pm 14$  years. After adjusting for potential confounders, the risk of female breast cancer was found to be associated with a history of periodontitis (OR, 1.12; 95% CI, 1.10–1.14). Such an association was significantly different between patients aged  $< 65$  years (OR, 1.09; 95% CI, 1.06–1.11) and patients aged  $\geq 65$  years (OR, 1.23; 95% CI, 1.18–1.28;  $p$  for interaction  $< 0.001$ ), as well as between patients where the CCI = 0 (OR, 1.17; 95% CI, 1.15–1.20) and patients with CCI  $> 0$  (OR, 0.99; 95% CI, 0.96–1.03;  $p$  for interaction  $< 0.001$ ). The highest level of urbanization was also associated with the risk of breast cancer.

**Conclusions:** This nationwide, population-based case-control study demonstrated that periodontitis was significantly associated with the risk of female breast cancer and such an association was modified by both age and comorbidities.

## Background

Female breast cancer is one of the most common malignancies among women worldwide [1]. In Taiwan, the age-standardized incidence rate of female breast cancer per 100,000 persons was 44.5 and significantly increased during 2000–2006 [2], with the mean hospital treatment cost and length of stay also having increased [3]. Prior studies have shown that the age of menarche, pregnancy, breastfeeding, late menopause, obesity, alcohol use and lack of physical activity were risk factors for breast cancer [4, 5], and a recent study has demonstrated that BRCA mutation carriers experience more severe disease and poorer outcomes [6].

Periodontitis is a chronic oral inflammation condition which is altered by microbiota and the microenvironment [7]. Several reports have shown the association between periodontitis and various chronic inflammatory diseases, including coronary heart disease, stroke, pneumonia, chronic obstructive pulmonary disease, chronic kidney disease, and diabetes mellitus [7–10], which may be due to an altered immune cell function [11–13]. Because immune cell function is affected by periodontitis, this response may theoretically correlate with the development of cancer. Certain studies have demonstrated that

periodontitis has also been revealed as having an association with an increased risk of several cancers, including esophageal cancer, head and neck cancer, as well as lung cancer [14–18].

In Taiwan, the prevalence of periodontitis also significantly increased from 11.5–19.59% during the period 1997 to 2013 [19]. The available data regarding the association between periodontitis and breast cancer is limited. To the best of our knowledge, only 2 cohort studies [20, 21] with small sample sizes have been reported. Soder et al. [20] revealed that severe periodontal disease increased the risk of breast cancer, while Sfreddo et al. [21] found there was a significant association between periodontitis and breast cancer. However, no population-based study with a large sample size has investigated the relationship. The data from the Taiwanese Health Insurance Research Database (NHIRD) is available for nationwide, population-based studies. Therefore, in this study we used data taken from the NHIRD to assess the relationship between periodontitis and female breast cancer.

## **Materials And Methods**

### **Ethics statement**

The study was permitted by the Institutional Review Board (IRB) of Taichung Veterans General Hospital (IRB Number: CE17100B).

The requirement for informed consent was waived given that personal information was anonymized.

### **Study design**

This study was a nationwide, population-based case-control study.

### **Data source**

The study data included the 1997–2013 administrative data from the NHIRD. The National Health Insurance (NHI) program currently covers over 99% of the Taiwanese population. The data found within the NHIRD includes medication prescription history, ambulatory care services, admission services and traditional medical services. Certain personal data and history data, such as body weight, body height, alcohol use, and smoking habits, are not available in the NHIRD. The National Health Research Institute (NHRI) manages the NHIRD and provides the database to researchers for research purposes after anonymization of personal information is assured.

We utilized NHIRD datasets to select newly diagnosed female breast cancer patients and matched patients found during the period 2003 to 2013. In 2000, the NHRI randomly selected and enrolled one million representative individuals from the NHIRD, establishing the Longitudinal Health Insurance Database (LHID2000). We selected non-breast cancer comparison cohorts from the population found in the LHID2000. We used LHID2000 claims data from 2003 to 2013 for analysis of the comparison cohorts.

# Identification of female breast cancer patients from the entire Taiwanese population

Female breast cancer patients were defined as those having a Catastrophic Illness Certificate (CIC) for breast cancer [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 174]. Using the NHIRD, we identified 87,738 newly diagnosed female breast cancer patients during the period of 2003–2013.

## Selection of matched female breast cancer patients and female non-breast cancer controls

A total of 60,756 matched patients were included in the female patient group during the period of 2003–2013. Patients who matched index date and age without the diagnosis of female breast cancer (ICD-9-CM code 174) were included in the non-breast cancer female group. There were 421,288 non-breast cancer females included in this dataset from 2003 to 2013. The ratio of female breast cancer patients and non-breast cancer females was 1:4, with a total of 243,024 patients enrolled in the matched non-breast cancer group during the period of 2003–2013.

## Definition of periodontitis

Patients with a diagnosis of periodontitis were defined as having ICD-9 code 523.3-523.5. We used the cumulative number of visits for periodontitis treatment and the cumulative cost of periodontitis related visits as proxies for the severity of periodontitis.

## Potential confounders

Potential confounders included level of urbanization and CCI. The CCI, as adapted by Deyo et al. (22), was used to represent the general level of comorbidity medical conditions. The presence of comorbidity was defined as a patient having at least three ambulatory visits or one inpatient visit with a corresponding ICD-9-CM code within 1 year prior to the index date. Sensitivity analyses were conducted based upon age (< 65 years, ≥ 65 years) and CCI.

## Dose-response relationship

In order to measure the relationship between the severity of periodontitis and breast cancer, the period between the last periodontitis visit date to breast cancer diagnosis date (ie, 0–3 months, 3–6 months, 6 months-1 year, 1–3 years, > 3 years), the number of visits required for acute or chronic periodontitis according to the 25th, 50th and 75th centiles, and the cumulative cost of acute or chronic periodontitis-related visits according to the 25th, 50th and 75th centiles were incorporated into the analysis.

## Statistical analysis

We tested the differences in the continuous variables through use of the Student's *t*-test and the categorical variables by using the Pearson's  $\chi^2$  test. A conditional logistic regression analysis was used to examine the association between periodontitis exposure and the risk of breast cancer development after

adjustment for potential confounders. This analysis involved the Charlson Comorbidity Index (CCI), geographical region (i.e., northern, southern, western and eastern) and the level of urbanization (i.e., Level 1 to 4) (23). These statistical analyses were performed using SAS statistical software, version 9.3 (SAS Institute, Inc., Cary, NC, USA). A p value less than 0.05 was considered statistically significant.

## Results

Table 1 demonstrates the demographic data of the matched female breast cancer patients and the non-breast cancer female controls. The mean  $\pm$  SD age was 53 years in both groups. Female breast cancer patients had a higher proportion of having a history of periodontitis than the control group. Most female breast cancer patients lived in the northern region, while there was a higher incidence of breast cancer in the more urbanized regions.

Table 1  
Demographic data of patients with breast cancer and non-breast cancer controls

	<b>Female Non- Breast Cancer patients</b>	<b>Female Brest Cancer patients</b>	
	(n = 243,024)	(n = 60,756)	<i>P-value</i>
<b>Age, years (mean ± SD)</b>	53 ± 14	53 ± 14	1
<b>Gingival and periodontal diseases (ICD9-CM: 523)</b>	106,081 (43.7)	28,358 (46.7)	< 0.001
Acute or chronic periodontitis (ICD9-CM: 523.3–4)	69,604 (28.6)	19,018 (31.3)	< 0.001
Chronic periodontitis (ICD9-CM: 523.4)	18,917 (7.8)	5,343 (8.8)	< 0.001
Periodontitis (ICD9-CM: 523.3–5)	94,477 (38.9)	25,357 (41.7)	< 0.001
<b>Geographic region</b>			< 0.001
Northern	124,252 (51.1)	33,455 (55.1)	
Central	44,956 (18.5)	10,593 (17.4)	
Southern	69,775 (28.7)	15,792 (26.0)	
Eastern	4,041 (1.7)	916 (1.5)	
<b>Level of urbanization</b>			< 0.001
0 most urbanization	81,755 (33.6)	23,091 (38.0)	
1	108,933 (44.8)	26,900 (44.3)	
2	35,724 (14.7)	7,680 (12.6)	
3 least urbanization	16,612 (6.8)	3,085 (5.1)	

Table 2

Comparison of previous existing periodontitis severity factors before index date between patients with breast cancer and non-breast cancer controls

	Female Non- Breast Cancer patients	Female Breast Cancer patients	
	(n = 243,024)	(n = 60,756)	<i>P</i> - <i>value</i>
<b>Last periodontitis visit date to breast cancer diagnosis date</b>			< 0.001
0–3 months	4,065 (1.7)	1,466 (2.4)	
3–6 months	4,080 (1.7)	1,201 (2.0)	
6 months–1 year	7,023 (2.9)	1,884 (3.1)	
1–3 years	19,505 (8.0)	5,162 (8.5)	
> 3 years	34,931 (14.4)	9,305 (15.3)	
<b>Number of visits for Acute or chronic periodontitis</b>			< 0.001
Q1Q2(1)	51,369 (21.1)	13,917 (22.9)	
Q3(2)	10,824 (4.5)	2,985 (4.9)	
Q4(> 2)	7,411 (3.0)	2,116 (3.5)	
<b>Cumulative cost of Acute or chronic periodontitis-related visits (US\$)</b>			< 0.001
Q1(13)	17,902 (7.4)	4,662 (7.7)	
Q2(16)	18,314 (7.5)	5,269 (8.7)	
Q3(43)	16,964 (7.0)	4,454 (7.3)	
Q4(> 43)	16,424 (6.8)	4,633 (7.6)	
<b>Comorbidity</b>			
<b>CCI group</b>	0.4 ± 1.0	1.2 ± 2.3	< 0.001
0	196,320 (80.8)	41,007 (67.5)	< 0.001
≥ 1	46,704 (19.2)	19,749 (32.5)	

Table 3  
Adjusted odds ratio with 95% confidence interval for the periodontitis

	OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
<b>Gingival and periodontal diseases</b> (ICD9-CM: 523)	1.14 (1.12–1.16)	< 0.001	1.11 (1.09–1.13)	< 0.001
Acute or chronic periodontitis (ICD9-CM: 523.3–4)	1.14 (1.12–1.17)	< 0.001	1.12 (1.10–1.14)	< 0.001
Chronic periodontitis (ICD9-CM: 523.4)	1.15 (1.11–1.18)	< 0.001	1.11 (1.07–1.15)	< 0.001
Periodontitis (ICD9-CM: 523.3–5)	1.13 (1.11–1.16)	< 0.001	1.10 (1.08–1.12)	< 0.001
Adjust for patient, CCI, geographic region, and Urban				

Table 2 compares the previously existing periodontitis severity factors prior to the index date between the patients with breast cancer and the non-breast cancer controls. After having matched the index date and ages, the period between the last periodontitis visit date to the breast cancer diagnosis date was shorter in the female breast cancer patients than in the matched non-breast cancer females ( $p < 0.001$ ). The number of visits for periodontitis treatment were more for the female breast cancer patients than in the matched non-breast cancer females ( $p < 0.001$ ). Additionally, the cumulative cost of periodontitis related visits was higher in the female breast cancer patients than in the matched non-breast cancer females ( $p < 0.001$ ). And finally, the female breast cancer patients had more comorbidities than the matched non-breast cancer females ( $p < 0.001$ ).

As shown in Table 3, the association between periodontitis and breast cancer was consistent using various definitions of periodontitis, implying that acute and/or chronic periodontitis was associated with breast cancer.

Table 4 shows the adjusted odds ratio (OR) of breast cancer. After adjusting for age and index date, the risk of female breast cancer was associated with a history of periodontitis (OR, 1.12; 95% CI, 1.10–1.14]. A short interval period between the last periodontitis visit date to the breast cancer diagnosis date (OR, 1.46; 95% CI, 1.37–1.55), more periodontitis visits (OR, 1.17; 95% CI, 1.11–1.23), a higher cumulated periodontitis-related cost (OR, 1.15; 95% CI, 1.11–1.19), and higher urbanization level were all associated with the risk of breast cancer.

Table 4

Crude and Adjusted odds ratio with 95% confidence interval for the association between the variables and periodontitis

	Crude	p value	Adjusted	p value
<b>Last periodontitis visit date to breast cancer diagnosis date</b>				
None	Ref.		Ref.	
0–3 months	1.51 (1.42–1.60)	< 0.001	1.46 (1.37–1.55)	< 0.001
3–6 months	1.23 (1.15–1.31)	< 0.001	1.20 (1.12–1.28)	< 0.001
6 months–1 year	1.12 (1.07–1.18)	< 0.001	1.10 (1.04–1.16)	< 0.001
1–3 years	1.11 (1.07–1.14)	< 0.001	1.08 (1.05–1.12)	< 0.001
> 3 years	1.11 (1.09–1.14)	< 0.001	1.10 (1.07–1.13)	< 0.001
<b>Number of visits for Acute or chronic periodontitis</b>				
None	Ref.		Ref.	
Q1Q2(1)	1.13 (1.11–1.16)	< 0.001	1.11 (1.09–1.14)	< 0.001
Q3(2)	1.15 (1.11–1.20)	< 0.001	1.12 (1.07–1.17)	< 0.001
Q4(> 2)	1.20 (1.14–1.26)	< 0.001	1.17 (1.11–1.23)	< 0.001
<b>Cumulative cost of Acute or chronic periodontitis-related visits (US\$)</b>				
None	Ref.		Ref.	
Q1(13)	1.09 (1.05–1.12)	< 0.001	1.08 (1.04–1.11)	< 0.001
Q2(16)	1.21 (1.17–1.25)	< 0.001	1.19 (1.15–1.23)	< 0.001

Adjust for CCI and level of urbanization and index year

	Crude	p value	Adjusted	p value
Q3(43)	1.10 (1.06–1.14)	< 0.001	1.06 (1.03–1.10)	< 0.001
Q4(> 43)	1.18 (1.14–1.22)	< 0.001	1.15 (1.11–1.19)	< 0.001
<b>CCI group</b>				
0	Ref.		Ref.	
≥ 1	2.31 (2.26–2.36)	< 0.001	2.32 (2.27–2.38)	< 0.001
<b>Level of urbanization</b>				
0 most urbanization	Ref.		Ref.	
1	0.87 (0.86–0.89)	< 0.001	0.89 (0.87–0.91)	< 0.001
2	0.76 (0.74–0.78)	< 0.001	0.78 (0.75–0.80)	< 0.001
3 least urbanization	0.65 (0.63–0.68)	< 0.001	0.68 (0.65–0.71)	< 0.001
Adjust for CCI and level of urbanization and index year				

Table 5 shows that the association was significantly different between patients < 65 years of age (OR, 1.09; 95% CI, 1.06–1.11) and patients ≥ 65 years of age (OR, 1.23; 95% CI, 1.18–1.28; p for interaction < 0.001), as well as between patients without the CCI (OR, 1.17; 95% CI, 1.15–1.20) and patients with the CCI (OR, 0.99; 95% CI, 0.96–1.03; p for interaction < 0.001).

Table 5  
stratified analyses on the basis of age and CCI group

	OR (95% CI)	P-value	Effect modification P value
<b>Age</b>			< 0.001
Age < 65	1.09 (1.06–1.11)	< 0.001	
Age ≥ 65	1.23 (1.18–1.28)	< 0.001	
<b>CCI group</b>			< 0.001
0	1.17 (1.15–1.20)	< 0.001	
≥ 1	0.99 (0.96–1.03)	0.726	
Adjust for patient's Age, Comorbidity, Urban			

## Discussion

This is the first nationwide, population-based case control study which assesses the association between a history of periodontitis and the risk of breast cancer development in Asia, and we have demonstrated that breast cancer risk increased in periodontitis patients. Soder et al. [20] selected 3,273 patients aged between 30–40 years and found that chronic periodontitis indicated by missing molars seemed to be associated with breast cancer. Sfreddo et al. [21] selected 67 breast cancer patients and 134 controls and found a significant association between periodontitis and breast cancer. Freudenheim et al. [24] analyzed the cohort of 73,737 postmenopausal women and revealed that periodontitis increased the risk of postmenopausal breast cancer. We enrolled 60,756 breast cancer patients and 243,024 matched female non-breast cancer patients in this study and found that there was a strong correlation between periodontitis and breast cancer.

The shorter the interval period between the last periodontitis visit date to the breast cancer diagnosis date, the more number of visits for periodontitis, and the higher cumulative cost of periodontitis related visits implied that there was more active and severe periodontitis. Additionally, we discovered that there was a higher risk of breast cancer in the patients who had more active and severe periodontitis. Soder et al. [20] defined missing molars as severe periodontitis, with severe periodontitis increasing the risk of breast cancer.

Another important finding was that the association between periodontitis and female breast cancer was significantly different on the basis of age and CCI. In subgroup analysis, elderly patients 65 years or older had a higher risk of breast cancer than younger patients. The reason for this may be that elderly patients may have had a longer history of periodontitis, along with greater exposure to bacteria and chronic inflammation over a longer period of time. Periodontitis effects decreased in patients who had multiple comorbidity diseases. Other diseases or comorbidities had different mechanisms which affected breast cancer. Cao et al. [25] revealed that overall survival and progression-free survival of breast cancer were impacted by age and CCI, implying that age and CCI play an important role in breast cancer. In this study, one important finding is that the risk of breast cancer is modified by both age and comorbidities. Periodontitis had more effect on female breast cancer, particularly for patients without any comorbidities and older than 65 years of age. Closer follow up of these higher risk patients may be helpful in future cancer surveillance studies.

The mechanism of periodontitis induced breast cancer still remain unclear.

Oral cavity bacteria may play a role in the potential mechanism.

Previous studies [26–28] have found that breast duct tissue was exposed to various bacteria, with bacteria also being found in breast tumors. The long-term bacteria stimulation and inflammation seems to lead to cancer formation. Periodontitis is a chronic inflammation condition and its associated systemic inflammation status may play a role as another mechanism. Certain studies [29–33] have revealed that periodontal disease increased systemic inflammation markers, including C-reactive protein (CRP), cytokines and chemokines. Chan et al. [29] reviewed the meta-analysis of several studies and found that

circulating CRT, a low grade inflammation marker, was associated breast cancer development. Noack et al. [31] showed CRP levels increased in periodontitis patients. Hayashi et al. [32] demonstrated oral pathogens can induce and maintain a chronic state of inflammation at sites distant from oral infection. Elinav et al. [33] showed that microbials played an important role in inflammation induced cancer, and also affected cancer development. These inflammation markers had an impact on carcinogenesis and could explain the association between periodontitis and breast cancer.

Some limitations were noted in this study. First, some confounders, including menarche, pregnancy, breastfeeding, menopause, body weight, body height, alcohol use, and smoking, were not made available in this study, and all these factors can affect the risk of breast cancer. Second, the severity of periodontitis may affect one's inflammation status, which could lead to breast cancer. In order to overcome these limitations, we enrolled large numbers of matched patients and stratified patients by their number of visits for periodontitis treatment and the cumulative cost of their periodontitis related visits. A higher number of visits for periodontitis treatment, along with a higher cumulative cost for periodontitis related visits, resulted in patients being considered as having more active and severe periodontitis.

## Conclusion

Periodontitis is significantly associated with breast cancer and the effect of periodontitis is modified by both age and comorbidities.

## Abbreviations

NHIRD

National Health Insurance Research Database

OR

odds ratio.

CI

confidence interval.

CCI

Charlson Comorbidity Index.

IRB

Institutional Review Board.

NHI

National Health Insurance.

NHRI

National Health Research Institute.

LHID2000

Longitudinal Health Insurance Database.

CIC

Catastrophic Illness Certificate.

## Declarations

### Acknowledgements

This study was supported by Taichung Veterans General Hospital.

### Conflict of interests

The authors declare that there are no conflicts of interest.

### DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article.

### ETHICS STATEMENT

The study reviewed and approved by Ethics Committee in Taichung Veterans General hospital.

### AUTHOR CONTRIBUTIONS

**CCC** writing original draft and acquisition of data.

**WLH** contributed to the data collection and advised the analysis.

**CHL** contributed to the data collection and advised the manuscript.

**HHC** data analysis and interpretation, and revising article and study supervision.

### FUNDING

This study was supported by grants from Taichung Veterans General hospital.

### Consent for publication

Not applicable.

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