

## Survivors of Childhood Cancer in the United States: Prevalence and Burden of Morbidity

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### Abstract

**Background:** No studies have estimated the population-level burden of morbidity in individuals diagnosed with cancer as children (ages 0–19 years). We updated prevalence estimates of childhood cancer survivors as of 2011 and burden of morbidity in this population reflected by chronic conditions, neurocognitive dysfunction, compromised health-related quality of life, and health status (general health, mental health, functional impairment, functional limitations, pain, and fear/anxiety).

**Methods:** Surveillance, Epidemiology, and End Results (SEER) Program data from 1975 to 2011 were used to update the prevalence of survivors of childhood cancers in the United States. Childhood Cancer Survivor Study data were used to obtain estimates of morbidity burden indicators, which were then extrapolated to SEER data to obtain population-level estimates.

**Results:** There were an estimated 388,501 survivors of childhood cancer in the United States as of January 1, 2011, of whom

83.5% are  $\geq 5$  years after diagnosis. The prevalence of any chronic condition among  $\geq 5$ -year survivors ranged from 66% (ages 5–19) to 88% (ages 40–49). Estimates for specific morbidities ranged from 12% (pain) to 35% (neurocognitive dysfunction). Generally, morbidities increased by age. However, mental health and anxiety remained fairly stable, and neurocognitive dysfunction exhibited initial decline and then remained stable by time since diagnosis.

**Conclusions:** The estimated prevalence of survivors of childhood cancer is increasing, as is the estimated prevalence of morbidity in those  $\geq 5$  years after diagnosis.

**Impact:** Efforts to understand how to effectively decrease morbidity burden and incorporate effective care coordination and rehabilitation models to optimize longevity and well-being in this population should be a priority. *Cancer Epidemiol Biomarkers Prev*; 24(4): 653–63. ©2015 AACR.

### Introduction

Estimates of the overall 5-year survival rates for childhood cancers have steadily increased since the 1970s and are currently over 80% (1). Although increased survival rates are promising, the low specificity of curative treatments for childhood cancer often results in long-term and late effects due to their impact on normal healthy tissues (2). Thus, survivors of childhood cancer are at an increased risk of adverse health and quality of life outcomes compared with individuals without a cancer history (3). These include increased number and severity of chronic health conditions (4, 5), health limitations (6, 7), hospitalizations (8, 9),

premature frailty (10), psychologic distress (11), neurocognitive dysfunction (11, 12), and reduced productivity (i.e., inability to work or limitation in amount/kind or work) due to health problems (6). Adult survivors of childhood cancers also report poorer overall health (6, 13) and physical health-related quality of life (HRQOL; ref. 11). Prevalence for most of these adverse outcomes is estimated from individual cohort studies with less known about the burden of morbidity in childhood cancer survivors at the population level. As the number of survivors is expected to continue to increase due to increased incidence (14) and advances in lifesaving treatments, defining the public health and healthcare implications of childhood cancer survivors is an important next step.

Although no U.S. population-based study of childhood cancer survivors exists, the Childhood Cancer Survivor Study (CCSS) provides rich, high-quality data on a range of potential adverse and late effects of cancer treatment (15–17). CCSS is a large, geographically, and socioeconomically diverse, retrospectively established cohort study that prospectively follows health and disease outcomes in individuals from 26 North American pediatric cancer hospitals who were diagnosed with cancer during childhood or adolescence and survived at least 5 years. Using statistical models, data relevant to morbidity can be extrapolated from CCSS and applied to population-level survivorship prevalence data from the Surveillance Epidemiology and End Results (SEER) program, a collection of population-based registries of cancer incidence and survival in the United States (<http://seer.cancer.gov>). Combining CCSS and SEER data can provide an

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estimation of the population-level burden of morbidity in absolute numbers of affected childhood cancer survivors rather than relying only on CCSS data.

The purpose of the present study is 2-fold: (i) to update previously published (16) prevalence estimates of childhood cancer survivors in the United States through 2011 using SEER and (ii) to estimate the burden of morbidity among  $\geq 5$ -year survivors of childhood cancer in the United States.

## Materials and Methods

### Data sources

**SEER data.** SEER (18) data on incidence and survival from cancers diagnosed in individuals  $\leq 19$  years of age from 1975 to 2011 in 9 SEER registries including the states of Connecticut, Hawaii, Iowa, New Mexico, and Utah and the metropolitan areas of Atlanta, Detroit, San Francisco-Oakland, and Seattle/Puget Sound were used to estimate prevalence. These registries represent approximately 10% of the U.S. population. Cancer sites considered for prevalence estimates are those identified by the International Classification for Childhood Cancer ICD-O3 codes consistent with other publications using these data (19, 20). To match CCSS and SEER data, cancer sites were restricted to those in the CCSS study: leukemia, brain and central nervous system tumors, Hodgkin lymphoma, non-Hodgkin lymphoma, renal tumors, neuroblastoma, soft tissue, and bone tumors. CCSS brain tumors that were either germ cells or benign/borderline were excluded from CCSS data to better align with the SEER histology data. We used population estimates from the U.S. Census Bureau in the SEER\*stat software (21).

**CCSS burden of morbidity data.** The CCSS cohort includes over 14,000 long-term survivors of childhood cancer diagnosed between 1970 and 1986. Since enrollment in 1994 to 1998, participants have been periodically surveyed to track health outcomes, healthcare use patterns, and health behaviors and practices. The CCSS cohort study design and methodology have been previously described (15–17). The prevalence of factors contributing to the morbidity burden in survivors of childhood cancer 5 or more years following diagnosis was estimated using self-reported CCSS cohort data. These factors include chronic health conditions, neurocognitive functioning, HRQOL, and health status indicators. Table 1 summarizes the measures, cutoff values, and assessment time points used to estimate morbidity burden in the present study. For the purposes of this study, only CCSS survivors diagnosed between 1970 and 1986, who were ages 0 to 19 at diagnosis, were included to provide as similar a population to that in SEER as possible. Survivors with germ cell tumors ( $n = 62$ ) were excluded because these tumor types were only captured for central nervous system patients and brain in the CCSS cohort. Survivors with benign or borderline brain and central nervous system tumors were also removed ( $n = 35$ ) because these data were not incorporated into SEER until 2004.

### Data analyses

**Prevalence of childhood cancer survivors.** Data on incidence and survival from 1975 to 2011 from the SEER registries were used to update prevalence estimates of childhood cancer survivors by anatomic sites and all cancer sites, combined, in the United States through January 1, 2011. The number of people in the United States alive in 2011 and diagnosed with cancer between ages 0

and 19 years was calculated in 3 steps. First, the proportion of survivors alive in the SEER-9 areas diagnosed with childhood cancer at ages 0 to 19 years between the years 1975 and 2011 was calculated by cancer site, sex, race (white, black, other; where unknown race was grouped with white race), and age using the SEER\*Stat software (21) and the counting method (22). Second, to estimate complete U.S. childhood cancer survivor prevalence, the site/sex/race/age-specific SEER cancer prevalence proportions were multiplied by the respective U.S. sex/race/age-specific populations. To obtain overall prevalence, these categories were summed. Third, complete prevalence of childhood cancer, which includes childhood cancers diagnosed before 1975 (i.e., with  $\geq 36$  years from prevalence date), was calculated using the CHILDPREV method (16, 23). Briefly, this method estimates the long-term childhood cancer survivors, diagnosed before 1975, using age and period parametric cancer site/sex-specific incidence and survival models fitted to SEER data. Prevalence was examined by sex, age at prevalence estimate (0–19, 20–29, 30–39, 40–49, 50–59, and  $\geq 60$  years), and cancer type (leukemia, acute lymphocytic leukemia, acute myelogenous leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, brain/central nervous system, neuroblastoma and other peripheral nervous cell tumor, renal tumors, malignant bone tumors, osteosarcoma, Ewing tumor and related sarcomas of bone, soft tissue and other extraosseous sarcomas, germ cell and trophoblastic tumors, and neoplasms of gonads).

**Representativeness of CCSS.** To ensure that the CCSS data were representative of the larger U.S. population of childhood cancer survivors, prevalence of all cancers by age at diagnosis (0–4, 5–9, 10–14, and 15–19 years), sex and race (white/unknown, black or other), and each cancer type listed, above, were calculated and compared for the SEER population-based and CCSS samples.

**Burden of morbidity.** To estimate the burden of morbidity of U.S. childhood cancer survivors, data on chronic conditions, neurocognitive dysfunction, HRQOL, and health status indicators were extrapolated from CCSS to U.S. prevalence data. Some adjustments were made to combine morbidity proportions from CCSS and SEER prevalence data to reflect the CCSS sample: (i) prevalence estimates were restricted to people who survived  $\geq 5$  years; (ii) complete prevalence up to 36 years duration was used instead of complete prevalence because this was the maximum length of follow-up for CCSS data; and (ii) only cancers considered in CCSS were included.

We used a logistic regression model to estimate prevalence of morbidities as the proportion of subjects who had experienced the binary outcome of interest as of a specified postdiagnosis period (or age). At-risk subjects were classified into prevalent cases versus noncases at each interval using reported age at onset (chronic conditions, assessed retrospectively) or age at assessment time point (all other variables). Given the follow-up time frame for the CCSS cohort, we were only able to estimate the burden of morbidity indicators up to 36 years after diagnosis for survivors 5 to 49 years of age. Binary outcome variables examined included presence of (a) any (grades 1–4) chronic conditions; (b) any grade 1 (mild) or grade 2 (moderate), and any grade 3 (severe) or grade 4 (life-threatening or disabling) chronic conditions; (c) multiple ( $\geq 2$  and  $\geq 3$ ) grade 3 or 4 chronic conditions (4); (d) neurocognitive dysfunction; (e) compromised mental or physical HRQOL; and (f) moderate to extreme impairments in health status

**Table 1.** Measures, cutoff values, and time schedule of data collection for burden of morbidity outcomes in CCSS

Morbidity outcome	Measure description	Cutoff value used to indicate compromised functioning, impairment or severity	Assessment time point			Number of records in model
			Baseline (1994-98)	2000	2003	
Chronic conditions/second cancers (4)	Self-reported or proxy-reported (if <18 years of age or deceased at the time of the questionnaire): a) physical health conditions and age at condition onset b) second cancer reports were verified by pathology report review	Severity determined by the Common Terminology for Adverse Events (version 4.03; ref. 39): a) Grade 1: Mild b) Grade 2: Moderate c) Grade 3: Severe d) Grade 4: Life-threatening or disabling - If condition not listed: categorized as "other, specify" according to organ system affected - If not enough information to distinguish between grades, lower score selected	X	X	X	13,974
Neurocognitive functioning: CCSS Neurocognitive Questionnaire (12, 40, 41)	Assesses degree (never, sometimes, often) to which participants experience any of 25 problems over the past 6 months. Has 4 subscales: a) Task efficiency b) Emotional regulation c) Organization d) Memory	T score <10th percentile of sibling groups' norm (i.e., ≥63) on any subscale (12)	X			7,228
HRQOL: SF-36 (42, 43)	Assesses 8 health-related dimensions: physical functioning, physical limitations, pain, behavior disturbances due to emotional problems, mental capacity, perceptions of health, social functioning, and feelings of energy/fatigue. Yields 2 component measures: a) Physical component score (PCS) b) Mental component score (MCS)	Score ≤40 on either PCS or MCS subscales	X			7,228
Health status indicators (24) General health	In general, would you say that your health is excellent, very good, good, fair, or poor?	Report fair/poor health	X	X	X	11,634
Mental health	Brief Symptom Inventory 18 (BSI-18) to assess psychological symptoms on 3 symptom-specific subscales: depression, somatization, and anxiety	T scores ≥63 on any of the 3 symptom-specific subscales (24)	X	X	X	20,994
Functional impairment	Any impairment (yes/no) or health problems resulting in: a) needing help with personal care needs, such as eating, bathing, dressing, or getting around your home b) needing help in handling routine needs, such as every-day household chores, doing necessary business, shopping, or getting around for other purposes c) keeping you from holding a job or attending school	Positive response to a, b, or c	X			15,569
Limitations in activity	How long (≥3 months, <3 months, or not at all), over the last 2 years, was your health limited in: a) kinds or amounts of moderate activities you can do, such as moving a table, carrying groceries, or bowling b) walking uphill or climbing a few flights of stairs c) walking one block	Report limitation on a, b, or c for ≥3 months	X		X	15,569
Pain	Do you currently have pain as a result of your cancer or its treatment? (yes/no)	Reported medium to excruciating pain	X	X	X	11,111
Anxiety/fear	Do you currently have anxiety/fears as a result of your cancer or its treatment?	Reported medium to very many, extreme anxiety/fears	X	X	X	11,634
						20,994

indicators (24), including general health, mental health, functional status, functional limitations, pain, and anxiety/fear.

Chronic conditions were assessed at multiple time points. Thus, a participant could contribute observations in more than one follow-up/age period. Survivors with the onset of the condition before a given time period were assumed to have the condition in subsequent periods. The remainder of the health outcomes were obtained from one or more questionnaire time points (see Table 1) and were evaluated at the time points after diagnosis at which they were assessed. If a survivor completed two questionnaires within the same age or time since diagnosis interval, data from the later questionnaire were used. Table 1 provides detailed information on the number of unique cases and number of records used in analyses for each morbidity indicator. As chronic conditions were the most frequently assessed morbidity indicator, the sample and record size was largest for these outcomes. Because the remaining morbidity outcomes were obtained at varying frequencies, the denominators for these outcomes differ. Estimates for health status indicators do not include the 5- to 19-year age group because the Brief Symptom Inventory (BSI) assessment was limited to those subjects  $\geq 18$  years of age. Neurocognitive functioning and HRQOL were only assessed at 2003 follow-up when all survivors were  $\geq 14$  years after diagnosis. Consequently, estimates for these factors were limited to survivors 15 to 36 years after diagnosis.

Logistic regression models were fit for each binary outcome, incorporating years after diagnosis and age at that observation time, controlling for impact of sex, as needed. Because most individuals contributed multiple records to the analysis via the multiple time point scenario developed for the morbidity indicators assessed at multiple time points, the analysis utilized generalized linear models, with generalized estimating equations and robust sandwich variance estimates to account for intraperson correlation (25). Predicted probability estimates from the models provided estimates of the prevalence of morbidity indicators, along with associated confidence intervals and *P* values for comparisons between groups defined by covariate levels. Once final models were obtained for U.S. cancer prevalence and CCSS morbidity prevalence, combined estimates of the burden of morbidity after cancer for this subset of the U.S. population were obtained by multiplying the CCSS morbidity prevalence by the relevant number of SEER cancer survivors within the equivalent age/follow-up periods.

## Results

### SEER prevalence estimates

A total of 388,501 survivors of childhood cancer are estimated to be alive in the United States as of January 1, 2011 (Table 2). Of these, 83.5% had survived  $\geq 5$  years since their original diagnosis and 44.9% had survived  $\geq 20$  years. The cancer sites with the largest number of survivors were leukemia (75,677), brain (60,540), germ cell and trophoblastic tumors and neoplasms of gonads (38,439), and renal tumors (23,990). The proportion of long-term ( $\geq 20$  years) survivors varied by cancer site. Sites with the largest proportions of longer-term survivors were as follows: germ cell, trophoblastic tumors, and neoplasms of gonads (58%); renal (58%); soft tissues (57%); and Hodgkin lymphoma (48%). Acute lymphocytic leukemia was the site with the smallest proportion of long-term survivors with only 23% surviving  $\geq 20$  years. Childhood cancer survivors  $\geq 60$  years represented 5% of

all childhood cancer survivors. Germ cell, trophoblastic tumors and neoplasms of gonads (17.7%), and soft tissues (14.6%) cancer sites had the largest proportion of survivors  $\geq 60$  years of age.

### Representativeness of CCSS

CCSS participants were similar in terms of age at diagnosis, gender, race, and cancer type by time interval since diagnosis (see Table 3) to those reported in SEER, indicating CCSS was representative of the larger U.S. population of childhood cancer survivors to which the burden of morbidity data were extrapolated.

### Estimated burden of morbidity

Table 4 displays estimates of the number of prevalent cases for each morbidity indicator by age and time since diagnosis.

**Chronic conditions.** Approximately 70% of childhood cancer survivors were estimated to have a grade 1 or 2 (mild/moderate) chronic condition, and about one third (32%) were estimated to have a grade 3 or 4 (severe, disabling, or life-threatening) chronic condition. An estimated two thirds (68%) of childhood cancer survivors had any chronic condition 5 to 14 years after diagnosis with this number increasing to 77% and 85% at 15 to 24 and 25 to 36 years after diagnosis, respectively. Two thirds (66%) of childhood cancer survivors ages 5 to 19 years were projected to have any chronic condition (grades 1–4; see Fig. 1). This proportion increased with increasing age to 88% at ages 40 to 49 years (see Fig. 1), reflecting the consistent increase in the proportion of survivors with a grade 3 or 4 condition across age categories. Almost half (48%) of those ages 40 to 49 had a grade 3 or 4 chronic condition. An estimated 11% of survivors had two or more grade 3 or 4 conditions, over half of which (55%) occur in those ages 30 to 49. Finally, an estimated 4% of childhood cancer survivors had three or more grade 3 or 4 chronic conditions with just over half (57%) observed in those ages 30 to 49.

Grade 1 or 2 condition prevalence estimates were similar for males and females across age categories ranging from 38% to 44% (see Fig. 1). Grade 3 and 4 conditions increased for both males and females with increasing age, but the proportion of women in each age category was higher (*P* value < 0.001).

**Neurocognitive functioning.** An estimated 35% of childhood cancer survivors ages 20 to 49 had neurocognitive dysfunction. The estimated number of prevalent cases decreased by age category ranging from 40% to 33% (see Fig. 2) and was stable by time since diagnosis (36% and 35% at 15–24 and 25–36 years after diagnosis, respectively).

**HRQOL.** Estimated prevalence for compromised physical (PCS) and mental (MCS) HRQOL scores in survivors 20 to 49 years of age was 16% and 18%, respectively. The proportion of prevalent cases with compromised PCS scores increased across time since diagnosis and age categories from 14% to 19% and 10% to 23% (see Fig. 2), respectively. The proportion of survivors with MCS scores indicative of emotional problems was relatively consistent by time since diagnosis (18%–19%) and age category (16%–20%). In contrast with PCS, the prevalence of compromised MCS declined with increasing age (see Fig. 2).

**Health status.** Prevalence estimates for self-reported poor or fair health (13%), functional impairment (14%), activity limitations

**Table 2.** SEER estimates of the number of people previously diagnosed with cancer as children (ages 0–19 years) in the United States and alive January 1, 2011, by International Classification of Childhood Cancer (ICCC) group, age, time since diagnosis, and gender

Site	Gender/ age	Complete prevalence counts by age at prevalence						All ages	Time since diagnosis (in years)					
		0–19	20–29	30–39	40–49	50–59	60+		<5	5–10	10–<15	15–<20	≥20	≥36
All sites	Both	114,469	96,086	63,670	56,072	39,055	19,149	388,501	64,105	56,369	49,311	44,394	174,322	73,757
	Male	61,300	50,413	31,574	25,285	16,475	9,976	195,023	33,865	30,060	25,669	22,928	82,501	32,774
	Female	53,169	45,673	32,096	30,787	22,580	9,173	193,478	30,241	26,309	23,642	21,465	91,821	40,983
Leukemia (I)	Both	35,982	20,750	11,794	5,282	1,659	210	75,677	15,512	13,991	11,847	10,349	23,977	4,269
	Male	19,822	10,941	6,006	2,737	766	92	40,364	8,401	7,946	6,368	5,498	12,151	1,924
	Female	16,160	9,809	5,788	2,545	893	118	35,313	7,111	6,045	5,479	4,851	11,826	2,345
Acute lymphocytic leukemia	Both	30,395	16,935	9,972	4,732	564	3	62,601	12,299	11,277	10,063	8,626	20,335	3,265
	Male	16,803	9,125	5,220	2,611	308	2	34,069	6,818	6,440	5,441	4,735	10,635	1,696
	Female	13,592	7,810	4,752	2,121	256	1	28,532	5,481	4,838	4,622	3,891	9,700	1,569
Acute myelogenous leukemia (Ib)	Both	3,992	2,528	1,185	690	245	4	8,644	2,221	1,944	1,298	1,167	2,015	499
	Male	2,075	1,183	498	321	137	3	4,217	1,028	1,099	694	515	881	265
	Female	1,917	1,345	687	369	108	1	4,427	1,193	845	604	652	1,134	234
Hodgkin lymphoma (IIa)	Both	4,863	8,832	8,058	7,834	5,056	1,353	35,996	5,622	4,267	4,742	4,002	17,364	5,424
	Male	2,693	4,544	4,009	3,829	2,504	702	18,281	2,994	2,246	2,249	1,844	8,948	2,910
	Female	2,170	4,288	4,049	4,005	2,552	651	17,715	2,627	2,021	2,493	2,158	8,416	2,514
Non-Hodgkin lymphoma (IIb,c,e)	Both	6,654	6,888	4,353	2,908	1,759	1,146	23,708	4,949	4,190	3,446	2,837	8,285	3,441
	Male	4,405	4,445	3,060	1,852	937	672	15,371	3,071	2,637	2,410	2,018	5,235	1,865
	Female	2,249	2,443	1,293	1,056	822	474	8,337	1,879	1,553	1,036	818	3,050	1,576
Brain/central nervous system (III)	Both	20,913	15,272	9,006	8,615	5,044	1,690	60,540	10,660	9,349	8,185	7,230	25,116	10,996
	Male	11,275	8,482	4,792	4,318	2,269	751	31,887	5,586	5,114	4,428	4,009	12,750	5,011
	Female	9,638	6,790	4,214	4,297	2,775	939	28,653	5,074	4,235	3,757	3,221	12,366	5,985
Neuroblastoma and other peripheral nervous cell tumor (IV)	Both	9,632	3,883	2,119	1,741	1,446	830	19,651	3,096	2,971	2,222	2,464	8,899	3,991
	Male	4,936	2,015	988	588	438	216	9,181	1,655	1,485	1,095	1,222	3,724	1,252
	Female	4,696	1,868	1,131	1,153	1,008	614	10,470	1,441	1,486	1,127	1,241	5,176	2,739
Renal tumors (VI)	Both	7,787	4,702	3,809	4,280	2,554	858	23,990	2,439	2,336	2,711	2,610	13,894	7,904
	Male	3,862	2,174	1,729	2,403	1,379	500	12,047	1,158	1,137	1,276	1,352	7,124	4,473
	Female	3,925	2,528	2,080	1,877	1,175	358	11,943	1,282	1,199	1,434	1,257	6,771	3,431
Malignant bone tumors (VIII)	Both	3,567	4,417	3,167	2,568	2,417	907	17,043	3,110	2,421	1,871	2,051	7,591	3,570
	Male	2,066	2,569	1,787	1,290	1,053	472	9,237	1,986	1,208	1,259	1,089	3,695	1,645
	Female	1,501	1,848	1,380	1,278	1,364	435	7,806	1,123	1,213	612	962	3,896	1,925
Osteosarcoma (VIIIa)	Both	1,859	2,253	1,777	1,293	1,237	829	9,248	1,594	1,292	1,039	1,001	4,323	2,123
	Male	1,002	1,265	1,014	657	499	396	4,833	965	601	685	495	2,087	965
	Female	857	988	763	636	738	433	4,415	629	690	354	506	2,235	1,158
Ewing tumor and related sarcomas of bone (VIIIc)	Both	1,347	1,467	972	728	358	148	5,020	1,146	772	599	721	1,781	600
	Male	819	872	487	336	197	43	2,754	747	387	436	386	798	248
	Female	528	595	485	392	161	105	2,266	399	385	163	335	983	352
Soft tissue and other extraosseous sarcomas (IX)	Both	6,799	7,126	4,166	4,913	4,267	4,670	31,941	4,270	3,518	3,404	2,645	18,105	10,464
	Male	3,724	3,812	2,131	2,424	1,995	2,608	16,694	2,225	2,005	1,755	1,401	9,309	5,344
	Female	3,075	3,314	2,035	2,489	2,272	2,062	15,247	2,045	1,513	1,649	1,244	8,796	5,120
Germ cell and trophoblastic tumors and neoplasms of gonads (X)	Both	5,233	7,869	5,634	6,245	6,641	6,817	38,439	4,760	4,359	3,557	3,503	22,260	13,953
	Male	2,749	5,143	3,461	3,322	3,301	3,136	21,112	2,985	2,822	2,236	2,086	10,983	6,605
	Female	2,484	2,726	2,173	2,923	3,340	3,681	17,327	1,775	1,536	1,321	1,417	11,277	7,348

(14%), impaired mental health (17%), pain (12%), and anxiety/fear (13%) were similar for childhood cancer survivors ages 20 to 49 years. The proportion of prevalent cases for impaired overall health status, activity limitations, and pain increased by age ranging from 11% to 17%, 12% to 21%, and 10% to 15%, respectively (see Fig. 2). Impaired overall health status and pain remained stable by time since diagnosis while activity limitation remained stable up to 24 years after diagnosis and then declined at 25 to 36 years after diagnosis (12% vs. 18%). Impaired mental health and anxiety estimates remained stable by age and time since diagnosis. Finally, functional impairment prevalence estimates remained stable for survivors <40 years of age (13%) and increased for those 40 to 49 years (17%), and increased by time since diagnosis interval from 11% to 16%.

## Discussion

It is estimated that there were 388,501 childhood cancer survivors alive in the United States as of January 1, 2011, an increase of 59,849 from the previous (2005) estimate (20). Findings of this analysis indicate that 83.5% of those diagnosed with childhood cancer survived  $\geq 5$  years after their cancer diagnosis, with almost 45% surviving  $\geq 20$  years. Moreover, 5% of childhood cancer survivors were  $\geq 60$  years of age. The increased prevalence of childhood cancer survivors through 2011 reflects ongoing treatment successes for a variety of childhood cancers. Moreover, by applying rates for selected adverse outcomes obtained from the CCSS cohort, we present the first population-level estimates of the number of survivors experiencing morbidity.

**Table 3.** Demographic and disease characteristics of the CCSS sample compared with U.S. survivors<sup>a</sup> diagnosed with childhood cancer by time since diagnosis

Characteristic	Times since diagnosis, years					
	5 to 14		15 to 24		25 to 36	
	CCSS (N = 13,974)	U.S. population <sup>a</sup> (N = 81,470)	CCSS (N = 12,031)	U.S. population <sup>a</sup> (N = 62,741)	CCSS (N = 6,466)	U.S. population <sup>a</sup> (N = 42,200)
Age at primary diagnosis (n, %, y)						
0–4	5,738 (41%)	29,298 (36%)	5,031 (42%)	23,963 (38%)	2,586 (40%)	15,286 (36%)
5–9	3,175 (23%)	16,767 (21%)	2,694 (22%)	13,033 (21%)	1,470 (23%)	9,021 (21%)
10–14	2,877 (21%)	16,819 (21%)	2,460 (20%)	11,429 (18%)	1,349 (21%)	8,779 (21%)
15–19	2,184 (16%)	18,586 (23%)	1,846 (15%)	14,316 (23%)	1,061 (16%)	9,115 (22%)
Gender (n, %)						
Male	7,514 (54%)	44,617 (55%)	6,339 (53%)	34,089 (54%)	3,354 (52%)	21,892 (52%)
Female	6,460 (46%)	36,853 (45%)	5,692 (47%)	28,651 (46%)	3,112 (48%)	20,309 (48%)
Race (n, %)						
White/unknown	12,392 (89%)	69,021 (85%)	10,770 (89%)	53,819 (86%)	5,948 (92%)	37,686 (89%)
Black	739 (5%)	8,731 (11%)	587 (5%)	6,348 (10%)	218 (4%)	3,288 (8%)
Other	843 (6%)	3,719 (5%)	674 (6%)	2,574 (4%)	300 (5%)	1,226 (3%)
Cancer type (n, %)						
Leukemia	4,808 (34%)	25,854 (32%)	4,084 (34%)	18,390 (29%)	2,115 (33%)	11,460 (27%)
Brain and central nervous system tumor	1,761 (13%)	17,538 (22%)	1,441 (12%)	13,243 (21%)	692 (11%)	7,493 (18%)
Hodgkin lymphomas (IIa)	1,779 (13%)	9,009 (11%)	1,553 (13%)	8,058 (13%)	910 (14%)	6,289 (15%)
Non-Hodgkin lymphomas (IIa)	1,059 (8%)	7,634 (9%)	925 (8%)	5,269 (8%)	503 (8%)	3,329 (8%)
Renal tumors (VI)	1,255 (9%)	5,047 (6%)	1,145 (10%)	4,826 (8%)	598 (9%)	3,740 (9%)
Neuroblastoma	953 (7%)	5,174 (6%)	863 (7%)	4,247 (7%)	474 (7%)	3,120 (7%)
Soft tissue	1,211 (9%)	6,921 (8%)	1,055 (9%)	5,164 (8%)	617 (10%)	4,583 (11%)
Bone tumors (VIII)	1,148 (8%)	4,294 (5%)	965 (8%)	3,543 (6%)	557 (9%)	2,187 (5%)

<sup>a</sup>U.S. survivors are estimated using the prevalence proportions of people diagnosed with cancer between 1975 and 2010 and ages 0 and 19 in the SEER-9 areas and applied to the respective U.S. population to generate U.S. counts.

Our results further define the magnitude of the health challenges faced by childhood cancer survivors. Over two thirds of survivors exhibited at least one chronic health condition 5 to 14 years after diagnosis with almost half of survivors ages 40 to 49 years estimated to have a severe or life-threatening chronic condition. Following a similar trajectory, though with lower prevalence, population estimates suggest a significant plurality of childhood cancer survivors experiencing compromised physical HRQOL, poor or fair overall health, functional impairments, activity limitation, and pain. In contrast, emotional distress and anxiety prevalence remained relatively stable by age and time since diagnosis, whereas mental HRQOL and neurocognitive dysfunction demonstrated somewhat lower prevalence by age. From these projected trends, we begin to see the burden of morbidity faced by these survivors generally increased as they age and move further from time of diagnosis, a trend recently described by the CCSS (26).

### Implications of findings

Harkening back to earlier warnings (27), a clear message emerges from these findings: a singular focus on curing cancer yields an incomplete picture of childhood cancer survivorship. The burden of chronic conditions in this population is profound, both in occurrence and severity. Because of their young age at diagnosis and their longevity, the consequences of these morbidities have implications for both survivors and the healthcare system. Survivors are likely challenged by the demand of managing multiple chronic conditions and the resulting limitations in their daily life, especially in the context of potential lack of awareness of their long-term health risks (28). These limitations in physical, cognitive, and mental functioning can disrupt typical development of personal relationships, education, and occupation, establishing independence, and negotiating family demands. Facing typical developmental milestones in the context

of managing multiple morbidities is a challenge for which limited personal and healthcare system resource and support may exist. Childhood cancer survivors may also face challenges in their interactions with the healthcare system (3) as they may represent high service users requiring the management of multiple teams of specialists, appointments, medication regimens, and financial outlays. Typical population guidelines for preventive behaviors such as cancer screening may not apply to this group (29), further complicating clinical pathways of care. Moreover, the complex morbidity in these survivors challenges healthcare system communication, cost, and care coordination processes.

Given the emerging picture of significant chronic condition burden for these childhood cancer survivors occurring within the context of functional and cognitive limitations as well as psychosocial distress for a significant subset, the resulting challenges form the basis of key directions for suggested research.

**Susceptibility to multiple chronic conditions.** Essential to improving our understanding of morbidity susceptibility is the question: what factors are associated with increased susceptibility? This question calls for examination from multiple perspectives in addition to oncology, including genomics, personalized medicine, treatment regimen-specific toxicities, behavioral medicine, psychology, cardiology, and endocrinology. A related question is the extent and mechanisms by which cancer treatments interact with the natural aging process. Although the high morbidity prevalence suggests childhood survivors' functional age may be older than their chronological age suggests (3), elucidating potential mechanisms underlying these processes is an important next step. In addition, further explication of morbidity trajectories, and determinants of these trajectories, is necessary. However, it is important to move beyond the description of a single chronic comorbidity (e.g., cardiac), and construct a picture of parallel and interactive trajectories, given our findings suggest that older

**Table 4.** Estimates of the number of prevalent cases of chronic conditions, cognitive dysfunction, compromised HRQOL, and health status in childhood cancer survivors in the United States who survived a minimum of 5 years as of January 1, 2011

	Current age	Total	Number of prevalent cases		
			Years since diagnosis		
			5 to 14 (n = 105,697)	15 to 24 (n = 81,519)	25 to 36 (n = 55,996)
<b>Chronic conditions</b>					
Any grade 1-4 condition	5-19 (n = 61,882)	41,059 (66%)	35,208	5,851	N/A
	20-29 (n = 84,589)	60,392 (71%)	30,406	25,592	4,394
	30-39 (n = 61,461)	48,796 (79%)	5,822	24,891	18,083
	40-49 (n = 35,280)	30,986 (88%)	N/A <sup>a</sup>	6,122	24,867
	Total (N = 243,212)	181,236 (75%)	71,436 (68%)	62,456 (77%)	47,344 (85%)
Any grade 1-2 (mild/moderate) condition	5-19 (n = 61,882)	38,401 (62%)	32,780	5,621	N/A
	20-29 (n = 84,589)	55,297 (66%)	27,644	24,087	4,196
	30-39 (n = 61,461)	45,753 (74%)	5,271	23,303	17,179
	40-49 (n = 35,280)	29,542 (84%)	N/A	5,778	23,764
	Total (N = 243,212)	169,263 (70%)	65,695 (62%)	58,789 (72%)	45,139 (81%)
Any grade 3-4 (severe/life-threatening or disabling) condition	5-19 (n = 61,882)	16,152 (26%)	13,787	2,365	N/A
	20-29 (n = 84,589)	24,492 (29%)	12,109	10,572	1,811
	30-39 (n = 61,461)	22,331 (36%)	2,565	11,434	8,332
	40-49 (n = 35,280)	16,902 (48%)	N/A	3,315	13,587
	Total (N = 243,212)	79,877 (33%)	28,461 (27%)	27,686 (34%)	23,730 (42%)
<b>Multiple chronic health conditions</b>					
≥2 grade 3-4	5-19 (n = 61,882)	4,528 (7%)	3,753	775	N/A
	20-29 (n = 84,589)	7,090 (8%)	3,150	3,319	621
	30-39 (n = 61,461)	7,585 (12%)	711	3,827	3,047
	40-49 (n = 35,280)	7,057 (20%)	N/A	1,291	5,766
	Total (N = 243,212)	26,260 (11%)	7,614 (7%)	9,212 (11%)	9,434 (17%)
≥3 grade 3-4	5-19 (n = 61,882)	1,511 (2%)	1212	299	N/A
	20-29 (n = 84,589)	2,296 (3%)	911	1,148	237
	30-39 (n = 61,461)	2,635 (4%)	200	1,296	1,139
	40-49 (n = 35,280)	2,939 (8%)	N/A	495	2,444
	Total (N = 243,212)	9,381 (4%)	2,323 (2%)	3,238 (4%)	3,820 (7%)
<b>Impaired neurocognitive functioning</b>					
Impaired neurocognitive functioning	20-29 (n = 40,353)	15,946 (40%)	N/A <sup>b</sup>	13,522	2,424
	30-39 (n = 53,644)	18,399 (34%)	N/A	10,383	8,016
	40-49 (n = 35,280)	11,518 (33%)	N/A	2,137	9,381
	Total (N = 129,277)	45,863 (35%)	N/A	26,042 (36%)	19,821 (35%)
	<b>HRQOL</b>				
Physical component score	20-29 (n = 40,353)	4,231 (10%)	N/A	3,626	605
	30-39 (n = 53,644)	8,788 (16%)	N/A	5,134	3,654
	40-49 (n = 35,280)	8,220 (23%)	N/A	1,636	6,584
	Total (N = 129,277)	21,239 (16%)	N/A	10,396 (14%)	10,843 (19%)
	Mental component score	20-29 (n = 40,353)	7,956 (20%)	N/A	6,790
30-39 (n = 53,644)		9,897 (18%)	N/A	5,708	4,189
40-49 (n = 35,280)		5,691 (16%)	N/A	1,103	4,588
Total (N = 129,277)		23,544 (18%)	N/A	13,601 (19%)	9,943 (18%)
<b>Health status indicators</b>					
Poor/fair general health	20-29 (n = 84,589)	9,388 (11%)	4,685	4,007	696
	30-39 (n = 61,461)	8,310 (14%)	961	4,222	3,127
	40-49 (n = 35,280)	5,973 (17%)	N/A	1,152	4,821
	Total (N = 181,330)	23,671 (13%)	5,646 (11%)	9,381 (13%)	8,644 (15%)
	Impaired mental health	20-29 (n = 84,589)	14,965 (18%)	7,969	6,125
30-39 (n = 61,461)		10,639 (17%)	1,445	5,719	3,475
40-49 (n = 35,280)		5,701 (16%)	N/A	1,284	4,417
Total (N = 181,330)		31,305 (17%)	9,414 (18%)	13,128 (18%)	8,763 (16%)
Functional impairment		20-29 (n = 84,589)	10,612 (13%)	5071	4,617
	30-39 (n = 61,461)	8,018 (13%)	825	3,874	3,319
	40-49 (n = 35,280)	6,030 (17%)	N/A	1,036	4,994
	Total (N = 181,330)	24,660 (14%)	5,896 (11%)	9,527 (13%)	9,237 (16%)

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**Table 4.** Estimates of the number of prevalent cases of chronic conditions, cognitive dysfunction, compromised HRQOL, and health status in childhood cancer survivors in the United States who survived a minimum of 5 years as of January 1, 2011 (Cont'd)

	Current age	Total	Years since diagnosis		
			5 to 14 (n = 52,053)	15 to 24 (n = 73,281)	25 to 36 (n = 55,996)
Limitations in activity	20–29 (n = 84,589)	10,182 (12%)	5369	4,066	747
	30–39 (n = 61,461)	8,802 (14%)	1106	4,318	3,378
	40–49 (n = 35,280)	7,249 (21%)	N/A	1,343	5,906
	Total (N = 181,330)	26,233 (14%)	6,475 (12%)	9,727 (13%)	10,031 (18%)
Pain (moderate to excruciating)	20–29 (n = 84,589)	8,149 (10%)	4,672	3,009	468
	30–39 (n = 61,461)	7,533 (12%)	1,147	3,834	2,552
	40–49 (n = 35,280)	5,336 (15%)	N/A	1,117	4,219
	Total (N = 181,330)	21,018 (12%)	5,819 (11%)	7,960 (11%)	7,239 (13%)
Anxiety/fear (medium to extreme)	20–29 (n = 84,589)	10,807 (13%)	6,027	4,134	646
	30–39 (n = 61,461)	8,080 (13%)	1,171	4,143	2,766
	40–49 (n = 35,280)	4,773 (14%)	N/A	998	3,775
	Total (N = 181,330)	23,660 (13%)	7,198 (14%)	9,275 (13%)	7,187 (13%)

<sup>a</sup>All participants were diagnosed between 1970 and 1986 at ages 0 to 19 years. Therefore, participants age 40 or older at completion of the questionnaires were at least 15 years after diagnosis (earliest questionnaire November 1992).

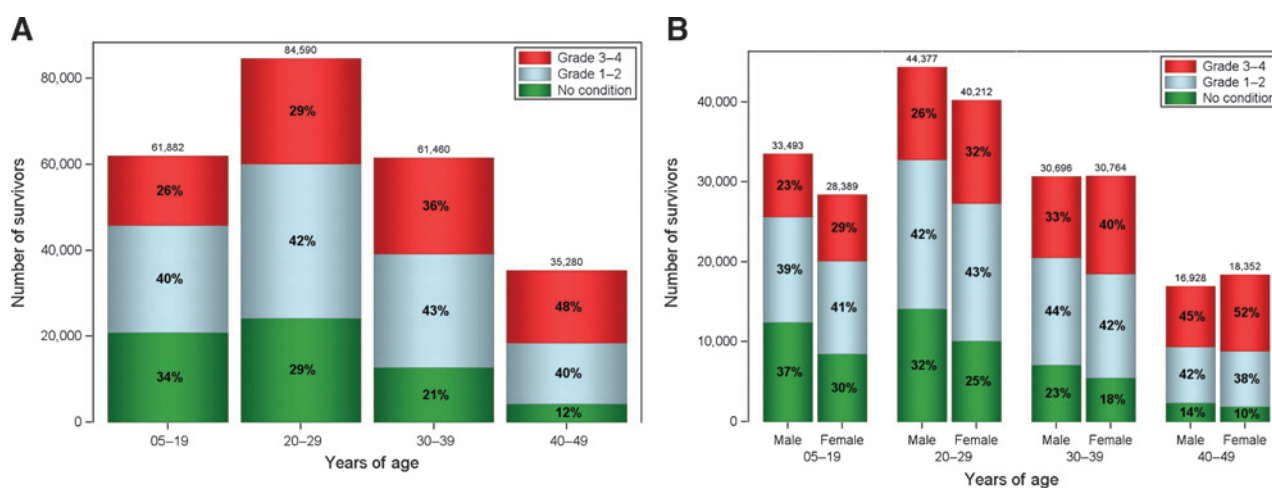
<sup>b</sup>Estimates for impaired neurocognitive dysfunction and HRQOL do not include survivors 5 to 14 years after diagnosis because at data collection (see Table 1), all participants in this category were at least 15 years after diagnosis.

survivors may be experiencing multiple, serious chronic conditions, and limitations.

Broadening the scope beyond chronic conditions to include other morbidity indicators (i.e., HRQOL, health status, and neurocognitive functioning), the question of susceptibility remains vital. What biomarkers or mechanistic processes are associated with decrements in cognitive functioning and health status? What are the susceptibilities for the consistent subset of patients experiencing impaired mental health? How do physical and psychologic factors interact to influence morbidity burden? Answering these questions could result in improved care via risk stratification and intervention development, but will require detailed longitudinal assessments to understand the pathophysiology of outcome-specific conditions.

**Prevention of chronic diseases morbidity.** Our data illustrate an increased prevalence of poor health status including functional

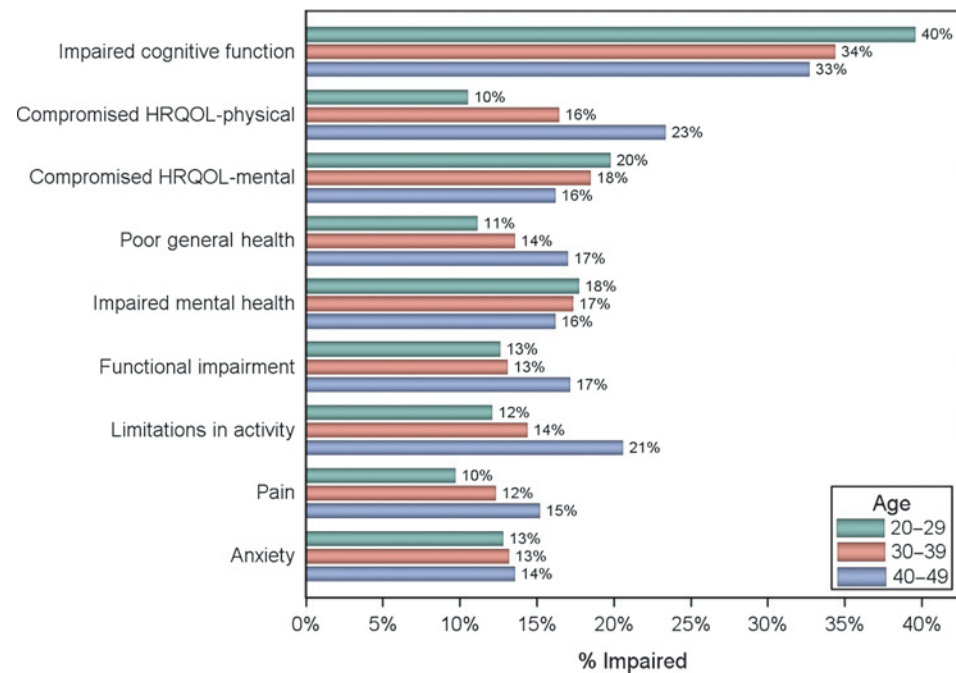
impairment and activity limitations in those ages 40 to 49 years. Approaches focused on preventing and ameliorating this health trajectory are essential. For example, physical activity, weight management, social support, and cognitive stimulation have been shown to be key components of healthy aging across disease prevention and management, cognition, and quality of life domains (30). Understanding the role of these factors in the prevention and trajectories of development of morbidity in childhood cancer survivors is essential. Current childhood cancer survivor screening guidelines recommend screening for second cancer and chronic conditions (29). However, these guidelines will need to be updated as cancer survivors age and could be expanded to include the additional endpoints explored in this study. Lastly, multiple studies have cited age-associated declines in cognitive abilities as a concern in the general population (31). Because approximately one third of childhood cancer survivors  $\geq 15$  years beyond diagnosis are estimated to experience



**Figure 1.** A, estimates of the prevalence of chronic health conditions in childhood cancer survivors in the United States who survived a minimum of 5 years as of January 1, 2011, by age. B, estimates of the prevalence of chronic conditions in childhood cancer survivors in the United States who survived a minimum of 5 years as of January 1, 2011, by gender and age.



**Figure 2.** Estimates of the prevalence of compromised neurocognitive function, compromised HRQOL, and health status in childhood cancer survivors in the United States who survived a minimum of 5 years by age as of January 1, 2011.



neurocognitive dysfunction, investigation into possible prophylactic strategies and interventions warrants further investigation.

**Care coordination.** Childhood cancer survivors need comprehensive follow-up care to address their complex healthcare needs (32, 33). Their needs do not end with cancer treatment. The burden of managing multiple chronic conditions and the accompanying need to coordinate care between multiple professionals and care teams becomes even more complicated for childhood cancer survivors and the healthcare system with the added need for incorporation of risk-based survivorship care. The emerging focus on survivorship care planning is in direct response to growing appreciation of the multiple chronic and late effects of cancer experienced by both childhood and adult cancer survivor populations and their care coordination needs (34–36). Much emphasis has been placed on documentation of treatments and toxicities, the transmission of screening schedules, and information on health behaviors. Although documentation of this information is important, it is imperative to move to more active survivorship care planning and coordination to simultaneously address the prevalence of chronic conditions, impairments, and limitations presented here, and the dynamic, complex active prevention, and treatment necessary for childhood cancer survivors.

**Rehabilitation model focused on integrated care.** Determining the most effective and efficient clinical models of care for this population is an important next step (3, 37). Conceptualizing survivorship care through a rehabilitation model focused on optimization of function and quality of life and the coordination of complex care (38) offers rich opportunities for determining how best to address morbidity burden across the childhood cancer survivorship trajectory, especially since the significant chronic condition burden may be further complicated by compromised mental health and physical and cognitive dysfunction. Future research is needed to determine the

feasibility and efficacy of this approach to address childhood cancer survivors' needs.

#### Limitations

Although study strengths include the use of multiple indicators of morbidity burden and extrapolation of these data to obtain population-level prevalence estimates, it is not without limitations. First, because the granularity and reliability of SEER data are limited in terms of secondary treatment and specific treatment agents and dosages, we were not able to directly link our findings to treatment data. Thus, we assumed treatment for childhood cancers was similar for the 1970 to 1986 CCSS treatment era as for the 1975 to 2005 diagnosis era used for SEER and are unable to comment on how these outcomes may differ based on treatment received. Most of our morbidity burden measures were based on self-report and thus are subject to possible under- and over-reporting. Our estimates of morbidity prevalence included only those who survived a minimum of 5 years and a maximum of 36 years and do not represent all childhood survivors. Future research is warranted to explore these relationships further by treatment and varying times since diagnosis to obtain a richer, more accurate picture of the burden of morbidity in this population and provide further insight into how morbidity may be prevented or delayed.

#### Conclusions and Impact

The estimated prevalence of childhood cancer survivors is increasing, as is the estimated morbidity prevalence in those  $\geq 5$  years beyond diagnosis. Taken together, these data paint a picture of a population experiencing co-occurring treatment benefits and morbidity. These findings call for future research focused not only on decreasing the morbidity burden, but also incorporating effective clinical models of care coordination and rehabilitation to reduce morbidity burden and optimize childhood cancer survivors' HRQOL, physical and neurocognitive functioning, and mental health.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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