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Original Article

Women with breast cancer exhibit a higher risk for periodontitis: A nationwide cohort study

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Abstract *Background/purpose:* Epidemiologic research has linked periodontitis to several types of cancer, particularly breast cancer. Although clinical evidence indicates a higher risk of breast cancer in women with periodontitis than in those without, few studies have explored whether the risk of periodontitis is higher in women with breast cancer than in those without. In this study, we examined the incidence of periodontitis in patients with breast cancer and identified potential interventions for its prevention.
Materials and methods: This retrospective cohort study included data from the National Health Insurance Research Database of Taiwan. We identified women who received a diagnosis of breast cancer between 2010 and 2019 and included a 1:1 matched control cohort with no breast cancer. Subsequently, we analyzed the risk of periodontitis by using Cox proportional-hazards models while adjusting for sociodemographic factors, comorbidities, and treatment regimens.
Results: In 82,146 matched pairs, the breast cancer cohort was at a 51 % higher risk of periodontitis compared with the control cohort (adjusted hazard ratio = 1.51, 95 % confidence interval = 1.43–1.60). The stratified analysis revealed the same results. The risk of breast cancer was higher in younger patients than in older patients, whereas the risk of periodontitis was significantly lower in patients who underwent surgery, radiotherapy, chemotherapy, or hormone therapy compared with those who did not.

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Conclusion: Breast cancer increases the risk of periodontitis, particularly in younger patients. These patients should receive regular dental care to prevent and manage periodontitis. Anticancer treatments may mitigate the risk of periodontitis in patients with breast cancer.

Introduction

Breast cancer is the most common malignancy in women and the second leading cause of cancer-related deaths worldwide.[1] The yearly incidence of breast cancer has substantially increased, with the number of global cases nearly doubling from 870,200 in 1990 to 1,937,600 in 2017.[2] Of the treatment modalities available for breast cancer are surgery, radiotherapy, chemotherapy, and hormone therapy, which have improved the survival rates of patients in recent years. Although the overall mortality rate associated with breast cancer increased by 0.4 % every year from 1975 to 1989, it decreased by 43 % between 1989 and 2020,[3] which indicates the importance of long-term survivorship as a critical topic after treatment for breast cancer.

Research has elucidated several mechanisms underlying the etiology and progression of breast cancer. One of the most widely accepted hypotheses is that breast cancer is an inflammation-related condition.[4] Chronic inflammation plays a crucial role in the initiation and progression of cancer and increases the risk of metastasis.[5] The tumor microenvironment during inflammation comprises immune cells and activated fibroblasts, which secrete cytokines, chemokines, growth factors, and DNA-damaging agents.[6]

Periodontitis is a common chronic inflammatory disease characterized by gradual detachment of the periodontium, which subsequently progresses to alveolar bone loss and eventual tooth loss.[7] In Taiwan, approximately 40 %—60 % of the population have periodontitis, with the rate being higher among older adults.[8] Although microbial dental plaque is regarded as the primary cause of periodontitis, the severity and pattern of destruction in hard and soft periodontal tissues depend on the host's immune response to bacterial stimulation.[9]

Multiple epidemiologic studies have indicated an association between periodontitis and many types of cancer, including oral, colorectal, gastrointestinal, breast, and lung cancers.[10] Of these types of cancer, breast cancer has particularly attracted major attention, with postmenopausal women with periodontitis exhibiting an increased risk of breast cancer.[11] A meta-analysis of eight studies involving 168,111 individuals revealed increased susceptibility to breast cancer in women with periodontitis [risk ratio = 1.18; 95 % confidence interval (CI) = 1.11—1.26].[12]

While clinical evidence suggests that periodontitis may increase the risk of breast cancer in women, no studies have yet explored whether a diagnosis of breast cancer subsequently raises the risk of developing periodontitis. Furthermore, large-scale epidemiological data is lacking to confirm or disprove this potential association. This population-based cohort study in Taiwan investigates the incidence of periodontitis among women with breast cancer. We want to find whether breast cancer is associated with a higher prevalence of periodontitis. Further understanding the relationship between breast cancer and periodontitis can aid in the identification of targeted strategies aimed at maintaining oral health and potentially reducing the incidence of periodontitis in patients with breast cancer.

Materials and methods

Data source

This study acquired data from the National Health Insurance Research Database (NHIRD) of Taiwan, which contains the medical records of approximately 99 % of the Taiwanese population (23.75 million people). This database is established and maintained by the National Health Research Institutes (NHRI), with data released publicly on an annual basis for research purposes. These data include hospital admissions, comprehensive outpatient and inpatient healthcare information, diagnostic codes, prescription medication status, and beneficiary registries since 1996. Diseases in the claims data are classified by the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD*-9-CM) guidelines for 1996—2015 and the *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD*-10-CM) guidelines for 2016—2021. To ensure patient privacy, all personal identification numbers are encrypted by the NHRI before the data are released. This study was approved by the Research Ethics Committee of China Medical University Hospital (CMUH109-REC2-031(CR-3). Given the retrospective nature of this study, the requirement for informed consent was waived (CMUH109-REC2-031(CR-3).

Study population

Patients with breast cancer holding a catastrophic illness card are exempt from copayments. For the period January 1, 2010, to December 31, 2019, women with breast cancer (*ICD*-9-CM code 714; *ICD*-10-CM code C50) in the claims data were identified from the Registry for Catastrophic Illness Patient Database, with the date of the first breast cancer diagnosis defined as the index date. Women with and without breast cancer were propensity-score-matched at a 1:1 ratio in terms of age, monthly income, urbanization level, comorbidities, and index year. Patients who had a history of periodontitis before the index date or any other type of cancer (*ICD*-9-CM codes 140—173 and 175—208; *ICD*-

10-CM codes C00—C49 and C51—C99), who were under 20 years of age, as well as males and subjects with incomplete sex data at baseline, were excluded from both cohorts.

Outcomes and covariates

The person-years of follow-up were estimated for the two cohorts from the index date until the date of periodontitis diagnosis (*ICD*-9-CM codes 523.4—523.5, *ICD*-10-CM code K05.30) and were censored in cases of death, withdrawal from the insurance program, or follow-up until December 31, 2021. To ensure the accurate enrollment of patients with periodontitis, we defined patients with periodontitis as those who received a diagnosis of periodontitis at least three visits within a 1-year period. Sociodemographic factors and baseline comorbidities were regarded as covariates. These sociodemographic factors included age, monthly income, and urbanization level.

We considered several comorbidities associated with periodontal diseases and breast cancer that were diagnosed before the index date. Baseline comorbidities were considered to exist if at least three of the following ambulatory or inpatient claims were recorded: type 2 diabetes mellitus (T2DM; *ICD*-9-CM codes 250.×0 and 250.×2; *ICD*-10-CM code E11), hyperlipidemia (*ICD*-9-CM code 272; *ICD*-10-CM codes E71.30, E75.21, E75.22, E75.24, E75.3, E75.5, E75.6, E77, E78.0—E78.6, E78.70, E78.79, E78.8, and E78.9), hypertension (*ICD*-9-CM codes 401—405; *ICD*-10-CM codes I10—I13, I15, and N26.2), congestive heart failure (*ICD*-9-CM code 428; *ICD*-10-CM code I50), coronary artery disease (*ICD*-9-CM codes 410—414; *ICD*-10-CM codes I20—I22, I24, and I25), and chronic obstructive pulmonary disease (COPD; *ICD*-9-CM codes 491, 492, and 496; *ICD*-10-CM codes J41, J42, J43, and J44). Treatment data were obtained for patients with breast cancer who underwent radiotherapy, chemotherapy, surgery, tamoxifen therapy, or aromatase inhibitor therapy (anastrozole, exemestane, or letrozole).

Statistical analysis

Categorical variables are presented as frequencies and percentages, and continuous variables are presented as means and standard deviations (SDs). Standardized mean differences were used to determine the distribution differences between the two cohorts, with a standardized mean difference of 0.1 or less indicating a negligible difference. The incidence density of periodontitis per 1,000 person-years was calculated for each cohort. Univariate and multivariate Cox proportional-hazards models were used to calculate the hazard ratios (HRs) and 95 % CIs of periodontitis in the two cohorts, with sociodemographic characteristics and comorbidities adjusted for in the multivariate models. Further data analyses were conducted to determine the risk factors for periodontitis in patients with breast cancer undergoing radiotherapy, chemotherapy, breast surgery, and receiving tamoxifen, anastrozole, exemestane, or letrozole treatment. The cumulative incidence of periodontitis in the two cohorts was plotted using the Kaplan—Meier method, and the difference was determined using a log-rank test. All statistical analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC, USA) for Windows. All tests were two-tailed, with the level of significance set at 0.05.

Results

Figure 1 demonstrates the selection of the study population from Taiwan's NHIRD. There are a total of 82,146 female

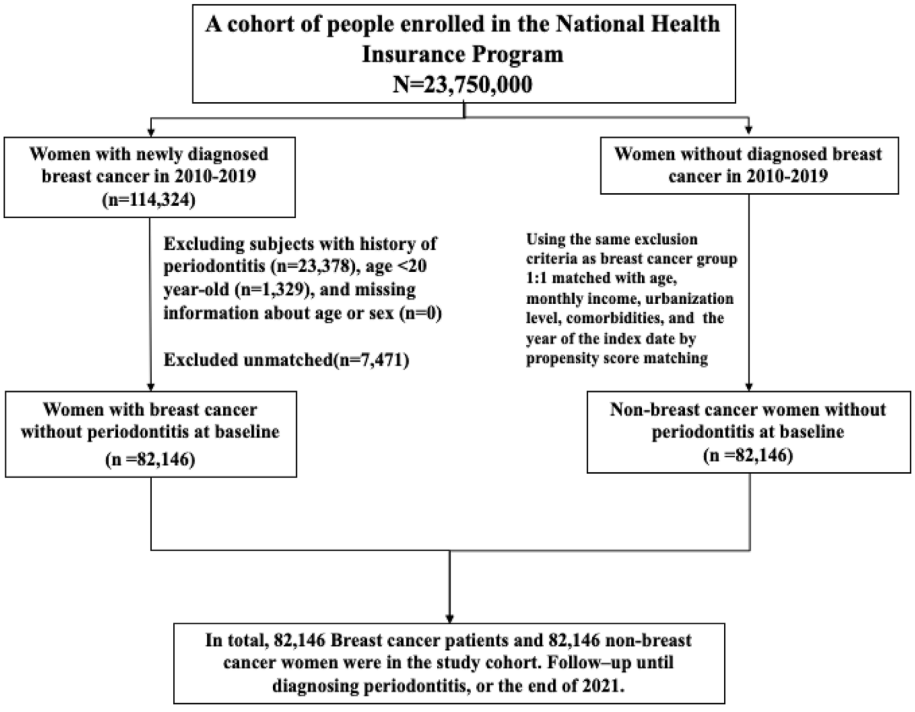

Figure 1 Selection of the study population from Taiwan's National Health Insurance Research Database.

Table 1 Demographic and clinical characteristics in patients with and without breast cancer between 2010 to 2019.

Variable	Breast cancer		SMD[a]
	No n (%)/Mean ± SD	Yes n (%)/Mean ± SD	
All	82146	82146	
Age (year)			
≦49	30279 (36.9)	29302 (35.7)	0.025
50-64	34636 (42.2)	35300 (43.0)	0.016
≧65	17231 (21.0)	17544 (21.4)	0.009
Mean ± SD	55.6 ± 14.7	55.1 ± 12.3	0.037
Monthly income			
<20,000 NTD	19919 (24.3)	20617 (25.1)	0.02
20,000–40000 NTD	38691 (47.1)	37750 (46.0)	0.023
>40,000 NTD	23536 (28.7)	23779 (29.0)	0.007
Urbanization level[b]			
1	44929 (54.7)	45123 (54.9)	0.005
2	30981 (37.7)	30828 (37.5)	0.004
3+	6236 (7.59)	6195 (7.54)	0.002
Comorbidities			
Type 2 diabetes mellitus	12483 (15.2)	14011 (17.1)	0.051
Hyperlipidemia	20039 (24.4)	22112 (26.9)	0.058
Hypertension	24912 (30.3)	26937 (32.8)	0.053
Congestive heart failure	1933 (2.35)	1954 (2.38)	0.002
Coronary artery disease	6809 (8.29)	7864 (9.57)	0.045
COPD	4524 (5.51)	5472 (6.66)	0.048
Treatment			
Radiotherapy		50836 (61.9)	
Chemotherapy		52684 (64.1)	
Operations on the breast		72623 (88.4)	
Tamoxifen		42746 (52.0)	
Anastrozole		5524 (6.72)	
Exemestane		5705 (6.94)	
Letrozole		35654 (43.4)	
Follow-up year, Mean ± SD	6.15 ± 3.01	5.68 ± 3.07	0.153

SD: standard deviation; NTD: New Taiwan Dollar; COPD: chronic obstructive pulmonary disease.
[a] A standardized mean difference (SMD) of ≤0.10 indicates a negligible difference between the two cohorts.
[b] The urbanization level was categorized by the population density of the residential area into 3 levels, with level 1 as the most urbanized and level 3 as the least urbanized.

subjects with breast cancer and matched the same number of female control subjects without breast cancer. Table 1 presents the demographic characteristics and comorbidities of the breast cancer cohort and control cohort. The mean ages of the breast cancer cohort and control cohort were 55.1 ± 12.3 years and 55.6 ± 14.7 years, respectively, with approximately 36 % of the patients aged 49 years or younger. More than half of the patients lived in an urban area, and 29 % had a monthly income greater than 40,000 New Taiwan Dollars. In all patients, the prevalence of preexisting comorbidities—including hypertension, hyperlipidemia, and T2DM—was high. For the treatment modalities, breast cancer patients were more likely to have undergone breast surgery, radiotherapy, and chemotherapy and to have received tamoxifen and letrozole treatment. The mean follow-up duration for periodontitis was 5.68 years (SD = 3.07 years) for the breast cancer cohort and 6.15 years (SD = 3.01 years) for the control cohort. At the end of the 12-year follow-up period, the cumulative incidence of periodontitis was significantly higher in the breast cancer cohort than in the control cohort (log-rank test: $P < 0.001$, Fig. 2).

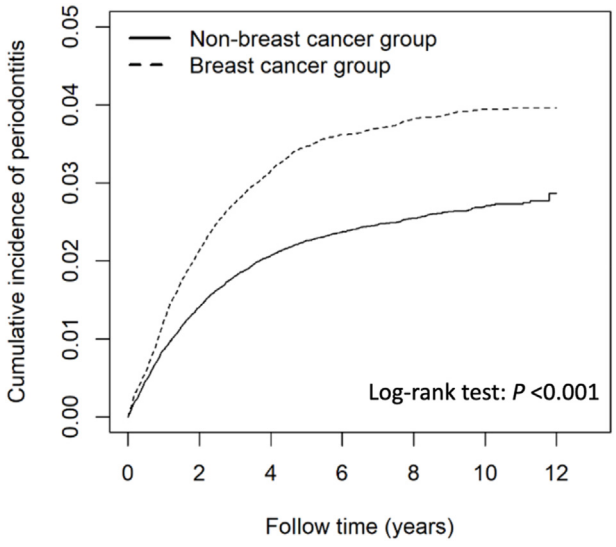

Figure 2 Cumulative incidence of periodontitis in breast cancer group compared to non-breast cancer group.

Table 2 presents the HRs of periodontitis associated with breast cancer, age, monthly income, urbanization level, and comorbidities. The overall incidence of periodontitis was 51 % higher in the breast cancer cohort than in the control cohort (5.74 vs. 3.67 per 1,000 person-years), with an adjusted HR (aHR) of 1.51 (95 % CI = 1.43−1.60). The risk of periodontitis was increased in younger patients (aHR = 1.32, 95 % CI = 1.19−1.47 for patients aged 49 years or younger; aHR = 1.48, 95 % CI = 1.35−1.63 for patients aged 50−64 years; comparison subgroup was those aged 65 years or older).

The risk of periodontitis was decreased in patients with breast cancer who underwent radiotherapy, chemotherapy, breast surgery or received tamoxifen, anastrozole, exemestane, or letrozole treatment (Table 3). Table 4 presents a comparison of the incidence rates and HRs of periodontitis in the breast cancer and control cohorts, stratified by age, monthly income, urbanization level, and comorbidities. The age-specific aHR of periodontitis for the breast cancer to non-breast cancer cohorts was significant for all age subgroups. Analysis of the monthly income−specific HRs of periodontitis revealed that, the breast cancer cohort exhibited higher risk at all income levels. Patients with breast cancer living in an urban area had higher risk of periodontitis compared with patients without breast cancer. Regarding comorbidities, patients with breast cancer and a comorbid disorder had higher risk of periodontitis compared with those with that comorbid disorder and without breast cancer (aHR = 1.53 for T2DM, aHR = 1.52 for hyperlipidemia, aHR = 1.59 for hypertension, aHR = 1.72 for coronary artery disease, and aHR = 1.41 for COPD).

Table 2 Risk of periodontitis associated with breast cancer, demographics, and comorbidities in the Cox risk models presented by hazard ratio (HR) and 95 % CI.

Variable	Event	1,000 person-years	IR	Crude		Adjusted[a]	
	N = 4533			HR (95 % CI)	*P*-value	HR (95 % CI)	*P*-value
Breast cancer							
No	1854	505133	3.67	1 (Reference)		1 (Reference)	
Yes	2679	466903	5.74	1.51 (1.42,1.60)	<0.001	1.51 (1.43,1.60)	<0.001
Age (year)							
≦49	1757	377068	4.66	1.49 (1.36,1.63)	<0.001	1.32 (1.19, 1.47)	<0.001
50-64	2160	419758	5.15	1.59 (1.46, 1.74)	<0.001	1.48 (1.35, 1.63)	<0.001
≧65	616	175210	3.52	1 (Reference)		1 (Reference)	
Monthly income							
<20,000 NTD	1132	230249	4.92	1 (Reference)		1 (Reference)	
20,000−40000 NTD	1984	455365	4.36	0.89 (0.83, 0.96)	0.0028	0.85 (0.79, 0.91)	<0.001
>40,000 NTD	1417	286422	4.95	1.02 (0.94, 1.1)	0.6012	0.94 (0.87, 1.02)	0.1246
Urbanization level[a]							
1	2517	533057	4.72	1.10 (0.98, 1.24)	0.097	1.06 (0.94, 1.19)	0.3249
2	1703	365610	4.66	1.09 (0.97, 1.23)	0.1503	1.06 (0.94, 1.20)	0.3246
3+	313	73369	4.27	1 (Reference)		1 (Reference)	
Comorbidities							
Type 2 diabetes mellitus							
No	3976	831703	4.78	1 (Reference)		1 (Reference)	
Yes	557	140334	3.97	0.78 (0.71,0.85)	<0.001	0.92 (0.83, 1.01)	0.0915
Hyperlipidemia							
No	3557	737231	4.82	1 (Reference)		1 (Reference)	
Yes	976	234806	4.16	0.81 (0.76,0.87)	<0.001	0.91 (0.83, 0.99)	0.0225
Hypertension							
No	3335	686807	4.86	1 (Reference)		1 (Reference)	
Yes	1198	285229	4.2	0.82 (0.77,0.88)	<0.001	0.99 (0.91, 1.07)	0.7963
Congestive heart failure							
No	4481	956418	4.69	1 (Reference)		1 (Reference)	
Yes	52	15619	3.33	0.60 (0.46,0.79)	<0.001	0.82 (0.62, 1.08)	0.1612
Coronary artery disease							
No	4235	895934	4.73	1 (Reference)		1 (Reference)	
Yes	298	76103	3.92	0.77 (0.68,0.87)	<0.001	0.96 (0.85, 1.09)	0.5425
COPD							
No	4333	921543	4.7	1 (Reference)		1 (Reference)	
Yes	200	50493	3.96	0.77 (0.67,0.89)	<0.001	0.87 (0.75, 1.003)	0.0548

IR, incidence rate, per 1000 person-years; HR, hazard ratio; COPD: chronic obstructive pulmonary disease.
[a] Multivariable analysis including age, income, urbanization level, diabetes mellitus, hyperlipidemia, hypertension, congestive heart failure, coronary artery disease, and COPD.

Table 3 Risk of periodontitis associated with treatment among breast cancer patient in the Cox risk models presented by hazard ratio (HR) and 95 % CI.

Variable	Event N = 2679	1,000 person-years	IR	Crude		Adjusted[a]	
				HR (95 % CI)	*P*-value	HR (95 % CI)	*P*-value
Radiotherapy							
No	1322	175076	7.55	1 (Reference)		1 (Reference)	
Yes	1357	291827	4.65	0.6 (0.56,0.65)	<0.001	0.57 (0.53,0.62)	<0.001
Chemotherapy							
No	1003	160466	6.25	1 (Reference)		1 (Reference)	
Yes	1676	306437	5.47	0.9 (0.83, 0.98)*	0.0103	0.84 (0.78,0.91)	<0.001
Operations on the breast							
No	299	34691	8.62	1 (Reference)		1 (Reference)	
Yes	2380	432212	5.51	0.77 (0.69,0.87)	<0.001	0.77 (0.69,0.87)	<0.001
Tamoxifen							
No	1311	195487	6.71	1 (Reference)		1 (Reference)	
Yes	1368	271416	5.04	0.86 (0.79,0.93)	<0.001	0.83 (0.76, 0.9)	<0.001
Anastrozole							
No	2588	433004	5.98	1 (Reference)		1 (Reference)	
Yes	91	33899	2.68	0.47 (0.38,0.58)	<0.001	0.47 (0.38,0.58)	<0.001
Exemestane							
No	2604	435806	5.98	1 (Reference)		1 (Reference)	
Yes	75	31097	2.41	0.38 (0.3, 0.48)	<0.001	0.37 (0.3, 0.47)	<0.001
Letrozole							
No	2094	266977	7.84	1 (Reference)		1 (Reference)	
Yes	585	199926	2.93	0.35 (0.32, 0.39)	<0.001	0.34 (0.31,0.37)	<0.001

IR, incidence rate, per 1000 person-years; COPD: chronic obstructive pulmonary disease; HR, hazard ratio.
[a] Multivariable analysis including age, income, urbanization level, diabetes mellitus, hyperlipidemia, hypertension, congestive heart failure, coronary artery disease, and COPD.

Discussion

To the best of our knowledge, this is the first study to employ a nationwide population-based cohort to examine the incidence of periodontitis in patients with breast cancer. Our results indicated that female patients with breast cancer were at higher risk of periodontitis compared with those without (aHR = 1.51, 95 % CI = 1.43–1.60). Multiple studies have revealed that the inflammatory microenvironment created in periodontitis is associated with an increased risk of cancer, including breast cancer.[10,13,14] Despite the potential association between periodontitis and breast cancer, the mechanism underlying this association remains unclear.[14] Both periodontitis and breast cancer occur in a transitory physiological inflammatory microenvironment.[15,16] In a mouse model of lipopolysaccharide-induced periodontitis, periodontal inflammation was found to stimulate luciferase-expressing 4T1 breast cancer cells.[17] The mechanism underlying this process was speculated to involve the recruitment of myeloid-derived suppressor cells, which induce the generation of interleukin-1β (IL-1β) and promote proinflammatory chemokine CCL2, CCL5, and CXCL5 signaling in the metastatic progression of breast cancer. Notably, research suggests a link between breast carcinogenesis and osteoimmunological disorders, such as osteoarthritis, rheumatoid arthritis, and periodontitis.[18] These osteoimmunological disorders and breast carcinogenesis activate a bone resorption microenvironment in response to inflammatory disequilibrium. This evidence implies a strong connection between periodontitis and breast cancer.

Our subgroup analysis revealed a significantly higher incidence of periodontitis in the breast cancer cohort than in the control cohort in young and middle-aged patients compared with those aged 65 years (patients aged ≤49 years, aHR = 1.32, 95 % CI = 1.19–1.47; patients aged 50–64 years, aHR = 1.48, 95 % CI = 1.35–1.63). A previous study reported that, compared with older women, younger women were more prone to tumors with negative clinicopathological characteristics, including a high histological grade or high likelihood of HER2/neu overexpression.[19] These results indicate that the effects of inflammation resulting from breast cancer may be stronger in younger women than in older ones. Taken together, the evidence underscores the importance of screening for periodontitis in younger patients with breast cancer.

In this study, we adjusted for several confounding variables (Table 2). Periodontal disease and breast cancer share many risk factors, such as hypertension,[20,21] T2DM,[22,23] hyperlipidemia,[24,25] congestive heart failure and coronary artery disease,[26,27] and COPD.[28,29] In this study, these comorbidities were incorporated as covariates to evaluate breast cancer as a potential risk factor for periodontitis. Comparison of the prevalence of periodontitis in patients with versus those without breast cancer revealed that patients with breast cancer were at higher

Table 4 Risk of periodontitis associated with breast cancer and control cohorts, stratified by age, monthly income, urbanization level, and comorbidities.

Variable	Non-breast cancer			Breast cancer			Compared to non-breast cancer			
							Crude		Adjusted[a]	
	Event N = 1854	1000 person-years	IR	Event N = 2679	1000 person-years	IR	HR (95 % CI)	*P*-value	HR (95 % CI)	*P*-value
Age (year)										
≦49	770	198784	3.87	987	178283	5.54	1.38 (1.26,1.52)	<0.001	1.38 (1.26,1.52)	<0.001
50-64	882	217730	4.05	1278	202028	6.33	1.5 (1.37, 1.63)	<0.001	1.51 (1.38,1.64)	<0.001
≧65	202	88619	2.28	414	86591	4.78	2.05 (1.73,2.42)	<0.001	2.07 (1.75,2.45)	<0.001
Monthly income (NTD)										
<20,000 NTD	389	121214	3.21	743	109035	6.81	1.99 (1.76,2.25)	<0.001	2.02 (1.78,2.28)	<0.001
20,000−40000 NTD	841	237374	3.54	1143	217991	5.24	1.44 (1.31,1.57)	<0.001	1.44 (1.32,1.57)	<0.001
>40,000 NTD	624	146546	4.26	793	139877	5.67	1.3 (1.17, 1.44)	<0.001	1.32 (1.18,1.46)	<0.001
Urbanization level[a]										
1	1042	276641	3.77	1475	256416	5.75	1.47 (1.36,1.59)	<0.001	1.49 (1.38,1.62)	<0.001
2	688	190214	3.62	1015	175396	5.79	1.54 (1.4, 1.7)	<0.001	1.55 (1.41,1.71)	<0.001
3+	124	38278	3.24	189	35091	5.39	1.6 (1.28, 2.01)	<0.001	1.58 (1.26,1.98)	<0.001
Comorbidities										
Type 2 diabetes mellitus										
No	1644	437216	3.76	2332	394487	5.91	1.52 (1.42,1.61)	<0.001	1.52 (1.43,1.62)	<0.001
Yes	210	67918	3.09	347	72416	4.79	1.5 (1.27, 1.78)	<0.001	1.53 (1.29,1.82)	<0.001
Hyperlipidemia										
No	1480	390596	3.79	2077	346635	5.99	1.52 (1.42,1.63)	<0.001	1.52 (1.42,1.62)	<0.001
Yes	374	114538	3.27	602	120268	5.01	1.5 (1.32, 1.7)	<0.001	1.52 (1.34,1.73)	<0.001
Hypertension										
No	1408	364886	3.86	1927	321921	5.99	1.49 (1.39, 1.6)	<0.001	1.49 (1.39, 1.6)	<0.001
Yes	446	140247	3.18	752	144982	5.19	1.59 (1.42, 1.79)	<0.001	1.59 (1.41, 1.79)	<0.001
Congestive heart failure										
No	1833	497758	3.68	2648	458660	5.77	1.51 (1.42, 1.6)	<0.001	1.52 (1.44, 1.62)	<0.001
Yes	21	7376	2.85	31	8243	3.76	1.35 (1.78, 2.35)	0.028	1.32 (0.75, 2.3)	0.034
Coronary artery disease										
No	1754	469686	3.73	2481	426248	5.82	1.5 (1.41, 1.6)	<0.001	1.51 (1.42, 1.6)	<0.001
Yes	100	35447	2.82	198	40655	4.87	1.71 (1.34, 2.17)	<0.001	1.72 (1.36, 2.19)	<0.001
COPD										
No	1781	482320	3.69	2552	439223	5.81	1.52 (1.43,1.61)	<0.001	1.53 (1.44,1.62)	<0.001
Yes	73	22813	3.2	127	27680	4.59	1.42 (1.07, 1.9)	0.017	1.41 (1.06, 1.88)	0.019

IR, incidence rate, per 1000 person-years; COPD: chronic obstructive pulmonary disease; HR, hazard ratio.

[a] Multivariable analysis including age, income, urbanization level, diabetes mellitus, hyperlipidemia, hypertension, congestive heart failure, coronary artery disease, and COPD.

risk of periodontitis, regardless of the stratification (Table 4). Despite these findings, further research is required to identify any unexplored interplay between these diseases.

The current study discovered that radiotherapy, chemotherapy, surgery, and hormone therapy had protective effects against periodontitis in patients with breast cancer. Despite the well-established association between radiotherapy and periodontitis in patients with head and neck cancer,[30] routine breast cancer radiotherapy, which does not involve the oral cavity, is assumed to be unrelated to the incidence of periodontitis. In our study, we found that radiotherapy mitigated the risk of periodontitis, presumably because of the indirect effect of radiation on breast cancer. Generally, radiation-induced cancer cell death is predominantly caused by breaks in DNA strands.[31] Research indicates that radiotherapy may induce antitumor immune responses, which can result in the regression of metastases or distant tumors, a phenomenon referred to as the abscopal effect.[32] A recent study revealed that patients who demonstrated a positive response to radiotherapy had substantially lower serum IL-6 and IL-8 levels.[33] Notably, IL-6 and IL-8 are specific inflammatory factors influencing periodontitis.[34] Future studies should explore this association in more detail to understand its complex mechanism.

In this study, hormone therapy had a protective effect against periodontitis in patients with breast cancer. Tamoxifen and aromatase inhibitors are typically used as the primary medications in hormone therapy for patients with breast cancer. Aromatase inhibitors have a negative effect on the periodontal health of patients with breast cancer,[35] but tamoxifen has a different effect on the periodontal status of these patients.[36] Specifically, tamoxifen can mimic the effects of estrogen and inhibit the production of osteoclasts,[37] potentially mitigating the risk of periodontitis-associated alveolar bone resorption. The different results obtained in our study may be attributable to the different control group. Specifically, our control group had breast cancer but did not undergo hormone therapy, unlike the healthy control groups employed in these previous studies. Hence, further research is required to determine the unique effects of different hormone therapy drugs on periodontal health. In patients with breast cancer, the patients' health condition must be comprehensively evaluated before surgery or chemotherapy is administered. Patients who are not eligible for surgery (e.g., high risk of complications from anesthesia) or chemotherapy (e.g., poor renal or hepatic function) may face certain limitations in dental care. In Taiwan, patients with breast cancer tend to comply with their physician-prescribed treatment, suggesting that these patients prefer regular clinical checkups and have strong health awareness. These factors will positively influence their likelihood of seeking proactive oral health care, in turn lowering their risk of periodontitis.

Although this study's strength lies in its population-based design, which yielded generalizable findings, certain limitations must be acknowledged. First, this study had a retrospective design, which is prone to confounding variables, such as negligence and misdiagnoses, although diseases were primarily diagnosed by medical professionals. Many scholars have attempted to enhance the diagnostic accuracy of the coding system, with one of the recommendations being to include only patients with more than two instances of the target diagnosis in their records.[38] Notably, our current definition of periodontitis is consistent with that used in other research: patients must have at least three outpatient visit records to mitigate the likelihood of a classification error.[39] This approach provided valuable insights into the correlation between periodontitis and breast cancer. Second, patients receiving treatment should have had more frequent clinical check-ups and may have visited the dental department more frequently to prevent periodontitis. As mentioned earlier, patients undergoing surgery may experience stronger cardiopulmonary function than those without surgery, and undergoing chemotherapy may possess better hepatic and renal function than those without chemotherapy. In addition, their good performance status should make them eligible for full anticancer treatment. However, this information is not available in the NHIRD. Therefore, we were unable to adjust for these potential confounding effects. Finally, this study involved patients from a single country. Therefore, our findings may not be applicable to other countries with different genetic, environmental, and lifestyle factors.

In conclusion, this study suggests that breast cancer increases the risk of periodontitis. Regular dental care, including routine recall visits, is crucial for the prevention and management of periodontitis. Pharmaceutical interventions may also mitigate the risk of periodontitis. In patients with breast cancer, anticancer treatment may reduce the risk of periodontitis. Further randomized controlled trials are required to determine the efficacy of routine periodontal examinations in patients with breast cancer.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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