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ORIGINAL REPORT

Long-Term Risk of Subsequent Malignant Neoplasms After Treatment of Childhood Cancer in the DCOG LATER Study Cohort: Role of Chemotherapy

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ABSTRACT

Purpose
Childhood cancer survivors (CCSs) are at increased risk for subsequent malignant neoplasms (SMNs). We evaluated the long-term risk of SMNs in a well-characterized cohort of 5-year CCSs, with a particular focus on individual chemotherapeutic agents and solid cancer risk.

Methods
The Dutch Childhood Cancer Oncology Group–Long-Term Effects After Childhood Cancer cohort includes 6,165 5-year CCSs diagnosed between 1963 and 2001 in the Netherlands. SMNs were identified by linkages with the Netherlands Cancer Registry, the Dutch Pathology Registry, and medical chart review. We calculated standardized incidence ratios, excess absolute risks, and cumulative incidences. Multivariable Cox proportional hazard regression analyses were used to evaluate treatment-associated risks for breast cancer, sarcoma, and all solid cancers.

Results
After a median follow-up of 20.7 years (range, 5.0 to 49.8 years) since first diagnosis, 291 SMNs were ascertained in 261 CCSs (standardized incidence ratio, 5.2; 95% CI, 4.6 to 5.8; excess absolute risk, 20.3/10,000 person-years). Cumulative SMN incidence at 25 years after first diagnosis was 3.9% (95% CI, 3.4% to 4.6%) and did not change noticeably among CCSs treated in the 1990s compared with those treated earlier. We found dose-dependent doxorubicin-related increased risks of all solid cancers ($P_{trend} < .001$) and breast cancer ($P_{trend} < .001$). The doxorubicin-breast cancer dose response was stronger in survivors of Li-Fraumeni syndrome–associated childhood cancers (leukemia, CNS, and non-Ewing sarcoma) versus survivors of other cancers ($P_{difference} = .008$). In addition, cyclophosphamide was found to increase sarcoma risk in a dose-dependent manner ($P_{trend} = .01$).

Conclusion
The results strongly suggest that doxorubicin exposure in CCSs increases the risk of subsequent solid cancers and breast cancer, whereas cyclophosphamide exposure increases the risk of subsequent sarcomas. These results may inform future childhood cancer treatment protocols and SMN surveillance guidelines for CCSs.

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INTRODUCTION

Childhood cancer survivors (CCSs) are at increased risk for long-term adverse health outcomes, including subsequent malignant neoplasms (SMNs).[1-5] Research among CCSs has shown a clear role of radiotherapy, with established dose-effect relationships for breast cancer,[6,7] thyroid cancer,[8,9] colorectal cancer,[10] sarcoma,[11-14] CNS tumors,[15,16] and basal cell skin cancer.[17]

For chemotherapy, an increased risk of acute myeloid leukemia within 10 years of childhood cancer treatment has been well established for alkylating agents, epipodophyllotoxins, and anthracyclines.[18,19] The role of chemotherapy in the etiology of solid cancers is less clear. Alkylating agents and anthracyclines were linked to an increased risk of subsequent sarcoma.[11,14,20,21] In addition, a recent Childhood Cancer Survivor Study among nonirradiated CCSs showed dose-dependent increases in breast cancer risk for these

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Appendix
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two classes of agents, particularly after childhood sarcoma and leukemia.[22,23] Not much is known, however, about the effects of specific chemotherapy agents on breast cancer and sarcoma risk. To examine the role of specific chemotherapeutic agents, we evaluated the long-term risk of SMNs in the Dutch Childhood Cancer Oncology Group–Long-Term Effects After Childhood Cancer (DCOG LATER) cohort of 5-year CCSs.

METHODS

The DCOG LATER cohort includes 5-year CCSs treated before the age of 18 years in one of seven Dutch pediatric oncology and stem cell transplant centers between January 1, 1963, and December 31, 2001. Eligible 5-year CCSs were identified from prospective registries (Emma Children's Hospital/Academic Medical Center[24]) and listings of pediatric patients with newly diagnosed cancer; the clinic-specific starting year varied (1963 to 1977) on the basis of completeness of the source. The study protocol was declared exempt from review of medical intervention research by institutional review boards of all participating centers.

Data Collection

Details on prior cancer diagnosis and treatment of primary tumor and all recurrences were collected by trained data managers. Chemotherapy details included start and end dates, drug names, and cumulative doses. For radiotherapy, details on prescribed dose, field, and boost/surdosage were recorded. In addition, names of other drugs and details on hematopoietic cell transplantation (HCT) were recorded. In case of missing chemotherapy doses when we knew the agent was given, we imputed mean doses of the agents administered to survivors within the same treatment protocol or to survivors from the same diagnosis group and diagnosis period (Appendix, online only).

Vital and emigration status were obtained by tracing CCSs through the Central Office for Genealogy register (which keeps records of Dutch decedents) and in the digital Municipal Personal Records Database that includes personal information of all inhabitants of the Netherlands since 1994. CCSs without a Municiple Personal Records Database record were traced through the last known municipality of residence before 1994.

SMNs until January 1, 2013, were identified as follows: We linked the cohort to the population-based Netherlands Cancer Registry (NCR), with nationwide coverage since 1989,[25] and, for the pre-1989 era, to the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA [Dutch Pathology Registry]).[26] Furthermore, we reviewed hospital medical records. Discrepancies between SMN sources were resolved by review of pathology reports. SMNs excluded myelodysplastic syndrome and basal cell carcinoma of the skin (not systematically ascertained by the NCR). We did include ductal carcinomas in situ in multivariable models on female breast cancer risk.

Statistical Analyses

Time at risk started 5 years after childhood cancer diagnosis and ended on the date of SMN diagnosis, date of death, date of emigration, date of loss to follow up, or end of study (January 1, 2013), whichever occurred first. SMNs diagnosed $\geq$ 5 years after childhood cancer diagnosis were included as the outcome of interest. For survivors with multiple SMNs, only the first SMN was counted in the analyses of all SMNs, and follow-up ended at the diagnosis of the first SMN. In cancer site–specific analyses, survivors contributed time at risk until the diagnosis of interest occurred, irrespective of possible preceding cancers. Standardized incidence ratios (SIRs) were calculated as the ratio of observed and expected number of SMNs. Excess absolute risks (EARs) were calculated as observed minus expected number of SMNs per 10,000 person-years of follow-up. Age-, sex-, and calendar year–specific rates from the Eindhoven Cancer Registry until 1988 and the NCR from 1989 onward were used to calculate expected numbers.[25,27]

Cumulative incidences of SMNs were estimated in the presence of death as a competing risk.[28] Cumulative incidences of any SMN after 15 years were compared for childhood cancer diagnosis period with use of pairwise Pepe-Mori tests.[29] Expected cumulative incidence was derived from expected cancer incidence adjusted for overall mortality in the general population. The effects of potential risk factors for all solid cancers combined and for the two most frequent solid cancers (breast cancer and sarcoma) were analyzed by using multivariable Cox proportional hazards regression models, with attained age as the time scale because cancer incidence varies by age.[30] All variables with $P < .1$ in univariable analyses were tested in multivariable models, except for chemotherapy agents with fewer than five exposed cases for the outcome of interest (Appendix Table A1, online only). Agents with at least 10 exposed cases were additionally categorized according to dose tertiles. Radiotherapy exposure was evaluated as yes/no variables and in prescribed dose categories if at least 10 exposed cases for the outcome of interest occurred (Appendix). All variables that remained significantly associated with the outcome of interest in multivariable analyses ($P < .05$) or that considerably changed the effect of other variables in the model were included in the final model. Besides specific chemotherapeutic agents, we tested categories of chemotherapy exposure.[31,32] Tests for trend were based on the likelihood ratio–based P value for a model with the respective continuous variable on the basis of exposed patients only, unless otherwise specified. The assumption of proportional hazards was checked in all models and was not violated. Childhood cancer treatments for initial treatment and all recurrences were summed in analysis variables. The default childhood cancer type categories were leukemia, lymphoma, CNS tumor, bone sarcoma, soft tissue sarcoma, and other. Analyses on subsequent sarcoma used leukemia, bone and soft tissue sarcoma, and other. Finally, we assessed the effect of treatment-related risk factors separately for survivors of Li-Fraumeni syndrome (LFS)–associated childhood cancers (leukemia, CNS tumor, and sarcoma [except Ewing sarcoma][33-35]) versus that in other CCSs as a surrogate for genetic susceptibility for second cancers. All analyses were performed with Stata 13 software (StataCorp, College Station, TX).

RESULTS

The cohort included 6,165 5-year CCSs who contributed 103,949 person-years of follow-up. Leukemia (34%), lymphoma (16%), and CNS tumors (14%) were the most frequent childhood cancers (Table 1). The median time since childhood cancer diagnosis was 20.7 years (range, 5.0 to 49.8 years); 20% of CCSs were followed for $\geq$ 30 years. Median attained age at the end of follow-up was 28.1 years (range, 5.3 to 65.1 years). Approximately 10% of the total cohort was deceased. Of all survivors, 48% received chemotherapy without radiotherapy, 8% received radiotherapy without chemotherapy, 33% received a combination of chemotherapy and radiotherapy, and 6% received HCT. The proportion of survivors treated with radiotherapy strongly decreased over time (75%, 43%, and 28% for those diagnosed in 1963 to 1979, 1980 to 1989, and 1990 to 2001, respectively), whereas the contribution of chemotherapy to treatment increased from 72% of survivors in 1963 to 1979 to $>$ 80% after 1980 (data not shown).

Comparison With General Population

In total, 261 survivors developed at least one SMN, including 24 with two SMNs and three with three SMNs. Risk of any SMN was significantly elevated compared with cancer incidence in the general population (SIR, 5.2; 95% CI, 4.6 to 5.8), with 20.3 excess

Table 1. Characteristics of the Total DCOG LATER Cohort (1963 to 2001) and of Five-Year Childhood Cancer Survivors With an SMN

Characteristic	Total Cohort (N = 6,165)*		Survivors With an SMN (n = 261)†	
	No.	%	No.	%
Sex				
Male	3,434	55.7	123	47.1
Female	2,731	44.3	138	52.9
Age at childhood cancer diagnosis, years				
0-4	2,781	45.1	92	35.3
5-9	1,673	27.1	66	25.3
10-14	1,310	21.2	78	29.9
15-17	401	6.5	25	9.6
Primary childhood cancer diagnosis‡				
Leukemia	2,092	33.9	63	24.1
Non-Hodgkin lymphoma§	578	9.4	18	6.9
Hodgkin lymphoma	404	6.6	21	8.0
CNS	843	13.7	29	11.1
Neuroblastoma	324	5.3	9	3.4
Retinoblastoma	33	0.5	6	2.3
Renal tumors	596	9.7	29	11.1
Hepatic tumors	52	0.8	1	0.4
Bone tumors	370	6.0	32	12.2
Soft tissue tumors	450	7.3	32	12.2
Germ cell tumors	232	3.8	8	3.1
Other and unspecified‖	191	3.1	13	5.0
Period of childhood cancer diagnosis				
1963-1969	119	1.9	11	4.2
1970-1979	978	15.9	89	34.1
1980-1989	1,931	31.3	105	40.2
1990-2001	3,137	50.9	56	21.5
Time since childhood cancer diagnosis, years				
5-9	386	6.3	44	16.9
10-19	2,529	41.0	90	34.5
20-29	1,993	32.3	74	28.4
≥ 30	1,257	20.4	53	20.3
Attained age at end of follow-up, years				
< 20	1,344	21.8	69	26.4
20-29	2,157	35.0	72	27.6
30-39	1,786	29.0	79	30.3
≥ 40	878	14.2	41	15.7
Vital status				
Alive	5,561	90.2	156	59.8
Dead	604	9.8	105	40.2
Childhood cancer treatment¶				
Surgery only	597	9.7	16	6.1
Chemotherapy, no radiotherapy	2,970	48.2	65	24.9
Radiotherapy, no chemotherapy	481	7.8	40	15.3
Radiotherapy and chemotherapy	2,024	32.8	133	51.0
No treatment or treatment unknown	93	1.5	7	2.7
Radiotherapy field¶#				
Head/cranium	1,413	22.9	83	31.8
Spinal	443	7.2	29	11.1
Thorax	395	6.4	26	10.0
Abdomen/pelvis	467	7.6	40	15.3
Neck	240	3.9	16	6.1
Extremities	133	2.2	12	4.6
Total body irradiation	221	3.6	19	7.3
Chemotherapy¶				
Alkylating agents	3,136	50.9	137	52.5
Anthracyclines	2,788	45.2	119	45.6
Epipodophyllotoxins	1,300	21.1	42	16.1
Vinca alkaloids	4,431	71.9	172	65.9
Platinum agents	804	13.0	24	9.2
Antimetabolites	2,885	46.8	96	36.8
Hematopoietic cell transplantation¶	386	6.3	25	9.6

Abbreviations: DCOG LATER, Dutch Childhood Cancer Oncology Group–Long-Term Effects After Childhood Cancer; SMN, subsequent malignant neoplasm.
*For 139 survivors (2.3% of total cohort), follow-up was incomplete; this group contributed 1,842 person-years until the date of last follow-up.
†Twenty-four survivors developed two SMNs, and three survivors developed three SMNs.
‡Diagnostic groups included all malignancies covered by the third edition of the International Classification of Childhood Cancer (ICCC-3) as well as multifocal Langerhans cell histiocytosis and selected nonmalignant ependymomas and astrocytomas.
§Includes all morphology codes specified in the ICCC-3 under lymphomas and reticuloendothelial neoplasms, except for Hodgkin lymphomas.
‖Includes all morphology codes specified in the ICCC-3 under other malignant epithelial neoplasms and malignant melanomas and other and unspecified malignant neoplasms as well as nonmalignant multifocal Langerhans cell histiocytosis.
¶Treatment data included primary treatment and all recurrences; chemotherapy (yes/no), radiotherapy (yes/no), surgery (yes/no), and hematopoietic cell transplantation (yes/no) data were missing for 48, 41, 73, and 90 survivors, respectively.
#Radiotherapy includes external beam radiotherapy, brachytherapy, and systemic radiotherapy.

cancers per 10,000 person-years (Table 2). EARs ≥ 2.0/10,000 person-years were observed for female breast, thyroid, soft tissue sarcoma, and CNS malignancies. SIRs decreased with increasing age at childhood cancer diagnosis and decreased gradually with increasing time since diagnosis, although the SIR was still significantly increased after > 30 years (SIR, 3.8; Appendix Table A2, online only). Conversely, EARs increased with increasing follow-up time. SIRs and EARs for solid cancers followed the time pattern for all SMNs, whereas those for hematologic malignancies peaked 5 to 9 years since childhood cancer and dropped afterward (Appendix Table A3, online only). The cumulative incidence of SMNs 25 years after childhood cancer was 3.9% (95% CI, 3.3% to 4.5%). For all solid cancers, female breast cancer, and sarcoma, 25-year cumulative incidences were 3.4% (95% CI, 2.9% to 4.0%), 1.5% (95% CI, 1.0% to 2.2%), and 1.0% (95% CI, 0.7% to 1.3%), respectively. The cumulative incidence of any SMN 15 years after childhood cancer for CCSs diagnosed in the 1990s was similar to that for CCSs treated in earlier decades (1.4%, 1.7%, and 1.6% for 1963 to 1979, 1980 to 1989, and 1990 to 2001, respectively; Fig 1).

Treatment-Related Risk Factors

Risk factors for subsequent breast cancer (n = 49, including five ductal carcinomas in situ), sarcoma (n = 55), and all solid tumors combined (n = 230) were evaluated in multivariable Cox proportional hazard regression analyses (Table 3). Doxorubicin was associated with a dose-dependent increased risk of female breast cancer, with hazard ratios (HRs) of 1.1 (95% CI, 0.4 to 2.9), 2.6 (95% CI, 1.1 to 6.5), and 5.8 (95% CI, 2.7 to 12.5) for ≤ 270, 271 to 443, and > 443 mg/m^2, respectively (P_{trend} < .001). Ifosfamide was also associated with breast cancer risk (any *v* none

Table 2. SIR, EAR, 25-Year Cumulative Incidence, and Time Since Childhood Cancer Diagnosis of Selected SMNs

Site of SMN	ICD-10 Code	Obs. No. of Cases	SIR (95% CI)	EAR/ 10,000 PY	25-Year Cumulative Incidence, % (95% CI)	Latency, Median (range)
All second cancers combined[a]	C00-C96	261	5.2 (4.6 to 5.8)	20.3	3.9 (3.4 to 4.6)	19.4 (5.1-45.0)
Solid cancers combined[a,b]	C00-C80	230	5.5 (4.8 to 6.2)	18.1	3.4 (2.9 to 4.0)	20.6 (5.2-45.0)
Head and neck[c]	C00-C14, C30-C32, C69	16	10.7 (6.1 to 17.4)	1.4	0.3 (0.2 to 0.5)	18.2 (5.2-34.5)
Digestive organs[d]	C15-C26	17	4.1 (2.4 to 6.6)	1.2	0.2 (0.1 to 0.4)	26.0 (13.1-45.0)
Lung and bronchus[e]	C34	8	4.3 (1.9 to 8.5	0.6	0.1 (0.0 to 0.3)	27.4 (17.3-37.7)
Mesothelioma	C45	4	88.6 (24.1 to 226.7)	0.4	0.0 (0.0 to 0.0)	30.1 (28.0-34.5)
Bone and articular cartilage	C40-C41	21	17.1 (10.6 to 26.1)	1.9	0.3 (0.2 to 0.5)	16.3 (5.4-33.0)
Melanoma	C43	19	2.6 (1.6 to 4.0)	1.1	0.3 (0.2 to 0.5)	24.3 (6.3-35.8)
Nonmelanoma skin, excluding BCC	C44	9	8.7 (4.0 to 16.5)	0.8	0.1 (0.0 to 0.2)	27.1 (7.2-39.5)
Soft tissue[f]	C47-C49	24	19.3 (12.4 to 28.7)	2.2	0.5 (0.3 to 0.7)	16.7 (7.8-35.9)
Female breast[a,g,h,i]	C50	45	5.1 (3.8 to 6.9)	7.6	1.5 (1.0 to 2.2	24.3 (12.8-40.6)
Female genital organs[h]	C51-C58	8	2.4 (1.0 to 4.7)	1.0	0.2 (0.1 to 0.5	18.1 (6.7-43.8)
Male genital organs[j]	C60-C63	9	1.5 (0.7 to 2.8)	0.5	0.3 (0.1 to 0.5)	16.5 (6.0-34.1)
Testis[j]	C62	8	1.4 (0.6 to 2.8)	0.4	0.3 (0.1 to 0.5)	16.5 (6.0-27.6)
Urinary tract	C64-C68	6	5.6 (2.1 to 12.2)	0.5	0.0 (0.0 to 0.1)	35.7 (15.2-40.2)
CNS[k]	C70-C72	24	8.5 (5.4 to 12.6)	2.0	0.4 (0.2 to 0.6	18.5 (5.8-37.6)
Meninges (malignant)	C70	6	154.0 (56.5 to 335.3)	0.6	0.0 (0.0 to 0.1)	27.4 (10.6-37.6)
Brain	C71	16	6.5 (3.7 to 10.6)	1.3	0.3 (0.2 to 0.6)	15.7 (5.8-28.6)
Other CNS	C72	2	11.8 (1.4 to 42.7)	0.2	0.0 (0.0 to 0.1)	9.8 (6.3-13.3)
Thyroid	C73	25	17.1 (11.1 to 25.3)	2.2	0.5 (0.3 to 0.7)	16.2 (6.2-33.8)
Hematologic malignancies combined	C81-C96	34	3.8 (2.6 to 5.3)	2.4	0.5 (0.3 to 0.7)	13.4 (5.1-40.2)
Hodgkin lymphoma	C81	6	1.9 (0.7 to 4.1)	0.3	0.1 (0.0 to 0.2)	16.0 (6.3-30.4)
Non-Hodgkin lymphoma	C82-C88	11	3.9 (2.0 to 7.0)	0.8	0.1 (0.1 to 0.3)	15.7 (5.7-40.2)
Leukemia	C91-C96	17	6.1 (3.6 to 9.8)	1.3	0.3 (0.2 to 0.5)	9.8 (5.1-29.7)

Abbreviations: BCC, basal cell carcinoma; EAR, excess absolute risk per 10,000 person-years; Obs., observed; PY, person-year; SIR, standardized incidence ratio; SMN, subsequent malignant neoplasm.
[a]Ductal carcinoma in situ (five women, one man) was excluded from all analyses in this table.
[b]Includes three solid cancers after a subsequent hematologic malignancy.
[c]Includes one head and neck cancer after a subsequent cancer of the bladder.
[d]Includes three digestive organ cancers after a subsequent cancer of breast, corpus uteri, and bone.
[e]Includes four lung and bronchus cancers after a subsequent cancer of head and neck (mouth), breast, thyroid, and leukemia.
[f]Includes one soft tissue cancer after a subsequent cancer of head and neck (tongue).
[g]Includes one breast cancer after a subsequent cancer of corpus uteri.
[h]Only women were included (n = 2,731) in calculating SIR, EAR, and cumulative incidence.
[i]One man developed a malignant breast cancer (SIR, 30.4; 95% CI, 0.8 to 169.5).
[j]Only men were included (n = 3,434) in calculating SIR, EAR, and cumulative incidence.
[k]Includes two CNS cancers after a subsequent Hodgkin lymphoma and thyroid cancer.

HR, 3.4; 95% CI, 1.3 to 8.8). Furthermore, both total body irradiation (TBI; HR, 10.6; 95% CI, 3.7 to 30.2) and chest radiotherapy (HR, 2.5; 95% CI, 1.3 to 4.9) were risk factors for female breast cancer. When we restricted the cohort to 2,451 female CCSs who had no chest radiotherapy or TBI (n = 31 with breast cancer), HRs for doxorubicin dose tertiles were 1.3 (95% CI, 0.3 to 6.1), 5.6 (95% CI, 1.9 to 16.2), and 9.9 (95% CI, 4.2 to 23.8), respectively (P_{trend} = .002), whereas risk associated with ifosfamide was no longer significant (HR, 2.3; 95% CI, 0.6 to 8.0; data not shown). We found a significant dose-related risk for anthracyclines (P_{trend} = .004) but not for the cyclophosphamide equivalent dose (CED; P_{trend} = 0.99; Table 3, female breast cancer model 2).

Incidence of subsequent sarcoma (Appendix Table A4, online only) was increased in survivors who received cyclophosphamide, with HRs of 0.2 (95% CI, 0.0 to 0.9), 1.7 (95% CI, 0.7 to 4.2), and 3.1 (95% CI, 1.5 to 6.0) for ≤ 4,800, 4,801 to 9,400, and > 9,400 mg/m^2, respectively (P_{trend} = .01). Ifosfamide was also associated with increased risk of subsequent sarcoma (any *v* none HR, 2.6; 95% CI, 1.3 to 5.2) without a clear dose effect (P_{trend} = .24). Other risk factors were TBI (HR, 4.5; 95% CI, 1.5 to 13.4) and any radiotherapy other than TBI (HR, 2.7; 95% CI, 1.5 to 4.9). The separate evaluation of risk for bone sarcoma and soft tissue or other extraosseous sarcoma showed that cyclophosphamide was associated with an increased risk of subsequent bone sarcoma, with HRs of 2.6 (95% CI, 0.6 to 11.1) and 8.2 (95% CI, 3.1 to 21.5) for medium and high dose, respectively (no low-dose–exposed survivors; P_{trend} = .007), but not with an increased risk of other sarcomas, with HRs of 0.3 (95% CI, 0.1 to 1.2), 1.4 (95% CI, 0.5 to 4.3), and 1.1 (95% CI, 0.3 to 3.6) for low, medium, and high dose, respectively (P_{trend} = 0.58; data not shown). We then restricted the cohort to CCSs treated without radiotherapy and found that sarcoma risks associated with cyclophosphamide dose were lower, with HRs of 0.9 (95% CI, 0.1 to 7.0) and 1.3 (95% CI, 0.2 to 10.1) for median and high dose, respectively (P_{trend} = .69; data not shown). A model with the CED showed a significant alkylating agent dose response (P_{trend} = .003; Table 3, sarcoma model 2).

For all subsequent solid cancers, treatment effects were observed for TBI (HR, 4.7; 95% CI, 2.7 to 8.4); any radiotherapy other than TBI (HR, 1.9; 95% CI, 1.4 to 2.6); and doxorubicin dose, with HRs of 0.8 (95% CI, 0.5 to 1.2), 1.8 (95% CI, 1.1 to 2.9), and 2.5 (95% CI, 1.6 to

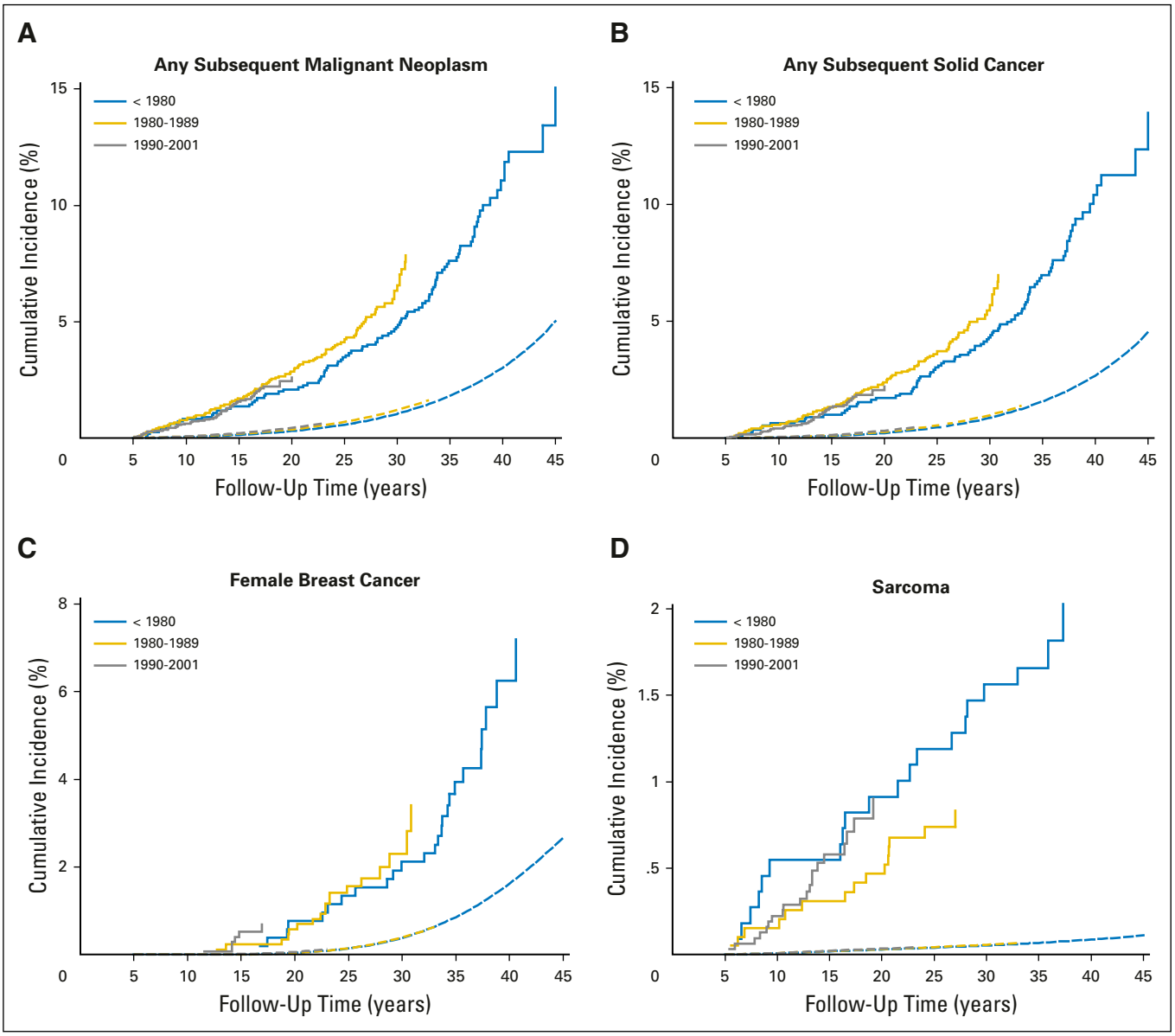

Fig 1. Cumulative incidence of subsequent malignant neoplasms in the DCOG LATER (Dutch Childhood Cancer Oncology Group–Long-Term Effects After Childhood Cancer) cohort (solid lines) and expected cumulative incidence in the general population (dashed lines) by childhood cancer treatment period. The range of the *y*-axis differs across panels. Pepe-Mori test *P* values for comparison of cumulative incidences of any subsequent malignant neoplasm up to 15 years after diagnosis for each childhood cancer diagnosis period are as follows: .67 for < 1980 *v* 1980 to 1989, .84 for < 1980 *v* 1990 to 2001, and .44 for 1980 to 1989 *v* 1990 to 2001.

3.9) for ≤ 270, 271 to 443, and > 443 mg/m^2, respectively (P_{trend} < .001). For ifosfamide, some evidence of increased risk was observed in the highest dose tertile, with dose-tertile–specific HRs of 1.8 (95% CI, 0.9 to 3.8), 1.4 (95% CI, 0.7 to 2.6), and 2.5 (95% CI, 1.2 to 5.0), respectively (P_{trend} = .15). Additional sensitivity analyses are reported in Appendix Table A5 (online only). We found no significant CED dose response (P_{trend} = .09), but we did for the anthracycline agents as a group (P_{trend} = .006). Women whose childhood cancer treatment included anthracycline ≥ 250 mg/m^2 had a significantly higher risk than those treated without anthracyclines (HR, 1.9; 95% CI, 1.3 to 2.7; Table 3, solid cancer model 2).

Finally, mercaptopurine and methotrexate, mainly used in leukemia and non-Hodgkin lymphoma protocols, were associated with decreased risks of subsequent solid cancers and sarcoma, respectively. After additional adjustment by childhood cancer type, these findings disappeared (data not shown).

We performed separate analyses for leukemia, CNS tumor, and sarcoma survivors (except Ewing sarcoma; n = 3,578) because combinations of these cancer types are specific for LFS, and many of these survivors (especially of sarcoma) were exposed to high-dose cyclophosphamide and/or doxorubicin (Appendix Table A6, online only). The doxorubicin dose-response trend for breast cancer was stronger ($P_{difference}$ = .008) among female survivors of potentially LFS-associated childhood cancers (P_{trend} < .001) versus other CCSs (P_{trend} = .94; Table 4). The cyclophosphamide dose-response trend for subsequent sarcoma was not materially different ($P_{difference}$ = .98).

Table 3. Multivariable Cox Proportional Hazards Regression Analysis for Female Breast Cancer (n = 49), Sarcoma (n = 55), and All Solid Cancers (n = 230)

Variable	Total No. of Patients	No. of Cancers	HR	95% CI	P_{trend}*
Female breast cancer†					
Model 1: single chemotherapy agents					
Chest radiotherapy					
No	2,526	36	1.0 (ref)		
Yes	183	13	2.5	1.3 to 4.9	
TBI					
No	2,632	44	1.0 (ref)		
Yes	77	5	10.6	3.7 to 30.2	
Ifosfamide					
No	2,415	43	1.0 (ref)		
Yes	290	6	3.4	1.3 to 8.8	
Doxorubicin dose,‡ mg/m^2					
None	1,877	25	1.0 (ref)		
≤ 270	563	6	1.1	0.4 to 2.9	
271-443	149	7	2.6	1.1 to 6.5	
> 443	106	10	5.8	2.7 to 12.5	< .001
Model 2: chemotherapy groups					
CED, mg/m^2					
No alkylating agents	1,433	18	1.0 (ref)		
< 6,000	651	14	2.0	0.9 to 4.8	
6,000-17,999	493	15	1.7	0.7 to 3.9	
≥ 18,000	94	2	1.0	0.2 to 4.5	.99
Anthracyclines, mg/m^2					
None	1,514	20	1.0 (ref)		
1-249	680	9	1.3	0.5 to 3.2	
≥ 250	492	19	3.1	1.4 to 6.5	.004
Sarcoma§					
Model 1: single chemotherapy agents					
Any radiotherapy other than TBI					
No	3,793	17	1.0 (ref)		
Yes	2,331	36	2.7	1.5 to 4.9	
TBI					
No	5,886	47	1.0 (ref)		
Yes	221	5	4.5	1.5 to 13.4	
Ifosfamide					
No	5,392	41	1.0 (ref)		
Yes	714	14	2.6	1.3 to 5.2	
Cyclophosphamide dose,‡ mg/m^2					
None	3,784	32	1.0 (ref)		
≤ 4,800	1,340	2	0.2	0.0 to 0.9	
4,801-9,400	557	9	1.7	0.7 to 4.2	
> 9,400	398	12	3.1	1.5 to 6.0	.01
Model 2: chemotherapy groups					
CED, mg/m^2					
No alkylating agents	3,020	23	1.0 (ref)		
< 6,000	1,537	3	0.2	0.0 to 0.8	
6,000-17,999	1,245	21	2.0	1.1 to 3.8	
≥ 18,000	227	8	4.2	1.9 to 9.6	.003
Solid cancer‖					
Model 1: single chemotherapy agents					
Sex					
Male	3,434	100	1.0 (ref)		
Female	2,731	130	1.7	1.3 to 2.2	
Any radiotherapy other than TBI					
No	3,793	78	1.0 (ref)		
Yes	2,331	149	1.9	1.4 to 2.6	
TBI					
No	5,886	209	1.0 (ref)		
Yes	221	16	4.7	2.7 to 8.4	
Ifosfamide dose,‡ mg/m^2					
None	5,392	196	1.0 (ref)		
≤ 9,467	189	10	1.8	0.9 to 3.8	
9,468-54,000	392	12	1.4	0.7 to 2.6	
> 54,000	125	9	2.5	1.2 to 5.0	.15

(continued on following page)

Table 3. Multivariable Cox Proportional Hazards Regression Analysis for Female Breast Cancer (n = 49), Sarcoma (n = 55), and All Solid Cancers (n = 230) (continued)

Variable	Total No. of Patients	No. of Cancers	HR	95% CI	P_{trend}*
Doxorubicin dose,‡ mg/m^2					
None	4,149	153	1.0 (ref)		
≤ 270	1,350	25	0.8	0.5 to 1.2	
271-443	359	23	1.8	1.1 to 2.9	
> 443	228	24	2.5	1.6 to 3.9	< .001
Model 2: chemotherapy groups					
CED, mg/m^2					
No alkylating agents	3,020	106	1.0 (ref)		
< 6,000	1,537	39	0.9	0.6 to 1.4	
6,000-17,999	1,245	65	1.3	0.9 to 1.9	
≥ 18,000	227	16	1.5	0.9 to 2.7	.09
Anthracyclines, mg/m^2					
None	3,288	123	1.0 (ref)		
1-249	1,620	35	0.9	0.6 to 1.4	
≥ 250	1,157	67	1.9	1.3 to 2.7	.006

NOTE. All factors in model 1 have been adjusted for simultaneously. Model 2 was similar to model 1, except that the chemotherapy agents have been substituted by chemotherapy groups. The other variables are not shown in model 2 for clarity. Attained age was used as the time scale in all models. Numbers do not always add up to the total because of missing values.

Abbreviations: CED, cyclophosphamide equivalent dose; HR, hazard ratio; ref, reference; TBI, total body irradiation.

*Test for trend in continuous dose variable among exposed survivors.

†Eligible patients include five women with a ductal carcinoma in situ of the breast (one before a breast carcinoma) and one breast cancer after a nonbreast subsequent malignant neoplasm (endometrial carcinoma treated without radiotherapy or chemotherapy 7 years before breast cancer).

‡Categories were based on approximate tertiles among exposed patients with subsequent solid cancer.

§Eligible patients were 21 survivors with a subsequent bone sarcoma and 34 with a subsequent soft tissue or other extraosseous sarcoma. Two survivors had a sarcoma after a nonsarcoma subsequent malignant neoplasm (acute lymphoblastic leukemia treated with TBI and chemotherapy 2 years before sarcoma and squamous cell carcinoma of the tongue treated without radiotherapy or chemotherapy 3 months before sarcoma).

||Eligible patients include three with solid cancers after a nonsolid subsequent malignant neoplasm (acute lymphoblastic leukemia treated with TBI and chemotherapy 2 years before solid cancer, acute lymphoblastic leukemia treated with TBI and chemotherapy 2 years before solid cancer, and one Hodgkin lymphoma treated with mantle field radiotherapy and chemotherapy 22 years before solid cancer).

DISCUSSION

This study in a well-characterized cohort of Dutch CCSs strongly suggests that chemotherapeutic agents can increase the risk of solid cancers independently of radiotherapy. Doxorubicin was associated with a dose-dependent increased risk of female breast cancer, whereas cyclophosphamide increased subsequent sarcoma risk in a dose-dependent manner. These findings are based on > 6,000 5-year survivors, with a median follow-up of 20.7 years since primary diagnosis, detailed therapy information, and highly complete follow-up for SMNs.

Doxorubicin exposure was associated with female breast cancer in a dose-dependent manner, particularly for women who may have had LFS-associated childhood cancer types. These findings independently validate and extend a recent Childhood Cancer Survivor Study report on a dose-dependent increased breast cancer risk with cumulative anthracycline exposure (relative SIRs, 2.6 and 3.8 for 1 to 249 and ≥ 250 mg/m^2, respectively; P_{trend} = .004) in female CCSs treated without chest radiotherapy, which was stronger among survivors of leukemia and sarcoma.[22] The current findings of a stronger doxorubicin dose response among survivors of LFS-associated cancer types compared with other CCSs suggest a gene-anthracycline interaction in the development of breast cancer, perhaps with the inclusion of LFS or LFS-like syndromes, as hypothesized by Henderson et al.[22] Future collaborative studies that include family history of cancer and/or *TP53* status are needed to truly disentangle the role that childhood cancer type, treatment details, and genetic factors play in the development of subsequent female breast cancer. We observed no effects of epirubicin and idarubicin, with only one and zero breast cancers occurring among exposed women, respectively. For daunorubicin (seven cases of breast cancer), risk was only increased in the multivariable model for the subcohort of LFS-associated childhood cancers (HR, 3.8; 95% CI, 1.1 to 13.2). An association between anthracyclines and (breast) cancer risk was previously suggested by smaller follow-up studies, particularly for doxorubicin,[36-38] and is supported by studies in rodents.[39-44] We observed an increased risk of sarcoma after high-dose doxorubicin treatment in univariable analyses but not after multivariable adjustment that included cyclophosphamide. This observation seemingly contrasts an earlier report on anthracycline-related sarcoma risk, which only crudely adjusted for other chemotherapy and not specifically for alkylating agents.[21] In all, the current result of a dose-dependent increased risk of solid cancer, particularly breast cancer, irrespective of radiotherapy treatment suggests that anthracyclines play a role in the etiology of breast cancer and perhaps other solid cancers.

Alkylating agents have been associated with many different solid cancers among (childhood) cancer survivors.[9-11,14,45-52] However, only a few studies identified specific agents (eg, procarbazine for GI cancer[45-48,51] and cyclophosphamide for bladder and pancreatic cancer[45,53,54]). We did not find an increased risk of solid cancer after procarbazine exposure on the basis of data from 17 patients with a GI cancer. Cyclophosphamide, however, showed a dose-response relation with subsequent sarcoma, particularly bone sarcoma, in accordance with previous SMN studies[11,14,45,53,54] and experimental data.[55,56] Previous treatment with ifosfamide also resulted in increased risks of female breast cancer, sarcoma, and all solid cancers among CCSs. We interpret this finding with caution

Table 4. Multivariable Cox Proportional Hazards Regression Analyses for Female Breast Cancer, Sarcoma, and All Solid Cancers Among Five-Year Survivors of Childhood Cancer for Subcohorts of LFS-Associated and Other Childhood Cancer Types

	Childhood Cancer-Based Subcohort									
	LFS Associated*					Other†				
SMN of Interest	Total No. of Patients	No. of Cancers	HR	95% CI	P_{trend}‡	Total No. of Patients	No. of Cancers	HR	95% CI	P_{trend}‡	$P_{difference}$§
Female breast cancer‖											
Chest radiotherapy											.77
No	1,568	21	1.0 (ref)			1,342	16	1.0 (ref)			
Yes	25	2	2.0	0.4 to 9.7		158	11	2.3	1.0 to 5.1		
TBI											NE
No	1,520	18	1.0 (ref)			1,496	27	1.0 (ref)			
Yes	73	5	23.3	7.1 to 76.4		4	0	0			
Ifosfamide											.64
No	1,421	19	1.0 (ref)			1,369	25	1.0 (ref)			
Yes	167	4	2.8	0.9 to 8.8		133	2	5.1	1.1 to 24.3		
Doxorubicin dose, mg/m^2											.008
None	1,132	8	1.0 (ref)			1,127	18	1.0 (ref)			
≤ 270	324	2	0.6	0.1 to 3.2		239	4	1.9	0.6 to 6.2		
271-443	64	5	9.1	2.5 to 32.8		86	2	1.1	0.2 to 4.9		
> 443	62	7	14.8	5.1 to 43.2	< .001	45	3	2.4	0.7 to 8.4	.94	
Sarcoma¶											
Any radiotherapy other than TBI											.03
No	2,225	13	1.0 (ref)			1,568	4	1.0 (ref)			
Yes	1,336	15	1.4	0.6 to 3.2		995	21	6.8	2.3 to 20.2		
TBI											NE
No	3,347	22	1.0 (ref)			2,539	25	1.0 (ref)			
Yes	207	5	2.8	0.8 to 10.6		14	0	0			
Ifosfamide											.15
No	3,142	19	1.0 (ref)			2,250	22	1.0 (ref)			
Yes	403	10	3.7	1.5 to 9.1		311	4	1.4	0.4 to 4.7		
Cyclophosphamide dose, mg/m^2											.98
None	2,104	14	1.0 (ref)			1,680	18	1.0 (ref)			
≤ 4,800	1,001	2	0.3	0.1 to 1.6		339	0	0			
4,801-9,400	249	8	3.3	1.1 to 10.0		308	1	0.6	0.1 to 4.4		
> 9,400	181	5	3.9	1.4 to 10.9	.10	217	7	2.6	1.1 to 6.3	.15	
Solid cancer#											
Sex											.04
Male	1,979	62	1.0 (ref)			1,455	38	1.0 (ref)			
Female	1,608	63	1.3	0.9 to 1.9		1,123	67	2.1	1.4 to 3.2		
Any radiotherapy other than TBI											.03
No	2,225	52	1.0 (ref)			1,568	26	1.0 (ref)			
Yes	1,336	57	1.7	1.1 to 2.6		995	77	2.6	1.6 to 4.2		
TBI											NE
No	3,347	106	1.0 (ref)			2,436	103	1.0 (ref)			
Yes	207	16	5.0	2.7 to 9.3		14	0	0			
Ifosfamide dose, mg/m^2											.80
None	3,142	104	1.0 (ref)			2,250	92	1.0 (ref)			
≤ 9,467	141	9	1.7	0.8 to 3.8		48	1	1.5	0.2 to 11.0		
9,468-54,000	207	9	1.4	0.7 to 2.9		185	3	0.8	0.2 to 3.3		
> 54,000	51	2	1.4	0.3 to 5.7	.62	74	7	5.1	2.0 to 12.9	.02	
Doxorubicin dose, mg/m^2											.002
None	2,559	80	1.0 (ref)			1,590	73	1.0 (ref)			
≤ 270	703	15	0.8	0.4 to 1.4		637	10	0.9	0.4 to 1.7		
271-443	143	12	2.4	1.2 to 4.6		205	11	1.2	0.6 to 2.5		
> 443	128	16	3.9	2.2 to 7.1	< .001	92	8	1.3	0.6 to 2.9	.61	

NOTE. All factors in the models have been adjusted for simultaneously. Attained age was used as the time scale in all models. Numbers do not always add up to the total because of missing values.

Abbreviations: HR, hazard ratio; LFS, Li-Fraumeni syndrome; NE, not estimable; SMN, subsequent malignant neoplasm; TBI, total body irradiation.

*The LFS-associated childhood cancer subcohort includes 5-year survivors of childhood leukemia and CNS tumors as well as survivors of sarcoma, except for Ewing sarcoma (n = 3,587). For breast cancer, only women were included (n = 1,608).

†Includes all other 5-year childhood cancer survivors (n = 2,578). For breast cancer, only women were included (n = 1,123).

‡Test for trend in continuous dose variable among exposed survivors.

§Test for difference in strength of the reported risk factor associations between LFS-associated childhood cancers and other childhood cancers. For variables with dose categories, this *P* value is for the difference in trend in continuous dose variable among exposed survivors. For dichotomous variables, this *P* value is for the difference in risk estimates for the yes category of the dichotomous variable.

‖Eligible patients were 23 and 26 female survivors with a subsequent breast cancer (including one and four women with ductal carcinomas in situ) for the subcohorts of LFS-associated *v* other childhood cancers, respectively.

¶Eligible patients were 29 and 26 survivors with a subsequent sarcoma (11 and 10 with a subsequent bone sarcoma and 18 and 16 with a subsequent soft tissue or other extraosseous sarcoma) for the subcohorts of LFS-associated *v* other childhood cancers, respectively.

#Eligible patients were 125 and 105 survivors with a subsequent solid cancer for the subcohort of LFS-associated *v* other childhood cancers, respectively.

because the seemingly elevated overall risk was not paralleled by clear dose-response patterns or is supported by other epidemiologic studies on carcinogenicity of ifosfamide, although some evidence from animal studies exists.[57,58]

We chose to focus on agent-specific dose information because the various agents collated in chemotherapy agent categories on the basis of structure and/or antitumor mechanism may not necessarily have similar carcinogenic properties. Moreover, aggregate measures of chemotherapy exposures are based on acute hematologic toxicity[32] or late cardiac toxicity,[59] or they are cohort specific, which limits comparability across cohorts.[14,60] Although we observed significant associations between anthracycline dose and risk of breast cancer and all solid cancers, they were confined to doxorubicin. For sarcoma, we observed a significant dose response for the CED, but when we examined specific agents, only cyclophosphamide dose seemed to be associated with sarcoma. Radiotherapy was associated with solid cancer risk, with stronger effects for TBI than for other radiotherapy, which may be related to the large volume of the body treated in TBI, a high dose per fraction, or HCT-related immunologic alterations.[61]

Despite the reduction of radiotherapy exposure over time, the findings indicate that the risk of SMN did not decrease noticeably in patients treated between 1990 and 2001 (median follow-up, 16 years) compared with those treated earlier. SMNs that occur relatively soon after childhood cancer diagnosis conceivably have a genetic basis, whereas treatment-related (mainly solid) SMNs occur later. Longer follow-up is needed to evaluate SMN risk among recently treated patients.

The major strengths of this study are the large cohort size, detailed information on individual treatments, and availability of highly complete SMN follow-up by record linkage and medical information. A limitation of the study is that the number of events for most SMN sites were fairly low as a result of the age distribution at the end of follow-up. In addition, as in other survivorship cohorts, correlations between patient and treatment factors, which reflect clinical reality, sometimes hampered the ability to disentangle effects in multivariable analysis.[22] Furthermore, we tested many variables in our models and performed various post hoc tests to validate the findings, so we cannot exclude the possibility that some of the findings are based on chance.

In conclusion, the results strongly suggest that CCSs who received treatment, including TBI, other radiotherapy, doxorubicin, or cyclophosphamide, are at the highest risk for developing subsequent solid cancers. In addition, our observations indicate that genetic susceptibility may influence doxorubicin-associated breast cancer risk. The results of this study will inform future childhood cancer treatment protocols as well as SMN surveillance guidelines for former patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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Appendix

Methods

Radiotherapy exposure assessment. For every individual in the cohort who had radiotherapy for initial cancer and/or recurrences, we collected information on body compartment of the radiotherapy and prescribed dose per body compartment. Radiotherapy, which excluded total body irradiation (TBI), was evaluated in the models as yes/no variables (any radiotherapy for sarcoma and for all solid cancers; chest radiotherapy for female breast cancer) and in prescribed dose categories if at least 10 exposed cases for the outcome of interest occurred (maximum dose to any body compartment for any solid cancer and sarcoma, maximum dose to the chest for breast cancer). Chest radiotherapy was defined as any field that included the thoracic region, which excluded spinal irradiation and TBI. TBI was evaluated separately from other radiotherapy.

Imputation missing chemotherapy doses. Of all survivors treated with chemotherapy, we did not know the exact dose in 17.8% of the administrations. For those missing dosage administrations, we knew which agent was given but not the exact dose. The number of survivors for whom chemotherapy doses were missing for all administrations was 1%. In cases of missing dose administration, we imputed these data. For survivors with a known treatment protocol, we imputed the mean dose of other survivors who had the same protocol (if at least three survivors had the same protocol). For survivors without a known protocol, we imputed the mean dose of all survivors with the same diagnosis group and diagnosis period (5-year period).

The number of missing data varied strongly between agents. For example, for doxorubicin and cyclophosphamide, two commonly used agents of main interest, only 3% and 6% of the dose administration data were missing, respectively. We performed sensitivity analyses without the imputed doses (which excluded survivors with a missing dose for one of the variables in the model), and this did not materially change the results.

Table A1. Chemotherapy Agents Tested in Multivariable Cox Proportional Hazard Regression Models*

Chemotherapy Agent†	All Solid Cancers	Female Breast Cancer	Sarcoma
Ifosfamide	X	X	X
Mechlorethamine	X	X	
Procarbazine	X	X	
Dacarbazine	X		
Cyclophosphamide	X	X	X
Doxorubicin	X	X	X
Daunorubicin	X	X	X
Epirubicin	X		
Etoposide	X	X	X
Teniposide	X		X
Vincristine	X	X	X
Vindesine	X		
Vinblastine	X		
Cisplatin	X		
Carboplatin	X		
Cytarabine	X	X	X
Methotrexate	X	X	X
Thioguanine	X	X	
Mercaptopurine	X	X	X

*As presented in Table 3.
†Only agents with at least five exposed survivors of the outcome of interest were tested.

Table A2. SIRs and EARs of All Subsequent Malignant Neoplasms According to Patient and Disease Characteristics

Characteristic	Person-Years	Observed No. of Cases	SIR	95% CI	EAR
Sex					
Male	57,127	123	5.2	4.3 to 6.2	17.4
Female	46,822	138	5.1	4.3 to 6.1	23.7
Age at childhood cancer diagnosis, years					
< 5	48,204	92	6.1	4.9 to 7.4	15.9
5-9	27,589	66	5.4	4.2 to 6.9	19.5
10-14	21,380	78	5.0	3.9 to 6.2	29.2
15-17	6,776	25	3.3	2.2 to 4.9	25.9
Period of childhood cancer diagnosis					
1963-1969	3,752	11	2.1	1.1 to 3.8	15.5
1970-1979	25,984	89	4.9	3.9 to 6.0	27.2
1980-1989	39,749	105	5.9	4.9 to 7.2	22.0
1990-2001	34,464	56	6.0	4.5 to 7.7	13.5
Childhood cancer diagnosis					
Leukemia	33,276	63	4.7	3.6 to 6.0	14.9
Acute lymphoblastic leukemia	29,323	47	4.0	2.9 to 5.3	12.0
Acute myeloid leukemia	2,858	12	10.4	5.4 to 18.2	38.0
Other leukemia	1,095	4	10.4	2.8 to 26.5	33.0
Non-Hodgkin lymphoma	10,129	18	3.6	2.2 to 5.8	12.9
Hodgkin lymphoma	6,767	21	5.2	3.2 to 8.0	25.1
CNS	12,555	29	4.7	3.2 to 6.8	18.2
Renal tumors	11,580	29	6.7	4.5 to 9.6	21.3
Bone/soft tissue sarcoma	14,531	64	6.5	5.0 to 8.3	37.3
Other neoplasms	15,111	37	4.7	3.3 to 6.5	19.3
Time since diagnosis, years					
5-9	29,677	44	9.5	6.9 to 12.8	13.3
10-19	45,572	90	6.2	5.0 to 7.6	16.6
20-29	21,946	74	4.3	3.4 to 5.4	25.8
≥ 30	6,754	53	3.8	2.8 to 4.9	57.7
Attained age (< 10 years at childhood cancer diagnosis), years					
< 20	42,129	63	10.5	8.0 to 13.4	13.5
20-29	23,089	43	4.6	3.4 to 6.2	14.6
30-39	9,109	38	4.3	3.1 to 5.9	32.1
≥ 40	1,466	14	4.3	2.3 to 7.2	73.1
Attained age (10-17 years at childhood cancer diagnosis), years					
< 30	17,199	35	5.8	4.1 to 8.1	16.9
30-39	7,753	41	5.6	4.0 to 7.6	43.4
40-49	2,663	20	3.2	1.9 to 4.9	51.4
≥ 50	541	7	2.0	0.8 to 4.2	65.4

Abbreviations: EAR, excess absolute risk per 10,000 person-years; SIR, standardized incidence ratio.

Table A3. SIRs and EARs of Subsequent Solid Cancers and Hematologic Malignancies According to Patient and Disease Characteristics

Characteristic	All Solid Cancers					All Hematologic Malignancies				
	Person-Years	Obs. No. of Cases	SIR	95% CI	EAR	Person-Years	Obs. No. of Cases	SIR	95% CI	EAR
Sex										
Male	57,233	100	5.5	4.5 to 6.7	14.3	57,585	25	4.6	3.0 to 6.8	3.4
Female	46,929	130	5.5	4.6 to 6.5	22.7	47,659	9	2.6	1.2 to 4.9	1.2
Age at childhood cancer diagnosis, years										
< 5	48,274	84	7.2	5.7 to 8.9	15.0	48,662	11	3.1	1.6 to 5.6	1.5
5-9	27,673	51	5.1	3.8 to 6.7	14.8	27,916	15	6.3	3.5 to 10.4	4.5
10-14	21,439	70	5.2	4.0 to 6.5	26.3	21,796	8	3.6	1.6 to 7.1	2.6
15-17	6,776	25	3.7	2.4 to 5.5	27.1	6,873	0	0.0	0.0 to 4.5	−1.2
Period of childhood cancer diagnosis										
1963-1969	3,789	8	1.7	0.7 to 3.3	8.3	3,797	3	6.3	1.3 to 18.5	6.7
1970-1979	26,042	84	5.3	4.2 to 6.5	26.1	26,483	6	2.5	0.9 to 5.4	1.4
1980-1989	39,826	92	6.4	5.2 to 7.9	19.5	40,327	14	4.1	2.2 to 6.9	2.6
1990-2001	34,505	46	6.8	5.0 to 9.1	11.4	34,639	11	4.1	2.1 to 7.4	2.4
Childhood cancer diagnosis										
Leukemia	33,330	53	4.9	3.7 to 6.4	12.7	33,585	11	4.1	2.1 to 7.4	2.5
Acute lymphoblastic leukemia	29,364	43	4.5	3.3 to 6.1	11.4	29,551	5	2.1	0.7 to 5.0	0.9
Acute myeloid leukemia	2,869	8	8.7	3.8 to 17.1	24.7	2,926	4	16.7	4.5 to 42.7	12.8
Other leukemia	1,097	2	6.6	0.8 to 24.0	15.5	1,108	2	23.2	2.8 to 83.9	17.3
Non-Hodgkin lymphoma	10,166	15	3.7	2.1 to 6.1	10.8	10,245	3	3.2	0.7 to 9.4	2.0
Hodgkin lymphoma	6,772	19	5.7	3.4 to 8.9	23.1	6,830	2	3.0	0.4 to 10.7	1.9
CNS	12,564	25	5.0	3.2 to 7.3	15.9	12,647	4	3.7	1.0 to 9.4	2.3
Renal tumors	11,614	24	6.9	4.5 to 10.3	17.7	11,703	5	5.7	1.8 to 13.2	3.5
Bone/soft tissue sarcoma	14,569	60	7.0	5.3 to 9.0	35.3	14,934	5	3.5	1.1 to 8.1	2.4
Other neoplasms	15,146	34	5.1	3.5 to 7.1	18.1	15,303	4	3.2	0.9 to 8.3	1.8
Treatment										
Surgery only	10,190	11	2.5	1.3 to 4.5	6.5	10,176	5	5.8	1.9 to 13.6	4.1
Chemotherapy, no radiotherapy	45,289	50	3.9	2.9 to 5.2	8.2	45,508	16	4.4	2.5 to 7.2	2.7
Radiotherapy, no chemotherapy	9,967	37	4.9	3.4 to 6.7	29.5	10,154	4	3.8	1.0 to 9.7	2.9
Radiotherapy and chemotherapy	37,715	125	7.6	6.3 to 9.0	28.8	38,395	9	2.7	1.2 to 5.2	1.5
No treatment or treatment unknown	1,002	7	10.5	4.2 to 21.5	63.2	1,014	0	0.0	0.0 to 40.2	−0.9
Time since diagnosis, years										
5-9	29,703	31	10.7	7.2 to 15.1	9.5	29,740	14	8.2	4.5 to 13.7	4.1
10-19	45,647	80	7.3	5.8 to 9.0	15.1	45,969	11	3.1	1.5 to 5.5	1.6
20-29	22,007	69	4.6	3.6 to 5.8	24.5	22,453	6	2.5	0.9 to 5.5	1.6
≥ 30	6,806	50	3.9	2.9 to 5.1	54.4	7,084	3	2.4	0.5 to 6.9	2.4
Attained age (< 10 years at childhood cancer diagnosis), years										
< 20	42,176	48	13.4	9.9 to 17.8	10.5	42,297	16	6.5	3.7 to 10.6	3.2
20-29	23,143	40	5.5	4.0 to 7.5	14.2	23,399	4	1.9	0.5 to 4.9	0.8
30-39	9,136	35	4.5	3.1 to 6.2	29.8	9,348	4	3.9	1.0 to 9.9	3.2
≥ 40	1,492	12	3.9	2.0 to 6.8	59.8	1,535	2	6.7	0.8 to 24.1	11.1
Attained age (10-17 years at childhood cancer diagnosis), years										
< 30	17,221	30	6.5	4.4 to 9.3	14.7	17,293	5	3.6	1.2 to 8.4	2.1
30-39	7,765	39	6.0	4.3 to 8.2	41.8	7,955	2	2.4	0.3 to 8.5	1.4
40-49	2,672	19	3.3	2.0 to 5.1	49.4	2,833	1	1.8	0.0 to 10.2	1.6
≥ 50	549	7	2.1	0.9 to 4.4	68.0	588	0	0.0	0.0 to 14.5	−4.3

Abbreviations: EAR, excess absolute risk per 10,000 person-years; Obs., observed; SIR, standardized incidence ratio.

Table A4. Frequency of Included Types of Subsequent Sarcomas (n = 55)*

Morphology Code	Morphology Description	Frequency
8800/3	Sarcoma, NOS	4
8801/3	Spindle cell sarcoma	1
8802/3	Giant cell sarcoma	2
8803/3	Small cell sarcoma	1
8810/3	Fibrosarcoma, NOS	1
8830/3	Malignant fibrous histiocytoma	4
8850/3	Liposarcoma, NOS	1
8858/3	Dedifferentiated liposarcoma	1
8890/3	Leiomyosarcoma, NOS	4
8900/3	Rhabdomyosarcoma, NOS	2
8910/3	Embryonal rhabdomyosarcoma, NOS	1
8920/3	Alveolar rhabdomyosarcoma	1
9040/3	Synovial sarcoma, NOS	3
9041/3	Synovial sarcoma, spindle cell	1
9120/3	Hemangiosarcoma	1
9140/3	Kaposi sarcoma	1
9150/3	Hemangiopericytoma, malignant	1
9180/3	Osteosarcoma, NOS	14
9181/3	Chondroblastic osteosarcoma	3
9182/3	Fibroblastic osteosarcoma	1
9220/3	Chondrosarcoma, NOS	3
9540/3	Malignant peripheral nerve sheath tumor	1
9560/3	Neurilemmoma, malignant	1
9561/3	Malignant peripheral nerve sheath tumor with rhabdomyoblastic differentiation	2

Abbreviation: NOS, not otherwise specified.
*Eligible sarcomas were all included in the third edition of the International Classification of Childhood Cancer under VIII. Malignant bone tumors, and IX. Soft tissue and extraosseous sarcoma.

Table A5. Sensitivity Analyses for Multivariable Cox Proportional Hazard Regression Analyses for Outcome of All Solid Cancers

	Solid Cancer Total			Solid Cancer Except Breast			Solid Cancer Adjustment Radiotherapy Dose*		
Variable	HR	95% CI	P_{trend}†	HR	95% CI	P_{trend}†	HR	95% CI	P_{trend}†
Sex									
Male	1.0 (ref)			1.0 (ref)			1.0 (ref)		
Female	1.7	1.3 to 2.2		1.1	0.8 to 1.4		1.6	1.3 to 2.2	
Any radiotherapy other than TBI									
No	1.0 (ref)			1.0 (ref)			1.0 (ref)		
Yes	1.9	1.4 to 2.6		2.2	1.6 to 3.1		0.3	0.0 to 2.4	
TBI									
No	1.0 (ref)			1.0 (ref)			1.0 (ref)		
Yes	4.7	2.7 to 8.4		3.9	2.0 to 7.7		1.1	0.2 to 8.4	
Ifosfamide dose,‡ mg/m^2									
None	1.0 (ref)			1.0 (ref)			1.0 (ref)		
≤ 9,467	1.8	0.9 to 3.8		1.3	0.6 to 3.3		1.7	0.8 to 3.6	
9,468-54,000	1.4	0.7 to 2.6		1.4	0.7 to 2.8		1.3	0.7 to 2.6	
> 54,000	2.5	1.2 to 5.0	.15	2.4	1.1 to 5.4	.15	2.3	1.1 to 4.7	.15
Doxorubicin dose,‡ mg/m^2									
None	1.0 (ref)			1.0 (ref)			1.0 (ref)		
≤ 270	0.8	0.5 to 1.2		0.7	0.4 to 1.2		0.8	0.5 to 1.2	
271-443	1.8	1.1 to 2.9		1.4	0.8 to 2.5		1.8	1.1 to 2.9	
> 443	2.5	1.6 to 3.9	< .001	1.7	1.0 to 3.0	.004	2.4	1.5 to 3.8	.02

NOTE. All factors in the models were adjusted for simultaneously. Attained age was used as the time scale in all models.
Abbreviations: HR, hazard ratio; TBI, total body irradiation.
*Adjusted for tertiles of radiotherapy dose. Tertile-specific HRs were 5.9 (95% CI, 0.8 to 46.4), 6.5 (95% CI, 0.8 to 54.8), and 7.9 (95% CI, 1.0 to 64.2) for ≤ 25 Gy, 26-45 Gy, and > 45 Gy, respectively.
†Test for trend in continuous dose variable among exposed survivors.
‡Categories were based on approximate tertiles among exposed survivors with subsequent solid cancer.

Table A6. Distribution of Selected Treatment Variables Across Childhood Cancer Types

Treatment Characteristic*	Childhood Cancer Type, No. (%)					
	Leukemia	Lymphoma	CNS Tumor	Bone Tumor	Soft Tissue Sarcoma	Other
No. of patients	2,092	982	843	370	450	1,428
Any radiotherapy other than TBI						
No	1,480 (70.8)	606 (61.7)	346 (41.0)	210 (56.8)	243 (54.0)	908 (63.6)
Yes	599 (28.6)	370 (37.7)	487 (57.8)	158 (42.7)	205 (45.6)	512 (35.9)
TBI						
No	1,869 (89.3)	953 (97.1)	830 (98.5)	368 (99.5)	447 (99.3)	1,419 (99.4)
Yes	207 (9.9)	14 (1.4)	0 (0)	0 (0)	0 (0)	0 (0)
Alkylating agents						
No	931 (44.5)	128 (13.0)	616 (73.1)	129 (34.9)	114 (25.3)	1,057 (74.0)
Yes	1,142 (54.6)	847 (86.3)	213 (25.3)	239 (64.6)	332 (73.8)	363 (25.4)
Cyclophosphamide dose in tertiles, mg/m^2						
None	953 (45.6)	422 (43.0)	723 (85.8)	229 (61.9)	269 (59.8)	1,188 (83.2)
≤ 4,800	867 (41.4)	243 (24.8)	62 (7.4)	41 (11.1)	38 (8.4)	89 (6.2)
4,801-9,400	177 (8.5)	225 (22.9)	19 (2.3)	18 (4.9)	38 (8.4)	80 (5.6)
> 9,400	65 (3.1)	79 (8.0)	24 (2.9)	76 (20.5)	99 (22)	55 (3.9)
Ifosfamide dose in tertiles, mg/m^2						
None	1,933 (92.4)	891 (90.7)	802 (95.1)	247 (66.8)	241 (53.6)	1,278 (89.5)
≤ 9,467	120 (5.7)	33 (3.4)	10 (1.2)	5 (1.4)	8 (1.8)	13 (0.9)
9,468-54,000	14 (0.7)	47 (4.8)	11 (1.3)	49 (13.2)	147 (32.7)	124 (8.7)
> 54,000	1 (0.1)	1 (0.1)	3 (0.4)	67 (18.1)	49 (10.9)	4 (0.3)
Anthracyclines						
No	862 (41.2)	253 (25.8)	819 (97.2)	63 (17.0)	251 (55.8)	1,075 (75.3)
Yes	1,212 (57.9)	722 (73.5)	9 (1.1)	305 (82.4)	195 (43.3)	345 (24.2)
Doxorubicin dose in tertiles, mg/m^2						
None	1,371 (65.5)	362 (36.9)	823 (97.6)	64 (17.3)	321 (71.3)	1,208 (84.6)
≤ 270	646 (30.9)	497 (50.6)	1 (0.1)	32 (8.7)	36 (8.0)	138 (9.7)
271-443	29 (1.4)	78 (7.9)	2 (0.2)	139 (37.6)	54 (12.0)	57 (4.0)
> 443	15 (0.7)	35 (3.6)	1 (0.1)	131 (35.4)	33 (7.6)	13 (0.9)
High-dose cyclophosphamide and doxorubicin†						
No	2,043 (97.7)	908 (92.5)	826 (98.0)	283 (76.5)	372 (82.7)	1,395 (97.7)
Yes	21 (1.0)	67 (6.8)	2 (0.2)	82 (22.2)	72 (16.0)	22 (1.5)

NOTE. Percentages do not always add up to 100% because of missing data.
Abbreviation: TBI, total body irradiation.
*Treatment data included primary treatment and all recurrences; chemotherapy (yes/no), radiotherapy (yes/no), surgery (yes/no), and hematopoietic cell transplantation (yes/no) data were missing for 48, 41, 73, and 90 survivors, respectively.
†High dose was defined according to the second or third tertile of exposure (ie, a dose of > 4,800 mg/m^2 cyclophosphamide and a dose of > 270 mg/m^2 doxorubicin).