

# Health Status of Adult Long-term Survivors of Childhood Cancer

## A Report From the Childhood Cancer Survivor Study

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THE DEVELOPMENT OF CURATIVE therapy for most pediatric malignancies provides the opportunity to investigate the impact of cancer treatment on health status of large numbers of long-term survivors. Numerous studies have established that cancer and its treatment predispose to late morbidity and increase the risk of early mortality in long-term childhood cancer survivors.<sup>1-8</sup> In general, children with aggressive tumor histologies have required more intensive treatment, which predispose them to heightened risks of physical morbidity. Treatment-related late sequelae with significant potential impact on physical functioning include neurocognitive dysfunction, cardiopulmonary toxicity, endocrinopathy,

For editorial comment see p 1641.

**Context** Adult survivors of childhood cancer are at risk for medical and psychosocial sequelae that may adversely affect their health status.

**Objectives** To compare the health status of adult survivors of childhood cancer and siblings and to identify factors associated with adverse outcomes.

**Design, Setting, and Participants** Health status was assessed in 9535 adult participants of the Childhood Cancer Survivor Study, a cohort of long-term survivors of childhood cancer who were diagnosed between 1970 and 1986. A randomly selected cohort of the survivors' siblings (n=2916) served as a comparison group.

**Main Outcome Measures** Six health status domains were assessed: general health, mental health, functional status, activity limitations, cancer-related pain, and cancer-related anxiety/fears. The first 4 domains were assessed in the control group.

**Results** Survivors were significantly more likely to report adverse general health (odds ratio [OR], 2.5; 95% confidence interval [CI], 2.1-3.0;  $P<.001$ ), mental health (OR, 1.8; 95% CI, 1.6-2.1;  $P<.001$ ), activity limitations (OR, 2.7; 95% CI, 2.3-3.3;  $P<.001$ ), and functional impairment (OR, 5.2; 95% CI, 4.1-6.6;  $P<.001$ ), compared with siblings. Forty-four percent of survivors reported at least 1 adversely affected health status domain. Sociodemographic factors associated with reporting at least 1 adverse health status domain included being female (OR, 1.4; 95% CI, 1.3-1.6;  $P<.001$ ), lower level of educational attainment (OR, 2.0; 95% CI, 1.8-2.2;  $P<.001$ ), and annual income less than \$20000 (OR, 1.8; 95% CI, 1.6-2.1;  $P<.001$ ). Relative to those survivors with childhood leukemia, an increased risk was observed for at least 1 adverse health status domain among those with bone tumors (OR, 2.1; 95% CI, 1.8-2.5;  $P<.001$ ), central nervous system tumors (OR, 1.7; 95% CI, 1.5-2.0;  $P<.001$ ), and sarcomas (OR, 1.2; 95% CI, 1.1-1.5;  $P=.01$ ).

**Conclusion** Clinicians caring for adult survivors of childhood cancer should be aware of the substantial risk for adverse health status, especially among females, those with low educational attainment, and those with low household incomes.

JAMA. 2003;290:1583-1592

www.jama.com

and second malignancy. The frequency and severity of many of the common sequelae have been corre-

lated with sex, age at diagnosis, and cumulative dose-exposures of specific treatment modalities.<sup>9-12</sup>

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In contrast, the impact of cancer and its therapy on the health status of long-term childhood cancer survivors has not been widely studied.<sup>13-15</sup> Cancer-related medical sequelae represent only 1 of many factors contributing to survivors' health status. The childhood cancer experience also may produce chronic psychological and cognitive impairments that hinder posttreatment adjustment and adversely affect quality of life. Although the majority of studies indicate that psychosocial functioning in childhood cancer survivors is very good, 10% to 20% of individuals show signs of psychological maladjustment, manifested as mood disturbances, behavioral problems, and somatic distress.<sup>16-19</sup> Higher levels of psychological distress in childhood cancer patients have been associated with academic underachievement, underemployment, and functional limitations that may adversely affect health status.<sup>16-19</sup> General anxiety and fears may persist after cancer treatment and undergo periodic exacerbations.<sup>20,21</sup> In extreme situations, intrusive cancer-related memories may trigger intense emotional and physiological reactions akin to posttraumatic stress reactions.<sup>20,21</sup> Therefore, health status assessment should consider general health, mental health, and functional limitations resulting from both medical and psychosocial sequelae.

The goal of this study was to describe the health status of long-term survivors of childhood cancer. Using a large, retrospective cohort of young adult survivors of childhood cancer living at the time of interview, the 3 objectives of this cross-sectional study were to (1) determine the prevalence of adverse health status, (2) compare the health status of survivors with that of a cohort of siblings, and (3) identify factors associated with adverse health status in survivors.

## METHODS

### Patient Selection and Contact

The Childhood Cancer Survivor Study (CCSS) included individuals from many institutions who survived for 5 or more

years after treatment for cancer, leukemia, tumor, or similar illness diagnosed during childhood or adolescence. This report from the CCSS is restricted to those adults ( $\geq 18$  years of age) who participated in the study and met the following eligibility criteria: (1) diagnosis of leukemia, central nervous system (CNS) tumors (all histologies), Hodgkin disease, non-Hodgkin lymphoma, kidney tumor, neuroblastoma, soft tissue sarcoma, or bone tumor; (2) diagnosis and initial treatment at 1 of 25 collaborating CCSS institutions; (3) diagnosis date between January 1, 1970, and December 31, 1986; (4) age younger than 21 years at diagnosis; and (5) survival at least 5 years from diagnosis. The CCSS protocol and contact documents were reviewed and approved by the human subjects committee at each participating institution and informed consent was obtained for study participation. A detailed description of the methods and cohort characteristics have been reported previously.<sup>22</sup>

Of the 20304 childhood cancer survivors included in the cohort, 2996 (14.8%) could not be located and were considered lost to follow-up. Among the 17308 participants located, 14193 (82%) completed a baseline questionnaire, including 9535 of participants who were alive and 18 years or older at time of interview.

To allow comparisons with a representative noncancer population, a random sample of participating survivors were chosen and asked to identify their nearest age living sibling. From those identified, 3585 siblings to date have been interviewed, of whom 2916 were aged 18 years or older at interview and included in this analysis. Demographics of the survivors and siblings are provided in TABLE 1.

### Cancer Treatment Information

Information on the characteristics of the original cancer diagnosis was obtained on all eligible cases from the treating institution. For all CCSS participants who returned a signed medical release, information on primary cancer therapy was collected, including

initial treatment, treatment for relapse, and preparatory regimens for bone marrow transplantation (if applicable). Qualitative information was abstracted from the medical record for 42 specific chemotherapeutic agents; quantitative information was abstracted from 22 of these agents. Data also were obtained on surgical procedures performed from the time of diagnosis onward, on tumor site, and fields and doses of radiation therapy. Copies of the baseline questionnaire and the treatment abstraction form are available for review and downloading at <http://www.cancer.umn.edu/ccss>.

### Health Status Measures

Six domains of health status were measured for this study: general health, mental health, functional status, limitations of activity, pain as a result of the cancer or its treatment, and anxiety/fears as a result of the cancer or its treatment. For general health, participants were asked, "Would you say that your health is excellent, very good, good, fair, or poor?" The 18-item Brief Symptom Inventory (BSI-18), a self-report measure of psychological symptoms, was used for the mental health domain.<sup>23,24</sup> Responses were scored according to the published manual with each participant receiving a T-score (mean=50, SD=10) on the Global Severity Index, as well as the 3-symptom specific subscales—depression, somatization, and anxiety.<sup>23,24</sup> For each scale a T-score of 63 or higher represents the upper 10th percentile of scores reported in a community sample and is considered to be significantly elevated. Using this cutoff, participants' scores were classified as elevated vs not elevated on each of the 4 scales. Participants who had a significant elevation on any of the 3 symptom specific subscales were classified as having adverse mental health, and this was used as the primary mental health outcome for this analysis.

Questions assessing general health, functional status, and limitations of activity were adapted from the National Health Interview Survey and the Behavioral Risk Factor Surveillance Sys-

tem Survey Questionnaire.<sup>25,26</sup> Functional status was determined from 3 questions that asked respondents if they had any impairment or health problem that resulted in (1) needing “help with personal care needs, such as eating, bathing, dressing, or getting around your home”; (2) needing “help in handling routine needs, such as everyday household chores, doing necessary business, shopping, or getting around for other purposes”; or (3) “keeping you from holding a job or attending school.” Activity status was determined from 3 questions that asked respondents if in the last 2 years their health was limited for more than 3 months in (1) the kinds or amounts of moderate activities you can do, like moving a table, carrying groceries, or bowling; (2) walking upstairs or climbing a few flights of stairs; or (3) walking 1 block. For pain as a result of the cancer or its treatment, survivors were asked, “Do you currently have pain as a result of your cancer or its treatment?” with responses recoded as a dichotomous variable. Participants reporting no pain or a small amount of pain were compared with those with a medium amount of pain, a lot of pain, or very bad excruciating pain. In a similar fashion, survivors were asked about anxiety/fears as a result of the cancer or its treatment and responses were recorded as a dichotomous variable of no or small amount of anxiety/fears vs medium amount, a lot of, or very many, extreme anxiety/fears. Each pair of the 6 outcomes was correlated, with weak correlations ranging from 0.12 to 0.41.

Siblings were asked the same questions as survivors regarding general health, mental health, activities, and functional impairment, but they were not asked the cancer-related questions related to pain or anxiety/fears.

### Independent Variables

Demographic and socioeconomic variables considered in the analysis included age at time of interview, sex, race and ethnicity, highest level of educational attainment, health insurance, and household income. Because there were

relatively few black non-Hispanic, and Hispanic survivors, they were combined with other race/ethnic minorities and analyzed as a single group. Cancer-related variables included cancer type, age at diagnosis, and interval from

cancer diagnosis to baseline interview. Cancer treatment variables included in the analysis were surgery (yes/no), radiation therapy (yes/no; radiation field including brain/head, chest/mantle, abdomen, pelvis), and chemotherapy

**Table 1.** Demographics of Adult Survivors of Childhood Cancer and Siblings\*

Variables	Survivors, No. (%)	Siblings, No. (%)
<b>Sex</b>	<b>n = 9535</b>	<b>n = 2916</b>
Female	4452 (46.7)	1537 (52.7)
Male	5083 (53.3)	1379 (47.3)
<b>Race/ethnicity</b>	<b>n = 9511</b>	<b>n = 2814</b>
White, non-Hispanic	8312 (87.4)	2589 (92.0)
Black, non-Hispanic	501 (5.3)	91 (3.2)
Hispanic	425 (4.5)	68 (2.4)
Other	273 (2.9)	66 (2.4)
<b>Education†</b>	<b>n = 9017</b>	<b>n = 2790</b>
High school or less	2998 (33.3)	685 (24.6)
High school + some college	6019 (66.8)	2105 (75.5)
<b>Household income</b>	<b>n = 8362</b>	<b>n = 2658</b>
<\$20 000	1893 (22.6)	336 (12.6)
≥\$20 000	6469 (77.4)	2322 (87.4)
<b>Health insurance</b>	<b>n = 9374</b>	<b>n = 2884</b>
No	1448 (15.5)	311 (10.8)
Yes or Canadian	7926 (84.6)	2573 (89.2)
<b>Cancer diagnosis</b>	<b>n = 9535</b>	NA
Leukemia	2865 (30.1)	NA
Central nervous system	1186 (12.4)	NA
Hodgkin disease	1666 (17.5)	NA
Non-Hodgkin lymphoma	867 (9.1)	NA
Wilms tumor	636 (6.7)	NA
Neuroblastoma	403 (4.2)	NA
Sarcoma	902 (9.5)	NA
Bone	1010 (10.6)	NA
<b>Cancer treatment</b>	<b>n = 8214</b>	NA
Surgery only	604 (7.3)	NA
Radiation only	23 (0.3)	NA
Chemotherapy only	340 (4.1)	NA
Chemotherapy + radiation	959 (11.6)	NA
Chemotherapy + surgery	1362 (16.5)	NA
Radiation + surgery	1172 (14.2)	NA
Chemotherapy + radiation + surgery	3754 (45.5)	NA
<b>Age at interview, y</b>		
Mean (SD)	26.8 (6.2)	29.2 (7.4)
Range	18-48	18-56
<b>Age at cancer diagnosis, y</b>		NA
Mean (SD)	10.0 (5.6)	NA
Range	0.1-20.9	NA
<b>Interval from diagnosis, y</b>		NA
Mean (SD)	17.4 (4.6)	NA
Range	6-29	NA

Abbreviation: NA, not applicable.

\*No. (%) is based on the total participants with available data for each variable. Percentages may not equal 100 due to rounding.

†High school or less means some high school or high school graduate; high school + some college means high school graduate with either some college courses or other training.

(yes/no and cumulative dose of anthracyclines, alkylating agents, bleomycin, and epipodophyllotoxins).

### Analysis

The prevalence of adverse outcomes in each of the health status domains was determined for survivors and siblings. Multiple logistic regression models with each

health status domain serving as the dependent variable were used to compare the odds of adverse outcomes between survivors and siblings, adjusting for age, sex, and race. Generalized estimating equations for correlated data were used to account for potential within-family correlation between the survivor and his/her sibling from the same family.<sup>27</sup>

Univariate analyses were performed to describe associations among demographic and cancer-related variables with the health status measures. To determine the strength of association between the outcome variables and the demographic and cancer-related factors that were hypothesized to be important a priori, multiple logistic re-

**Table 2.** Siblings and Adult Survivors of Childhood Cancer Who Reported Moderate to Extreme Adverse Health Status\*

Variables	No.	Siblings, %				No.	Survivors, %						
		General Health	Mental Health†	Functional Impairment	Activity Limitations		General Health	Mental Health†	Functional Impairment	Activity Limitations	Pain‡	Anxiety§	Any Domain
Total population	2916	4.9	10.2	2.5	5.6	9535	10.9	17.2	12.0	12.5	10.2	13.2	43.6
Age at interview, y													
18-24	899	4.8	11.9	2.4	4.5	3917	9.5	17.8	11.9	10.6	8.5	12.5	45.1
25-29	673	3.6	10.0	2.2	5.8	2541	10.9	17.0	11.9	13.0	9.7	13.3	40.8
30-34	625	4.7	10.8	1.9	5.6	1871	12.1	17.0	12.4	13.5	12.8	13.4	43.6
≥35	719	6.3	8.0	3.4	6.7	1206	13.7	16.5	12.0	16.4	12.8	15.4	45.3
Sex													
Male	1378	3.9	9.6	2.2	4.2	5083	10.2	16.2	10.6	9.9	9.8	10.6	39.7
Female	1537	5.8	10.6	2.8	6.8	4452	11.7	18.4	13.7	15.5	10.7	16.2	48.0
Race/ethnicity													
White, non-Hispanic	2589	8.2	12.8	4.5	6.7	8312	10.4	17.2	11.5	12.4	10.0	13.3	43.2
Minorities	225	4.6	9.9	2.4	5.4	1199	14.5	17.2	15.1	14.0	11.7	12.5	46.5
Education¶													
High school or less	685	7.6	12.4	3.7	7.3	2998	16.1	20.6	21.5	16.5	12.1	13.9	55.5
High school + some college	2105	3.8	9.1	1.8	4.9	6019	8.0	15.5	6.2	10.0	9.1	13.0	37.5
Household income													
<\$20 000	336	8.1	17.3	7.2	7.8	1893	19.5	26.1	22.8	19.6	15.2	17.1	57.6
≥\$20000	2322	4.4	9.3	1.5	5.1	6469	7.8	15.3	8.0	10.1	8.7	12.5	39.2
Health insurance													
No	311	8.4	15.9	3.6	5.8	1448	14.7	23.3	12.8	13.0	12.9	14.5	48.8
Yes or Canadian	2573	4.5	9.4	2.4	5.6	7926	10.0	16.0	11.7	12.5	9.7	13.0	42.5

\*Questions about pain or anxiety/fears as a result of the cancer were not applicable to the siblings. Because these 2 domains were not included for siblings, the "Any Domain" was not applicable. No. (%) is based on the total with available data for each variable.

†Mental health is adverse outcome (T-score ≥63) in any of the 3 Brief Symptom Inventory 18-item subscales (depression, somatization, or anxiety).

‡Pain as a result of the cancer or its treatment.

§Anxiety/fears as a result of the cancer or its treatment.

||Minorities included black, non-Hispanic, and Hispanic and other.

¶High school or less means some high school or high school graduate; high school + some college means high school graduate with either some college courses or other training.

**Table 3.** Moderate to Extreme Adverse Health Status Outcomes in Adult Survivors of Childhood Cancer Compared With Siblings, Adjusted for Age, Sex, and Race

Cancer Diagnosis	Odds Ratio (95% Confidence Interval)				BSI-18 Scales, Odds Ratio (95% Confidence Interval)			
	General Health	Functional Impairment	Activity Limitations	Mental Health*	Global	Depression Domain	Somatization Domain	Anxiety Domain
Total population	2.5 (2.1-3.0)	5.2 (4.1-6.6)	2.7 (2.3-3.3)	1.8 (1.6-2.1)	2.2 (1.8-2.8)	1.7 (1.4-2.0)	2.2 (1.8-2.7)	1.9 (1.5-2.4)
Leukemia	2.2 (1.8-2.8)	3.8 (2.9-5.0)	1.8 (1.5-2.3)	1.7 (1.5-2.1)	2.1 (1.6-2.7)	1.6 (1.3-2.0)	1.9 (1.5-2.5)	2.0 (1.5-2.6)
Central nervous system	3.5 (2.7-4.4)	18.0 (13.8-23.6)	4.1 (3.3-5.1)	2.0 (1.6-2.4)	2.5 (1.9-3.4)	2.2 (1.7-2.8)	2.1 (1.6-2.9)	1.7 (1.3-2.4)
Hodgkin disease	2.7 (2.2-3.4)	2.4 (1.8-3.3)	2.1 (1.7-2.7)	2.0 (1.6-2.4)	2.3 (1.8-3.0)	1.7 (1.3-2.1)	2.5 (1.9-3.2)	1.9 (1.4-2.5)
Non-Hodgkin lymphoma	2.3 (1.7-3.2)	3.0 (2.1-4.4)	2.0 (1.5-2.6)	1.8 (1.4-2.3)	2.2 (1.6-3.1)	1.8 (1.4-2.4)	1.9 (1.3-2.6)	1.8 (1.3-2.6)
Wilms tumor	1.8 (1.3-2.7)	3.2 (2.1-4.8)	2.0 (1.4-2.8)	1.3 (1.0-1.7)	1.7 (1.1-2.6)	1.1 (0.7-1.6)	1.7 (1.1-2.5)	1.7 (1.1-2.6)
Neuroblastoma	2.1 (1.3-3.2)	3.8 (2.3-6.2)	2.7 (1.9-4.0)	1.4 (1.0-2.0)	1.3 (0.8-2.1)	1.4 (0.9-2.1)	1.6 (1.0-2.6)	1.5 (0.9-2.4)
Sarcoma	2.2 (1.6-2.9)	4.2 (3.1-5.9)	2.3 (1.8-3.0)	1.7 (1.3-2.1)	2.1 (1.5-2.9)	1.5 (1.1-2.0)	2.1 (1.6-2.9)	1.7 (1.2-2.4)
Bone	2.6 (2.0-3.4)	7.4 (5.5-10.0)	6.4 (5.2-8.0)	1.8 (1.5-2.3)	2.2 (1.6-3.0)	1.6 (1.2-2.1)	2.2 (1.6-3.0)	2.1 (1.5-2.8)

Abbreviation: BSI-18, Brief Symptom Inventory 18-item.

\*Mental health is adverse outcome (T-score ≥63) in any of the 3 BSI-18 subscales.

gression models were constructed estimating odds ratios (ORs) with 95% confidence intervals (CIs) for adverse health status. Compared with survivors with a higher prevalence of late effects (CNS tumor, bone tumor) and those with a lower prevalence (Wilms tumor, neuroblastoma), leukemia survivors are generally considered an intermediate risk group. Thus, for regression analyses related to type of cancer, leukemia survivors were used as the reference group. Statistical significance was set as  $P < .05$ . Data were analyzed with the SAS PC software package version 8 (SAS Institute, Cary, NC).

## RESULTS

The mean age at interview for survivors was 26.8 years (range, 18-48 years). The mean age at cancer diagnosis was 10.0 years (range, 0.1-20.9 years), with a mean and median interval from diagnosis to completion of questionnaire of 17.4 years and 17.2 years (range, 6-29 years). Forty-seven percent of the participating survivors were female, and 87.4% were white, non-Hispanic. Compared with the siblings, survivors were younger, more likely to be male, and less likely to be white, non-Hispanic, to have a higher level of education, a household income level of \$20 000 or

more, and some form of health insurance (Table 1).

TABLE 2 shows the percentage of survivors and siblings with an adverse outcome in the different health status domains for various demographic categories. Overall, 43.6% of survivors had at least 1 adversely affected domain. TABLE 3 shows the OR estimates with 95% CIs for the 4 comparative domains, adjusted for age, sex, and race.

The percentage of survivors with adverse health status, by domain, for different cancer and cancer treatment variables are provided in TABLE 4. Multiple regression model fits including demo-

**Table 4.** Percentage of Adult Survivors of Childhood Cancer With Adverse Health Status, by Cancer Diagnosis and Cancer Treatment\*

Variables	No.	General Health	Mental Health†	Functional Impairment	Activity Limitations	Pain‡	Anxiety§	Any Domain
Total population	9535	10.9	17.2	12.0	12.5	10.2	13.2	43.6
Cancer diagnosis								
Leukemia	2865	9.6	17.5	9.3	8.6	8.3	11.9	40.3
Central nervous system	1186	14.6	19.0	31.7	17.8	9.3	12.1	54.2
Hodgkin disease	1666	12.7	17.8	6.4	11.3	6.6	15.9	40.2
Non-Hodgkin lymphoma	867	9.6	17.2	7.2	9.0	7.3	11.6	37.4
Wilms tumor	636	8.2	14.1	7.7	8.8	8.4	11.2	37.5
Neuroblastoma	403	8.6	15.6	8.3	11.7	7.6	10.7	41.2
Sarcoma	902	9.9	16.1	9.8	11.3	14.8	16.0	43.2
Bone	1010	12.1	17.0	16.2	26.8	23.0	15.2	55.7
Age at diagnosis, y								
0-4	2409	9.4	16.9	12.9	10.7	8.5	11.7	44.1
5-9	2359	10.1	17.7	12.4	10.6	8.6	12.7	42.6
10-14	2577	11.4	17.7	11.3	13.4	11.1	13.9	43.4
15-21	2190	12.8	16.5	11.6	15.7	12.9	14.7	44.4
Radiotherapy								
Any	5925	11.4	17.8	12.6	11.9	9.5	13.9	44.0
Brain	2632	11.3	17.9	17.6	11.4	8.8	12.3	46.5
Chest	1912	11.8	18.1	7.4	12.3	8.9	15.6	42.2
Abdomen	1076	10.2	17.4	8.2	11.7	9.4	13.5	40.5
Pelvis	787	11.6	19.1	10.7	12.4	11.7	13.9	42.2
Chemotherapy								
Any chemotherapy	6434	10.5	17.8	10.7	11.8	9.8	13.8	43.4
Alkylating agent								
None	2181	8.3	16.3	9.8	9.7	8.3	11.3	40.6
Intensity								
Low	1590	11.3	18.9	10.5	12.8	11.7	13.9	45.1
Moderate	1173	10.5	17.5	10.4	12.1	11.4	14.4	43.6
High	886	12.0	18.7	11.2	11.4	7.7	16.1	41.1
Anthracycline								
None	3320	10.1	17.5	10.8	9.7	7.4	12.9	41.5
Intensity								
Low	831	11.9	18.5	9.9	10.4	11.0	13.5	42.9
Moderate	970	10.5	19.1	10.3	15.0	11.5	14.4	46.1
High	1058	10.3	16.7	10.6	14.9	14.1	16.5	45.0

\*No. (%) is based on the total participants with available data for each variable.

†Mental health is adverse outcome (T-score  $\geq 63$ ) in any of the 3 Brief Symptom Inventory 18-item subscales (depression, somatization, or anxiety).

‡Pain as a result of the cancer or its treatment.

§Anxiety/fears as a result of the cancer or its treatment.



graphic and cancer-related factors associated with adverse outcomes in each of the domains are provided in TABLE 5. Reporting at least 1 adversely affected health status domain was associated with being female (OR, 1.4; 95% CI, 1.3-1.6;  $P<.001$ ), not completing high school or being a high school graduate without further training or education (OR, 2.0; 95% CI, 1.8-2.2;  $P<.001$ ), and an annual household income of less than \$20 000 (OR, 1.8; 95% CI, 1.6-2.1;  $P<.001$ ). Compared with leukemia survivors, increased risks for an adverse health status was noted in survivors of bone tumors (OR, 2.1; 95% CI, 1.8-2.5;  $P<.001$ ), CNS tumors (OR, 1.7; 95% CI, 1.5-2.0;  $P<.001$ ),

and sarcomas (OR, 1.2; 95% CI, 1.1-1.5;  $P=.01$ ).

Being female was associated with adverse outcomes in all of the domains except for cancer-related pain. Survivors aged 35 years or older were more likely to report adverse outcomes in general health (OR, 1.7; 95% CI, 1.4-2.2;  $P<.001$ ), functional status (OR, 1.4; 95% CI, 1.1-1.8;  $P=.03$ ), activity status (OR, 1.6; 95% CI, 1.3-1.9;  $P<.001$ ), and pain as a result of the cancer or its treatment (OR, 1.6; 95% CI, 1.3-2.1;  $P<.001$ ), compared with survivors aged 18 to 24 years. A lower level of educational attainment was associated with adverse outcomes in each domain, especially functional status (OR, 3.9; 95%

CI, 3.3-4.5;  $P<.001$ ) and activity status (OR, 1.9; 95% CI, 1.6-2.2;  $P<.001$ ). Similarly, an annual household income of less than \$20 000 was associated with adverse health status in all domains, especially functional status (OR, 2.9; 95% CI, 2.5-3.4;  $P<.001$ ) and general health (OR, 2.6; 95% CI, 2.2-3.0;  $P<.001$ ). Of note, racial and ethnic minority status as a group was associated with adverse outcomes in general health (OR, 1.2; 95% CI, 1.1-1.5;  $P=.04$ ), but not in any of the other domains. There were 2266 survivor-sibling pairs in the study. When analyzing only these pairs, excluding the 76% of survivors without a sibling, the conclusions were unchanged (data not shown).

**Table 5.** Multiple Regression Results of Demographic and Socioeconomic Factors for Adverse Health Status, by Domain in 9535 Adult Survivors of Childhood Cancer

Variables	Odds Ratio (95% Confidence Interval)						
	General Health	Mental Health*	Functional Impairment	Activity Limitations	Pain†	Anxiety‡	Any Domain
Age at interview, y							
18-24	1.0	1.0	1.0	1.0	1.0	1.0	1.0
25-29	1.3 (1.1-1.5)	1.0 (0.8-1.1)	1.2 (1.0-1.4)	1.3 (1.1-1.5)	1.2 (1.0-1.4)	1.1 (0.9-1.2)	0.9 (0.8-1.0)
30-34	1.5 (1.2-1.8)	1.0 (0.8-1.1)	1.2 (1.0-1.5)	1.2 (1.0-1.5)	1.6 (1.3-1.9)	1.0 (0.8-1.2)	1.0 (0.8-1.1)
≥35	1.7 (1.4-2.2)	0.9 (0.8-1.1)	1.4 (1.1-1.8)	1.6 (1.3-1.9)	1.6 (1.3-2.1)	1.1 (0.9-1.3)	1.0 (0.9-1.2)
Sex							
Male	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Female	1.2 (1.0-1.4)	1.2 (1.1-1.3)	1.4 (1.2-1.6)	1.7 (1.5-1.9)	1.1 (0.9-1.2)	1.6 (1.4-1.9)	1.4 (1.3-1.6)
Race/ethnicity							
White, non-Hispanic	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Minorities§	1.2 (1.1-1.5)	0.9 (0.8-1.1)	1.1 (0.9-1.4)	1.0 (0.8-1.2)	1.0 (0.9-1.3)	0.9 (0.7-1.1)	1.0 (0.9-1.1)
Education							
High school or less	2.0 (1.7-2.3)	1.3 (1.1-1.5)	3.9 (3.3-4.5)	1.9 (1.6-2.2)	1.4 (1.2-1.6)	1.1 (1.0-1.3)	2.0 (1.8-2.2)
High school + some college	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Household income							
<\$20 000	2.6 (2.2-3.0)	1.8 (1.5-2.0)	2.9 (2.5-3.4)	2.0 (1.8-2.4)	1.8 (1.5-2.1)	1.4 (1.2-1.7)	1.8 (1.6-2.1)
≥\$20 000	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Health insurance							
No	1.2 (1.0-1.4)	1.4 (1.2-1.6)	0.8 (0.6-0.9)	0.9 (0.7-1.1)	1.2 (1.0-1.5)	1.1 (0.9-1.3)	1.1 (1.0-1.2)
Yes or Canadian	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Cancer diagnosis							
Leukemia	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Central nervous system	1.5 (1.2-1.8)	1.1 (0.9-1.3)	4.7 (3.9-5.7)	2.2 (1.8-2.7)	1.0 (0.8-1.3)	1.0 (0.8-1.3)	1.7 (1.5-2.0)
Hodgkin disease	1.4 (1.2-1.8)	1.1 (1.0-1.4)	0.8 (0.6-1.0)	1.4 (1.1-1.8)	0.7 (0.6-0.9)	1.4 (1.2-1.8)	1.1 (1.0-1.3)
Non-Hodgkin lymphoma	1.0 (0.8-1.4)	1.0 (0.8-1.3)	0.9 (0.6-1.2)	1.2 (0.9-1.6)	0.8 (0.6-1.1)	1.1 (0.8-1.4)	1.0 (0.8-1.2)
Wilms tumor	0.9 (0.6-1.2)	0.8 (0.6-1.0)	0.8 (0.6-1.1)	1.0 (0.8-1.4)	1.1 (0.8-1.5)	0.9 (0.7-1.2)	0.9 (0.7-1.1)
Neuroblastoma	1.0 (0.7-1.4)	0.9 (0.6-1.2)	1.0 (0.6-1.4)	1.5 (1.1-1.8)	1.0 (0.7-1.5)	0.9 (0.6-1.2)	1.1 (0.8-1.3)
Sarcoma	1.1 (0.8-1.4)	1.0 (0.8-1.2)	1.2 (0.9-1.6)	1.4 (1.1-1.8)	1.9 (1.5-2.3)	1.4 (1.2-1.8)	1.2 (1.1-1.5)§
Bone	1.3 (1.0-1.7)	1.0 (0.9-1.3)	2.3 (1.8-2.9)	4.1 (3.4-5.1)	3.1 (2.5-3.8)	1.4 (1.1-1.7)	2.1 (1.8-2.5)

\*Mental health is adverse outcome (T-score ≥63) in any of the 3 Brief Symptom Inventory 18-item subscales (depression, somatization, or anxiety).

†Pain as a result of the cancer or its treatment.

‡Anxiety/fears as a result of the cancer or its treatment.

§Minorities included black non-Hispanic, Hispanic, and other.

||High school or less means some high school or high school graduate; high school + some college means high school graduate with either some college courses or other training.

Compared with leukemia survivors, adjusting for demographic/socioeconomic variables, survivors of bone tumor were more likely to report adverse health in each domain (except mental health), especially activity status (OR, 4.1; 95% CI, 3.4-5.1;  $P < .001$ ), functional status (OR, 2.3; 95% CI, 1.8-2.9;  $P < .001$ ), and pain as a result of the cancer or its treatment (OR, 3.1; 95% CI, 2.5-3.8;  $P < .001$ ). Similarly, survivors of CNS tumor were more likely to report adverse outcomes in functional status (OR, 4.7; 95% CI, 3.9-5.7;  $P < .001$ ), activity status (OR, 2.2; 95% CI, 1.8-2.7;  $P < .001$ ), and general health (OR, 1.5; 95% CI, 1.2-1.8;  $P = .002$ ).

The relationship of treatment to health domains is summarized in TABLE 6. Treatment with surgery (OR, 1.2; 95% CI, 1.1-1.4;  $P = .01$ ), radiation involving the head/brain (OR, 1.4; 95% CI, 1.2-1.6;  $P < .001$ ), chest/mantle radiation (OR, 1.2; 95% CI, 1.1-1.4;  $P = .05$ ), or alkylating agent chemotherapy (OR, 1.2; 95% CI, 1.1-1.4;  $P = .02$ ) was associated with a mild excess risk of reporting at least 1 adversely affected health status domain. Even after accounting for treatment effects, survivors of both CNS and bone tumors had an approximately 2-fold odds of having at least 1 adversely

affected health status compared with survivors of leukemia (Table 5). No interaction was observed between chemotherapy and radiation therapy with any of the outcomes. Of note, era of diagnosis was not significantly associated with any of the adverse health status outcomes other than functional impairment.

Within the survivor cohort, 313 had a confirmed second malignant primary neoplasm, excluding nonmelanoma skin cancer. Compared with survivors who did not have a second malignant primary neoplasm, this subset of survivors were more likely to report moderate to extreme adverse outcomes for each health status domain: any domain (OR, 1.8; 95% CI, 1.4-2.3;  $P < .001$ ); general health (OR, 1.8; 95% CI, 1.3-2.6;  $P < .001$ ); mental health (OR, 1.7; 95% CI, 1.3-2.3;  $P < .001$ ); functional impairment (OR, 2.0; 95% CI, 1.3-3.0;  $P < .001$ ); activity limitations (OR, 1.8; 95% CI, 1.3-2.6;  $P < .001$ ); pain as a result of cancer (OR, 1.5; 95% CI, 1.1-2.3;  $P = .03$ ); and anxiety as a result of the cancer (OR, 1.6; 95% CI, 1.2-2.2;  $P = .002$ ).

## COMMENT

This study provides information about the health status of the largest cohort

of adults surviving childhood cancer. Through the resource of the CCSS, a more precise and comprehensive assessment of health status was possible because of the number and diversity of study participants and the varied expertise of the investigators. Important study findings include the general health as perceived by adults surviving childhood cancer is very good with only 10.9% reporting fair or poor health, long-term adverse effects in specific aspects of health were relatively common as reflected by 43.6% of the cohort reporting impairment in 1 or more of the health domains evaluated in the study, and factors associated with impaired health status included being female, not completing high school, having a household income less than \$20 000, and having a diagnosis of bone tumor, CNS tumor, sarcoma, or Hodgkin disease. These findings help characterize the high-risk childhood cancer survivor who is more likely to require intervention to optimize long-term health outcomes.

Previous reports of global health have less relevance to the general population of childhood cancer survivors because most describe outcomes in small, heterogeneous patient popu-

**Table 6.** Multiple Regression Results of Cancer-Related Risk Factors for Adverse Health Status, by Domain, Adjusted for Age, Sex, Race, and Diagnosis

Variable	Odds Ratio (95% Confidence Interval)						
	General Health	Mental Health*	Functional Impairment	Activity Limitations	Pain†	Anxiety‡	Any Domain
Surgery							
No	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Yes	1.2 (0.9-1.5)	1.1 (0.9-1.3)	1.2 (0.9-1.5)	1.1 (0.9-1.4)	1.3 (1.0-1.7)	1.2 (1.0-1.6)	1.2 (1.1-1.4)
Radiation therapy							
None	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Head/brain	1.5 (1.2-1.8)	1.0 (0.8-1.2)	2.1 (1.7-2.6)	1.3 (1.0-1.6)	1.5 (1.1-1.9)	1.1 (0.9-1.3)	1.4 (1.2-1.6)
Chest/mantle	1.4 (1.0-1.8)	1.1 (0.9-1.3)	1.1 (0.8-1.4)	1.3 (1.0-1.6)	1.4 (1.1-1.9)	1.2 (0.9-1.5)	1.2 (1.1-1.4)
Brain/chest	1.4 (0.8-2.5)	1.1 (0.7-1.7)	3.6 (2.2-5.9)	2.0 (1.2-3.4)	3.4 (2.1-5.5)	1.2 (0.7-2.0)	2.1 (1.4-3.0)
Other	1.4 (1.1-1.8)	1.1 (0.9-1.3)	1.4 (1.1-1.8)	1.2 (1.0-1.5)	1.5 (1.2-1.9)	1.2 (1.0-1.5)	1.2 (1.0-1.4)
Chemotherapy							
None	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Alkylating agent	1.3 (1.1-1.7)	1.2 (1.0-1.4)	1.4 (1.1-1.8)	1.1 (0.9-1.4)	1.0 (0.8-1.3)	1.2 (1.0-1.5)	1.2 (1.1-1.4)
Anthracycline	1.2 (0.9-1.7)	1.1 (0.8-1.5)	1.5 (1.1-2.1)	1.3 (1.0-1.8)	1.2 (0.9-1.7)	1.1 (0.8-1.5)	1.2 (0.9-1.5)
Alkylating agent + anthracycline	1.4 (1.1-1.8)	1.2 (1.0-1.5)	1.5 (1.1-1.9)	1.4 (1.1-1.8)	1.3 (1.0-1.7)	1.5 (1.2-1.9)	1.3 (1.1-1.5)
Other	1.1 (0.8-1.4)	1.0 (0.8-1.3)	1.4 (1.1-2.0)	1.1 (0.8-1.5)	0.9 (0.6-1.2)	1.1 (0.9-1.5)	1.2 (1.0-1.4)

\*Mental health is adverse outcome (T-score  $\geq 63$ ) in any of the 3 Brief Symptom Inventory 18-item subscales (depression, somatization, or anxiety).

†Pain as a result of the cancer or its treatment.

‡Anxiety/fears as a result of the cancer or its treatment.

lations, who did not receive contemporary antineoplastic treatment.<sup>13-15</sup> Garre et al<sup>14</sup> evaluated the health status of 288 survivors treated for childhood cancer from 1962 to 1982 at a single institution using medical and neuropsychological assessments. Health status was defined relative to the incidence of medical sequelae and graded according to severity and corrective interventions, and did not include other aspects of health.

Only 1 previous investigation described health status of adults surviving childhood cancer in the context of medical and psychosocial sequelae and health-related quality of life. Crom et al<sup>13</sup> examined the influence of psychosocial demographic factors and patient and cancer-related variables on health status and related quality of life in 220 adults who were 15 or more years from diagnosis of a childhood solid tumor. Among the group, 59.1% reported at least 1 serious toxic effect (infertility, thyroid dysfunction, scoliosis most common). Despite the frequency of cancer-related toxicity, two thirds of survivors reported moderately good to excellent quality of life.

Health status in this group of individuals is likely to be determined by the unique response of the survivor and family to a multitude of physical and emotional insults associated with the cancer experience. While health status is generally poorer in survivors with more frequent or serious medical sequelae, resilient survivors with significant cancer-related medical issues may paradoxically view their overall health as good. Conversely, health status may be significantly impaired in survivors with less serious or no medical sequelae who have psychosocial issues interfering with post-treatment psychological adaptation. To integrate the impact of both medical and psychosocial factors on survivor health outcomes, in the present study we defined health status in the context of 6 domains that assessed general health, mental health, functional impairment, activity limitations, cancer-related pain, and anxiety/fears. This definition permitted the evaluation of medical and psychosocial

sequelae on health status of long-term childhood cancer survivors.

Sociodemographic factors that were consistently associated with adverse outcomes across all health domains included being female, lower levels of educational attainment, and household income less than \$20 000. These factors have been previously associated with a higher risk of emotional sequelae after childhood leukemia and lymphoma.<sup>16,19</sup> Mental health problems also have been observed more frequently in the general population with these same sociodemographic features.<sup>28,29</sup> Racial and ethnic minority status also was associated with a slight excess risk of impaired general health (OR, 1.2; 95% CI 1.1-1.5), but was not associated with adverse outcomes in any of the other health domains. The use of a sibling control group permitted comparison of cancer survivors with a demographically and genetically similar cohort. Predictably, survivors exhibited significantly more adverse outcomes in all of the domains studied compared with sibling controls, suggesting a major role of treatment effects in determining health status.

Our findings of poor health outcomes in survivors of primary malignancies treated with more intensive multimodality therapy concur with previous investigations of long-term childhood cancer survivors.<sup>13,14</sup> It is not surprising that survivors of pediatric bone tumors and sarcoma treated with chemotherapy and aggressive surgery or radiation more frequently reported cancer-related pain and activity limitations. Treatment for these tumors generally includes high cumulative doses of anthracyclines and alkylating agents, which predispose to cardiomyopathy, infertility, and second malignancy, as well as surgical interventions and/or radiation therapy that may limit musculoskeletal development and function and produce chronic pain. Functional impairment was more commonly endorsed in survivors of bone tumors, who encountered chronic health issues following amputation or limb-sparing surgeries, and survivors of CNS

tumors who experienced a variety of disabling neurocognitive complications related to tumor location and CNS therapy. Among all disease groups studied, adverse health outcomes in cancer-related pain, functional impairment, and activity limitations were associated with older age at interview. These results suggest that a higher degree of chronic disability may develop in aging childhood cancer survivors or that earlier treatment produces more morbidity than contemporary therapies.

Moderate to severe impairment in some aspect of mental health was observed across all diagnostic groups analyzed. In particular, patients with Hodgkin disease, sarcomas, and bone tumors had significantly higher levels of cancer-related anxiety and fears adversely affecting health status. These malignancies commonly present during adolescence and young adulthood when patients developmentally and cognitively can better appreciate the gravity of a cancer diagnosis and risks of cancer treatment sequelae. Recent studies indicate that a significant minority of young adult survivors of childhood cancer experience symptoms of posttraumatic stress related to residual anxiety about their cancer experience.<sup>21</sup> In severely affected patients, external reminders of diagnosis and treatment may stimulate an exacerbation of anxiety and distress that interferes with daily functioning. Often this anxiety is manifest as somatic distress regarding the body, current state of health, and related fears of recurrence or severe late toxic effects. These issues make it difficult to determine if somatic complaints such as fatigue, lethargy, chronic pain, or chronic health worries are physical or psychological in etiology. Therefore, all symptoms should be evaluated from a multifaceted viewpoint that considers physical and psychological issues in the differential diagnoses.<sup>30</sup>

Appreciation of sociodemographic and treatment characteristics associated with physical morbidity and psychosocial maladjustment is an important first step in developing interventions to improve the health status of long-term survivors. Health care profession-



als are challenged with the responsibility of educating survivors about anxiety-provoking cancer-related risks using methods that encourage continued health monitoring and motivate lifestyle practices that promote risk reduction. This task is particularly difficult considering the fact that many primary care clinicians and young-adult cancer survivors lack knowledge about their cancer treatment, its associated health risks, and appropriate screening measures.<sup>31</sup>

The process can be further undermined if a survivor is experiencing unresolved cancer-related anxiety or post-traumatic stress symptoms. Hobbie et al<sup>21</sup> recommended that clinicians promote competence of young adult cancer survivors in dealing with potential and unknown health risks after cancer. To do so effectively, health care professionals and pediatric cancer centers must communicate with each other to obtain accurate information about treatment exposures and their potential long-term adverse effects. Periodic evaluations of survivors should include a thorough psychosocial and physical assessment for cancer-related medical and emotional sequelae that require further intervention. During the evaluation, the clinician should candidly discuss cancer-related health risks, correct misperceptions, and encourage the survivor to stay informed about this rapidly evolving area of medical research. Modifiable behavioral risk factors that may exacerbate cancer-related risks should be emphasized in an effort to shift perspective from potential uncontrollable aspects of illness and motivate behaviors that maintain wellness.<sup>21</sup> Clinicians should likewise be prepared to assist with referrals to other health care professionals that can ameliorate or facilitate adaptation to physical or emotional disabilities related to childhood cancer.

This study has some methodological limitations that should be considered when interpreting the results. First, there are inherent difficulties in describing health outcomes in childhood cancer

survivors with heterogeneous cancer diagnoses, ages/developmental stages at diagnosis, and treatments during a 16-year period. Second, health status was, in part, determined by self-report of medical complications that were not validated externally. Third, we did not use a single validated instrument for assessment of health status, but derived this measure from a combination of various instruments. Although we believe that the health domains assessed provide a reasonable measure of health status, we recognize that the questionnaire did not provide an entirely global view of health status. Fourth, incomplete participation of the eligible adult cohort could result in more favorable health status if healthier survivors were more likely to join the cohort study. Conversely, health status deficits may be overestimated if survivors with chronic health problems participated more frequently than healthy survivors. Fifth, because of the small proportion of minority study participants in the CCSS, these results have limited generalizability to ethnic and minority population.

Finally, the use of a sibling cohort also could pose problems with interpretation of health status outcomes that should be considered. A growing body of literature exists describing psychological outcomes in siblings of cancer survivors.<sup>32-37</sup> While some investigators have reported that siblings of childhood cancer patients experience more emotional and behavioral problems compared with age-matched controls,<sup>33,38</sup> others indicate no significant differences in emotional status.<sup>34,35</sup> Some studies have observed positive psychological outcomes in siblings of survivors who were noted to be more thoughtful, sensitive, compassionate, mature, and responsible because of their cancer experience.<sup>34,36,37</sup> The BSI-18 scores of our sibling cohort, which incorporate a comparison with a normative control group, did not reflect more mental health problems than the average person.<sup>23,24</sup>

In summary, although the vast majority of adults surviving childhood cancer perceive their overall health as good,

deficits in specific health domains are common. Sociodemographic factors predicting poor health are similar to those identified in the general population and include being female, those with low income, and those with low educational achievement. Survivors of CNS tumors, bone tumors, and sarcomas predictably reported functional impairments and/or activity limitations likely related to the aggressive nature of anti-neoplastic therapy, especially those directed at local tumor control. Lingering cancer-related anxiety and fears were more common in long-term survivors of Hodgkin disease, sarcomas, and bone tumors possibly reflecting a greater appreciation of their vulnerability to cancer-related health risks. Primary care clinicians should anticipate health deficits in these clinical and sociodemographic groups when evaluating adults who are childhood cancer survivors and be prepared to address physical and psychosocial sequelae adversely impacting health status.

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**Funding/Support:** This work was supported by grant 5U24-CA-55727 from the Department of Health and Human Services and funding to the University of Minnesota from the Children's Cancer Research Fund. Dr Hudson is supported by Cancer Center Support (CORE) grant CA 21765 from the National Cancer Institute and by the American Lebanese Syrian Associated Charities (ALSAC).

**Previous Presentations:** Presented at the Proceedings of the 2002 Annual Meeting of the American Society of Clinical Oncology, Orlando, Fla, May 18-21, 2002; Proceedings of the 7th International Conference on the Long-Term Complications of Treatment of Children and Adolescents for Cancer, Niagara-on-the-Lake, Ontario, Canada, June 28-29, 2002; Conference on Cancer Survivorship: Resilience Across the Lifespan, Washington, DC, June 2002; and Proceedings of the American Institute for Cancer Research and World Cancer Research Fund International: International Research Conference on Food, Nutrition and Cancer, Washington, DC, July 17-18, 2003.

**Acknowledgment:** We thank John Whitton, MS, and Pauline Mitby, MPH, for their assistance with the CCSS database and Sandra Mulkey, RD, and Barbara Cruchon for their assistance with manuscript preparation.

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