The risk of developing acute non-lymphocytic leukemia in women with breast cancer

Zhong Wang[1#], Zhiyu Li[1#], Qi Wu[1], Si Sun[2], Juanjuan Li[1], Dongcheng Gao[1], Yimin Zhang[1], Shengrong Sun[1]

[1]Department of Breast and Thyroid Surgery, [2]Department of Clinical Laboratory, Renmin Hospital of Wuhan University, Wuhan 430060, China
Contributions: (I) Conception and design: Z Wang, Z Li; (II) Administrative support: Y Zhang, S Sun; (III) Provision of study materials or patients: Z Wang, Z Li, Q Wu; (IV) Collection and assembly of data: Z Wang, Z Li, Q Wu, S Sun, J Li, D Gao; (V) Data analysis and interpretation: Z Wang, Z Li; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.
[#]These authors contributed equally to this work.
Correspondence to: Shengrong Sun; Yimin Zhang. Department of Breast and Thyroid Surgery, Renmin Hospital of Wuhan University, 238 Ziyang Road, Wuhan 430060, China. Email: sun137@sina.com; dryiminzhang@163.com.

Background: This study had the purpose of examining the incidences, risk factors, and survival outcome of developing subsequent acute non-lymphocytic leukemia (ANLL) among a large group of breast cancer survivors.
Methods: We analyzed data from the Surveillance, Epidemiology, and End Results (SEER) program for standardized incidence ratio (SIR), risk factors, and survival of subsequent ANLL, focusing on the period between 2000 and 2014.
Results: There was an increased SIR among breast cancer patients for subsequent ANLL (SIR: 2.41; 95% CI: 2.26–2.58). Risk factors of subsequent ANLL were age at first cancer diagnosis (40+ *vs.* 15–39 years, aHR =1.572, P=0.003), tumor size (21–50 *vs.* ≤20 mm, aHR =1.332, P=0.003; 50+ *vs.* ≤20 mm, aHR =1.735, P<0.001), chemotherapy exposure (yes *vs.* no, aHR =1.692, P<0.001), and radiation exposure (yes *vs.* no, aHR =1.232, P=0.002). Meanwhile, following subsequent ANLL, survivors had an adverse overall survival (OS) compared with patients who did not develop ANLL (aHR =3.359, P<0.001).
Conclusions: Breast cancer survivors have a higher risk of developing subsequent ANLL compared to the general population. Increased vigilance should be shown towards the potential development of ANLL due to older age, larger tumor size, chemotherapy, and radiation exposure in survivors.

Keywords: Breast cancer; acute non-lymphocytic leukemia (ANLL); the Surveillance, Epidemiology, and End Results (SEER); risk factor; survival outcomes

Introduction

Among women around the world, breast cancer is the malignancy most frequently diagnosed and is also the leading contributor to cancer-associated mortality among females (1). Attributed to early screening, advanced detection, and efficient treatment, breast cancer patients are now more likely to achieve long-term survival and better life expectancy. However, in their prolonged lifetime, survivors face the rising problem of second primary malignancies, which are independent tumors subsequent to the first breast tumor, which may be related to the shared etiology or side-effects of treatment (2). In comparison with the population generally, cancer patients have a heightened risk of developing a subsequent primary cancer, and around 10% of individuals with breast cancer go on to develop a second primary cancer, with second hematopoietic diseases as one example (3). Therefore, it is pivotal for breast cancer patients to manage subsequent primary problems (4).

Previous investigations have suggested a 30% excess risk of second primary tumors, excluding breast cancer as second cancer, and the excess was more apparent for hematopoietic diseases such as myeloid leukemia (5,6). Acute non-lymphocytic leukemia (ANLL), including acute myeloid leukemia (AML), is the predominant subsequent hematopoietic disease among breast cancer survivors. The second ANLL developed by breast cancer survivors is possibly associated with the side effects of adjuvant therapy or etiological associations with various forms of malignancy. Moreover, several studies reported that breast cancer patients treated with chemotherapy and/or radiation therapy had an increased risk of developing AML, which was called therapy-related acute myeloid leukemia (t-AML) (7).

Here, we systemically assessed subsequent primary leukemia incidence among a large cohort of subjects with breast cancer, and we identified risk factors and outcomes for subsequent primary ANLL among breast cancer patients. We calculated the standardized incidence ratio (SIR) for subsequent primary cancers following breast cancer based on the Surveillance, Epidemiology, and End Results (SEER) database. Multivariate analysis was conducted to investigate the risk factors behind developing a second primary ANLL following breast cancer and to assess survival outcomes.

Methods

Data sources and study design

Data were collected from the SEER 18 Registries database, which brings together cancer survival, incidence, and tumor characteristics information from a number of geographical areas across the United States.

From this database, female patients with breast cancer alone and patients who had survived breast cancer but went on to develop second leukemia who received their diagnosis between January 1, 2000, and December 31, 2014, were selected. Patients who received their second primary cancer diagnosis in the 6 months after initially being diagnosed with breast cancer were not included as these had a high possibility of being pre-existing or synchronous cancers (8). The follow-up period lasted up to the date any second cancer was diagnosed, death occurred due to any cause, the date of last known vital status, or when the study concluded (December 31, 2014). None of the follow-up data were excluded from the Cox proportional hazards regression model analyses of risk factors and outcomes for the

subsequent development of ANLL after breast cancer.

We found data of 617,083 women who had breast cancer along and 1,555 patients who developed subsequent leukemia after being diagnosed with primary breast cancer. Overall, 926 individuals who developed a second ANLL, and 919 patients with follow-up data were included in the analyses of risk factors and outcomes. Furthermore, we performed analyses on the characteristics of the first breast cancer, including the year of diagnosis (2000–2004, 2005–2009, and 2010–2014), age at diagnosis (aged under 14, 15–39, and 40+ years) (9), latency period (6–11, 12–59, 60–119, and 120+ months), subtype (ER+PR+, ER+PR–, ER–PR+, or ER–PR–), radiation (none or yes), and chemotherapy (none or yes).

Statistical analysis

Estimating the SIR

The SEER*Stat Multiple primary-standardized incidence ratios (MP-SIR) tool (version 8.3.4) was employed to draw comparisons with the relative risk in the population generally. The tool enables the SIRs to be calculated by dividing the observed numbers of second primary cancers by the anticipated numbers of second primary cancers based on the rates seen in the general population, along with the 95% confidence interval (95% CI). CIs and P values were at 0.05 significance alpha levels and were two-sided based on Poisson exact methods. In cases where the number of observed cases was zero, the SIRs and CIs of the 0–14 age group were not put forward, with the intention of avoiding estimations with statistical instability (10).

Risk factor analysis

Chi-square tests were carried out to compare the characteristics of the women in both groups (breast cancer alone and second primary ANLL). Evaluations of the hazard ratios (HRs) and corresponding 95% CIs were performed by crude semi-parametric Cox proportional hazards regression analyses, which also showed the risk factors behind developing second primary ANLL following breast cancer. The latency period was commenced at the initial diagnosis of breast cancer diagnosis and censored at the diagnosis of second cancer.

Survival outcomes

To allow for adjustment for other prognostic indicators, the association with survival was analyzed by multivariable Cox regression. Overall survival (OS) was the main endpoint.

Table 1 Standardized incidence ratios for second acute non-lymphocytic leukemia risk in breast cancer patients by characteristic

Characteristics	Acute non-lymphocytic leukemia	
	O	SIR (95% CI)
Calendar year of breast cancer diagnosis		
2000–2004	114	2.90*# (2.40–3.49)
2005–2009	308	2.59*# (2.31–2.90)
2010–2014	504	2.24*# (2.05–2.44)
Attained age, years		
15–39	30	18.12*# (12.23–25.87)
40+	896	2.35*# (2.20–2.51)
Latency period, months		
6–11	33	1.21 (0.83–1.70)
12–59	571	3.23*# (2.97–3.50)
60–119	244	1.86*# (1.63–2.10)
120+	75	1.74*# (1.37–2.18)
Unknown	3	0.58 (0.12–1.17)
Subtype		
ER+PR+	517	2.25*# (2.06–2.45)
ER+PR–	91	2.06*# (1.66–2.53)
ER–PR+	11	3.27*# (1.63–5.84)
ER–PR–	199	3.98*# (3.45–4.58)
Unknown	108	1.77*# (1.39, 2.21)
Radiation		
None	354	2.00*# (1.80–2.22)
Yes	524	2.91*# (2.67–3.17)
Unknown	48	2.95*# (1.80–4.56)
Chemotherapy		
None	383	1.42*# (1.28–1.57)
Yes	543	4.98*# (4.57–5.42)
Adjuvant treatment		
R + chemotherapy	356	5.75*# (5.17–6.38)
R only	168	1.42*# (1.21–1.65)
Chemotherapy only	158	3.84*# (3.27–4.49)
None	196	1.44*# (1.25–1.66)
Unknown	48	2.95*# (1.80–4.56)

#, these values indicate the SIR (risk) for developing a second primary cancer was significantly increased. *P<0.05; confidence intervals are 95%. O, observed numbers; SIR, standardized incidence ratio; HR, hormone receptor; ER, estrogen receptor; PR, progesterone receptor; R, radiotherapy.

OS was defined as the period from surgery up to the date of death (due to any cause) or the date of the last follow-up. SPSS 19.0 (IBM Corporation, Armonk, NY, USA) generated all statistical analyses and charts. P<0.05 signified statistical significance. Every test conducted was two-sided.

Results

SIRs for ANLL among breast cancer survivors

A total of 1,555 patients developed leukemia after the breast cancer diagnosis, including 926 women who suffered from ANLL, which was comprised predominately of AML and a small amount of acute monocytic leukemia (AMoL). The SIRs for leukemia are shown in *Table S1*. Increased SIRs were observed in breast cancer survivors with second ANLL (SIR: 2.41; 95% CI: 2.26–2.58), including second AML, AMoL, and other (SIR: 2.45; 95% CI: 2.28–2.62, SIR: 3.34; 95% CI: 2.55–4.30, and SIR: 1.30; 95% CI: 0.89–1.84, respectively).

Table 1 shows the SIRs for second primary ANLL among breast cancer survivors. A total of 926-second primary ANLL were examined and analyzed in our study. Across every year of breast cancer diagnosis, ANLL patients had increased SIRs, although this declined in more recent years (2000–2004 SIR: 2.90; 2005–2009 SIR: 2.59; 2010–2014 SIR: 2.24). Meanwhile, elevated SIRs were observed in the adolescent and young adult group (15–39 years, SIR: 18.12; 95% CI: 12.23–25.87), and the SIRs decreased with increasing age, as seen in the older adult group (40+ years, SIR: 2.35; 95% CI: 2.20–2.51). The SIRs were elevated for each latency period excluding the first 6–11 months post-diagnosis, and these decreased according to the time period (12–59 SIR: 3.23; 60–119 SIR: 1.86; 120+ SIR: 1.74). Overall, patients with 12–59 months' latency had the highest SIR for developing ANLL. In addition, patients with all breast cancer subtypes had elevated SIRs for ANLL (SIR: ER+PR+ 2.25, ER+PR– 2.06, ER–PR+ 3.27, ER–PR– 3.98). Patients who underwent chemotherapy/radiation showed higher SIR for ANLL than those who did not receive chemotherapy/radiation. Meanwhile, breast cancer patients who were treated with combined chemotherapy and radiation had the highest risk for subsequent ANLL in comparison with the population generally (SIR: 5.75; 95% CI: 5.17–6.38).

Risk factors for developing ANLL after breast cancer

Table 2 shows the clinical characteristics of the female patients who had breast cancer alone, together with those of the women who developed second primary ANLL. Women with subsequent ANLL differed significantly from patients with breast cancer only in terms of the race, grade, tumor size, ER and PR status, radiation, and chemotherapy, according to Chi-square tests (*Table 2*). In relation to age at diagnosis, no statistically significant differences were observed between women who had breast cancer alone and those with second primary ANLL.

We then examined the risk factors of developing subsequent ANLL after breast cancer (*Table 3*) and found the risk of developing subsequent ANLL to be positively associated with age at breast cancer diagnosis (40+ *vs.* 15–39 years, aHR =1.572, P=0.003, *Figure 1A*), and tumor size (21–50 *vs.* ≤ 20 mm, aHR =1.332, P=0.003; 50+ *vs.* ≤ 20 mm, aHR =1.735, P<0.001; *Figure 1B*). Moreover, our study also suggested that the risk of developing ANLL among breast cancer patients was positively associated with adjuvant treatment. Compared with survivors who did not receive radiation treatment, women who were treated with radiation had an increased risk of developing ANLL (yes *vs.* no, aHR =1.232, P=0.002; *Figure 1C*). Similarly, patients who received chemotherapy had a higher risk of subsequent ANLL compared to those who did not receive chemotherapy (yes *vs.* no, aHR =1.692, P<0.001; *Figure 1D*). However, *Table 3* showed that race, grade, and ER and PR status had no association with the risk.

Outcomes following ANLL development

OS was defined as the period of time from breast cancer diagnosis to death due to any cause, including breast cancer-specific death or disease progression to ANLL or other related complications. Patients with breast cancer alone and those with breast cancer who developed subsequent ANLL were analyzed in our study. *Table S2* shows that the multivariable Cox regression model was analyzed to adjust for other prognostic indicators of OS. Breast cancer survivors who developed ANLL had a significantly worse OS compared with patients who did not develop ANLL (aHR =3.359, P<0.001; *Figure 2*). The survival of breast cancer patients with second ANLL was comparable between those who received chemotherapy/radiation and those who did not receive chemotherapy/radiation (both P>0.05, not present).

Discussion

ANLL is one of the most common subsequent myeloid neoplasms (MNs) encountered by breast cancer survivors, and it comprises a predominant number of AML and a small amount of acute monocytic leukemia (AMoL). In this study, the comprehensive, retrospective-based analysis of a large population revealed dynamic changes in the risk of subsequent ANLL with first primary breast cancer. The results observed indicated that patients with breast cancer had an increased risk of developing ANLL compared to the general population. In particular, we found that adults with lower age, a short latency period (1–5 years), and ER-PR-subtype had higher SIR for subsequent ANLL, and patients with adjuvant treatment including chemotherapy and radiation also had significantly elevated SIR compared to the general population. Meanwhile, the risk of subsequent ANLL was positively associated with age, tumor size, chemotherapy, and radiation in women with first breast cancer. In addition, a truncated OS was observed in breast cancer patients who developed ANLL, which was adjusted for other independent prognostic factors.

Our results showed that, in correlation with previous studies, breast cancer survivors have an increased risk of developing ANLL compared with the population generally (5,6). Our study also unveiled the trend, which shows the decline in SIR of subsequent ANLL in more recent years. However, this trend could be a mere reflection of the shortened latency period for breast cancer survivors witnessed over the same period. Previous studies observed the highest absolute excess risk of second primary cancers in adolescents and young adult survivors (AYAs), compared with all age groups (11). In addition, another study demonstrated that young women with breast cancer had the highest risk of developing therapy-related myeloid neoplasm (t-MN) (12), our study also suggested AYAs had significantly higher SIR of subsequent ANLL compared to older adult patients after the first breast cancer. There was an age-dependent SIR of subsequent ANLL in AYAs and older adult survivors, which could be potentially be attributed to young females with early on-set breast cancer having a germline mutation in BRAC1 or BRAC2, which leads to enhanced susceptibility (13,14). Although subsequent ANLL is less common among AYAs with breast cancer, the fact that AYAs had such a high SIR for developing ANLL is of clinical importance (15). As found in prior studies, subsequent leukemia may not present within 1 year and may occur at a few latency period (16).

Table 2 Breast cancer patient characteristics within subgroups

Variables	Women with breast cancer only, N=617,083 (%)	Women with second acute non-lymphocytic leukemia, N=919 (%)	P value*
Age at diagnosis, y			0.550
≤14 years	11 (0.0)	0 (0.0)	
15–39 years	36,796 (6.0)	47 (5.1)	
40+ years	580,276 (94.0)	872 (94.9)	
Race			0.028#
White	495,712 (80.3)	758 (82.5)	
Black	66,054 (10.7)	97 (10.5)	
Other	50,761 (8.2)	64 (7.0)	
Unknown	4,556 (0.8)	0 (0.0)	
Grade			<0.001#
Well	118,814 (19.3)	154 (16.8)	
Moderately	236,676 (38.4)	341 (37.1)	
Poorly	199,579 (32.3)	349 (38.0)	
Undifferentiated	6,632 (1.0)	18 (2.0)	
Unknown	55,382 (9.0)	57 (6.1)	
Tumor size (mm)			<0.001#
≤20	256,856 (41.6)	263 (28.6)	
21–50	142,188 (23.0)	202 (22.0)	
50+	35,293 (5.7)	55 (6.0)	
Unknown	182,746 (29.7)	399 (43.4)	
ER			0.007#
Negative	114,117 (18.5)	210 (22.8)	
Positive	445,788 (72.3)	630 (68.6)	
Borderline	852 (0.1)	2 (0.2)	
Unknown	56,326 (9.1)	77 (8.4)	
PR			<0.001#
Negative	174,424 (28.3)	289 (31.4)	
Positive	377,994 (61.3)	528 (57.5)	
Borderline	2,615 (0.4)	11 (1.2)	
Unknown	62,050 (10.0)	91 (9.9)	
Radiation			<0.001#
None	315,573 (51.1)	376 (40.9)	
Yes	301,510 (48.9)	543 (59.1)	
Chemotherapy			<0.001#
None/unknown	361,386 (58.6)	382 (41.6)	
Yes	255,697 (41.4)	537 (58.4)	

*, P values calculated by Pearson Chi squared testing; #, if statistically significant, P<0.05.

Table 3 Cox proportional hazards regression model analysis of risk factors for second acute non-lymphocytic leukemia after breast cancer: adjusted hazard ratio (aHR) and 95% confidence interval (95% CI)

Variables	Acute non-lymphocytic leukemia	
	aHR (95% CI)	P value*
Age at diagnosis, y		
15–39 years	Reference	
40+ years	1.572 (1.168–2.115)	0.003#
Race		
White	Reference	
Black	1.023 (0.826–1.266)	0.837
Other	0.842 (0.652–1.087)	0.188
Grade		
Well	Reference	
Moderately	1.008 (0.830–1.223)	0.938
Poorly	1.102 (0.890–1.364)	0.371
Undifferentiated	1.458 (0.887–2.399)	0.137
Tumor size (mm)		
≤20	Reference	
21–50	1.332 (1.101–1.611)	0.003#
50+	1.735 (1.289–2.334)	<0.001#
ER		
Negative	Reference	
Positive	0.865 (0.688–1.086)	0.211
PR		
Negative	Reference	
Positive	1.037 (0.846–1.270)	0.728
Radiation		
None	Reference	
Yes	1.232 (1.077–1.409)	0.002#
Chemotherapy		
None/unknown	Reference	
Yes	1.692 (1.463–1.958)	<0.001#

*, P values calculated by Log-rank testing; #, if statistically significant, P<0.05.

Meanwhile, ER-PR- breast cancer patients had the highest SIR of the second ANLL, which could be explained by different genetic predisposition among different subtypes, and greater chemotherapy exposure for breast cancer in ER-PR- patients, according to more probable aggressive biologic behaviors (17).

Adjuvant therapy, such as chemotherapy and radiation, plays a pivotal role in the management of breast cancer patients, with the adverse impact of therapy-related complications considered in recent years. As is known, t-MN is a typical complication of chemotherapy and radiation for breast cancer (18), and therapy-related acute non-lymphocytic leukemia (t-ANLL) is believed to be the consequence of metabolism alteration and genomic changes induced by therapy (19,20). The tumor type related to chemotherapy is mainly t-AML in patients with t-ANLL, with exposure to cyclophosphamide and epirubicin, but not to taxanes (21,22). Despite this, we did not carry out the evaluation of the impact of different doses and regimens of chemotherapy as dose and regimen information to is not available from the SEER database. Prior observations reported that radiation therapy has a stronger relation to acute promyelocytic leukemia (APL) than to other ANLL types, and the latency period of radiation-associated ANLL can vary (23). However, the risk of t-MN after exposure to radiation (external beam radiation) is probably lower in comparison with chemotherapy or combined chemotherapy and radiation, as shown by our study (24).

We had extensive information on risk factors and survival outcomes for developing subsequent ANLL among breast cancer survivors. For breast cancer survivors, in the development of subsequent ANLL, older age (40+ years), larger tumor size, chemotherapy, and radiation treatment were in the main related to a heightened risk of subsequent ANLL. Meanwhile, this study corresponds well with previous findings that the development of subsequent MNs among survivors of first unrelated primary cancer can increase mortality and worsen OS (9).

Our study had both strengths and limitations. Contributing to its reliability was having data from a large, well-established and standardized population as its foundation. However, it was also a retrospective study, focusing on a heterogeneous population from the SEER
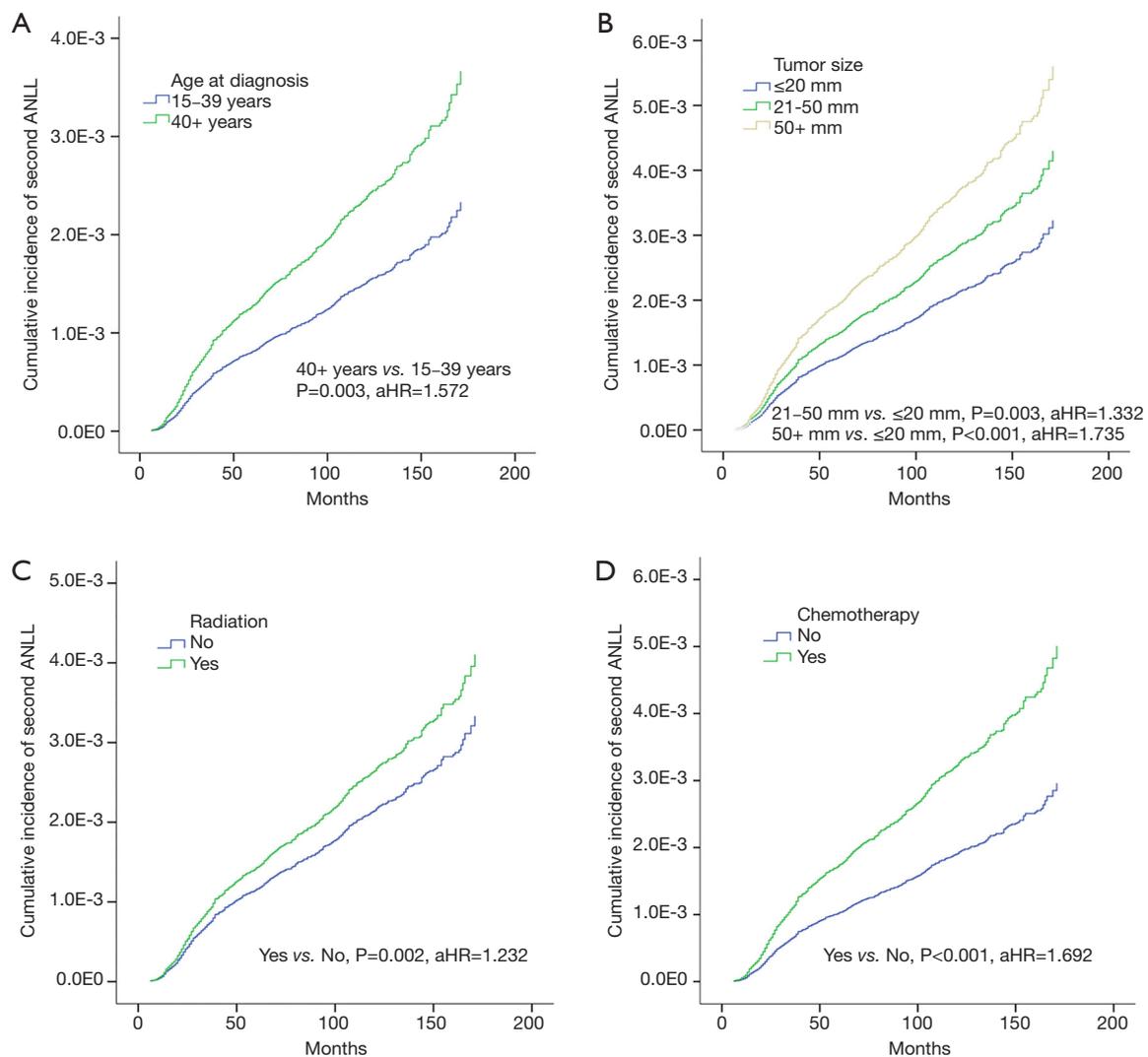
Figure 1 Cumulative incidence curves of subsequent ANLL among breast cancer survivors: (A) in different age groups; (B) in different tumor sizes; (C) in patients receiving radiation compared to those not receiving radiation; (D) in patients receiving chemotherapy compared to those not receiving chemotherapy. ANLL, acute non-lymphocytic leukemia.

data collection. Furthermore, as breast cancer survivors are likely to be given more attention in relation to potential complications than the population as a whole, it is plausible that a surveillance bias might exist for survivors. Therefore, we focused on a 15-year period and conducted an analysis of data from 18 registries, with these systemic errors non-differential. Another limitation was potentially pre-existing or synchronous cancers. To address these issues, this study excluded patients with subsequent leukemia diagnosed within 6 months of a breast cancer diagnosis. Moreover, there is a lack of detailed adjuvant therapy information and

genetic information. Lastly, due to the composition of the dataset, the numbers of AYAs for subsequent ANLL among breast cancer survivors were small. Our findings, therefore, require further confirmation.

In conclusion, we found breast cancer survivors to have a higher risk of developing subsequent ANLL compared to the population as a whole. The heightened risk of developing subsequent ANLL could possibly be related to the biological behavior of the tumor, therapy exposure, and gene susceptibility. In addition, age, tumor size, chemotherapy, and radiation are risk factors for the
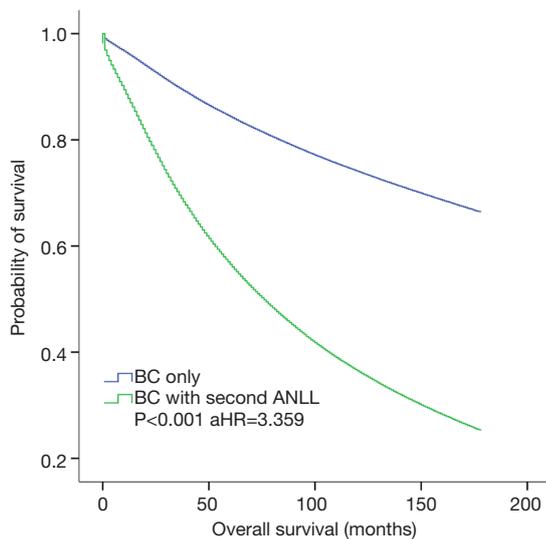
Figure 2 Overall survival for patients with breast cancer only and breast cancer patients with subsequent ANLL. ANLL, acute non-lymphocytic leukemia.

development of subsequent ANLL among breast cancer survivors. Older age, larger tumor size, chemotherapy, and radiation in survivors are positively associated with a higher risk of subsequent ANLL. Meanwhile, survivors following a subsequent ANLL had an adverse survival outcome. These findings are useful for health planning, including monitoring and the development of specific guidelines for both the general population and breast cancer patients.

Acknowledgments

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2020.02.62). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Table S1 Standardized incidence ratios for second leukemia risk in breast cancer patients

Sites	O	SIR (95% CI)
Leukemia	1,555	1.43*[#] (1.36–1.51)
Lymphocytic leukemia	414	0.80*[&] (0.73–0.88)
Acute lymphocytic leukemia	84	1.95*[#] (1.56–2.42)
Chronic lymphocytic leukemia	318	0.70*[&] (0.63–0.79)
Other lymphocytic leukemia	12	0.55*[&] (0.29–0.97)
Non-lymphocytic leukemia	1,141	2.01*[#] (1.89–2.13)
Acute non-lymphocytic leukemia	926	2.41*[#] (2.26–2.58)
Acute myeloid leukemia	834	2.45*[#] (2.28–2.62)
Acute monocytic leukemia	60	3.34*[#] (2.55–4.30)
Other	32	1.30 (0.89–1.84)
Chronic non-lymphocytic leukemia	167	1.25*[#] (1.07–1.45)
Other	48	1.66*[#] (1.03–2.54)

[#], these values indicate the SIR (risk) for developing a second primary cancer was significantly increased; [&], these values indicate the SIR (risk) for developing a second primary cancer was significantly decreased; *P<0.05; confidence intervals are 95%. O, observed numbers; SIR, standardized incidence ratio; NHL, non-Hodgkin lymphoma.

Table S2 Cox proportional hazards regression model analysis of overall survival for patients with breast cancer only and breast cancer patients with second ANLL: adjusted hazard ratio (aHR) and 95% confidence interval (95% CI)

Variables	Acute non-lymphocytic leukemia	
	aHR (95% CI)	P value
Patients		
Breast cancer only	Reference	
With second ANLL	3.359 (3.123–3.614)	<0.001[#]
Age at diagnosis, y		
15–39 years	Reference	
40+ years	1.497 (1.460–1.534)	<0.001[#]
Race		
White	Reference	
Black	1.303 (1.283–1.324)	<0.001[#]
Other	0.672 (0.656, 0.688)	<0.001[#]
Grade		
Well	Reference	
Moderately	1.346 (1.322–1.371)	<0.001[#]
Poorly	1.795 (1.761–1.830)	<0.001[#]
Undifferentiated	2.399 (2.349–2.450)	<0.001[#]
Tumor size (mm)		
≤20	Reference	
21–50	2.241 (2.202–2.281)	<0.001[#]
50+	4.928 (4.821–5.038)	<0.001[#]
ER		
Negative	Reference	
Positive	0.914 (0.898–0.931)	<0.001[#]
PR		
Negative	Reference	
Positive	0.756 (0.744–0.768)	<0.001[#]
Radiation		
None	Reference	
Yes	0.595 (0.588–0.602)	<0.001[#]
Chemotherapy		
None/unknown	Reference	
Yes	0.674 (0.666–0.683)	<0.001[#]

*, P values calculated by Log-rank testing; [#], if statistically significant, P<0.05.