

Aging and Risk of Severe, Disabling, Life-Threatening, and Fatal Events in the Childhood Cancer Survivor Study

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A B S T R A C T

Purpose

The first generation of childhood cancer survivors is now aging into their fourth and fifth decades of life, yet health risks across the aging spectrum are not well established.

Methods

Analyses included 14,359 5-year survivors from the Childhood Cancer Survivor Study, who were first diagnosed when they were younger than 21 years old and who received follow-up for a median of 24.5 years after diagnosis (range, 5.0 to 39.3 years) along with 4,301 of their siblings. Among the survivors, 5,604 were at least 35 years old (range, 35 to 62 years) at last follow-up. Severe, disabling, life-threatening, and fatal health conditions more than 5 years from diagnosis were classified using the Common Terminology Criteria for Adverse Events, grades 3 to 5 (National Cancer Institute).

Results

The cumulative incidence of a severe, disabling, life-threatening, or fatal health condition was greater among survivors than siblings (53.6%; 95% CI, 51.5 to 55.6; v 19.8%; 95% CI, 17.0 to 22.7) by age 50 years. When comparing survivors with siblings, hazard ratios (HR) were significantly increased within the age group of 5 to 19 years (HR, 6.8; 95% CI, 5.5 to 8.3), age group of 20 to 34 years (HR, 3.8; 95% CI, 3.2 to 4.5), and the ≥ 35 years group (HR, 5.0; 95% CI, 4.1 to 6.1), with the HR significantly higher among those ≥ 35 years versus those 20 to 34 years old ($P = .03$). Among survivors who reached age 35 years without a previous grade 3 or 4 condition, 25.9% experienced a subsequent grade 3 to 5 condition within 10 years, compared with 6.0% of siblings ($P < .001$).

Conclusion

Elevated risk for morbidity and mortality among survivors increases further beyond the fourth decade of life, which affects the future clinical demands of this population relative to ongoing surveillance and interventions.

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INTRODUCTION

Improvement in survival rates of childhood cancer over the last half-century is one of the major achievements of modern medicine. The relative 5-year survival for children with cancer, which was less than 30% in 1960, is now over 80%.¹ There are currently more than 363,000 survivors of childhood cancer in the United States.¹ The impact of this growing number of cancer survivors is particularly apparent when one considers that one in 680 people between the ages of 20 and 50 years in the United States is a survivor of childhood cancer.²

Previous research has documented that childhood cancer survivors are at increased risk for a broad range of serious health conditions.³⁻⁶ How-

ever, it is not clear what the prevalence of adverse health conditions will be as this at-risk population ages into middle and late adulthood. Our current analysis was undertaken to address two questions that are important for the clinical care of aging childhood cancer survivors: what is the risk of future serious health problems for survivors who developed at least one serious health condition during their childhood or young adult years, and do survivors who have reached their third decade of life without developing a serious condition have an elevated risk of serious morbidity? The Childhood Cancer Survivor Study (CCSS) performed follow-up for more than 7,600 survivors and siblings older than 35 years, providing the opportunity to address these important questions in aging survivors of childhood cancer.^{7,8}

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METHODS

Population

The CCSS is a multi-institutional retrospective cohort study, with longitudinal follow-up of survivors of childhood cancer who were treated at 26 institutions in the United States and Canada. Study eligibility included diagnosis of cancer before age 21 years; initial treatment between January 1, 1970, and December 31, 1986; and survivors had to be alive at 5 years after diagnosis of leukemia, CNS malignancy, Hodgkin lymphoma, non-Hodgkin lymphoma, Wilms tumor, neuroblastoma, soft-tissue sarcoma, or a bone tumor. A random sample of siblings of CCSS participants served as a comparison population ($n = 4,031$). The cohort methodology and study design have been previously described in detail.^{7,9} The CCSS was approved by the institutional review boards at the 26 participating centers. Participants provided informed consent.

All participants completed a baseline survey (administered between 1994 and 1999) that included demographics, personal/family medical history, and chronic health conditions, including assessment of subsequent malignant neoplasms. A surrogate (parent, spouse, or next of kin) completed the baseline survey for survivors who died more than 5 years after diagnosis, who were under age 18 years, or who were unable to complete the survey. Sex and race/ethnicity characteristics were available from the surveys. Subsequently, there have been four additional follow-up surveys (Appendix Fig A1 [online-only]). Study surveys can be viewed at <http://ccss.stjude.org>.

Health Condition Outcomes

At baseline and at subsequent follow-up evaluations, participants completed a multi-item survey, which included participant's age at onset of organ-based health conditions. Severity scoring was applied based on the Common Terminology Criteria for Adverse Events (version 4.0, National Cancer Institute), which is used to score both acute and chronic conditions in patients and survivors of cancer.¹⁰ This system grades conditions as mild (grade 1), moderate (grade 2), severe or disabling (grade 3), life-threatening (grade 4), or fatal (grade 5). Our current analysis was restricted to conditions grades 3 to 5 that developed at least 5 years after the cancer diagnosis (thus, conditions that developed during therapy or shortly thereafter were not included). When not enough information was available to distinguish between grades, the lower grade was assigned. Subsequent malignant neoplasms, not including recurrence of the primary childhood malignancy, were initially ascertained through self- or proxy-report questionnaires and/or death certificates and were confirmed by pathology report or, when not available, other medical records. Only subsequent malignant neoplasms occurring 5 or more years after childhood cancer diagnoses were evaluated.^{11,12} For assessment of mortality, the CCSS cohort was linked with the National Death Index to ascertain date and cause of death.

Cancer diagnosis and treatment data (including chemotherapy and radiotherapy) were abstracted from medical records at the treating institutions for the 12,593 patients who provided a signed medical release.^{8,13}

Statistical Analysis

Cox proportional hazards models were used to compare severe, disabling, life-threatening, or fatal health conditions among survivors, versus siblings, and were reported as hazard ratios (HR) and

95% CI. Age was used as the time scale to account for the increasing risk of severe, disabling, life-threatening, or fatal health conditions owing to age. Survivors entered the analysis at an age equivalent to 5 years postdiagnosis; siblings entered at age 5 years. Because participants could have reported multiple grade 3 to 5 conditions, the models used a counting-process approach, using all reported unique conditions for each participant, and accounting for intra-participant correlations using sandwich SE estimates.^{14,15} Separate analyses were conducted to compare overall grade 3 to 5 conditions, plus each of 13 organ systems of interest between survivors and siblings. Additional analyses compared rates of grade 3 to 5 health conditions for subgroups of survivors who received specific treatments or combinations of treatments with siblings. Finally, a supplemental multivariable analysis was undertaken among survivors to evaluate how treatment factors affected the hazards of developing grade 3 to 5 health conditions after the age of 35 years. All analyses were adjusted for sex and race/ethnicity.

To compare the HRs between age periods, age was added as a time-varying covariate, categorized in three periods (participants ages 5 to 19 years, 20 to 34 years, and 35 years and older). The interaction between age period and group provided HRs for survivors versus siblings within each age interval. Late onset of specific severe, disabling, life-threatening, or fatal health conditions was compared in additional Cox proportional hazards models, with both survivors and siblings entering at age 35 years. We completed a sensitivity analysis to evaluate the potential impact of participants dropping out from the CCSS before age 35 years and analyzed participants who, based on birth and death dates, survived past age 35 years using the Inverse Probability Censored Weighting method to weight analyses to account for differences between participants who dropped out of our study before age 35 years versus those who did not.¹⁶

Person-years and number of events were calculated for survivors and siblings within each age period and across all ages. To calculate incidence rates (per 1,000 person-years) of severe, disabling, life-threatening, or fatal health conditions for survivors and siblings, person-years and number of events were fit with Poisson regression models. Models based on all ages included a restricted cubic spline for age,¹⁷ and parameter estimates from these models were used to calculate predicted incidence rates per 1,000 person-years at a median age of 31 years.

Cumulative incidence rates for each of the primary outcomes were calculated separately for survivors and siblings, with deaths other than those as a result of fatal health conditions of interest (ie, recurrence of primary cancer or external causes such as accidents, injuries, or suicide) treated as competing risk events.¹⁸ Similar to the Cox models, age was used as the time scale with appropriately staggered age of entry to the cohort.¹⁹ For each outcome, the cumulative incidence was computed based on time to the earliest reported age of the event of interest. In addition to unconditional curves, conditional cumulative incidence curves were evaluated, conditioning for survival free of a grade 3-5 condition up to ages 26, 35, and 45 years. *P* values for comparisons between cumulative incidence for survivors and siblings at specific ages were calculated using Wald tests. Data were analyzed with SAS software, version 9.3 (SAS Institute, Cary, NC) and Stata/SE 12.1 (StataCorp, College Station, TX).

Table 1. Demographic and Treatment Characteristics for Survivors and Siblings

Characteristic	Total Cohort				Age 35 or Older at Last Follow-Up			
	Survivors		Siblings		Survivors		Siblings	
	No. of Participants (n = 14,359)	%	No. of Participants (n = 4,031)	%	No. of Participants (n = 5,604)	%	No. of Participants (n = 1,969)	%
Sex								
Female	6,645	46.3	2,088	51.8	2,660	47.5	1,074	54.5
Male	7,714	53.7	1,943	48.2	2,944	52.5	895	45.5
Race/ethnicity*								
Non-Hispanic white	12,397	86.6	3,509	90.4	5,063	90.6	1,768	92.8
Hispanic	749	5.2	149	3.8	219	3.9	55	2.9
Non-Hispanic black	733	5.1	123	3.2	192	3.4	49	2.6
Other	429	3.0	101	2.6	114	2.0	34	1.8
Age at last contact, years								
0-19	1,524	10.6	267	6.6	—	—	—	—
20-29	4,493	31.3	1,136	28.2	—	—	—	—
30-39	5,226	36.4	1,396	34.6	2,488	44.4	737	37.4
40-49	2,747	19.1	979	24.3	2,747	49.0	979	49.7
≥ 50	369	2.5	253	6.3	369	6.6	253	12.8
Age at primary diagnosis, years								
0-4	5,754	40.1	—	—	686	12.2	—	—
5-9	3,201	22.3	—	—	1,052	18.8	—	—
10-14	2,913	20.3	—	—	1,887	33.7	—	—
15-20	2,491	17.3	—	—	1,979	35.3	—	—
Primary diagnosis								
Acute lymphoblastic leukemia	4,329	30.1	—	—	1,195	21.3	—	—
Acute myeloid leukemia	356	2.5	—	—	128	2.3	—	—
Other leukemia	145	1.0	—	—	46	0.8	—	—
CNS tumors	1,876	13.1	—	—	654	11.7	—	—
Hodgkin lymphoma	1,927	13.4	—	—	1,341	23.9	—	—
Non-Hodgkin lymphoma	1,080	7.5	—	—	557	9.9	—	—
Kidney tumors	1,256	8.7	—	—	221	3.9	—	—
Neuroblastoma	955	6.7	—	—	120	2.1	—	—
Soft tissue sarcoma	1,246	8.7	—	—	579	10.3	—	—
Bone tumors	1,189	8.3	—	—	763	13.6	—	—
Therapy for primary diagnosis								
Surgery*								
Any surgery	10,234	81.3	—	—	4,368	86.5	—	—
Nephrectomy	1,091	8.7	—	—	203	4.0	—	—
Splenectomy	1,257	10.0	—	—	915	18.1	—	—
Surgery only	909	7.3	—	—	372	7.4	—	—
Chemotherapy*								
Any chemotherapy	10,137	80.6	—	—	3,813	75.5	—	—
Alkylator	6,826	54.3	—	—	2,749	54.4	—	—
Anthracycline	5,190	41.3	—	—	1,841	36.5	—	—
Bleomycin	756	6.0	—	—	425	8.4	—	—
Cisplatin	738	5.9	—	—	193	3.8	—	—
Methotrexate	5,676	45.1	—	—	2,042	40.4	—	—
Radiotherapy*								
Any radiotherapy	8,547	68.0	—	—	3,709	73.4	—	—
Brain	4,010	32.6	—	—	1,393	28.1	—	—
Chest	2,467	20.1	—	—	1,458	29.4	—	—
Abdomen	2,200	17.9	—	—	1,126	22.7	—	—
Pelvis	1,863	15.2	—	—	887	17.9	—	—
Combinations*								
Chest RT plus bleomycin	339	2.8	—	—	188	3.8	—	—
Chest RT plus abdominal/pelvic RT	1,435	11.7	—	—	851	17.2	—	—
Alkylator plus abdominal/pelvic RT	1,636	13.3	—	—	762	15.4	—	—
Chest RT plus anthracyclines	966	7.9	—	—	395	8.0	—	—
Anthracyclines plus an alkylator	5,190	41.3	—	—	1,841	36.5	—	—

Abbreviations: RT, radiotherapy.

*Percentages calculated on total No. of participants on whom information was available.

RESULTS

As listed in Table 1 and Appendix Figures A1A and A1B, 14,359 5-year survivors and 4,031 siblings completed the baseline survey. Demographic and treatment characteristics for the entire cohort and for those participants who were at least age 35 years at last follow-up are included. For survivors who were 35 years or older at the last follow-up, longitudinal recruitment and retention rates

(Appendix Fig A1C) and a description of nonparticipation are also included (Appendix Table A1). For survivors, the median age at last follow-up was 31 years (range, 5 to 58; interquartile range, 13 years), at a median of 24.5 years from primary cancer diagnosis (range, 5 to 39.3; interquartile range, 9.6 years). Of survivors, 5,604 were 35 years old or older at last follow-up. The median age at last follow-up of siblings was 34 years (range, 3 to 62; interquartile range, 14 years).

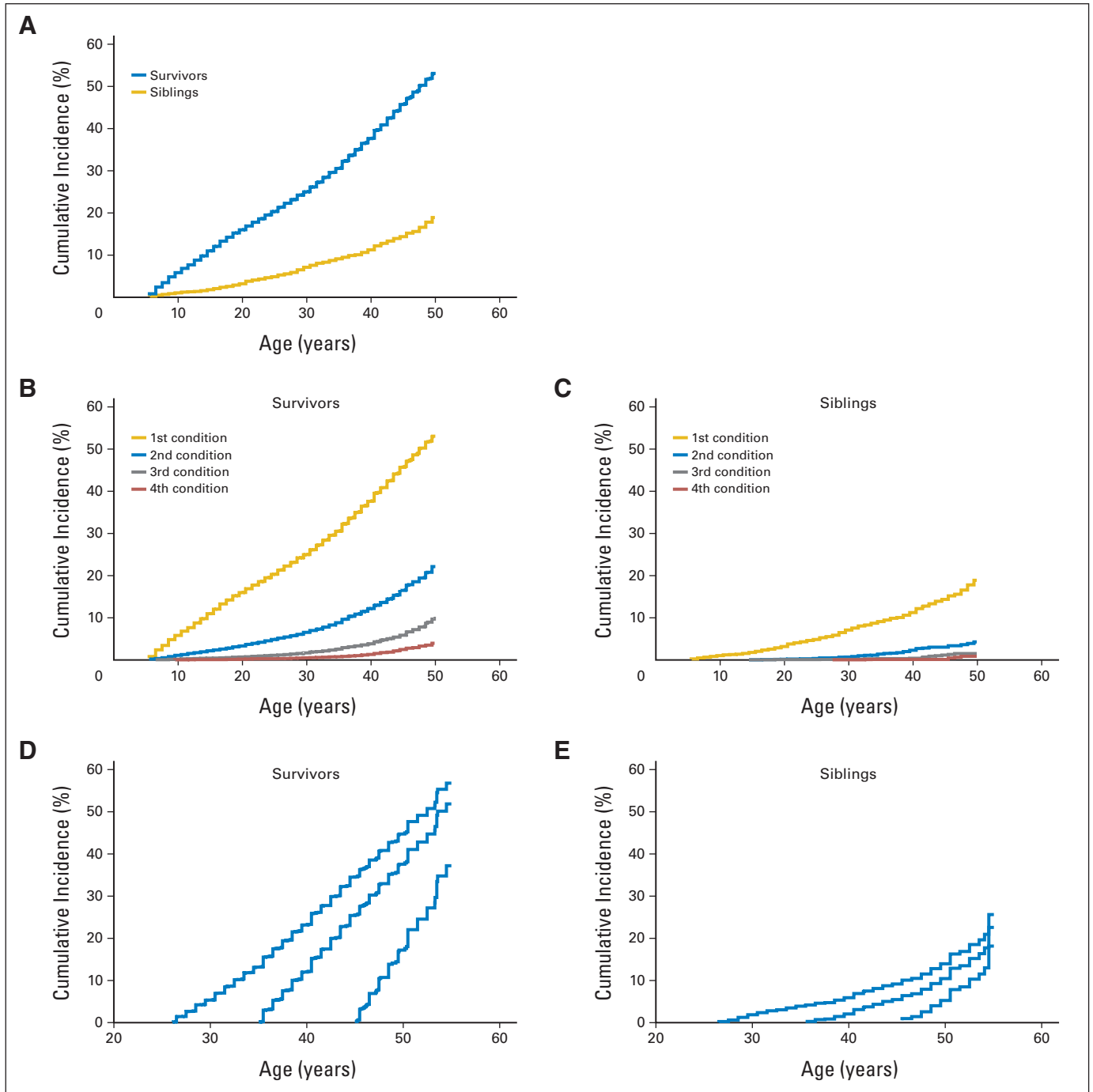


Fig 1. Cumulative incidence of chronic health conditions for (A) grades 3 to 5 chronic health conditions, (B) multiple grade 3 to 5 conditions in survivors, (C) multiple grade 3 to 5 conditions in siblings, (D) conditioned based on no previous grade 3 to 5 conditions among survivors by ages 25, 35, or 45, and (E) conditioned based on no previous grade 3 to 5 conditions among siblings by ages 25, 35, or 45.

Table 2. Incidence Rates and Hazard Ratios by Organ System for Severe, Disabling, Life-Threatening, or Fatal Health Conditions for Survivors Compared With Siblings Among All Survivors and Age-Specific Strata of Survivors

Organ System*	All Participants		Ages 5-19 Years		Ages 20-34 Years		Ages ≥ 35 Years		Pt
	Survivors (n = 14,359)	Siblings (n = 4,031)	Survivors (n = 11,868)	Siblings (n = 4,031)	Survivors (n = 12,835)	Siblings (n = 3,764)	Survivors (n = 5,604)	Siblings (n = 1,969)	
All conditions									
PY	271,148	117,251	101,644	59,370	13,5061	43,161	34,443	14,719	
No. of events	5,588	490	1,509	134	2,510	209	1,569	147	
IR	15.4	3.0	12.7	2.1	15.9	4.6	38.9	9.3	
95% CI	14.7 to 16.1	2.5 to 3.5	11.8 to 13.6	1.6 to 2.6	15.0 to 16.9	3.8 to 5.6	36.2 to 41.8	7.4 to 11.7	
HR	4.9	1.0	6.8	1.0	3.8	1.0	5.0	1.0	.03
95% CI	4.3 to 5.5		5.5 to 8.3		3.2 to 4.5		4.1 to 6.1		
Subsequent malignancy									
PY	270,609	117,248	101,619	59,370	134,791	43,161	34,200	14,717	
No. of events	999	47	172	3	460	22	367	22	
IR	3.9	0.5	1.3	0.1	2.6	0.5	8.1	1.3	
95% CI	3.5 to 4.3	0.3 to 0.9	1.1 to 1.5	0.0 to 0.2	2.3 to 2.9	0.3 to 0.8	7.2 to 9.9	0.8 to 2.3	
HR	8.5	1.0	29.5	1.0	6.7	1.0	7.5	1.0	.71
95% CI	6.4 to 11.4		9.3 to 93.1		4.3 to 10.2		4.9 to 11.5		
Hearing									
PY	270,173	117,248	101,578	59,370	134,617	43,161	33,979	14,717	
No. of events	394	44	150	16	164	17	80	11	
IR	0.7	0.1	1.5	0.4	1.3	0.6	2.4	1.2	
95% CI	0.6 to 0.9	0.1 to 0.2	1.3 to 1.8	0.3 to 0.7	1.0 to 1.5	0.3 to 1.0	1.9 to 3.1	0.6 to 2.3	
HR	4.3	1.0	6.5	1.0	3.1	1.0	3.2	1.0	.95
95% CI	3.1 to 5.9		3.8 to 11.0		1.9 to 5.2		1.7 to 6.0		
Vision									
PY	270,173	117,248	101,578	59,370	134,617	43,161	33,979	14,717	
No. of events	333	61	152	35	133	18	48	8	
IR	0.6	0.1	1.4	0.6	0.9	0.4	1.3	0.5	
95% CI	0.4 to 0.7	0.1 to 0.2	1.1 to 1.7	0.3 to 0.9	0.7 to 1.1	0.2 to 0.7	0.9 to 1.7	0.2 to 1.3	
HR	2.6	1.0	2.8	1.0	2.3	1.0	2.8	1.0	.68
95% CI	2.0 to 3.5		1.8 to 4.1		1.4 to 3.8		1.2 to 7.0		
Endocrine									
PY	270,186	117,248	101,581	59,370	134,622	43,161	33,984	14,717	
No. of events	976	89	308	31	478	36	190	22	
IR	3.7	0.9	1.7	0.2	2.0	0.4	3.2	0.6	
95% CI	3.3 to 4.1	0.6 to 1.3	1.5 to 2.0	0.1 to 0.4	1.8 to 2.3	0.2 to 0.6	2.7 to 3.7	0.3 to 1.2	
HR	4.5	1.0	5.3	1.0	4.3	1.0	3.8	1.0	.65
95% CI	3.6 to 5.6		3.6 to 5.6		3.1 to 6.0		2.4 to 5.8		
Respiratory									
PY	270,291	117,248	101,582	59,370	134,668	43,161	34,036	14,716	
No. of events	212	17	39	3	98	7	75	7	
IR	0.7	0.1	0.3	0.1	0.6	0.2	1.9	0.5	
95% CI	0.5 to 0.9	0.0 to 0.3	0.2 to 0.5	0.0 to 0.2	0.5 to 0.8	0.1 to 0.4	1.5 to 2.5	0.2 to 1.1	
HR	5.0	1.0	6.6	1.0	4.4	1.0	5.0	1.0	.81
95% CI	3.0 to 8.2		2.1 to 21.2		2.1 to 9.4		2.3 to 10.8		
Cardiac									
PY	270,407	117,251	101,585	59,370	134,718	43,161	34,105	14,718	
No. of events	1,158	73	189	13	463	28	506	32	
IR	3.1	0.3	1.7	0.3	3.2	0.7	14.0	2.5	
95% CI	2.8 to 3.5	0.2 to 0.5	1.5 to 2.0	0.1 to 0.5	2.8 to 3.7	0.4 to 1.2	12.3 to 16.0	1.6 to 4.0	
HR	6.9	1.0	8.6	1.0	5.2	1.0	7.8	1.0	.15
95% CI	5.2 to 9.1		4.2 to 17.3		3.4 to 7.9		5.4 to 11.5		
GI									
PY	270,233	117,248	101,583	59,370	134,645	43,161	34,005	14,717	
No. of events	285	14	91	3	133	6	61	5	
IR	0.6	0.1	0.9	0.1	1.0	0.2	1.8	0.4	
95% CI	0.5 to 0.8	0.0 to 0.2	0.7 to 1.2	0.0 to 0.3	0.8 to 1.2	0.1 to 0.5	1.3 to 2.4	0.1 to 1.1	
HR	9.3	1.0	18.3	1.0	6.9	1.0	6.7	1.0	.96
95% CI	5.3 to 16.5		5.7 to 59.1		3.0 to 15.6		2.4 to 18.5		

(continued on following page)

Aging Survivors of Childhood Cancer and Serious Health Conditions

Table 2. Incidence Rates and Hazard Ratios by Organ System for Severe, Disabling, Life-Threatening, or Fatal Health Conditions for Survivors Compared With Siblings Among All Survivors and Age-Specific Strata of Survivors (continued)

Organ System*	All Participants		Ages 5-19 Years		Ages 20-34 Years		Ages ≥ 35 Years		Pt
	Survivors (n = 14,359)	Siblings (n = 4,031)	Survivors (n = 11,868)	Siblings (n = 4,031)	Survivors (n = 12,835)	Siblings (n = 3,764)	Survivors (n = 5,604)	Siblings (n = 1,969)	
Renal									
PY	270,183	117,248	101,578	59,370	134,625	43,161	33,981	14,717	
No. of events	112	10	46	3	50	6	16	1	
IR	0.2	0.1	0.5	0.0	0.4	0.1	0.5	0.1	
95% CI	0.1 to 0.3	0.0 to 0.3	0.4 to 0.7	0.0 to 0.2	0.3 to 0.6	0.0 to 0.3	0.3 to 0.9	0.0 to 0.7	
HR	5.3	1.0	13.1	1.0	2.6	1.0	7.5	1.0	.35
95% CI	2.6 to 10.8		3.2 to 54.3		1.1 to 6.0		1.0 to 58.4		
Musculoskeletal									
PY	270,182	117,248	101,578	59,370	134,626	43,162	33,979	14,717	
No. of events	217	17	59	2	116	8	42	7	
IR	0.5	0.1	0.7	0.0	1.0	0.2	1.5	0.6	
95% CI	0.4 to 0.6	0.0 to 0.1	0.6 to 1.0	0.0 to 0.2	0.8 to 1.3	0.1 to 0.6	1.1 to 2.1	0.3 to 1.3	
HR	4.9	1.0	14.9	1.0	4.4	1.0	2.8	1.0	.38
95% CI	3.0 to 8.1		3.5 to 63.0		2.2 to 9.1		1.3 to 5.9		
Neurologic									
PY	270,193	117,248	101,578	59,370	134,628	43,162	33,986	14,717	
No. of events	479	60	190	12	199	31	90	17	
IR	0.9	0.5	1.8	0.2	1.5	0.7	2.6	1.1	
95% CI	0.7 to 1.0	0.3 to 0.8	1.5 to 2.2	0.1 to 0.4	1.2 to 1.7	0.4 to 1.1	2.0 to 3.2	0.6 to 2.1	
HR	3.5	1.0	10.6	1.0	2.0	1.0	2.2	1.0	.78
95% CI	2.6 to 4.8		5.8 to 19.3		1.3 to 3.0		1.2 to 3.8		
Other hematologic									
PY	270,178	117,248	101,578	59,370	134,619	43,162	33,982	14,717	
No. of events	374	58	103	13	188	30	83	15	
IR	1.1	0.5	0.8	0.2	1.1	0.6	2.0	0.8	
95% CI	0.9 to 1.3	0.3 to 0.9	0.7 to 1.0	0.1 to 0.3	0.9 to 1.4	0.4 to 1.0	1.5 to 2.5	0.4 to 1.5	
HR	2.7	1.0	4.8	1.0	2.0	1.0	2.6	1.0	.43
95% CI	2.0 to 3.6		2.6 to 8.9		1.3 to 2.9		1.5 to 4.5		
Other infectious/immunologic									
PY	270,238	117,248	101,580	59,370	134,665	43,162	33,994	14,717	—
No. of events	48	0	10	0	27	0	11	0	
IR	0.2	—	0.1	—	0.2	—	0.3	—	
95% CI	0.1 to 0.3		0.0 to 0.2		0.1 to 0.3		0.1 to 0.5		
HR	—		—		—		—		
95% CI									

NOTE. Incidence rates are per 1,000 person-years. Em-dashes represent not enough events to analyze.

Abbreviations: HR, hazard ratio; IR, incidence rate; PY, person-years.

*Each organ system represents a multivariable model, with separate models for all survivors and age-specific strata. Models allow for repeated events across age categories and are adjusted for race and sex, and age is used as a time-dependent variable.

†P value for difference in HR between ages 20-34 and ages ≥ 35 years.

Compared with siblings, survivors had an increased cumulative incidence of severe, disabling, life-threatening, or fatal health conditions (Fig 1 [overall]; Appendix Fig A2, Appendix Table A2 [by primary childhood cancer diagnosis]). The increase in cumulative incidence between survivors and siblings evident at 20 years (survivors: 16.0%; 95% CI, 14.9 to 17.2; ν siblings: 3.3%; 95% CI, 2.8 to 3.9; Fig 1A) increased with age (at 50 years: 53.6% of survivors; 95% CI, 51.5 to 55.6; ν 19.8% of siblings; 95% CI, 17.0 to 22.7). Notably, 24-year-old survivors of childhood cancer had the same cumulative incidence of grade 3 to 5 health conditions (19.6%) as the 50-year-old siblings. Multivariable analysis confirmed that the HR for a severe, disabling, life-threatening, or fatal health condition increased for survivors 35 years old and older compared with survivors 20 to 34 years old (HR, 5.0 ν 3.8; $P = .03$; Table 2).

By age 50 years, 22.5% of survivors (95% CI, 20.7 to 24.4) had two or more severe, disabling, life-threatening, or fatal health conditions compared with 4.3% of siblings (95% CI, 3.0 to 5.8; Figs 1B and 1C). Among survivors who reached age 35 years without a previous severe, disabling, life-threatening, or fatal health condition, 25.9% experienced a new grade 3 to 5 condition within 10 years, compared with 6.0% of healthy siblings ($P < .001$; Figs 1D and 1E; Appendix Table A3).

Beyond age 35 years, survivors experienced a marked increase in cumulative incidence (Fig 2; Appendix Fig A3) and incidence rates of grade 3 to 5 cardiac events (Table 2) and the development of malignant neoplasms that were not observed in other organ systems. This observation remained consistent even when restricting analyses to grade 3 to 4 events (ie, excluding mortality, data not shown). Notably,

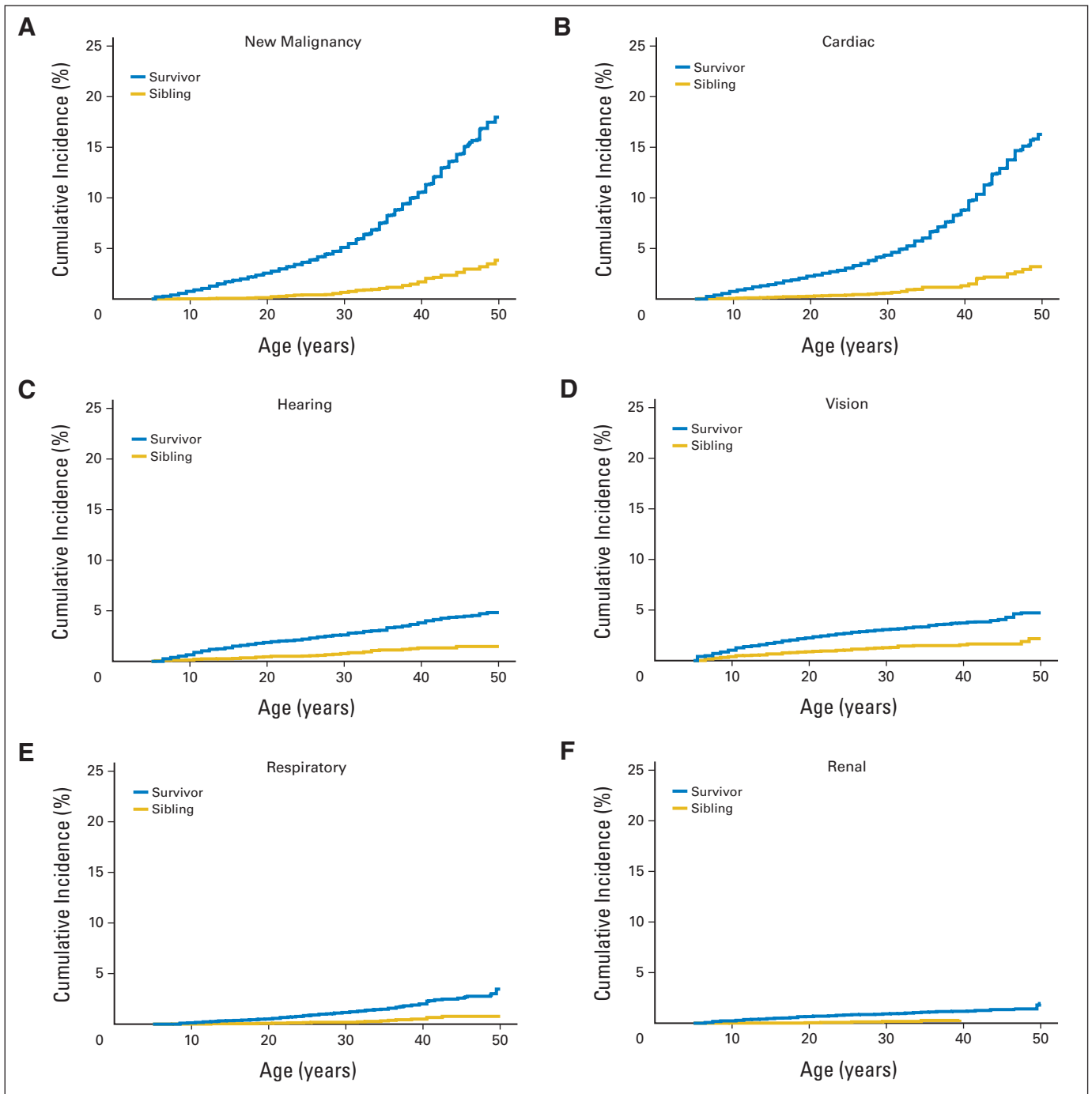


Fig 2. Cumulative incidence of selected grade 3 to 5 conditions by organ system. (A) New malignancy, (B) cardiac, (C) hearing, (D) vision, (E) respiratory, and (F) renal.

at age 50 years, certain organ systems had a low cumulative incidence of severe, disabling, life-threatening, or fatal health conditions (renal: 1.8%; 95% CI, 1.3 to 2.5; pulmonary: 3.8%; 95% CI, 3.0 to 4.7).

Specific chronic conditions were assessed (Fig 3, Appendix Fig A4). Survivors 35 years and older experienced increased risk for first occurrence of stroke, heart attack, and congestive heart failure compared with siblings (Fig 3). Evidence for an increase in risk for new onset joint replacement, renal failure, blindness, gonadal failure, and lung fibrosis did not achieve statistical significance. Even beyond age

35 years, primary cancer therapy was associated with a new onset of severe, disabling, life-threatening, or fatal health conditions (any radiotherapy: HR, 5.7; 95% CI, 4.6 to 7.0; any chemotherapy: HR, 4.9; 95% CI, 4.0 to 6.0; surgery alone: HR, 1.8; 95% CI, 1.2 to 2.7; Table 3). In addition, survivors exposed to radiation to the chest or neck (HR, 2.8; 95% CI, 2.3 to 3.4), brain (HR, 2.1; 95% CI, 1.6 to 2.7), or total body (HR, 3.9; 95% CI, 2.3 to 6.7) and survivors who were exposed to bleomycin (HR, 1.4; 95% CI, 1.1 to 1.9) or ≥ 300 mg/m² of anthracycline chemotherapy were at increased risk for

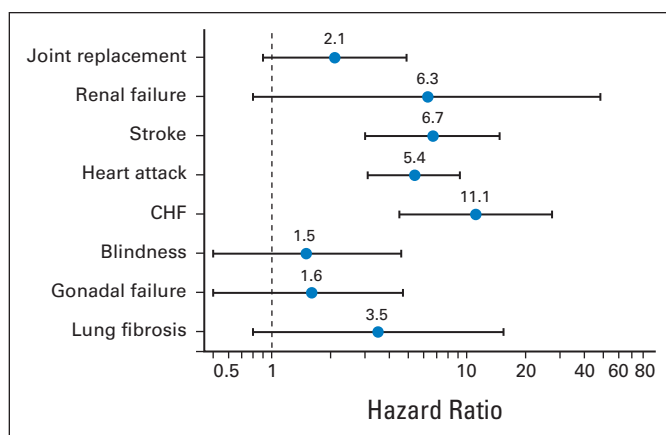


Fig 3. Hazard ratios and 95% CIs of survivors versus siblings for specific chronic conditions that first occurred at or after age 35 years, adjusted for age, race, and sex. CHF, congestive heart failure.

grade 3 to 5 conditions compared with survivors not exposed to those therapies (Appendix Table A4).

Using the Inverse Probability Censored Weighting analysis method, we replicated our analyses for grade 3 to 5 conditions in participants who were at least 35 years old. We calculated HRs to compare survivors with siblings, for the complete age ≥ 35 years cohort (Appendix Table A5), and subgroups defined by treatment

DISCUSSION

Health outcomes research conducted over the last three decades has established that survivors of childhood cancer are at increased risk for morbidity and mortality during their childhood and young adult years, largely as a result of adverse effects of the therapies that cured their primary malignancies.^{3-6,20,21} We previously reported that for survivors of childhood cancer at a mean age of 26 years, 62% had at least one chronic health condition with about one-quarter of survivors having a severe, life-threatening, or disabling condition.⁴ Others subsequently confirmed our observation of the substantial burden of morbidity experienced among young adults who had survived a childhood cancer.^{20,21} We now identify that elevated risk for severe, disabling, life-threatening, or fatal health conditions extends across the aging spectrum into the fourth and fifth decades of life, increasing significantly beyond age 35 years versus a sibling comparison population. After assessing more than 18,000 participants contributing over 388,000 person-years of time, survivors 35 years old and older were five-fold more likely than same-age, same-sex siblings to experience a new onset of a severe, disabling, life-threatening, or fatal health condition. Indeed, even as the general population ages and accumulates age-related chronic health conditions, there seems to be no point in time where the morbidity and mortality seen in a noncancer population is equivalent to that of survivors of childhood cancer.

In addition, the absolute magnitude of this burden of morbidity in middle age is striking. By age 50 years, 50% of survivors of childhood cancer will have experienced severe, disabling, or life-threatening morbidity or death, most commonly as a result of cardiovascular, pulmonary, hepatic, renal, and gonadal dysfunction, along with the development of subsequent malignant neoplasms. Furthermore, those who survive a first new condition remain at risk for developing additional conditions, such that by 50 years old, 22.5% have had at least two and 10.1% have had three or more grade 3 to 5 events. The National Academies' Institute of Medicine (Washington, DC) has previously recommended that these survivors receive "risk-based" care.²² Our current findings provide a compelling rationale for continuation of risk-based health care through adulthood.

These findings have important implications for cancer screening and prevention. Though the cumulative incidence of events increased across all organ systems, after age 35 years survivors had a disproportionate increase in the incidence of subsequent malignant neoplasms and cardiac events. Although the occurrence of new malignancies has been well documented,^{6,23} we now demonstrate that this profound rise in incidence occurs during an important window of vulnerability, before the age-threshold when general population screening guidelines recommend screenings to start (eg, breast cancer at age 40 years; colon cancer at age 50 years).^{24,25} This finding highlights the importance of disseminating established guidelines for follow-up care from the Children's Oncology Group.²⁶ Similarly, early detection of cardiomyopathy and medical intervention may mitigate progression to heart

Table 3. Hazard Ratios and 95% CIs for Development of Grade 3-5 Health Conditions at or Beyond Age 35 Years, After Specific Therapy for Primary Cancer, Compared With Siblings

Therapy for Treatment of Primary Cancer	HR	95% CI
Surgery		
Any surgery	5.0	4.1 to 6.1
Surgery only	1.8	1.2 to 2.7
Nephrectomy	3.1	1.9 to 5.1
Splenuctomy	7.4	6.0 to 9.1
Radiation		
Any radiation	5.7	4.6 to 7.0
Chest RT	7.0	5.7 to 8.6
CNS RT	4.9	3.8 to 6.3
Abdominal RT	7.1	5.7 to 8.7
Pelvic RT	6.6	5.3 to 8.2
No radiation	2.6	2.0 to 3.3
Chemotherapy		
Any chemotherapy	4.9	4.0 to 6.0
Cisplatin	4.5	2.9 to 6.9
Alkylator	5.5	4.4 to 6.7
Anthracycline	4.6	3.7 to 5.8
Methotrexate	3.6	2.9 to 4.6
Bleomycin	6.9	5.1 to 9.2
Combinations		
Chest RT plus bleomycin	9.1	6.5 to 12.7
Chest RT plus abdominal or pelvic RT	7.7	6.2 to 9.5
Abdominal or pelvic RT plus alkylator	6.9	5.5 to 8.6
Chest RT plus anthracyclines	7.3	5.5 to 9.7
Anthracyclines plus an alkylator	4.6	3.7 to 5.8

NOTE. Each row represents a separate multivariable model adjusted for sex and race. Age is used as the time scale. Models allow for multiple events and participants may have had another grade 3-4 event before age 35 years. Abbreviations: HR, hazard ratio; RT, radiation therapy.

failure in survivors exposed to anthracycline chemotherapy or chest-directed radiotherapy.²⁷⁻²⁹ Finally, the risk for stroke and myocardial infarction, identified in this study to have increased more than five-fold in survivors older than 35 years, may be modified by promoting a healthy lifestyle that can reduce rates of certain traditional cardiovascular risk factors (obesity, dyslipidemia, hypertension, diabetes, and smoking).

In our study, 24-year-old survivors of childhood cancer have the same cumulative incidence of grade 3 to 5 health conditions as 50-year-old siblings. In addition, survivors are known to have higher rates of physical impairment and fatigue³⁰⁻³² and early onset of age-related memory impairment,³³ which raises the question of whether exposure to systemic chemotherapy or even focal radiotherapy at a young age may accelerate the aging process. In our study, even healthy survivors (ie, no previous health condition before age 45 years) had a significant increase in risk for future conditions, indicating an underlying predisposition for early onset of poor outcomes. Mechanisms for aging such as telomere shortening, accumulation of free-radical mediated injury, and cellular senescence have been hypothesized to be operative in cancer survivors, but this has yet to be established.³⁴

The CCSS has uniquely provided the first systematic, longitudinal characterization of overall physical health in a large, geographically diverse population of survivors aging through middle adulthood with comparison to a sibling population. Despite these strengths, a number of limitations should be considered. First, all outcomes were self-reported, with validation of only the subsequent malignant neoplasms. Therefore, we excluded mild and moderate events from this analysis (grades 1 and 2), expecting improved validity from higher grade outcomes. Second, therapies for many childhood malignancies have evolved over time and, thus, results from this study may not be directly generalizable to more recently treated populations. However, traditional chemotherapeutics and radiotherapy continue to be the backbone of cancer treatment for most childhood malignancies.^{35,36} Finally, though analysis of a subset of the CCSS cohort that is now at least 35 years old has the potential for participation bias, the similarity between the unweighted and weighted analyses accounting for differences between participants and nonparticipants provide strong evidence that drop-out after the age 35 years has little impact on our analytic results. Comparisons of demographic distributions and cancer-related characteristics between overall participants (n =

14,359) and nonparticipants have been previously published.⁹ In general, participant and nonparticipants were similar regarding sex, cancer diagnosis, age at diagnosis, age at contact, and type of cancer treatment. However, the rate of nonparticipation was significantly higher among the next-of-kin of survivors who were deceased at the baseline evaluation compared with next of kin of survivors who were alive at baseline. Comparisons between those who completed baseline and those who were lost to follow-up (ie, could not be located for baseline completion) were not statistically significant except for vital status.

In summary, we have identified that risk for morbidity and mortality continues across the life span for cancer survivors and actually increases beyond age 35 years when compared with a population of siblings. By age 50 years, more than half of survivors have experienced a severe, disabling, or life-threatening event, including death. These data raise concerns for acceleration of the aging process in this population; highlight the need for longitudinal, risk-based follow-up; and identify the increasing health burden on this population as they age.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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Appendix

Table A1. CCSS Participants Expected to Be Age \geq 35 Years at Time of Last Attempted Follow-Up Survey

Characteristic	Completed Baseline		Died Before Age 35		Alive at Age 35 Years and Eligible for Follow-Up		Completed Follow-Up \geq Age 35 Years		Did Not Have Follow-Up by Age 35 Years	
	No. of Participants (n = 7,809)	%	No. of Participants (n = 980)	%	No. of Participants (n = 6,829)	%	No. of Participants (n = 5,604)	%	No. of Participants (n = 1,225)	%
Sex*										
Female	3,565	45.7	393	40.1	3,172	46.4	2,660	47.5	512	41.8
Male	4,244	54.3	587	59.9	3,657	53.6	2,944	52.5	713	58.2
Race/ethnicity*†										
Non-Hispanic white	6,924	88.9	860	87.8	6,064	89.1	5,063	90.6	1,001	82.2
Hispanic	347	4.5	41	4.2	306	4.5	219	3.9	87	7.1
Non-Hispanic black	326	4.2	52	5.3	274	4.0	192	3.4	82	6.7
Other	188	2.4	26	2.7	162	2.4	114	2.0	48	3.9
Age at first diagnosis, years*										
0-4	1,123	14.4	142	14.5	981	14.4	686	12.2	295	24.1
5-9	1,590	20.4	208	21.2	1,382	20.2	1,052	18.8	330	26.9
10-14	2,605	33.4	314	32.0	2,291	33.5	1,887	33.7	404	33.0
15-20	2,491	31.9	316	32.2	2,175	31.8	1,979	35.3	196	16.0
Primary diagnosis*										
Acute lymphoblastic leukemia	1,748	22.4	221	22.6	1,527	22.4	1,195	21.3	332	27.1
Acute myeloid leukemia	178	2.3	29	3.0	149	2.2	128	2.3	21	1.7
Other leukemia	89	1.1	28	2.9	61	0.9	46	0.8	15	1.2
CNS tumors	979	12.5	175	17.9	804	11.8	654	11.7	150	12.2
Hodgkin lymphoma	1,757	22.5	208	21.2	1,549	22.7	1,341	23.9	208	17.0
Non-Hodgkin lymphoma	734	9.4	50	5.1	684	10.0	557	9.9	127	10.4
Kidney tumors	330	4.2	29	3.0	301	4.4	221	3.9	80	6.5
Neuroblastoma	191	2.4	21	2.1	170	2.5	120	2.1	50	4.1
Soft tissue sarcoma	778	10.0	91	9.3	687	10.1	579	10.3	108	8.8
Bone tumors	1,025	13.1	128	13.1	897	13.1	763	13.6	134	10.9
Therapy for primary diagnosis										
Surgery†										
Any surgery*	5,890	86.3	745	89.2	5,145	85.9	4,368	86.5	777	82.3
Nephrectomy*	300	4.4	29	3.5	271	4.5	203	4.0	68	7.2
Splenectomy*	1,159	17.0	133	15.9	1,026	17.1	915	18.1	111	11.8
Surgery alone	455	6.7	19	2.3	436	7.3	372	7.4	64	6.8
Chemotherapy†										
Any chemotherapy*	5,310	77.7	726	86.9	4,584	76.4	3,813	75.5	771	81.5
Alkylator	3,897	57.1	628	75.5	3,269	54.5	2,749	54.4	520	55.1
Anthracycline	2,676	39.2	474	57.0	2,202	36.7	1,841	36.5	361	38.2
Bleomycin	622	9.1	123	14.8	499	8.3	425	8.4	74	7.8
Cisplatin*	367	5.4	126	15.1	241	4.0	193	3.8	48	5.1
Methotrexate*	2,820	41.3	348	41.7	2,472	41.2	2,042	40.4	430	45.5
Radiotherapy†										
Any RT	5,127	75.0	720	86.1	4,407	73.5	3,709	73.4	698	74.1
Brain*	2,020	30.2	331	40.9	1,689	28.7	1,393	28.1	296	32.3
Chest*	1,953	29.2	287	35.5	1,666	28.3	1,458	29.4	208	22.7
Abdomen	1,515	22.7	205	25.3	1,310	22.3	1,126	22.7	184	20.1
Pelvis*	1,234	18.5	216	26.7	1,018	17.3	887	17.9	131	14.3
Chest RT + bleomycin	297	4.5	85	10.5	212	3.6	188	3.8	24	2.6
Chest RT + abdominal/pelvic RT*	1,152	17.2	194	24.0	958	16.3	851	17.2	107	11.7
Alkylator + abdominal/pelvic RT	1,121	16.8	232	28.7	889	15.1	762	15.4	127	13.9
Chest RT + anthracyclines	647	9.7	171	21.2	476	8.1	395	8.0	81	8.9
Anthracyclines + alkylator	2,676	39.2	474	57.0	2,202	36.7	1,841	36.5	361	38.2

(continued on following page)

Aging Survivors of Childhood Cancer and Serious Health Conditions

Table A1. CCSS Participants Expected to Be Age ≥ 35 Years at Time of Last Attempted Follow-Up Survey (continued)

Characteristic	Completed Baseline		Died Before Age 35		Alive at Age 35 Years and Eligible for Follow-Up		Completed Follow-Up ≥ Age 35 Years		Did Not Have Follow-Up by Age 35 Years	
	No. of Participants (n = 7,809)	%	No. of Participants (n = 980)	%	No. of Participants (n = 6,829)	%	No. of Participants (n = 5,604)	%	No. of Participants (n = 1,225)	%
Age at baseline, years*										
0-19	287	3.7	281	29.0	6	0.1	6	0.1	0	0.0
20-29	4,276	54.8	580	59.8	3,696	54.1	2,733	48.8	963	78.6
30-39	2,904	37.2	109	11.2	2,795	40.9	2,533	45.2	262	21.4
40-49	332	4.3	0	0.0	332	4.9	332	5.9	0	0.0
Health status at baseline*										
Excellent	1,265	18.3	16	8.8	1,249	18.6	1,012	18.4	237	19.6
Very good	2,633	38.1	45	24.7	2,588	38.5	2,176	39.5	412	34.1
Good	2,204	31.9	64	35.2	2,140	31.8	1,747	31.7	393	32.5
Fair	677	9.8	42	23.1	635	9.4	494	9.0	141	11.7
Poor	123	1.8	15	8.2	108	1.6	82	1.5	26	2.2
Education at baseline*										
Patient age < 18 years	217	2.9	217	23.3	0	0.0	0	0.0	0	0.0
High school or less	1,989	27.0	314	33.8	1,675	26.0	1,257	23.8	418	36.4
Completed high school/some college	2,536	34.4	355	38.2	2,181	33.9	1,769	33.4	412	35.9
College graduate	2,627	35.6	44	4.7	2,583	40.1	2,264	42.8	319	27.8

NOTE. For this analysis, we identified the eligible population as individuals who reached age 35 years after entering our cohort and before the last follow-up questionnaire was administered (2007). Among these, the participant population included individuals who contributed data to our analysis after age 35 years via a questionnaire or with cause of death information. Prediction models were built separately for survivors and siblings to calculate predicted probabilities of participation. The prediction model for survivors used the 6,829 alive (as of age 35) and eligible survivors (5,604 participants) and was based on the following covariates: age at diagnosis, race, sex, diagnosis group, any surgery, any chemotherapy, any brain radiation, any chest RT plus abdomen or pelvis RT, age at baseline, education at baseline, and self-reported health status at baseline. The prediction model for siblings used the 2,270 alive and eligible siblings (1,969 participants) and was based on the following covariates: race, sex, age at baseline, education at baseline, and self-reported health status at baseline.

Abbreviations: CCSS, Childhood Cancer Survivor Study; RT, radiotherapy.

* $P < .05$ for comparison of participants who completed follow-up at age ≥ 35 years with those who did not complete follow up, based on χ^2 test.

†Percentages calculated on total No. of patients on whom information was available.

Table A2. Grade 3-5 Conditions

Category	Grade	Condition	Occurring More Than 5 Years After Diagnosis				Occurring at or After Age 35 Years			
			Survivors (n = 14,359)		Siblings (n = 4,031)		Survivors (n = 5,604)		Siblings (n = 1,969)	
			No. of Participants	%	No. of Participants	%	No. of Participants	%	No. of Participants	%
Subsequent neoplasms	3	Benign meningioma with surgery, thyroid cancer	153	1.1	10	0.2	29	0.5	4	0.2
	4	Breast carcinoma-in-situ	63	0.4	3	0.1	51	0.9	3	0.2
		Malignancy other than non-melanoma skin cancer or thyroid cancer	657	4.6	35	0.9	229	4.1	15	0.8
	5	Malignancy, death	360	2.5	5	0.1	139	2.5	2	0.1
		Total	1,233	8.6	53	1.3	448	8.0	24	1.2
Hearing	3	Hearing loss requiring a hearing aid	387	2.7	42	1.0	77	1.4	10	0.5
	4	Deafness in both ears not corrected by hearing aid	45	0.3	3	0.1	9	0.2	2	0.1
		Total	432	3.0	45	1.1	86	1.5	12	0.6
Vision	3	Cataracts, requiring surgery	142	1.0	8	0.2	33	0.6	4	0.2
		Legally blind in one eye	150	1.0	38	0.9	9	0.2	3	0.2
		Moderate, severe and profound impairment in one eye	5	0.0	0	0.0	0	0.0	0	0.0
	4	Legally blind in both eyes or loss of an eye	36	0.3	12	0.3	6	0.1	1	0.1
		Moderate, severe and profound impairment in both eyes	4	0.0	3	0.1	0	0.0	0	0.0
	Total	337	2.3	61	1.5	48	0.9	8	0.4	
Speech	3	Aphonia	1	0.0	0	0.0	0	0.0	0	0.0
		Total	1	0.0	0	0.0	0	0.0	0	0.0
Endocrine	3	Corticoadrenal insufficiency	4	0.0	0	0.0	1	0.0	0	0.0
		Panhypopituitarism	4	0.0	0	0.0	0	0.0	0	0.0
		Diabetes insipidus	9	0.1	0	0.0	0	0.0	0	0.0
		Diabetes, requiring insulin therapy and/or diabetic end organ disease	129	0.9	22	0.5	34	0.6	8	0.4
		Ovarian failure	334	2.3	45	1.1	14	0.2	3	0.2
		Testicular hypofunction	78	0.5	4	0.1	4	0.1	1	0.1
		Thyroid nodules, requiring surgery	480	3.3	25	0.6	139	2.5	11	0.6
	5	Diabetes with ketoacidosis, death	4	0.0	0	0.0	1	0.0	0	0.0
		Metabolic death	3	0.0	0	0.0	1	0.0	0	0.0
		Total	1,045	7.3	96	2.4	194	3.5	23	1.2
Respiratory	3	Emphysema	24	0.2	2	0.0	11	0.1	0	0.0
		Emphysema, requiring medication	15	0.1	1	0.0	9	0.2	1	0.1
		Lung fibrosis, requiring oxygen	39	0.3	6	0.1	16	0.3	2	0.1
		Pulmonary hypertension	8	0.1	0	0.0	3	0.1	0	0.0
	4	Other diseases of lung	41	0.3	2	0.0	8	0.1	1	0.1
		Pulmonary embolism	13	0.1	4	0.1	4	0.1	3	0.2
		Respiratory arrest	9	0.1	3	0.1	2	0.0	0	0.0
	5	Pulmonary death	73	0.5	0	0.0	27	0.5	0	0.0
		Total	222	1.5	18	0.4	80	1.4	7	0.4
Cardiac	3	Arrhythmia, requiring pacemaker	83	0.6	11	0.3	41	0.7	3	0.2
		Cerebral embolism	5	0.0	0	0.0	1	0.0	0	0.0
		Congestive heart failure requiring medication	302	2.1	11	0.3	120	2.1	5	0.3
		Heart attack, angina or coronary heart disease not requiring a cardiac catheterization	184	1.3	16	0.4	103	1.8	13	0.7
		Hypertension, severe	8	0.1	2	0.0	0	0.0	0	0.0
		Hypotension	18	0.1	3	0.1	3	0.1	0	0.0
		Pericardial disease requiring surgical intervention	22	0.2	0	0.0	13	0.2	0	0.0
	4	Endocarditis	14	0.1	1	0.0	5	0.1	0	0.0
		Heart attack requiring cardiac catheterization or angioplasty or CABG	169	1.2	20	0.5	101	1.8	12	0.6
		Heart transplantation	30	0.2	0	0.0	3	0.1	0	0.0
		Heart valve replacement	59	0.4	3	0.1	48	0.9	0	0.0
		Stroke/CVA	302	2.1	18	0.4	89	1.6	7	0.4
		Ventricular fibrillation/flutter	1	0.0	1	0.0	1	0.0	1	0.1
	5	Cardiovascular death	156	1.1	2	0.0	73	1.3	2	0.1
		Total	1,353	9.4	88	2.2	601	10.7	43	2.2

(continued on following page)

Aging Survivors of Childhood Cancer and Serious Health Conditions

Table A2. Grade 3-5 Conditions (continued)

Category	Grade	Condition	Occurring More Than 5 Years After Diagnosis				Occurring at or After Age 35 Years			
			Survivors (n = 14,359)		Siblings (n = 4,031)		Survivors (n = 5,604)		Siblings (n = 1,969)	
			No. of Participants	%	No. of Participants	%	No. of Participants	%	No. of Participants	%
GI	3	Cirrhosis of liver	70	0.5	2	0.0	19	0.3	1	0.1
		Surgery for intestinal obstruction	185	1.3	12	0.3	30	0.5	4	0.2
	4	Liver transplantation	2	0.0	0	0.0	0	0.0	0	0.0
		Gastrointestinal death	30	0.2	0	0.0	13	0.2	0	0.0
		Total	287	2.0	14	0.3	62	1.1	5	0.3
Renal	3	Acute renal failure	3	0.0	1	0.0	2	0.0	0	0.0
		Nephrotic syndrome	3	0.0	3	0.1	1	0.0	0	0.0
		Neurogenic bladder	6	0.0	1	0.0	2	0.0	0	0.0
	4	Chronic renal failure	41	0.3	2	0.0	3	0.1	1	0.1
		Dialysis or kidney transplantation	81	0.6	4	0.1	9	0.2	0	0.0
		End-stage renal disease	2	0.0	0	0.0	0	0.0	0	0.0
	5	Death as a result of renal failure	10	0.1	0	0.0	1	0.0	0	0.0
Total		146	1.0	11	0.3	18	0.3	1	0.1	
Musculoskeletal	3	Amputation	102	0.7	3	0.1	12	0.2	0	0.0
		Joint replacement	187	1.3	14	0.3	54	1.0	7	0.4
	5	Musculoskeletal death	8	0.1	0	0.0	0	0.0	0	0.0
		Total	297	2.1	17	0.4	66	1.2	7	0.4
Neurologic	3	Multiple sclerosis	6	0.0	11	0.3	1	0.0	3	0.2
		Paralysis	16	0.1	0	0.0	1	0.0	0	0.0
		Problems with balance or ability to manipulate objects, severe	51	0.4	6	0.1	19	0.3	3	0.2
		Problems with learning or memory, severe	40	0.3	3	0.1	7	0.1	2	0.1
	4	Coma and stupor	22	0.2	1	0.0	2	0.0	0	0.0
		Mental retardation, problems with memory or learning, disabling	36	0.3	3	0.1	3	0.1	0	0.0
		Paralysis, severe	321	2.2	36	0.9	49	0.9	10	0.5
	5	Problems with balance or ability to manipulate objects, disabling	14	0.1	4	0.1	5	0.1	1	0.1
		Neurologic death	25	0.2	0	0.0	5	0.1	0	0.0
		Total	531	3.7	64	1.6	92	1.6	19	1.0
Hematologic	3	Blood clot in head, lung, arm, leg, or pelvis	361	2.5	60	1.5	80	1.4	16	0.8
		Aplastic anemia NOS	1	0.0	0	0.0	0	0.0	0	0.0
	5	Hematologic death	8	0.1	0	0.0	1	0.0	0	0.0
		Thromboembolic death	6	0.0	0	0.0	2	0.0	0	0.0
		Total	376	2.6	60	1.5	83	1.5	16	0.8
Infectious disease	5	Death as a result of infection	47	0.3	0	0.0	10	0.2	0	0.0
		Total	47	0.3	0	0.0	10	0.2	0	0.0

Abbreviations: CABG, coronary artery bypass grafting; CVA, stroke; NOS, not otherwise specified.

Table A3. No. of Survivors With Multiple Conditions, Based On Having No Previous Conditions Before Age Listed

Age Reached With No Previous Conditions (years)	No. of Survivors	No. of Chronic Health Conditions				
		0	1	2	3	≥ 4
26	9,348	7,578	1,259	327	113	71
35	4,483	3,657	611	137	45	33
45	842	715	104	14	5	4

Table A4. Multivariable HRs and 95% CIs for Development of Grade 3-5 Health Conditions at or After Age 35 Years, Within the Survivor Population After Specific Therapy for Primary Cancer

Therapy for Treatment of Primary Cancer	HR*	95% CI
Surgery		
Any surgery	1.1	0.8 to 1.5
Radiation		
Chest/neck RT	2.8	2.3 to 3.4
CNS RT	2.1	1.6 to 2.7
Abdominal RT	1.1	0.7 to 1.6
Total body RT	3.9	2.3 to 6.7
Other RT	1.7	1.7 to 2.3
Chemotherapy		
Anthracycline, 1-299 mg/m ² †	0.9	0.7 to 1.2
Anthracycline, ≥ 300 mg/m ² †	1.2	1.0 to 1.5
Methotrexate	0.7	0.6 to 0.9
Bleomycin	1.4	1.1 to 1.9

Abbreviations: HR, hazard ratio; RT, radiation therapy.

*From a multivariable model including all covariates listed, plus sex and race, with age as the time scale. Model allows for multiple events and participants may have had a different grade 3-4 event before age 35 years.

†Referent group received no exposure to anthracycline.

Table A5. HRs by Organ System and for Specific Severe, Disabling, Life-Threatening, or Fatal Health Conditions at or After Age 35 Years for Survivors Versus Siblings With Weighting Based on Nonparticipation Rates, and Without Weighting (for comparison to Table 2)

Condition	With Weights		Without Weights	
	HR	95% CI	HR	95% CI
Organ system				
All conditions	5.0	4.1 to 6.1	5.0	4.1 to 6.1
Subsequent malignancy	7.7	5.0 to 11.7	7.5	4.9 to 11.5
Hearing	3.3	1.8 to 6.3	3.2	1.7 to 6.0
Vision	2.8	1.2 to 6.9	2.8	1.2 to 7.0
Endocrine	3.8	2.4 to 5.9	3.8	2.4 to 5.8
Respiratory	5.3	2.5 to 11.5	5.0	2.3 to 10.8
Cardiac	7.9	5.4 to 11.6	7.8	5.4 to 11.5
GI	7.0	2.5 to 19.5	6.7	2.4 to 18.5
Renal	8.6	1.1 to 67.4	7.5	1.0 to 58.3
Musculoskeletal	2.8	1.3 to 6.0	2.8	1.3 to 5.9
Neurologic	2.2	1.2 to 3.8	2.2	1.2 to 3.8
Other hematologic	2.6	1.4 to 4.5	2.6	1.5 to 4.5
Specific conditions				
Joint replacement	2.2	1.0 to 4.6	2.2	1.0 to 4.6
Renal failure	6.9	0.9 to 55.3	6.0	0.6 to 47.7
Stroke	7.0	3.3 to 14.8	6.6	3.1 to 14.1
Heart attack	5.0	3.0 to 8.3	5.0	3.1 to 8.3
Congestive heart failure	11.4	4.7 to 27.3	10.9	4.5 to 26.0
Blindness	1.6	0.5 to 4.5	1.6	0.5 to 4.6
Gonadal failure	1.3	0.4 to 4.3	1.5	0.5 to 4.5
Lung fibrosis	3.6	0.8 to 16.0	3.5	0.8 to 15.7

NOTE. Each row represents a separate multivariable model, adjusted for sex and race, with age as the time scale. Models allow for multiple events and participants may have had a grade 3-4 event before age 35 years.

Abbreviation: HR, hazard ratio.

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Table A6. HRs and 95% CIs for Development of Grade 3-5 Health Conditions at or After Age 35 Years, After Specific Therapy for Primary Cancer, Versus Siblings Both With and Without Weighting for Nonparticipation

Therapy for Treatment of Primary Cancer	With Weights		Without Weights	
	HR	95% CI	HR	95% CI
Surgery				
Any surgery	5.1	4.2 to 6.2	5.0	4.1 to 6.1
Surgery only	1.8	1.2 to 2.7	1.8	1.2 to 2.7
Nephrectomy	3.3	2.0 to 5.3	3.1	1.9 to 5.1
Splenectomy	7.5	6.1 to 9.3	7.4	6.0 to 9.1
Radiation				
Any radiation	5.8	4.7 to 7.0	5.7	4.6 to 7.0
Chest RT	7.1	5.8 to 8.7	7.0	5.7 to 8.6
CNS RT	5.0	3.9 to 6.4	4.9	3.8 to 6.3
Abdominal RT	7.1	5.7 to 8.8	7.1	5.7 to 8.7
Pelvic RT	6.6	5.3 to 8.2	6.6	5.3 to 8.2
No radiation	2.6	2.0 to 3.3	2.6	2.0 to 3.3
Chemotherapy				
Any chemotherapy	4.9	4.0 to 6.1	4.9	4.0 to 6.0
Cisplatin	4.8	3.1 to 7.5	4.5	2.9 to 6.9
Alkylator	5.5	4.5 to 6.8	5.5	4.4 to 6.7
Anthracycline	4.7	3.7 to 5.9	4.6	3.7 to 5.8
Methotrexate	3.7	2.9 to 4.7	3.6	2.9 to 4.6
Bleomycin	7.0	5.3 to 9.4	6.9	5.1 to 9.2
Combinations				
Chest RT + bleomycin	9.3	6.7 to 13.0	9.1	6.5 to 12.7
Chest RT + abdominal or pelvic RT	7.8	6.3 to 9.6	7.7	6.2 to 9.5
Abdominal or pelvic RT + alkylator	6.9	5.5 to 8.7	6.9	5.5 to 8.6
Chest RT + anthracyclines	7.4	5.6 to 9.9	7.3	5.5 to 9.7
Anthracyclines + an alkylator	4.7	3.7 to 5.9	4.6	3.7 to 5.8

NOTE. Each row represents a separate multivariable model adjusted for sex and race, with age as the time scale. Models allow for multiple events and participants may have had a grade 3-4 event before age 35 years.
Abbreviations: HR, hazard ratio; RT, radiation therapy.

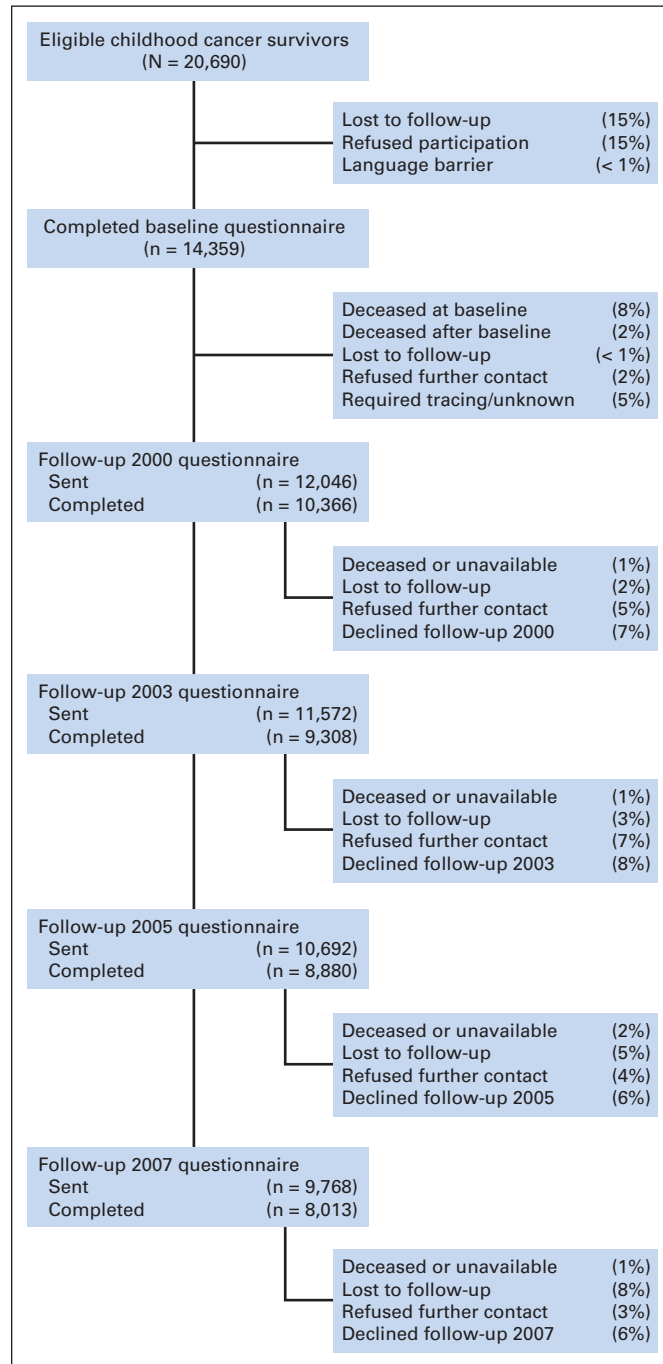


Fig A1. (A) Study population: survivor recruitment and longitudinal participation among those ages 35 years or older as of last follow-up in 2007. (continued)

Aging Survivors of Childhood Cancer and Serious Health Conditions

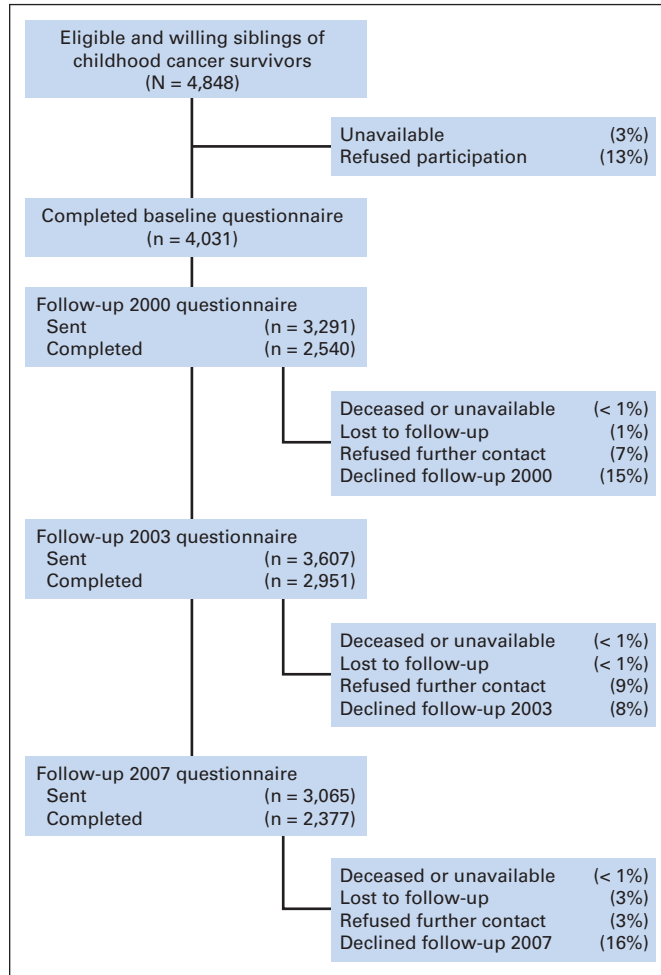


Fig A1. (B) Study population: sibling recruitment and longitudinal participation among those ages 35 years or older as of last follow-up in 2007. (continued)

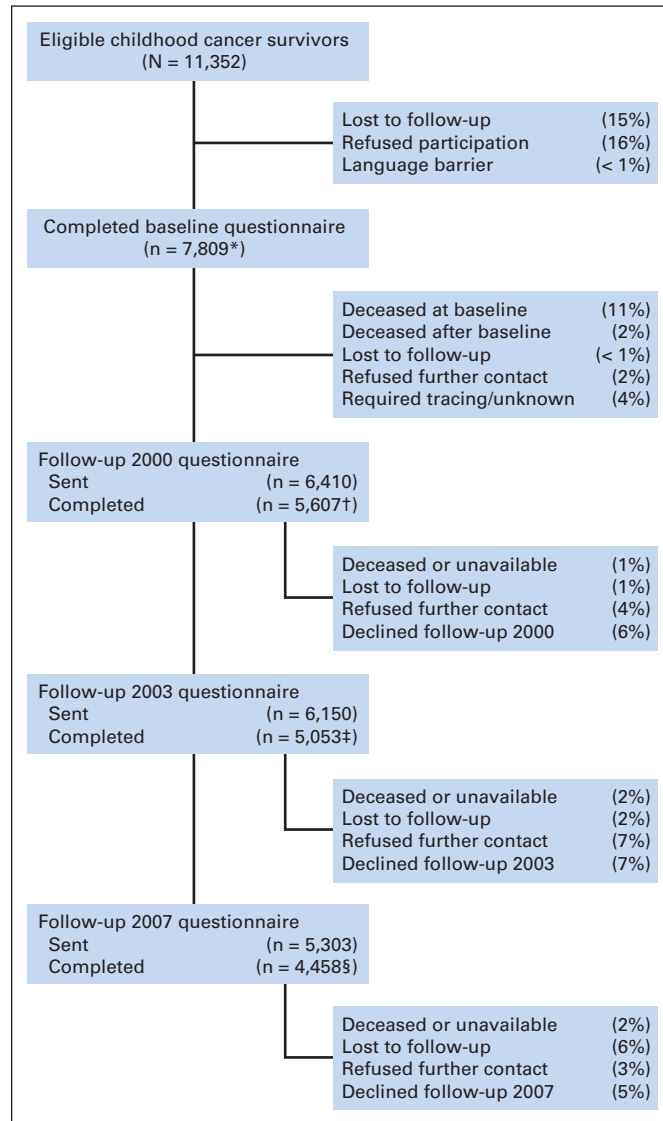


Fig A1. (C) Study population: survivor recruitment and longitudinal participation among those ages 35 years or older as of last follow-up in 2007. (*) For 228 participants, age at baseline \geq 35 years and baseline was the last follow-up. Median follow-up time since age 35 years was 3 years, with a maximum of 18 years. (†) For 322 participants, age at follow-up in 2000 was \geq 35 years and follow-up 2000 was the last follow-up; median follow-up time since age 35 years was 3 years, with a maximum of 15 years. (‡) For 596 participants, age at follow-up in 2003 was \geq 35 years and follow-up in 2003 was the last follow-up; median follow-up time since age 35 years was 5 years, with a maximum of 20 years. (§) For 4,458 participants, age at follow-up in 2007 was \geq 35 years and follow-up in 2007 was the last follow-up; median follow-up time since age 35 years was 6 years, with a maximum of 23 years. Overall, for the 5,604 participants in the subcohort, median follow-up time since age 35 years was 5 years.

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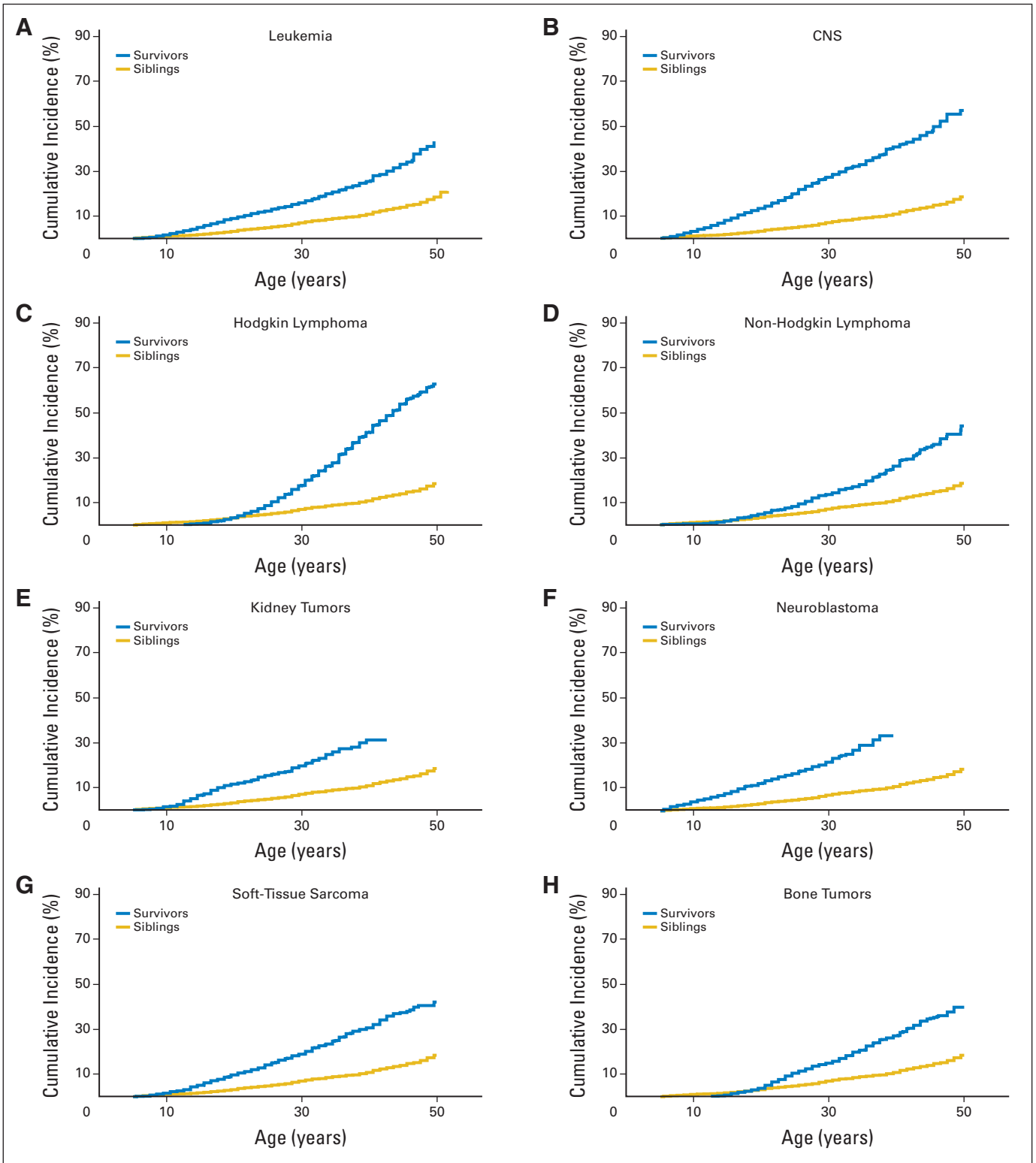


Fig A2. Cumulative incidence of chronic health conditions for severe, disabling, life-threatening, or fatal health conditions, by primary childhood cancer diagnosis. (A) leukemia, (B) CNS tumors, (C) Hodgkin lymphoma, (D) non-Hodgkin lymphoma, (E) kidney tumors, (F) neuroblastoma, (G) soft-tissue sarcoma, and (H) bone tumors.

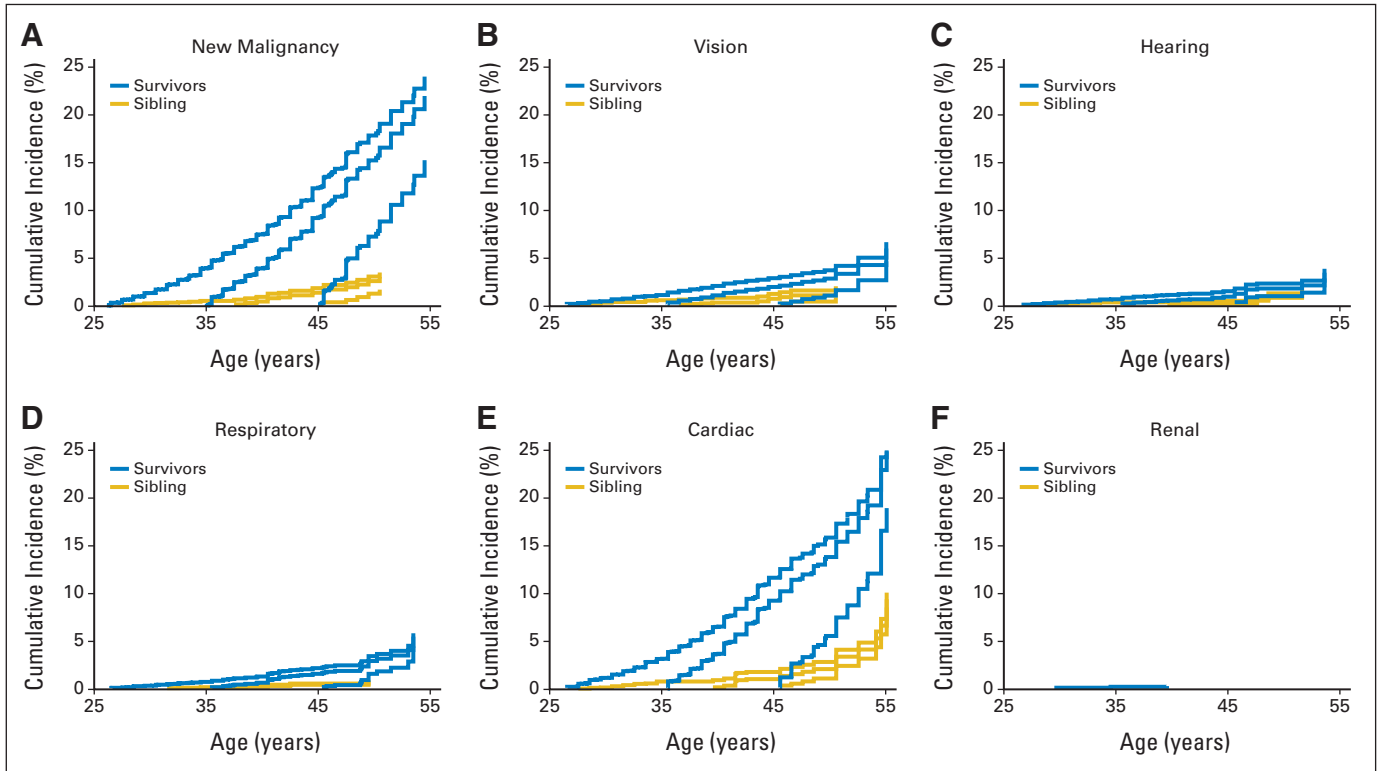


Fig A3. Cumulative incidence of selected grade 3 to 5 conditions by organ system, based on having no previous grade 3 to 5 events among survivors and siblings. (A) New malignancy, (B) vision, (C) hearing, (D) respiratory, (E) cardiac, and (F) renal.

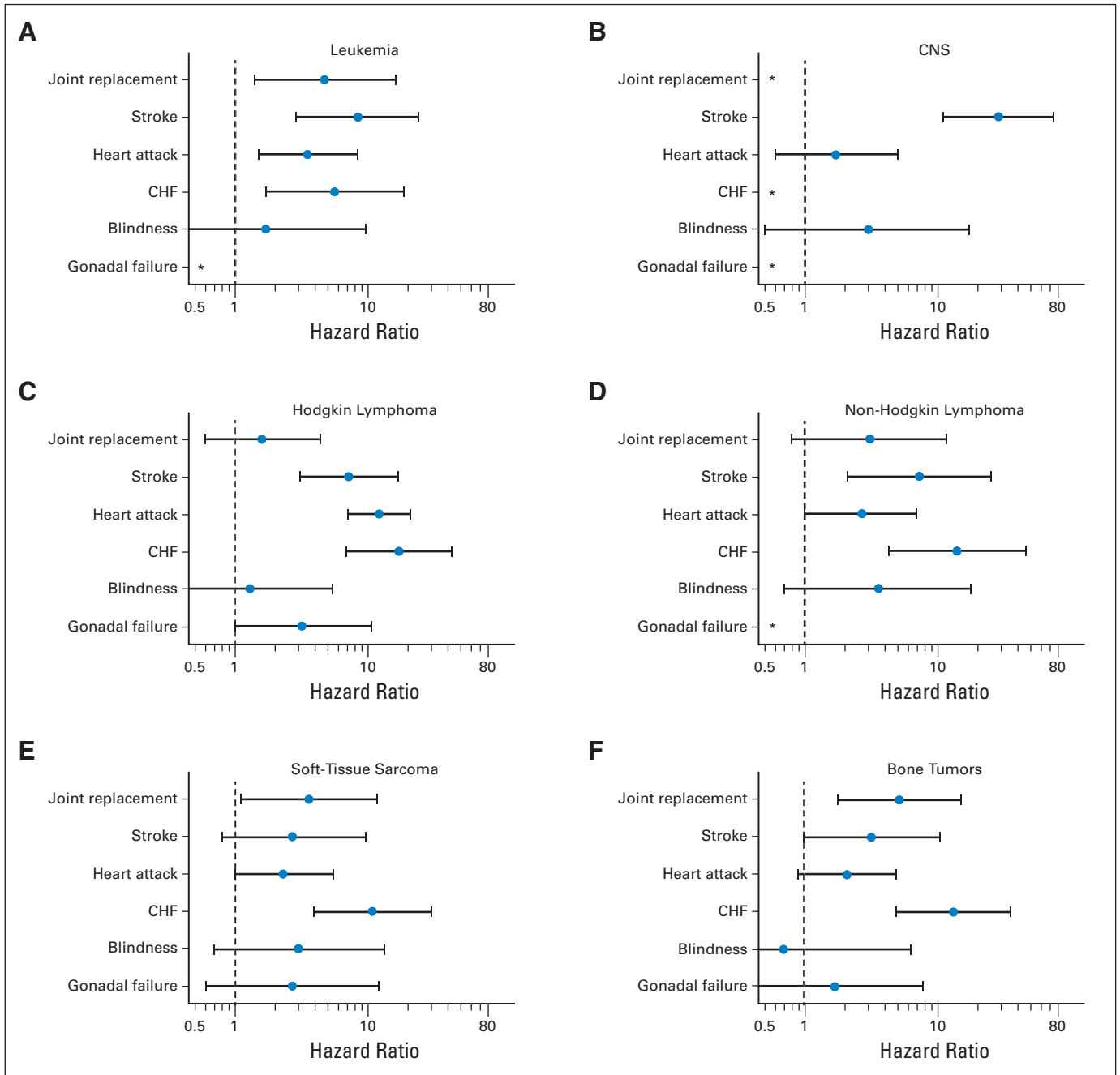


Fig A4. Hazard ratios and 95% CIs for specific chronic conditions that first occurred on or after age 35 years, adjusted for age and sex for survivors of (A) leukemia, (B) CNS tumors, (C) Hodgkin lymphoma, (D) non-Hodgkin lymphoma, (E) soft-tissue sarcomas, and (F) bone tumors. CHF, congestive heart failure. (*) No events.