

Therapy related acute myeloid leukemia in breast cancer survivors, a population-based study

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Abstract The aim of this study was to determine the association between age and stage at diagnosis of breast cancer with the subsequent development of acute myeloid leukemia (AML). The National Cancer Institute's Surveillance, Epidemiology, and End Results program were analyzed for incidence of second malignancies by age and stage at diagnosis of breast cancer. 420,076 female patients were identified. There was an age dependent risk of a subsequent diagnosis of AML in women younger than 50 years old (RR 4.14; $P < 0.001$) and women 50–64 years old (RR 2.19; $P < 0.001$), but not those 65 and older (RR 1.19;

$P = 0.123$) when compared with the expected incidence of AML. A similar age dependent pattern was observed for second breast and ovarian cancers. There was also a stage dependent increase in risk of subsequent AML in younger women with stage III disease when compared with stage I disease (RR 2.92; $P = 0.004$), and to a lesser extent in middle age women (RR 2.24; $P = 0.029$), but not in older women (RR 0.79; $P = 0.80$). Younger age and stage III disease at the time of breast cancer diagnosis are associated with increased risk of a subsequent diagnosis of AML. This association maybe explained by either greater chemotherapy exposure or an interaction between therapy and genetic predisposition.

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Keywords Therapy-related acute myeloid leukemia · Breast cancer · Chemotherapy · SEER · Epidemiology · Radiation therapy

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Background

Breast cancer is common and often curable, making second malignancies a concern. These second cancers may represent: (1) independent events, (2) genetic predisposition to multiple malignancies (such as ovarian cancer in patients with germline BRCA mutations), (3) the consequences of chemotherapy and radiation treatment, or (4) a combination of the above. While several groups have described the incidence of second malignancies in breast cancer survivors, myeloid leukemia after breast cancer has not been systematically studied in large numbers of patients to determine whether risk factors can be identified [1–6].

Therapy-related acute myeloid leukemia (t-AML) is a lethal iatrogenic complication of radiation therapy and chemotherapy [7]. t-AML is believed to be the direct

consequence of genomic changes (i.e., deletions, mutations, translocations) induced by these therapies [7, 8]. It is unclear whether t-AML represents a truly stochastic event, or if individuals have different degrees of susceptibility [7]. Several groups have described polymorphisms that alter the metabolism of chemotherapy, which may contribute to the incidence of t-AML [9–11]. Alternatively, it is possible that germline variations in DNA repair genes may contribute to the risk of t-AML [12].

Using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, we tested the hypotheses that younger women with higher stage breast cancer were more likely to develop t-AML. Acknowledging the inherent limits of such a database based study, we used stage I vs. III disease as a proxy for exposure to and intensity of chemotherapy, and age as a proxy for genetic susceptibility to breast cancer. We also examined the impact of external beam radiation therapy on the incidence of AML in breast cancer survivors.

Methods

Data sources

Data from nine tumor registries participating in SEER program were studied. SEER is the only population-based source of comprehensive cancer data in the United States [13]. This registry gathers information from approximately 10% of cancer patients in the United States. SEER tracks demographic and disease specific information including stage, age at diagnosis, and second malignancies. The data used for this study was collected from 1973 to 2002, which provides at least 5 years of follow-up in order to capture the majority of t-AML cases (typical latency 3–5 years).

Cohort selection

All women with a primary diagnosis of breast cancer (sequence number code equal to 0 or 1) in the SEER database were selected and information was obtained for their age at diagnosis, diagnosis of second malignancies, and stage of disease. Age cohorts were defined as 15–49, 50–64, and 65 and older based on the median age of diagnosis of BRCA and other genetically associated breast cancers. Subsequent acute myeloid leukemia (AML) was defined as a diagnosis of AML or acute myelomonocytic leukemia occurring at least 2 months after a diagnosis of breast cancer. Data was retrieved from the SEER database using the SEER*Stat 6.4.4 frequency and MP-SIR modules. The MP-SIR module only allows the retrieval of certain second malignancies and therefore precluded an analysis of the rates of myelodysplastic syndrome

following a diagnosis of breast cancer. Cancers are coded in the SEER registry according to the International Classification of Diseases for Oncology, third edition. Since SEER does not contain detailed records of chemotherapy, we used the incidence of second malignancies in patients with stage I vs. stage III breast cancer to infer a possible impact of chemotherapy. Women with stage I disease are more likely to receive less intensive or no chemotherapy, and women with stage III disease are more likely to receive more intensive chemotherapy. Women with stage II and IV disease were excluded due to treatment variability and life expectancy, respectively. Stage is defined according to SEER's American Joint Cancer Committee third edition criteria. Stage was available starting in 1988. Radiation therapy was treated as a dichotomous variable (external beam radiation therapy vs. no radiation therapy).

Statistical analysis

Using the SEER*Stat 6.4.4 MP-SIR module, the actual numbers of second malignancy were determined by age at diagnosis of breast cancer and stage. This module also provides observed over expected ratios, allowing calculation of the expected number of cases for each second malignancy for a particular age. Contingency tables were formulated and relative risks (RR) and 95% confidence intervals for developing a second malignancy were calculated for patients diagnosed with a primary malignancy when compared with the expected incidence within an age interval, and for stage III patients compared with stage I patients. Two-sided *P*-values from Chi-square test, or Fisher's exact test if <5 subjects per cell, were reported. *P*-values <0.05 were considered statistically significant. All analyses were performed in SAS 9.1.

Results

Patients

422,915 cases of primary breast cancer were identified in the SEER database 9 Nov 2004 data set. Of these 2,839 were cases of male breast cancer and 420,076 were cases of female breast cancer. Given the low total number of male breast cancer cases and subsequent AMLs (4 observed cases vs. 1 expected case), males were excluded from further analyses. Of the 420,076 women with a primary diagnosis of breast cancer, 95,217 (23%) were 15–49 years, 136,396 (33%) were 50–64 and 188,463 (44%) were 65 and older. Within these cohorts, 20,959 (22%) of young women were diagnosed with stage I breast cancer and 4,639 (5%) were diagnosed with stage III disease; 36,120 (27%) of middle age women were diagnosed with stage I breast cancer and

4,691 (3%) were diagnosed with stage III disease; and 52,422 (28%) of older women were diagnosed with stage I breast cancer and 6,285 (3%) were diagnosed with stage III disease.

Impact of age on second malignancies

When compared with older women, younger women with breast cancer were at the greatest risk of developing subsequent ovarian cancers, breast cancers, and AML. The risk of being diagnosed with ovarian cancer was increased in the younger and middle cohorts (RR 2.29; 95% confidence interval 1.92–2.73, $P < 0.001$ and RR 1.25; 1.11–1.41, $P = 0.004$, respectively) but not in the older cohort (RR 0.93; 0.82–1.05, $P = 0.250$). The risk of a second breast cancer was elevated across all age groups, but decreased with increasing age: younger cohort (RR 2.5; 2.40–2.68, $P < 0.001$), middle cohort (RR 1.46; 1.40–1.52, $P < 0.001$) and older cohort (RR 1.25; 1.20–1.30, $P < 0.001$). The risk of a subsequent diagnosis of AML followed the same pattern that was observed with subsequent ovarian cancers: increased in younger (108 cases in 95,109 women vs. an expected of 26 cases in 94,827 women; RR 4.14; 2.70–6.35, $P < 0.001$) and middle age women (175 cases in 136,221 women vs. an expected of 80 cases in 136,316 women; RR 2.19; 1.68–2.85, $P < 0.001$), but not older women (167

cases in 188,296 women vs. 140 cases in 188,323 women; RR 1.19; 0.95–1.49, $P = 0.123$) (Table 1).

The incidence of uterine cancer was increased across all age groups, which was likely the result of therapy with tamoxifen [14]. The incidence of lung cancer was increased in younger women diagnosed with breast cancer (RR1.37; 1.22–1.54, $P < 0.001$) and decreased in older women (RR 0.82; 0.77–0.87, $P < 0.001$), as was the incidence of pancreatic cancer (RR 0.83; 0.74–0.93, $P = 0.001$). A diagnosis of breast cancer was associated with a decreased risk of cervical cancer and chronic lymphocytic leukemia. No other malignancy showed an age specific trend following a diagnosis of breast cancer.

We also examined the age dependent risk of a subsequent diagnosis of AML following exposure to alkylator chemotherapy used to treat other (non-breast cancer) primary malignancies. Compared with breast cancer, there was the opposite age-dependent trend of a subsequent diagnosis of AML in patients with multiple myeloma (RR in young cohort 3.16; 0.35–28.22, $P = 0.392$; in middle cohort 9.33; 1.27–68.53, $P = 0.004$; in older cohort 6.00; 2.70–13.35, $P < 0.001$), but there was a similar trend observed in patients with non-Hodgkin lymphoma (RR in young cohort 10.33; 3.16–33.80, $P < 0.001$; in middle cohort 4.23; 2.31–7.74, $P < 0.001$; in older cohort 2.12; 1.33–3.37, $P = 0.001$) (Table 2).

Table 1 Relative risk of the diagnosis of specific malignancies following a diagnosis of breast cancer in the SEER database

Site	15–49 years RR (95% CI)	<i>P</i> -value	50–64 years RR (95% CI)	<i>P</i> -value	65 years plus RR (95% CI)	<i>P</i> -value
AML	4.14 (2.70–6.35)	<0.001	2.19 (1.68–2.85)	<0.001	1.19 (0.95–1.49)	0.123
Breast	2.53 (2.40–2.68)	<0.001	1.46 (1.40–1.52)	<0.001	1.25 (1.20–1.30)	<0.001
Ovarian	2.29 (1.92–2.73)	<0.001	1.25 (1.11–1.41)	<0.001	0.93 (0.82–1.05)	0.250
ALL	1.60 (0.47–5.48)	0.553	1.13 (0.43–2.92)	0.808	0.80 (0.34–1.88)	0.602
CLL	1.15 (0.65–2.03)	0.633	0.85 (0.64–1.13)	0.270	0.60 (0.47–0.75)	<0.001
CML	1.41 (0.67–2.95)	0.359	1.06 (0.66–1.69)	0.811	1.09 (0.78–1.51)	0.617
Lymphoma	0.93 (0.74–1.17)	0.542	0.87 (0.76–0.99)	0.038	0.88 (0.79–0.98)	0.019
Myeloma	0.87 (0.54–1.39)	0.550	0.85 (0.67–1.07)	0.170	0.97 (0.82–1.15)	0.724
Lung	1.37 (1.22–1.54)	<0.001	1.01 (0.94–1.07)	0.857	0.82 (0.77–0.87)	<0.001
Uterine	1.30 (1.12–1.51)	<0.001	1.22 (1.12–1.33)	<0.001	1.51 (1.39–1.64)	<0.001
Cervical	0.62 (0.46–0.82)	0.001	0.56 (0.44–0.71)	<0.001	0.69 (0.55–0.88)	0.002
Bladder	1.44 (1.08–1.94)	0.014	1.11 (0.96–1.29)	0.165	0.97 (0.86–1.08)	0.555
Gastric (stomach)	1.55 (1.04–2.31)	0.031	1.21 (0.98–1.48)	0.078	1.05 (0.91–1.21)	0.517
Bones and joints	2.53 (0.91–7.02)	0.065	0.97 (0.43–2.16)	0.932	0.97 (0.43–2.15)	0.931
Esophageal	1.63 (0.90–2.94)	0.104	1.46 (1.09–1.96)	0.011	1.20 (0.94–1.53)	0.138
Oral cavity	1.25 (0.92–1.68)	0.151	1.09 (0.91–1.31)	0.327	1.00 (0.85–1.18)	0.981
Thyroid	1.19 (0.92–1.54)	0.180	1.21 (0.95–1.53)	0.116	1.20 (0.91–1.58)	0.189
Pancreatic	1.16 (0.84–1.59)	0.380	0.93 (0.80–1.09)	0.377	0.83 (0.74–0.93)	0.001
Kidney	0.95 (0.69–1.30)	0.734	1.00 (0.84–1.20)	1.00	1.11 (0.95–1.29)	0.199
Colorectal	0.99 (0.86–1.15)	0.929	1.02 (0.95–1.10)	0.516	1.01 (0.96–1.06)	0.761
All	1.70 (1.64–1.76)	<0.001	1.07 (1.04–1.09)	<0.001	0.92 (0.90–0.94)	<0.001

RR relative risk, NHL non-hodgkin lymphoma, CI confidence interval, ALL acute lymphoblastic leukemia

Impact of stage on second malignancies

The risk of AML was elevated in younger women with stage III disease when compared with younger women with stage I disease (11 cases in 4,639 women with stage III disease vs. 17 cases in 20,959 women with stage I disease; RR 2.92; 1.37–6.24, $P = 0.004$), and when compared with the expected incidence of AML in younger women without breast cancer (RR 8.65; 4.28–17.50, $P < 0.001$) (Table 3). A significant, though weaker stage dependent increased risk was observed in the middle age cohort (RR 2.24; 1.07–4.69, $P = 0.029$). This is similar to the trend in age dependent risk seen with ovarian cancer, but there was no stage dependent increase in risk for ovarian cancer.

The risk of AML in younger women with stage III disease was significantly higher than in older women with stage III disease (RR 3.73; 1.19–11.70, $P = 0.031$), suggesting a genetic risk factor may exist. There was no difference in the risk of AML between older patients with stage I and stage III disease (RR 0.79; 0.26–2.33, $P = 0.800$).

Latency of a subsequent diagnosis of AML

The median latency from a diagnosis of breast cancer to a subsequent diagnosis of AML for the entire study was

5 years, with patients <50 years old having a median latency of 3 years (range <1 year–25 years), and patients ≥ 65 years old having a median latency of 5 years (range <1 year–24 years). There was no difference in latency between patients <50 years old when compared with those ≥ 65 years old (mean 5.9 vs. 5.7 years, respectively, $P = 0.798$). The median overall survival for patients ≥ 65 years old was 7.8 years from the time of their breast cancer diagnosis.

Impact of radiation therapy on risk of AML

External beam radiation therapy was associated with an increased risk of t-AML in older women, but not younger women (Table 4).

Discussion

Using the SEER database, we described a pronounced increased risk of AML in young breast cancer survivors with stage III disease. The age dependent incidence of a subsequent diagnosis of AML was similar to that observed for a second diagnosis of ovarian or breast cancer. This suggests a common susceptibility for developing subsequent AML, ovarian and breast cancer, which may be

Table 2 Relative risk of AML by age following exposure to alkylator chemotherapy for the treatment of myeloma and NHL

Site	<i>N</i>	15–49 years RR (95% CI)	<i>P</i> -value	<i>N</i>	50–64 years RR (95% CI)	<i>P</i> -value	<i>N</i>	65 years plus RR (95% CI)	<i>P</i> -value
Myeloma	2,324	3.16 (0.35–28.22)	0.392	8,906	9.33 (1.27–68.53)	0.004	22,204	6.0000 (2.70–13.35)	<0.001
NHL	21,976	10.33 (3.16–33.80)	<0.001	26,543	4.23 (2.31–7.74)	<0.001	53,869	2.1154 (1.33–3.37)	0.001

RR relative risk, NHL non-hodgkin lymphoma, CI confidence interval, *N* number of patients

Table 3 Relative risk of various malignancies following a diagnosis of breast cancer for women diagnosed with stage III versus stage I disease

Site	15–49 years RR (95% CI)	<i>P</i> -value	50–64 years RR (95% CI)	<i>P</i> -value	65 years plus RR (95% CI)	<i>P</i> -value
AML	2.92 (1.37–6.24)	0.004	2.24 (1.07–4.69)	0.029	0.78 (0.26–2.33)	0.800
Breast	1.25 (1.05–1.48)	0.011	1.19 (0.99–1.42)	0.065	0.85 (0.71–1.03)	0.092
Ovarian	0.71 (0.34–1.49)	0.362	0.71 (0.36–1.41)	0.332	0.48 (0.24–0.99)	0.041
Oral cavity	1.39 (0.45–4.26)	0.531	0.81 (0.29–2.27)	1.000	1.25 (0.64–2.42)	0.517
Esophageal	4.52 (0.28–72.22)	0.330	0.59 (0.08–4.53)	0.610	0.45 (0.11–1.87)	0.432
Gastric (stomach)	0.75 (0.09–6.25)	1.000	0.77 (0.18–3.29)	1.000	0.88 (0.42–1.82)	0.726
Colorectal	1.05 (0.46–2.40)	0.900	0.92 (0.60–1.42)	0.713	0.81 (0.63–1.04)	0.099
Pancreatic	1.00 (0.22–4.65)	1.00	0.86 (0.30–2.40)	1.00	0.25 (0.09–0.67)	0.001
Lung	0.90 (0.49–1.68)	0.748	0.54 (0.36–0.81)	0.003	0.47 (0.33–0.68)	<0.001
Lymphoma	0.27 (0.04–2.00)	0.226	0.64 (0.26–1.60)	0.336	0.36 (0.18–0.74)	0.003
ALL	2.26 (0.20–24.91)	0.451	0 NA	0.549	4.17 (0.38–45.99)	0.288
Myeloma	4.52 (0.64–32.07)	0.153	0.70 (0.16–2.98)	1.000	0.57 (0.23–1.41)	0.220
All	1.17 (1.03–1.34)	0.020	0.91 (0.81–1.03)	0.142	0.68 (0.61–0.76)	<0.001

RR relative risk, NHL non-hodgkin lymphoma, CI confidence interval, ALL acute lymphoblastic leukemia

Table 4 Influence of external beam radiation therapy on incidence of AML following a diagnosis of breast cancer

Site	15–49 years RR (95% CI)	<i>P</i> -value	50–64 years RR (95% CI)	<i>P</i> -value	65 years plus RR (95% CI)	<i>P</i> -value
AML	0.91 (0.61–1.37)	0.649	1.14 (0.83–1.55)	0.414	1.76 (1.29–2.41)	<0.001

RR relative risk, AML acute myeloid leukemia, CI Confidence interval

genetic. These findings are in contrast to other primary malignancies where the risk of a subsequent diagnosis of AML increases with age, but agrees with the majority of the published breast cancer literature [1–6, 8]. Furthermore, women with stage III breast cancer were at a significantly higher risk of developing AML compared to women with stage I disease, arguing that AML may be the sequela of treatment (consistent with therapy-related AML). This risk of AML was significantly greater in younger women, suggesting an interaction between age and therapy.

This interaction has two plausible explanations. First, young women with stage III breast cancer may receive more intensive chemotherapy resulting in a higher rate of t-AML. As SEER does not provide information on chemotherapy regimens we cannot rule out this possibility. Interestingly though, older age, rather than younger age, is considered a risk factor for t-AML in the general cancer population [8]. Consistent with this, we observed an age-dependent increase in AML in older patients with multiple myeloma, a malignancy commonly treated with alkylating chemotherapy. However, we observed that younger patients with NHL were also at a greater risk for AML when compared with older patients. This may be due to a yet incompletely elucidated difference in young vs. old patients with NHL, such as a genetic risk factor not yet identified. Second, young women with breast cancer may have a germline mutation or polymorphism in a gene leading to an increased risk of t-AML following chemotherapy exposure. Because SEER does not contain genetic information, age was used to define a population that maybe enriched for alleles associated with a genetic predisposition for breast cancer [15, 16]. Mutations in the BRCA1 and BRCA2 genes are strong candidates that may explain this enhanced susceptibility, given their association with breast cancer and importance in DNA repair. Working with the Fanconi anemia family of proteins, the BRCA1 and BRCA2 proteins are involved in maintaining the integrity of DNA [12]. Mutations in these genes lead to genomic instability and faulty DNA repair, specifically homologous recombination. Other DNA repair genes, or genes/pathways associated with an increased risk of breast and ovarian cancer, may also be involved [17]. Further evidence for this possibility is suggested by the similar age dependent risk of ovarian cancer and second breast cancer in these women, which are known to be associated with mutations in BRCA1 and BRCA2. The possible association

between germline mutations in BRCA1 or BRCA2 and an increased risk of t-AML in women with breast cancer that are treated with adjuvant chemotherapy needs to be validated in genotyping studies.

The median latency of AML in our study was 5 years. Patients in the older cohort had a median overall survival of 7.8 years from the time of their breast cancer diagnosis, making it unlikely that the lower incidence of AML in this cohort was solely due to attrition before AML had the opportunity to develop. This may have contributed to the decreased incidence of other malignancies in the older age cohort, such as chronic lymphocytic leukemia, but these cancers are not as strongly associated with prior chemotherapy when compared with AML.

Other groups have examined second cancers in breast cancer survivors, but they differ from this study in several ways. Three studies considered leukemia as a diagnosis, but did not analyze AML separately. They grouped together chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL) and AML, and sometimes also including lymphomas [3, 4, 6]. As these other leukemias are not typically considered to be therapy-related, including them in the analysis would reduce the power to detect an association between breast cancer and t-AML. Two groups considered AML as a unique diagnosis but did not attempt to further characterize the incidence of AML based on breast cancer stage or radiation exposure [1, 2]. One study did attempt to further dissect risk factors for AML but were unable to reach statistical significance for an association between subsequent AML diagnosis and age due to their small sample size (13 cases of AML in women younger than 50 compared to 108 cancers described here) [5]. No group has reported an association between a specific genetic variant and risk of t-AML after breast cancer.

In conclusion, we described an increased risk of t-AML following a diagnosis of breast cancer largely confined to young women with stage III disease. These results suggest there may be an interaction between chemotherapy intensity and a germline ability to manage the genotoxic stress of chemotherapy used to treat breast cancer. We believe that germline mutations in BRCA1, BRCA2 or other genes involved in DNA repair may be important for determining whether a woman with breast cancer will develop t-AML. Definitive studies incorporating a woman's genotype and chemotherapy intensity are ongoing.

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