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Risk of secondary cancers in women with breast cancer and the influence of radiotherapy

A national cohort study in Taiwan

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Abstract

Breast cancer is the most common cancer in women worldwide; thus, the prolongation of survival, and the incidence and risk factors, including radiotherapy, for developing secondary malignancies are important. We compared the incidence of secondary and new primary cancers in women with breast cancer (CA^{Pos}) and well-matched for age, geographic region, and monthly income cancer-free controls (CA^{Neg}). The risk for secondary cancers with and without radiotherapy was also compared in CA^{Pos} women. We enrolled 2422 CA^{Pos} patients and CA^{Neg} 12,110 controls. In a 4-year follow-up, the secondary cancers risk was significant in the CA^{Pos} group (adjusted hazard ratio [AHR]: 1.59; 95% confidence interval [CI]: 1.17–2.18). Only the risk of uterine cancer was significant compared with the controls (AHR: 6.30; 95% CI: 2.28–17.38). CA^{Pos} patients and <50 years old had a higher risk for secondary cancers. Developing secondary cancers was significant in the first follow-up year (AHR: 1.51; 95% CI: 1.11–2.06). Radiotherapy had no significant effect on the CA^{Pos} group, but it was significant ($P=0.0298$) in women ≥60 years old (elderly). We recommend monitoring secondary cancers in CA^{Pos} women, especially those <50 years old, and during the first year of follow-up. Radiotherapy should be used more carefully in elderly CA^{Pos} women.

Abbreviations: AHR = adjusted hazard ratio, CA^{Neg} = cancer-free controls, CA^{Pos} = diagnosed with breast cancer, CI = confidence interval, CIPD = Catastrophic Illness Patient Database, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification, LHID2000 = Longitudinal Health Insurance Database 2000, NHI = National Health Insurance, PY = person-years.

Keywords: breast cancer, radiotherapy, secondary cancers

1. Introduction

Breast cancer is one of the most common cancers worldwide. It is the leading cancer in women in developed western countries[1,2] and in Asia, because of the westernization of the daily diet, increased urbanization, the adoption of western lifestyles, and prolonged life expectancy, the incidence of breast cancer is also increasing.[3–6] Because of the promotion of public health infrastructure, the establishment of screening programs, and improvements in breast cancer treatments, the mortality rates of breast cancer have decreased in Western Europe, the United States, Australia, Japan, and Taiwan.[7,8] With the improvement of survival after being diagnosed with breast cancer, there has been an increasing interest in the long-term effects of therapy. Because of shared genetic, hormonal, environmental, and other factors,[9] the prevalence and risk factors for secondary and second primary malignancies after being diagnosed with breast cancer (CA^{Pos}) have become an important concern for clinicians, patients, and their families.[10,11]

Several population-based studies have reported the risk of secondary malignancies in breast cancer. The majority of those studies analyzed western populations[12,13] or a few Asian countries in 1 study.[14] Because of the ethnic differences and variant study designs, their results were inconsistent. One Taiwan report included only patients in hospitals with more than 50 beds.[15] Moreover, most of those studies evaluated the risk of secondary malignancies by comparing expected numbers based on population rates. Therefore, those estimated data may not reflect the true incidence of cancer.

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Radiotherapy has been recommended as a primary conservative treatment for early breast cancer.[16–18] In addition, for nonmetastatic, locally advanced breast cancer with a high risk, such as local lymph node metastasis, radiotherapy is also suggested to diminish local recurrence and even prolong survival.[19–21] However, low-dose ionizing radiation itself is carcinogenic in humans. The risk of developing secondary cancers after being exposed to ionizing radiation is also necessary to clarify the possible negative effects in CA^{Pos} patients.

In this cohort study, we extracted CA^{Pos} women from Taiwan's National Health Insurance Research Database, which provides comprehensive national medical claims records. A randomly selected well-matched control group of women without cancer (CA^{Neg}) was the comparison cohort. The risk for secondary cancers in CA^{Pos} patients given radiotherapy was also evaluated. We expect this evaluation method to provide a more precise risk evaluation for secondary cancers in Asian populations.

2. Materials and methods

2.1. Database

In Taiwan, a single-payer National Health Insurance (NHI) program was launched in 1995. The database contains the medical claims information of 99% of Taiwan's 23 million legal residents registered between March 1995 and December 2012.[22] The data used in this study were taken from the NHI Longitudinal Health Insurance Database 2000 (LHID2000). The LHID2000 contains original claims data of 1 million individuals randomly selected from the 2000 Registry of NHI Beneficiaries database. There was no significant difference in the gender distribution, age, and healthcare costs between the LHID2000 and the original NHI database. The LHID2000 contains the registration data of everyone who was an NHI beneficiary between 1998 and 2007. International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes are used for diagnoses, procedures, and the Catastrophic Illness Patient Database (CIPD). A formal written wavier for ethical approval was obtained from the Chi-Mei Medical Center Institutional Review Board (applicant number: 10306-E03).

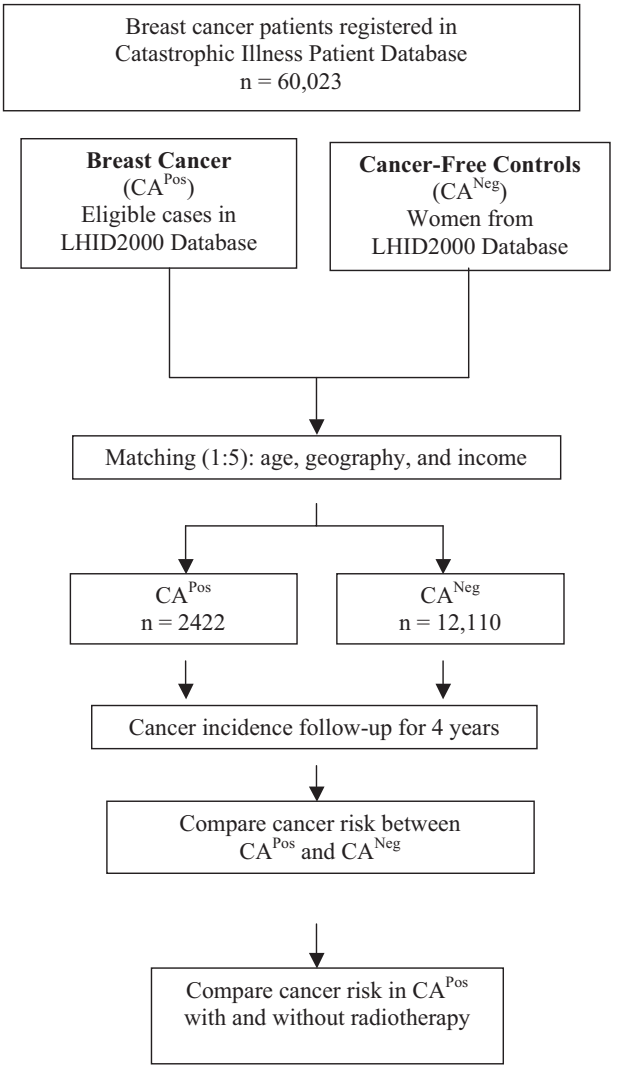

Figure 1. Diagram of risk evaluation for new secondary and primary cancers between eligible women already diagnosed with breast cancer (CA^{Pos}) and age-, residence area-, and monthly insurance-income-matched cancer-free control group (CA^{Neg}). LHID2000 = Longitudinal Health Insurance Database 2000.

2.2. Study participants

This retrospective cohort study included 2 study groups: women who were breast cancer-positive (CA^{Pos}) study group and a matched control group of women who were CA-negative (CA^{Neg}). The NHI program requires that histologically and pathologically confirmed malignancies be registered in the CIPD, which covers 1998 to 2007. From the CIPD, we selected CA^{Pos} women and linked the eligible cases to the LHID2000. The CA^{Pos} group was composed of women with newly diagnosed breast cancer (ICD-9-CM code 174). We excluded CA^{Pos} men, females younger than 18 years when diagnosed with their first breast cancer, and CA^{Pos} women with a history of prior cancer before documented breast cancer. The control group was composed of 5 times as many CA^{Neg} women matched for age, geographic region, and monthly income were randomly selected from LHID2000 (Fig. 1). We also identified CA^{Pos} women who had undergone inpatient or outpatient radiotherapy (ICD-9-CM code V58.0) within 1 year after their breast cancer diagnosis. The index date for the CA^{Pos} group was the date of their first breast cancer registry. Each eligible case was followed-up for 4 years starting from the index date. Follow-up time was calculated in person-years (PY) for each case. The final follow-up date was defined as death, the full 4 years, or the day a secondary cancer was diagnosed in the CA^{Pos} group or a first cancer diagnosed in the CA^{Neg} group. The secondary malignancies (excluding female breast cancer) were head and neck (ICD-9-CM code: 140–149), digestive (150–159), respiratory (160–165), bone, connective tissue, skin (170–173, 176), genitourinary (179–189), hematological (200–208), and other unspecified (190–199).

2.3. Statistical analyses

Pearson χ^2 test was used to compare differences in baseline age, geographic region, and monthly incomes between the study and control groups. The incidence rate was calculated as the number and location of anatomic sites of identified secondary cancers in the CA^{Pos} group or first diagnosed cancers in the CA^{Neg} group during the 4-year follow-up. The relevant data were divided by the total PY for each group by age and follow-up year. Cox

Table 1

Baseline characteristics of patients with breast cancer and cancer-free controls.

Characteristics	CA^{Pos} (n = 2422), n (%)	CA^{Neg} (n = 12,110), n (%)	P^*
Age, y			
18–39	335 (13.83)	1652 (13.64)	0.97
40–49	829 (34.23)	4201 (34.69)	
50–59	667 (27.54)	3296 (27.22)	
≥60	591 (24.40)	2961 (24.45)	
Geographic region			
Northern	1300 (53.67)	6500 (53.67)	>0.99
Central	403 (16.64)	2015 (16.64)	
Southern	667 (27.54)	3335 (27.54)	
Eastern	52 (2.15)	260 (2.15)	
Monthly income, NT$			
<15,840	813 (33.57)	4065 (33.57)	>0.99
15,840–24,999	1140 (47.07)	5700 (47.07)	
≥25,000	469 (19.36)	2345 (19.36)	

Data are number (%).

CA^{Neg} = cancer-free controls, CA^{Pos} = diagnosed with breast cancer, NT$ = New Taiwan Dollars.

* P derived using Pearson χ^2.

proportional hazard models were used to evaluate the crude and adjusted hazard ratios (AHR) plus 95% confidence interval (CI) to determine the risk for secondary cancers in the CA^{Pos} group and first cancers in the CA^{Neg} group and for CA^{Pos} patients with and without radiotherapy. All AHRs were adjusted by age group, geographic region, and monthly income. Cox proportional hazards regression analyses and Kaplan–Meier analyses were used to calculate the cumulative incidence rates of secondary cancers in the CA^{Pos} group and first-diagnosed cancers in the CA^{Neg} group. Fisher exact test was used to compare differences in CA^{Pos} patients with and without radiotherapy. SAS 9.2 for Windows (SAS Institute, Cary, NC) was used for all analyses. Significance was set at $P < 0.05$ (2-sided).

3. Results

3.1. Baseline characteristics of CA^{Pos} patients and CA^{Neg} controls

We identified 60,023 CA^{Pos} patients in the CIPD. The data of 2422 eligible women were extracted based on the insurance claims data from the LHID2000. For the CA^{Neg} control group, the data of 12,110 patients, matched in age ($P = 0.97$), geographic region ($P > 0.99$), and monthly insurance incomes ($P > 0.99$) (Table 1), were randomly selected.

3.2. Secondary cancer risk for CA^{Pos} patients during the 4-year follow-up

In the 4-year follow-ups, 51 secondary cancers were detected in the CA^{Pos} group and 175 newly diagnosed cancers in the CA^{Neg} group. The incidence of new cancer was higher in the CA^{Pos} group (5.71 vs 3.64 per 1000 PY) and the differences in both crude and AHRs (1.57; 95% CI: 1.15–2.14 and 1.59; 95% CI: 1.17–2.18, respectively) (Table 2). By the end of the follow-ups, the incidence of new cancer development was significantly higher in the CA^{Pos} group ($P < .01$) (Fig. 2A).

In the analysis for the risk stratified by age and follow-up years, younger CA^{Pos} patients had risks of developing secondary cancers than did the CA^{Neg} group. The crude and AHRs were significant in the 18 to 40 and 40 to 50 age ranges of the CA^{Pos} group (Fig. 2B). The risk for CA^{Pos} patients >50 years was not significantly different from that of the CA^{Neg} group, and only within 1-year follow-up was there a significant risk of secondary cancers risk (AHR: 1.51; 95% CI: 1.11–2.06) (Table 2).

3.3. Crude and AHRs for cancer types in CA^{Pos} and CA^{Neg} patients

Digestive tract cancers were the most common secondary new cancers in both groups. However, in multivariate Cox proportional hazard regression analysis adjusted for age, geographic region, and monthly insurance income, only uterine cancer was significantly different between the 2 groups (AHR: 6.30; 95% CI: 2.28–17.38) (Table 3).

3.4. Incidence and secondary cancer types in CA^{Pos} patients who underwent radiotherapy

Of the total 216 CA^{Pos} patients who had undergone radiotherapy, 8 (3.7%) developed secondary cancers of the digestive tract (4), uterus (2), respiratory tract (1), and other areas of the genitourinary tract (1). The mean follow-up was 1.86 ± 0.99 years (Table 4). The incidence was nonsignificantly

Table 2

The risk of new cancers for patients with breast cancer and cancer-free controls during the 4-year follow-up.

	CA^{Pos}				CA^{Neg}					
Characteristics	n	CA^{Pos}	PY	Rate†	n	CA^{Pos}	PY	Rate†	Crude HR (95% CI)	AHR‡ (95% CI)
All	2422	51	8937.56	5.71	12,110	175	47,953.86	3.64	1.57* (1.15–2.14)	1.59* (1.17–2.18)
Age, y										
18–39	335	4	1262.90	3.17	1652	5	6604.23	0.76	4.30* (1.15–16.02)	4.18* (1.12–15.56)
40–49	829	14	3164.39	4.42	4201	35	16,741.75	2.09	2.12* (1.14–3.94)	2.12* (1.14–3.94)
50–59	667	11	2460.86	4.47	3296	44	13,064.19	3.37	1.33 (0.69–2.58)	1.34 (0.69–2.59)
≥60	591	22	2049.40	10.73	2961	91	11,543.68	7.88	1.36 (0.85–2.17)	1.36 (0.85–2.17)
Follow-up, y										
<1	2422	16	2377.03	6.73	12,110	39	12,079.10	3.23	1.50* (1.10–2.05)	1.51* (1.11–2.06)
1–2	2332	14	2274.70	6.15	12,049	33	12,025.78	2.74	1.38 (0.95–2.00)	1.40 (0.97–2.03)
2–4	2224	21	4285.83	4.90	11,998	103	23,848.98	4.32	1.13 (0.71–1.81)	1.16 (0.73–1.86)

AHR = adjusted hazard ratio, CA^{Neg} = cancer-free controls, CA^{Pos} = diagnosed with breast cancer, CI = confidence interval, HR = hazard ratio, PY = person-years.

† Per 1000 person-years.

‡ Adjusted by age group, geographic region, and monthly income.

* $P < 0.05$.

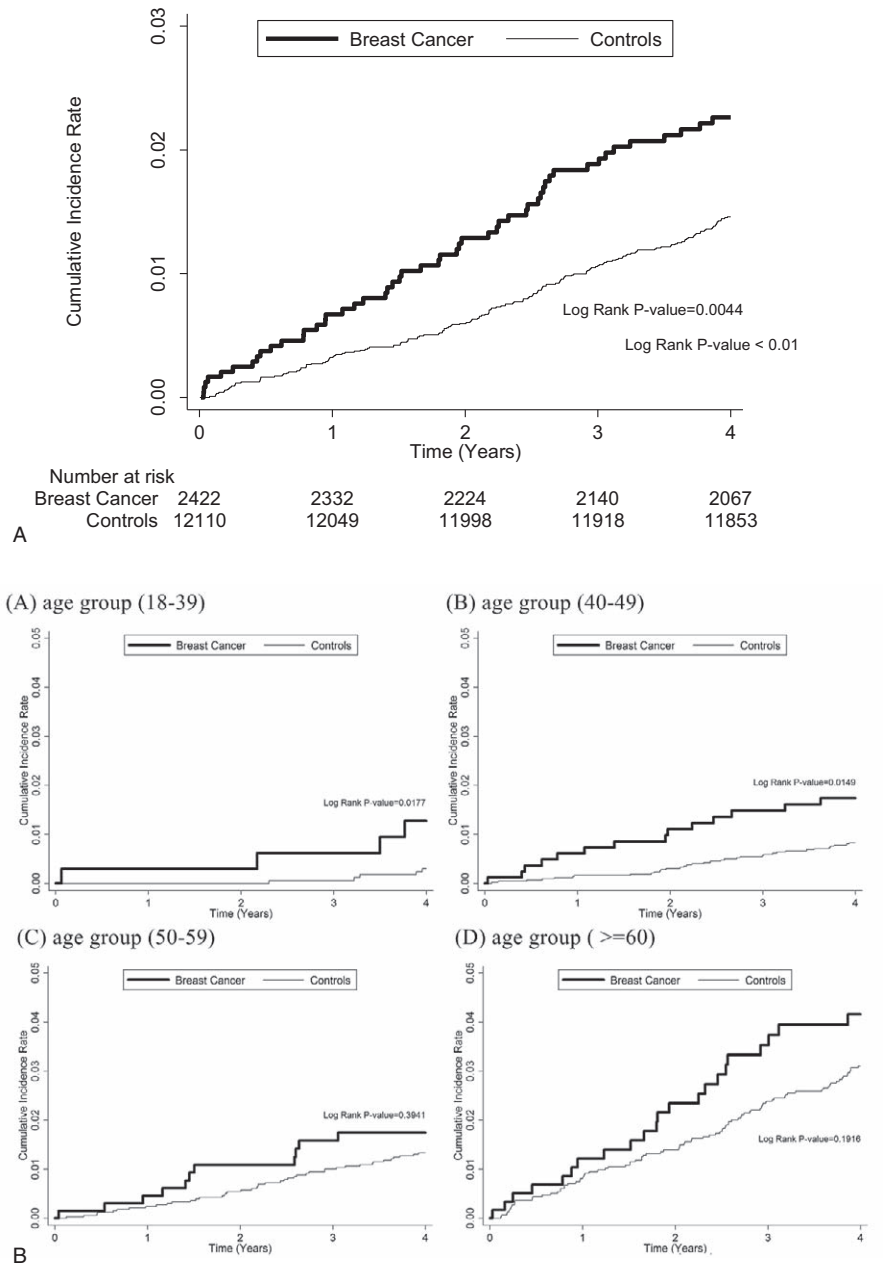

Figure 2. (A) The cumulative incidence of developing new cancers was significantly higher in the CA^{Pos} patients than the CA^{Neg} patients ($P<0.01$). (B) The difference was significant in the age <50 years. CA^{Neg} = cancer-free controls, CA^{Pos} = diagnosed with breast cancer.

higher than for CA^{Pos} patients who had not undergone radiotherapy (1.95%; 43/2206) (Table 5). The cumulative incidence rate within the 4-year follow-ups was not significant ($P=0.08$) (Fig. 3).

3.5. Hazard ratio of secondary cancer CA^{Pos} patients who underwent radiotherapy

In the analysis of the possible risk factors for secondary cancer in CA^{Pos} patients who had and had not undergone radiotherapy, the crude hazard ratio (HR) was not significant (crude HR: 1.93; 95% CI: 0.91–4.10), but when adjusted age, geographic region, and monthly insurance income, CA^{Pos} patients who had undergone radiotherapy had a significantly higher risk of secondary cancer (AHR: 2.23; 95% CI: 1.04–4.81; $P=0.04$). The stratified analysis showed that only CA^{Pos} patients ≥60 years had a higher risk of secondary cancer than did other patient groups (AHR: 3.37; 95% CI 1.13–10.11; $P=0.03$) (Table 6).

4. Discussion

In the 4-year follow-up of this cohort study, we found that the incidence of secondary cancers was 1.59 times higher in CA^{Pos}

Table 3

Crude and adjusted hazard ratios for cancer types in patients with breast cancer and in cancer-free controls.

Cancer type (ICD-9-CM code)	CA^{Pos} (n = 2422), n (%)	CA^{Neg} (n = 12,110), n (%)	Crude HR (95% CI)	AHR† (95% CI)
All (140–208)‡	51 (2.11)	175 (1.45)	1.57* (1.15–2.14)	1.59* (1.17–2.18)
Head and neck (140–149)	1 (1.96)	5 (2.86)	1.08 (0.13–9.21)	1.09 (0.13–9.32)
Digestive (150–159)	18 (35.29)	68 (38.86)	1.42 (0.84–2.39)	1.46 (0.87–2.45)
Respiratory (160–165)	6 (11.76)	22 (12.57)	1.45 (0.59–3.58)	1.48 (0.60–3.65)
Bone and skin (170–173, 176)	1 (1.96)	5 (2.86)	1.07 (0.12–9.13)	1.07 (0.13–9.19)
Other_GU (179, 185–189)	4 (7.84)	14 (8.00)	1.51 (0.50–4.60)	1.54 (0.51–4.67)
F_uterus (182)	8 (15.69)	7 (4.00)	6.23* (2.26–17.19)	6.30* (2.28–17.38)
F_ovarian (183)	4 (7.84)	12 (6.86)	1.80 (0.58–5.57)	1.79 (0.58–5.57)
F_cervical (180)	2 (3.92)	19 (10.86)	0.56 (0.13–2.39)	0.56 (0.13–2.41)
Hematological (200–208)	3 (5.88)	11 (6.29)	1.46 (0.41–5.22)	1.45 (0.40–5.19)
Others	4 (7.84)	12 (6.86)	1.78 (0.58–5.53)	1.80 (0.58–5.59)

AHR = adjusted hazard ratio, CA^{Neg} = cancer-free controls, CA^{Pos} = diagnosed with breast cancer, CI = confidence interval, F = female, GU = genitourinary, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification.

† Adjusted by age group, geographic region, and monthly income.

‡ Except breast cancer (174).

* $P < 0.05$.

patients than the incidence of new primary cancers in CA^{Neg} controls matched for age, area of residence, and monthly insurance incomes. We also found that CA^{Pos} patients <50 years old had a higher risk of secondary cancer than did elderly CA^{Pos} patients within 1 year after breast cancer had been diagnosed. Radiotherapy may not be a strong risk factor for developing secondary cancers; however, a Cox regression analysis showed that, in elderly (≥60 years) CA^{Pos} patients, radiotherapy and age were independent predictors of secondary cancers.

Age is an important predictor that CA^{Pos} patients will develop secondary cancers. The finding that younger CA^{Pos} patients tend to have a higher carcinogenic risk was reported in studies[13,14] that compared expected numbers based on population rates. We confirmed that the carcinogenic risk was also higher when compared with the cancer-free general population. Moreover, this is the case in Asian and in Western countries.[12–15] People <50 years old are considered a risk group. In Asian countries, the age at onset (median age: 45–49 years) of female breast cancer is younger than in western countries.[6,23–25] Therefore, our findings, in addition to prior findings, highlight the importance of secondary cancer surveillance in female breast cancer survivors.

The latency between a diagnosis of primary breast cancer and the development of secondary cancers is also important. A cohort study[12] using 4 Scandinavian cancer registries reported that the standardized incidence ratios for secondary nonhematological malignancies increased with the number of years from the diagnosis of primary breast cancer. However, the study collected data at least 1 year after the primary breast cancer diagnosis; therefore, secondary cancers that developed within 1 year after the breast cancer diagnosis were omitted. Another study,[14] which used multinational population-based cancer registries, also indicated that the overall secondary cancer risk increased with increasing time after the primary breast cancer diagnosis. We found that the time interval was significant only within 1 year after the primary breast cancer diagnosis and in the subsequent 2 to 4 years, which is inconsistent with the above studies. This might be attributable to the cancer incidence risk of both studies above having been compared with the expected numbers of cancers calculated based upon population rates. In our study, however, the cancer incidence risk was compared with an age-, residence area-, and monthly insurance income-matched cancer-free population in the same study period. Therefore, we emphasize the importance of monitoring secondary cancers within 1 year of a documented diagnosis of primary breast cancer.

Because of the divergent results of the studies on this topic, it is difficult to conclude which are the most common types of secondary cancers. The divergence might be attributable to different ethnicities, nations, and regions investigated, breast cancer therapy strategies and data analysis methods used, or to a combinations of these. Because the high prevalence of specific cancer types in local regions or national populations would affect the possibilities of secondary cancer types, we eliminated this confounding factor by comparing matched CA^{Pos} and CA^{Neg} samples. We found that only secondary uterine cancers were significantly more common in CA^{Pos} patients than in the general population. Because female sex hormones and menstruation cycles are associated with both breast cancer and endometrial

Table 4

Secondary cancer types in patients with breast cancer who underwent radiotherapy.

Cancer type (ICD-9-CM code)	n (%)	Follow-up (y), mean ± SD
Digestive (150–159)	4	
Respiratory (160–165)	1	
Other_GU (179, 185–189)	1	
F_uterus (182)	2	
Total	8 (3.70*)	1.86 ± 0.99

F = female, GU = genitourinary, ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification, SD = standard deviation.

* Total 216 patients with breast cancer who underwent radiotherapy.

Table 5

Incidence of secondary primary cancers in patients with breast cancer who did and did not undergo radiotherapy.

Second primary cancers	Radiotherapy		P^*
	No	Yes	
No	2163	208	0.13
Yes	43	8	

* P derived using Fisher exact test.

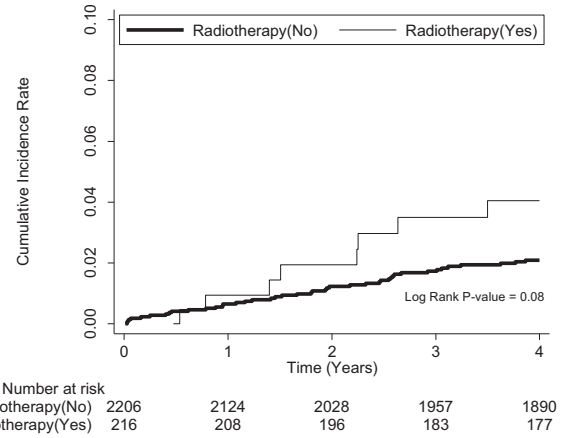

Figure 3. The cumulative incidence of secondary cancers in CA^{Pos} patients given radiotherapy was not significantly higher than that in CA^{Pos} patients without radiotherapy ($P=0.08$). CA^{Neg} = cancer-free controls, CA^{Pos} = diagnosed with breast cancer.

Table 6

Hazard ratios of secondary cancers derived from a Cox regression model for patients with breast cancer.

	Crude HR (95% CI)	AHR (95% CI)	*P*
Radiotherapy			
Yes	1.93 (0.91–4.10)	2.23* (1.04–4.81)	0.04*
No	1.00	1.00	
Age, y			
18–39	1.00	1.00	
40–49	1.40 (0.46–4.25)	1.61 (0.53–4.92)	0.40
50–59	1.41 (0.45–4.42)	1.62 (0.51–5.13)	0.41
≥60	3.36* (1.16–9.75)	3.37* (1.13–10.11)	0.03*
Geographic region			
Northern	1.00	1.00	
Central	0.36 (0.13–1.03)	0.37 (0.13–1.04)	0.06
Southern	0.60 (0.31–1.18)	0.58 (0.29–1.14)	0.11
Eastern	—	—	
Monthly income, NT$			
<15,840	1.00	1.00	
15,840–24,999	0.45* (0.25–0.84)	0.61 (0.32–1.16)	0.13
≥25,000	0.50 (0.23–1.11)	0.61 (0.26–1.41)	0.25

AHR = adjusted hazard ratio, CI = confidence interval, HR = hazard ratio, NT$ = New Taiwan Dollars.
* $P<0.05$.

cancers,[26,27] it is reasonable to link CA^{Pos} patients with a higher secondary uterine cancer risk. Thus, regular and close evaluation of the gynecological area, especially the uterus, is indicated by our findings.

Breast-conserving surgery is a current trend in breast cancer therapy and is being promoted more than has radical mastectomy in early breast cancer because of the cosmetic benefit with equivalent recurrence and survival.[17,18,28] For this reason, radiotherapy is expected to be a more common adjuvant therapy in CA^{Pos} patients. Conclusions about the association of radiotherapy with secondary cancers CA^{Pos} are inconsistent. One study[29] of 1253 CA^{Pos} women with unilateral stage I to II breast cancer who underwent wide excision, axillary dissection, and radiation concluded that the majority of patients given conservative surgery and radiation with or without adjuvant systemic therapy did not have a higher risk of developing secondary cancers. In contrast, a study[16] of 1079 CA^{Pos} women with clinically negative axillary nodes, and treated with radical mastectomy, total mastectomy, or total mastectomy plus postoperative irradiation, reported that patients given radiotherapy had the highest percentage of secondary cancers: 6%, 5%, and 8%, respectively. Yet another study[30] of 1884 stage I or II CA^{Pos} patients given radiotherapy reported that 8% developed secondary nonbreast malignancies within the first 8 years of follow-up. That number is higher than estimates from the Surveillance, Epidemiology, and End Results databases, but it is not significant ($P=0.05$). Therefore, radiotherapy might be associated with more frequent secondary cancers in CA^{Pos} women than in the general population. We also showed that radiotherapy did not induce a higher risk of secondary cancers in CA^{Pos} patients without radiotherapy. However, we found that radiotherapy has a higher HR when adjusted for age, region, and incomes, and that the major difference was in elderly CA^{Pos} patients. This finding is important for clinical practice, because in elderly early CA^{Pos} patients given breast-conserving surgery, the radiotherapy may be omitted due to a low local recurrence rate.[31] Taking our findings and those of the clinical studies of other researchers provides more evidence which indicates that radiotherapy should be used more carefully in elderly CA^{Pos} women with early-stage breast cancer.

The present study used a large-scale, nationally representative sample. The large sample size affords statistical power and the precision of risk appraisal with a minimal tendency for selection bias. More important, we compared the target patients with well-matched randomly selected control patients so that the results would express the more realistic risks of CA^{Pos} patients. However, there are limitations in the population-based study. First, several types of cancer-associated information are not recorded in the insurance claims data; for example, breast cancer markers, menstrual periods, lifestyle, smoking, family history, and body weight. Besides, secondary cancer in case subjects is more tendency to screen than controls, there might be different diagnosis rates between cases and controls. Thus, there might be some bias. Second, the breast cancer stage, histopathological characteristics, and complete breast cancer therapy strategies used for each CA^{Pos} patient were not available in this study; we cannot exclude the possibility that different kinds of chemotherapy or hormone drugs had different effects. Third, a population-based study cannot provide exact reasons or explain the possible underlying mechanism of breast cancer and secondary malignancies.

5. Conclusions

Our study showed that younger (<50 years old) CA^{Pos} patients had a higher risk of developing secondary cancers, especially uterine cancer. Close monitoring and evaluation plans are necessary for these younger patients. For CA^{Pos} women ≥60, radiotherapy should be used more carefully. Furthermore, additional genetic and biological studies to determine the possible mechanisms of secondary cancers and breast cancer are necessary.

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