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Risk Factors Associated with Secondary Sarcomas in Childhood Cancer Survivors: A Report from the *Childhood Cancer Survivor Study*

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Abstract

Purpose—Childhood cancer survivors have an increased risk of secondary sarcomas. To better identify those at risk, the relationship between therapeutic dose of chemotherapy and radiation and secondary sarcoma should be quantified.

Methods and Materials—We conducted a nested case-control study of secondary sarcomas (105 cases, 422 matched controls) in a cohort of 14,372 childhood cancer survivors. Radiation dose at the second malignant neoplasm (SMN) site and use of chemotherapy were estimated from detailed review of medical records. Odds ratios (ORs) and 95% confidence intervals were estimated by conditional logistic regression. Excess odds ratio (EOR) was modeled as a function of radiation dose, chemotherapy, and host factors.

Results—Sarcomas occurred a median of 11.8 years (range: 5.3-31.3 years) from original diagnosis. Any exposure to radiation was associated with increased risk of subsequent sarcoma (OR = 4.1, 95% CI = 1.8-9.5). A dose-response relation was observed, with elevated risks at doses between 10 - 29.9 Gy (OR = 15.6, 95% CI = 4.5-53.9), 30 - 49.9 Gy (OR = 16.0, 95% CI 3.8-67.8) and >50 Gy (OR = 114.1, 95% CI 13.5-964.8). Anthracycline exposure was associated with sarcoma risk (OR = 3.5, 95% CI = 1.6-7.7) adjusting for radiation dose, other chemotherapy, and primary cancer. Adjusting for treatment, survivors with a first diagnosis of Hodgkin lymphoma (HL; OR=10.7, 95% CI = 3.1-37.4) or primary sarcoma (OR=8.4, 95% CI = 3.2-22.3) were more likely to develop a sarcoma.

Conclusions—Of the risk factors evaluated, radiation exposure was the most important for secondary sarcoma development in childhood cancer survivors; anthracycline chemotherapy exposure was also associated with increased risk.

Keywords

Childhood cancer survivors; secondary sarcomas; radiation late effects

Introduction

A significant health risk in childhood cancer survivors is the development of second malignant neoplasms (SMN), with a 30-year cumulative incidence approaching 8%.[1] Almost 2% of childhood cancer survivors develop secondary sarcomas that have high associated mortality rates.[1-3] A detailed understanding of risk factors for secondary sarcomas is essential for clinicians and researchers to identify at-risk cancer survivors. We previously observed an association between any exposure to radiation and risk of subsequent sarcomas in the Childhood Cancer Survivor Study (CCSS).[2] However, our earlier study did not include quantitative radiation dose-response analysis, and a full understanding of the effect of clinical and treatment factors were limited insofar as dose of radiation was not evaluated. In the current report, we present the results from a nested case-control study of secondary sarcoma designed to investigate dose-response relationships for radiation and chemotherapy treatment.

Methods and Materials

Description of the CCSS Cohort

Detailed methods for the CCSS cohort have been published previously.[4] The CCSS is a retrospective cohort of 14,358 5-year childhood cancer survivors at 26 North American centers. Each participating institution identified patients who fulfilled the following eligibility criteria: 1) diagnosis and initial treatment of leukemia, CNS malignancy, Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), neuroblastoma, soft-tissue sarcoma

(STS), kidney cancer, or bone cancer; 2) diagnosis date between January 1, 1970 and December 31, 1986; 3) < 21 years at diagnosis; and, 4) alive 5 years post-diagnosis.

The human subjects committees at each participating institution approved the CCSS protocol. Data used in this analysis were collected using a baseline and three follow-up questionnaires in 2000, 2002 and 2005. Next of kin, typically a parent or spouse, was contacted for those eligible subjects who were known to have died after achieving 5-year survivorship. The questionnaires addressed social and demographic information, medical conditions, health behaviors, cancer recurrence, development of SMN, and family history. Survey questionnaires are available at: http://ccss.stjude.org.

For all CCSS participants who signed a medical record release, a detailed summary of prior cancer treatment was prepared. Information was abstracted according to a standardized protocol to capture exposure to 49 specific chemotherapy agents and cumulative exposure for 22 agents. Doses (in milligrams/m^2) of daunorubicin, doxorubicin, and idarubicin (multiplied by 3 to approximate doxorubicin equivalence) were summed to determine cumulative anthracycline exposure, as were doses of etoposide and teniposide for cumulative epipophyllotoxin exposure. The cumulative dose of carboplatin was divided by 4 and added to the cisplatin dose to assess exposure to platinum compounds. Alkylating agent scores were calculated with the use of methods previously described.[5] Radiation therapy records from the treating institution were used by M.D. Anderson Cancer Center's Department of Radiation Physics to calculate site-specific radiation doses.

Ascertainment of Secondary Sarcoma Cases and Selection of Control Subjects

Secondary sarcoma cases were ascertained through self- or proxy-report of a history of secondary malignancy via baseline and follow-up questionnaires; cause of death reported on death certificate and/or reporting by next of kin. Positive responses were screened, and those representing a likely SMN were verified by the CCSS Pathology Review Center. The CCSS pathologist (*S.H.*) reviewed pathology reports to confirm a SMN. If the pathology report could not be obtained, the questionnaire response, death certificate and/or institutional records were reviewed to determine if cases were sufficiently documented to confirm case status. Data collected for secondary sarcoma cases included histology and specific location(s) of the tumor. The sarcoma had to have occurred at least five years after the primary cancer diagnosis. All patients with secondary sarcomas identified before February 1, 2007 were included in this analysis. Four survivors without a secondary sarcoma (controls) for each case were randomly selected from the cohort and matched to case patients (by age at original diagnosis; time since primary cancer diagnosis; and sex). As compared to Henderson's cohort study, 9 additional sarcomas were identified while twelve sarcomas in the previous report were histologically reclassified following a central CCSS review committee meeting in 2008, and therefore not included in this analysis.[2]

Tumor Localization and Radiation Dosimetry

Available records for each case were reviewed by two pediatric oncologists (*T.H., L.D.)* to determine the secondary sarcoma location. Records reviewed included operative notes, pathology reports, radiology reports, and any relevant correspondence available. Original imaging studies were not obtained. Location and extent of sarcomas were sketched onto diagrams of children. If the tumor location or laterality was unknown the site was specified as a more general body region (leg, head, abdomen, trunk, etc).

Radiation records for all cases and controls were reviewed to determine the treatment details, including: dates of therapy, beam energy, field size, field location, field blocking and total dose to each field. The overall approach in determining doses from radiation therapy

was based on a mathematical phantom, and is detailed in a previous report.[6] Doses were calculated to all points within the SMN location. Average, minimum and maximum dose over the SMN location were reported for each subject in each case set. In fifteen case patients and 2 control subjects, the quality of the records available did not permit a radiation dose assignment (as in some cases it is not confirmed if the survivor received radiation at all).

Statistical Analysis

STATA 11.0 and the Epicure module PECAN were used to estimate odds ratios (ORs), model dose-response relations, perform likelihood ratio tests, and calculate 95% likelihood-based confidence intervals (CI).[7] Statistical tests were two-sided and based on an α-level of 0.05. The risk of secondary sarcoma was evaluated with conditional logistic regression (to calculate ORs) in relation to radiotherapy and chemotherapy for the initial cancer, as well as other host characteristics. Analyses were adjusted for primary cancer and the matching factors of age at original diagnosis, time between first cancer and sarcoma diagnoses, and sex. Radiation dose-response models that were considered were simplifications of the general model: $EOR = (\beta_1 D + \beta_2 D^2) \exp(\beta_3 D + \beta_4 D^2)$, in which EOR is the excess odds ratio (= odds ratio – 1), D=dose, and β_1- β_4 are regression coefficients. The exponential term allows for possible curvature of the dose-response relationship at high doses. The model $EOR = \beta_1 D$, corresponds to a straight-line dose-response relation, and β_1 equals the slope (EOR/Gy). Risk estimates were adjusted for type of first cancer (HL, bone or STS, other), use of anthracyclines (yes/no), and other chemotherapy use (yes/no). Analyses were limited to examining first secondary sarcomas only. Cases with recurrences (n=8) or other types of SMNs (n=8) intervening between the primary diagnosis and sarcoma were included in the analysis, but a sensitivity analysis dropping any subjects with intervening SMNs or recurrences was conducted. A sensitivity analysis was also performed to examine those cases that had the highest quality radiation data (n=78; 68 with known radiation and dose plus 10 patients confirmed not to have received radiation for primary cancer).

Results

Characteristics of the Case Patients and Controls

Included in the current analysis are 105 secondary sarcomas that were identified among CCSS participants as of February 1, 2007 (**Table 1**). Five subjects each developed two distinct secondary sarcomas – only the first sarcoma was considered in the analysis.

Characteristics of the case patients and matched controls (n=422) are shown in **Table 2**. The median age for case subjects was 8.6 years (range 6 months to 20.8 years) at primary diagnosis, and 20.8 years (range 8.6 years to 49.2 years) at secondary sarcoma diagnosis. The median interval from first cancer to secondary sarcoma was 11.8 years (range 5.3 to 31.3 years). STS was the initial cancer in 27.6% of cases versus 9.2% of controls. HL was the initial cancer in 26.7% of cases and 15.9% of controls. Bone cancer, kidney cancer and leukemia were the next most common types of first cancer among cases. There were no significant differences between cases and controls in treatment era or ethnicity.

Detailed Therapy-Related Risk Factors for Secondary Sarcomas

We determined the ORs for the occurrence of a secondary sarcoma following radiation or chemotherapy (**Table 3**). Eighty case patients (89%) and 290 (69%) control subjects had received confirmed radiation for primary cancer treatment. Radiation therapy exposure was associated with a significantly increased risk for the secondary sarcoma development (OR = 4.1, 95% CI: 1.8 – 9.5) after adjustment for primary cancer diagnosis, anthracycline exposure, and use of other chemotherapeutic agents.

Significant increased secondary sarcoma risk was observed at radiation doses over 10 Gy, (with no radiation exposure as the reference). In the dose categories 10-29.9 Gy, 30-49.9 Gy, and 50 Gy or higher, secondary sarcoma risk was elevated 15.6-fold (95% CI: 4.5-53.9), 16.0-fold (95% CI: 3.8-67.8), and 114.1-fold (95% CI: 13.5-964.8) respectively, with a statistically significant increasing trend between radiation dose and sarcoma risk (p-trend < 0.001).

Patients with a primary diagnosis of HL or sarcoma were more likely to develop a secondary sarcoma, when compared with primary leukemia patients, after adjustment for radiation dose, use of anthracyclines and other chemotherapeutic agents (See **Table 3**). While exposure to any chemotherapy was associated with a 3-fold increase in sarcoma risk, this relationship was driven by exposure to anthracyclines (no statistically significant association remained after adjustment for anthracycline use). Exposure to anthracyline therapy was associated with an increased risk of sarcoma, adjusting for radiation dose, primary cancer diagnosis, and other chemotherapy (OR 3.5, 95% CI: 1.6-7.7). This increased risk was seen after exposure to both doxorubicin and daunorubicin, and with higher dose anthracycline exposure (**Table 3**). No statistically significant associations were seen between risk of subsequent sarcomas and chemotherapy overall or exposure to bleomycin, epipodophyllotoxins, platinum drugs or dactinomycin, after adjusting for radiation dose, primary cancer, and anthracycline exposure. Although exposure to alkylating agents was statistically significant when controlling for radiation dose and first diagnosis only (OR=2.2, 95% CI=1.1-4.5), this relationship was no longer significant after adjustment for use of anthracyclines (OR=1.3, 95% CI=0.6-2.9).

Dose Response Modeling and Modification of Radiation Effect by Host Characteristics

Model fit for excess risk per Gy for secondary sarcoma was adequately described by a linear model for radiation dose, with an excess odds ratio per Gy (EOR/Gy) of 1.32 (0.44, 4.22) after controlling for primary cancer diagnosis, any anthracyclines, and any other chemotherapy. Model fit was not significantly better when dose was described as a pure quadratic or a linear-quadratic, and we observed no evidence of a downturn of risk at the highest dose category (maximum dose in our study was 76 Gy). We found no evidence of effect modification by sex, age at diagnosis or attained age (data not shown).

Sensitivity Analyses Considering Data Quality and Intervening Cancers

Restricting our analysis to subjects with the highest quality radiation data (n = 78 cases, 381 controls) yielded similar risks and no change in this trend. Estimates for radiation-related risks were also similar when subjects with intervening cancers or recurrences were dropped from the analysis, with the point estimate for the highest category (>50 Gy) dropping to 57.0, with smaller confidence intervals (95% CI: 6.0-543.1). There were 30 secondary bone sarcomas and 50 STS for which there were adequate estimates of radiation dose at the sarcoma site. Risk of secondary bone sarcomas was similar to risk of STS (results not shown).

Discussion

To our knowledge, this is the largest study to date of secondary sarcomas among childhood cancer survivors for which detailed treatment data are available and site-specific radiation dosimetry has been performed. Exposure to therapeutic radiotherapy for the primary cancer was the most significant risk factor observed in secondary sarcoma development. Of interest, we observed significantly elevated risk for secondary sarcomas even in those survivors exposed to relatively lower dose radiation, starting at 10 Gy. In addition, we observed a sharp increase in risk in patients who received radiation over 50 Gy. Exposure to

anthracycline chemotherapy in this cohort was associated with secondary sarcoma development. After controlling for radiation dose, alkylator exposure was not associated with increased risk of secondary sarcoma as compared to our previous analysis. Finally, after adjusting for treatment, we observed that those who survived HL or sarcoma were more likely to develop a secondary sarcoma as compared to leukemia survivors.

Prior studies of secondary sarcomas in childhood cancer survivors are limited by single histologies, inclusion of large proportions of retinoblastoma survivors, and small numbers.[2,5,8-10] Consistent with our findings (EOR/Gy=1.32), a French study of secondary osteosarcoma (n=32), reported the excess relative risk of radiation as 1.4 per Gy.[9] Two older studies of secondary STS (n=25 and n=39) found that risk for development of sarcoma was associated with increasing dose of radiation over 10-30 Gy, with no down-turn in risk in the highest dose categories.[11,12] These findings are consistent with a Swedish Cancer Registry study of 116 STS in breast cancer survivors where risk of secondary sarcoma increased linearly with the integral dose of 150-200J and stabilized at higher energies.[13] A recent European study of childhood cancer survivors reported an elevated risk of death from secondary sarcomas (n=41) with exposure to over 150 J of radiation, when retinoblastoma survivors were excluded from the analysis.[14] A study of retinoblastoma survivors reported an excess relative risk of 1.19 per Gy for all sarcoma, again with no downturn in risk.[10] Two studies of secondary bone sarcomas (n=64 and n=55) also demonstrated substantial increases in risk with increasing doses of radiation, but, in contrast to our findings, these studies found suggestions of downturns in risk in the highest dose categories over 50 Gy.[5,15] Important to note, these two studies included substantial subgroups (25% and 44%) of retinoblastoma survivors, who have known underlying genetic predisposition to sarcomas both within and outside of radiation fields. The CCSS does not include retinoblastoma survivors.

After controlling for radiation dose, we found that anthracycline exposure is associated with an increased risk of secondary sarcomas. Our findings are consistent with early laboratory-based studies suggesting that anthracyclines are tumorigenic *in vivo* and *in vitro.*[16,17] Prior studies of the additional risk of chemotherapy exposure on development of solid tumors have suggested that alkylating agent exposure is a risk factor for secondary tumors.[2,5,9,11,12,15] Given that alkylators and anthracyclines are very often given in combination for the treatment of many childhood tumors, it is difficult to fully assess independent effects for the two classes of agents. Our data suggest that it may be that anthracyclines, rather than alkylators, are associated with secondary sarcomas. Most other prior studies of treatment-related sarcoma did not have sufficient numbers to assess the independent effect of anthracycline exposure.[5,9,12,15,18] In a series of 91 sarcomas from the Late Effects Study Group (LESG) consortium, time to development of bone sarcomas was associated with exposure to anthracyclines.[5,8] However, doses of anthracyclines were not examined in the LESG. A study of subsequent breast cancer in the CCSS study similarly observed a significant association between anthracycline exposure and the development of subsequent breast cancer, but no significant association was observed with alkylator exposure.[19] While we did not observe independent effects of other chemotherapy agents, given the small numbers and correlations between many of the agents, we cannot rule out the possibility that such effects may exist.

As combined modality therapies have become the standard of care for most childhood cancers, the use of chemotherapy has contributed to decreases in radiation dose. Our data suggest that even with relatively lower dose radiation treatment, there is still an increased risk of these tumors, perhaps in part because the higher doses of adjuvant chemotherapy used in combination with the low dose radiation have their own carcinogenic effects. A recent study of a small number of HL survivors with secondary malignancies supports this

notion, as the investigators found an increased rate of sarcomas even in those exposed to doses of radiation below 20 Gy in combination with anthracycline-containing multi-agent chemotherapy (MOPP/ABVD).[20]

Our data present the most comprehensive assessment to date of the role of therapy pertinent to secondary sarcoma development in childhood cancer survivors. The study findings are strengthened by the large number of cases, long duration of follow-up, detailed review of medical records, and central review of all pathology reports for SMN. Of particular importance, individual dosimetry was conducted for each case patient and control subject in order to assign a specific radiation dose to each tumor site.

Despite the size and completeness of this analysis and the CCSS cohort in general, there are some study limitations. The CCSS outcomes depend on self-report and thus, the outcome of interest may be under-reported. Further, the analysis includes only sarcomas identified after the 5-year survival point and excludes those sarcomas that develop prior to 5 years. In considering these data, physicians must consider the relative primitiveness of radiation therapeutics in the treatment era of these survivors (1970-1986). Finally, the dosimetry data are limited by incomplete information about the precise location of the secondary sarcomas in a small number of subjects resulting in wide confidence intervals in our radiation dosimetry analysis.

With improved survival rates, the population of childhood cancer survivors is continuing to expand. It is of great importance that survivors who are at high risk for second malignancies are identified and monitored to detect these morbidities as early as possible. For secondary sarcomas, early detection is the best hope for cure. This investigation indicates that clinicians need to be alert to the possibility of these tumors, even in survivors exposed to lower doses of radiation in combination with high dose chemotherapy. As new protocols are developed for pediatric cancers, physicians need to continue to strive to reduce or eliminate radiation when possible. However, investigators must further consider the tumorigenic effects of high dose chemotherapy agents, such as anthracyclines, when making these treatment decisions, as these agents may incur increased risk of second malignancies even with reduced or eliminated radiation. Finally, as the genetics of cancer predisposition and radio-sensitivity becomes better defined, this information combined with previous detailed cancer treatment, family history and health behavior data will further refine the ability to identify at-risk individuals and provide appropriate long-term risk-based health care in order to improve survival.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Secondary Sarcoma Histologic Subtypes*

Secondary Sarcoma Histology	N (%)
Non-rhabdomyosarcoma soft tissue sarcoma**	43 (39%)
Osteosarcoma	34 (31%)
Malignant peripheral nerve sheath tumor	12 (11%)
Ewing's/primitive neuroectodermal tumor	5 (5%)
Rhabdomyosarcoma	4 (4%)
Sarcoma Not Otherwise Specified	12 (11%)

* **N=110 in 105 survivors.** In the patients who developed two sarcomas, one patient had a primary diagnosis of a CNS tumor with 2 subsequent malignant peripheral nerve sheath tumors (MPNST). One patient had a primary osteosarcoma, followed by 2 distinct leiomyosarcomas. One survivor had a CNS tumor followed by MPNST and osteosarcoma. One survivor had a primary rhabdomyosarcoma followed by malignant fibrous histiocytoma and osteosarcoma. Lastly, one patient had a rhabdomyosarcoma followed by MPNST and osteosarcoma.

** Non-rhabdomyosarcoma soft tissue sarcomas included chondrosarcoma (n=3), dermatofibrosarcoma (n=2), epitheliod sarcoma (n=1), fibromyxosarcoma (n=2), fibrosarcoma (n=3) hemangiosarcoma (n=2), leiomyosarcoma (n=9), malignant fibrous histocytoma (n=10), myxoid liposarcoma (n=1), rhabdoid (n=1), spindle cell sarcoma (n=7), and synovial sarcoma (n=2).

Table 2

CCSS survivor characteristics with a secondary sarcoma and matched control subjects

Characteristic, n (%)	Patients with second sarcoma (n=105)		Controls (n=422)	
Sex[†]				
Male	60	57.1%	241	57.1%
Female	45	42.9%	181	42.9%
Ethnicity				
White	95	90.5%	374	88.6%
Black	4	3.8%	19	4.5%
Hispanic	5	4.8%	15	3.6%
Other	0	0.0%	12	2.8%
Primary Diagnosis				
Leukemia	10	9.5%	140	33.2%
CNS tumor	8	7.6%	52	12.3%
Hodgkin lymphoma	28	26.7%	67	15.9%
Non-Hodgkin lymphoma	4	3.8%	34	8.1%
Kidney (Wilms)	10	9.5%	30	7.1%
Neuroblastoma	3	2.9%	25	5.9%
Soft tissue sarcoma	29	27.6%	39	9.2%
Bone cancer	13	12.4%	35	8.3%
Year of initial diagnosis				
1970-1974	30	28.6%	114	27.0%
1975-1979	31	29.5%	108	25.6%
1980-1986	44	41.9%	200	47.4%
Age at primary cancer (years)[†]				
<1	5	4.8%	20	4.7%
1-3	27	25.7%	109	25.8%
4-7	19	18.1%	76	18.0%
8-10	15	14.3%	60	14.2%
11-14	19	18.1%	77	18.2%
15-20	20	19.0%	80	19.0%
Age at sarcoma (years)				
5-14	25	23.8%	n/a	
15-19	22	21.0%	n/a	
20-24	27	25.7%	n/a	
25-29	13	12.4%	n/a	
30-34	7	6.7%	n/a	
35+	11	10.5%	n/a	
Time between first cancer diagnosis and sarcoma diagnosis (years)				
5-9	42	40.0%	n/a	
10-14	27	25.7%	n/a	

Characteristic, n (%)	Patients with second sarcoma (n=105)		Controls (n=422)	
15-19	18	17.1%	n/a	
20+	18	17.1%	n/a	
Treatment for primary malignancy*				
Neither radiotherapy nor chemotherapy	1	1.0%	30	7.1%
Radiotherapy only	8	7.6%	55	13.0%
Chemotherapy only	9	8.6%	100	23.7%
Both radiotherapy and chemotherapy	71	67.6%	235	55.7%
Radiation but chemotherapy unknown	1	1.0%	0	0%
Missing radiation treatment information	15	14.3%	2	0.5%
Vital status, number alive	47	44.8%	405	96.0%

*% based on non-missing values

†matching factor

Table 3

Treatment-related risk for secondary sarcoma development

	Cases (n=90)	Controls (n=420)	Odds Ratio (95% CI)
Radiotherapy*			
No	10	130	1.0 (ref)
Yes	80	290	4.1 (1.8, 9.5)
Missing	15	2	
Radiation to sarcoma site, Gy* (mean within category for controls)			
0 (0)	10	130	1.0 (ref)
<10 (0.6)	22	212	1.3 (0.5, 3.6)
10-29.9 (19.2)	23	32	15.6 (4.5, 53.9)
30-49.9 (37.3)	17	23	16.0 (3.8, 67.8)
50+ (52.9)	12	3	114.1 (13.5, 964.8)
Missing	21	22	
			p-trend<0.001[a]
Any chemotherapy†			
No	9	86	1.0 (ref)
Yes	80	336	3.0 (1.2, 7.9)
Missing	16	0	
Anthracyclines††			
No	36	264	1.0 (ref)
Yes	53	156	3.5 (1.6, 7.7)
Missing	16	2	
Anthracycline cumulative dose, mg/m^2††			
1-100	9	34	2.8 (0.8, 9.9)
101-300	15	61	2.1 (0.8, 5.7)
>300	24	49	6.8 (2.4, 19.6)
Missing	21	14	
			p-trend=0.004
Doxorubicin††			
No	40	288	1.0 (ref)
Yes	49	132	2.7 (1.3, 5.7)
Missing	16	2	
Daunorubicin††			
No	80	379	1.0 (ref)
Yes	9	41	4.2 (1.2, 14.3)
Missing	16	2	
Bleomycin†††			
No	76	403	1.0 (ref)
Yes	13	17	1.5 (0.4, 5.2)

	Cases (n=90)	Controls (n=420)	Odds Ratio (95% CI)
Missing	16	2	
Dactinomycin†††			
No	48	341	1.0 (ref)
Yes	41	81	0.9 (0.4, 2.5)
Missing	16	2	
Alkylating agents†††			
No	23	207	1.0 (ref)
Yes	66	213	1.3 (0.6, 2.9)
Missing	16	2	
Alkylating agent score†††			
1	15	79	1.5 (0.5, 4.0)
2	26	57	1.9 (0.7, 5.3)
3	16	45	1.0 (0.3, 2.9)
Missing	25	34	
			p-trend=0.8
Decarbazine†††			
No	84	408	1.0 (ref)
Any	5	12	1.4 (0.3, 7.2)
Missing	16	2	
Epipodophyllotoxins†††			
No	82	394	1.0 (ref)
Yes	7	26	1.8 (0.4, 7.1)
Missing	16	2	
Platinum drugs†††			
No	82	406	1.0 (ref)
Yes	7	14	0.7 (0.2, 3.2)
Missing	16	2	
First diagnosis†††			
Leukemia	10	140	1.0 (ref)
Hodgkin lymphoma	28	67	10.8 (3.1, 38.4)
Sarcoma	42	74	8.9 (3.3, 23.8)
Other	25	141	3.9 (1.3, 11.4)

*Adjusted for any use of anthracyclines, any chemotherapy, and type of first cancer (leukemia, Hodgkin lymphoma, sarcoma, other)

†Adjusted for radiation dose and type of first cancer

††Adjusted for radiation dose, any chemotherapy, and type of first cancer

†††Adjusted for radiation dose, any use of anthracyclines, and type of first cancer

[a]all p-trends based on non-missing values of ordinal variable