

## Psychological Status in Childhood Cancer Survivors: A Report From the Childhood Cancer Survivor Study

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### A B S T R A C T

Psychological quality of life (QOL), health-related QOL (HRQOL), and life satisfaction outcomes and their associated risk factors are reviewed for the large cohort of survivors and siblings in the Childhood Cancer Survivor Study (CCSS). This review includes previously published manuscripts that used CCSS data focused on psychological outcome measures, including the Brief Symptom Inventory (BSI-18), the Medical Outcomes Survey Short Form-36 (SF-36), the Cantril Ladder of Life, and other self-report questionnaires. Comparisons and contrasts are made between siblings and survivors, and to normative data when available, in light of demographic/health information and abstracted data from the medical record. These studies demonstrate that a significant proportion of survivors report more symptoms of global distress and poorer physical, but not emotional, domains of HRQOL. Other than brain tumor survivors, most survivors report both good present and expected future life satisfaction. Risk factors for psychological distress and poor HRQOL are female sex, lower educational attainment, unmarried status, annual household income less than \$20,000, unemployment, lack of health insurance, presence of a major medical condition, and treatment with cranial radiation and/or surgery. Cranial irradiation impacted neurocognitive outcomes, especially in brain tumor survivors. Psychological distress also predicted poor health behaviors, including smoking, alcohol use, fatigue, and altered sleep. Psychological distress and pain predicted use of complementary and alternative medicine. Overall, most survivors are psychologically healthy and report satisfaction with their lives. However, certain groups of childhood cancer survivors are at high risk for psychological distress, neurocognitive dysfunction, and poor HRQOL, especially in physical domains. These findings suggest targeting interventions for groups at highest risk for adverse outcomes and examining the positive growth that remains despite the trauma of childhood cancer.

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### INTRODUCTION

Long-term follow-up of childhood cancer survivors provides unique opportunities to study psychological outcomes, as diagnosis and treatment take place during formative development of organ systems, cognition, emotions, and life experiences. On the basis of a median age at diagnosis of 6 years, survivors can expect to live another 66 years,<sup>1</sup> and issues pertinent to quality of life (QOL) and emotions will vary across the adult age spectrum. Factors that impact educational attainment, employment, marriage and intimacy, fertility, and other life values differ in the emerging young adult compared with the older adult.<sup>2</sup> These factors in adults who are childhood cancer survivors, along with delayed health sequelae for some, may explain the differing psychological outcomes reported in this population. Because of the vastness of salient potential risk factors, large

cohorts of survivors are needed to examine the impact of specific diagnoses and treatments in relation to age, sex, other demographic factors, and physical health that can each and together impact long-term psychological outcomes.

A review of the literature on the psychosocial outcomes of childhood cancer survivors demonstrates varied, and sometimes contradictory, results. This inconsistency in outcomes is likely caused by small sample sizes, varied outcome measures used across studies, and selection of population norms for the comparison group. Studies in which survivors report no differences in psychological outcomes compared with those of population norms may be viewed as having been influenced by response bias.<sup>3</sup> In addition, normative data with which survivors are compared in many studies have their own limitations, especially in terms of demographic characteristics of the control group that may be quite different from those in the survivor cohort that is

studied. Siblings of long-term survivors may provide a better comparison group for psychological health outcomes, particularly given the similarities in ethnicity, culture, community, socioeconomic status, genetics, and family environment. Although subgroups of siblings may have their own set of psychological effects, such comparison data might at least provide a conservative estimate of risks for negative psychological sequelae, which would help to direct targeted intervention.

For reasons thus noted, the Childhood Cancer Survivor Study (CCSS) offers the opportunity to move beyond barriers not only to examine the psychological QOL and health-related QOL (HRQOL) of adult survivors of childhood cancer, but also to compare these outcomes to a matched cohort of adult siblings and to population norms. Additionally, by having diagnoses and treatment-documented data, as well as self-report data from standardized measures, the CCSS offers the opportunity to have a broad view on psychological QOL and HRQOL and to identify at-risk subgroups of survivors who may benefit from psychosocial intervention. This report provides an overview of the findings from the CCSS in relation to psychological outcomes, neurocognitive function, QOL, and life expectations. Specific recommendations for targeted interventions, disease prevention, and health promotion are suggested.

## REVIEW OF PSYCHOLOGICAL MEASURES IN CCSS

### Brief Symptom Inventory–18

The Brief Symptom Inventory–18 (BSI-18) measures psychological distress by using 18 items related to symptoms experienced during the previous 7 days.<sup>4</sup> The BSI-18 has been validated in healthy volunteers,<sup>5</sup> in cancer patients,<sup>4</sup> and in the CCSS cohort of survivors.<sup>3</sup> The BSI-18 has a summary scale, the global distress index, and three subscales: depression, anxiety, and somatization. Raw scores are converted to T scores on the basis of normative data. The T scores are then dichotomized, in which a T score  $\geq 63$  classified a respondent as having psychological distress.<sup>3</sup>

### Medical Outcomes Short Form–36

The Medical Outcomes Short Form–36 (SF-36) measures HRQOL by using 36 questions on general health, well-being, and QOL during the previous 4 weeks.<sup>6</sup> The SF-36 has two summary scales and eight subscales that represent different aspects of well-being.<sup>6</sup> Data are presented as T scores with a mean score of 50 and a standard deviation (SD) of 10, in which a higher score indicates better HRQOL.<sup>7</sup> T scores are dichotomized, in which a T score at least one SD below the population mean ( $\leq 40$ ) classified a respondent as having reported poor HRQOL. Reulen et al<sup>8</sup> studied the psychometric properties of the SF-36 in more than 10,000 adult survivors of childhood cancer, which confirmed its validity and reliability for this population.<sup>8</sup>

### Cantril Ladder of Life

The Ladder of Life (LOL) assesses respondents' life satisfaction with three self-report items that indicate life satisfaction in the past, present, and future.<sup>9</sup> Ratings are made on a 10-point scale that ranges from best possible life to worst possible life,<sup>9</sup> which provides a global rating of life satisfaction used previously in population studies and clinical samples of cancer survivors.<sup>10,11</sup>

### Childhood Cancer Survivor Study Neurocognitive Questionnaire

The Childhood Cancer Survivor Study Neurocognitive Questionnaire (CCSS-NCQ) was developed and validated within the CCSS cohort as a neurocognitive measure specifically designed for cancer survivors.<sup>12</sup> It was constructed to assess skills reported to be sensitive to the effects of radiation and/or antimetabolite chemotherapy and skills included in established measures of executive functioning. The CCSS-NCQ was developed by selecting a subset of items represented in an investigational version of the Brief Rating Inventory of Executive Function–Adult (BRIEF-A), to which additional items were added.<sup>13</sup> Exploratory factor analysis in 382 siblings of cancer survivors revealed four factors that demonstrated good internal consistency: task efficiency (ie, initiating and completing tasks in a rapid manner), emotional regulation (ie, emotional reactivity and frustration tolerance), organization (ie, organization of the individual's environment), and memory (ie, working memory and long-term memory).

Construct and concurrent validities of the four CCSS-NCQ factors were demonstrated through correlation with factors from other established measures, including the Behavior Problem Index (BPI) and the BSI, respectively.<sup>4,14</sup> The task efficiency factor from the CCSS-NCQ was highly correlated with the BPI domain of attention deficits. In addition, the depression/anxiety domain from the BPI was correlated more strongly with the CCSS-NCQ emotional regulation factor.<sup>12</sup> Similarly, this emotional regulation factor correlated more highly with the BSI factors than did any of the other CCSS-NCQ factors.

Discriminant validity of the CCSS-NCQ was examined by comparing the factor scores between cancer survivors who were at high risk versus low risk for neurocognitive dysfunction. The high-risk groups were comprised of individuals who had a history of cerebrovascular stroke or epilepsy (ie, neurologic group [ $n = 172$ ]) or who received high-dose cranial radiation (ie,  $\geq 35$  Gy; chemoradiotherapy group [ $n = 247$ ]), whereas the low-risk group ( $n = 688$ ) included healthy survivors who had no history of central nervous system (CNS) disease, CNS treatment, or major organ complications or procedures. Compared with siblings, the high-risk groups demonstrated significantly increased rates of problems in task efficiency, memory, emotional regulation, and organization.<sup>12</sup> Equally important is that the low-risk group of healthy survivors demonstrated no significant increase in problems compared with the sibling sample.

## PSYCHOLOGICAL HEALTH STATUS IN RELATION TO CANCER DIAGNOSIS

Overall, childhood cancer survivors are relatively healthy, both physically and emotionally, compared with siblings. However, within-group comparisons demonstrate that a significant subset of patients report impaired physical health status, poor psychological health, and low HRQOL.<sup>15,16</sup> In reference to national norms, survivors are 80% more likely than their siblings to report clinically relevant impairment in mental health QOL (odds ratio [OR], 1.8; 95% CI, 1.6 to 2.1), and greater than five times more likely to report functional impairment in HRQOL (OR, 5.2; 95% CI, 4.1 to 6.6).<sup>15</sup> In addition, survivors are twice as likely to report clinical levels of emotional distress compared with their siblings (OR, 2.2; 95% CI, 1.8 to 2.8).<sup>15</sup> Some of the important differences within cancer diagnostic groups are highlighted in this

section, as are differences compared with siblings. One of the strengths of the CCSS cohort is the large sample size of long-term survivors, which can result in statistically significant differences when actual group differences are generally small. As such, emphasis in the survivor-type sections will be placed on comparisons of rates of clinically relevant impairment within diagnostic and/or treatment groups. In each instance, impairment is defined by scores that exceed established thresholds on validated clinical instruments. The section with a discussion of instruments explains specific threshold determinants. As an example, for the BSI-18, the clinical cutoff T score of  $\geq 63$  was used to assess increased risk for any of the subscales (eg, depression, anxiety, or somatic distress).

### **Leukemia Survivors**

Compared with siblings, leukemia survivors demonstrate elevated rates of psychological distress (OR, 2.1; 95% CI, 1.6 to 2.7).<sup>16,17</sup> During patient adolescence, parents report that leukemia survivors experience increased rates of depression and anxiety (response rate [RR], 1.6; 95% CI, 1.2 to 2.2) and social-skills deficits (RR, 1.4; 95% CI, 1.1 to 1.8) compared with sibling controls.<sup>18</sup>

### **Brain Tumor Survivors**

Brain tumor survivors demonstrate higher rates of impaired physical health compared with siblings (OR, 3.5; 95% CI, 2.7 to 4.4)<sup>15</sup> and compared with leukemia survivors.<sup>15,16,19</sup> This impairment includes a lower capacity to fulfill physical roles as well as lower expectations of future life satisfaction.<sup>16</sup> Additionally, survivors of astrocytomas report lower HRQOL within the mental health domain compared with siblings, which demonstrates the largest effect size with respect to impairment within this domain.<sup>16</sup> Brain tumor survivors also endorse more psychological distress, including depression and somatization,<sup>16,20</sup> and more symptoms of fatigue and daytime sleepiness (OR, 1.6; 95% CI, 1.0 to 2.8).<sup>21</sup>

### **Neuroblastoma Survivors**

Neuroblastoma survivors do not report impaired physical health compared with leukemia or kidney tumor survivors but do report higher rates of psychological distress, including depression, somatization, and anxiety, compared with siblings.<sup>19,22</sup> However, no differences in psychological distress have been found between neuroblastoma survivors and survivors of other solid tumors, including kidney tumor, bone tumor, or sarcoma.<sup>18</sup>

### **Bone Tumor and Sarcoma Survivors**

Bone tumor and sarcoma survivors demonstrate higher rates of impaired physical health (OR, 2.6; 95% CI, 2.0 to 3.4) and increased reports of pain compared with siblings, norms, and leukemia survivors.<sup>15,16,19</sup> More specifically, osteosarcoma survivors demonstrate the largest effect size with respect to impaired physical functioning compared with siblings and norms.<sup>16</sup> Both osteosarcoma and Ewing sarcoma survivors demonstrate the largest effect size with respect to bodily pain compared with siblings and norms.<sup>16</sup> In addition, location of primary tumor site impacts these health outcomes. Pelvic tumors are associated with poorer outcomes compared with extremity tumors.<sup>23</sup> Bone tumor survivors, but not survivors of other solid tumors (eg, kidney tumors, neuroblastoma), demonstrate more psychological distress, including anxiety (OR, 2.1; 95% CI, 1.5 to 2.8) and somatization (OR, 2.2; 95% CI, 1.6 to 3.0) compared with siblings and popu-

lation norms.<sup>16,18</sup> Additionally, osteosarcoma survivors report lower mean scores on emotional role functioning and mental health domains compared with siblings.<sup>16</sup> Sarcoma survivors also endorse more symptoms of sleep disruption (OR, 1.9; 95% CI, 1.1 to 3.2) compared with siblings.<sup>21</sup>

### **Wilms Tumor Survivors**

Wilms tumor survivors report higher rates of impaired general health compared with siblings (OR, 1.8; 95% CI, 1.3 to 2.7), but no differences are found compared with leukemia or neuroblastoma survivors.<sup>15,16,22</sup> In addition, no differences in psychological health are reported by Wilms tumor survivors compared with neuroblastoma, bone tumors, or other sarcoma survivors.<sup>18</sup>

### **Lymphoma Survivors**

Lymphoma survivors report higher rates of psychological distress, including anxiety (OR, 1.8; 95% CI, 1.3 to 2.6) and somatization (OR, 1.9; 95% CI, 1.3 to 2.6), compared with siblings and population norms.<sup>16</sup> More specifically, survivors of Hodgkin's lymphoma report impaired physical health compared with leukemia survivors<sup>15,19</sup> and more symptoms of somatization compared with leukemia and non-Hodgkin's lymphoma survivors.<sup>24</sup> With respect to somatization, Hodgkin's lymphoma survivors also demonstrate higher rates of clinically significant somatization compared with siblings (OR, 2.5; 95% CI, 1.9 to 3.2).<sup>16</sup> They also endorse more complaints of fatigue, sleep disruption, and daytime sleepiness compared with siblings.<sup>21</sup> Non-Hodgkin's lymphoma survivors report lower vitality in assessment of their HRQOL scores compared with siblings and norms, which demonstrates the largest effect size with respect to impaired vitality.<sup>16</sup>

## PSYCHOLOGICAL HEALTH STATUS IN RELATION TO CANCER TREATMENT

Treatments such as irradiation, chemotherapy, and surgical intervention may themselves exert long-term effects on survivors' psychological outcomes. Tables 1 and 2 present data on psychological distress (ie, BSI) and HRQOL (ie, SF-36) by treatment factors.

### **Irradiation**

Irradiation is associated with psychological distress, including somatization, in survivors (Table 1).<sup>16</sup> Solid tumor survivors exposed to irradiation—including those diagnosed with kidney tumors, neuroblastoma, bone tumors, and sarcomas—report more psychological distress, including somatization.<sup>18</sup> Survivors treated with irradiation endorse more fatigue than those treated without irradiation, with the exception of survivors of Hodgkin's disease who are treated with mediastinal radiation therapy.<sup>21</sup>

Pelvic irradiation is associated with poorer HRQOL compared with nonirradiated cohorts.<sup>23</sup> Kidney tumor survivors who had received pelvic irradiation report poorer emotional role functioning compared with those treated without irradiation.<sup>22</sup>

CNS irradiation is linked to impairment in physical health in survivors when compared with non-CNS-irradiated survivors (Table 2).<sup>15,16,19</sup> Impairment includes poor general health, poor physical functioning, lower fulfillment of roles physically, more functional impairment, and more activity limitations. CNS-irradiated leukemia

**Table 1.** Frequencies and Percentages of Survivors Who Had Poor Outcomes on the BSI

Variable	Sample Size (n)	Scale Outcome																
		Depression				Anxiety				Somatization				Global Status Index				
		No.	%	OR	95% CI	No.	%	OR	95% CI	No.	%	OR	95% CI	No.	%	OR	95% CI	
Sex																		
Male	3,481	351	10.8	—		206	6.3	—		343	10.5	—		278	8.5	—		
Female	3,666	472	13.6	1.3	1.1 to 1.5	347	10.0	1.7	1.4 to 2.0	575	16.6	1.7	1.5 to 2.0	427	12.3	1.53	1.3 to 1.8	
Age at diagnosis, years																		
0-3	2,211	261	12.5	1.0	0.8 to 1.2	184	8.8	1.1	0.8 to 1.4	248	11.9	0.8	0.6 to 0.9	222	10.6	1.1	0.8 to 1.4	
4-9	2,137	251	12.6	1.0	0.8 to 1.2	170	8.5	1.1	0.8 to 1.5	277	13.9	0.9	0.7 to 1.1	219	11.0	1.1	0.9 to 1.4	
10-14	1,497	160	11.3	0.9	0.7 to 1.1	103	7.3	0.9	0.7 to 1.2	204	14.5	1.0	0.8 to 1.2	141	10.0	1.0	0.8 to 1.3	
15-20	1,302	151	12.2	—		96	7.7	—		189	15.2	—		123	9.9	—		
Survival time, years																		
< 20	1,985	243	12.9	1.0	0.8 to 1.3	171	9.1	1.1	0.8 to 1.6	249	13.2	0.8	0.7 to 1.1	207	11.0	0.9	0.7 to 1.2	
20-24	2,432	280	11.8	0.9	0.7 to 1.2	195	8.2	1.0	0.8 to 1.4	311	13.1	0.8	0.6 to 1.0	222	9.3	0.7	0.6 to 1.0	
25-29	1,829	207	12.1	1.0	0.7 to 1.2	129	7.5	1.0	0.7 to 1.3	239	13.9	0.9	0.7 to 1.1	185	10.8	0.9	0.7 to 1.1	
≥ 30	801	93	12.3	—		58	7.7	—		119	15.8	—		91	12.1	—		
Surgery																		
Yes	5,403	652	12.1	1.1	0.9 to 1.4	435	8.1	1.1	0.8 to 1.4	733	13.6	1.0	0.8 to 1.2	566	10.5	1.2	0.9 to 1.5	
No	1,334	171	12.8	—		118	8.8	—		185	13.9	—		139	10.4	—		
Chemotherapy																		
Yes	5,326	646	12.1	1.0	0.8 to 1.2	450	8.4	1.2	0.9 to 1.5	736	13.8	1.1	0.9 to 1.4	565	10.6	1.1	0.9 to 1.4	
No	1,411	177	12.5	—		103	7.3	—		182	12.9	—		140	9.9	—		
Radiation																		
Cranial	2,057	287	14.0	1.2	1.0 to 1.5	159	7.7	0.9	0.7 to 1.1	275	13.4	1.1	1.0 to 1.4	214	10.4	1.0	0.8 to 1.2	
Other than cranial	2,415	264	10.9	0.9	0.7 to 1.1	189	7.8	0.9	0.7 to 1.1	372	15.4	1.3	1.1 to 1.5	251	10.4	1.0	0.8 to 1.2	
None	2,265	272	12.0	—		205	9.1	—		271	12.0	—		240	10.6	—		

NOTE. Models adjusted for all variables in left column of the table. Odds ratios and 95% confidence intervals compared poor outcomes by treatment variables. Abbreviations: BSI, Brief Symptom Inventory; OR, odds ratio.

survivors report no differences in fatigue, sleep disruption, or daytime sleepiness,<sup>21</sup> although they report more functional limitations.<sup>17</sup>

In contrast to leukemia survivors, brain tumor survivors do not link treatment effects to psychological distress, whether predictors are the examination of brain radiation dosage or the use of concomitant chemotherapy.<sup>20</sup> One explanation for this finding may be that the impact of the location and invasion of the brain tumor itself might be more salient than specific treatments. For brain tumor survivors who had received CNS irradiation, there is an increase in sleep disruption.<sup>21</sup>

**Surgical Therapy**

Surgical therapy is associated with impairment in physical health (Table 2)<sup>15</sup>; yet, in bone tumor survivors, no differences were noted in recipients of amputation versus recipients of limb-sparing procedures in both overall functioning and HRQOL.<sup>23</sup> Interestingly, amputees report less functional impairment and lower levels of anxiety and somatization compared with nonamputees.<sup>18,23</sup> Although limb-sparing procedures originally were intended to provide better psychological outcomes and function, a study in 1982, in fact, found no difference in QOL in extremity sarcoma patients who underwent amputation or limb-sparing procedures.<sup>25</sup>

**Chemotherapy**

Chemotherapy exposures, including alkylating agents and anthracyclines, are associated with an increase in physical impairment and psychological distress, including anxiety.<sup>15</sup> Survivors of leukemia

and lymphoma exposed to intensive chemotherapy report more psychological distress, including depression and somatization.<sup>24</sup> Among survivors of neuroblastoma, kidney tumors, bone tumors, and sarcomas, exposure to alkylators also is associated with more psychological distress, including depression.<sup>18</sup>

**NEUROCOGNITIVE OUTCOMES**

Neurocognitive dysfunction is demonstrated in up to 40% of childhood cancer survivors in one or more specific domains (eg, processing speed, attention, memory).<sup>26,27</sup> Impairment in these domains can impede the ability to learn new information, and the maintenance of previously learned information, and ultimately can lead to declines in global intellect.<sup>28</sup> This, in turn, can result in poor academic and vocational success, low self-esteem, and behavioral or emotional disorders.

Attention problems have been reported in adolescents who are long-term survivors of childhood cancer. In a comparison of 2,979 survivors and 649 siblings between 12 and 17 years of age, Schultz et al<sup>18</sup> reported that survivors were more likely to demonstrate attention problems on the basis of parent report (RR, 1.4; 95% CI, 1.1 to 1.9). In particular, compared with siblings, elevated rates of attention problems were reported in survivors of leukemia (RR, 1.5; 95% CI, 1.2 to 2.0) and CNS tumors (RR, 1.8; 95% CI, 1.2 to 2.5). In addition, such problems were more common in patients treated with cranial radiation alone (RR, 1.8; 95% CI, 1.2 to 2.6) or when combined with

**Table 2.** Frequencies and Percentages of Survivors With Poor Outcomes on the SF-36

Variable	Sample Size (n)	Physical Function				Physical Role				Bodily Pain				General Health				Vitality			
		No.	%	OR	95% CI	No.	%	OR	95% CI	No.	%	OR	95% CI	No.	%	OR	95% CI	No.	%	OR	95% CI
<b>Sex</b>																					
Male	3,481	292	8.9	—	549	16.8	—	346	10.6	—	511	15.7	—	1,031	31.6	—					
Female	3,666	457	13.2	1.7	1.4 to 2.0	791	22.8	1.5	1.3 to 1.7	539	15.5	1.6	1.4 to 1.8	794	22.9	1.6	1.4 to 1.9	1,653	47.6	2.0	1.8 to 2.2
<b>Age at diagnosis, years</b>																					
0-3	2,211	171	8.2	0.5	0.4 to 0.6	323	15.5	0.5	0.4 to 0.7	217	10.4	0.5	0.4 to 0.7	346	16.6	0.6	0.5 to 0.8	790	37.8	0.9	0.8 to 1.0
4-9	2,137	189	9.5	0.5	0.4 to 0.7	374	18.7	0.7	0.6 to 0.8	232	11.6	0.6	0.5 to 0.8	362	18.1	0.7	0.6 to 0.9	785	39.3	1.0	0.8 to 1.1
10-14	1,497	188	13.3	0.8	0.6 to 1.0	330	23.4	0.9	0.7 to 1.1	221	15.7	0.9	0.7 to 1.0	292	20.7	0.8	0.7 to 1.0	607	43.0	1.1	1.0 to 1.3
15-20	1,302	201	16.2	—	—	313	25.2	—	—	215	17.3	—	—	305	24.6	—	—	502	40.5	—	—
<b>Survival time, years</b>																					
< 20	1,985	164	8.7	0.5	0.4 to 0.7	340	18.0	0.7	0.6 to 0.9	225	11.9	0.7	0.5 to 0.9	322	17.1	0.6	0.5 to 0.8	723	38.3	0.9	0.8 to 1.1
20-24	2,432	247	10.4	0.6	0.5 to 0.8	456	19.1	0.8	0.6 to 0.9	290	12.2	0.7	0.5 to 0.9	448	18.8	0.7	0.6 to 0.8	937	39.3	1.0	0.8 to 1.1
25-29	1,829	223	13.0	0.8	0.6 to 1.0	364	21.2	0.8	0.7 to 1.0	243	14.2	0.8	0.6 to 1.0	338	19.7	0.7	0.6 to 0.8	717	41.8	1.0	0.9 to 1.3
≥ 30	801	115	15.2	—	—	180	23.8	—	—	127	16.8	—	—	197	26.1	—	—	307	40.7	—	—
<b>Surgery</b>																					
Yes	5,403	653	12.1	1.9	1.5 to 2.5	1106	20.5	1.2	1.0 to 1.5	726	13.4	1.2	1.0 to 1.4	1063	19.7	1.1	0.9 to 1.3	2149	39.8	1.1	1.0 to 1.3
No	1,334	96	7.2	—	—	234	17.5	—	—	159	11.9	—	—	242	18.1	—	—	535	40.1	—	—
<b>Chemotherapy</b>																					
Yes	5,326	565	10.6	1.0	0.9 to 1.2	1033	19.4	1.0	0.8 to 1.1	696	13.1	1.1	0.9 to 1.4	1,036	19.5	1.1	1.0 to 1.6	2,093	39.3	0.9	0.8 to 1.1
No	1,411	184	13.0	—	—	307	21.8	—	—	189	13.4	—	—	269	19.1	—	—	591	41.9	—	—
<b>Radiation</b>																					
Cranial	2,057	239	11.6	1.3	1.1 to 1.6	434	21.1	1.4	1.2 to 1.6	263	12.8	1.1	0.9 to 1.3	387	18.8	1.3	1.1 to 1.6	872	42.4	1.1	1.0 to 1.3
Other than cranial	2,415	281	11.6	0.9	0.7 to 1.1	523	21.7	1.2	1.0 to 1.4	345	14.3	1.0	0.9 to 1.2	572	23.7	1.6	1.3 to 1.8	981	40.6	1.1	0.9 to 1.2
None	2,265	229	10.1	—	—	383	16.9	—	—	277	12.2	—	—	346	15.3	—	—	831	36.7	—	—

  

Variable	Sample Size (n)	Emotional Role				Social Function				Mental Health				Physical Component Summary				Mental Component Summary			
		No.	%	OR	95% CI	No.	%	OR	95% CI	No.	%	OR	95% CI	No.	%	OR	95% CI	No.	%	OR	95% CI
<b>Sex</b>																					
Male	3,481	505	15.5	—	408	12.5	—	244	7.5	—	422	12.9	—	556	17.0	—					
Female	3,666	763	22.0	1.6	1.4 to 1.8	600	17.3	1.5	1.3 to 1.7	352	10.1	1.4	1.2 to 1.7	646	18.6	1.6	1.4 to 1.9	802	23.1	1.5	1.3 to 1.7
<b>Age at diagnosis, years</b>																					
0-3	2,211	397	19.0	1.0	0.9 to 1.3	320	15.3	1.0	0.8 to 1.3	201	9.6	1.2	0.9 to 1.6	239	11.4	0.4	0.3 to 0.5	436	20.9	1.2	1.0 to 1.5
4-9	2,137	378	18.9	1.1	0.9 to 1.3	289	14.5	1.0	0.8 to 1.2	182	9.1	1.2	0.9 to 1.5	272	13.6	0.5	0.4 to 0.6	415	20.8	1.2	1.0 to 1.5
10-14	1,497	266	18.9	1.0	0.9 to 1.3	213	15.1	1.0	0.8 to 1.2	118	8.4	1.1	0.8 to 1.4	266	18.9	0.7	0.7 to 0.9	283	20.1	1.2	1.0 to 1.4
15-20	1,302	227	18.3	—	—	186	15.0	—	—	95	7.7	—	—	291	23.5	—	—	224	18.1	—	—
<b>Survival time, years</b>																					
< 20	1,985	356	18.9	0.9	0.7 to 1.2	277	14.7	0.9	0.7 to 1.1	173	9.2	0.9	0.7 to 1.2	235	12.5	0.5	0.4 to 0.6	379	20.1	1.2	1.0 to 1.5
20-24	2,432	437	18.3	0.9	0.7 to 1.1	331	13.9	0.8	0.6 to 1.0	192	8.1	0.8	0.6 to 1.1	356	14.9	0.7	0.6 to 0.9	478	20.1	1.2	1.0 to 1.5
25-29	1,829	325	19.0	0.9	0.8 to 1.2	272	15.9	0.9	0.7 to 1.2	159	9.3	1.0	0.7 to 1.3	306	17.9	0.7	0.6 to 0.9	355	20.7	1.2	1.0 to 1.4
≥ 30	801	150	19.9	—	—	128	17.0	—	—	72	9.5	—	—	171	22.6	—	—	146	19.3	—	—
<b>Surgery</b>																					
Yes	5,403	1024	19.0	1.2	1.0 to 1.4	821	15.2	1.2	1.0 to 1.5	472	8.7	1.1	0.9 to 1.4	906	16.8	1.5	1.2 to 1.8	1,097	20.3	1.2	1.0 to 1.4
No	1,334	244	18.3	—	—	187	14.0	—	—	124	9.3	—	—	162	12.1	—	—	261	19.6	—	—
<b>Chemotherapy</b>																					
Yes	5,326	1001	18.8	1.0	0.9 to 1.2	785	14.7	1.0	0.8 to 1.1	480	9.0	1.1	0.9 to 1.4	821	15.4	1.1	0.9 to 1.3	1,071	20.1	1.0	0.9 to 1.2
No	1,411	267	18.9	—	—	223	15.8	—	—	116	8.2	—	—	247	17.5	—	—	287	20.3	—	—
<b>Radiation</b>																					
Cranial	2,057	381	18.5	1.0	0.8 to 1.1	318	15.5	1.1	1.0 to 1.4	186	9.0	1.0	0.8 to 1.2	330	16.0	1.4	1.2 to 1.6	400	19.4	0.9	0.8 to 1.1
Other than cranial	2,415	447	18.5	0.9	0.8 to 1.1	364	15.1	1.0	0.9 to 1.2	200	8.3	0.9	0.7 to 1.1	438	18.1	1.1	1.0 to 1.4	481	19.9	0.9	0.8 to 1.1
None	2,265	440	19.4	—	—	326	14.4	—	—	210	9.3	—	—	300	13.2	—	—	477	21.1	—	—

NOTE. Models adjusted for all variables in left column of the table. Odds ratios and 95% confidence intervals compared poor outcomes by treatment variables. Abbreviations: SF-36, Medical Outcomes Survey Short Form-36; OR, odds ratio.

intrathecal methotrexate (RR, 1.6; 95% CI, 1.2 to 1.6) compared with those survivors who were not receiving CNS treatment.

Neurocognitive problems have been reported to extend into adulthood for long-term survivors of childhood cancer. In an examination of functional limitations in 7,147 adult survivors, Ness et al<sup>19</sup> indicated that 14% of survivors reported impairment in executive functioning (ie, abilities required for the planning, implementing, monitoring, and adaptation of behavior for success in one's environment). In addition, in a comparison of healthy survivors who received no CNS treatment and the siblings of survivors, those survivors who received high-dose cranial radiation to frontal areas of their brains (ie, ≥ 35 Gy) reported significantly more problems with attention and processing speed, memory, and emotional regulation (Table 3).<sup>12</sup> Thus, neurocognitive problems appear prevalent in this cohort, particularly for those treated with cranial radiation when measured by the CCSS-NCQ. See the Childhood Cancer Survivor Study Neurocognitive Questionnaire section for review of the validation process of this new instrument. The specific treatment factors that lead to increased neurocognitive problems, and the functional consequences of these problems, are yet to be determined. In addition, although the validity of self-reported ratings of neurocognitive impairment has been previously demonstrated,<sup>29</sup> data collection currently is ongoing to compare the CCSS-NCQ to formal neuropsychological testing.

PSYCHOLOGICAL FUNCTION AND HEALTH BEHAVIORS

Psychological functioning appears related to health behaviors in long-term survivors of childhood cancer. In an examination of smoking behavior in survivors, Emmons et al<sup>30</sup> reported that 28% of survivors had a history of being a smoker and that 17% were current smokers at the time of long-term follow-up. Predictors of smoking initiation include a household income less than \$20,000 (RR, 1.6; 95% CI, 1.3 to 1.8) and less than a high school education (RR, 2.8; 95% CI, 2.3 to 3.3). A reduced risk of smoking initiation was related to cancer diagnosis before 10 years of age (RR, 0.81; 95% CI, 0.72 to 0.91), receipt of pulmonary-toxic treatment (RR, 0.88; 95% CI, 0.79 to 0.98), and receipt of brain radiation (RR, 0.61; 95% CI, 0.53 to 0.69). In a follow-up study in which the survivors identified as current smokers, the number of cigarettes smoked was related to older age at diagnosis, lower educational attainment, and increased total emotional distress, as measured by the BSI.<sup>30</sup>

Alcohol use has also been examined in long-term survivors of childhood cancer. Lown et al<sup>31</sup> examined alcohol consumption patterns in 10,398 survivors and 3,034 of their siblings. Drinking behavior was also compared with 4,774 individuals from the National Alcohol Survey.<sup>32</sup> Compared with the siblings, survivors were less likely to be current drinkers (OR, 0.6; 95% CI, 0.5 to 0.6) and were less likely to be risky or heavy drinkers (OR, 0.7; 95% CI, 0.6 to 0.8).<sup>31</sup> Among those survivors who did report drinking, heavy drinking was more likely in those who reported poor health (OR, 1.5; 95% CI, 1.1 to 1.9), depression (OR, 1.7; 95% CI, 1.4 to 2.2), anxiety (OR, 1.4; 95% CI, 1.1 to 1.9), and somatic distress (OR, 1.7; 95% CI, 1.2 to 2.2). Compared with survivors of leukemia, survivors of Wilms tumor had greater reports of heavy drinking (OR, 1.5; 95% CI, 1.1 to 2.1), neuroblastoma (OR, 1.6; 95% CI, 1.1 to 2.3), and bone cancers (OR, 1.7; 95% CI, 1.2 to 2.2).

Thus, emotional distress is related to health behaviors in long-term survivors. Specifically, smoking initiation is higher in survivors with low socioeconomic status, who themselves are at increased risk for emotional distress. It is not surprising, therefore, to find that the degree of emotional distress is related to the intensity of smoking behavior. Such distress is also related to the intensity of alcohol consumption in current drinkers.

RELATIONSHIP BETWEEN PHYSICAL HEALTH AND PSYCHOLOGICAL STATUS

Chronic health conditions have been associated with psychological outcomes. In a comparison of 1,101 survivors of CNS tumors, Zebrack et al<sup>20</sup> reported a correlation between health status and psychological functioning. Those survivors who rated their own health as poor also reported significantly more symptoms of depression, anxiety, and somatic distress. In addition, experience of a major medical condition within the past 2 years was related to the degree of reported somatic distress. Zeltzer et al<sup>16</sup> reported a similar association in a larger group of cancer survivors. When 7,147 survivors of various cancer diagnoses were compared with 388 sibling controls, those survivors with a history of a major medical condition reported more symptoms of depression (OR, 1.2; 95% CI, 1.0 to 1.4), anxiety (OR, 1.2; 95% CI, 1.0 to 1.6), and somatic distress (OR, 1.3; 95% CI, 1.1 to 1.6).

Poor health also has been associated with self-reported QOL. Nagarajan et al<sup>23</sup> examined HRQOL in 528 survivors of lower-extremity osteosarcoma and Ewing sarcoma. Of these survivors, 9.7%

Table 3. Mean CCSS-NCQ Scores for Various Survivor Risk Groups

Variable	Risk Group*								F	Group Comparison†
	CRT ≥ 35 Gy		Neurologic		Healthy		Sibling			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Task efficiency	16.5	5.18	16.2	5.17	11.8	3.26	11.9	3.12	127.65	1, 2 > 3, 4
Emotional regulation	5.5	1.81	5.7	1.81	5.1	1.67	5.0	1.60	11.82	1, 2 > 3, 4
Organization	4.9	1.77	5.0	1.80	4.4	1.50	4.6	1.61	12.03	2 > 3, 4; 1 > 2
Memory	7.6	2.47	7.1	2.36	5.8	1.85	5.8	1.77	71.41	1, 2 > 3, 4

NOTE. Analyses were adjusted for age and sex through covariate analysis.

Abbreviations: CCSS-NCQ, Childhood Cancer Survivor Study Neurocognitive Questionnaire; CRT, chemoradiotherapy; SD, standard deviation.

\*Healthy indicates survivor with no history of central nervous system–based diagnosis or treatment and no chronic health conditions. Neurologic indicates survivor with history of stroke and/or epilepsy post–cancer treatment.

†Significant differences were based on *P* < .05 with Bonferroni correction for multiple comparisons.

reported experiencing poor health. In this study, HRQOL was evaluated in areas of physical, psychological, social, and spiritual functioning. Poor health was significantly related to reduced QOL (OR, 7.5; 95% CI, 3.7 to 15.2). In a related study, Ness et al<sup>19</sup> examined the association between physical mobility and emotional outcomes. When this relation was compared in 7,147 survivors of various cancer diagnoses, these investigators demonstrated a link between limitations in physical performance and emotional QOL. Specifically, those patients with limitations in physical mobility more often reported emotional problems that additionally limited their functioning (OR, 1.5; 95% CI, 1.3 to 1.8).

Sleep quality and fatigue also have been examined in long-term survivors. In a comparison of 1,897 long-term survivors of childhood cancer with 369 of their siblings, Mulrooney et al<sup>21</sup> reported that survivors were significantly more fatigued than their sibling controls (OR, 1.9; 95% CI, 1.3 to 2.9).<sup>21</sup> However, no significant group differences were reported for the presence of sleep disorders (OR, 1.4; 95% CI, 0.9 to 1.9) or daytime sleepiness (OR, 1.0; 95% CI, 0.7 to 1.4). Within the group of survivors, increased fatigue was related to depression (OR, 7.5; 95% CI, 5.1 to 10.9) and being unmarried (OR, 2.7; 95% CI, 2.0 to 3.6). The presence of depression was also associated with the report of more sleep disorders (OR, 4.4; 95% CI, 3.1 to 6.3) and of increased daytime sleepiness (OR, 3.4; 95% CI, 2.3 to 5.0). Interestingly, the presence of congestive heart failure was also independently related to increased fatigue (OR, 2.9; 95% CI, 1.4 to 6.1), sleep disorders (OR, 4.0; 95% CI, 2.0 to 8.0), and increased daytime sleepiness (OR, 4.2; 95% CI, 2.0 to 8.7).

Thus, in addition to the direct role of cancer diagnosis and specific treatments, the subsequent role of recovery and chronic health conditions, and fatigue and sleep, can impact psychological functioning and adjustment in the long-term survivor.

#### FUTURE DIRECTIONS: IMPLICATIONS FOR INTERVENTION

Although the contributions made by the CCSS to the study of psychosocial outcomes of childhood cancer survivors have been significant, the ultimate goal for better understanding of these outcomes must be to develop interventions to improve them. An expressed goal of psychosocial oncology research and intervention is to facilitate patients' and family members' adjustment to the short- and long-term consequences of treatment, recovery, and survivorship.<sup>33</sup> Studies of psychosocial outcomes in the CCSS cohort indicate that childhood cancer confers some increased risk of problems in psychosocial adaptation, even many years after completion of therapy. Although most individual survivors can expect to achieve positive psychosocial adjustment and life satisfaction in adulthood, many survivors will experience limitations in social and psychological well-being. Moreover, many survivors, even those apparently doing quite well on distress scales, may continue to have concerns related to their treatment—including concerns about their physical health, body image, or self-concept, access to life and health insurance, jobs and career options, and continued care from a skilled and attentive medical system.<sup>34-36</sup> By reporting on the long-term psychosocial outcomes of childhood cancer survivors, reports from the CCSS can identify the significant areas of difficulty these survivors experience and can identify the groups of vulnerable survivors who are at greatest risk for poor outcomes.

Findings from the CCSS indicate that fatigue and psychological distress, including symptoms of depression and anxiety, are significant issues for a subgroup of adult survivors of childhood cancers, particularly among those who are women, are unemployed, have low income levels, and are struggling with late or delayed effects of cancer therapy. This finding is similar to that reported in studies of survivors of adult cancers, in which many adults are psychologically healthy but in which younger adults and those more heavily treated, such as those in a bone marrow transplant group, show the most pronounced psychological effects.<sup>37-39</sup> These findings in both adult and childhood cancer survivors suggest that a subgroup of long-term survivors may benefit from psychological assessments and targeted interventions as part of long-term follow-up care. The caveat in the QOL and psychological outcome findings from the CCSS is the issue of clinical versus statistical significance. Clearly, studies that involve a large cohort may be overpowered to provide statistical significance in many domains. In the CCSS, siblings were used as a closer-matched control group than just normative data for comparisons. Although there are some areas in which siblings might indicate more problems than the general population, such survivor-sibling comparisons would make significant differences clinically meaningful and conservative. In this series of studies, normative data were also used for comparisons, when available, and risk estimates were made by using clinically significant cutoff scores, such as  $T \geq 63$  for the subscales of the BSI-18. The issue of clinical versus statistical significance in the assessment of QOL is discussed by Cella et al.<sup>40</sup>

Ideally, late psychological effects in survivors would be prevented best during childhood cancer treatment. Clinic-based family interventions have shown efficacy in the promotion of psychological adaptation and reduction of distress in pediatric cancer patients.<sup>41</sup> Continued research of these interventions will lead to better understanding of their potential to affect long-term adjustment. In addition to interventions aimed at the prevention of long-term adjustment problems, research also needs to focus on addressing these concerns when they develop in childhood cancer survivors. Psychological interventions to help survivors of adult cancers cope with anxiety and depression have been developed,<sup>42-44</sup> and adaptation of these programs for survivors of childhood cancers may be a promising strategy to pursue. Interventions to address fatigue in childhood cancer survivors may similarly benefit from research on adult survivors.<sup>45,46</sup> Such interventions will need to address the potential contribution of medical factors (eg, endocrine, metabolic, cardiac, neurologic). Adaptation of existing exercise and other lifestyle interventions developed to reduce fatigue in other cancer populations should be a priority for research in the childhood cancer survivor population.

Survivors with medical morbidities and poor overall health were identified in several CCSS studies as having increased risk for poor psychosocial adaptation. These results indicate that intervention for these survivors will need to target several aspects of cancer therapy and aftercare. Pediatric oncology research continues to focus on decreasing toxicity of therapies, and these findings have the potential to succeed at primary prevention for these medical late-effects of treatment.<sup>47</sup> Secondary and tertiary prevention of the psychosocial consequences of these morbidities may be realized by interventions that help survivors optimize their medical care for their conditions as well as interventions aimed at helping them cope more effectively with the burden of illness. Several programs for patient education, decision

support, and positive coping have been developed for other aspects of cancer care<sup>48,49</sup> and other diseases,<sup>50,51</sup> and research should now focus on adapting these approaches to survivors of childhood cancer who face similar medical problems—including pain and limitations in daily living, such as limited mobility.

Results from the CCSS clearly identify brain tumor survivors as a particularly vulnerable group, whose members report more psychological distress, fatigue, cognitive problems, and diminished life satisfaction. Neuropsychological problems seen in these survivors, and, to a lesser extent in survivors of other diseases who also received cranial radiation, have been previously characterized,<sup>52,53</sup> but CCSS findings demonstrate the ongoing difficulties faced by these survivors and the associated risk for psychological problems. Targets of intervention for these survivors should include ongoing efforts to reduce toxicities of therapy as well as interventions aimed at helping these survivors receive the specialized cognitive, educational, and vocational services they require. Several clinical programs that address these survivor needs have been developed,<sup>54,55</sup> but more research is needed to evaluate their effectiveness. Intervention addressed at public policy-makers to ensure the availability of special education programs for patients who miss school or who have cognitive and emotional disabilities should be encouraged. Policies that ensure nondiscrimination in survivors' access to advanced educational opportunities and nondiscrimination in employment should be encouraged also. Cognitive remediation trials aimed at helping survivors improve their cognitive abilities have reported some positive results,<sup>56</sup> and future research in this area is particularly promising. In several of the CCSS reports, limited educational achievement and lower income were associated with a variety of psychosocial problems, which highlights the need to make interventions that promote cognitive functioning and educational achievement priority areas.

In addition to identifying the priority areas for psychosocial intervention research with childhood cancer survivors, the CCSS itself can be used for development and evaluation of interventions for these

survivors. Because of its large and representative cohort of survivors in whom treatment exposures and post-treatment outcomes have already been documented, the CCSS represents a valuable resource to support this work. Emmons et al<sup>57</sup> successfully used the CCSS cohort to develop a clinically effective telephone intervention for smoking cessation, and other intervention trials are expected to be developed. Health interventions increasingly use telephone, internet, DVD, or other methods to make interventions deliverable to large groups of geographically dispersed participants,<sup>58,59</sup> and these methods can be developed and tested quite efficiently by using the CCSS. Telephone interventions have already been developed for adult cancer survivors to reduce psychological distress and fatigue<sup>43-45</sup> and to promote a variety of health behaviors,<sup>60,61</sup> and these should be used as models for developing interventions for childhood cancer survivors. With more of these intervention studies in place, the CCSS will expand the current evidence-based interventions available for childhood cancer survivors and will demonstrate how they can be extended to the broader community and to a more diverse population of survivors. Ultimately, this research must answer the questions of where best to offer which supportive care interventions, and to whom, to definitively support implementation of and reimbursement for these intervention services.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

#### AUTHOR CONTRIBUTIONS

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