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ORIGINAL ARTICLE

Survival and chemotherapy-related risk of second primary malignancy in breast cancer patients: a SEER-based study

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Abstract

Background With the improvement in the survival of breast cancer, developing second primary malignancy becomes a serious health issue. The aim of this study was to explore the survival of breast cancer patients with second primary malignancy, and to evaluate the impact of chemotherapy on the risk of different cancer sites.

Method Obtaining data from the Surveillance, Epidemiology, and End Results database, we calculated the standardized incidence ratio (SIR) for second primary malignancy in breast cancer survivors between 2000 and 2014. Overall survival and cancer-specific survival were analyzed with Kaplan–Meier method. Then, we further conducted stratified sub-analyses according to chemotherapy.

Results The overall risk of second primary cancer for all sites was significantly elevated in breast cancer patients (SIR = 1.15, 95% CI 1.14–1.16). Overall survival and cancer-specific survival of the patients with breast cancer only were significantly better than the patients with multiple primary cancers (both $P < 0.001$). Chemotherapy was associated with increased incidences for all sites, except lymphoma, myeloma, and chronic lymphocytic leukemia (SIR = 0.80, 95% CI 0.72–0.88; SIR = 0.85, 95% CI 0.71–1.01; SIR = 0.57, 95% CI 0.43–0.74, respectively). The risk for developing second acute myeloid leukemia after chemotherapy in breast cancer patients varied with age and latency.

Conclusion Female breast cancer patients showed higher incidence of second primary malignancy, which was associated with poorer prognosis. Chemotherapy benefits should be weighed against the risks of second primary malignancy.

Keywords Breast cancer · Second primary malignancy · Chemotherapy · Survival

Introduction

Breast cancer (BC) is the most commonly diagnosed cancer among US women (excluding skin cancers). Based on National Cancer Institutes (NCI's) Surveillance, Epidemiology, and End Results (SEER) program and the Centers for Disease Control and Prevention's National Program of Cancer Registries, nearly 252,710 new cases of invasive female BC would be diagnosed in 2017 [1]. Statistically, the risk for a 60-year-old, cancer-free woman being diagnosed with BC over the next 10 years is 3.4% [1]. Fortunately, due to earlier detection through systematic screening and increased awareness, as well as improvements in treatments, the survival rate for female BC patients has increased, with the 5-year, 10-year, and 15-year relative survival rates being 89%, 83%, and 78%, respectively [2]. Over 3.5 million US women with a history of BC were estimated to be alive on January 1, 2016 [2].

Because of the high incidence and good prognosis of BC, the risk of developing a second primary malignancy (SPM) thereafter may turn into a serious health issue both for the patients and health caring system. According to a meta-analysis, women with a first primary BC had a 17% higher risk of developing a second primary cancer compared to the general population [3]. The previous studies

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have evaluated the standardized incidence ratios (SIR) of developing an SPM according to cancer sites [4–8], racial and ethnic difference [9], different hormone receptor status [8, 10–12], and various study cohort [7, 13–16]. However, a few literatures explored the effect of treatment modalities [5, 17–19], or the survival of these patients with multiple malignancies. The role of chemotherapy on different second primary malignancies followed BC, especially the lymphatic and hematopoietic system, remained unelucidated.

The aims of our study were to systemically evaluate the incidence of SPM in BC patients, to assess the survival of this cohort, and to explore the effect of chemotherapy on subsequent malignancies among BC survivors.

Materials and methods

We utilized the SEER database to construct a retrospective study of women diagnosed with a first primary, pathologically confirmed, invasive, stages I–III BC between January 1, 2001 and December 31, 2014. The SEER 18 registry database with additional treatment information collects information on patient demographics, clinical characteristics, survival, and treatment modality in the United States. We retrieved data of cases with BC only and BC survivors with subsequent malignancies. According to the "Multiple Primary and Histology Coding Rules", multiple tumors, that fit certain rules and are not described as metastases, are classified as multiple primaries in SEER registries [20]. Patients with unknown hormone status, unknown laterality, unknown tumor Grade, and a survival shorter than 6 months were excluded. Second primary cancers that were diagnosed within 6 months of BC, and cases derived from death certificates or autopsy were also excluded. Data extraction was performed by SEER*Stat software version 8.3.5 based on the November 2016 data submission [21], last follow-up time being December 31, 2014.

There were 406,115 women with BC only and 36,119 survivors with multiple cancers (38,897 subsequent malignancies) in this database fitting our criteria. We ascertained data including year of diagnosis, age at diagnosis, marital status (married, not married, and unknown), laterality of BC, race (white, black, other and unknown), latency (the time interval between the first breast cancer diagnosis and the second cancer diagnosis), American Joint Committee on Cancer (AJCC) stage, estrogen receptor (ER) status, progesterone receptor (PR) status, tumor Grade (four-grade system), and chemotherapy recode (yes or no/unknown).

The independent ethical committee/institutional review board of Fudan University Shanghai Cancer Center Ethical Committee reviewed our study and declared it exempt from approval.

Statistical analysis

Using the SEER*Stat Multiple primary-standardized incidence ratios (MP-SIR) tool (version 8.3.5), we estimated SIRs and 95% confidence intervals (CI) to compare the relative risk with the general population. SIRs for "all sites" or specific cancers were calculated through dividing the observed numbers by the expected numbers of second primary cancers based on the rates of the general population. Breast cancer-specific survival (BCSS), calculated from the date of diagnosis to the date of BC death, and overall survival (OS), defined as the interval from BC diagnosis to the death from any cause, were compared with the Kaplan–Meier method. Accumulated risk curve was also constructed by the Kaplan–Meier method. Multivariate Cox regression models were built to assess the independent association with BCSS and OS. Hazard ratios (HR) and their 95% CI were estimated using the Cox models. Statistical analyses were performed using SPSS 22.0 (Chicago, IL, USA) and All P values were two-sided and considered of statistical significance when $P < 0.05$.

Results

SIRs and survival of the whole cohort

Table 1 showed the SIRs for SPM risk in BC patients by patient characteristic. The overall risk of second primary cancer for all sites was significantly elevated in BC patients (SIR = 1.15, 95% CI 1.14–1.16). Increased risks were observed in all years of diagnosis, all races (except unknown race), all marital status, all age at diagnosis, all latency periods, all tumor Grade, all hormone status, and all tumor stage. For patients younger than 75 years old, the SIRs decreased significantly as the age at diagnosis of BC increased (SIR = 7.33, 95% CI 6.30–8.49; SIR = 3.09, 95% CI 2.93–3.25; SIR = 1.58, 95% CI 1.54–1.63; SIR = 1.16, 95% CI 1.14–1.19; SIR = 1.04, 95% CI 1.02–1.06; respectively). In addition, the risk for second primary cancer ascended as the latency period between the diagnosis of two primary cancers extended (SIR = 1.02, 95% CI 0.98–1.06; SIR = 1.07, 95% CI 1.05–1.08; SIR = 1.25, 95% CI 1.23–1.28; SIR = 1.33, 95% CI 1.14–1.16, respectively). Similarly, patients with higher tumor Grade, negative hormone receptor expression, and more advanced stage presented higher SIRs, as shown in Table 1.

82,048 patients died during follow-up, 39,480 of which died from the first BC. Both the BCSS and OS of the patients with BC only were significantly better than the patients with multiple primary cancers (both $P < 0.001$),

Table 1 Standardized incidence ratios for second malignancy risk in breast cancer patients by characteristic

Characteristic	*O*	SIR (95% CI)
Total	38,897	1.15* (1.14–1.16)
Age at diagnosis, years		
< 35	178	7.33* (6.30–8.49)
35–44	1477	3.09* (2.93–3.25)
45–54	5035	1.58* (1.54–1.63)
55–64	8451	1.16* (1.14–1.19)
65–74	10,846	1.04* (1.02–1.06)
≥ 75	12,910	1.04* (1.02–1.06)
Calendar year of diagnosis		
2000–2004	3477	1.11* (1.07–1.15)
2005–2009	12,688	1.14* (1.12–1.16)
2010–2014	22,732	1.17* (1.15–1.18)
Latency period, months		
6–11	2647	1.02 (0.98–1.06)
12–59	17,797	1.07* (1.05–1.08)
60–119	14,222	1.25* (1.23–1.28)
≥ 120	4231	1.33* (1.14–1.16)
Race		
White	32,447	1.10* (1.09–1.12)
Black	3914	1.48* (1.44–1.53)
Other	2513	1.57* (1.51–1.63)
Unknown	23	0.20* (0.13–0.30)
Laterality		
Right	19,280	1.16* (1.14–1.18)
Left	19,617	1.15* (1.13–1.16)
Grade		
I	8838	1.05* (1.03–1.07)
II	16,692	1.11* (1.09–1.13)
III	12,868	1.30* (1.27–1.32)
IV	499	1.32* (1.21–1.44)
ER		
Positive	30,552	1.09* (1.08–1.11)
Negative	8345	1.43* (1.40–1.46)
PR		
Positive	26,363	1.10* (1.09–1.12)
Negative	12,533	1.27* (1.25–1.29)
Stage		
I	20,820	1.11* (1.10–1.13)
IIA	9814	1.16* (1.14–1.19)
IIB	3860	1.20* (1.16–1.24)
III NOS	64	1.30* (1.00–1.66)
III A	2432	1.22* (1.17–1.27)
III B	751	1.43* (1.33–1.53)
III C	1156	1.44* (1.36–1.53)

O observed numbers, *SIR* standardized incidence ratio, *ER* estrogen receptor, *PR* progesterone receptor, *NOS* not otherwise specified

*$P < 0.05$; confidence intervals are 95%

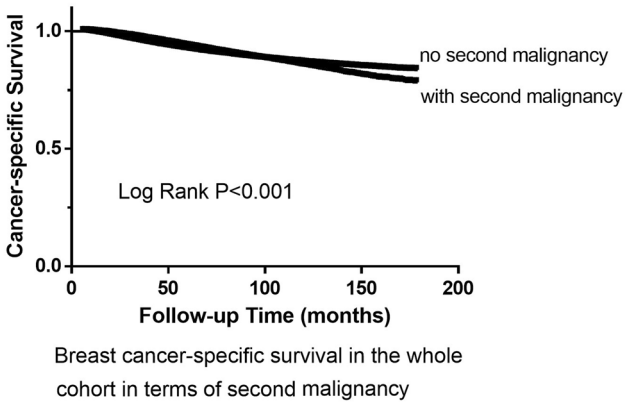

Fig. 1 Breast cancer-specific survival in the whole cohort in terms of second malignancy

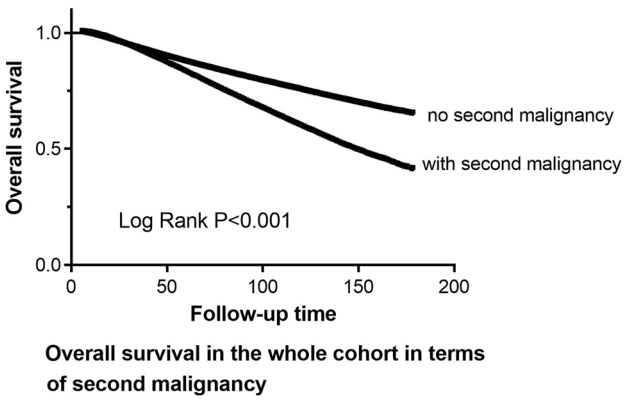

Fig. 2 Overall survival in the whole cohort in terms of second malignancy

as shown in Figs. 1 and 2. After adjusting age at diagnosis, race, marital status, tumor Grade, stage, ER and PR status, and treatment modality, multivariate Cox regression models indicated that developing SPM was statistically associated with BCSS and OS (HR = 1.059, 95% CI 1.026–1.093, $P < 0.001$; HR = 2.782, 95% CI 2.731–2.833, $P < 0.001$; respectively, as shown in Supplement Table 1).

Of the 442,234 BC patients, 36,119 patients had multiple primary malignancies. The most frequent observed second primary cancer was BC (33.4%), followed by cancer of digestive system (16.9%), lung and bronchus (13.4%), genital system (10.4%), lymphatic and hematopoietic system (7.6%), urinary system (5.1%), and thyroid (3.3%). Figure 3 showed the accumulated risk of developing second primary malignancies in BC patients according to cancer sites.

SIRs stratified by chemotherapy

To evaluate the impact of chemotherapy on the risk of different second primary malignancies, we further conducted

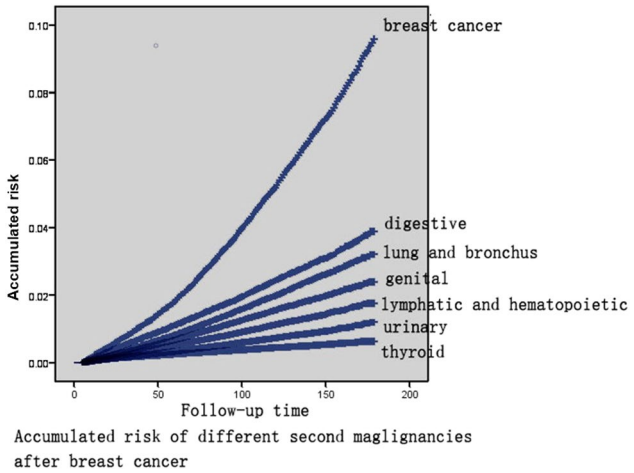

Fig. 3 Accumulated risk of different second malignancies after breast cancer

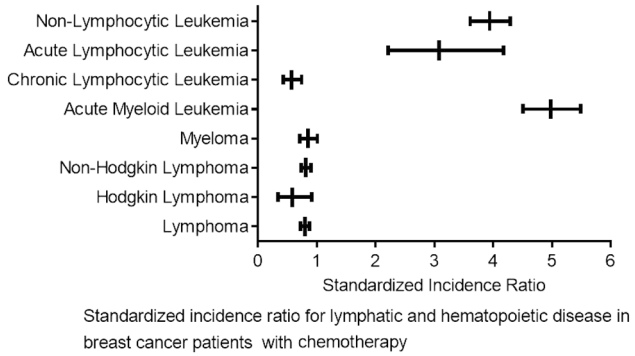

Fig. 4 Standardized incidence ratio for lymphatic and hematopoietic disease in breast cancer patients with chemotherapy

stratified sub-analyses to estimate site specific SIRs. Table 2 demonstrates that chemotherapy increased SIRs for all systems, the highest being thyroid (SIR = 1.58, 95% CI 1.46–1.70). Compared with patients with no/unknown chemotherapy, the cases who did receive chemotherapy all presented higher SIRs. Multivariate Cox regression model confirmed chemotherapy as an independently prognostic factor for developing second lymphatic and hematopoietic disease following BC, after adjusting other variables (HR = 1.218, 95% CI 1.115–1.330, $P < 0.001$, as shown in Supplement Table 2).

Risk evaluations for different second primary lymphatic and hematopoietic diseases in BC patients treated with chemotherapy are displayed in Fig. 4. Patients were at significantly increased risk of second primary acute lymphocytic leukemia, acute myeloid leukemia (AML), and non-lymphocytic leukemia (SIR = 3.08, 95% CI 2.21–4.18; SIR = 4.98, 95% CI 4.51–5.49; SIR = 3.94, 95% CI 3.61–4.29, respectively). On the other hand, findings suggested significantly decreased SIRs for lymphoma, myeloma, and chronic lymphocytic leukemia (SIR = 0.80, 95% CI 0.72–0.88; SIR = 0.85, 95% CI 0.71–1.01; SIR = 0.57, 95% CI 0.43–0.74, respectively).

673 cases of AML were observed, 402 of which happened to patients with chemotherapy. Since AML was the most common malignancy among the second primary lymphatic and hematopoietic disease, we further analyzed the risk by latency period and age at diagnosis of BC, as shown in Table 3. SIR descended with age at diagnosis except for the 5–10 year interval. For patients younger than 60 years old, the incidence peaked in 1–2 years after diagnosis of BC, and then decreased with latency, while patients older than 60 had the highest risk during 2–5 years following BC. Compared with general population, all

Table 2 Standardized incidence ratios (SIR) for different second malignancy risk in breast cancer patients by chemotherapy

Cancer sites	Chemotherapy			
	Yes		No/Unknown	
	O	SIR (95% CI)	*O*	SIR (95% CI)
All sites	14,913	1.26* (1.24–1.28)	23,984	1.10* (1.08–1.11)
All solid tumors	13,491	1.26* (1.24–1.28)	21,621	1.12* (1.10–1.13)
Breast	5548	1.45* (1.41–1.49)	7454	1.25* (1.22–1.28)
Digestive system	2037	1.05* (1.01–1.10)	4528	1.04* (1.01–1.07)
Lung and bronchus	1710	1.09* (1.04–1.14)	3520	1.03 (0.99–1.06)
Female genital system	1673	1.12* (1.07–1.18)	2382	1.04 (1.00–1.08)
Urinary system	644	1.11* (1.03–1.20)	1332	1.07* (1.01–1.13)
Thyroid	651	1.58* (1.46–1.70)	627	1.40* (1.29–1.51)
All lymphatic and hematopoietic disease	1136	1.28* (1.20–1.35)	1827	0.96 (0.91–1.00)

O observed numbers, *SIR* standardized incidence ratio, *CI* confidence intervals

*$P < 0.05$

Table 3 Standardized incidence ratios (SIR) with 95% confidence intervals for acute myeloid leukemia in breast cancer patients treated with chemotherapy by latency and age at diagnosis of breast cancer

Age, years	Latency, months				
	6–11	12–23	24–59	60–119	≥120
≤49	3.91 (0.79–11.43)	29.19* (20.75–39.90)	10.79* (7.23–15.50)	3.06 (0.99–7.14)	4.81 (0.06–26.77)
50–59	2.38 (0.48–6.96)	11.91* (7.91–17.22)	9.87* (7.45–12.81)	4.13* (2.59–6.26)	2.48 (0.50–7.24)
60–69	2.26 (0.61–5.79)	5.91* (3.61–9.13)	7.52* (5.82–9.57)	3.08* (2.08–4.40)	2.15 (0.86–4.44)
≥70	1.30 (0.15–4.71)	1.30 (0.35–3.32)	3.52* (2.41–4.97)	3.06* (2.16–4.20)	1.92 (0.92–3.53)

*$P < 0.05$

patients exhibited no significant difference of incidence after 10 years.

Discussion

Increase in the incidence rate and decrease in the mortality rate of BC have been documented by DeSantis et al. [1], yielding more BC survivors exposed at the high risk of developing second primary cancers. Our study found that the SIR for second primary cancers (all sites) was 1.15 (95% CI 1.14–1.16), which was consistent with the previous literatures [3, 22]. The increased risk might be attributed to behavioral factors, long-term side effects of treatment regimens, and the presence of an inherited genetic predisposition, such as BRAC1/2 mutation, PTEN mutation, and Cowden Disease [23].

In our analysis, patients with BC only presented significant better BCSS and OS than the patients with multiple primary cancer, and developing second primary tumor was an independent prognostic factor. Our findings were consistent with the other studies which addressed the survival of BC patients with multiple primary malignancies [23–25]. The study in 2018 reported that the 10-year survival rates for the BC only patients and the multiple primary cancer patients were 87.5% and 70.4%, respectively, with significant difference. The other Korean research demonstrated that the survival advantage of the BC only patients was more obvious in the first 5 years. These results were contrary to the conclusion of the study by Liu et al. [26]. After analyzing 28 patients with subsequent primary tumors after BC, the authors found that multiple primary carcinoma was not a prognostic factor. However, this study was blighted by the small study cohort in one center. The OS divergence went beyond explanation, while the BCSS difference in our study, as far as we are concerned, was first to be reported. Since we had adjusted some prognostic factors in our multivariate Cox regression model, plausible suggestions might include: the patients with multiple primary malignancies bore other prognostic factors, for example HER2 expression [27]; treatment cessation due to bad compliance as well as treatment confliction with subsequent cancer caused the recurrence and metastasis of BC. Therefore, stricter surveillance should be administrated to BC patients with high risk to facilitate the early diagnosis of SPM, and more professional and comprehensive treatment could be offered.

Certain studies discussed the impact of chemotherapy on the risk of developing SPM after BC, yet the results were conflicting and unspecific. During a follow-up period that included 529,782 person-years, 3,153 cases out of 100,915 female and 578 male BC patients developed SPM. After adjusting other risk factors, only chemotherapy remained significantly associated with SPM for all cancer in general [28]. To the contrary, some other literatures failed to identify the correlation between chemotherapy and SPM after BC [23, 29, 30]. In addition to these, chemotherapy had been found to be related with increased risk of uterine cancer [31], non-Hodgkin's lymphoma (NHL) [32], ovary cancer, bladder cancer and leukemia [17], and decreased risk of bowel and thyroid cancer [33], together with contralateral BC [34]. Our research demonstrated that the incidence was higher among the patients with chemotherapy in all the malignancies except lymphoma, myeloma, and chronic lymphocytic leukemia. The fact that we explored some malignancies in a whole system and different study cohort may justify some of our findings.

We specifically focused on the incidence of the lymphatic and hematopoietic system. The incidence for AML was significantly elevated. Other retrospective studies had reported similar results [35–37]. Clinical studies had tried to obtain some possible explanation for the correlation of chemotherapy and AML, such as the usage of DNA-damaging chemicals, and granulocyte colony-stimulating factors (G-CSF). Shenolikar et al [35] conducted a study with data from a large, commercially insured cohort in a real-world setting in America. They found that the incidence of AML in BC patients was significantly associated with the duration of exposure to DNA-damaging regimen, which included alkylating agents, antimetabolites, platinum-based antineoplastic drugs, and topoisomerase inhibitors. The latest meta-analysis indicated that patients, who were assigned to chemotherapy with primary G-CSF

support, experienced 85% higher risk of developing secondary malignancies (RR = 1.85; 95% CI 1.19–2.88; $P < 0.01$) [38]. With prior exposure to chemotherapy, 19 of the 27 patients with available marrow cytogenetics had abnormal marrow cytogenetics, and 5 patients with AML displayed translations in the mixed-lineage leukemia gene [37]. Certainly, correlation did not guarantee causation. On one hand, studies with larger cohort and longer follow-up are demanded to verify the association between chemotherapy and AML; on the other hand, more fundamental research is needed to expound the mechanics and confirm the relevance.

Noticeable, the risk for developing second AML varied with age and latency in our study. Patients aged younger than 60 bore the highest risk within 12–59 months after the diagnosis of BC. Another SEER-based study of chemotherapy-related AML after six different primary malignancies, including BC, also indicated that the risks were significantly higher in the first 5 years and among the patients at younger ages [39]. Since younger patients were more prone to receive chemotherapy, the risks for AML should be weighed against the benefits of chemotherapy. Besides, during the follow-up program for these patients, blood routine is supposed to be monitored regularly.

All studies have their limitations, so does our research. Similar to other studies based on SEER database, our study suffered from the lack of specific information on chemotherapy and hormone treatment, and thus, we could not perform the analysis on different regimen. However, we focused our analysis on the patients who did received chemotherapy to increase the credibility of this research. Further investigation is warranted to assess the risks based on the exposure to specific chemical agents. And as a retrospective study, systemic errors like surveillance bias and data input error existed. To address this issue, we extracted the relatively new data in the late 14 years from 18 different registries. In addition, cases with some unknown variables were excluded. Besides, we could not totally rule out the possibility that second primary BC were actually metastases or recurrences rather than true SPM, even though SEER registry established strict rules for documenting multiple primary tumors.

In general, our large population-based study indicated that BC patients had higher risk of developing SPM. The survival for women with SPM was significantly poorer. Chemotherapy was associated with increased risk for SPM in different system, particularly in the hematopoietic system. These findings may facilitate more individualized treatment and surveillance programming.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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