

Breast Cancer after Childhood Cancer: A Report from the Childhood Cancer Survivor Study

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Background: Survivors of childhood cancer are at risk for secondary breast cancer. Other than previous chest radiation therapy, risk factors for secondary breast cancer have not been established.

Objective: To identify risk factors for breast cancer among female survivors of childhood cancer.

Design: Retrospective cohort study.

Setting: The Childhood Cancer Survivor Study (CCSS), a multi-center study of persons who survived more than 5 years after childhood cancer diagnosed from 1970 to 1986.

Participants: Among 6068 women in the CCSS, 95 women had 111 confirmed cases of breast cancer.

Measurements: Standardized incidence ratios for breast cancer were calculated by using age-specific incidence rates in the general population. Breast cancer incidence was evaluated with respect to primary cancer diagnosis and therapy, age at and time since primary diagnosis, menstrual and reproductive history, and family history of cancer.

Results: Breast cancer risk was increased in survivors who were

treated with chest radiation therapy (standardized incidence ratio, 24.7 [95% CI, 19.3 to 31.0]) and survivors of bone and soft-tissue sarcoma who were not treated with chest radiation therapy (standardized incidence ratios, 6.7 and 7.6, respectively). Family history of breast cancer (relative rate, 2.7 [CI, 1.3 to 5.0]) and history of thyroid disease (relative rate, 1.7 [CI, 1.1 to 2.6]) were independently associated with increased risk, and exposure to pelvic radiation was protective (relative rate, 0.6 [CI, 0.4 to 0.9]). Age at primary cancer diagnosis and menstrual and reproductive histories did not statistically significantly modify risk.

Limitations: This cohort has not yet attained an age at which breast cancer risk is greatest.

Conclusion: Survivors of childhood sarcomas and those who received chest radiation therapy are at risk for secondary breast cancer. When assessing a survivor's risk, clinicians should consider primary diagnosis, previous radiation therapy, family cancer history, and history of thyroid disease.

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Women treated with chest radiation therapy for childhood and adolescent Hodgkin disease are at increased risk for developing breast cancer at a young age (1–12). However, case reports and preliminary studies indicate that survivors of childhood cancer other than Hodgkin disease may also be at risk for secondary breast cancer (1, 13, 14). Practitioners caring for the growing population of young female survivors of childhood cancer are challenged with assessing breast cancer risk in order to recommend screening and preventive strategies. Although recent studies have shown that the risk for radiation-induced breast cancer is directly related to dose of chest radiation, specific details of previous treatment are not always available to clinicians and may not affect screening decisions (11, 12). In addition, whether primary cancer diagnosis, previous treatment other than chest radiation, or other well-established breast cancer risk factors contribute to a childhood cancer survivor's risk for breast cancer is unknown.

Studies of Hodgkin disease survivors have shown that clinical examination and screening mammography can detect early-stage secondary breast cancer in young women (15–17), and although treatment options may be limited by previous therapy, early-stage secondary breast cancer is curable (16, 17). Thus, identifying specific groups of childhood cancer survivors who would benefit from early mam-

mographic screening might reduce the morbidity and mortality of breast cancer in these young women.

In this study, we analyzed a large series of women with secondary breast cancer from a cohort of childhood cancer survivors, the Childhood Cancer Survivor Study (CCSS), to describe clinical and pathologic features of breast cancer and to determine breast cancer risk relative to the general population. We hypothesized that breast cancer risk would be modified by previous treatment and factors unrelated to treatment. Thus, in this large cohort of women, we assessed the influence of primary cancer, previous treatment, family cancer history, and menstrual and reproductive history on breast cancer risk.

METHODS

Study Sample: Childhood Cancer Survivors Study

The CCSS is a follow-up study of childhood cancer survivors established in 1994. Eligibility criteria included diagnosis at an age younger than 21 years with leukemia, brain tumor, Hodgkin disease, non-Hodgkin lymphoma, renal tumor, neuroblastoma, or soft-tissue or bone sarcoma and survival of at least 5 years after diagnosis. The 20 276 eligible participants received a diagnosis from 1 January 1970 to 31 December 1986 at 1 of 25 collaborating institutions (Appendix, available at www.annals.org). Participants ($n = 14\ 054$) completed a self-report questionnaire,

providing information about their medical history, family medical history, reproductive history, and socioeconomic status. Follow-up questionnaires were sent to patients reporting second cancer diagnoses. Information on the cohort was updated in 2000. We used data available as of May 2002 for this analysis. No men in the CCSS reported breast cancer by that date; thus, this analysis was restricted to women. Detailed information on the study methods and cohort characteristics has been reported (18). The human subjects committee at each participating institution approved the CCSS protocol.

Clinical Data

We abstracted treatment data from medical records, including chemotherapeutic agents and dose, and radiation therapy dose, and site for primary cancer and relapses. We asked participants who self-reported breast cancer to sign a medical release to confirm the diagnosis. We confirmed all cases of breast cancer in this report and obtained the tumor size, histologic characteristics, hormone receptor status, involvement of axillary nodes, and metastatic sites from pathology records.

Statistical Analysis

We compared survivors who had breast cancer with those who did not have breast cancer with respect to primary cancer diagnosis, age at diagnosis, years of follow-up, and therapy for the primary cancer. We calculated standardized incidence ratios for breast cancer by using age-, sex-, and calendar-year-specific incidence rates of the general population (Surveillance, Epidemiology, and End Results Program [SEER], National Cancer Institute, Bethesda, Maryland [19]). We considered survivors to be at risk for breast cancer from 5 years after the childhood cancer diagnosis until 1 of the following 3 events: death, breast cancer diagnosis, or completion of the CCSS questionnaire. To make the definition of incidence comparable in the calculation of the observed and expected numbers, we included only the first primary breast cancer diagnosis. We calculated cumulative incidences of breast cancer by attained age (20).

We used Poisson multiple regression models for standardized incidence ratios to assess the modification of risk for developing breast cancer by several variables chosen a priori (21). We considered the following risk factors for breast cancer: age at and years since primary cancer diagnosis; age at menarche (<12 years or \geq 12 years); age at first live birth (never, <20 years, 20 to 24 years, or \geq 25 years), as queried in the CCSS questionnaire; history of breast cancer in first-degree female relatives (yes or no); exposure to chest radiation (yes or no); exposure to pelvic radiation (yes or no); family history of sarcoma (yes or no); history of thyroid disease (thyroid nodules, overactive or underactive thyroid, or enlarged thyroid); and exposure to an alkylating agent (alkylating agent score, measured as previously described, accounted for several drug exposures and dose) (22). The Poisson multiple regression incorpo-

Context

Adult survivors of childhood cancer are at risk for developing breast cancer and other secondary cancer. Knowing the risk factors for breast cancer in these women may help to formulate screening policies for them.

Contribution

Among 6068 women who survived childhood cancer, 95 developed breast cancer at a median age of 35 years. Childhood sarcoma, chest irradiation, family history of breast cancer, and personal history of thyroid disease increased the risk for breast cancer.

Implications

Women who survived childhood cancer and had sarcoma, chest irradiation, family history of breast cancer, or personal history of thyroid disease should consider early, vigilant screening for breast cancer.

—The Editors

rated all time-dependent factors by splitting each survivor's follow-up period into several time intervals, wherein each factor was assumed constant. We initially evaluated the relative rate of developing breast cancer for each risk factor, adjusting for the exposure to chest radiation (yes or no). We then stratified the analysis by the exposure to chest radiation and assessed the modification of risk with age at and years since primary cancer diagnosis, family history of breast cancer or sarcoma, history of thyroid disease, and exposure to pelvic radiation. The years since primary cancer diagnosis variable was the baseline time factor of the model for which we obtained fitted standardized incidence ratios relative to SEER data. For other variables, we calculated relative rates by comparing standardized incidence ratios across categories of each variable. All significance tests were 2-sided. We used SAS software, version 8 (SAS Institute Inc., Cary, North Carolina), and S-PLUS software, version 6 (Insightful Corp.), for this analysis.

Role of the Funding Sources

The funding sources had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

RESULTS

Cohort Characteristics

Of the 20 276 survivors eligible for the CCSS cohort, 9062 were women. Of those, 6498 women participated, 6068 of whom had signed medical record release to be eligible for this analysis. Of the 6068 eligible women, 95 women had 111 confirmed cases of breast cancer. Primary cancer diagnosis and age at treatment were similar between participants and nonparticipants (Table 1). Survivors with breast cancer were older at diagnosis of primary cancer and at follow-up than those without breast cancer. As expected,

Table 1. Characteristics of Women Who Did and Did Not Develop Breast Cancer and of Eligible Nonparticipants

Characteristic	Breast Cancer (n = 95)	No Breast Cancer (n = 5973)	Nonparticipants (n = 2994)
Primary cancer, n (%)			
Hodgkin disease	65 (68.4)	741 (12.4)	350 (11.7)
Bone sarcoma	10 (8.6)	511 (8.6)	273 (9.1)
Soft-tissue sarcoma	8 (8.4)	535 (9.0)	276 (9.2)
Non-Hodgkin lymphoma	4 (4.2)	280 (4.7)	146 (4.9)
Wilms tumor	3 (3.2)	593 (9.9)	294 (9.8)
Leukemia	3 (3.2)	2097 (35.1)	963 (32.2)
Brain tumors	2 (2.1)	763 (12.8)	491 (16.4)
Neuroblastoma	0 (0)	453 (7.6)	201 (6.7)
Median age at diagnosis of primary cancer (range), y	16 (5–20)	6 (0–20)	8 (0–20)
Therapy for primary cancer			
Chest radiation therapy, n (%)	73 (76.8)	1185 (19.8)	—
Alkylating agents, n (% yes)	47 (49.5)	2939 (49.2)	—
Median age at last follow-up (range), y	39 (26–50)	27 (5–51)	—
Median duration of follow-up (range), y	19 (6–29)	18 (5–31)	—

Table 2. Clinical and Pathologic Characteristics of Breast Cancer Cases

Characteristic	Patients
Median age at diagnosis of breast cancer (range), y	35 (20–49)
Age at diagnosis of breast cancer, n (%)	
20–24 y	4 (4.2)
25–29 y	14 (14.7)
30–34 y	27 (28.4)
35–39 y	34 (35.8)
40–44 y	11 (11.6)
45–50 y	5 (5.3)
Median time from primary cancer to breast cancer (range), y	19 (6–29)
Laterality of breast cancer, n (%)	
Right	37 (38.9)
Left	42 (44.3)
Bilateral	16 (16.8)
Stage of breast cancer, n (%)	
Known	87 (78.4)
Ductal carcinoma in situ	21 (24.1)
Stage I	30 (34.5)
Stage II	27 (31.0)
Stage III	4 (4.6)
Stage IV	5 (5.7)
Unknown	24 (21.6)
Pathologic features of invasive breast cancer, n (%)	
Invasive ductal carcinoma	77 (85.6)
Lobular carcinoma	4 (4.4)
Mixed ductal or lobular carcinoma	3 (3.3)
Poorly differentiated carcinoma	2 (2.2)
Malignant phylloides tumor	2 (2.2)
Breast angiosarcoma	1 (1.1)
Malignant fibrosarcoma	1 (1.1)
Estrogen receptor status of invasive breast cancer, n (%)	
Known	37 (41.1)
Positive	28 (75.6)
Negative	9 (24.3)
Unknown	53 (58.9)

a large proportion of the women with breast cancer (65 of 95 [68%] women) were Hodgkin disease survivors, and all but 2 of the 65 women were known to have received chest radiation therapy. However, 30 of 95 (32%) women with breast cancer were survivors of other childhood cancer, and 20 of 95 (21%) women did not receive chest radiation therapy. The proportion of patients exposed to alkylating agents was similar in both groups (49.5% vs. 49.2%) (Table 1).

Since the oldest survivors in this cohort were 51 years of age, all cases of breast cancer were diagnosed in relatively young women (median age at diagnosis, 35 years [range, 20 to 49 years]) (Table 2). However, 19% (18 of 95 women) of the breast cancer cases occurred in women 20 to 29 years of age and 64% (61 of 95 women) of cases occurred in women 30 to 39 years of age. Median time from childhood cancer diagnosis to breast cancer diagnosis was 19 years; however, the range extended from 6 years to 29 years after primary cancer diagnosis (Table 2).

Of the 111 cases of breast cancer, 21 cases were ductal carcinoma in situ (Table 2). Of those 21 cases, 19 were diagnosed in Hodgkin disease survivors and 2 in soft-tissue sarcoma survivors. Table 2 shows the distribution of histologic characteristics in the invasive cases. We determined the stage in 66 of 90 (73%) invasive cases from pathology reports (Table 2). Twenty-six (29%) cases involved axillary lymph nodes, and 5 (6%) cases involved distant metastatic disease. Estrogen receptor status was available in 37 cases, and 76% of those were positive.

There was no predominant laterality. Sixteen cases (17%) were bilateral, 5 were synchronous, and 11 involved an asynchronous primary lesion in the opposite breast. Twelve women had a prophylactic contralateral mastectomy after receiving a unilateral breast cancer diagnosis (7 ductal carcinoma in situ and 5 invasive ductal carcinoma). These 12 women were all Hodgkin disease survivors treated with chest radiation therapy. No occult lesions were detected in the 10 prophylactic mastectomy specimens for which pathology reports were available. Of the 79 women who were not known to have had bilateral mastectomies,

11 (14%) developed second primary breast cancer in the contralateral breast. The median time from first breast cancer diagnosis to diagnosis of cancer in the opposite breast was 31 months (range, 4 to 94 months). Seventy-two women were alive at the last follow-up. Of the 23 women who died, the causes of death were breast cancer ($n = 15$), other ($n = 4$), and unknown ($n = 4$).

Analysis of Breast Cancer Incidence

We analyzed breast cancer incidence by primary cancer and stratified the analysis by whether survivors had previous treatment with chest radiation therapy (Table 3). We found that survivors who were treated with chest radiation therapy for Hodgkin disease, bone sarcoma, soft-tissue sarcoma, non-Hodgkin lymphoma, and Wilms tumor were at increased risk for breast cancer compared with the age-matched general population. Survivors of childhood bone sarcoma and soft-tissue sarcoma who were not exposed to previous chest radiation therapy also had increased risk (standardized incidence ratios, 6.7 and 7.6, respectively). Standardized incidence ratios did not increase in women surviving leukemia or brain tumors. For Hodgkin disease survivors, the standardized incidence ratios were 92.4 (95% CI, 55.6 to 144.3) for ductal carcinoma in situ and 17.8 (CI, 13.1 to 23.8) for invasive breast cancer.

In the Figure, the estimated cumulative incidence of breast cancer for survivors of Hodgkin disease, sarcoma

(both bone sarcoma and soft-tissue sarcoma), and other primary cancer as a function of age is shown separately for women exposed and not exposed to chest radiation therapy. Because of the eligibility requirements for this cohort (<21 years of age at initial diagnosis and 5-year survivor), we evaluated cumulative incidence after 26 years of age. Primary diagnosis, age, and exposure to chest radiation influenced the cumulative incidence of breast cancer in this cohort (Figure). In Hodgkin disease survivors who received chest radiation, the cumulative incidence of breast cancer at 40 years of age is 12.9% (CI, 9.3 to 16.5) and continues to increase dramatically over the subsequent decade. For survivors without previous chest radiation, cumulative incidence of breast cancer is highest in sarcoma survivors, reaching 3.3% (CI, 1.2 to 5.4) at 40 years of age.

Table 4 shows the results of a Poisson regression analysis of breast cancer risk factors, adjusted for chest radiation therapy. Factors associated with increased breast cancer risk were family history of breast cancer in first-degree relatives and previous history of thyroid disease. Exposure to pelvic radiation was associated with a decreased risk. Risk was not modified by age at menarche or first live birth. Exposure to alkylating agents was not associated with a statistically significant change in risk. Women who were prepubertal at primary diagnosis (5 to 9 years of age) did

Table 3. Standardized Incidence Ratios of Breast Cancer by Primary Diagnosis and Exposure to Chest Radiation Therapy

Primary Diagnosis	Observed, <i>n</i>	Expected, <i>n</i>	Standardized Incidence Ratio (95% CI)	<i>P</i> Value
All diagnoses				
Chest radiation therapy	73	3.0	24.7 (19.3–31.0)	<0.001
No chest radiation therapy	20	4.2	4.8 (2.9–7.4)	<0.001
Unknown	2	0.4	4.8 (0.53–17.17)	0.13
Hodgkin disease				
Chest radiation therapy	63	2.4	26.3 (20.2–33.7)	<0.001
No chest radiation therapy	0	0.2	—	—
Bone sarcoma				
Chest radiation therapy	3	0.2	19.4 (3.9–56.5)	0.001
No chest radiation therapy	7	1.0	6.7 (2.7–13.8)	<0.001
Soft-tissue sarcoma				
Chest radiation therapy	2	0.1	20.4 (2.3–73.6)	0.009
No chest radiation therapy	6	0.8	7.6 (2.8–16.6)	<0.001
Non-Hodgkin lymphoma				
Chest radiation therapy	3	0.2	16.3 (3.3–47.7)	0.002
No chest radiation therapy	1	0.2	4.2 (0.1–23.3)	>0.2
Wilms tumor				
Chest radiation therapy	2	0.04	45.8 (5.15–165.4)	0.002
No chest radiation therapy	1	0.1	9.5 (0.1–53.0)	0.20
Acute leukemia				
Chest radiation therapy	0	0.1	—	—
No chest radiation therapy	3	1.1	2.7 (0.53–7.8)	0.21
Brain tumor				
Chest radiation therapy	0	0.01	—	—
No chest radiation therapy	2	0.6	3.4 (0.4–12.3)	0.2

Table 4. Relative Rate Associated with Each Risk Factor for Breast Cancer among Childhood Cancer Survivors after Adjustment for Chest Radiation Therapy

Risk Factor	Relative Rate (95% CI)	P Value
Age at original diagnosis		
5–9 y	0.9 (0.4–2.4)	0.16
10–14 y	1.3 (0.8–2.0)	
≥15 y	1.0 (reference)	
Years since original diagnosis		
5–9 y	1.0 (reference)	0.06
10–14 y	1.9 (0.7–8.1)	
15–19 y	1.5 (0.6–6.4)	
≥20 y	1.0 (0.4–4.0)	
Age at menarche		
12 y	1.2 (0.6–2.2)	>0.2
≥12 y	1.0 (reference)	
Age at first live birth		
<20 y	0.7 (0.3–1.4)	>0.2
20–24 y	0.9 (0.5–1.5)	
≥25 y	1.1 (0.7–1.8)	
Never	1.0 (reference)	
Family history of breast cancer		
Yes	2.7 (1.3–5.0)	0.01
No	1.0 (reference)	
Family history of sarcoma		
Yes	5.0 (0.8–15.9)	0.07
No	1.0 (reference)	
Family history of several cancer lesions		
Yes	1.2 (0.4–2.9)	>0.2
No	1.0 (reference)	
Pelvic radiation therapy		
Yes	0.6 (0.4–0.9)	0.03
No	1.0 (reference)	
Alkylating agent score*		
0	1.0 (reference)	>0.2
1–2	0.8 (0.4–1.6)	
3–4	0.8 (0.4–1.4)	
≥5	1.11(0.6–2.0)	
History of thyroid disease		
Yes	1.7 (1.1–2.6)	0.02
No	1.0 (reference)	

* Calculated categorical variable that accounts for exposure to various alkylating agents and a range of doses (22).

not have a statistically significant reduction in breast cancer risk. Family history of sarcoma was associated with an increased risk for secondary breast cancer, although this was not statistically significant (relative rate, 5.0 [CI, 0.8 to 15.9]; $P = 0.07$).

Because secondary breast cancer not associated with chest radiation therapy might have different risk factors, we stratified the cohort by exposure to chest radiation therapy and examined breast cancer risk modification by various factors in a Poisson regression analysis (Table 5). Age at original diagnosis has no effect in either group. As expected, survivors with radiation-associated secondary breast cancer had the greatest risk for breast cancer relative to the

general population 10 to 14 years after their original diagnosis (standardized incidence ratio, 26.0 [CI, 14.0 to 48.2]), and this risk remained statistically significantly high for 20 years or more after diagnosis (standardized incidence ratio, 13.9 [CI, 8.1 to 24.0]). Survivors who were not treated with chest radiation therapy were at greatest risk for breast cancer relative to the general population as soon as 5 to 9 years after initial diagnosis (standardized incidence ratio, 10.0 [CI, 2.3 to 42.7]). When cases were stratified by previous exposure to chest radiation therapy, the effect of family history of sarcoma in survivors who were not exposed to chest radiation therapy increased (relative rate, 9.3 [CI, 1.2 to 70.4]) and was statistically significant ($P = 0.03$). History of previous thyroid disease (relative rate, 1.8 [CI, 1.1 to 2.9]), family history of breast cancer (relative rate, 2.6 [CI, 1.2 to 5.4]), and history of exposure to pelvic radiation therapy (relative rate, 0.6 [CI, 0.4 to 1.0]) inde-

Figure. Cumulative incidence of breast cancer in survivors of Hodgkin disease, bone sarcoma and soft-tissue sarcoma, and other cancer diagnosis as a function of attained age in women exposed and not exposed to chest radiation therapy.

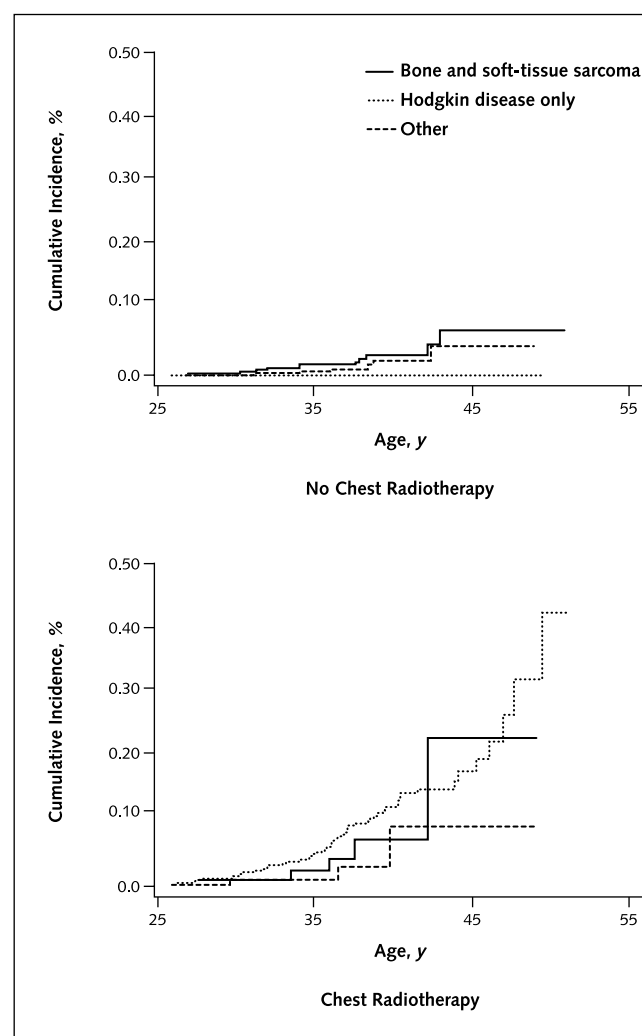


Table 5. Poisson Multiple Regression Models of Breast Cancer Incidence Rates in Women Exposed and Not Exposed to Chest Radiation Therapy

Variable	All Patients (n = 95)		Patients Exposed to Chest Radiation Therapy (n = 73)		Patients Not Exposed to Chest Radiation Therapy (n = 20)	
	Standardized Incidence Ratio (95% CI)	P Value	Standardized Incidence Ratio (95% CI)	P Value	Standardized Incidence Ratio (95% CI)	P Value
Years since original diagnosis						
5–9 y	6.3 (2.0–20.3)	0.002	6.0 (0.8–43.7)	0.08	10.0 (2.3–42.7)	0.002
10–14 y	11.8 (7.0–19.8)	<0.001	26.0 (14.0–48.2)	<0.001	6.3 (2.3–17.1)	<0.001
15–19 y	9.2 (5.8–14.5)	<0.001	22.8 (13.2–39.3)	<0.001	3.4 (1.3–8.9)	0.01
≥20 y	6.0 (3.8–9.4)	<0.001	13.9 (8.1–24.0)	<0.001	2.7 (1.1–6.7)	0.03
Relative Rate (95% CI)						
Pelvic radiation therapy						
Yes	0.6 (0.4–1.0)	0.05	0.6 (0.4–1.0)	0.05	0.7 (0.1–5.2)	>0.2
No	1.0 (reference)		1.0 (reference)		1.0 (reference)	
Family history of breast cancer						
Yes	2.9 (1.5–5.7)	0.001	2.6 (1.2–5.4)	0.01	2.7 (0.6–11.6)	0.19
No	1.0 (reference)		1.0 (reference)		1.0 (reference)	
Family history of sarcoma						
Yes	5.3 (1.3–21.5)	0.02	4.1 (0.6–29.9)	0.16	9.3 (1.2–70.4)	0.03
No	1.0 (reference)		1.0 (reference)		1.0 (reference)	
History of thyroid disease						
Yes	3.0 (2.0–4.6)	<0.001	1.8 (1.1–2.9)	0.02	1.7 (0.6–5.3)	>0.2
No	1.0 (reference)		1.0 (reference)		1.0 (reference)	
Age at original diagnosis						
5–9 y	0.8 (0.3–2.1)	>0.2	1.6 (0.5–5.1)	>0.2	1.0 (0.2–4.9)	>0.2
10–14 y	1.3 (0.8–2.0)	>0.2	1.4 (0.8–2.3)	>0.2	1.6 (0.7–4.0)	>0.2
≥15 y	1.0 (reference)		1.0 (reference)		1.0 (reference)	

pendently modified risk for survivors treated with chest radiation therapy in this model.

DISCUSSION

We found that young female survivors of childhood sarcomas and those treated with chest radiation are at an increased risk for breast cancer compared with women in the age-matched general population. Breast cancer risk is increased by a family history of breast cancer or sarcoma, and history of pelvic radiation is protective. Thyroid disease is an indicator of increased risk in these young women, and unlike in the general population, menstrual and reproductive histories did not statistically significantly modify risk. Unexpectedly, almost one quarter of the breast cancer cases were diagnosed in women who had not been exposed to previous chest radiation. Thus, Hodgkin disease survivors treated with chest radiation therapy are not the only childhood cancer survivors who should be considered at risk for secondary breast cancer.

Breast cancer risk in childhood Hodgkin disease survivors treated with chest radiation therapy has been extensively studied (2–6), and the relative risks we observed (standardized incidence ratio, 26.3) are similar to estimates from other studies (standardized incidence ratio, 15 to 30) (3–6). Our report describes the largest series of secondary

breast cancer to date, provides risk estimates on various primary diagnoses, describes pathologic findings, and analyzes non-treatment-related variables (such as menstrual, reproductive, and family history). Our analysis confirms that survivors of childhood Hodgkin disease and other types of childhood cancer are at increased risk for secondary breast cancer (1) and identifies risk factors that were not previously reported.

Prolonged exposure to endogenous cycling estrogens because of aging, early menarche, delayed menopause, and older age at first live birth is consistently associated with an increased risk for breast cancer in the general population (23, 24). In a large case-control study of Hodgkin disease survivors, Travis and colleagues (11) investigated the role of estrogens in radiation-induced breast cancer. They reported reduced risk for secondary breast cancer in women treated with radiation to the ovaries, consistent with our finding that pelvic radiation decreased risk. Travis and colleagues also showed that increasing cycles of alkylating agent chemotherapy attenuated radiation-related risk; however, for women treated when they were 21 years of age or younger, this trend was not statistically significant (11). We did not find a protective effect of alkylating agents in our study, even at the highest dose level. These findings suggest that the effect of chemotherapy-induced premature

menopause on breast cancer risk is influenced by age at exposure (25) and that the protective effect might not become evident until this cohort ages.

Breast cancer risk was not modulated by age at first birth or age at menarche in our cohort or in van Leeuwen and colleagues' study of Hodgkin disease survivors (12). The protective effect of pregnancy on premenopausal breast cancer risk in young women with competing risk is unclear (26). Studies of young women with hereditary predisposition for breast cancer suggest that age at menarche does not influence risk and that early pregnancy might actually increase breast cancer risk (27, 28). Additional studies with detailed measures of estrogen exposures would be useful to further define breast cancer risk in this population.

Our findings suggest that some survivors of childhood cancer are genetically predisposed to secondary breast cancer. Among survivors with breast cancer who did not receive chest radiation therapy, risk was independently associated with family history of sarcoma. These cases are suggestive of hereditary cancer predisposition syndromes, such as the Li-Fraumeni syndrome, an inherited or de novo mutation in the tumor suppressor gene *TP53* expressed as multiple lesions in affected individuals, including breast cancer, sarcoma, adrenal cancer, and brain tumors (29, 30). The young age at cancer diagnosis, occurrence of bilateral cancer, and influence of family cancer history on risk are consistent with this hypothesis. Analysis of the genetic pedigrees in these study participants could provide information on an individual survivor's cancer susceptibility and the prevalence of familial cancer predisposition syndromes in childhood cancer survivors.

A history of previous thyroid disease may be a useful clinical marker for assessing a survivors' breast cancer risk. Our observed association between previous thyroid disease (probably radiation-induced) (31) and breast cancer might reflect exposure to higher doses of previous radiation therapy. Alternatively, the association we observed might reflect enhanced susceptibility to radiation toxicity due to mutations or polymorphisms of genes affecting DNA stability or repair (32, 33). Thus, genetic analysis of polymorphisms in radiation-repair genes may provide information on individual susceptibility to radiation-induced cancer.

The histologic features, stage, and hormone receptor status of secondary breast cancer in this study are similar to those seen in breast cancer in the general population (34) and secondary breast cancer in other reports (15–17). However, a larger portion of our cases were ductal carcinoma in situ, and some rare pathologic subtypes were seen. The increased risk for ductal carcinoma in situ in Hodgkin disease survivors might represent a trend toward early screening for breast cancer in this group. Previous reports have noted rates of bilateral disease from 10% to 30%, compared with 4% to 6% in the general population (35). Our study confirms the higher rate (17%) of bilateral disease observed by other studies (2, 16, 17). These findings

have important implications when considering preventive strategies and breast cancer treatment options.

In most survivors, breast cancer was diagnosed at an age at which women are usually not considered to be at risk (<40 years of age). Although the relative risks for breast cancer reported in this cohort of young adult women are high, they must be considered in the context of the rarity of breast cancer in young adult women in the general population (19). In addition, the risk estimates might be biased because the health status of the nonparticipants is unknown. However, when interpreting the results of our study, readers should recognize that the disease burden of breast cancer to childhood cancer survivors is probably underestimated because survivors in this cohort have not yet attained the age at which breast cancer risk is greatest (19).

Recent case-control studies of survivors of Hodgkin disease that used radiation dosimetry confirm the association between radiation dose and secondary breast cancer risk (11, 12). We are exploring the relationship between radiation dose to the breast and development of breast cancer in this cohort, determining the precise dose at the site of breast cancer development in each case. Current regimens for childhood cancer have reduced radiation exposure by limiting treatment volume and dose and relying more on combined-modality therapy (36, 37). The success of this strategy in reducing breast cancer risk is not yet determined. Thus, radiation dose is not currently used to guide breast cancer screening recommendations for childhood cancer survivors.

Secondary breast cancer risk should be assessed in all young women who are childhood cancer survivors, with particular attention to survivors of sarcoma and those treated with previous chest radiation therapy. Early screening should be recommended to survivors at increased risk. Future studies should prospectively evaluate the utility of breast cancer risk education, screening, and prevention strategies in this unique population.

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