Am J Cancer Res 2022;12(6):2744-2756
www.ajcr.us /ISSN:2156-6976/ajcr0142447

Original Article

Risk factors and specific cancer types of second primary malignancies in patients with breast cancer receiving adjuvant radiotherapy: a case-control cohort study based on the SEER database

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Received February 19, 2022; Accepted May 14, 2022; Epub June 15, 2022; Published June 30, 2022

Abstract: Patients with breast cancer can survive and live a long, cancer-free life; however, late complications of treatment, such as second primary malignancies (SPMs), have emerged as a competing cause of death and morbidity. We conducted a long-term population-based cohort study to identify the risk factors for SPMs and specific secondary cancer types after various latency periods of irradiated breast cancer. Cox proportional hazards regression was used to calculate the hazard ratio (HR) and 95% confidence interval (95% CI) for independent risk factors for SPM. We also calculated the HR of each specific cancer type and the latency time to specific SPMs. The risk of SPM was statistically significantly higher in patients with adjuvant RT than in patients without adjuvant RT (adjusted HR [aHR]: 1.105, 95% CI: 1.013-1.206). Compared with the control group, the case group had significantly increased risks of contralateral breast cancer (aHR: 1.268, 95% CI: 1.112-1.445), lung cancer (aHR: 1.218, 95% CI: 1.049-1.565), and urinary system cancer (aHR: 1.702, 95% CI: 1.140-2.543). Adjuvant RT for breast cancer increases the risk of SPM. Contralateral breast cancer, lung cancer, and bladder cancer were significant SPMs after breast RT, although the cumulative risk of SPM was low, at approximately 6, 10, and 13 cancers per 1000 women with irradiated breasts at latency periods of 5, 10, and 15 years, respectively, after breast RT.

Keywords: Second primary malignancies, radiotherapy, risk factor, breast cancer, latency time

Introduction

Radiotherapy (RT)-induced secondary primary malignancy (SPM) is a critical late complication of RT, and it has an impact on optimal treatment and collaborative decision-making by physicians and patients, particularly regarding specific cancers, such as breast cancer, prostate cancer, and lymphoma, with a long-term life expectancy associated with the medical progression of cancer treatments [3-5]. Many factors contribute to the development of RT-induced SPM, such as the patient's age at radiation [6, 7], dose and volume of the irradiated area [8], type of irradiated organ and tissue [9], radiation technique, and individual and family history of cancer [10, 11]. The exact mechanism of radiation-induced SPM is unknown [3], and radiation-induced SPM is a growing concern because of the increased number of cancer survivors. Efforts are being made to prevent or decrease the incidence of RT-induced SPM.

Adjuvant breast RT eradicates remaining tumor deposits after surgery [12], reducing the risk of locoregional recurrence and improving breast

cancer-specific and overall survival rates [12]. However, adjuvant RT can also result in long-term complications, including cardiotoxicity, lung injury, and SPM [13, 14], which can occur many years after treatment completion. Considerable progression has been made in breast cancer treatment, which has resulted in high long-term, cancer-free survival rates [15, 16]. However, late treatment complications, such as second malignancies or cardiovascular disease, have emerged as competing causes of death and morbidity [17-21]. The development of SPM appears to be related to the use of adjuvant breast RT [19-21]. Because of conflicting data on SPM after breast RT, particularly for contralateral breast cancer, additional research is required [12, 17-21].

The risk factors for SPM, such as patient characteristics and the incidence of specific cancers at years after breast irradiation, have thus far been unclear. Therefore, we conducted a long-term population-based cohort study to identify the risk factors for SPM and specific secondary cancer types after various latency periods.

Patients and methods

Database description

The data analyzed in this paper were extracted from the Surveillance, Epidemiology, and End Results (SEER) database, an authoritative database of cancer incidence and prognosis information in the United States. SEER was initiated in 1973 and contains cancer diagnosis, treatment, and survival data on Americans with cancer. It is a vital population-based resource for oncologists in the United States that can be used to study pathological diagnoses across demographic characteristics, geographic regions, and time. Because the SEER database is available to all clinical researchers, no ethical review was required for this study.

Study cohort

We investigated the National Cancer Institute's SEER 9 Regulations Custom data (November 2018 Sub; 1975-2016; Katrina/Rita Population Adjustment) to evaluate the risk of SPM after RT for breast cancer. A total of 31 500 patients with breast cancer were selected according to the following diagnosis criteria: (1) International Classification of Diseases for Oncology, Third Edition (ICD-0-3) histologic codes for adenocarcinoma (8140, 8147, 8290, 8310, 8410, 8440, 8480, 8525, 8550, and 8491), adenoid cystic carcinoma (8200), or other carcinomas (8012, 8041, 8082, 8430, 8562, 8980, and 8982). (2) ICD-0-3 primary sites code for nipple (C50.0), central portion of breast (C50.1), upper-inner quadrant of breast (C50.2), lower-inner quadrant of breast (C50.3), upper-outer quadrant of breast (C50.4), lower-outer quadrant of breast (C50.5), axillary tail of breast (C50.6), or overlapping lesion of breast (C50.8).

First, we excluded 118 patients with a diagnosis of a benign tumor. Then, we excluded 379 patients with a missing or unknown cause of death, 339 male patients, 73 patients with unknown ethnicity, 14 354 patients aged <40 or >70 years, and 277 patients with an unknown RT status. We also excluded 665 patients who died less than 12 months after the primary breast cancer diagnosis, 294 patients without histologic confirmation of a tumor, and 1954 patients whose breast cancer was not primary. A total of 13 047 patients were thus included in our study cohort, and the selection of study participants is presented in Supplementary Figure 1. <40 years BC patients were rare with more aggressive cancer behavior contributed to shorter survival time, and >70 years BC patients might have too short life-expected time to develop SPM. Therefore, we removed these patients.

Covariates and outcomes

The covariates explored in this study were age group at primary diagnosis (40-49, 50-59, and 60-69 years), ethnicity (White, Black, and Asian), SEER stage of tumor (localized, regional, distant, and unstaged), tumor grade (well differentiated, moderately differentiated, poorly differentiated, undifferentiated, and unknown), primary sites (nipple, central portion, upper-inner, lower-inner, upper-outer, lower-outer, axillary tail, overlapping lesion, and not otherwise specified), and histologic type (adenocarcinoma, adenoid cystic carcinoma, and other). The outcome of interest was the diagnosis of SPM including all types of solid cancers.

Statistics

Statistical analysis was performed using R software (version 4.0.0). The case-control study

consisted of a case group of women with breast cancer who were receiving adjuvant breast RT and a control group of women with breast cancer who did not receive adjuvant breast RT. We compared the differences in distribution between the adjuvant breast RT (case) and non-adjuvant breast RT (control) groups in terms of baseline characteristics using a chi-squared test. We applied the Kaplan-Meier estimator to calculate the cumulative incidence of SPM in women with irradiated breast cancer. We used univariate and multivariate Cox proportional hazards regression models to calculate the hazard ratio (HR) and 95% confidence interval (95% CI) for the risk of developing SPMs among participants. For multivariate analysis, we adjusted potential confounders, namely age, ethnicity, SEER stage, grade, primary site, and histological type (**Table 2**). Because the reference group in the categorical variables were non-RT group within the same category, all mentioned covariates in **Table 2** might be the confounding factors between RT and non-RT groups. Therefore, all variables were included in the multivariate analysis. A *P* value of <0.05 was deemed statistically significant. We conducted subgroup analyses in the strata of clinical interest and latency time (≥5, ≥10, and ≥15 years) to SPM to identify possible prognostic factors (**Table 4**). We also calculated the HR of each specific cancer (**Table 3**) and the latency time (≥5, ≥10, and ≥15 years) to specific SPMs for each group (**Table 5**).

Results

Study cohort

The results of the descriptive analysis of baseline characteristics are displayed in **Table 1**. Of the 13 407 patients identified from the SEER database, 7667 patients were included in the control group, and 5380 patients were included in the case group. No significant differences were observed in age (P=0.501) or histological type (P=0.853), but significant differences were noted in ethnicity (P<0.001), SEER stage (P<0.001), grade (P<0.001), primary site (P< 0.001), and SPM (P<0.001). Risk factors for SPM were black or Asian ethnicity, localized tumor stage, well or moderate differentiation of breast cancer, and a upper-inner or lower-inner primary breast cancer site. We also supplied the Supplementary Table 1 for the readers to compare the features between BC patients with RT developing SPM and not (case is BC patients with RT developing SPM, while control is without SPM).

Cumulative incidence of second primary cancers

The cumulative risk of SPM in the case group, as presented in **Figure 1**, persistently increased until 30 years after breast RT treatment, at which point, the risk level plateaued. Kaplan-Meier curves and log rank test (P<0.001) showing the cumulative risk of SPM in adjuvant RT group were significant higher than non-adjuvant RT group.

Risk factors for SPM after breast RT

The risk factors for SPM among women receiving breast irradiation were analyzed using univariate and multivariate Cox regression models, as presented in **Table 2**. After adjusting for confounders, we determined a significant increased risk of SPM in the case group compared with the control group (adjusted HR [aHR]: 1.105, 95% CI: 1.013-1.206, P=0.024). The aHR (95% CI) of SPM for women aged 40-49 years was 1.36 (95% CI: 1.106-1.589, P=0.002) in the case group compared with that in the control group (**Table 2**). Of all the SEER stages, patients with the regional stage of irradiated breast cancer had a significantly increased risk of SPM (aHR: 1.206, 95% CI: 1.020-1.425, P=0.028). Among the primary sites of breast cancer, a significantly increased risk of SPM was observed in the upper-outer group (aHR: 1.244, 95% CI: 1.067-1.449, P= 0.005) in the case group, and among the various pathologic types, patients with adenocarcinoma had a significantly increased risk of SPM (aHR: 1.105, 95% CI: 1.011-1.207, P=0.028).

Cancer types of SPMs after breast RT

The HR of each cancer in each group is presented in **Table 3**. Compared with the control group, the case group had significantly increased risks of contralateral breast cancer (aHR: 1.268, 95% CI: 1.112-1.445, P<0.001), lung cancer (aHR: 1.218, 95% CI: 1.049-1.565, P=0.022), and urinary system cancer (aHR: 1.702, 95% CI: 1.140-2.543, P=0.009). However, adjuvant breast RT was not significantly associated with other cancers, such as respiratory system cancer (P=0.122), female genital system cancer

Table 1. Characteristics of patients with breast cancer with or without radiotherapy

	Non-adjuvant RT N (%)	Adjuvant RT N (%)	*P* value
Overall	7667	5380	
Age			
40-49	1857 (24.22)	1272 (23.64)	0.501
50-59	2568 (33.49)	1853 (34.44)	
60-69	3242 (42.29)	2255 (41.91)	
Race			
White	6521 (85.05)	4375 (81.32)	<0.001
Black	679 (8.86)	535 (9.94)	
Asian	467 (6.09)	470 (8.74)	
SEER Stage			
Localized	4484 (58.48)	3314 (61.60)	<0.001
Regional	2168 (28.28)	1408 (26.17)	
Distant	630 (8.22)	544 (10.11)	
Unstaged	385 (5.02)	114 (2.12)	
Grade			
Well differentiated	899 (11.73)	1317 (24.48)	<0.001
Moderately differentiated	1118 (14.58)	1101 (20.46)	
Poorly differentiated	1365 (17.80)	879 (16.34)	
Undifferentiated	280 (3.65)	123 (2.29)	
Unknown	4005 (52.24)	1960 (36.43)	
Primary site			
Nipple	64 (0.83)	37 (0.69)	<0.001
Central portion	439 (5.73)	284 (5.28)	
Upper-inner	589 (7.68)	554 (10.30)	
Lower-inner	376 (4.90)	372 (6.91)	
Upper-outer	2265 (29.54)	1511 (28.09)	
Lower-outer	537 (7.00)	374 (6.95)	
Axillary tail	73 (0.95)	66 (1.23)	
Overlapping lesion	1517 (19.79)	1128 (20.97)	
Not otherwise specified	1807 (23.57)	1054 (19.59)	
Histology			
adenocarcinoma	7386 (96.33)	5173 (96.15)	0.853
adenoid cystic carcinoma	173 (2.26)	126 (2.34)	
other	108 (1.41)	81 (1.51)	
SPM			
No	6225 (81.19)	4504 (83.72)	<0.001
Yes	1442 (18.81)	876 (16.28)	
Follow-up time			
years (mean ± SD)	13.45±3.42	13.99±4.10	0.642
years (Median; IQR Q1, Q3)	14 (11.31, 16.62)	14 (11.79, 17.32)	

SPM: second primary malignancy; RT: radiotherapy; SEER: Surveillance, Epidemiology, and End Results; N: number; SD, standard deviation; IQR, interquartile range.

(P=0.1162), rectum and rectosigmoid junction cancers (P=0.62), skin (excluding basal and squamous) cancer (P=0397), endocrine cancer (P=0.215), lymphoma (P=0.827), leukemia (P=0.25), and other cancers (P=0.206).

Risk factors for second primary cancers after breast RT by latency time

The HRs of the two groups according to the latency time since breast cancer treatment

Table 2. Univariate and multivariate Cox regression models of the hazard ratio of SPM after radiotherapy compared with non-radiotherapy for breast cancer

	Crude HR	*P* value	aHR*	*P* value
Overall	1.099 (1.010-1.197)	0.028	1.105 (1.013-1.206)	0.024
Age				
40-49	1.333 (1.117-1.590)	0.001	1.326 (1.106-1.589)	0.002
50-59	1.044 (0.899-1.212)	0.57	1.047 (0.898-1.220)	0.557
60-69	1.041 (0.917-1.183)	0.531	1.052 (0.924-1.199)	0.443
Race				
White	1.090 (0.994-1.195)	0.066	1.094 (0.995-1.202)	0.063
Black	1.219 (0.905-1.643)	0.193	1.259 (0.924-1.715)	0.114
Other	1.102 (0.793-1.530)	0.564	1.136 (0.807-1.599)	0.464
SEER stage				
localized	1.072 (0.967-1.188)	0.188	1.084 (0.974-1.205)	0.138
regional	1.199 (1.017-1.413)	0.031	1.206 (1.020-1.425)	0.028
distant	0.749 (0.441-1.274)	0.286	0.747 (0.437-1.275)	0.285
unstaged	1.550 (0.907-2.648)	0.109	1.452 (0.823-2.564)	0.198
Grade				
Well differentiated	1.091 (0.879-1.353)	0.43	1.095 (0.879-1.363)	0.418
Moderately differentiated	1.212 (0.987-1.489)	0.067	1.229 (0.999-1.511)	0.051
Poorly differentiated	1.071 (0.855-1.341)	0.552	1.087 (0.865-1.365)	0.474
Undifferentiated	1.337 (0.824-2.170)	0.239	1.409 (0.830-2.394)	0.204
Unknown	1.067 (0.942-1.209)	0.31	1.063 (0.937-1.206)	0.342
Primary site				
Nipple	0.957 (0.351-2.612)	0.932	0.925 (0.282-3.030)	0.897
Central portion	1.147 (0.785-1.675)	0.479	1.113 (0.749-1.655)	0.595
Upper-inner	1.113 (0.831-1.490)	0.474	1.135 (0.841-1.530)	0.408
Lower-inner	1.150 (0.838-1.577)	0.387	1.030 (0.801-1.533)	0.534
Upper-outer	1.227 (1.057-1.426)	0.007	1.244 (1.067-1.449)	0.005
Lower-outer	1.204 (0.891-1.628)	0.227	1.209 (0.884-1.653)	0.235
Axillary tail	0.458 (0.179-1.170)	0.103	0.457 (0.175-1.196)	0.111
Overlapping lesion	0.981 (0.811-1.186)	0.843	1.039 (0.855-1.262)	0.699
Not otherwise specified	0.995 (0.809-1.224)	0.965	0.976 (0.790-1.206)	0.822
Histology				
Adenocarcinoma	1.099 (1.008-1.198)	0.033	1.105 (1.011-1.207)	0.028
Adenoid cystic carcinoma	0.907 (0.481-1.709)	0.763	1.003 (0.498-2.02)	0.992
Other	1.464 (0.683-3.138)	0.327	1.707 (0.698-4.173)	0.241

*All covariate in **Table 2** were adjusted. SPM: second primary malignancy; SEER: Surveillance, Epidemiology, and End Results; RT: radiotherapy; HR: hazard ratio; CI: confidence interval; aHR: adjusted hazard ratio.

are presented in **Table 4**. The aHRs of SPMs increased with time since breast RT and were 1.273 (1.150-1.409), 1.358 (1.200-1.536), and 1.366 (1.158-1.611) for latency times of ≥5, ≥10, and ≥15 years, respectively, compared with <5 years for those receiving adjuvant breast RT. For the latency periods of 5, 10, and 15 years after treatment for irradiated breast cancer, significant risk factors for SPM were noted, such as a young age, black or white ethnicity, localized or regional SEER stage, well and moderate differentiation, an upper-outer breast cancer site, and adenocarcinoma (**Table 4**).

HRs of secondary cancer types after RT by latency time

The HRs according to irradiated breast cancer latency time periods of ≥5, ≥10, and ≥15 years

Table 3. The hazard ratio of each specific cancer for RT cohort compared with non-RT cohort

	Crude HR	*P* value	aHR*	*P* value
Contralateral Breast Cancer	1.251 (1.101-1.421)	<0.001	1.268 (1.112-1.445)	<0.001
Digestive System Cancer	0.793 (0.631-0.997)	0.047	0.804 (0.637-1.015)	0.067
Lung Cancer	1.157 (0.906-1.479)	0.243	1.218 (1.049-1.565)	0.022
Female Genital System Cancer	0.825 (0.641-1.061)	0.134	0.832 (0.643-1.077)	0.162
Rectum and Rectosigmoid Junction Cancer	0.890 (0.438-1.806)	0.746	0.830 (0.398-1.731)	0.620
Skin excluding Basal and Squamous Cancer	1.301 (0.747-2.267)	0.353	1.279 (0.724-2.257)	0.397
Bladder Cancer	1.711 (1.155-2.533)	0.007	1.702 (1.140-2.543)	0.009
Endocrine System	0.643 (0.309-1.339)	0.238	0.619 (0.290-1.321)	0.215
Lymphoma	0.938 (0.554-1.587)	0.811	0.942 (0.552-1.609)	0.827
Leukemia	0.693 (0.363-1.322)	0.265	0.680 (0.353-1.311)	0.250
Sarcoma	1.325 (0.839-2.093)	0.227	1.350 (0.848-2.151)	0.206

*All covariates in **Table 3** were adjusted. SPM: second primary malignancies; SEER: Surveillance, Epidemiology, and End Results; RT: radiotherapy; HR: hazard ratio; CI: confidence interval; aHR: adjusted hazard ratio.

Table 4. The hazard ratio of SPM after radiotherapy compared with non-radiotherapy for breast cancer according to latency time to SPM

	Time since treatment ≥5 years		Time since treatment ≥10 years		Time since treatment ≥15 years	
	aHR*	*P* value	aHR*	*P* value	aHR*	*P* value
Overall	1.273 (1.150-1.409)	<0.001	1.358 (1.200-1.536)	<0.001	1.366 (1.158-1.611)	<0.001
Age						
40-49	1.448 (1.184-1.773)	<0.001	1.550 (1.224-1.962)	<0.001	1.611 (1.207-2.149)	0.001
50-59	1.186 (0.992-1.417)	0.061	1.289 (1.042-1.594)	0.020	1.242 (1.136-1.647)	0.013
60-69	1.250 (0.967-1.464)	0.076	1.302 (1.064-1.592)	0.010	1.363 (1.016-1.830)	0.039
Race						
White	1.207 (1.081-1.348)	<0.001	1.302 (1.139-1.488)	<0.001	1.293 (1.082-1.546)	0.005
Black	1.999 (1.371-2.913)	<0.001	2.242 (1.379-3.647)	0.001	3.392 (1.729-6.653)	<0.001
Asian	1.692 (0.9212.554)	0.112	1.484 (0.905-2.433)	0.118	1.402 (0.720-2.731)	0.320
SEER stage						
localized	1.250 (1.106-1.413)	<0.001	1.305 (1.124-1.515)	<0.001	1.310 (1.072-1.602)	0.008
regional	1.359 (1.111-1.661)	0.003	1.530 (1.197-1.956)	<0.001	1.571 (1.138-2.167)	0.006
distant	1.824 (0.848-3.922)	0.124	1.673 (0.585-4.784)	0.337	2.499 (0.548-11.39)	0.237
unstaged	1.358 (0.615-3.002)	0.449	2.417 (0.903-6.467)	0.079	2.339 (0.401-13.63)	0.345
Grade						
Well differentiated	1.393 (1.067-1.818)	0.015	1.414 (1.093-2.014)	0.025	2.044 (1.188-3.518)	0.01
Moderately differentiated	1.427 (1.121-1.815)	0.004	1.593 (1.183-2.146)	0.002	1.513 (1.051-2.409)	0.021
Poorly differentiated	1.139 (0.872-1.486)	0.339	1.205 (0.864-1.683)	0.272	1.190 (0.785-1.803)	0.412
Undifferentiated	1.404 (0.761-2.592)	0.278	1.247 (0.563-2.762)	0.586	1.301 (0.486-3.483)	0.600
Unknown	1.214 (0.747-1.408)	0.114	1.331 (0.919-1.584)	0.081	1.369 (1.098-1.706)	0.075
Primary site						
Central portion	1.342 (0.838-2.151)	0.221	1.523 (0.833-2.784)	0.172	2.609 (0.925-6.636)	0.144
Upper-inner	1.331 (0.945-1.875)	0.102	1.488 (0.992-2.232)	0.055	1.369 (0.805-2.329)	0.247
Lower-inner	1.295 (0.885-1.893)	0.183	1.478 (0.924-2.365)	0.103	1.302 (0.721-2.351)	0.382
Upper-outer	1.418 (1.191-1.689)	<0.001	1.393 (1.131-1.715)	0.002	1.320 (1.193-1.756)	0.036
Lower-outer	1.405 (0.972-2.031)	0.071	1.324 (0.819-2.142)	0.252	1.216 (0.638-2.317)	0.552
Overlapping lesion	1.157 (0.917-1.459)	0.218	1.178 (0.880-1.576)	0.270	1.215 (0.941-2.205)	0.130
Nipple, Axillary tail, and Breast, NOS	1.094 (0.855-1.401)	0.475	1.391 (0.931-1.875)	0.131	1.375 (0.927-2.040)	0.113
Histology						
Adenocarcinoma	1.273 (1.148-1.412)	<0.001	1.359 (1.198-1.541)	<0.001	1.374 (1.162-1.624)	<0.001
Adenoid cystic carcinoma	0.999 (0.425-2.352)	0.998	1.081 (0.347-3.368)	0.893	0.881 (0.269-2.887)	0.834
Other	2.201 (0.301-9.946)	0.064	3.171 (0.602-16.70)	0.173	3.0191 (0.712-14.21)	0.294

*All covariates in **Table 4** were adjusted. SPM: second primary malignancy; SEER: Surveillance, Epidemiology, and End Results; RT: radiotherapy; HR: hazard ratio; CI: confidence interval; aHR: adjusted hazard ratio.

Table 5. The hazard ratio of each specific cancer after radiotherapy compared with non-radiotherapy according to latency time to SPM

	Time since treatment ≥5 years		Time since treatment ≥10 years		Time since treatment ≥15 years	
	aHR*	*P* value	aHR*	*P* value	aHR*	*P* value
Contralateral Breast Cancer	1.492 (1.277-1.744)	<0.001	1.811 (1.498-2.189)	<0.001	1.857 (1.443-2.389)	<0.001
Digestive System Cancer	0.965 (0.735-1.267)	0.796	1.032 (0.741-1.438)	0.852	0.821 (0.523-1.288)	0.390
Lung Cancer	1.326 (1.001-1.757)	0.049	1.364 (1.072-1.914)	0.042	1.303 (0.834-2.037)	0.245
Female Genital System Cancer	1.002 (0.741-1.355)	0.992	0.921 (0.624-1.361)	0.680	1.139 (0.650-1.994)	0.649
Rectum and Rectosigmoid Junction Cancer	0.926 (0.353-2.426)	0.875	0.198 (0.025-1.555)	0.123	1.625 (0.567-4.655)	0.366
Skin excluding Basal and Squamous Cancer	1.318 (0.645-2.695)	0.449	1.298 (0.566-2.977)	0.538	2.034 (0.987-4.193)	0.054
Bladder cancer	1.808 (1.156-2.828)	0.009	1.783 (1.043-3.047)	0.034	0.332 (0.040-2.739)	0.306
Endocrine System	0.777 (0.293-2.058)	0.611	0.542 (0.149-1.973)	0.353	1.491 (0.677-3.281)	0.321
Lymphoma	1.043 (0.599-1.816)	0.881	0.994 (0.523-1.889)	0.985	0.458 (0.128-1.634)	0.229
Leukemia	0.801 (0.360-1.780)	0.586	0.619 (0.223-1.722)	0.358	0.804 (0.343-1.883)	0.615
Sarcoma	1.222 (0.724-2.065)	0.453	1.085 (0.557-2.115)	0.810	1.857 (1.443-2.389)	<0.001

*All covariates in **Table 5** were adjusted. SPM: second primary malignancy; SEER: Surveillance, Epidemiology, and End Results; RT: radiotherapy; HR: hazard ratio; CI: confidence interval; aHR: adjusted hazard ratio.

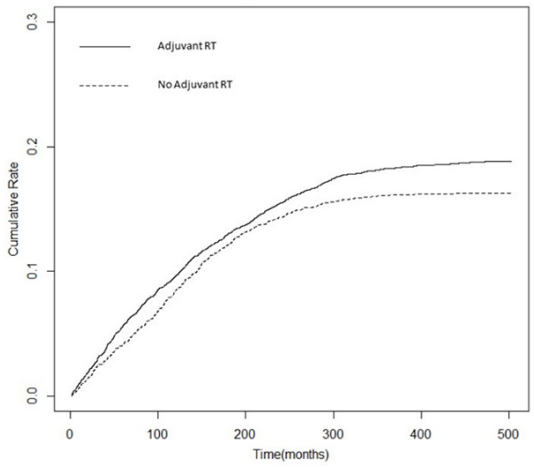

Figure 1. Cumulative incidence of cancers in patients with irradiated and non-irradiated breast cancer.

of each specific cancer are presented in **Table 5**. In women with latency periods of ≥5 and ≥10 years, contralateral breast cancer, lung cancer, and urinary system cancer were significant specific cancer types of SPMs. In women with a latency period of ≥15 years, contralateral breast cancer and sarcoma were significant specific types of SPMs. The aHRs (95% CI) of contralateral breast cancer, lung cancer, and urinary cancer in the case group were 1.811 (1.498-2.189), 1.364 (1.072-1.914), and 1.783 (1.043-3.047), respectively, for the latency period of ≥10 years. The aHRs of contralateral breast cancer and sarcoma in the case group were 1.857 (1.443-2.389) and 1.857 (1.443-2.389), respectively, for the latency period of ≥15 years (**Table 5**).

Discussion

In the multivariable Cox proportional model in this study, the independent risk factors for SPM for women with breast cancer women who were receiving adjuvant breast RT were young age (40-49 years), SEER regional stage, upper-outer primary breast cancer site, and adenocarcinoma (**Table 2**). These factors may be crucial for young patients with a prolonged anticipated survival, for whom a heterogeneous irradiation dose-volume may result in a higher incidence of SPM or unintended consequences [22-24]. Adjuvant breast RT for patients with breast cancer was associated with a significant increase in SPM, which is consistent with the results of previous studies [19-21].

No study has determined the SEER regional stage, upper-outer primary breast cancer site, or adenocarcinoma as independent risk factors for SPM in patients with breast cancer receiving adjuvant breast RT [19-21]. The association of the SEER regional stage and upper-outer breast cancer with a high risk of SPM (**Tables 2** and **4**) might be due to the effects of radiation. A large irradiation volume and a number of scatter radiation doses to the lymphatic and upper-outer areas are highly possible because the RT portals are designed and oriented to encompass a wide area of the breast; therefore, lymphatic regions have a high risk of absorbing some of the radiation, as illustrated through the SEER regional stages and in patients with upper-outer breast cancer [25, 26]. The potential mechanism of a high risk of SPM

in women with irradiated breast cancer with adenocarcinoma might involve an unknown genetic susceptibility, such as rs4946728 or rs1040411, noncoding single nucleotide polymorphisms located on chromosome 6q21, a loss of chromosome 5 or 7, or a mutation of the *TP53* gene [3, 27]. Future genome-wide association studies for breast adenocarcinoma should be conducted [3]. Our findings provide fundamental knowledge for future studies of genetic susceptibility.

We also surveyed the risk factors for SPM by latency periods of ≥5, ≥10, and ≥15 years (**Table 4**) and determined that individuals of black or white ethnicity might be more susceptible to SPM after breast RT than Asians, a result similar to those displayed in **Table 2**. Our study is the first to demonstrate that black and white populations are more susceptible to a breast irradiation-induced SPM risk than the Asian population. The special genetic susceptibility in the black and white populations should be further examined. Patients aged 50-59 and 60-69 years with a remaining life expectancy of ≥10 years exhibited a significantly increased risk of SPM (**Table 4**). Similar results were noted for patients with a potentially long life expectancy with a localized SEER stage, well differentiation, or moderate differentiation [28, 29].

The absolute risk of SPM because of adjuvant breast RT is small [19-21]. In a cohort study of 58 000 patients treated for invasive breast cancer, approximately 13 of 1000 women developed second nonbreast primary cancer within 10 years, representing an elevated rate (RR: 1.22, 95% CI: 1.17-1.27) compared with the general population [30]. Additionally, the risk of SPM after receiving breast RT varied according to the elapsed time since treatment completion. For example, secondary leukemias tend to occur within 5-7 years; solid tumors, such as those of esophageal cancer, usually present at least 10 years after RT [31-33]. However, RT-induced angiosarcoma typically presents after 5 to 8 years [34]. As presented in **Table 3**, contralateral breast cancer, lung cancer, and bladder cancer were the significant specific secondary cancer types; this result is compatible with those of previous studies [31-33]. Sarcoma was not a significant secondary cancer type (**Table 3**). Studies have indicated that RT for breast cancer contributes little to the already high risk of second cancer in the opposite breast, a result that is compatible with our study findings (**Tables 3** and **5**) [35-38]. Moreover, some studies have determined a low, albeit significant, risk of second primary lung cancer in women after RT for breast cancer [19, 39, 40].

Further subgroup analysis of the latency periods revealed that the significant specific secondary cancers were contralateral breast cancer, lung cancer, and bladder cancer in women with a latency period of ≥10 years. Sarcoma and contralateral breast cancer were significant specific secondary cancers in women with a latency period of ≥15 years. Our findings revealed that secondary contralateral breast cancer, lung cancer, and bladder cancer tended to occur ≥5-10 years after breast RT [19, 35-40]. Sarcoma usually presents at least 15 years after breast RT [34]. Limited data suggest a slight increase in the incidence of contralateral breast cancers following breast or chest wall RT. Our study and long-term follow-up revealed a significant increased risk of contralateral breast cancer (**Tables 3** and **5**) [12, 35, 36, 41-43].

Our study is the first study with a long-term follow-up period that examined the risk factors and specific secondary cancers according to latency period in patients with breast cancer who received adjuvant breast RT (**Tables 4** and **5**). Patients had an increased risk of bladder cancer, despite bladder RT not being in the same field as breast cancer RT. Consistent with previous studies, we determined an increased risk of second primary kidney or bladder cancer after breast RT [5, 44, 45]. The bladder absorbs a considerable amount of scattered radiation during RT for breast cancer treatment [46], which contributes to the risk of SPM after breast RT. However, we still have some doubts about this correlation of the link between postoperative breast/chest wall plus/minus regional node RT and the risk of bladder cancer. Because the references were old [5, 44, 45], the contemporary RT techniques might be not associated with this kind. We suggest further analyses of the correlation of the link in the future.

As presented in **Figure 1**, the cumulative risk of SPM was low, at approximately 6, 10, and 13 cancers per 1000 women with irradiated breast cancer after latency periods of 5, 10,

and 15 years, respectively, after breast RT, a result consistent with those of previous studies [30-34]. The incidence of SPM increased in women after 20 to 30 years and plateaued at approximately 16 cancers per 1000 women at 30 years after breast RT (**Figure 1**). Our study is the first to reveal these findings. In **Table 1** the crude SPM risk seemed likely little high in non-adjuvant RT group and less risk of SPM in adjuvant RT group. The crude risk of SPM might be bias by competing risk of mortality [47], because there might be higer mortality for patients with breast cancer with adjuvant RT. The National Comprehensive Cancer Network guidelines do not recommend standard adjuvant RT in some subgroups of patients with favorable histology and a very low risk of relapse [48]. Therefore, there mihgt be more favorable histology, less advanced stages, and a very low risk of relapse patients in non-RT group. A competing risk is an event whose occurrence precludes the occurrence of the primary event of interest [47], the higher mortality in RT group cannot met the occurrence of the primary event of interest [47]. Therefore, after adjustement of age group at primary diagnosis (40-49, 50-59, and 60-69 years), ethnicity (White, Black, and Asian), SEER stage of tumor (localized, regional, distant, and unstaged), tumor grade (well differentiated, moderately differentiated, poorly differentiated, undifferentiated, and unknown), primary sites (nipple, central portion, upper-inner, lower-inner, upper-outer, lower-outer, axillary tail, overlapping lesion, and not otherwise specified), and histologic type (adenocarcinoma, adenoid cystic carcinoma, and other), the risk of SPM between case and control gropus might be more close to the the real. In the future, patients should be made aware of the risk of SPM in women with breast cancer receiving adjuvant breast RT, so they can make informed decisions about their future.

RT is an important component of breast cancer treatment that reduces local recurrence and improves survival after breast surgery, especially in breast conservative surgery [49]. Breast conservation rates have increased significantly since the late 1980s and techniques have improved with greater awareness of the impact of radiation on the heart [50]. Several randomized controlled trials of breast conservation using standard whole breast irradiation, whole breast hypofractionation, accelerated partial breast irradiation and intraoperative radiation are ongoing [51-53]. Selection criteria for breast conservation and the utility of adding a boost dose to the primary tumor site are also performed in the past ten years [54]. Modern dose constraints are different and 10 different radiation techniques from the 1980s through to modern volumetric modulated arc therapy are progression for a patient where the breast and internal mammary nodes are treated [50]. Short courses of RT over 3-4 weeks are generally as effective as longer courses [50-53]. Short-term follow-up of trials of accelerated partial breast irradiation show promise for selected good prognosis subgroups [50-53]. The role of intraoperative radiation remains controversial [50]. In the last 30 years, there have been significant advances in radiation techniques [55]. Modern radiotherapy equipment and techniques will reduce complications and improve survival rates [55]. The long-term side effects like SPM for several modern techniques should be monitored carefully.

Our study has several strengths, including the use of a population-based registry with detailed baseline information. This is the first study with a large cohort and long-term follow-up to examine the risk factors for SPM and specific secondary cancer types for patients with breast cancer receiving adjuvant breast RT. Few long-term studies have analyzed patient characteristics that are independent risk factors for SPM by various latency periods, and ours is the first to determine these specific risk factors and to identify the emergence of specific secondary cancers in patients after various latency periods.

This study also has several limitations. First, the patients in our study were categorized by SEER stages, but the SEER stages are not the routine cancer stages used by physicians. Many studies using SEER stages have been published, and they have illustrated a notable association and validation between SEER stages and the stages in the *AJCC Cancer Staging Handbook: TNM Classification of Malignant Tumors* [1, 2]. Moreover, there were no hormones receptor status, or human epidermal growth factor receptor 2 status in the SEER database. Nevertheless, there is no solid data to report the association of human epidermal

growth factor receptor 2 status, hormones receptor status, and SPM. Second, the SEER database did not include comorbid conditions. However, because patients could receive standard breast cancer surgery and adjuvant treatments, we believe that the patients in our study might be relatively healthy. Third, the exact irradiation dose-volume for normal tissue could not be calculated using the data from the SEER database. Nevertheless, the standard breast irradiation dose-volume was approximately 50 Gy [56], and most breast cancer patients completed breast irradiation. Thus, the irradiation dose-volume might be similar for most patients receiving adjuvant breast RT, although the specific chest wall anatomy of some patients might have contributed to additional areas of irradiated normal tissue because they were near the irradiation field. However, the small population of patients with this specific anatomy could be disregarded under the law of large numbers [57, 58]. Fourth, the comprehensive RT equipment and techniques were missing in the current SEER database. The differences of SPM risk and RT techniques like 2D, 3D, intensity modulated radiation therapy, image-guided radiation therapy, proton, standard whole breast irradiation, whole breast hypofractionation, accelerated partial breast irradiation and intraoperative radiation are missing in the current study. Fifth, the biases of our retrospective study with a very long accrual period for radiation induced SPM might be possible, because radiation induced SPM is late complications. To obtain information on population specificity and disease occurrence, a large-scale randomized controlled trial (RTC) comparing meticulously selected patients undergoing adjuvant breast RT and with those without adjuvant breast RT is necessary. Performing this type of RTC to assess the effects of adjuvant breast RT is difficult if patients are treated according to treatment guidelines, including the National Comprehensive Cancer Network guidelines that do not recommend standard adjuvant RT in some subgroups of patients with favorable histology and a very low risk of relapse [48]. Finally, the SEER database does not contain information regarding dietary habits or body mass index, both of which may be risk factors for SPM and specific secondary cancers. Considering the magnitude and statistical significance of the observed effects in the current study, these limitations are unlikely to affect our conclusions.

Conclusions

Adjuvant breast RT, black or white ethnicity, diagnosis of adenocarcinoma, young age (40-49 years), SEER regional stage, and upper-outer breast cancer site were independent risk factors for SPM in women with irradiated breast cancer, regardless of the latency period. Contralateral breast cancer, lung cancer, and bladder cancer were secondary cancers after breast RT and a latency period of ≥10 years. After a latency period of ≥15 years, sarcoma and contralateral breast cancer were significant specific secondary cancer types. The incidence of SPM was persistent 30 years after breast RT and increased to approximately 16 cancers per 1000 women who had irradiated breast cancer.

Acknowledgements

Lohsu Medical Foundation, LotungPoh-Ai Hospital, supports Szuyuan Wu's work (Funding Number: 10908, 10909, 11001, 11002, 11003, 11006, and 11013). Lei Qin's work is supported by University of International Business and Economics (UIBE) Huiyuan distinguished young scholars research fund (grant 20JQ07). This research was funded by Fu Jen Catholic University (A0110180 and A0110182) from Prof. Ben-Chang Shia.

Disclosure of conflict of interest

None.

Abbreviations

SPM, Second primary malignancies; SEER, Surveillance, Epidemiology, and End Results; RT, Radiotherapy; HR, Hazard ratio; CI, Confidence interval; ICD-O-3, International Classification of Diseases for Oncology, third edition; aHR, Adjusted hazard ration; SNPs, Single nucleotide polymorphisms; GWAS, Genome-wide association studies.

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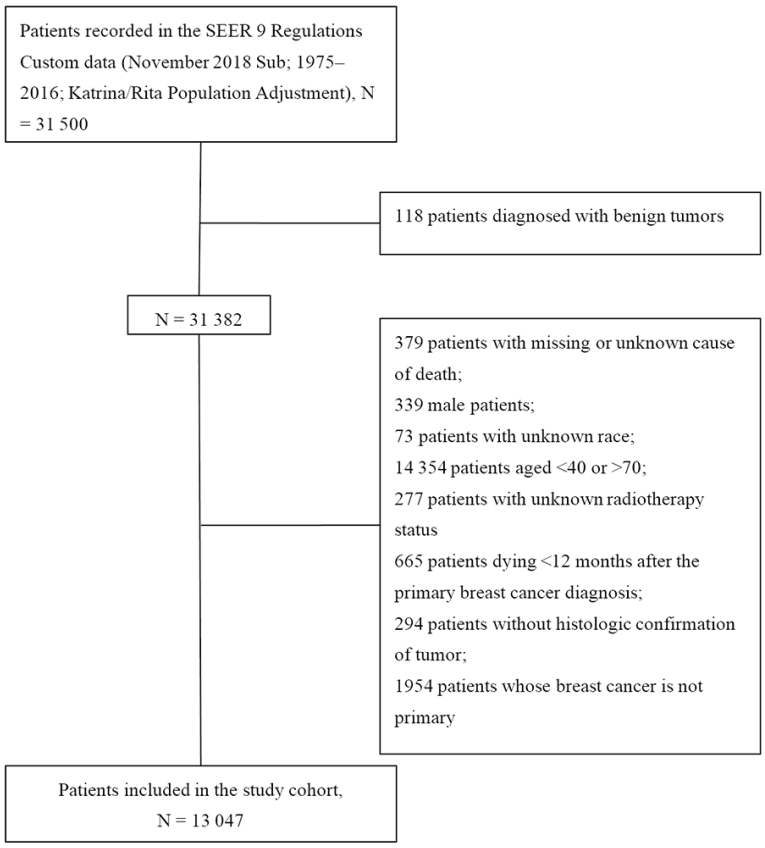

Supplementary Figure 1. Patient enrollment in the study.

Supplementary Table 1. Characteristics of patients with breast cancer with or without SPM

	Non-SPM N (%)	SPM N (%)	*P* value
Overall	10729	2318	
Age			
40-49	2594 (24.18%)	535 (23.08%)	0.05
50-59	3667 (34.18%)	754 (32.53%)	
60-69	4468 (41.64%)	1029 (44.39%)	
Race			
White	8905 (83.00%)	1991 (85.89%)	0.002
Black	1035 (9.65%)	179 (7.72%)	
Asian	789 (7.35%)	148 (6.38%)	
SEER Stage			
Localized	6210 (57.88%)	1588 (68.51%)	<0.001
Regional	2983 (27.80%)	593 (25.58%)	
Distant	1111 (10.36%)	63 (2.72%)	
Unstaged	425 (3.96%)	74 (3.19%)	
Grade			
Well differentiated	1871 (17.44%)	345 (14.88%)	<0.001
Moderately differentiated	1845 (17.20%)	374 (16.13%)	
Poorly differentiated	1904 (17.75%)	340 (14.67%)	
Undifferentiated	325 (3.03%)	78 (3.36%)	
Unknown	4784 (44.59%)	1181 (50.95%)	
Primary site			
Nipple	83 (0.77%)	18 (0.78%)	<0.001
Central portion	605 (5.64%)	118 (5.09%)	
Upper-inner	953 (8.88%)	190 (8.20%)	
Lower-inner	593 (5.53%)	155 (6.69%)	
Upper-outer	3034 (28.28%)	742 (32.01%)	
Lower-outer	729 (6.79%)	182 (7.85%)	
Axillary tail	115 (1.07%)	24 (1.04%)	
Overlapping lesion	2177 (20.29%)	468 (20.19%)	
Not otherwise specified	2440 (22.74%)	421 (18.16%)	
Histology			
adenocarcinoma	10322 (96.21%)	2237 (96.51%)	0.668
adenoid cystic carcinoma	247 (2.30%)	52 (2.24%)	
other	160 (1.49%)	29 (1.25%)	
Adjuvant RT			
No	6670 (62.17%)	997 (43.01%)	<0.001
Yes	4059 (37.83%)	1321 (56.99%)	
Follow-up time			
years (mean ± SD)	14.68±9.99	11.10±8.13	<0.001
years (Median; IQR Q1, Q3)	15.33 (4.00, 19.50)	9.75 (4.27, 16.17)	

SPM: second primary malignancy; RT: radiotherapy; SEER: Surveillance, Epidemiology, and End Results; N: number; SD, standard deviation; IQR, interquartile range.