Breast Cancer After Chest Radiation Therapy for Childhood Cancer

Chaya S. Moskowitz, Joanne F. Chou, Suzanne L. Wolden, Jonine L. Bernstein, Jyoti Malhotra, Danielle Novetsky Friedman, Nidha Z. Mubdi, Wendy M. Leisenring, Marilyn Stovall, Sue Hammond, Susan A. Smith, Tara O. Henderson, John D. Boice, Melissa M. Hudson, Lisa R. Diller, Smita Bhatia, Lisa B. Kenney, Joseph P. Neglia, Colin B. Begg, Leslie L. Robison, and Kevin C. Oeffinger

Author affiliations appear at the end of this article.

Published online ahead of print at www.jco.org on April 21, 2014.

Processed as a Rapid Communication manuscript.

Supported by Grants No. U24CA55727, R01CA136783, K05CA160724, R01CA134722, U01CA83178, R01CA097397, and R01CA129639 from the National Cancer Institute and by the Meg Berté Owen Foundation; support to St Jude Children's Research Hospital was also provided by the American Lebanese-Syrian Associated Charities.

Presented at the 48th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, June 1-5, 2012; 54th Annual Meeting of the American Society of Hematology, Atlanta, GA, December 8-11, 2012; and 45th Congress of the International Society of Paediatric Oncology, Hong Kong, Special Administrative Region, People's Republic of China, September 25-28, 2013.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Chaya S. Moskowitz, PhD, Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, 307 E 63rd St, 3rd Floor, New York, NY 10065; e-mail: moskowc1@mskcc.org.

© 2014 by American Society of Clinical Oncology

0732-183X/14/3221w-2217w/\$20.00

DOI: 10.1200/JCO.2013.54.4601

ABSTRACT

Purpose

The risk of breast cancer is high in women treated for a childhood cancer with chest irradiation. We sought to examine variations in risk resulting from irradiation field and radiation dose.

Patients and Methods

We evaluated cumulative breast cancer risk in 1,230 female childhood cancer survivors treated with chest irradiation who were participants in the CCSS (Childhood Cancer Survivor Study).

Results

Childhood cancer survivors treated with lower delivered doses of radiation (median, 14 Gy; range, 2 to 20 Gy) to a large volume (whole-lung field) had a high risk of breast cancer (standardized incidence ratio [SIR], 43.6; 95% CI, 27.2 to 70.3), as did survivors treated with high doses of delivered radiation (median, 40 Gy) to the mantle field (SIR, 24.2; 95% CI, 20.7 to 28.3). The cumulative incidence of breast cancer by age 50 years was 30% (95% CI, 25 to 34), with a 35% incidence among Hodgkin lymphoma survivors (95% CI, 29 to 40). Breast cancer-specific mortality at 5 and 10 years was 12% (95% CI, 8 to 18) and 19% (95% CI, 13 to 25), respectively.

Conclusion

Among women treated for childhood cancer with chest radiation therapy, those treated with whole-lung irradiation have a greater risk of breast cancer than previously recognized, demonstrating the importance of radiation volume. Importantly, mortality associated with breast cancer after childhood cancer is substantial.

J Clin Oncol 32:2217-2223. © 2014 by American Society of Clinical Oncology

INTRODUCTION

Young women treated for childhood cancer with chest irradiation have an elevated risk of breast cancer.¹⁻¹² The incidence of breast cancer in this population, with estimates in the range of 5% to 14% by age 40 years,^{1,3,5,7,13} is among the highest described for any population. Historically, the highest risk group was survivors of childhood Hodgkin lymphoma treated with high doses of radiation to an extended mantle field.^{1,14,15} However, studies have also reported an increased breast cancer risk among Hodgkin lymphoma survivors treated with contemporary therapy using reduced volumes and lower doses.^{6,14,16} Women treated for other childhood cancers with high doses of radiation to breast tissue also have an elevated risk.^{3,5,13,17}

As a result, several national and international organizations have issued recommendations for long-term breast cancer surveillance.^{13,18-21} The International Late Effects of Childhood Cancer Guide-

line Harmonization Group recently released recommendations for breast cancer surveillance in this high-risk population. It recommended that women treated for cancer before age 30 years with chest irradiation ≥ 20 Gy be screened with an annual mammogram and breast magnetic resonance imaging starting at age 25 years or 8 years after radiation treatment, whichever occurs last. The group called for research to study the risk associated with chest radiation doses < 20 Gy, particularly 10 to 19 Gy, because this is a common dose range with contemporary therapy.²²

Here we investigate the long-term outcomes of female survivors of a childhood cancer treated with chest irradiation to extend our understanding of the incidence of and risk factors for breast cancer. Aiming to further inform screening guidelines, we explored the role of both the delivered dose of radiation and the volume of exposed breast tissue in contributing to breast cancer risk in childhood cancer survivors.

PATIENTS AND METHODS

Study Population

The CCSS (Childhood Cancer Survivor Study) is a retrospective cohort study with longitudinal follow-up of survivors of childhood cancer treated at 26 institutions in the United States and Canada. Eligibility for participation in the CCSS included diagnosis of cancer before age 21 years, initial treatment between 1970 and 1986, and alive at 5 years after diagnosis of leukemia, CNS tumor, Hodgkin or non-Hodgkin lymphoma, Wilms tumor, neuroblastoma, soft tissue sarcoma, or bone tumor. The cohort methodology and study design have been previously described.^{23,24} The CCSS was approved by institutional review boards at the participating centers. Participants provided informed consent.

We restricted our analysis to female participants who had received chest irradiation within 5 years of their childhood cancer diagnosis. We defined chest irradiation to include treatment with any one of the following fields: mantle, mediastinal (including involved field), hemithorax (or anterior fields on one side of chest), whole-lung irradiation (WLI), posterior thoracic/paravertebral, abdominal (with extension above diaphragm), and total-body irradiation (TBI). Of the CCSS participants, 1,230 met these criteria.

Ascertainment of Treatment Information

Data on the primary childhood cancer diagnosis and therapeutic exposures were abstracted from medical records obtained from the treating institutions, including information on fields of irradiation and maximum tumor doses listed in the radiation therapy record or treatment summary for all chest irradiation fields (ie, delivered radiation dose), including those used for recurrent disease. We ascertained complete radiation treatment information for all but seven participants. Treatment abstraction included radiation to the ovaries and chemotherapeutic exposures including alkylating agent chemotherapy.

Identification and Confirmation of Breast Cancer

Breast cancers, invasive cancers, or ductal carcinoma in situ were initially identified through self- or proxy report. They were confirmed by pathology reports if available or alternatively by other medical records. New breast cancers in deceased persons were ascertained through family members and the National Death Index. Only the first primary breast cancer diagnosis was included in our analysis.

Statistical Analysis

Childhood cancer survivors were considered at risk of breast cancer beginning at entry into the CCSS cohort, 5 years after their childhood cancer diagnosis, until a confirmed diagnosis of breast cancer, death, or date of most recent contact. Cumulative incidences of breast cancer overall and by treatment exposure were calculated with a nonparametric estimate considering death as a competing risk.^{25,26} The six CCSS participants for whom we had information on irradiation field but were missing radiotherapy dose were excluded from the dose analyses. One participant for whom radiation therapy records were unavailable was excluded from the dose and field analyses. We defined the primary chest irradiation field as the initial field used. If a woman received mantle field irradiation after previous chest field irradiation, we considered the mantle field to be the primary field because of the dose and volume encompassed by this field.

We measured increased risks of breast cancer by calculating standardized incidence ratios (SIRs), the ratios of the observed number of CCSS participants with breast cancer to the expected number of women with breast cancer in the general US population using age- and calendar year-specific rates from the SEER program.²⁷ For the calendar years after 2010, we used the 2010 rates (most recent rates reported in SEER). Poisson regression was used to assess the effect of factors adjusted for the delivered dose of radiation. We hypothesized that larger irradiation fields were associated with an increased breast cancer risk, whereas exposure to ovarian irradiation or alkylating agents was associated with a decreased risk.

To benchmark breast cancer risk in childhood cancer survivors, we present the expected population cumulative incidence of breast cancer and the risk of breast cancer in another high-risk population for whom intense breast cancer surveillance is recommended: carriers of *BRCA1* and *BRCA2* muta-

tions. Breast cancer risk in *BRCA1* and *BRCA2* mutation carriers was estimated using data from the published WECARE (Women's Environmental Cancer and Radiation Epidemiology) study.^{28,29} In this study, 1,394 1-year survivors of invasive unilateral breast cancer diagnosed before age 55 years between 1985 and 2000 were genotyped for *BRCA1* and *BRCA2* deleterious mutations, yielding 42 *BRCA1* and 31 *BRCA2* mutation carriers. Information on breast cancer incidence, age at breast cancer diagnosis, vital status, and date of death, where applicable, was obtained for 4,570 female first-degree relatives by telephone interview of participants. Among first-degree relatives with a median age of 52 years (range, 0 to 98 years), 324 had breast cancer. There were 21 breast cancers observed in 136 first-degree relatives of the 42 participants with a *BRCA1* mutation and 14 breast cancers observed among 108 first-degree relatives of the 31 participants with a *BRCA2* mutation. The median age at breast cancer diagnosis in the relatives was 55 years (range, 26 to 90 years). These data were used to impute lifetime risks of breast cancer in mutation carriers. The age-specific cumulative risks of breast cancer in *BRCA1* and *BRCA2* mutation carriers were estimated with the kin-cohort method, which uses the breast cancer history of first-degree female relatives together with the genotype data of the participants to produce population-based estimates of the cumulative risks of breast cancer in mutation carriers.³⁰ The expected population cumulative incidence was estimated using age-specific rates of female breast cancer from SEER weighted to take into account the calendar year in which members of the CCSS cohort were at risk of breast cancer.

All-cause mortality subsequent to breast cancer diagnosis in childhood cancer survivors was estimated using the Kaplan-Meier method. Breast cancer-specific mortality was estimated using the cumulative incidence function, treating death resulting from other causes as a competing risk. Age- and calendar year-specific mortality rates in the US population were obtained from the National Center for Health Statistics.³¹ Analyses were performed using STATA (version 12.0; STATA, College Station, TX) and the kin-cohort package (version 0.6) in R software (version 2.13.2; R Foundation for Statistical Computing; <http://www.r-project.org>).

RESULTS

Table 1 lists characteristics of the female childhood cancer survivors. With a median age at last contact of 37 years (range, 6 to 59 years), 203 women had a confirmed breast cancer diagnosis. The median time from childhood cancer diagnosis to onset of breast cancer was 23 years (range, 7 to 41 years). The median age at breast cancer diagnosis was 39 years (range, 24 to 59). Figure 1A shows breast cancer risk by age for the entire cohort. By age 50 years, the cumulative incidence of breast cancer was 30% (95% CI, 25 to 34).

Treatment Exposures

Figure 1B and Table 2 show breast cancer risk by delivered dose of radiation. Although our analysis confirms the high risk of breast cancer in women treated with ≥ 20 Gy, it also demonstrates that women treated with 10 to 19 Gy have an elevated risk of breast cancer (SIR, 30.6; 95% CI, 18.4 to 50.9).

In Figure 1C, breast cancer risk by the primary field of chest irradiation is provided. Women treated with WLI received lower doses of radiation (median, 14 Gy) but to a larger volume of breast tissue than women treated with mantle field (median, 40 Gy) or mediastinal field irradiation (median, 30 Gy). The cumulative incidence of breast cancer in women who received WLI was similar to those who received mantle field irradiation and elevated compared with women who were treated with mediastinal field irradiation. The incidence rate ratios adjusted for dose were 1.8 (95% CI, 0.9 to 3.7; $P = .07$) for comparing WLI with mantle field irradiation and 3.4 (95% CI, 1.6 to 7.2; $P = .001$) for comparing WLI with mediastinal irradiation (SIRs listed in Table 2).

Table 1. Demographic and Cancer-Related Characteristics of Female Childhood Cancer Survivors Treated With Chest Irradiation

Characteristic	All Participants (N = 1,230)		Breast Cancer (n = 203)		No Breast Cancer (n = 1,027)	
	No.	%	No.	%	No.	%
Primary childhood cancer						
Hodgkin lymphoma	678	55.1	167	82.3	511	49.7
Wilms tumor	143	11.6	7	3.4	136	13.2
Non-Hodgkin lymphoma	99	8.1	9	4.4	90	8.8
Neuroblastoma	90	7.3	1	0.5	89	8.7
Leukemia	81	6.6	4	2.0	77	7.5
Bone tumor	75	6.1	12	5.9	63	6.1
Soft tissue sarcoma	55	4.5	3	1.5	52	5.1
CNS tumor	9	0.7	0	0.0	9	0.9
Age at diagnosis of primary cancer, years						
Median	13.0		15.0		12.0	
Range	0-20		3-20		0-20	
Year of diagnosis						
1970-1974	299	24.3	73	36.0	226	22.0
1975-1979	379	30.8	75	37.0	304	29.6
1980-1984	412	33.5	43	21.1	369	36.0
1985-1986	140	11.4	112	5.9	128	12.4
Selected cancer therapies						
Alkylating agent chemotherapy	608	57.6	81	45.8	527	60.0
Pelvic radiation therapy	128	96.9	10	5.0	118	11.5
Race or ethnic group						
White, non-Hispanic	1,112	90.4	192	94.5	920	89.6
Black, non-Hispanic	25	2.0	2	1.0	23	2.2
Hispanic	65	5.3	8	4.0	57	5.6
Other	24	2.0	1	0.5	23	2.2
Unknown	4	0.3	0	0.0	4	0.4
Age at last follow-up, years						
Median	37.3		38.6		36.9	
Range	6.0-58.8		23.7-58.7		6.0-58.2	
Duration of follow-up, years						
Median	25.9		24.1		26.2	
Range	8.4-40.6		10.7-40.6		8.4-38.4	
Vital status						
Alive at last point of contact	925	75.2	141	69.5	784	76.3
Dead at last point of contact	305	24.8	62	30.5	243	23.6

Women treated with mediastinal irradiation had a significantly reduced risk of breast cancer relative to women treated with similar doses of mantle field radiation (incidence rate ratio adjusted for dose, 0.5; 95% CI, 0.3 to 0.9; $P = .013$). Nevertheless, their risk was still significantly increased relative to the general population (Table 2).

Treatment with an irradiation field that included the ovaries decreased the risk of breast cancer (Fig 1D). This decrease remained statistically significant after adjusting for the dose of chest radiation (adjusted incidence rate ratio, 0.3; 95% CI, 0.2 to 0.7; $P = .003$). In contrast, treatment with alkylating agent chemotherapy did not materially modify breast cancer risk (adjusted incidence rate ratio, 1.1; 95% CI, 0.8 to 1.4; $P = .75$; Fig 1E).

Four percent of women (54 of 1,230) received a boost to the primary field, and 37% (455 of 1,230) were treated with $\geq$ two fields. We found no evidence that including the second (or more) field or the radiation boost substantively changed our findings. There seemed to be an elevated breast cancer risk in women treated with TBI and abdominal field irradiation, although these results should be inter-

preted cautiously because of small numbers (Table 2). When these analyses were repeated censoring participants who had a relapse of their pediatric cancer, there were no substantive differences.

Comparison With BRCA1 and BRCA2 Carriers

Figure 2 shows the cumulative incidence of breast cancer for childhood cancer survivors separately for Hodgkin lymphoma survivors and survivors of other childhood cancers contrasted with *BRCA* mutation carriers. The cumulative risk of breast cancer among *BRCA1* and *BRCA2* mutation carriers by age 50 years was 31% (95% CI, 15 to 48) and 10% (95% CI, 1 to 23), respectively. In Hodgkin lymphoma survivors, the cumulative incidence of breast cancer by age 50 years was 35% (95% CI, 29 to 40). For survivors of childhood cancers other than Hodgkin lymphoma, the cumulative incidence of breast cancer by age 45 years was 15% (95% CI, 10 to 21). An estimate for the cumulative incidence by age 50 years for the other childhood cancer survivors is not provided, because the number of women who attained this age was too small for a reliable estimate.

Fig 1. Cumulative risk of breast cancer among women treated for childhood cancer with chest irradiation (A) overall and by childhood cancer therapy: (B) chest radiation dose; (C) chest irradiation field; (D) ovaries in concurrent irradiation field; (E) alkylating agents.

Mortality Among Childhood Cancer Survivors

Among women diagnosed with breast cancer after a childhood cancer, 62 died subsequent to a breast cancer diagnosis; 30 of these deaths were attributable to breast cancer. All-cause mortality at 5 and 10 years was 15% (95% CI, 11 to 22) and 32% (95% CI, 25 to 40), respectively; breast cancer–specific mortality was 12% (95% CI, 8 to 18) and 19% (95% CI, 13 to 25) at 5 and 10 years, respectively (Fig 3). We found no difference in survival by dose of chest radiation used for the childhood cancer.

DISCUSSION

With this work, we contribute novel and clinically important results, including demonstrating an increased breast cancer risk in women treated for a childhood cancer with lower doses of radiation applied to a broad field of breast tissue and describing a high mortality rate in childhood cancer survivors diagnosed with breast cancer. A linear relationship between the absorbed dose of radiation to the breast, as

Table 2. SIRs of Breast Cancer by Childhood Cancer Diagnosis and Treatment

Characteristic	No. of Participants	No. of Person-Years of Risk	No. of Breast Cancer Cases		SIR	95% CI
			Observed	Expected		
Total group	1,230	23,920	203	9.3	21.9	19.1 to 25.2
Primary field of chest irradiation, dose in Gy						
Mantle (median, 40; range, 5 to 54)	603	12,012	156	6.5	24.2	20.7 to 28.3
Mediastinal (median, 30; range, 3 to 54)	239	4,732	20	1.5	13.0	8.4 to 20.2
Whole lung (median, 14; range, 2 to 20)	116	2,198	17	0.4	43.6	27.1 to 70.1
Total body (median, 12; range, 4 to 16)	69	1,118	4	0.2	19.3	7.3 to 51.5
Abdominal (median, 20; range, 4 to 40)*	77	1,579	2	0.2	10.8	2.7 to 43.2
Posterior chest (median, 31; range, 6 to 54)†	54	982	0	0.2	0.0	—
Other one-sided anterior (median, 41; range, 10 to 61)	53	1,073	3	0.3	9.9	3.2 to 30.6
Dose of radiation to chest, Gy						
10-19‡	159	2,939	15	0.5	30.6	18.4 to 50.7
≥ 20	916	18,211	179	8.5	21.2	18.3 to 24.5
Ovaries irradiated						
No	1,102	21,259	193	8.1	23.7	20.6 to 27.3
Yes	128	2,661	10	1.1	8.8	4.7 to 16.4
Alkylating agents						
No	418	8,782	89	4.1	22.7	18.4 to 28.0
Yes	805	14,997	113	4.0	21.4	17.8 to 25.8
Childhood cancer group						
Hodgkin lymphoma	678	13,533	167	7.2	23.1	19.8 to 26.8
Other cancer	552	10,387	36	2.0	17.8	12.9 to 24.7
Age at diagnosis, years						
0-9	402	7,983	11	0.7	14.8	8.2 to 26.8
10-14	353	6,864	66	2.4	27.5	21.6 to 35.0
15-20	475	9,031	126	6.1	20.6	17.3 to 24.6

Abbreviation: SIR, standardized incidence ratio.

*Abdominal field extending above diaphragm.

†Posterior thoracic or paravertebral fields.

‡Irradiation fields represented in this group include mantle (n = 3), mediastinal (n = 30), whole lung (n = 46), hemithorax (n = 4), total body (n = 43), paravertebral/posterior chest (n = 11), and abdominal (n = 22).

estimated by radiation dosimetry, and the risk of breast cancer has been previously reported among childhood cancer survivors.^{3,4} This relationship was used in establishing the lower radiation dose threshold at 20 Gy in the breast cancer surveillance recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group.^{13,18} A clinically important and novel observation from our study is that lower-dose therapeutic radiation < 20 Gy (10 to 19 Gy) to a large volume of breast tissue is associated with a substantially elevated risk among young women. WLI, used to treat pulmonary metastases of pediatric solid malignancies most frequently for Wilms tumor and Ewing sarcoma, is generally delivered at a dose of 12 to 15 Gy, well below the 20 Gy cutoff for early initiation of breast cancer surveillance. However, as illustrated in Figures 1 and 2, the age at onset of breast cancer and the slope of the cumulative incidence are quite similar to those of Hodgkin lymphoma survivors. This suggests that women treated with 10 to 19 Gy of radiation, particularly those with WLI, would derive benefit from early initiation of breast cancer surveillance, similar to those currently screened according to the International Late Effects of Childhood Cancer Guideline Harmonization Group recommendations.²² Moreover, in extending the cumulative incidence rates to 50 years of age, our study confirms previous reports that reducing the volume of irradiated breast tissue from a mantle to mediastinal field is associated with a lower incidence of breast

cancer.^{6,14,16} However, this incidence is still significantly elevated relative to that in the general population, suggesting that female patients treated with contemporary therapy including 20 to 25 Gy to the mediastinal field will still benefit from breast cancer screening.

Although some have linked women treated for a childhood cancer with chest irradiation, particularly in terms of breast cancer surveillance, with another high-risk population, women with underlying genetic mutations,^{15,32,33} how the incidence of breast cancer differs between these two high-risk populations has not been well studied. We found that the magnitude of breast cancer risk by age 50 years in childhood cancer survivors is comparable to that of *BRCA* mutation carrier population-based estimates. The cumulative risk is remarkably similar between *BRCA1* carriers and Hodgkin lymphoma survivors. Our analysis further suggests that women treated with chest irradiation for a childhood cancer other than Hodgkin lymphoma, although varied with respect to the radiation treatment they received, have a lower but still substantially elevated risk profile. This first, to our knowledge, side-by-side comparison of these high-risk populations highlights the need to consider providing women treated as children with chest irradiation a model of care involving risk communication and counseling, breast cancer surveillance, and prevention strategies commensurate to the approach used with women who have a high familial risk.

Fig 2. Cumulative risk of breast cancer. Breast cancer risk among women treated for childhood cancer with chest irradiation contrasted with breast cancer risk in female carriers of *BRCA1* or *BRCA2* deleterious mutations and women in general US population, with a birth-year distribution reflective of CCSS (Childhood Cancer Survivor Study) participants. (*) Insufficient follow-up in this group to provide reliable estimates of cumulative risk of breast cancer by age 50 years.

Breast cancer after childhood cancer is associated with substantial mortality. The reasons for this high mortality rate warrant further study. Of note, we are limited by lack of information on breast cancer stage at diagnosis; in the general population, mortality is strongly associated with stage at diagnosis. Nevertheless, this seems to be an opportunity for lifesaving interventions.

Our study has several notable strengths. The study population represents the largest cohort of women treated with chest irradiation for a childhood cancer, with detailed information regarding their

childhood cancer therapy and confirmed cases of breast cancer. In contrast to earlier studies that assessed radiation exposure and risk of breast cancer using dosimetry based on detailed radiation oncology records to estimate radiation dose to the specific site of the breast cancer, we used information available in the medical records, namely the radiation treatment summary. By focusing on the summary of delivered radiation fields and doses, information that is generally available to the clinician, our results have direct clinical implications. Lastly, this is the first study to our knowledge to directly contrast risk between childhood cancer survivors and *BRCA* mutation carriers.

It is also important to recognize the limitations of the study. This is a relatively young cohort, with a median age of 37 years. As the participants age, breast cancer incidence may increase. Data for women treated with WLI were sparse after age 45 years, limiting our ability to draw conclusions beyond that age. Although the risk of breast cancer in women treated with TBI and abdominal irradiation seemed elevated, the numbers of women in each group were small. Larger samples, potentially obtainable by merging international studies in this area, are necessary to make definitive statements about risk in these women.

We previously estimated that there are approximately 20,000 to 25,000 women in the United States age > 25 years who have previously been treated with high doses (≥ 20 Gy) of chest radiation for a childhood cancer.³⁴ Breast cancer surveillance guidelines for women treated with chest irradiation for a prior malignancy have been limited in part by a lack of evidence with regard to information available to health care professionals that may modify breast cancer risk in this population. Our study contributes important insights in this respect and indicates that irradiation field is an important factor.

In conclusion, women treated with lower doses of radiation to large volumes of breast tissue for a childhood cancer have a risk of breast cancer that is higher than has previously been recognized, warranting consideration of initiating breast cancer surveillance at a young age. We found that childhood cancer survivors treated with chest irradiation have a risk of breast cancer similar to that of *BRCA* mutation carriers, a risk that is much higher than women in the general population. Finally, mortality associated with breast cancer after childhood cancer is substantial.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Chaya S. Moskowitz, Jonine L. Bernstein, Wendy M. Leisenring, Sue Hammond, John D. Boice, Melissa M. Hudson, Lisa R. Diller, Joseph P. Neglia, Colin B. Begg, Leslie L. Robison, Kevin C. Oeffinger

Financial support: Chaya S. Moskowitz, Jonine L. Bernstein, Leslie L. Robison, Kevin C. Oeffinger

Administrative support: Chaya S. Moskowitz, Leslie L. Robison, Kevin C. Oeffinger

Provision of study materials or patients: Lisa R. Diller, Leslie L. Robison

Collection and assembly of data: Chaya S. Moskowitz, Joanne F. Chou, Suzanne L. Wolden, Jonine L. Bernstein, Jyoti Malhotra, Danielle Novetsky Friedman, Nidha Z. Mubdi, Marilyn Stovall, Sue Hammond,

Fig 3. Death after breast cancer among childhood cancer survivors treated with chest irradiation. All-cause and breast cancer-specific mortality after breast cancer after chest radiotherapy for childhood cancer compared with expected mortality, age and year standardized to US population.

Susan A. Smith, Tara O. Henderson, Joseph P. Neglia, Leslie L. Robison, Kevin C. Oeffinger

Data analysis and interpretation: Chaya S. Moskowitz, Joanne F. Chou, Suzanne L. Wolden, Jonine L. Bernstein, Wendy M. Leisenring, Tara O.

Henderson, John D. Boice, Melissa M. Hudson, Lisa R. Diller, Smita Bhatia, Lisa B. Kenney, Colin B. Begg, Kevin C. Oeffinger

Manuscript writing: All authors

Final approval of manuscript: All authors

REFERENCES

- Bhatia S, Yasui Y, Robison LL, et al: High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: Report from the Late Effects Study Group. *J Clin Oncol* 21:4386-4394, 2003
- Constine LS, Tarbell N, Hudson MM, et al: Subsequent malignancies in children treated for Hodgkin's disease: Associations with gender and radiation dose. *Int J Radiat Oncol Biol Phys* 72:24-33, 2008
- Guibout C, Adjadj E, Rubino C, et al: Malignant breast tumors after radiotherapy for a first cancer during childhood. *J Clin Oncol* 23:197-204, 2005
- Inskip PD, Robison LL, Stovall M, et al: Radiation dose and breast cancer risk in the Childhood Cancer Survivor Study. *J Clin Oncol* 27:3901-3907, 2009
- Kenney LB, Yasui Y, Inskip PD, et al: Breast cancer risk after childhood cancer: A report from the Childhood Cancer Survivor Study. *Ann Intern Med* 141:590-597, 2004
- Swerdlow AJ, Cooke R, Bates A, et al: Breast cancer risk after supradiaphragmatic radiotherapy for Hodgkin's lymphoma in England and Wales: A national cohort study. *J Clin Oncol* 30:2745-2752, 2012
- Taylor AJ, Winter DL, Stiller CA, et al: Risk of breast cancer in female survivors of childhood Hodgkin's disease in Britain: A population-based study. *Int J Cancer* 120:384-391, 2007
- Travis LB, Hill DA, Dores GM, et al: Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. *JAMA* 290:465-475, 2003
- Reulen RC, Frobisher C, Winter DL, et al: Long-term risks of subsequent primary neoplasms among survivors of childhood cancer. *JAMA* 305:2311-2319, 2011
- Metayer C, Lynch CF, Clarke EA, et al: Second cancers among long-term survivors of Hodgkin's disease diagnosed in childhood and adolescence. *J Clin Oncol* 18:2435-2443, 2000
- Hudson MM, Ness KK, Gurney JG, et al: Clinical ascertainment of health outcomes among adults treated for childhood cancer. *JAMA* 309:2371-2381, 2013
- Ng AK, Bernardo MV, Weller E, et al: Second malignancy after Hodgkin disease treated with radiation therapy with or without chemotherapy: Long-term risks and risk factors. *Blood* 100:1989-1996, 2002
- Henderson TO, Amsterdam A, Bhatia S, et al: Systematic review: Surveillance for breast cancer in women treated with chest radiation for childhood, adolescent, or young adult cancer. *Ann Intern Med* 152:444-455, W144-W154, 2010
- De Bruin ML, Sparidans J, van't Veer MB, et al: Breast cancer risk in female survivors of Hodgkin's lymphoma: Lower risk after smaller radiation volumes. *J Clin Oncol* 27:4239-4246, 2009
- Travis LB, Hill D, Dores GM, et al: Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma. *J Natl Cancer Inst* 97:1428-1437, 2005
- O'Brien MM, Donaldson SS, Balise RR, et al: Second malignant neoplasms in survivors of pediatric Hodgkin's lymphoma treated with low-dose radiation and chemotherapy. *J Clin Oncol* 28:1232-1239, 2010
- Friedman DL, Whitton J, Leisenring W, et al: Subsequent neoplasms in 5-year survivors of childhood cancer: The Childhood Cancer Survivor Study. *J Natl Cancer Inst* 102:1083-1095, 2010
- Children's Oncology Group: Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancer (version 3.0). <http://www.survivorshipguidelines.org>
- UK Department of Health Cancer Policy Team: Increased risk of breast cancer after radiotherapy for Hodgkin's disease: Patient notification exercise. <http://www.cancerscreening.nhs.uk/breastscreen/>
- UK Children's Cancer Study Group Late Effects Group: Therapy based long term follow up practice statement. <http://www.cclg.org.uk/>
- Dutch Childhood Oncology Group: Richtlijn follow-up na kinderkanker meer dan 5 jaar na diagnose. <http://www.skion.nl/>
- Mulder RL, Kremer LCM, Hudson MM, et al: Recommendations for breast cancer surveillance for female childhood, adolescent and young adult cancer survivors treated with chest radiation: A report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Oncol* 14:e621-e629, 2013
- Robison LL, Armstrong GT, Boice JD, et al: The Childhood Cancer Survivor Study: A National Cancer Institute-supported resource for outcome and intervention research. *J Clin Oncol* 27:2308-2318, 2009
- Robison LL, Mertens AC, Boice JD, et al: Study design and cohort characteristics of the Childhood Cancer Survivor Study: A multi-institutional collaborative project. *Med Pediatr Oncol* 38:229-239, 2002
- STATA: STATA Survival Analysis and Epidemiological Tables Reference Manual. College Station, TX, STATA Press, 2011
- Coviello V, Boggess M: Cumulative incidence estimation in the presence of competing risks. *Stata J* 4:103-112, 2004
- National Cancer Institute: Surveillance, Epidemiology, and End Results Program: SEER*Stat Database—Incidence: SEER 9 regs research data—November 2012 submission: Vintage 2009 populations (1973-2010). www.seer.cancer.gov
- Begg CB, Haile RW, Borg A, et al: Variation of breast cancer risk among BRCA1/2 carriers. *JAMA* 299:194-201, 2008
- Bernstein JL, Langholz B, Haile RW, et al: Study design: Evaluating gene-environment interactions in the etiology of breast cancer—The WECARE study. *Breast Cancer Res* 6:R199-R214, 2004
- Chatterjee N, Wacholder S: A marginal likelihood approach for estimating penetrance from kin-cohort designs. *Biometrics* 57:245-252, 2001
- National Center for Health Statistics: Centers for Disease Control and Prevention: United States Life Tables, 1983-2008
- US Preventive Services Task Force: Screening for breast cancer: US Preventive Services Task Force recommendation statement. *Ann Intern Med* 151:716-726, W236, 2009
- Saslow D, Boetes C, Burke W, et al: American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA Cancer J Clin* 57:75-89, 2007
- Oeffinger KC, Ford JS, Moskowitz CS, et al: Breast cancer surveillance practices among women previously treated with chest radiation for a childhood cancer. *JAMA* 301:404-414, 2009

Affiliations

Chaya S. Moskowitz, Joanne F. Chou, Suzanne L. Wolden, Jonine L. Bernstein, Danielle Novetsky Friedman, Nidha Z. Mubdi, Colin B. Begg, and Kevin C. Oeffinger, Memorial Sloan Kettering Cancer Center; Jyoti Malhotra, Mount Sinai Medical Center, New York, NY; Wendy M. Leisenring, Fred Hutchinson Cancer Research Center, Seattle, WA; Marilyn Stovall and Susan A. Smith, University of Texas MD Anderson Cancer Center, Houston, TX; Sue Hammond, Nationwide Children's Hospital, Columbus, OH; Tara O. Henderson, University of Chicago Medicine Comer Children's Hospital, Chicago, IL; John D. Boice, Vanderbilt-Ingram Cancer Center, Nashville; Melissa M. Hudson and Leslie L. Robison, St Jude Children's Research Hospital, Memphis, TN; Lisa R. Diller and Lisa B. Kenney, Dana-Farber Cancer Institute, Boston, MA; Smita Bhatia, City of Hope National Medical Center, Duarte, CA; and Joseph P. Neglia, University of Minnesota Masonic Cancer Center, Minneapolis, MN.

Acknowledgment

We thank Flora van Leeuwen and Lois B. Travis for sharing their comments and insight.