

SPECIAL ARTICLE

Chronic Health Conditions in Adult Survivors of Childhood Cancer

Kevin C. Oeffinger, M.D., Ann C. Mertens, Ph.D., Charles A. Sklar, M.D., Toana Kawashima, M.S., Melissa M. Hudson, M.D., Anna T. Meadows, M.D., Debra L. Friedman, M.D., Neyssa Marina, M.D., Wendy Hobbie, C.P.N.P., Nina S. Kadan-Lottick, M.D., Cindy L. Schwartz, M.D., Wendy Leisenring, Sc.D., and Leslie L. Robison, Ph.D., for the Childhood Cancer Survivor Study*

ABSTRACT

BACKGROUND

From Memorial Sloan-Kettering Cancer Center, New York (K.C.O., C.A.S.); the University of Minnesota, Minneapolis (A.C.M.); the Fred Hutchinson Cancer Research Center, Seattle (T.K., D.L.F., W.L.); St. Jude Children's Research Hospital, Memphis, TN (M.M.H., L.L.R.); Children's Hospital of Philadelphia, Philadelphia (A.T.M., W.H.); Stanford University Medical Center, Palo Alto, CA (N.M.); Yale University School of Medicine, New Haven, CT (N.S.K.-L.); and Brown Medical School, Providence, RI (C.L.S.). Address reprint requests to Dr. Oeffinger at the Department of Pediatrics, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021, or at oeffingk@mskcc.org.

Only a few small studies have assessed the long-term morbidity that follows the treatment of childhood cancer. We determined the incidence and severity of chronic health conditions in adult survivors.

METHODS

The Childhood Cancer Survivor Study is a retrospective cohort study that tracks the health status of adults who received a diagnosis of childhood cancer between 1970 and 1986 and compares the results with those of siblings. We calculated the frequencies of chronic conditions in 10,397 survivors and 3034 siblings. A severity score (grades 1 through 4, ranging from mild to life-threatening or disabling) was assigned to each condition. Cox proportional-hazards models were used to estimate hazard ratios, reported as relative risks and 95% confidence intervals (CIs), for a chronic condition.

RESULTS

Survivors and siblings had mean ages of 26.6 years (range, 18.0 to 48.0) and 29.2 years (range, 18.0 to 56.0), respectively, at the time of the study. Among 10,397 survivors, 62.3% had at least one chronic condition; 27.5% had a severe or life-threatening condition (grade 3 or 4). The adjusted relative risk of a chronic condition in a survivor, as compared with siblings, was 3.3 (95% CI, 3.0 to 3.5); for a severe or life-threatening condition, the risk was 8.2 (95% CI, 6.9 to 9.7). Among survivors, the cumulative incidence of a chronic health condition reached 73.4% (95% CI, 69.0 to 77.9) 30 years after the cancer diagnosis, with a cumulative incidence of 42.4% (95% CI, 33.7 to 51.2) for severe, disabling, or life-threatening conditions or death due to a chronic condition.

CONCLUSIONS

Survivors of childhood cancer have a high rate of illness owing to chronic health conditions.

*Members of the Childhood Cancer Survivor Study are listed in the Appendix.

N Engl J Med 2006;355:1572-82.
Copyright © 2006 Massachusetts Medical Society.

AS A RESULT OF ADVANCES IN TREATMENT, almost 80% of children and adolescents who receive a diagnosis of cancer become long-term survivors.¹ In the United States, there are approximately 270,000 survivors of pediatric cancer, or about 1 of every 640 adults between the ages of 20 and 39 years.² The large number of survivors has prompted studies of the long-term health consequences of treatments for childhood cancer.²⁻⁴ It is now clear that damage to the organ systems of children caused by chemotherapy and radiation therapy may not become clinically evident for many years.

To understand fully the health risks incurred by treatment of childhood cancer, it is important to measure three types of long-term outcomes: health status, mortality, and morbidity. Of these, the first two have been fairly well characterized.^{5,6} In a retrospective analysis of 20,227 5-year survivors of cancer, Mertens et al.⁵ found statistically significant excess rates of death from subsequent cancers (standardized mortality ratio [SMR], 19.4), from cardiac causes (SMR, 8.2), and from pulmonary causes (SMR, 9.2). In a study of 9535 adults who had survived childhood cancer, 44% reported having at least one domain of health status (general health, mental health, functional status, limitations in activity, cancer-related pain, and cancer-related fear or anxiety) that was moderately or severely affected.⁶

However, only a few small studies have assessed the long-term morbidity that follows the treatment of childhood cancer. Four studies, with a combined sample of 1330 survivors, reported an estimate of the prevalence of "late effects," or chronic conditions that were possibly associated with cancer therapy.⁷⁻¹⁰ The small sample limited the ability of these studies to assess the risk of chronic conditions associated with a particular treatment. Moreover, there were no comparison groups to provide perspective, and the outcomes were reported for survivors who were relatively young and still involved in follow-up care. The Institute of Medicine report *Childhood Cancer Survivorship: Improving Care and Quality of Life* highlights the need for further research to characterize the health of long-term survivors of childhood cancer and to determine the prevalence and incidence of adverse health outcomes and chronic conditions after cancer therapy.²

The purpose of this study was to investigate the large and geographically diverse cohort that is

followed in the Childhood Cancer Survivor Study (CCSS), with the goal of determining the prevalence, incidence, and severity of chronic health conditions in adult survivors of childhood cancer, and to determine the risk of chronic conditions in the survivors, as compared with their siblings. In addition, we sought to identify subpopulations of survivors at highest risk for severe, debilitating, or life-threatening chronic health conditions. In short, we sought to provide an estimate of the overall physical morbidity secondary to the type of cancer and cancer therapy.

METHODS

SUBJECTS

CCSS is a multi-institutional, retrospectively ascertained cohort of adults who have survived for at least 5 years after treatment for childhood cancer. Our study was restricted to participants who met the following criteria: a diagnosis of leukemia, central nervous system (CNS) tumor, Hodgkin's disease, non-Hodgkin's lymphoma, Wilms' (kidney) tumor, neuroblastoma, soft-tissue sarcoma, or bone tumor; a diagnosis and initial treatment at one of 26 collaborating CCSS institutions; a date of diagnosis between January 1, 1970, and December 31, 1986; an age of less than 21 years at diagnosis; and survival for at least 5 years after the date of diagnosis. The institutional review board at each participating center reviewed and approved the CCSS protocol and documents sent to participants. All study participants provided written informed consent for participation in the study and for the release of medical-record information. A detailed description of the study design and characteristics of the cohort was reported previously.¹¹ The questionnaire that was administered to all participants at baseline and the treatment abstraction form are available at www.cancer.umn.edu/research/ltfu/ccssquestionnaires.html and in Section A of the Supplementary Appendix, available with the full text of this article at www.nejm.org.

Of the 20,720 survivors of childhood cancer in the cohort, 3017 (14.6%) were lost to follow-up after extensive efforts failed to locate them. Among the remaining 17,703 subjects, 14,372 (81.2%), including 10,397 who were 18 years of age or older at the time they were interviewed, completed the baseline questionnaire. To determine the potential for introducing bias into the

Table 1. Demographic Characteristics of Adult Survivors of Childhood Cancer and Siblings.*

Characteristic	Survivors (N=10,397)	Siblings (N=3034)	P Value
Sex — no. (%)			<0.001
Female	4804 (46.2)	1605 (52.9)	
Male	5593 (53.8)	1429 (47.1)	
Race or ethnic group — no. (%)†			<0.001
Non-Hispanic white	8708 (84.0)	2692 (91.9)	
Other group	1654 (16.0)	238 (8.1)	
Education — no. (%)			<0.001
Did not complete high school	1099 (11.2)	189 (6.5)	
High-school graduate with no further education	2257 (23.0)	535 (18.4)	
High-school graduate plus some college or training	6477 (65.9)	2182 (75.1)	
Household income — no. (%)			<0.001
<\$20,000/yr	2063 (22.9)	353 (12.8)	
≥\$20,000/yr	6934 (77.1)	2397 (87.2)	
Health insurance — no. (%)			<0.001
No	1486 (15.5)	328 (10.9)	
Yes or Canadian resident	8118 (84.5)	2673 (89.1)	
Cancer diagnosis — no. (%)			
Leukemia	3061 (29.5)	NA	
Central nervous system tumor	1322 (12.7)	NA	
Hodgkin's disease	1876 (18.0)	NA	
Non-Hodgkin's lymphoma	928 (8.9)	NA	
Wilms' tumor	670 (6.5)	NA	
Neuroblastoma	416 (4.0)	NA	
Sarcoma	991 (9.5)	NA	
Bone tumor	1133 (10.9)	NA	

studied cohort, we previously compared demographic and cancer-related characteristics among participants, nonparticipants, and those who were lost to follow-up. We found that these three groups were similar with regard to sex, the type of cancer, the age at diagnosis, the age at which they were asked to participate in the study (or for those lost to follow-up, the age at which the cohort was assembled), and the type of cancer treatment.^{11,12}

To allow for comparisons with a population that had not been treated for cancer, we asked a random sample of participating survivors to identify a nearest-age living sibling. Of 4782 eligible siblings, 3846 (80.4%) participated; of these, 3034 were 18 years of age or older.

CANCER TREATMENT INFORMATION

We obtained information on the original cancer diagnosis from the treating institution. For the

12,752 participants who returned a signed medical release, the information on cancer therapy included their initial treatment, treatment for any relapse, and preparatory regimens for bone marrow transplantation (if applicable). Data regarding exposure to 42 chemotherapeutic agents (either yes or no) were abstracted from the medical record; cumulative doses were abstracted for 22 of these agents. Data were also obtained on surgical procedures performed for cancer treatment at any time from the date of diagnosis onward, as well as on the site of the tumor and on fields and doses of radiation therapy. (See Sections B through D in the Supplementary Appendix for details concerning these treatments.)

HEALTH CONDITION OUTCOMES

At enrollment, survivors and siblings completed a 289-item questionnaire that included questions regarding their physical health conditions, in-

Table 1. (Continued.)

Characteristic	Survivors (N = 10,397)	Siblings (N = 3034)	P Value
Cancer treatment — no. (%)			
No chemotherapy or radiation therapy	626 (6.0)	NA	
Chemotherapy			
Any chemotherapy	7012 (67.4)	NA	
Alkylating agent	3982 (38.3)	NA	
Anthracycline	3161 (30.4)	NA	
Other chemotherapy	3418 (32.9)	NA	
Radiation therapy			
Any radiation therapy	6469 (62.2)	NA	
Brain irradiation	2852 (27.4)	NA	
Chest irradiation	2266 (21.8)	NA	
Abdominal or pelvic irradiation	2259 (21.7)	NA	
Missing or unknown treatment	1518 (14.6)	NA	
Age at interview — yr			
Mean	26.6±6.1	29.2±7.3	<0.001
Range	18.0–48.0	18.0–56.0	
Interval between cancer diagnosis and study — yr			
Mean	17.5±4.6	NA	
Range	6.0–31.0	NA	

* Plus–minus values are means ±SD. All survivors were at least 18 years of age. Percentages are based on the total number of participants who provided data for each variable, rather than on the total number of subjects in each cohort; percentages may not total 100 because of rounding. NA denotes not applicable.

† Race or ethnic group was reported by the participant.

cluding their age at the onset of the condition. All second cancers that were ascertained from a participant or a physician's report were verified by a review of pathology reports performed by Dr. S. Hammond at the CCSS Pathology Center in Columbus, OH.

To determine the severity of the conditions, scoring was based on the Common Terminology Criteria for Adverse Events (version 3), a scoring system developed through the National Cancer Institute by a multidisciplinary group and intended for use in scoring both acute and chronic conditions in patients with cancer and survivors of all ages.¹³ The system grades conditions as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening or disabling (grade 4), or fatal (grade 5). For our study, a total of 137 health conditions were scored. As specified in the scoring system, when a particular condition was not listed, it was entered in the "Other, specify" category according to the organ system affected. If there was not enough information to distinguish between grades, the lower score was selected. Ad-

verse psychosocial outcomes, including depression and anxiety disorder, were not included in this analysis. Before data analysis, all the authors agreed on all scores.

The same scoring system was used to grade the conditions of siblings. However, because the design of the study included only living siblings at the time of study entry, there were no siblings with a grade 5 (fatal) condition.

STATISTICAL ANALYSIS

We determined the prevalence of chronic conditions among survivors and siblings. Three primary outcomes were assessed: any condition (grades 1 through 4), severe or life-threatening conditions (grade 3 or 4), and multiple conditions (≥2). For participants who had more than one condition, the maximum grade was used. For deceased survivors, the maximum grade of a condition reported before death was used for comparisons with siblings. For example, if a survivor died of a myocardial infarction, the grade for myocardial infarction (grade 4) was used rather than the

grade for a fatal condition (grade 5). Hazard ratios were estimated with the use of Cox regression and are reported as relative risks with 95% confidence intervals (CIs). Comparisons between survivors and siblings were adjusted for the age at enrollment, sex, and race or ethnic group. The analysis accounted for within-family correlations with the use of sandwich standard-error estimates.¹⁴ The risk associated with treatment with radiation and chemotherapy agents was analyzed with the use of specific classes of chemotherapeutic agents and according to specific anatomical sites of radiation therapy.

Cumulative incidence rates for each of the primary outcomes were calculated for the survivors, with death treated as a competing risk according to the method described by Gooley et al.¹⁵ Cumulative incidence rates for siblings were not calculated because the design of the study included only living siblings at the time of study entry.

The starting point for both survivors and sib-

lings was 5 years after the date of diagnosis of cancer. If the date of onset of an irreversible condition, such as blindness, occurred within the first 5 years after the date of diagnosis, the condition was considered to be present 5 years after diagnosis; for the purposes of analysis, the onset date was shifted forward to that time point. Data were analyzed with SAS software, version 9.0 (SAS Institute).

RESULTS

COMPARISONS OF SURVIVORS WITH SIBLINGS

Table 1 shows the characteristics of the survivor and sibling cohorts. The mean age of the survivors was 26.6 years (range, 18.0 to 48.0), and the mean interval from the date of diagnosis of cancer to the date of completion of the questionnaire was 17.5 years (range, 6.0 to 31.0). Of the survivors, 46.2% were women and 16.0% were members of minority groups. The mean age of the siblings was 29.2 years (range, 18.0 to 56.0); 52.9% were women, and 8.1% were members of minority groups (Table 1 lists relevant P values).

Among the survivors, 62.3% reported having at least one chronic health condition, with 27.5% reporting a grade 3 (severe) or grade 4 (life-threatening or disabling) condition (Table 2, and Section E of the Supplementary Appendix, which lists the 137 conditions reported in the health questionnaire). Among survivors, 37.6% reported having at least two conditions listed in Supplementary Appendix E, and 23.8% reported having three or more conditions. In contrast, among siblings, 36.8% reported having a chronic health condition, of which 5.2% reported having a condition of grade 3 or 4; 13.1% reported having at least two conditions, and 5.4% reported having three or more conditions. The relative risks of 10 selected conditions of grade 3 or 4 for survivors as compared with siblings are provided in Table 3.

After adjustment for the age at completion of the questionnaire or death, sex, and race or ethnic group, survivors were 3.3 times as likely as their siblings to have a chronic health condition of any grade (95% CI, 3.0 to 3.5) (Table 4). The relative risk of a survivor having any condition of grade 3 or 4, as compared with siblings, was 8.2 (95% CI, 6.9 to 9.7). Survivors were 4.9 times as likely to have two or more chronic health conditions (95% CI, 4.4 to 5.5). Groups at highest risk for having a condition of grade 3 or 4 were survivors of bone

Table 2. Cancer Survivors and Siblings with a Chronic Health Condition, According to the Severity Score.*

Health Condition	Survivors (N = 10,397)	Siblings (N = 3034)
	no. (%)	
No condition	3887 (37.4)	1917 (63.2)
Grade 1 (mild)	1931 (18.6)	610 (20.1)
Grade 2 (moderate)	1635 (15.7)	349 (11.5)
Grade 3 (severe)	2128 (20.5)	128 (4.2)
Grade 4 (life-threatening or disabling)	653 (6.3)	30 (1.0)
Grade 5 (fatal)	163 (1.6)	NA†
Any condition‡		
Grades 1–4	6482 (62.3)	1117 (36.8)
Grade 3 or 4	2858 (27.5)	158 (5.2)
Multiple health conditions		
≥2	3905 (37.6)	397 (13.1)
≥3	2470 (23.8)	163 (5.4)

* The severity of health conditions was scored according to the Common Terminology Criteria for Adverse Events (version 3). Health conditions of survivors did not include conditions the patients had before their cancer diagnosis or acute conditions they had within 5 years after the diagnosis. NA denotes not applicable.

† All siblings were alive at the time of enrollment. Survivors may have died in the interval between 5 years after their cancer diagnosis and the time of the study. The composite percentage for survivors with grade 3 or 4 conditions includes conditions that were reported before the time of death in the 163 survivors who died.

‡ The number of patients in each subgroup may not reflect the sum of the grades of conditions, since grades 1 through 5 were calculated by taking the maximum grade per subject. A subject with grade 5 may have had other lower grades.

tumors (relative risk, 38.9; 95% CI, 31.2 to 48.5), CNS tumors (relative risk, 12.6; 95% CI, 10.3 to 15.5), and Hodgkin's disease (relative risk, 10.2; 95% CI, 8.3 to 12.5). All cancer groups were significantly more likely to have any condition, a condition of grade 3 or 4, and two or more conditions, as compared with siblings ($P < 0.001$ for all comparisons).

The relative risks associated with various combinations of therapy for survivors, as compared with siblings, are listed in Table 4. (Sections B, C, and D of the Supplementary Appendix list the types of chemotherapy, surgery, and radiotherapy received by the survivors.) Exposure to one of five specific combinations was associated with a risk of having a condition of grade 3 or 4 that was at least 10 times the expected risk: chest radiation plus bleomycin (relative risk, 13.6; 95% CI, 9.8 to 18.7), chest radiation plus an anthracycline (relative risk, 13.0; 95% CI, 10.4 to 16.3), chest radiation plus abdominal or pelvic irradiation (relative risk, 10.9; 95% CI, 8.9 to 13.2), an anthracycline plus an alkylating agent (relative risk, 10.9; 95% CI, 9.0 to 13.1), and abdominal or pelvic irradiation plus an alkylating agent (relative risk, 10.0; 95% CI, 8.2 to 12.1). An increase in the cumulative dose of an alkylating agent was associated with an increased risk of any condition or multiple conditions. In a similar way, an increase in the cumulative dose of an alkylating

agent in combination with any type of irradiation was associated with an increased relative risk. In contrast, an increase in the cumulative dose of an anthracycline was not associated with an increased risk of any condition (grades 1 through 4) that we listed.

COMPARISONS AMONG SURVIVORS

The sex and age of the survivor at the time of the diagnosis of cancer modified the risk of having a condition of grade 3, 4, or 5. As compared with male survivors and with adjustment for the type of cancer, age at the time of the study, and race or ethnic group, female survivors were 1.5 times as likely to have any condition of grade 3 or higher (95% CI, 1.3 to 1.6). Female survivors were also more likely than male survivors to have any condition (grades 1 through 5; relative risk, 1.4; 95% CI, 1.3 to 1.5) and to have multiple conditions (relative risk, 1.5; 95% CI, 1.4 to 1.7). The age of the survivor at diagnosis also independently modified the risk when the analysis was adjusted for age at the time of the study, sex, and race or ethnic group. For each cancer group, survivors who received the diagnosis at an older age were significantly more likely to report any condition, conditions of grades 3 through 5, or multiple conditions ($P < 0.001$). The race or ethnic group of the survivor did not affect the likelihood of having a condition of grade 3 or higher. However, black non-Hispanic survivors

Table 3. Relative Risk of Selected Severe (Grade 3) or Life-Threatening or Disabling (Grade 4) Health Conditions among Cancer Survivors, as Compared with Siblings.

Condition	Survivors (N = 10,397)	Siblings (N = 3034)	Relative Risk (95% CI)
	percent		
Major joint replacement*	1.61	0.03	54.0 (7.6–386.3)
Congestive heart failure	1.24	0.10	15.1 (4.8–47.9)
Second malignant neoplasm†	2.38	0.33	14.8 (7.2–30.4)
Cognitive dysfunction, severe	0.65	0.10	10.5 (2.6–43.0)
Coronary artery disease	1.11	0.20	10.4 (4.1–25.9)
Cerebrovascular accident	1.56	0.20	9.3 (4.1–21.2)
Renal failure or dialysis	0.52	0.07	8.9 (2.2–36.6)
Hearing loss not corrected by aid	1.96	0.36	6.3 (3.3–11.8)
Legally blind or loss of an eye	2.92	0.69	5.8 (3.5–9.5)
Ovarian failure‡	2.79	0.99	3.5 (2.7–5.2)

* For survivors, major joint replacement was not included if it was part of cancer therapy.

† For both groups, this category excludes basal-cell and squamous-cell carcinoma (grade 2). For siblings, this category includes a first cancer.

‡ Values are for women only.

Table 4. Relative Risk of a Chronic Health Condition among Cancer Survivors, According to the Type of Tumor and Treatment, as Compared with Siblings.*

Cancer Diagnosis or Treatment Exposure	Relative Risk (95% Confidence Interval)		
	Grade 1–4	Grade 3 or 4	≥2 Conditions
Siblings	1.0	1.0	1.0
All cancer groups	3.3 (3.0–3.5)	8.2 (6.9–9.7)	4.9 (4.4–5.5)
Bone tumor	10.3 (8.9–12.0)	38.9 (31.2–48.5)	10.7 (8.9–12.8)
Central nervous system tumor	7.1 (6.3–8.2)	12.6 (10.3–15.5)	12.4 (10.5–14.6)
Hodgkin's disease	4.6 (4.2–5.1)	10.2 (8.3–12.5)	8.7 (7.4–10.2)
Sarcoma	3.5 (3.1–4.0)	8.9 (7.2–11.0)	5.2 (4.4–6.2)
Non-Hodgkin's lymphoma	3.2 (2.8–3.6)	6.8 (5.3–8.6)	4.3 (3.6–5.2)
Neuroblastoma	2.0 (1.7–2.4)	4.7 (3.5–6.4)	2.5 (2.0–3.2)
Leukemia	2.2 (2.0–2.4)	4.1 (3.4–5.1)	2.8 (2.5–3.3)
Wilms' tumor	1.9 (1.7–2.2)	4.1 (3.2–5.4)	2.5 (2.0–3.1)
No chemotherapy or radiation	1.5 (1.3–1.7)	1.2 (1.0–1.5)	1.3 (1.1–1.5)
Chemotherapy			
Any chemotherapy	3.2 (2.9–3.4)	8.1 (6.8–9.6)	4.5 (4.0–5.0)
Alkylating agent	3.8 (3.5–4.2)	9.9 (8.3–11.8)	5.6 (5.0–6.4)
Anthracycline	4.3 (3.9–4.7)	11.0 (9.2–13.1)	5.8 (5.0–6.6)
Radiation therapy			
Any irradiation	3.4 (3.1–3.6)	7.9 (6.6–9.4)	5.2 (4.6–5.9)
Brain irradiation	3.1 (2.8–3.3)	7.0 (5.8–8.5)	4.8 (4.2–5.5)
Chest irradiation	4.7 (4.3–5.2)	10.6 (8.8–12.7)	8.2 (7.1–9.4)
Abdominal irradiation	3.7 (3.3–4.0)	8.8 (7.3–10.6)	5.8 (5.1–6.7)
Pelvic irradiation	4.2 (3.8–4.7)	10.5 (8.6–12.7)	6.8 (5.9–7.9)
Surgery			
Splnectomy	4.7 (4.2–5.2)	10.2 (8.3–12.5)	8.5 (7.2–10.0)
Nephrectomy	2.1 (1.8–2.4)	4.7 (3.5–6.2)	2.7 (2.2–3.4)
Specific combinations			
Chest radiation plus bleomycin	7.8 (6.2–9.8)	13.6 (9.8–18.7)	13.3 (10.1–17.6)
Chest radiation plus anthracycline	6.0 (5.2–6.9)	13.0 (10.4–16.3)	9.7 (8.1–11.8)
Chest radiation plus abdominal or pelvic irradiation	4.7 (4.2–5.2)	10.9 (8.9–13.2)	8.5 (7.3–9.9)
Anthracycline plus an alkylating agent	4.3 (3.9–4.8)	10.9 (9.0–13.1)	6.0 (5.2–6.9)
Abdominal or pelvic irradiation plus an alkylating agent	4.0 (3.6–4.4)	10.0 (8.2–12.1)	6.2 (5.4–7.2)

* Each row represents an individual multivariate regression model, adjusted for the age at the time of the study, sex, and race or ethnic group.

were less likely than white non-Hispanic survivors to have any condition (grades 1 through 5; relative risk, 0.8; 95% CI, 0.6 to 0.9) or multiple conditions (relative risk, 0.7; 95% CI, 0.5 to 0.8) (data not shown).

Figure 1 shows the cumulative incidence of

chronic health conditions reported by survivors during the interval from the time of the diagnosis to the time of the study. The cumulative incidence of a chronic health condition was 66.8% 25 years after the diagnosis, with an estimated incidence of 73.4% (95% CI, 69.0 to 77.9) at 30

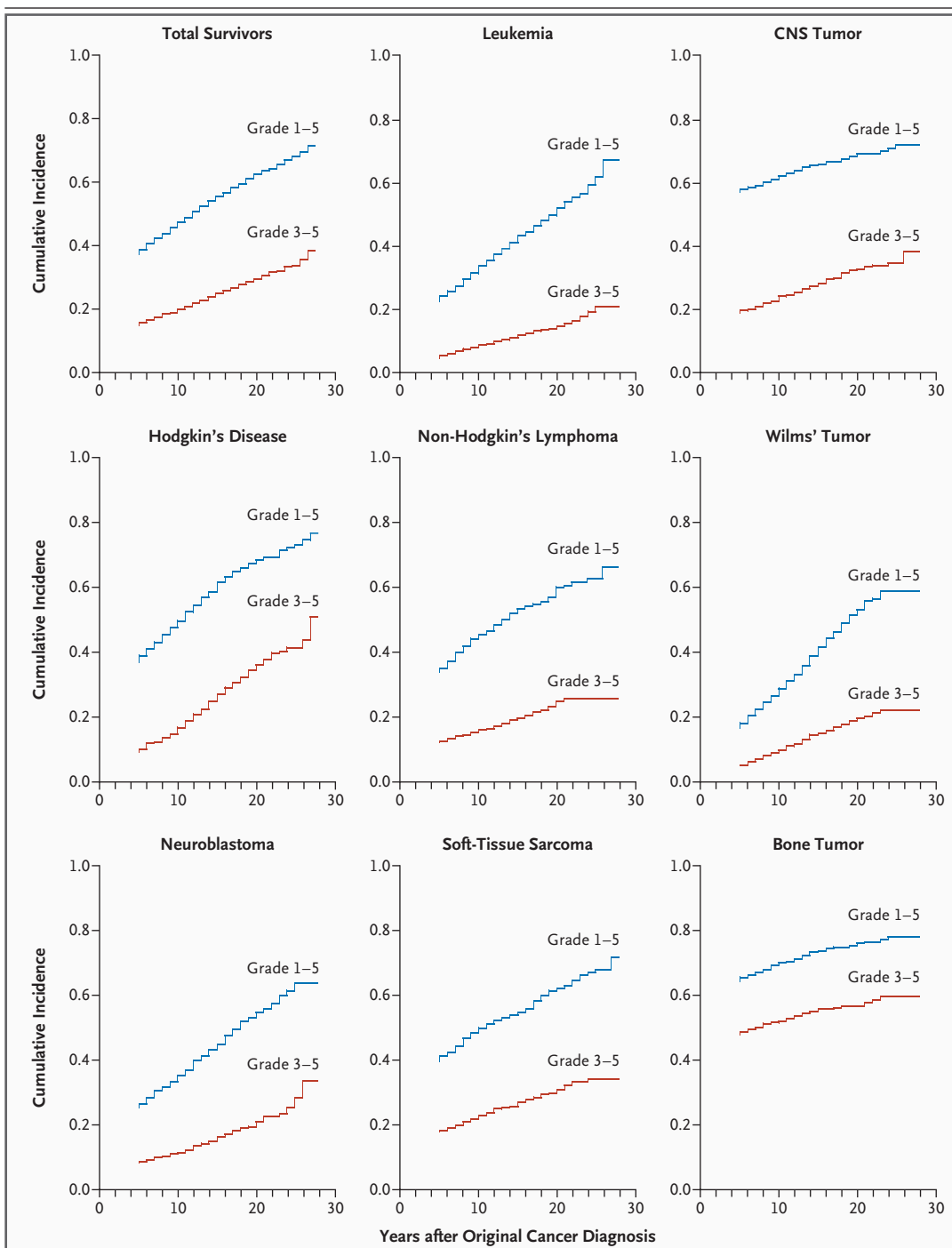


Figure 1. Cumulative Incidence of Chronic Health Conditions among 10,397 Adult Survivors of Pediatric Cancer, According to the Original Diagnosis and the Severity of the Later Condition.

Among the survivors of various types of childhood cancer, the severity of subsequent health conditions was scored according to the Common Terminology Criteria for Adverse Events (version 3) as either mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening or disabling (grade 4), or fatal (grade 5). For the total survivor cohort, the curves showing the cumulative incidence of the two outcomes by grade are truncated at 28 years, even though the text provides data up to 30 years after the original cancer diagnosis. This was done for consistency with the panels showing data for groups of patients with certain types of cancer, in which smaller samples yielded data that were not as robust at 30 years as they were at 28 years.

years. For conditions of grades 3 through 5 (severe, disabling, life-threatening, or fatal), the cumulative incidence 25 years after the diagnosis was 33.1%, with an estimated incidence of 42.4% (95% CI, 33.7 to 51.2) at 30 years. The cumulative incidence of multiple conditions (≥ 2) was 38.5% 25 years after diagnosis, with an estimated incidence of 39.2% (95% CI, 37.7 to 40.8) at 30 years.

DISCUSSION

Long-term survivors of pediatric cancer are more likely to have diminished health status and to die prematurely than are adults who never had childhood cancer, but only a few small studies have assessed the frequency and severity of chronic conditions in this population. In addition to small samples and selection bias, previous studies have been limited by their focus on the prevalence of health conditions that developed during a relatively short interval after the cancer diagnosis, thus limiting the assessment of whether the risk changes with time.⁷⁻¹⁰ Our study of more than 10,000 adult survivors of childhood cancer who were treated in the 1970s and 1980s shows that the risk of chronic health conditions is high, particularly for second cancers, cardiovascular disease, renal dysfunction, severe musculoskeletal problems, and endocrinopathies. Moreover, the incidence of chronic conditions, including these five groups of serious outcomes, increases over time and does not appear to plateau.

These findings underscore the necessity of continued follow-up of survivors of childhood cancer, with an emphasis on surveillance for second cancers (e.g., breast and colorectal cancer, melanoma, and nonmelanoma skin cancer), coronary artery disease, late-onset anthracycline-related cardiomyopathy, pulmonary fibrosis, and endocrinopathies (e.g., premature gonadal failure, thyroid disease, osteoporosis, and hypothalamic and pituitary dysfunction). Follow-up care of survivors should also include secondary and tertiary prevention (e.g., strategies to promote tobacco cessation or avoidance, physical activity, and proper weight management) and management of chronic disease.

As a group, cancer survivors were eight times as likely as their siblings to have severe or life-threatening chronic health conditions (e.g., myo-

cardial infarction, congestive heart failure, premature gonadal failure, second cancers, and severe cognitive dysfunction). Three groups were at highest risk: survivors of bone tumors, CNS tumors, and Hodgkin's disease. In addition to being at increased risk for particular health conditions, survivors of these tumors were also more likely to have multiple conditions. For example, bone-tumor survivors with multiple conditions more frequently had severe musculoskeletal problems, congestive heart failure, and hearing loss. CNS-tumor survivors with multiple conditions were more likely to have cognitive dysfunction, seizure disorders, and various endocrinopathies. Hodgkin's disease survivors with multiple conditions were more likely to have cardiovascular disease (coronary artery disease, cerebrovascular accident, valvular heart disease, or cardiomyopathy), second cancers (particularly breast cancer in women), lung disease, and thyroid disorders.

In the 1970s, effective treatment for osteosarcoma of the limbs generally included amputation. Even with modern limb-sparing procedures, the life-altering musculoskeletal morbidity faced by bone-tumor survivors is clinically significant and will increase as weight-bearing joints age more rapidly, owing to asymmetric stress and altered function.¹⁶⁻¹⁸ Since bone-tumor survivors are the group most likely to have severe limitations in activity,¹⁸ these limitations — and the resulting physical inactivity — may further compound the risk of cardiovascular disease as the survivors age. Survivors of CNS tumors — who often have significant cognitive, visual, and auditory impairment and endocrinopathies — are the group most likely to be functionally impaired.^{6,19-21} Hodgkin's disease survivors have the highest risk of second cancers and heart disease.²²⁻²⁷

Five treatment combinations were associated with a risk of severe or life-threatening conditions that was increased by a factor of at least 10; four of the treatment combinations included chest, abdominal, or pelvic irradiation. Survivors who were treated with any of these combinations should be identified for the purpose of surveillance, since many of the conditions can be diagnosed at an early and treatable stage (e.g., breast cancer, cardiomyopathy, and osteoporosis).²⁸

As compared with men, women who survive childhood cancer have been reported to have a greater risk of diminished health status,⁶ second

cancers,^{22,29} anthracycline-related cardiomyopathy and congestive heart failure,³⁰ and cranial radiotherapy-related cognitive dysfunction, growth hormone deficiency, and obesity.³¹⁻³⁴ Our study confirms this difference in outcomes between the sexes after cancer therapy. It has been reported that less than 20% of adult survivors of childhood cancer are followed at a cancer center or by an oncologist; the likelihood of follow-up in this setting decreases even more with time.³⁵ For this reason, it is important for general physicians and internists to be aware of the risks facing this population.

There are several considerations to keep in mind when interpreting these findings. First, the conditions were self-reported without external verification, with the exception of second cancers and death. Several key chronic conditions associated with cancer therapy, such as late-onset cardiomyopathy associated with previous anthracycline exposure, may remain clinically silent for long periods before becoming clinically apparent.³⁶ Other conditions that may be underreported are osteoporosis, hypertension, and insulin resis-

tance. Our list of chronic conditions, although comprehensive, is not all-inclusive; a notable omission is adverse mental health outcomes, an important component of morbidity after cancer in childhood.^{6,37,38}

In summary, adult survivors of pediatric cancer who were treated in the 1970s and 1980s are a high-risk population. Thirty years after a diagnosis of cancer, almost three fourths of survivors have a chronic health condition, more than 40% have a serious health problem, and one third have multiple conditions. The incidence of health conditions reported by this population increases with time and does not appear to plateau. The monitoring of survivors is an important part of their overall health care.

Supported by a grant (U24-CA-55727, to Dr. Robison) from the Department of Health and Human Services; by the Children's Cancer Research Fund (to the University of Minnesota); and by American Lebanese Syrian Associated Charities (St. Jude Children's Research Hospital).

Presented at the Proceedings of the 2005 Annual Meeting of the American Society of Clinical Oncology, Orlando, FL, May 13-17, 2005.

No potential conflict of interest relevant to this article was reported.

APPENDIX

The following investigators are members of the Childhood Cancer Survivor Study Group: *University of California, San Francisco* — R. Goldsby (principal investigator), A. Ablin (former principal investigator); *University of Alabama, Birmingham* — R. Berkow (principal investigator); *International Epidemiology Institute, Rockville, MD* — J. Boice (steering committee); *University of Washington, Seattle* — N. Breslow (steering committee); *University of Texas Southwestern Medical Center, Dallas* — G. Tomlinson (principal investigator), G.R. Buchanan (former principal investigator); *Cincinnati Children's Hospital Medical Center, Cincinnati* — S. Davies (steering committee); *Dana-Farber Cancer Institute, Boston* — L. Diller (principal investigator), H. Grier (former principal investigator), F. Li (steering committee); *Texas Children's Center, Houston* — Z. Dreyer (principal investigator); *Children's Hospital and Medical Center, Seattle* — D. Friedman (principal investigator), T. Pendergrass (former principal investigator); *Roswell Park Cancer Institute, Buffalo, NY* — D.M. Green (principal investigator and steering committee); *Hospital for Sick Children, Toronto* — M. Greenberg (principal investigator); *St. Louis Children's Hospital, St. Louis* — R. Hayashi (principal investigator), T. Vietti (former principal investigator); *St. Jude Children's Research Hospital, Memphis, TN* — L.L. Robison (principal investigator and steering committee), M. Hudson (principal investigator and steering committee); *University of Michigan, Ann Arbor* — R. Hutchinson (principal investigator); *Stanford University School of Medicine, Stanford, CA* — N. Marina (principal investigator), M.P. Link (former principal investigator), S.S. Donaldson (steering committee); *Emory University, Atlanta* — L. Meacham (principal investigator); *Children's Hospital of Philadelphia, Philadelphia* — A. Meadows (principal investigator and steering committee), B. Bayton (steering committee); *Children's Hospital, Oklahoma City* — J. Mulvihill (steering committee); *Children's Hospital, Denver* — B. Greffe (principal investigator), L. Odom (former principal investigator); *Children's Health Care-Minneapolis, Minneapolis* — J. Perkins (principal investigator), M. O'Leary (former principal investigator); *Columbus Children's Hospital, Columbus, OH* — A. Termuhlen (principal investigator), F. Ruymann (former principal investigator), S. Qualman (steering committee); *Children's National Medical Center, Washington, DC* — G. Reaman (principal investigator), R. Packer (steering committee); *Children's Hospital of Pittsburgh, Pittsburgh* — A. Ritchey (principal investigator), J. Blatt (former principal investigator); *University of Minnesota, Minneapolis* — A. Mertens (principal investigator and steering committee), J. Neglia (steering committee), M. Nesbit (steering committee); *Children's Hospital Los Angeles, Los Angeles* — K. Ruccione (principal investigator); *Memorial Sloan-Kettering Cancer Center, New York* — C. Sklar (principal investigator and steering committee), K. Oeffinger (steering committee); *National Cancer Institute, Bethesda, MD* — B. Anderson (steering committee), P. Inskip (steering committee); *Mayo Clinic, Rochester, MN* — V. Rodriguez (principal investigator), W. Smithson (former principal investigator), G. Gilchrist (former principal investigator); *University of Texas M.D. Anderson Cancer Center, Houston* — L. Strong (principal investigator and steering committee), M. Stovall (steering committee); *Riley Hospital for Children, Indianapolis* — T.A. Vik (principal investigator), R. Weetman (former principal investigator); *Fred Hutchinson Cancer Center, Seattle* — W. Leisenring (principal investigator and steering committee), J. Potter (former principal investigator and steering committee); *University of Alberta, Edmonton, AB, Canada* — Y. Yasui (steering committee); and *University of California, Los Angeles* — L. Zeltzer (principal investigator and steering committee).

REFERENCES

1. Ries LAG, Eisner MP, Kosary CL, et al., eds. SEER cancer statistics review, 1975-2002. Bethesda, MD: National Cancer Institute, 2005. (Accessed September 15, 2006, at http://seer.cancer.gov/csr/1975_2002/.)
2. Hewitt M, Weiner SL, Simone JV, eds. Childhood cancer survivorship: improving care and quality of life. Washington, DC: National Academies Press, 2003.
3. Oeffinger KC, Hudson MM. Long-term complications following childhood and adolescent cancer: foundations for providing risk-based health care for survivors. *CA Cancer J Clin* 2004;54:208-36.
4. Friedman DL, Meadows AT. Late effects of childhood cancer therapy. *Pediatr Clin North Am* 2002;49:1083-106.
5. Mertens AC, Yasui Y, Neglia JP, et al. Late mortality experience in five-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study. *J Clin Oncol* 2001;19:3163-72.
6. Hudson MM, Mertens AC, Yasui Y, et al. Health status of adult long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *JAMA* 2003;290:1583-92.
7. Garre ML, Gandus S, Cesana B, et al. Health status of long-term survivors after cancer in childhood: results of a uni-institutional study in Italy. *Am J Pediatr Hematol Oncol* 1994;16:143-52.
8. Stevens MC, Mahler H, Parkes S. The health status of adult survivors of cancer in childhood. *Eur J Cancer* 1998;34:694-8.
9. Sklar CA. Overview of the effects of cancer therapies: the nature, scale and breadth of the problem. *Acta Paediatr Suppl* 1999;88:1-4.
10. Oeffinger KC, Eshelman DA, Tomlinson GE, Buchanan GR, Foster BM. Grading of late effects in young adult survivors of childhood cancer followed in an ambulatory adult setting. *Cancer* 2000;88:1687-95.
11. Robison LL, Mertens AC, Boice JD, et al. Study design and cohort characteristics of the Childhood Cancer Survivor Study: a multi-institutional collaborative project. *Med Pediatr Oncol* 2002;38:229-39.
12. Mertens AC, Walls RS, Taylor L, et al. Characteristics of childhood cancer survivors predicted their successful tracing. *J Clin Epidemiol* 2004;57:933-44.
13. Cancer Therapy Evaluation Program. Common terminology criteria for adverse events, version 3.0. Bethesda, MD: National Cancer Institute, 2003. (Accessed September 15, 2006, at http://ctep.cancer.gov/reporting/ctc_v30.html.)
14. Therneau TM, Grambsch PM. Modeling survival data: extending the Cox model. New York: Springer-Verlag, 2000.
15. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med* 1999;18:695-706.
16. Eiser C, Darlington AS, Stride CB, Grimer R. Quality of life implications as a consequence of surgery: limb salvage, primary and secondary amputation. *Sarcoma* 2001;5:189-95.
17. Nagarajan R, Neglia JP, Clohisey DR, Robison LL. Limb salvage and amputation in survivors of pediatric lower-extremity bone tumors: what are the long-term implications? *J Clin Oncol* 2002;20:4493-501.
18. Ness KK, Mertens AC, Hudson MM, et al. Limitations on physical performance and daily activities among long-term survivors of childhood cancer. *Ann Intern Med* 2005;143:639-47.
19. Mulhern RK, Hancock J, Fairclough D, Kun L. Neuropsychological status of children treated for brain tumors: a critical review and integrative analysis. *Med Pediatr Oncol* 1992;20:181-91.
20. Mulhern RK, Reddick WE, Palmer SL, et al. Neurocognitive deficits in medulloblastoma survivors and white matter loss. *Ann Neurol* 1999;46:834-41.
21. Sklar CA, Constine LS. Chronic neuroendocrinological sequelae of radiation therapy. *Int J Radiat Oncol Biol Phys* 1995;31:1113-21.
22. Bhatia S, Yasui Y, Robison LL, et al. High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the Late Effects Study Group. *J Clin Oncol* 2003;21:4386-94.
23. Bisharat N, Omari H, Lavi I, Raz R. Risk of infection and death among post-splenectomy patients. *J Infect* 2001;43:182-6.
24. Travis LB, Gospodarowicz M, Curtis RE, et al. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. *J Natl Cancer Inst* 2002;94:182-92.
25. Hull MC, Morris CG, Pepine CJ, Mendenhall NP. Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of Hodgkin lymphoma treated with radiation therapy. *JAMA* 2003;290:2831-7.
26. Kenney LB, Yasui Y, Inskip PD, et al. Breast cancer after childhood cancer: a report from the Childhood Cancer Survivor Study. *Ann Intern Med* 2004;141:590-7.
27. Ng AK, Mauch PM. Late complications of therapy of Hodgkin's disease: prevention and management. *Curr Hematol Rep* 2004;3:27-33.
28. Oeffinger KC. Longitudinal risk-based health care for adult survivors of childhood cancer. *Curr Probl Cancer* 2003;27:143-67.
29. Neglia JP, Friedman DL, Yasui Y, et al. Second malignant neoplasms in five-year survivors of childhood cancer: Childhood Cancer Survivor Study. *J Natl Cancer Inst* 2001;93:618-29.
30. Lipshultz SE, Lipsitz SR, Mone SM, et al. Female sex and drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. *N Engl J Med* 1995;332:1738-43.
31. Waber DP, Tarbell NJ, Fairclough D, et al. Cognitive sequelae of treatment in childhood acute lymphoblastic leukemia: cranial radiation requires an accomplice. *J Clin Oncol* 1995;13:2490-6.
32. Robison LL, Nesbit ME Jr, Sather HN, Meadows AT, Ortega JA, Hammond GD. Height of children successfully treated for acute lymphoblastic leukemia: a report from the Late Effects Study Committee of Childrens Cancer Study Group. *Med Pediatr Oncol* 1985;13:14-21.
33. Melin AE, Adan L, Leverger G, Souberbielle JC, Schaison G, Brauner R. Growth hormone secretion, puberty and adult height after cranial irradiation with 18 Gy for leukaemia. *Eur J Pediatr* 1998;157:703-7.
34. Oeffinger KC, Mertens AC, Sklar CA, et al. Obesity in adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *J Clin Oncol* 2003;21:1359-65.
35. Oeffinger KC, Mertens AC, Hudson MM, et al. Health care of young adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Ann Fam Med* 2004;2:61-70.
36. Lipshultz SE, Lipsitz SR, Sallan SE, et al. Chronic progressive cardiac dysfunction years after doxorubicin therapy for childhood acute lymphoblastic leukemia. *J Clin Oncol* 2005;23:2629-36.
37. Zebrack BJ, Gurney JG, Oeffinger K, et al. Psychological outcomes in long-term survivors of childhood brain cancer: a report from the Childhood Cancer Survivor Study. *J Clin Oncol* 2004;22:999-1006.
38. Zebrack BJ, Zeltzer LK, Whitton J, et al. Psychological outcomes in long-term survivors of childhood leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma: a report from the Childhood Cancer Survivor Study. *Pediatrics* 2002;110:42-52.

Copyright © 2006 Massachusetts Medical Society.