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Original article

Breast cancer following spinal irradiation for a childhood cancer: A report from the Childhood Cancer Survivor Study

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ABSTRACT

It has been suggested that pediatric patients treated with spinal irradiation may have an elevated risk of breast cancer. Among a cohort of 363 long-term survivors of a pediatric central nervous system tumor or leukemia treated with spinal irradiation, there was little evidence of an increased breast cancer risk.

Spinal irradiation is essential for cure for many children with central nervous system (CNS) tumors, including medulloblastoma. It was also used until the 1980's to treat some children with leukemia. While breast cancer is not commonly thought to be a late sequela of spinal irradiation, we are not aware of studies that specifically address this question. Multiple studies assessing the occurrence of second neoplasms in leukemia and CNS tumor survivors report very few instances of breast cancer despite studying thousands of patients (with a maximum median follow-up of 18.7 years) [1–8]. None of these studies, however, present enough details to evaluate whether these breast cancers are occurring specifically among survivors treated with spinal irradiation.

Materials and methods

We analyzed participants in the Childhood Cancer Survivor Study (CCSS), a cohort of 5-year survivors of childhood cancer diagnosed before the age of 21 years between 1970 and 1986 at one of 26 participating institutions. Participants and data collection methods were described previously [9,10]. The institutional review board at each institution approved the CCSS protocol. Informed consent was obtained from all participants or their parents. We focus on female survivors of a pediatric CNS tumor or leukemia who were treated with spinal irradiation but with no other radiation field near breast tissue (women also treated with high abdominal fields or total body irradiation were excluded). Delivered spinal irradiation doses were abstracted from medical records. Average breast doses were calculated using radiation treatment parameters as previously described [11]. To summarize the average breast dose across all participants, we present a weighted average of the average nipple dose across cohort participants. Radiation doses to the left and right ovaries were also estimated. The right and left ovary doses were equivalent in all but four women, and the average is presented. The cyclophosphamide equivalent dose (CED) was used to quantify cumulative alkylating agent exposure and was calculated as has been described previously [12].

We estimated the relative risk of breast cancer with standardized incidence ratios (SIRs) using age- and calendar-year-specific incidence rates in the U.S. of invasive and in-situ carcinoma from the Surveillance, Epidemiology, and End Results (SEER) program. Only the first primary breast cancer diagnosis is included. CCSS participants were considered at risk of breast cancer starting 5 years after their childhood cancer diagnosis until a diagnosis of breast cancer, death, or date of last follow-up. All analyses were done in Stata 12.1 for Windows (StataCorp LP, College Station, TX).

Results

Among 363 survivors of leukemia and CNS tumors treated with spinal irradiation, the median age at diagnosis of the primary childhood cancer was five years (range = [0,19]). Among participants

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still alive, the median follow-up was 27 years (range = [10,38]). The median attained age was 35 years (range = [10,53]); 36 years among all leukemia survivors and 33 years among CNS tumor survivors. The majority of the participants in this sub-cohort were survivors of either (a) acute lymphoblastic leukemia (ALL) (n = 184) or (b) medulloblastoma or primitive neuroectodermal tumor (PNET) (n = 125). The median attained age of ALL survivors was 33 years (range = [6,52]), and the median follow-up among ALL survivors still alive was 27 years (range = [10,38]). The median attained age of medulloblastoma or PNET survivors was 33 years (range = [8,54]), and the median follow-up among those survivors still alive was 26 years (range = [11,38]). Additional characteristics of these participants are presented in Table 1.

Three women were diagnosed with breast cancer. One was diagnosed with invasive ductal carcinoma in the left breast, quadrant unknown, at 31 years of age after receiving 23 Gy Cobalt-60 craniospinal radiotherapy for acute lymphoblastic leukemia (ALL) at 13 years of age; average dose to the breast was 0.61 Gy. A second woman was diagnosed with ductal carcinoma in-situ in the upper outer quadrant of the right breast at age 41 years after receiving 18 Gy craniospinal radiotherapy with Cobalt-60 for ALL at age 15; average breast dose was 0.67 Gy. Both had no known family history of breast cancer. The third woman was diagnosed with invasive ductal carcinoma at age 41 years, location unknown, after receiving 25 Gy craniospinal radiotherapy with 4 MeV for a leukemia at age 12; average dose to the breast was 0.49 Gy. Her family history was unknown.

Table 1
Characteristics of CNS tumor and leukemia survivors treated with spinal irradiation.

Characteristic	Total (N = 363)		CNS tumor survivors[a] (N = 168)		Leukemia survivors[b] (N = 195)	
	No.	%	No.	%	No.	%
Age at diagnosis of primary cancer, years						
0–4	166	45.7	56	33.3	110	56.4
5–11	133	36.6	78	46.4	55	28.2
12 and older	64	17.6	34	20.2	30	15.4
Year of diagnosis of primary cancer						
1970–1974	115	31.7	16	9.5	99	50.8
1975–1979	74	20.4	42	25.0	32	16.4
1980–1986	174	47.9	110	65.5	64	32.8
Dose of spinal irradiation, Gy						
Less than 19	107	29.5	4	2.4	103	52.8
19–24	101	27.8	21	12.5	80	41.0
25–35	99	27.3	90	53.6	9	4.6
36+	56	15.4	53	31.6	3	1.5
Race						
White, non-hispanic	320	88.2	148	88.1	172	88.2
Minorities	42	11.6	20	11.9	22	11.3
Unknown	1	0.3	0	0	1	0.5
CED (mg/m^2)						
0	191	60.1	94	64.4	97	56.4
>0–3999	34	10.7	6	4.1	28	16.2
4000–7999	22	6.9	7	4.8	15	8.7
8000+	71	22.3	39	26.7	32	18.6
Average ovarian irradiation dose (Gy)						
0	9	2.5	0	0	9	4.6
0.01–0.9	34	9.5	9	5.5	25	12.9
1–9	273	76.0	139	84.2	134	69.1
10–19	26	7.2	9	5.5	17	8.8
20+	17	4.7	8	4.9	9	4.6
Vital status						
Alive	282	77.7	130	77.4	152	78.0
Deceased	81	22.3	38	22.6	43	22.0
Follow-up, years[c]						
Less than 20 years	84	23.1	42	25.0	42	21.5
20+ years	279	76.9	126	75.0	153	78.5
Age at analysis, years[d]						
Under 25	82	22.6	40	23.8	42	21.5
25–39	218	60.1	106	63.1	112	57.4
40+	63	17.4	22	13.1	41	21.0

[a] Diagnoses of CNS tumor survivors consist of medulloblastoma or primitive neuroectodermal tumor (n = 125), astrocytoma (n = 8), and other CNS tumor (n = 35).
[b] Diagnoses of leukemia survivors consist of acute lymphoblastic leukemia (n = 184), acute myeloid leukemia (n = 2), and other leukemia (n = 9). CED = cyclophosphamide equivalent dose (information is missing on n = 45 participants) Minimum ovarian irradiation dose missing on n = 4 participants.
[c] Evaluated in participants still alive at last contact.
[d] Defined as the age at breast cancer diagnosis, death, or last contact.

Leukemia survivors had lower delivered doses of spinal irradiation than CNS tumor survivors, a median of 18 Gy (range = [1.5,41.8]) compared with a median of 34.53 Gy (range = [4.8,65.0]) for CNS tumor survivors (Fig. 1), although their estimated doses to the breast were similar, an average of 1.1 Gy compared with 1.5 Gy for leukemia and CNS tumor survivors, respectively. The SIR was 2.4 (95% CI: 0.8–7.5) in all women treated with spinal irradiation, and 3.8 (95% CI: 1.2–11.7) in leukemia survivors.

CNS tumor survivors also tended to be treated with higher doses of alkylating agents than were leukemia survivors. Among the 74 (44%) CNS tumor survivors who were treated with alkylators, the median CED was 11,435 mg/m^2 (range = [1111.1,32,517.1]). Among the 98 (50%) leukemia survivors treated with alkylators, the median CED was 6756.8 mg/m^2 (range = [102.7,49,380.4]). Ovarian radiation doses were similar in the two groups, a median of 3.3 Gy for CNS tumor survivors (range = [0.01,34.0]) compared with 2.8 Gy for leukemia survivors (range = [0.02,34.7]).

Discussion

Several recent papers have used simulation and modeling strategies based on the estimated radiation dose to the breast to suggest there may be an increased breast cancer risk after spinal irradiation with conventional photon therapy for a pediatric malignancy particularly when compared to irradiation with proton therapy. These analyses have been taken to indicate that there may be a substantially elevated breast cancer risk after photon therapy [13,14], that proton therapy may significantly reduce this risk although the risk reduction may depend on the method of proton beam delivery [14–16], and that early breast cancer screening might be considered in women treated with high doses of spinal irradiation using conventional photon therapy [15].

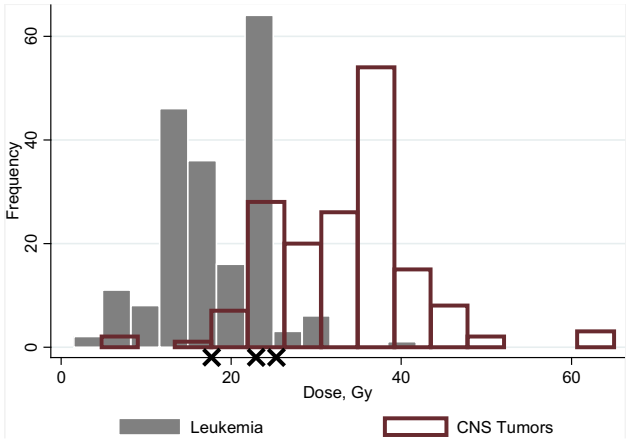

Fig. 1. Distribution of doses of spinal irradiation. The delivered doses of spinal irradiation are shown separately by childhood cancer diagnosis. The delivered doses for the three women diagnosed with breast cancer are denoted with an X.

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