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Secondary Gastrointestinal Cancer in Childhood Cancer Survivors

A Cohort Study

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Background: Childhood cancer survivors develop gastrointestinal cancer more frequently and at a younger age than the general population, but the risk factors have not been well-characterized.

Objective: To determine the risk and associated risk factors for gastrointestinal subsequent malignant neoplasms (SMNs) in childhood cancer survivors.

Design: Retrospective cohort study.

Setting: The Childhood Cancer Survivor Study, a multicenter study of childhood cancer survivors diagnosed between 1970 and 1986.

Patients: 14 358 survivors of cancer diagnosed when they were younger than 21 years of age who survived for 5 or more years after the initial diagnosis.

Measurements: Standardized incidence ratios (SIRs) for gastrointestinal SMNs were calculated by using age-specific population data. Multivariate Cox regression models identified associations between risk factors and gastrointestinal SMN development.

Results: At median follow-up of 22.8 years (range, 5.5 to 30.2 years), 45 cases of gastrointestinal cancer were identified. The risk for gastrointestinal SMNs was 4.6-fold higher in childhood cancer survivors than in the general population (95% CI, 3.4 to 6.1). The SIR for colorectal cancer was 4.2 (CI, 2.8 to 6.3). The highest risk for gastrointestinal SMNs was associated with abdominal radiation (SIR, 11.2 [CI, 7.6 to 16.4]). However, survivors not exposed to radiation had a significantly increased risk (SIR, 2.4 [CI, 1.4 to 3.9]). In addition to abdominal radiation, high-dose procarbazine (relative risk, 3.2 [CI, 1.1 to 9.4]) and platinum drugs (relative risk, 7.6 [CI, 2.3 to 25.5]) independently increased the risk for gastrointestinal SMNs.

Limitation: This cohort has not yet attained an age at which risk for gastrointestinal cancer is greatest.

Conclusion: Childhood cancer survivors, particularly those exposed to abdominal radiation, are at increased risk for gastrointestinal SMNs. These findings suggest that surveillance of at-risk childhood cancer survivors should begin at a younger age than that recommended for the general population.

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Between 5% and 15% of childhood cancer survivors will develop a subsequent malignant neoplasm (SMN) by 20 to 30 years after the diagnosis of their first cancer (1–5). Subsequent malignant neoplasms are the second leading cause of premature death in childhood cancer survivors, after recurrence of the primary cancer (6).

Emerging evidence shows that childhood cancer survivors develop gastrointestinal cancer more frequently and at a younger age than the general population (5, 7, 8). However, most published studies have been conducted in restricted groups of patients (for example, survivors of Hodgkin lymphoma or testicular cancer) (7–9) or have included survivors of both pediatric and adult cancer (10–12). Although studies frequently identify radiation exposure as a risk factor for gastrointestinal SMNs (5, 7, 8, 10–12), none has assessed the relationship between the radiation field and the site of the SMN or the specific effect of the chemotherapy used to treat the primary cancer.

Because surveillance can detect gastrointestinal cancer, particularly colorectal cancer, and potentially reduce morbidity and mortality, the Children's Oncology Group has published guidelines for colorectal cancer surveillance in childhood cancer survivors (13, 14). These guidelines recommend that survivors exposed to more than 30 Gy of abdominal radiation undergo colonoscopy at a minimum of every 5 years beginning 10 years after radiation or at age 35 years, whichever is later.

In our study, we evaluate the risk for gastrointestinal SMNs and the clinical and pathologic factors associated with their development in a large, North American cohort of childhood cancer survivors for whom we have detailed information about the specific therapies received for the primary cancer. The findings of our analysis will facilitate the refinement of the published surveillance guidelines by allowing more precise identification of which groups of childhood cancer survivors are at greatest risk for gastrointestinal SMN.

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Context

Survivors of childhood cancer are at increased risk of developing gastrointestinal (GI) cancer later in life. However, the tumor- or treatment-specific variables during childhood associated with an increased risk for subsequent GI cancer have not been defined.

Contribution

In this large cohort, survivors of childhood cancer were at increased risk for GI cancer, which occurred as soon as 5.5 years after diagnosis of childhood cancer. The highest risks were seen after childhood Hodgkin lymphoma or Wilms tumor and after abdominal radiation and treatment with procarbazine and platinum chemotherapies.

Implication

Screening for GI cancer earlier than is currently recommended may be warranted in survivors of childhood cancer, particularly those who were treated with abdominal radiation or procarbazine and platinum chemotherapy.

—The Editors

METHODS

Description of the Childhood Cancer Survivor Study Cohort

The CCSS (Childhood Cancer Survivor Study) is a retrospectively assembled and ongoing hospital-based cohort of 14 358 childhood cancer survivors treated at 26 centers in the United States and Canada, established in 1994 (15, 16). Eligibility criteria include diagnosis of leukemia, central nervous system cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, neuroblastoma, soft tissue sarcoma, Wilms tumor, or bone cancer; diagnosis between 1 January 1970 and 31 December 1986; age younger than 21 years at diagnosis; and survival 5 years from the diagnosis date.

Each institution identified eligible participants. All eligible survivors were recruited to the cohort. The study was approved by institutional review boards at each participating institution. Informed consent was obtained from each participant or a proxy (if the participant was younger than 18 years or deceased) at the time of enrollment by the CCSS Coordinating Center.

Data were collected from eligible participants by using a baseline questionnaire administered yearly from 1994 to 1998 and 3 follow-up questionnaires (available online at http://ccss.stjude.org) administered in 2000, 2003, and 2005. Next of kin, typically a parent or spouse, was contacted for participants who had died after achieving 5-year survivorship. The questionnaires addressed social and demographic factors, medical conditions, health behaviors, cancer recurrence, SMN development, and family history of cancer.

A detailed summary of exposures to cancer treatment was obtained from the hospital charts of participants who consented to release of medical records. Data on the cumulative dose were collected for 22 specific chemotherapy agents, and qualitative (yes or no) data were collected for 20 additional agents. Exposure to anthracyclines was expressed as the cumulative dose received. Scores for alkylating agents were calculated by using methods previously described (15). Radiation records were reviewed by the CCSS Radiation Physics Center for abstraction and exposure assessment.

Identification and Confirmation of Patients With Gastrointestinal SMN

We defined a gastrointestinal SMN as any cancer listed in the Surveillance, Epidemiology, and End Results (SEER) classification of tumors of the oral cavity and pharynx (excluding the salivary glands) or digestive system by using SEER*Stat software, version 6.3.6 (National Cancer Institute [NCI], Bethesda, Maryland; available at www.seer.cancer.gov/seerstat) (17). Gastrointestinal SMN cases were ascertained through self-report or proxy report by the baseline and follow-up questionnaires and by searches of National Death Index data for U.S. participants (the most recent linkage to the National Death Index occurred in 2010 and included all deaths through 2008).

All positive responses were screened, and those representing a probable SMN were verified by the CCSS Pathology Review Center. The pathologist reviewed a copy of the report to confirm the SMN. If the pathology report could not be obtained, the patient or proxy questionnaire response, death certificate (for deceased patients), or medical records were reviewed. Only gastrointestinal SMNs occurring 5 or more years after the primary cancer diagnosis were included in the analysis. Data collected about gastrointestinal SMN cases included histology and specific locations of the tumors. All SMNs identified and verified before November 2008 are included in this analysis.

Tumor Localization and Radiation Data

Two pediatric oncologists reviewed operative notes, pathology and radiology reports, and any substantial correspondence to determine SMN location. The locations were sketched onto an anatomical diagram and reviewed to determine proximity of the SMN to the radiation field of the primary tumor. The gastrointestinal cancer was assigned to 1 of 3 proximity categories: "in the beam" if the tumor was within the radiation field, "near the beam" if the tumor was 0 to 10 cm from the radiation field edge, or "out of the beam" if the tumor was more than 10 cm from the radiation field edge. Specific radiation doses to the site of each SMN were not estimated.

Statistical Analysis

Calculation of Standardized Incidence Ratios and Absolute Excess Risks

The incidence of gastrointestinal neoplasms in the survivor cohort was compared with that of the general U.S.

population by using the SEER database, which is generated from population-based cancer registries across the United States. The SEER data were used to ascertain the incidences of gastrointestinal cancer expected in a general population cohort with the same age and sex distribution as the CCSS cohort. Standardized incidence ratios (SIRs) were calculated as the ratio of the observed numbers of cases in the various subgroups of the cohort to the expected numbers in the general population.

Poisson regression models were used to calculate SIRs, their 95% CIs, and *P* values. Absolute excess risk was calculated as the difference between the number of observed and expected events divided by the number of person-years of follow-up and is expressed per 100 000 person-years. Analyses were performed by using SAS, version 9.1 (SAS Institute, Cary, North Carolina).

Calculation of Cumulative Incidence Rates

Cumulative incidence estimates for gastrointestinal SMNs were calculated by using the algorithm described by Kalbfleisch and Prentice (18). These estimates represent the cumulative number of gastrointestinal SMNs that had occurred by each time point beyond 5 years after the childhood cancer. A proportion of participants was included in the denominator, with appropriate accounting for censoring and treating death as a competing risk, such that follow-up for a participant who died was truncated at death (18).

Risk Factor Analysis

Univariate Cox regression analysis evaluated the association between gastrointestinal SMN development and primary cancer diagnosis, age at diagnosis of primary cancer, sex, race, treatment era, radiation therapy, chemotherapy (platinum drugs, alkylating agents, epipodophyllotoxins, antimetabolites, plant alkaloids, and anthracyclines), smoking history, and family history of cancer. A multivariate Cox regression model was constructed that included significant univariate factors ($P < 0.10$), coupled with variables not statistically significant but considered important to evaluate given our a priori hypotheses or their potential as confounders.

The initial multivariate model assessed the following factors that were significant in univariate analysis: primary diagnosis; radiation to the brain, neck, abdomen, or pelvis; or exposure to alkylating agents, platinum drugs, antimetabolites, and anthracyclines (**Appendix Table**, available at www.annals.org). Sex, race, treatment era, plant alkaloids, and epipodophyllotoxins were also included in the initial model, because we had hypothesized a priori that they would affect SMN risk.

The final model included covariates that modified the effect of other factors (as confounders) and excluded covariates that did not significantly affect time to gastrointestinal SMN development when included in the joint model. Only participants for whom we had complete data on primary cancer treatment were included in the final multivariate model. We subsequently performed sensitivity analyses in which we included participants with missing treatment data (procarbazine, platinum, anthracyclines, plant alkaloids, and abdominal radiation) in the final model under the assumptions that they received all treatments, no treatment, and the treatment pattern most common for their primary cancer.

Age was used as the time scale in all Cox models to account for the strong effect that increasing age has on SMN development (19). The proportional hazards assumption was examined for the effects of several radiation and chemotherapy risk factors, and no significant changes in hazard ratios were found over time. Standard asymptotic inference methods for Cox regression on the basis of the partial probability were used to construct CIs and to carry out 2-sided tests of statistical significance.

Role of the Funding Source

The CCSS is a multi-institutional study funded by the NCI. Additional support was provided by the Intramural Research Program of the National Institutes of Health and NCI and by the American Lebanese-Syrian Associated Charities. Dr. Henderson received support from the NCI.

RESULTS

Characteristics of CCSS Cohort Participants

Figure 1 shows the persons identified and included in each stage of the CCSS cohort development. The analytic data set with complete follow-up information included 14 337 survivors. Of note, medical records were available for 12 592 participants and thus constituted the data set used for all analyses involving treatment data.

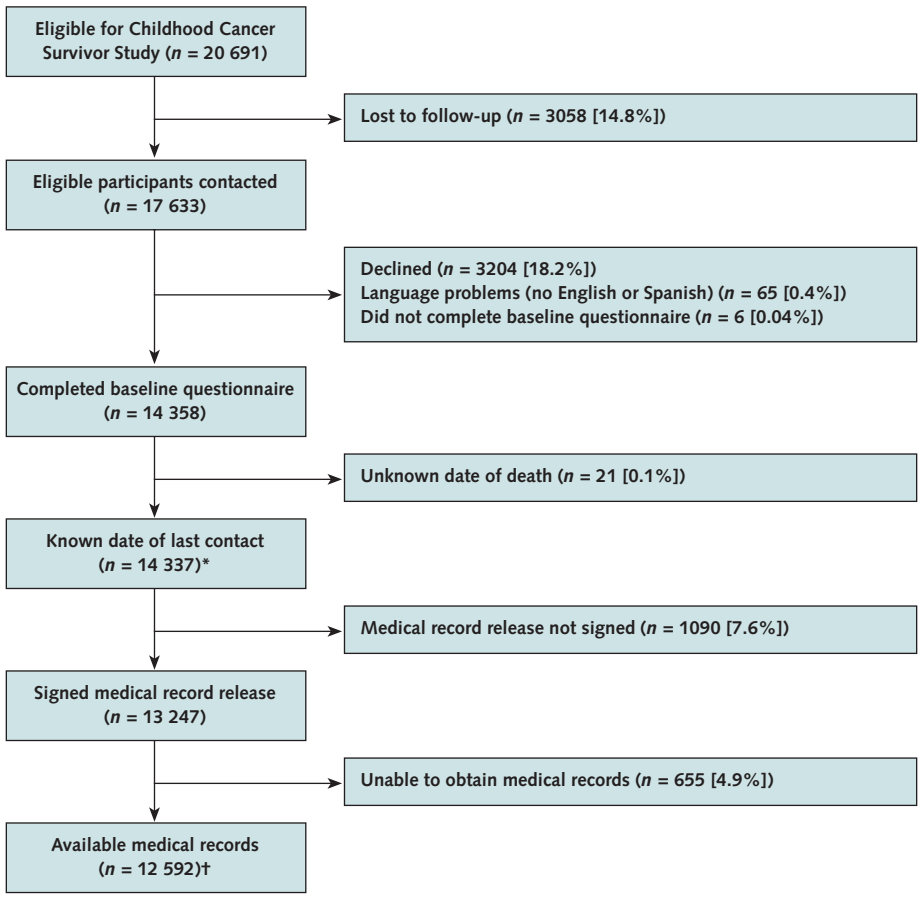
Characteristics of Survivors With Gastrointestinal SMNs

Among 14 337 childhood cancer survivors, 802 SMNs (not including nonmelanoma skin cancer) were identified in 732 persons. Of those, 45 (5.6%) gastrointestinal SMNs were identified in 45 persons at a median follow-up of 22.8 years (range, 5.5 to 30.2 years) from primary diagnosis. The median age at diagnosis of gastrointestinal SMNs was 33.5 years (range, 9.7 to 44.8 years).

As shown in **Table 1**, survivors who developed gastrointestinal SMN were similar to those who did not in terms of race, sex, family history of gastrointestinal cancer, and smoking history. The 2 populations differed statistically in their distribution among treatment eras, exposure to abdominal and pelvic radiation, primary cancer diagnosis, and vital status.

The characteristics of those who developed gastrointestinal SMN are shown in **Table 2**. Most SMNs (80%) occurred more than 24 years after the primary childhood cancer. The most frequent site was the colon, followed by the rectum or anus. Twenty-five (56%) of the 45 gastrointestinal SMNs were adenocarcinomas. Twenty-three of the

Figure 1. **Study flow diagram.**



* Data set used for calculation of overall cumulative incidence, standardized incidence ratios, and absolute excess risks.
† Data set used for all analyses involving treatment data.

45 patients (51%) were deceased, of whom 15 (65%) died of gastrointestinal SMN.

Thirty-nine (87%) childhood cancer survivors who developed gastrointestinal SMNs had confirmed radiation for their primary cancer. Eighty-two percent of these survivors developed SMNs "in" or "near" their previous radiation field, whereas 15% developed them "out" of the previous radiation field. The distribution of radiation fields relative to gastrointestinal SMN location among the 25 survivors who developed an adenocarcinoma of the gastrointestinal tract was similar to that observed among survivors with other types of gastrointestinal cancer histology (data not shown).

SIR and Absolute Excess Risk Analysis

We compared the incidence of gastrointestinal SMNs in the CCSS cohort with that of the general population by using the SEER database. As shown in **Table 3**, risk for gastrointestinal cancer was almost 5-fold higher in childhood cancer survivors than in the general population. Survivors with a history of abdominal radiation had a greater than 11-fold risk for gastrointestinal cancer.

Wilms tumor survivors had the highest risk, followed by Hodgkin lymphoma survivors. Risk for colorectal cancer was more than 4-fold higher in childhood cancer survivors than in the general population. Similar to all cases of gastrointestinal SMN, Wilms tumor survivors had the greatest risk for colorectal cancer.

Cumulative Incidence Rates

The cumulative incidence of gastrointestinal SMNs by 30 years after the primary cancer diagnosis was 0.64% (CI, 0.43% to 0.86%) (**Figure 2**). The cumulative incidence in persons who received abdominal radiation was 1.97% (CI, 1.15% to 2.80%) by 30 years (**Figure 2**). The 30-year cumulative incidence rates were highest among survivors of Hodgkin lymphoma at 2.08% (CI, 1.08% to 3.07%) and Wilms tumor at 1.20% (CI, 0.12% to 2.29%) (**Figure 2**). The cumulative incidence of colorectal SMNs by 30 years after the primary cancer diagnosis was 0.41% (CI, 0.22% to 0.59%). Abdominal radiation was associated with a cumulative incidence of colorectal SMN of 1.16% (CI, 0.47% to 1.85%) by 30 years (**Figure 2**).

Table 1. **Characteristics of the Childhood Cancer Survivor Study Cohort**

Characteristic	Cohort Members With GI SMNs (n = 45)		Cohort Members Without GI SMNs (n = 14 292)	
	Median	Range	Median	Range
Age at last follow-up, *y*	35.7	21.2–49.5	30.8	5.6–56.3
Duration of follow-up from primary diagnosis to last contact, *y*	23.9	6.8–36.0	22.9	5.0–36.0
	Number	Percentage	Number	Percentage
Sex				
Men	26	57.8	7675	53.7
Women	19	42.2	6617	46.3
Total	45	–	14 292	–
Race				
White	40	88.9	11 884	83.2
Black	2	4.4	665	4.7
Hispanic	2	4.4	749	5.2
Other	1	2.2	943	6.6
Unknown	0	0	51	0.4
Total	45	–	14 292	–
Age at primary cancer diagnosis				
<1 y	0	0	1004	7.0
1–3 y	5	11.1	3630	25.4
4–7 y	5	11.1	3226	22.6
8–10 y	5	11.1	1563	10.9
11–14 y	13	28.9	2399	16.8
15–20 y	17	37.8	2470	17.3
Total	45	–	14 292	–
Current age				
0–19 y	0	0	1491	10.4
20–29 y	11	24.4	5262	36.8
30–39 y	20	44.4	5172	36.2
>40 y	14	31.1	2367	16.6
Total	45	–	14 292	–
Primary diagnosis				
Leukemia	2	4.4	4823	33.7
CNS tumor	6	13.3	1866	13.1
Hodgkin lymphoma	20	44.4	1901	13.3
Non-Hodgkin lymphoma	2	4.4	1076	7.5
Wilms tumor	7	15.6	1248	8.7
Neuroblastoma	0	0	955	6.7
Soft tissue sarcoma	2	4.4	1243	8.7
Bone tumor	6	13.3	1180	8.3
Total	45	–	14 292	–
Treatment era				
1970–1974	15	33.3	2524	17.7
1975–1979	17	37.8	4045	28.3
1980–1986	13	28.9	7723	54.0
Total	45	–	14 292	–
Vital status				
Alive	22	48.9	12 318	86.2
Dead	23	51.1	1974	13.8
Total	45	–	14 292	–
Radiation therapy for primary cancer*				
Yes	39	88.6	8494	68.0
No	5	11.4	4002	32.0
Total	44	–	12 496	–
Abdominal radiation for primary cancer*				
Yes	26	63.4	2415	20.0
No	15	36.6	9640	80.0
Total	41	–	12 055	–
Chest radiation for primary cancer*				
Yes	22	53.7	2655	22.0
No	19	46.3	9404	78.0
Total	43	–	12 059	–
Pelvic radiation for primary cancer*				
Yes	20	48.8	2012	16.7
No	21	51.2	10 044	83.3
Total	41	–	12 056	–
Total body irradiation for primary cancer*				
Yes	0	0	264	2.2
No	41	100	11 778	97.8
Total	41	–	12 042	–
Chemotherapy for primary cancer				
Yes	37	84.1	10 084	80.6
No	7	15.9	2427	19.4
Total	44	–	12 511	–
Stem cell transplantation for primary cancer				
Yes	0	0	191	1.5
No	44	100	12 302	98.5
Total	44	–	12 493	–
Family history of cancer				
Yes	10	22.2	1760	12.3
No	35	77.8	12 525	87.7
Total	45	–	14 285	–
Family history of GI cancer				
Yes	1	2.2	200	1.4
No	44	97.8	14 085	98.6
Total	45	–	14 285	–

CNS = central nervous system; GI = gastrointestinal; SMN = subsequent malignant neoplasm.

* Of 45 survivors with GI SMNs, 1 participant had no medical record; therefore, that person's radiation status was unknown. Three participants had known radiation, but whether the radiation site included the abdomen was unknown. Of the 41 remaining participants, 26 received abdominal radiation and 15 did not. Ten out of 15 participants received radiation but not to the abdomen, and 5 out of 15 received no radiation at all.

Cox Model Risk Factor Analysis

Multivariate Cox regression analysis (**Table 4**) revealed that exposure to abdominal radiation was associated with a more than 5-fold increased risk for gastrointestinal SMNs. After abdominal radiation was controlled for, high-dose procarbazine and platinum exposure were independently associated with an increased risk for gastrointestinal SMNs. As described in the Methods section, sensitivity analyses to evaluate

Table 2. **Clinical and Pathologic Characteristics of Participants With GI SMN**

Characteristic	Median (Range), *y*
Age at primary diagnosis of childhood cancer	13.9 (1.7–19.9)
Time from primary diagnosis to GI SMN	22.8 (5.5–30.2)
Age at diagnosis of GI SMN	33.5 (9.7–44.8)
	GI SMN Cases, *n* (%)
Age at diagnosis of GI SMN	
5–14 y	1 (2.2)
15–24 y	8 (17.8)
25–34 y	17 (37.8)
>35 y	19 (42.2)
Pathologic subtype of GI SMN	
Adenocarcinoma	25 (56)
Neuroendocrine tumor	4 (9)
Leiomyosarcoma	2 (4)
Hepatocellular carcinoma	2 (4)
Linea plastica	1 (2)
Klatskin tumor	1 (2)
Islet cell carcinoma	1 (2)
Hemangiosarcoma	1 (2)
Gastrinoma	1 (2)
Goblet cell carcinoma	1 (2)
Endometrial stromal cell sarcoma	1 (2)
Carcinoma NOS	3 (7)
Neoplasm NOS	2 (4)
Site of GI SMN	
Esophagus	2 (4.4)
Stomach	6 (13.3)
Small intestine	4 (8.9)
Colon (excluding rectum)	17 (37.8)
Rectum or anus	7 (15.6)
Hepatobiliary tree or pancreas	8 (17.8)
NOS	1 (2.2)

Radiation exposure for treatment of primary cancer	GI SMN Cases, *n* (%)	Median Dose, *Gy* (Range)
GI SMN in radiation field	24 (53)	37.7 (20–55)
GI SMN near field (0–10 cm)	8 (18)	32.6 (10–44)
GI SMN out of field (>10 cm)	6 (13)	43.7 (20–55)
No history of radiation	5 (11)	–
Missing radiation data*	2 (4)	–

Cause of death of participants with GI SMN (*n* = 23)	GI SMN Cases, *n* (%)
Primary cancer	1 (4)
GI SMN	15 (65)
Other SMN	4 (17)
Cardiac toxicity	2 (4)
External causes	1 (4)

GI = gastrointestinal; NOS = not otherwise specified; SMN = subsequent malignant neoplasm.
* Missing radiation data from 1 participant with no available medical record and 1 participant with no available radiation record to determine site (radiation exposure noted in other part of medical record).

the effect of missing treatment variables (including procarbazine, platinum, anthracyclines, plant alkaloids, and abdominal radiation exposure data) were done and revealed risk estimates consistent with our final model (data not shown).

Because procarbazine was administered orally to all survivors who developed gastrointestinal SMN, we explored whether oral administration of other alkylating agents was associated with a greater risk for gastrointestinal SMNs than intravenous administration. No effect was observed (data not shown).

Discussion

To our knowledge, this is the largest study that has focused on the risk for gastrointestinal cancer in childhood cancer survivors and that considers detailed treatment information, including chemotherapy exposures and radiation fields. We observed that young survivors of childhood cancer, particularly Wilms tumor, Hodgkin lymphoma, and bone and brain tumors, are at increased risk for gastrointestinal cancer compared with the age-matched general population. Gastrointestinal SMNs presented in survivors as young as 9 years, and although all observed SMNs occurred before age 45 years, we expect the incidence to continue to increase as this population ages (17).

We observed that survivors exposed to abdominal radiation were at particularly increased risk for gastrointestinal SMNs. Furthermore, even survivors not exposed to radiation had increased risk for gastrointestinal SMNs.

Because radiation exposure is a well-established risk factor for SMN development, we anticipated that survivors treated with abdominal radiation would be at greatest risk for gastrointestinal cancer. However, 13 out of 45 of the gastrointestinal SMNs occurred outside of the radiation field or in survivors who did not receive radiation therapy as part of their primary cancer treatment. It is plausible that genetic predisposition may have contributed to these tumors, even though self-report of a family history of cancer was not associated with an increased risk for gastrointestinal SMNs.

Procarbazine and platinum drugs were independently associated with risk for gastrointestinal SMNs in the radiation field, suggesting that these 2 agents may potentiate the carcinogenic effects of radiation. This observation of an independent, dose-related risk of procarbazine with abdominal radiation supports van den Belt-Dusebout and colleagues' findings (9) of an association between procarbazine and gastric cancer in survivors of testicular and Hodgkin lymphoma who were treated with abdominal radiation. However, similar to their study, we did not find that procarbazine without abdominal radiation was associated with an increased risk for gastrointestinal SMNs. This result may have been because the number of persons treated with procarbazine without radiation was too small for analysis.

Results of another study by van den Belt-Dusebout and coworkers (20) suggest that cisplatin is associated with an increased risk for SMNs (all types) in survivors of testicular cancer treated without radiation. Whether cisplatin without abdominal radiation is associated with an increased risk for gastrointestinal SMNs cannot be ascertained in our study. It is important to note that cisplatin

Table 3. **SIRs and AERs for the Development of GI and Colorectal SMNs, According to Childhood Cancer Diagnosis and Treatment**

Childhood Cancer Characteristic	CCSS Cases With GI SMN	Observed Cases of GI and Colorectal SMN, *n*	Expected Cases of GI and Colorectal SMN, *n*	SIR (95% CI)*	AER per 100 000 Person-Years (95% CI)
Overall GI SMN					
All cases	14 337	45	9.9	**4.6 (3.4–6.1)**	14 (9–20)
Abdomen radiation	2441	26	2.3	**11.2 (7.6–16.4)**	53 (34–80)
No abdomen radiation	9655	15	6.3	**2.4 (1.4–3.9)**	5 (2–11)
Leukemia	4825	2	2.0	1.0 (0.3–3.9)	0
CNS cancer	1872	6	1.1	**5.7 (2.5–12.7)**	16 (5–40)
Hodgkin lymphoma	1921	20	2.8	**7.1 (4.6–11.0)**	49 (28–80)
Non-Hodgkin lymphoma	1078	2	1.0	2.1 (0.5–8.3)	5 (0–36)
Wilms tumor	1255	7	0.4	**19.7 (9.4–41.2)**	29 (13–62)
Neuroblastoma	955	0	<0.1	–	–
Soft tissue sarcoma	1245	2	1.1	1.9 (0.5–7.5)	4 (0–30)
Bone cancer	1186	6	1.4	**4.4 (2.0–9.8)**	22 (6–58)
Colorectal SMN					
All cases	14 337	24	5.5	**4.2 (2.8–6.3)**	7 (4–11)
Abdomen radiation	2441	12	1.3	**8.5 (4.7–15.4)**	24 (11–41)
No abdomen radiation	9655	9	3.5	**2.6 (1.3–4.9)**	3 (1–8)
Leukemia	4825	0	1.1	–	–
CNS cancer	1872	4	0.6	**6.8 (2.6–18.2)**	11 (3–32)
Hodgkin lymphoma	1921	9	1.6	**5.7 (3.0–11.0)**	21 (9–44)
Non-Hodgkin lymphoma	1078	2	0.5	3.8 (0.9–15.2)	8 (0–0.4)
Wilms tumor	1255	4	0.2	**15.5 (5.0–47.9)**	16 (3–39)
Neuroblastoma	955	0	<0.1	–	–
Soft tissue sarcoma	1245	2	0.6	3.3 (0.8–13.4)	6 (0–0.3)
Bone cancer	1186	3	0.8	**3.9 (1.3–5.4)**	11 (1–41)

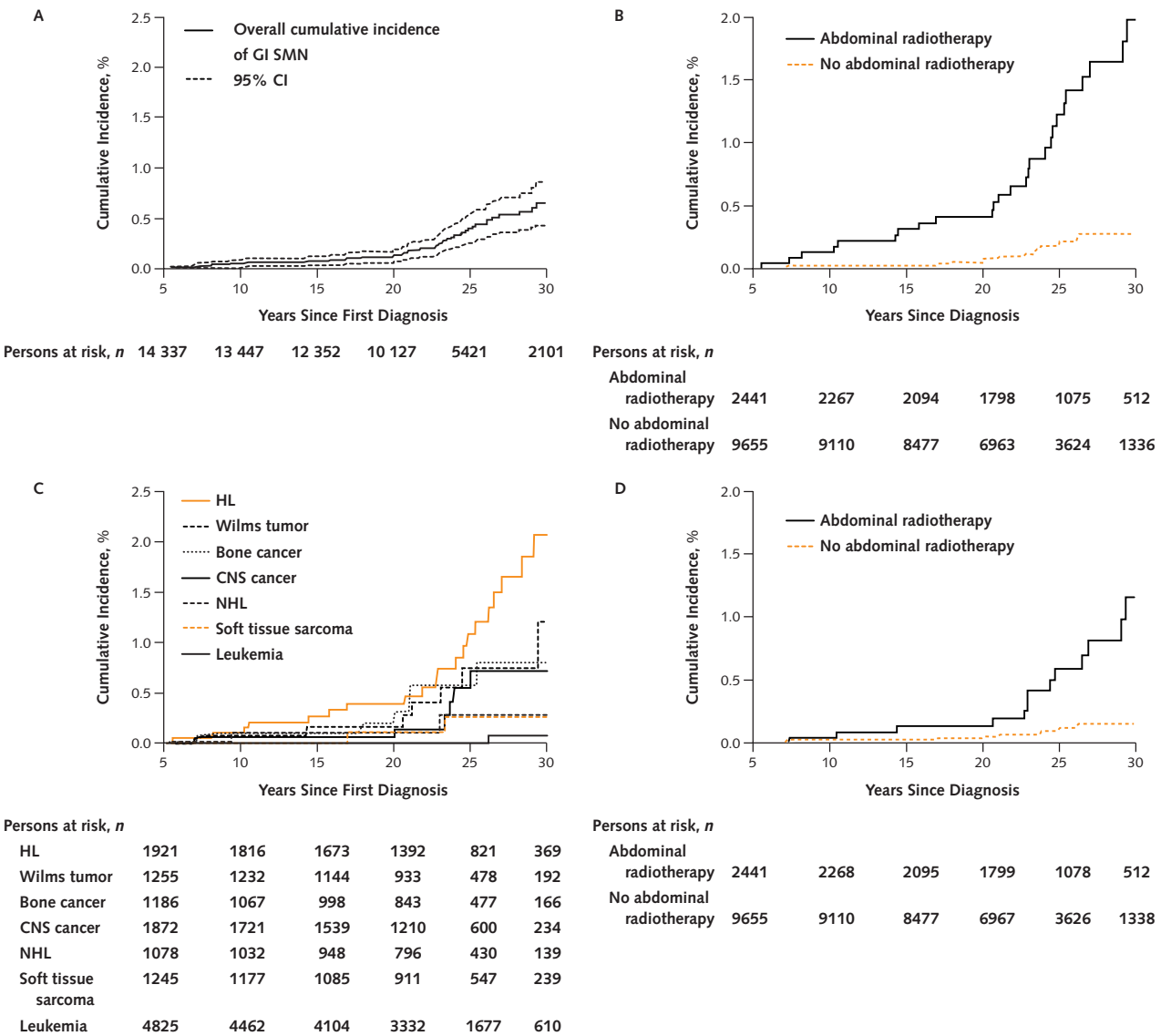
AER = absolute excess risk; CCSS = Childhood Cancer Survivor Study; CNS = central nervous system; GI = gastrointestinal; SIR = standardized incidence ratio; SMN = subsequent malignant neoplasm.
* SIRs that are statistically significantly greater than 1.0 at $P < 0.05$ are in boldface.

may simply be a proxy for an underlying germline mutation, such as *TP53*. Cisplatin is primarily used to treat osteosarcoma or central nervous system tumors, both of which are included in the classic definition of the Li–Fraumeni syndrome (21, 22). Both of the childhood cancer survivors treated with cisplatin without abdominal radiation who subsequently developed gastrointestinal SMN had osteosarcoma as their primary cancer diagnosis. Indeed, of the 11 survivors who had gastrointestinal SMN either outside of the radiation field or did not have a history of radiation, 9 had primary cancer that had been associated with a *TP53* germline mutation (osteosarcoma, 4; central nervous system tumor, 3; and leukemia 2). Recently, Ruijs and colleagues (23) reported an excess risk for colorectal and pancreatic cancer in *TP53*-positive families.

Our results were interpreted in the context of relevant findings from other published work. We briefly searched for English-language studies in MEDLINE, PubMed, OVID, and Embase from 1950 to 2011 and included the following search terms: *second primary neoplasms* and *abdominal*, *anal*, and *digestive neoplasms*. Most studies identified were in cohorts of adult survivors of Hodgkin lymphoma or testicular cancer and were not limited to childhood cancer survivors. None of these studies focused exclusively on gastrointestinal SMNs in childhood cancer survivors. The British Childhood Cancer Survivor Study, which consists of an older population of childhood cancer survivors than the CCSS, recently demonstrated that digestive SMNs contribute the largest absolute excess risk of any cancer in childhood cancer survivors older than 40 years. Digestive SMNs accounted for 18% of the excess cancer risk in older survivors in that cohort, suggesting that the incidence of gastrointestinal SMNs will continue to increase as the North American CCSS cohort ages (5).

Most published studies that found an increased risk for solid tumors in the gastrointestinal tract attributed the increased risk to the radiation therapy used to treat the primary cancer (7, 8, 10–12, 24). In the British Childhood Cancer Survivor Study, abdominopelvic radiation increased the risk for digestive SMNs by 3.3-fold, although detailed and validated radiation fields and chemotherapy exposures were not examined (5). Bhatia and colleagues (7) described SMNs among 1380 childhood Hodgkin lymphoma survivors and reported a significantly elevated excess risk for both gastric and colorectal cancer. In addition to radiation exposure in this study, younger age at primary cancer diagnosis significantly increased risk for gastrointestinal SMNs. In a British cohort of Hodgkin lymphoma survivors, Swerdlow and colleagues (10) observed only a borderline association between radiation therapy and gastrointestinal SMNs (SIR, 1.7 [CI, 1.0 to 2.5]). However, patients who received mixed-modality therapy (that is, radiation and chemotherapy) had a greater than 3-fold in-

Figure 2. **Cumulative incidence of GI and colorectal SMN.**



Persons at risk, *n*

Persons at risk, *n*	14 337	13 447	12 352	10 127	5421	2101

Persons at risk, *n*

Abdominal radiotherapy	2441	2267	2094	1798	1075	512
No abdominal radiotherapy	9655	9110	8477	6963	3624	1336

Persons at risk, *n*

HL	1921	1816	1673	1392	821	369
Wilms tumor	1255	1232	1144	933	478	192
Bone cancer	1186	1067	998	843	477	166
CNS cancer	1872	1721	1539	1210	600	234
NHL	1078	1032	948	796	430	139
Soft tissue sarcoma	1245	1177	1085	911	547	239
Leukemia	4825	4462	4104	3332	1677	610

Persons at risk, *n*

Abdominal radiotherapy	2441	2268	2095	1799	1078	512
No abdominal radiotherapy	9655	9110	8477	6967	3626	1338

CNS = central nervous system; GI = gastrointestinal; HL = Hodgkin lymphoma; NHL = non-Hodgkin lymphoma; SMN = subsequent malignant neoplasm. **A.** Overall cumulative incidence of GI SMN. **B.** Cumulative incidence of GI SMN, by abdominal radiation exposure. **C.** Cumulative incidence of GI SMN, by primary diagnosis. **D.** Cumulative incidence of colorectal SMN, by abdominal radiation exposure.

crease in risk compared with the general population (SIR, 3.3 [CI, 2.1 to 4.8]) (10).

Our study has limitations that must be considered when interpreting the results. The total number of observed gastrointestinal SMNs was small; therefore, it was not feasible to examine the effect of demographic factors, such as race and geography, on risk. Furthermore, analyses aimed at distinguishing between the effects of treatment and primary diagnoses (as representing inherent genetic propensity) were not possible given the small numbers of the outcome of interest, that is, gastrointestinal SMN.

Because SMNs are self-reported in the CCSS, underreporting is possible. Family history is also self-reported and may also be inaccurate. The analysis was limited to gastrointestinal SMNs that occurred 5 or more years after the primary cancer diagnosis; thus, our study could not identify risks for early gastrointestinal SMNs.

Because cure of the primary childhood cancer is a priority, we do not advocate for modification of the current treatment protocols used for childhood cancer to decrease the long-term risk for gastrointestinal SMNs. However, pediatric oncologists strive to reduce or eliminate late toxicity without affecting the probability of cure; therefore, the necessity of such therapies as radiation is under constant scrutiny. Our observations should enable researchers and clinicians to better identify survivors at highest

Table 4. **Final Cox Multivariate Model of Risk Factors for Development of GI SMN (n = 11 807)***

Risk Factor	Cohort Members With GI SMN, *n*		Hazard Ratio (95% CI)	*P* Value
	Yes	No		
Abdominal radiation				
No (referent)	13	9500	1.00	
Yes	23	2271	**5.38 (2.58–11.20)**	**<0.001**
Procarbazine dose†				
0 (referent)	25	10 875	1.00	
1	2	292	1.02 (0.22–4.80)	0.98
2	4	305	2.08 (0.64–6.78)	0.23
3	5	299	**3.15 (1.06–9.38)**	**0.040**
Platinum				
No (referent)	32	11 056	1.00	
Yes	4	715	**7.57 (2.25–25.51)**	**<0.001**
Anthracyclines				
No (referent)	27	6938	1.00	
Yes	9	4833	0.66 (0.27–1.63)	0.37
Plant alkaloids				
No (referent)	13	3158	1.00	
Yes	23	8613	0.84 (0.37–1.92)	0.68

GI = gastrointestinal; SMN = subsequent malignant neoplasm.
* Risk factors that were statistically significant at $P < 0.05$ are in boldface.
† Procarbazine cumulative dose categories are defined as follows: dose 0 = 0 mg/m^2; dose 1 = >0, ≤4200 mg/m^2; dose 2 = >4200, ≤7036 mg/m^2; dose 3 = >7036 mg/m^2.

risk for gastrointestinal SMNs, potentially facilitating the implementation of better surveillance in clinical practice.

Colorectal cancer is known to have improved outcomes with early detection in both the general and high-risk populations (25–28). As such, the Children's Oncology Group currently recommends that survivors exposed to more than 30 Gy of abdominal radiation have colonoscopy at a minimum of every 5 years, beginning 10 years after radiation or at age 35 years, whichever is later. If the findings of this study are confirmed, physicians should also consider chemotherapy exposures when determining the indications for early colorectal cancer surveillance in childhood cancer survivors.

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Appendix Table. **Initial Cox Multivariate Model of Risk Factors for Development of GI SMN**

Risk Factor	Hazard Ratio (95% CI)	*P* Value
Female sex	0.71 (0.38–1.33)	0.29
Nonwhite race	0.78 (0.28–2.21)	0.65
Hodgkin lymphoma	3.20 (0.72–14.29)	0.127
Wilms tumor	8.85 (2.00–39.20)	<0.01
Bone cancer	3.05 (0.74–12.60)	0.123
Treatment era		
1970–1974	0.79 (0.32–1.92)	0.60
1975–1979	0.96 (0.43–2.15)	0.92
Radiation area		
Neck	0.63 (0.14–2.82)	0.54
Chest	0.93 (0.30–2.89)	0.90
Abdomen	3.17 (1.08–9.32)	0.036
Spine	2.94 (0.53–16.19)	0.22
Pelvis	1.76 (0.78–3.95)	0.174
Alkylating agents	5.05 (1.86-13.71)	<0.02
Platinum drugs	4.60 (1.21–17.48)	0.025
Antimetabolites	0.51 (0.18–1.42)	0.20
Anthracyclines	0.58 (0.24–1.41)	0.23
Plant alkaloids	0.45 (0.18–1.13)	0.089
Epipodophyllotoxins	0.00 (0.00)	0.98

GI = gastrointestinal; SMN = subsequent malignant neoplasm.