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ORIGINAL REPORT

Breast Cancer Risk in Childhood Cancer Survivors Without a History of Chest Radiotherapy: A Report From the Childhood Cancer Survivor Study

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ABSTRACT

Purpose
Little is known about the breast cancer risk among childhood cancer survivors who did not receive chest radiotherapy. We sought to determine the magnitude of risk and associated risk factors for breast cancer among these women.

Patients and Methods
We evaluated cumulative breast cancer risk in 3,768 female childhood cancer survivors without a history of chest radiotherapy who were participants in the Childhood Cancer Survivor Study.

Results
With median follow up of 25.5 years (range, 8 to 39 years), 47 women developed breast cancer at a median age of 38.0 years (range, 22 to 47 years) and median of 24.0 years (range, 10 to 34 years) from primary cancer to breast cancer. A four-fold increased breast cancer risk (standardized incidence ratio [SIR] = 4.0; 95% CI, 3.0 to 5.3) was observed when compared with the general population. Risk was highest among sarcoma and leukemia survivors (SIR = 5.3; 95% CI, 3.6 to 7.8 and SIR = 4.1; 95% CI, 2.4 to 6.9, respectively). By the age of 45 years, the cumulative incidence of breast cancer in sarcoma and leukemia survivors was 5.8% (95% CI, 3.7 to 8.4) and 6.3% (95% CI, 3.0 to 11.3), respectively. No other primary cancer diagnosis was associated with an elevated risk. Alkylators and anthracyclines were associated with an increased breast cancer risk in a dose-dependent manner (*P* values from test for trend were both $< .01$).

Conclusions
Women not exposed to chest radiotherapy who survive childhood sarcoma or leukemia have an increased risk of breast cancer at a young age. The data suggest high-dose alkylator and anthracycline chemotherapy increase the risk of breast cancer. This may suggest a possible underlying gene-environment interaction that warrants further study.

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INTRODUCTION

The improvement in survival of childhood cancer achieved over the last half century is one of the great successes in modern medicine. Over 80% of children diagnosed with cancer before the age of 21 years will be cured.[1] There are now over 388,500 childhood cancer survivors in the United States.[2] Unfortunately, many survivors have a significantly elevated risk of premature mortality.[3,4] Subsequent malignant neoplasms (SMNs) are the leading cause of late mortality among survivors, excluding recurrence of the primary cancer.[3,5] Breast cancer is the most frequent SMN among female childhood cancer survivors.[6-10] It occurs at a relatively young age in this population and the cumulative incidence increases with age.[6] Evidence to date suggests female survivors exposed to chest radiotherapy are the women at high risk for these breast cancers; there is a well-established, dose-response association between chest radiotherapy and breast cancer risk.[9-16] Among these women, the cumulative incidence of breast cancer by the age of 50 years is 30%.[10]

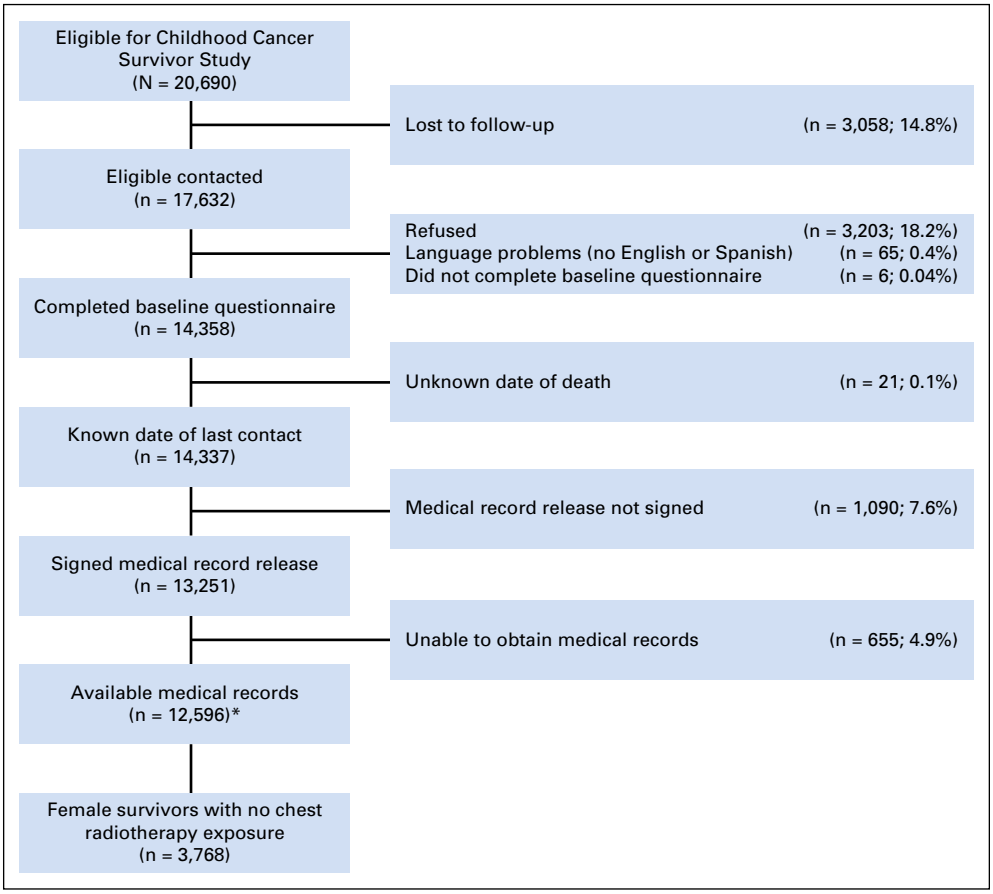

Fig 1. Study flow diagram. (*) Dataset used for all analyses involving treatment data.

Thus, for women exposed to chest radiotherapy, early initiation of breast cancer surveillance with yearly mammography and breast magnetic resonance imaging is recommended.[15,17,18]

In 2004, investigators from the Childhood Cancer Survivor Study (CCSS) reported on 20 breast cancer cases in women not exposed to chest radiotherapy. This study found an elevated breast cancer risk, with standardized incidence ratios (SIRs) of 6.7 and 7.6 among bone and soft tissue sarcoma survivors, respectively.[6] The small number of cases limited the ability to explore potential risk factors, but suggested some childhood cancer survivors may be at risk for breast cancer due to factors other than chest radiotherapy. In the current study, we evaluated breast cancer risk in women never exposed to chest radiotherapy and examined factors associated with this risk.

PATIENTS AND METHODS

Study Population

The CCSS is a retrospective cohort of 14,358 5-year childhood cancer survivors treated at 26 centers in North America.[19,20] Eligibility criteria included: diagnosis of leukemia, CNS malignancy, Hodgkin lymphoma (HL), non-HL, neuroblastoma, soft tissue sarcoma, kidney tumor, or bone cancer; diagnosis between January 1, 1970 and December 31, 1986; less than 21 years of age at diagnosis; and alive 5 years from diagnosis date. Institutional review boards at the participating centers approved the CCSS study. CCSS participants provided informed consent. The cohort methodology has been previously described.[19-21]

We restricted our analysis to 3,768 female participants who received no chest radiotherapy within 5 years of their childhood cancer diagnosis. We defined chest radiotherapy to include treatment with any of the following fields: mantle, mediastinal (including involved field), hemithorax (or anterior fields on one side of chest), whole-lung irradiation, spinal including posterior thoracic/paravertebral, abdominal (with extension above diaphragm), and total body irradiation. Figure 1 depicts the sample used for this analysis.

Ascertainment of Treatment Information

Therapeutic exposures were ascertained through abstraction of medical records of each participant by use of a standardized protocol.[20] This abstraction included diagnosis, chemotherapy, radiation therapy, and surgeries. Cumulative doses of anthracyclines, alkylators, and other chemotherapy agents were determined.[19,22,23]

Identification and Confirmation of Subsequent Breast Cancer

Breast cancer cases, including invasive cancers as well as ductal carcinoma in situ (DCIS), were ascertained through self- or proxy-report and the National Death Index. The CCSS pathologist reviewed pathology reports to confirm all cases. If the pathology report could not be obtained, medical records or death certificates were reviewed.

Statistical Analysis

Childhood cancer survivors were considered at risk for breast cancer beginning from entry into the CCSS cohort (5 years after their childhood cancer diagnosis) until either a recurrence, a confirmed diagnosis of breast cancer, an SMN other than breast cancer, death, or date of most recent contact. Individuals with a recurrence of their primary diagnosis or with an SMN other than breast cancer were censored at the date of diagnosis with the recurrence or neoplasm because we lacked complete medical records and knowledge of radiation exposure in these cases.

Table 1. Cancer Diagnosis, Clinical Characteristics, and Patient Demographic Data of Female Survivors of Childhood Cancer Without a History of Chest Radiotherapy Exposure

Characteristic	Total, N = 3,768	Breast Cancer, n = 47	No Breast Cancer, n = 3,721
Primary childhood cancer, No. (%)			
Leukemia	1,556 (41.3)	14 (29.8)	1,542 (41.4)
Acute lymphoblastic leukemia	1,411	10	1,401
Acute myelogenous leukemia	121	4	117
Others	24	0	24
CNS tumor	474 (12.6)	2 (4.3)	472 (12.6)
Hodgkin lymphoma	63 (1.7)	1 (2.1)	62 (1.7)
Non-Hodgkin lymphoma	155 (4.1)	1 (2.1)	154 (4.1)
Kidney tumor	408 (10.8)	1 (2.1)	407 (10.9)
Neuroblastoma	325 (8.6)	2 (4.2)	323 (8.7)
Sarcoma	787 (20.9)	26 (55.3)	761 (20.5)
Soft tissue sarcoma	418	10	408
Ewing sarcoma	99	6	93
Osteosarcoma	251	10	241
Other sarcoma	19	0	19
Race/ethnicity, No. (%)			
White, non-Hispanic	3,295 (87.4)	42 (89.4)	3,253 (87.4)
Black, non-Hispanic	152 (4.0)	3 (6.4)	149 (4.0)
Hispanic	192 (5.1)	2 (4.2)	190 (5.1)
Other	116 (3.1)	0 (0.0)	116 (3.1)
Unknown	13 (0.4)	0 (0.0)	13 (0.4)
Age at diagnosis of primary cancer, years			
Median	5.0	14.0	5.0
Range	0-20	3-20	0-20
Attained age, years			
Median	31	43	31
Range	8-58	29-56	8-58
Duration of follow up, years			
Median	25.5	26.0	25.5
Range	8.3-38.9	9.9-34.3	8.3-38.9
Age at breast cancer diagnosis, years			
Median		38.0	
Range		22-47	
Chemotherapy for primary cancer, No. (%)			
Alkylators	1,649 (43.8)	30 (63.8)	1,619 (43.5)
Cyclophosphamide	1,567	29	1,538
Other	467	13	454
Cyclophosphamide equivalent dose, mg/m^2, No. (%)			
0	2,116 (59.0)	17 (38.6)	2,099 (59.3)
1-5,999	624 (17.4)	4 (9.1)	620 (17.5)
6,000-17,999	675 (18.8)	16 (36.4)	659 (18.6)
≥ 18,000	169 (4.7)	7 (15.9)	162 (4.6)
Anthracycline cumulative dose, mg/m^2, No. (%)			
0	2,321 (63.4)	14 (31.8)	2,307 (63.8)
1-249	541 (14.8)	4 (9.1)	537 (14.9)
≥ 250	799 (21.8)	26 (59.1)	773 (21.3)
Platinum chemotherapy, No. (%)	181 (4.8)	2 (4.3)	179 (4.8)
Antimetabolites, No. (%)	1,962 (52.1)	24 (51.1)	1,938 (52.1)
Plant alkaloids, No. (%)	2,774 (73.6)	36 (76.6)	2,738 (73.6)
Epipodophyllotoxins, No. (%)	260 (6.9)	2 (4.3)	258 (6.9)
Radiation for primary cancer, No. (%)			
Any*	1,912 (50.7)	22 (46.8)	1,890 (50.8)
Pelvic	1,892 (50.2)	22 (46.8)	1,870 (50.2)
Vital status, No. (%)			
Alive at last point of contact	3,520 (93.4)	35 (74.5)	3,485 (93.6)
Deceased at last point of contact	248 (6.6)	12 (25.5)	236 (6.3)

*Includes all nonchest radiotherapy.

Calculation of SIRs and absolute excess risks. SIRs were calculated as the ratio of the observed numbers of women with breast cancer to the expected numbers in the general population (including both invasive breast cancer and DCIS). SEER Program data were used to ascertain the number of breast cancers expected in a general population female cohort with the same age and calendar-year distribution as eligible CCSS participants.[24] For both the CCSS cohort and SEER Program data, we included only the first primary breast cancer diagnosis. Absolute excess risk was calculated as the difference between the number of observed and expected events divided by the number of person-years follow-up, and is expressed per 10,000 person-years.

Risk factor analysis. We used Poisson regression analysis for SIRs, with age as the time scale to assess for variables that modify the risk of a

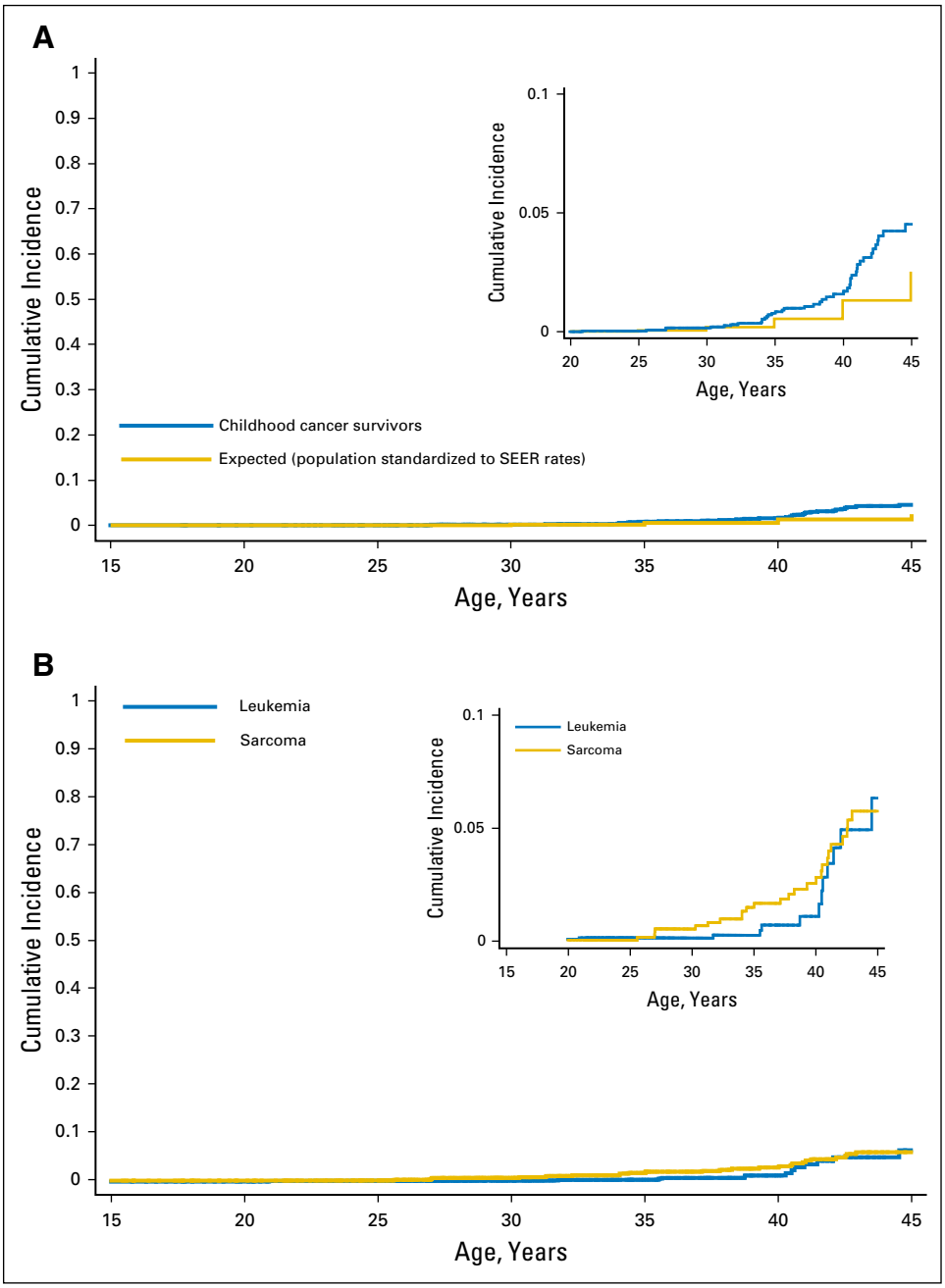

Fig 2. (A) Cumulative incidence of breast cancer in childhood cancer survivors without a history of chest radiotherapy. (B) Cumulative incidence of breast cancer in childhood sarcoma and leukemia survivors without a history of chest radiotherapy.

first breast cancer diagnosis. Relative SIRs (rSIRs) and 95% CIs are presented. A multivariate model was constructed including the main risk factors of interest, cumulative anthracycline dose, cyclophosphamide equivalent dose (CED),[22,23] and age at primary cancer diagnosis, adjusting for race/ethnicity (white, non-Hispanic, and other) and attained age. We explored inclusion of the primary cancer diagnosis (sarcoma/leukemia *v* other cancers); including it was not significant and did not meaningfully change the results. A test for trend for cumulative anthracycline dose and CED was performed by specifying the ordinal variables using orthogonal polynomial contrasts and testing the statistical significance of the linear contrast.

Calculation of cumulative incidence rates. Cumulative incidences of breast cancer overall and by primary diagnoses were calculated with a nonparametric estimate, using age as the time scale. Individuals were considered to be at breast cancer risk beginning 5 years after their primary diagnosis, and death was treated as a competing risk.[25,26] These estimates represent the cumulative proportion of survivors expected to experience a primary breast cancer according to attained age.

We used SAS software, version 9.2 (SAS Institute, Cary, NC), and Stata software, version 13.0 (StataCorp, College Station, TX).

RESULTS

Characteristics of Survivors With Breast Cancer

With a median follow up of 25.5 years (range, 8 to 39 years), 47 women developed primary breast cancer (41 invasive breast cancer cases; six DCIS cases). The median time from primary cancer to breast cancer was 24.0 years (range, 10 to 34 years). The median age at breast cancer diagnosis was 38.0 years (range, 22 to

Table 2. Breast Cancer Risk Compared With the General Population

Characteristic	No. Person-Years at Risk	O	E	SIR	95% CI	AER per 10,000 Person-Years	95% CI
Whole cohort	72,493	47	11.8	4.0	3.0 to 5.3	4.9	3.0 to 6.7
Age at primary diagnosis, years							
0-9	51,750	6	3.3	1.8	0.8 to 4.1	0.5	−0.4 to 1.4
10-20	20,743	41	8.5	4.8	3.5 to 6.5	15.4	9.4 to 21.5
Attained age, years							
0-19	1,803	0	0.0	NA		NA	
20-39	54,109	12	3.4	3.5	2.0 to 6.2	1.6	0.3 to 2.8
40-49	14,999	32	6.8	4.7	3.3 to 6.6	16.8	9.4 to 24.2
50-59	1,582	3	1.5	1.9	0.6 to 6.0	9.5	−12.0 to 30.9
Time since diagnosis, years							
5-14.9	35,625	7	0.6	11.0	5.3 to 23.1	1.8	0.3 to 3.3
15-24.9	28,171	17	4.8	3.6	2.2 to 5.8	4.3	1.5 to 7.2
≥ 25	8,669	23	6.4	3.6	2.4 to 5.4	19.1	8.3 to 30.0
Primary cancer diagnosis							
Leukemia	29,896	14	3.4	4.1	2.4 to 6.9	3.5	1.1 to 6.0
ALL	27,156	10	3.0	3.3	1.8 to 6.3	2.6	0.3 to 4.9
AML	2,377	4	0.4	9.8	3.6 to 26.1	15.1	−1.3 to 31.6
Others	361	0	0.5	NA		NA	
Sarcoma	15,262	26	4.8	5.3	3.6 to 7.8	13.9	7.4 to 20.5
Ewing	1,844	6	0.6	10.0	4.5 to 22.4	29.3	3.2 to 55.3
Soft tissue	8,086	10	2.1	4.8	2.6 to 9.1	9.8	2.1 to 17.4
Osteosarcoma	4,941	10	2.0	5.1	2.8 to 9.5	16.2	3.6 to 28.7
Other sarcoma	391	0	0.2	NA		NA	
CNS tumor	8,042	2	1.4	1.4	0.4 to 5.6	0.7	−2.7 to 4.2
Lymphoma*	4,379	2	1.3	1.6	0.4 to 6.3	1.6	−4.7 to 7.9
Embryonal tumors*	14,914	3	0.8	3.6	1.2 to 11.3	1.5	−0.8 to 3.8
Whole cohort							
CED, mg/m^2							
0	41,443	17	6.6	2.6	1.6 to 4.2	2.5	0.6 to 4.5
1-5,999	11,342	4	1.4	2.8	1.1 to 7.5	2.3	−1.2 to 5.7
6,000-17,999	12,524	16	2.0	7.9	4.8 to 12.9	11.2	4.9 to 17.4
≥ 18,000	3,551	7	0.7	9.4	4.5 to 19.7	17.7	3.1 to 32.3
Anthracycline, mg/m^2							
0	45,660	14	7.2	2.0	1.2 to 3.3	1.5	−0.1 to 3.1
1-249	9,778	4	1.0	4.0	1.5 to 10.7	3.1	−0.9 to 7.1
≥ 250	15,039	26	3.1	8.3	5.7 to 12.2	15.2	8.6 to 21.9
Among leukemia/sarcoma							
CED, mg/m^2							
0	22,404	12	4.4	2.8	1.5 to 4.8	3.4	0.4 to 6.4
1-5,999	9,563	4	1.2	3.3	1.2 to 8.7	2.9	−1.2 to 7.0
6,000-17,999	8,387	15	1.5	10.0	6.1 to 16.7	16.1	7.0 to 25.1
≥ 18,000	2,581	6	0.6	10.3	4.6 to 22.9	20.9	2.3 to 39.5
Anthracycline, mg/m^2							
0	24,752	8	4.4	1.8	0.9 to 3.6	1.5	−0.8 to 3.7
1-249	7,186	4	0.8	5.0	1.8 to 13.1	4.5	−1.0 to 9.9
≥ 250	11,695	25	2.6	9.5	6.4 to 14.0	19.2	10.8 to 27.5

NOTE. Breast cancer includes both invasive breast cancer (n = 41) and ductal carcinoma in situ.
Abbreviations: AER, absolute excess risk; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CED, cyclophosphamide equivalent dose; E, expected; NA, not applicable; O, observed; SIR, standardized incidence ratio.
*Lymphoma = Hodgkin lymphoma or non-Hodgkin lymphoma; embryonal tumors = kidney tumors or neuroblastoma.

47 years). The characteristics of the female childhood cancer survivors are presented in Table 1. Eighty-five percent of women with breast cancer were sarcoma (55%) or leukemia (30%) survivors. Twenty-six percent of women with breast cancer were subsequently deceased at last point of contact. Seven women (15%) with breast cancer had bilateral breast cancer; two women (4%) had synchronous breast cancer, and five women (11%) developed metachronous breast cancer (> 6 months from the first breast cancer diagnosis).

Cumulative Incidence Rates

The cumulative incidence of breast cancer by the age of 45 years was 4.5% (95% CI, 3.2 to 6.2) (Fig 2A), and was highest among sarcoma and leukemia survivors at 5.8% (95% CI, 3.7 to 8.4) and 6.3% (95% CI, 3.0 to 11.3), respectively (Fig 2B). Among all primary cancers except sarcoma and leukemia, the cumulative incidence by the age of 45 years was 1.8% (95% CI, 0.6 to 4.0).

SIR Analysis

Breast cancer risk was four-fold higher in childhood cancer survivors than the general population (Table 2; SIR = 4.0; 95% CI, 3.0 to 5.3). Notable high-risk groups included survivors of primary sarcoma (SIR = 5.3; 95% CI, 3.6 to 7.8) or leukemia (SIR = 4.1; 95% CI, 2.4 to 6.9), those who were older at primary cancer diagnosis (ages 10 to 20 years; SIR = 4.8; 95% CI, 3.5 to 6.5), and

Table 3. Multivariate Risk Factor Analysis

Variable	Whole Cohort			Leukemia/Sarcoma		
	No. of Patients With Breast Cancer	Relative SIRs (95% CI)	*P*	No. of Patients With Breast Cancer	Relative SIRs (95% CI)	*P*
Cyclophosphamide equivalent dose, mg/m^2						
0	15	—	.044	10	—	.045
1-5,999	4	0.6 (0.2 to 2.0)		4	0.7 (0.2 to 2.3)	
6,000-17,999	16	1.6 (0.7 to 3.5)		15	1.9 (0.8 to 4.5)	
≥ 18,000	7	3.0 (1.2 to 7.7)		6	3.4 (1.2 to 9.7)	
Anthracycline dose, mg/m^2						
0	12	—	.004	6	—	.005
1-249	4	2.6 (0.8 to 8.7)		4	4.3 (1.1 to 16.6)	
≥ 250	26	3.8 (1.7 to 8.3)		25	5.1 (1.9 to 13.7)	
Age at primary cancer diagnosis, years						
0-9	6	—	.077	4	—	.147
10-20	36	2.3 (0.9 to 5.8)		31	2.3 (0.7 to 7.0)	
Ethnicity			.849			.944
White, non-Hispanic	37	—		31	—	
Minorities	5	1.1 (0.4 to 2.8)		4	1.0 (0.4 to 3.0)	
Current age, years			.380			.661
5-29	4	—		4	—	
30-34	11	1.3 (0.4 to 4.1)		7	0.8 (0.2 to 2.7)	
35-39	8	0.6 (0.2 to 1.9)		7	0.5 (0.1 to 1.7)	
40+	19	0.8 (0.3 to 2.5)		17	0.7 (0.2 to 2.2)	

NOTE. Survivors with complete data on all risk factors were included.
Abbreviation: SIR, standardized incidence ratio.

those who were treated with anthracycline and alkylator chemotherapy (SIR = 8.6; 95% CI, 5.7 to 12.8). Sarcoma and leukemia survivors treated with both anthracyclines and alkylators had a 9.8-fold increased breast cancer risk (95% CI, 6.5 to 14.7). In contrast, an increased risk among sarcoma and leukemia survivors who did not receive alkylator or anthracycline chemotherapy was not observed (SIR = 1.2; 95% CI, 0.4 to 3.3). When we examined breast cancer risk among women diagnosed with a primary cancer other than sarcoma or leukemia, we did not observe a significantly increased risk (SIR = 1.9; 95% CI, 0.9 to 4.2).

Risk Factor Analysis for Subsequent Breast Cancer

By univariate analysis, breast cancer risk was not significantly different among white, non-Hispanic, and minority survivors. In contrast, survivors diagnosed with their primary cancer between the ages of 10 and 20 years had a higher risk than those diagnosed between 0 and 9 years (rSIR = 2.6; 95% CI, 1.1 to 6.2). Sarcoma and leukemia survivors had a 2.4-fold elevated breast cancer risk compared with all other survivors (95% CI, 1.1 to 5.4). Exposures to alkylator and anthracycline chemotherapy were associated with breast cancer development in a dose-dependent fashion (*P* values both $< .01$). Of note, this association persisted when restricting the analysis to only survivors of sarcoma or leukemia (n = 2,343). The number of cases in those who were not survivors of leukemia or sarcoma (n = 7) precludes a dose-response analysis; only two of these seven survivors received any alkylating agents.

To exclude the effect of scatter radiation (radiation from fields other than chest) on breast cancer risk, we examined the risk from exposure to any radiation for the primary cancer and found no association. Pelvic radiation, associated with a protective effect against breast cancer in women exposed to chest radiotherapy,[10-12] was not associated with a reduced breast cancer risk in this cohort.

Multivariable analysis (Table 3) revealed that exposure to high doses of alkylator (CED > 18,000 mg/m^2; rSIR = 3.0; 95% CI, 1.2 to 7.7) or anthracycline chemotherapy (> 250 mg/m^2; rSIR = 3.8; 95% CI, 1.7 to 8.3) was significantly associated with breast cancer development. When we restricted the analysis to only sarcoma or leukemia survivors, alkylators and anthracyclines were associated with breast cancer development in a dose-dependent fashion (test for trend, *P* values both $< .01$).

DISCUSSION

Overall, we observed that female childhood cancer survivors without a history of chest radiotherapy have a four-fold increased breast cancer risk compared with similar-age women in the general population. Breast cancer risk was particularly increased in sarcoma and leukemia survivors, with a 5.3-fold and 4.1-fold greater risk, respectively; among sarcoma and leukemia survivors exposed to both anthracycline and alkylator chemotherapy, risk was increased to almost 10-fold. To our knowledge, this is the largest study to date focused on breast cancer risk in female childhood cancer survivors who were not exposed to chest radiotherapy for their primary cancer.

A clinically relevant and novel finding observed in this study was the association of two classes of chemotherapy (anthracyclines and alkylators) and breast cancer risk. The association between anthracyclines or alkylators and breast cancer is suggestive of a dose-response relationship. We were limited in this study in our ability to assess the association between chemotherapy exposures and breast cancer risk in the primary cancer diagnoses other than leukemia and sarcoma, given the small number of cases of breast cancer among them (n = 7).

Although increased breast cancer risk has been noted among leukemia and sarcoma survivors, prior studies have not been able

to assess the association of chemotherapeutic exposures among these survivors.[6,27,28] Further, although the association of breast cancer among sarcoma and leukemia survivors has been observed in the British CCSS, this risk was only observed among survivors exposed to radiation therapy, not among survivors who never received radiation.[27,28]

Breast cancer presented in women as young as 22 years with a median age at breast cancer diagnosis of 38 years, which is much younger than the general population incidence. Fifteen percent of women presented with bilateral disease. This is a comparable proportion to that observed in previous reports of breast cancer in survivors exposed to chest radiotherapy[15]; it is higher than the incidence of bilateral disease observed in the general population.[29]

Prior work suggests an association between chemotherapy and solid SMNs, but these studies largely involved patients treated with radiotherapy.[11,30-37] For example, in a case-control study, Inskip et al[11] reported a potential independent association between breast cancer and anthracyclines (odds ratio = 1.86; 95% CI, 0.99 to 3.48), adjusted for an exposure to chest radiotherapy. Henderson et al[31,32] reported that exposure to alkylators or anthracyclines was independently associated with the development of secondary sarcomas in childhood cancer survivors treated with high doses of radiotherapy. This is consistent with earlier studies in the Late Effects Study Group.[36,37] Further, Veiga et al[35] reported that alkylator chemotherapy was independently associated with thyroid cancer development among survivors in the CCSS who received low doses of radiotherapy to the neck field.

There is a paucity of data suggesting a relationship between alkylators or anthracyclines and solid tumors developing in survivors not exposed to therapeutic radiation (or in areas distant from the radiation field). In a case-control study of HL survivors who developed lung cancer, Travis et al[33] reported that alkylator chemotherapy without radiotherapy was associated with increased lung cancer risk (relative risk = 4.2; 95% CI, 2.1 to 8.8). Similarly, Swerdlow et al[34] reported that in HL survivors exposed to chemotherapy alone, there was a significant association between chemotherapy exposure and the development of lung cancer and non-HL.

To our knowledge, this is the first large study that has identified an association between subsequent breast cancer development in a nonirradiated field and exposure to anthracyclines or alkylators. Moreover, our data suggest a possible dose-response relationship. Our findings are consistent with early laboratory-based studies suggesting that anthracycline and alkylator exposure are associated with mammary tumor development in vivo.[38-41] These studies confirmed the in vitro observations that anthracycline agents are potent in producing malignant transformation in mammalian cell systems by their binding interaction with DNA and subsequent disruption of the template functions of DNA.[42] Alkylators, by alkylating DNA to disrupt cancer growth, may also cause DNA damage in normal tissue such that replication is impaired, placing those exposed at risk for solid tumors.[43]

Our findings suggest potential gene-environment interactions causing SMN. Sarcoma (with the exception of Ewing sarcoma [EWS]) and leukemia are cancers known to be associated with Li-Fraumeni syndrome (LFS).[44,45] Eighty-five percent of breast cancers diagnosed in this cohort occurred among sarcoma and leukemia survivors. Additionally, two women with subsequent breast cancer were survivors of CNS tumors, which are also established to be associated with LFS. For survivors of LFS-associated tumors, it is possible that there are gene-chemotherapy interactions that result in increased breast cancer risk, given our observed dose-response association with alkylator and anthracycline chemotherapy exposure in this cohort. Although this hypothesis is supported by the relatively young ages at which women developed their breast cancer and the high incidence of bilateral disease, we lack the ability to evaluate this in detail. Further analyses of family pedigrees and genetic testing are warranted to provide additional insight into an individual's cancer predisposition and the prevalence of familial cancer predisposition syndromes in childhood cancer survivors' SMN risk. In addition, we observed 11 subsequent breast cancer cases in survivors of primary cancers not known to be associated with LFS, including six EWS survivors. Breast cancer after EWS has been described previously in the CCSS and in an analysis of SEER program data.[46,47] However, to date, no known cancer predisposition syndrome has been described that includes EWS. This study may lead to further exploration of an association between familial breast cancer and EWS.

Our study has limitations that need to be considered when interpreting the results. Our ability to evaluate the independent risks of primary diagnosis and therapeutic exposures was limited by the relatively small number of patients with the outcome of interest. For example, many sarcoma patients are treated with high doses of both alkylators and anthracyclines, and the role of exposure to each of these two agents cannot be easily dissected. Our exploratory analyses suggest there may be an association between these agents and a diagnosis of sarcoma or leukemia, but we are underpowered to explore this relationship.

In addition, family history data, important for defining familial cancer risk, are not available in sufficient detail in the CCSS to allow for meaningful analysis. We were unable to calculate scatter radiotherapy dose from therapeutic radiation to nonchest areas, although we did examine exposure to any nonchest radiotherapy in our analyses and found no impact on risk of breast cancer.

Last, we were not able to quantify exposure to diagnostic radiation (ie, computed tomography scans). Exposure to diagnostic and surveillance radiographic studies has not been quantified for the CCSS; the cumulative diagnostic radiation exposure may have influenced the breast cancer risk in this cohort.[48-50] This is of particular interest in sarcoma patients, whose highest recurrence risk is in the lungs and who undergo multiple chest x-rays and/or chest tomography as part of routine surveillance after completion of therapy.

Female sarcoma and leukemia survivors exposed to high doses of anthracyclines or alkylators may benefit from early breast cancer surveillance, even in the absence of a history of exposure to chest radiotherapy. The declining mortality rate in breast cancer in the United States over the past few decades has been attributed to both large-scale screening leading to the identification of earlier-stage disease and to an improvement in systemic treatment strategies,[51] seen in both the general and high-risk breast cancer populations.[15,17,52,53]

For all childhood cancer survivors, particularly sarcoma and leukemia survivors, our data highlight the potential value of clinicians obtaining a detailed family history of cancer and considering genetic counseling and possible genetic testing where

warranted. In women who are found to have an increased familial risk or genetic predisposition to breast cancer, clinicians should counsel them to initiate early breast cancer surveillance as outlined in the National Comprehensive Cancer Network Clinical Practice Guidelines.[54] Last, further study aimed at identifying underlying genetic factors in sarcoma and leukemia survivors that might lead to the development of solid tumors, such as breast cancer, and the potential interactions between these factors and anthracycline and alkylator chemotherapy, is warranted.

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Disclosures provided by the authors are available with this article at www.jco.org.

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