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Risk and survival of chronic myeloid leukemia after breast cancer: A population-based study

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ABSTRACT

Background: We aimed to investigate the risk and survival of chronic myeloid leukemia (CML) after breast cancer (BC) diagnosis.

Methods: We used the Surveillance, Epidemiology, and End Results 'SEER' database. Females, diagnosed with BC between 1992 and 2014, were selected and followed for the development of CML after a 6-month latency period from BC diagnosis. We used the Multiple Primary Standardized Incidence Ratios session of the SEER*Stat software (version 8.3.4) to calculate the Observed/Expected (O/E) ratios with 95% confidence intervals (CI). To calculate the overall survival, we performed an unadjusted Kaplan-Meier analysis using the SPSS software.

Abbreviations: AML, Acute Myeloid Leukemia; BC, Breast Cancer; CML, Chronic Myeloid Leukemia; O/E, Observed/Expected ratio; SEER, Surveillance, Epidemiology, and End Results.

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Results: We included 474,866 females with BC, of which 178 were later diagnosed with CML. We found the risk of CML to increase significantly after BC diagnosis (O/E = 1.26, 95% CI: 1.08-1.45) and the risk was specifically higher within the first 5 years of diagnosis (O/E = 1.45, 95% CI: 1.16-1.8). When the risk was stratified by cancer stage, localized BC was associated with a significant increase in CML risk within 5 years of diagnosis (O/E = 1.4, 95% CI: 1.06-1.82), while regional BC was associated with a significant increase in CML risk after more than 5 years of diagnosis (O/E = 1.59, 95% CI: 1.09-2.25). Moreover, radiotherapy, chemotherapy, and presence of hormonal receptors were associated with a significant increase in CML risk in BC patients. The median overall survival of CML after BC was 28 months.

Conclusion: Breast cancer patients have an increased risk of developing CML and further investigation is required to establish the causes of this finding.

Introduction

Breast cancer (BC) is the most common cancer in females worldwide and in the United States and is responsible for about one-third of cancer diagnoses among females.[1] Over the past 10 years, the incidence of BC has been increasing in the United States, with about 266,120 females expected to be diagnosed with BC in 2018. However, mortality rates have been decreasing due to improved treatment and care.[2] Radiotherapy is essential for the treatment of both localized and regional BC and its use has been increasing with continuous advances.[3]

With an improved life expectancy of females with BC, more cases of subsequent primary malignancies have been reported and several studies have linked BC with an increased risk of other malignancies.[1,4,5] Due to the wide use of radiotherapy for BC, it has been blamed for this increased risk; however, other factors, such as chemotherapy, tumor characteristics, or overlapping etiologies (genetic or environmental exposures) may also play a role.[4–8]

Several studies have reported an increased incidence of leukemias following BC treatment.[9,10] In particular, the risk of chronic myeloid leukemia (CML) has been suggested to increase among this population, but no large studies were conducted to prove this association and study the related demographics and tumor characteristics.[11] In this study, we estimated the risk of CML among females with BC diagnosis, compared to the general population, using the Surveillance, Epidemiology, and End Results (SEER) program. Further, we studied the characteristics associated with such risk and calculated the overall survival for CML after BC diagnosis.

Patients and methods

Data source

We obtained data from the SEER database of the US National Cancer Institute, using the SEER*Stat software (version 8.3.4).[12] We used the SEER 13 registries that cover about 13.4% (based on the 2010 census) of the US population between 1992 and 2014.[13]

Study population

We reviewed females who were diagnosed with BC between 1992 and 2014 and then diagnosed with a subsequent CML. We used the Site recode of Topographical ICD-O-3/WHO 2008 variable for this selection. We only included cases with histologic confirmation. In order to eliminate the possibility of simultaneous malignancy, we excluded cases with CML, diagnosed within 6 months from BC diagnosis. Within selected patients, we looked into the following variables: age at diagnosis of BC, race, marital status at BC diagnosis, histology, stage and grade of BC, progesterone, and estrogen receptors status of the breast tissue and exposure to chemotherapy and/or radiotherapy for BC treatment.

Outcomes

We calculated the observed/expected ratio (O/E) of CML following BC diagnosis. The 'Observed' value represents the number of CML cases diagnosed after BC diagnosis, while the 'Expected' value represents the number of CML cases expected to be diagnosed in a demographically similar population (regarding age, sex, and race) within the same period. The O/E ratio represents the change in CML risk following BC diagnosis when compared to the general US population. We also calculated the absolute excess risk per 10,000 person-years compared to the general population and the overall survival of included CML cases. Survival was measured as the interval in months between the date of CML diagnosis and the date of death as provided by the SEER database. Patients were followed until the respective dates of death or censored at the end of 2014 (last date of death in the 2016 SEER submission).

Statistical analysis

We used the Multiple Primary Standardized Incidence Ratios (MP-SIR) session of the SEER*stat software (version 8.3.4) to calculate the O/E ratios with 95% confidence intervals (CI). A significant positive increase in risk was defined as the number of observed CML cases being more than the number of expected CML cases in the general population with a p value less than 0.05. To calculate the overall and CML-specific survival, we performed an unadjusted Kaplan-Meier analysis using the SPSS software (version 23, IBM, NY). All statistical tests were two-sided.

Results

Baseline characteristics

We reviewed 474,866 females with BC, of which 178 developed CML. Most of these patients were white (84.8%) and had 65 years or older (54.5%) when they were diagnosed with BC. Table 1 summarizes the baseline characteristics of included patients. The median time to develop CML following BC diagnosis was 64.5 months.

The risk of CML following BC diagnosis

We found the risk of CML to increase significantly after the diagnosis of BC (O/E ratio = 1.26), with an excess risk of 0.1 per 10,000 person-years. When we analyzed patients according to

Table 1
Baseline characteristics of patients with CML after breast cancer.

Baseline characteristic	Cases, No (%)
Overall	178 (100)
Age	
<35	4 (2.24)
35-50	22 (12.35)
51-64	55 (30.89)
>64	97 (54.49)
Race	
White	151 (84.83)
Black	13 (7.3)
Asian or Pacific Islander	13 (7.3)
American Indian/Alaska Native	1 (0.56)
Marital status	
Married	112 (62.92)
Single	20 (11.23)
Widowed	25 (14.04)
Divorced	16 (8.98)
Separated	1 (0.56)
Unknown	4 (2.24)
State	
California	64 (36)
Connecticut	15 (8.4)
Michigan	28 (15.7)
Hawaii	9 (5.1)
Iowa	17 (9.6)
New Mexico	4 (2.2)
Washington	25 (14)
Utah	6 (3.4)
Georgia	10 (5.6)
Histology	
Ductal and lobular neoplasms	160 (89.88)
Others*	18 (10.11)
Grade	
Well differentiated; Grade I	28 (15.73)
Moderately differentiated; Grade II	82 (46.06)
Poorly differentiated; Grade III	37 (20.78)
Undifferentiated; anaplastic; Grade IV	3 (1.68)

* Include adenomas and adenocarcinomas, cystic, mucinous and serous neoplasms, fibromatous neoplasms, and adnexal and skin appendage neoplasms.

the latency period between the diagnosis of BC and CML, the risk of CML was significantly higher within the first 5 years of BC diagnosis (O/E = 1.45), with an excess risk of 0.15 per 10,000 person-years. Subgroup analysis by cancer stage showed that localized BC was associated with a significant increase in CML risk within 5 years of diagnosis (O/E = 1.4), with an excess risk of 0.14 per 10,000 person-years, while regional BC was associated with a significant increase in CML risk after > 5 years of diagnosis (O/E = 1.59), with an excess risk of 0.21 per 10,000 person-years.

When cases were analyzed according to progesterone and/or estrogen receptors status, 30 cases had an unknown status and were excluded from the analysis. Of the remaining, most cases had positive estrogen and progesterone receptors, and this was associated with a significant increase in CML risk within 5 years of BC diagnosis (O/E = 1.76), with an excess risk of 0.26 per 10,000 person-years. Moreover, the O/E ratio of CML risk increased in groups treated with chemotherapy (O/E = 1.59, 95% CI [1.2-2.07]) (excess risk was 0.15 per 10,000 person-years) or radiation (O/E = 1.55, 95% CI [1.27, 1.87]) (excess risk was 0.2 per 10,000 person-years). Table 2 summarizes the risk of CML in different studied groups.

Table 2
The risk of CML among breast cancer patients (overall and stratified according to stage and receptors status of breast cancer).

	Within 5 years			After 5 years			Total		
	Persons*	Observed†	O/E‡ (95% CI§)	Persons*	Observed†	O/E‡ (95% CI§)	Persons*	Observed†	O/E‡ (95% CI§)
Total	474,866	84	1.45ǀ (1.16-1.80)	302,583	94	1.12 (0.90-1.37)	474,866	178	1.26ǀ (1.08-1.45)
Stage									
Localized	298,664	56	1.40ǀ (1.06-1.82)	205,154	58	0.93 (0.71-1.21)	298,664	114	1.12 (0.92- 1.34)
Regional	144,016	23	1.53 (0.97-2.29)	87,894	32	1.59ǀ (1.09-2.25)	144,016	55	1.56ǀ (1.18-2.04)
Distant	24,082	4	2.35 (0.64-6.01)	5,718	2	2.34 (0.28-8.45)	24,082	6	2.34 (0.86-5.10)
Progesterone/Estrogen receptors Status									
Progesterone positive and estrogen positive	273,977	60	1.76ǀ (1.34-2.26)	174,367	59	1.27 (0.96-1.63)	273,977	119	1.47ǀ (1.22-1.76)
Progesterone positive only	7702	1	1.38 (0.03-7.69)	5294	4	2.65 (0.72-6.79)	7702	5	2.24 (0.73-5.23)
Estrogen positive only	49,978	5	0.76 (0.25-1.77)	30,436	9	1.04 (0.47-1.97)	49,978	14	0.92 (0.50-1.54)
Progesterone negative and estrogen negative	78,391	6	0.81 (0.30-1.77)	45,729	5	0.46 (0.15-1.08)	78,391	11	0.60 (0.30-1.08)

* Number of breast cancer patients who were at risk of developing CML at the beginning of this time interval
† Number of breast cancer patients who developed CML.
‡ The observed over expected ratio.
§ 95% confidence interval.
ǀ Significant O/E ratio.

Survival of CML following BC

The median overall survival of CML after BC was 28 months with a standard error of 8.6 (95% CI [11.1-44.8]). However, the median CML-specific survival of CML after BC could not be calculated due to the small number of patients (18 patients) who died due to CML itself (Fig 1).

Discussion

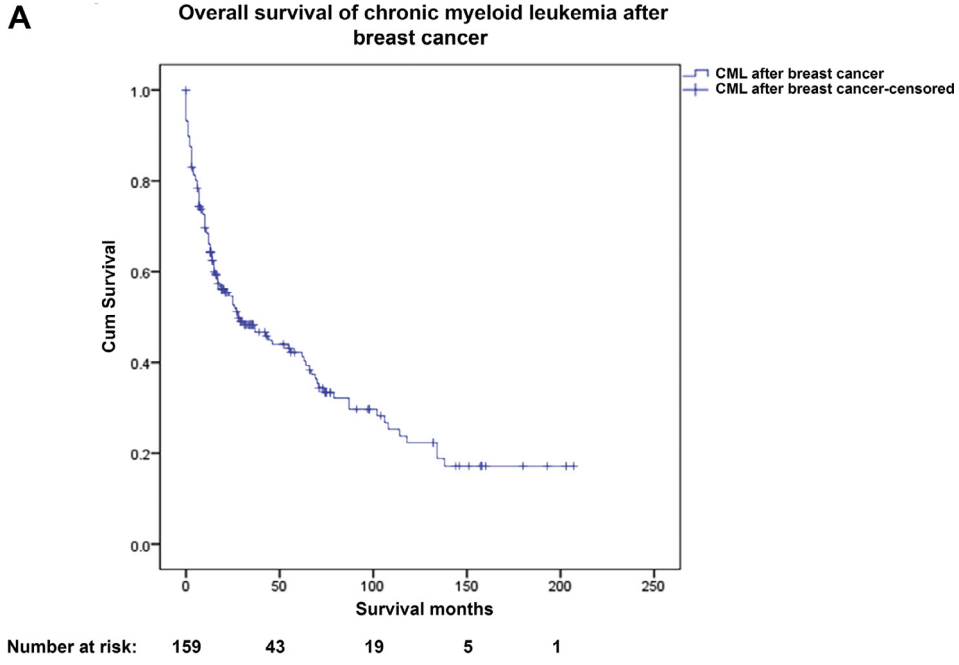
Multiple studies have investigated the impact of BC on the development of subsequent acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). However, only few publications reported detailed data on CML risk after BC.[14,15] To our knowledge, this study is the first SEER-based analysis and one of the largest on this issue (in terms of the number of BC and CML cases). We found BC patients to have 1.26 higher risk of developing CML than the general population, especially within the first 5 years of BC diagnosis. Most CML cases were older than 64 years, which may be explained by the fact that both BC and CML have a higher incidence in patients older than 64 years.[2]

This study supports the findings of prior investigations that observed an increased risk of CML after primary BC diagnosis.[9,11,14,16–18] In agreement with our results, Curtis et al observed that the risk of leukemia (mainly AML and MDS) was highest within the first 5 years of BC diagnosis.[16] While Howard et al reported that the risk remained high throughout the 25 years after the primary BC diagnosis and explained that other studies have failed to follow the patients for more than 10 years.[14] We found that localized BC cases were more likely to develop CML within the first 5 years of diagnosis, while regional BC cases were more likely to develop CML after more than 5 years. The observed risk of CML was higher than the expected risk in the regional BC group than the localized group, which confirms the findings of Smith et al.[9]

Our study has shown an increased risk of CML in patients who received radiotherapy or chemotherapy for the primary BC. However, we could not draw an accurate conclusion due to lack of sensitivity of the SEER database regarding radiation and chemotherapy data.[19] In accordance, several studies correlated the regimen of BC treatment to the development of subsequent leukemia.[9,11,14,16,17,20,21] Curtis et al reported that regional radiation and alkylating agents are linked to elevated risk of AML and MDS, while only radiation is related to an increased risk of CML.[16] Similarly, Rubino et al found a significant increase in leukemia risk in the group that received radiotherapy for the primary BC than the group that received neither radiotherapy nor chemotherapy.[18] Further, Diamandidou et al concluded that the risk of leukemia was higher specifically in patients receiving doxorubicin and radiotherapy.[22] In contrast, Haas et al[20] and Kaplan et al[15] found no association between the risk of leukemia and exposure to radiotherapy or doxorubicin, respectively. Ionizing radiation is a well-documented culprit for the development of leukemia**.** Although the genetic makeup of cancer survivors may predispose them to develop other malignancies, the risk of leukemia is probably increased by radiation therapy.[11]

Other authors have investigated the chromosomal aberrations following BC treatments, which may be implicated in the development of subsequent leukemias (mainly AML).[23] Carey et al suggested a viral origin as the common etiologic factor for the development of BC and AML in animal models.[24] Another interesting observation was that BC patients with positive estrogen and progesterone receptors had a significantly higher risk of CML, compared to the general population within 5 years of the initial BC diagnosis. This may be related to the hormonal treatment received by BC patients (not covered in detail in the SEER database and may reflect selection bias; therefore, data should be interpreted with caution). Further studies should examine the effect of hormonal treatment on CML risk.

Our study has some limitations including the lack of accurate data on the treatment modalities, received by BC patients in the SEER database; therefore, we cannot draw accurate conclusions about the relation between BC treatments and the development of subsequent CML.



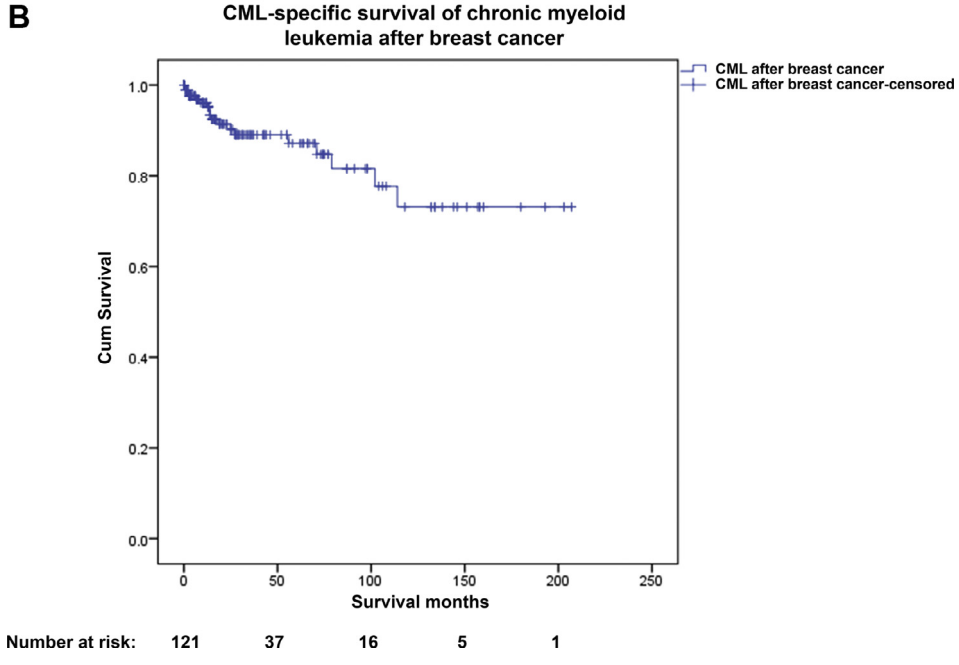


Fig. 1. (a) Overall and (b) CML-specific survival of chronic myeloid leukemia after breast cancer.

Moreover, the present data on systemic chemotherapy and radiation, although specific, is not sensitive enough. Therefore, it is not recommended to make comparisons between patients who did or did not receive chemotherapy and/or radiation.[19] Due to certain inherit characteristics of the SEER database, calculating the 5- and 10-year cumulative incidence in our cohort was not feasible. Moreover, the retrospective design and underrepresentation of some ethnic groups are limitations to this study.

In conclusion, this study showed a significantly increased risk of CML after BC diagnosis. Large clinical trials are needed to determine the exact chemotherapeutic agents, exact doses of radiotherapy and the role of therapy in inducing chromosomal abnormalities, which may be implicated in the development of CML. Moreover, future studies should investigate the potential benefits of screening and early detection programs on the survival of CML after BC.

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