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ORIGINAL PAPER

Hospitalization and mortality among pediatric cancer survivors: a population-based study

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Abstract

Purpose We examined serious long-term outcomes among childhood cancer survivors using population-based data.

Methods We used 1982–2014 Washington State data to compare hospitalization and/or death (including cause-specific) during up to 27 years follow-up among all 5+ year childhood cancer survivors <20 years at diagnosis ($n=3,152$) and a sample of comparison children within birth cohorts, with assessment by cancer type and child/family characteristics.

Results During follow-up (9 years median), 12% of survivors had hospitalizations; 4% died. Greatest absolute risks/1,000 person-years were for hospitalization/deaths due to cancers (8.1), infection (6.2), injuries (6.0), and endocrine/metabolic disorders (5.8). Hazard ratios (HR) and 95% confidence intervals (CI) for hospitalization (2.7, 95% CI 2.4–3.0) and any-cause death (14.7, 95% CI 11.3–19.1) were increased, and for all cause-specific outcomes examined, most notably cancer- (35.1, 95% CI 23.7–51.9), hematological- (6.7, 95% CI 5.3–8.5), nervous system- (6.4, 95% CI 5.2–7.8), and circulatory- (5.2, 95% CI 4.1–6.5) related outcomes. Hospitalizations occurred more often among females and those receiving radiation, with modest differences by urban/rural birth residence and race/ethnicity. Cause-specific outcomes varied by cancer type.

Conclusions This study suggests increased risks for the rarely-studied outcomes of long-term fracture and injury, and confirms increased risks of selected other conditions among survivors. Multi-state pooling of population-based data would increase the ability to evaluate outcomes for uncommon cancer types and by racial/ethnic groups under-represented in many studies.

Keywords Childhood cancer · Hospitalization · Late effects · Survivorship · Cohort · Morbidity

Introduction

Annually, more than 10,000 children less than 15 years old are diagnosed with malignancies in the US [1], with an estimated prevalence of more than 420,000 persons with a prior pediatric cancer [2, 3]. Among survivors, occurrence of cardiopulmonary diseases [4–6], subsequent cancers [7], and mortality [8] is increased, in part due to adverse treatment effects. Less is known about other less-studied outcomes, or for children with less common cancers, or within population-subgroups who typically are under-represented in cohort studies requiring repeated interactions or clinical visits for recruitment and follow-up [9, 10]. Characterization of serious morbidities within population-based studies will help in development of strategies for optimal care and follow-up for all children, including those who may be under-represented in many studies. We used linked population-based health registry data to compare late (5+ years after diagnosis) occurrence of hospitalization or death among

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childhood cancer cases in Washington State to that among children without cancer born in the same years, evaluating outcomes by cancer types and selected personal and family characteristics.

Methods

Institutional Review Board approvals including waivers of consent (due to use of existing health registry data) were received. We used population-based cancer registry data starting in 1974 from the Cancer Surveillance System of Western Washington (National Cancer Institute's Surveillance, Epidemiology and End Results Program; > 70% of state population), and starting in 1995 from the Washington State Cancer Registry (Centers for Disease Control and Prevention's National Program of Central Cancer Registries; statewide surveillance), both subject to comprehensive quality control activities for completeness and accuracy [11, 12], meeting the highest standards of the North American Association of Central Cancer Registries, which are the most comprehensive of any disease surveillance system [13]. Records of all persons < 20 years with cancer diagnosed 1974–2014 identified in the registries were linked to birth records 1974–2014 to identify children and adolescents born in-state ($n = 5{,}876$).

Cases surviving 5+ years after diagnosis ($n = 5{,}000$) were identified per registry follow-up. An "index date" was assigned (5 years after diagnosis). To account for earliest and latest years of complete follow-up data available (1987–2013) and the cases' survival eligibility requirement, analysis included diagnosis years 1982–2008 ($n = 3{,}589$). Excluding non-malignancies ($n = 437$) left 3,152 cases. For each case, 10 comparison subjects were selected from birth records, matched on birth year and sex, excluding those known to have died before their case's index date.

Hospitalizations and deaths were assessed by linking to state hospital discharge and death records. Washington State hospital discharge data include all inpatient and observation discharges in non-Federal facilities, with multiple International Classification of Disease, Version 9 codes (ICD9) for each episode using Medicare–Medicaid billing standards. The State Department of Health conducts steps to ensure complete hospital reporting, including tracking and verifying the number of records monthly, and following up with any delinquent reports. Deaths were identified in the death registry, which maintains agreements with the National Center for Health Statistics and the State Department to identify out-of-state deaths to residents; these include primary/contributing causes of death (ICD9, ICD10) information.

Outcomes assessed included any hospitalization, death, and occurrence of a hospitalization and/or death related to general outcome categories identified by relevant diagnosis codes in discharge/death records (Supplementary Table S1). Pregnancy-related hospitalizations (ICD9 630–679, 760–779) were excluded. We also evaluated selected outcome subsets: diabetes (ICD9 = 250; ICD10 = E109, E139, E141, E149) and fracture (ICD9 = 800–829, 733.1, 733.8, 733.93, 733.98; ICD10 = M48.4, M80, M84.0, M84.1, M84.2, M84.3, M84.4, M90.7, M96.6, S02, S12, S22, S32, S42, S52, S62, S72, S82, S92, T02, T08, T10, T12, T14.2). Because cancer-related hospitalizations at < 20 years of age would only have occurred among cases, analysis of this outcome was restricted to cases who survived to age 20 years without a cancer hospitalization (excluding the 5 years after diagnosis) and their comparison subjects, with left-truncation of follow-up at age 20 years.

Cancer registry data included: International Classification of Diseases for Oncology (ICD-O) morphology and topography codes, histology, diagnosis age, date, initial therapy (chemotherapy, radiotherapy), and vital status at quarterly follow-up. Cancer types were classified per the International Classification of Childhood Cancer, 3rd edition [14]. Birth data included maternal age, race/ethnicity, insurance, rurality (as defined using U.S. Census Bureau standards) [15], and infant gender.

Case follow-up accrued from the index date, with similar dates for comparison subjects, through December 2013, or death date if earlier. We estimated the incidence rate of outcomes per 1,000 person-years. Birth year- and sex-adjusted rate differences/1,000 person-years and their 95% confidence intervals (CI) for outcomes were estimated with Poisson regression. Proportional hazards were used to calculate hazard ratios (HR) estimates and 95% CIs for the hypothesis that survivors have increased hospitalization/death rates vs. comparison children. All-cause mortality HRs were calculated using death certificate data. Risk-set stratification accounted for matched set number; confounder evaluation was conducted by their inclusion in regressions. Race/ethnicity (White, Black, Hispanic, Asian, Native American/Alaska Native, Pacific Islander, Other); sex; urban/rural residence at birth; diagnosis year; maternal education (< 13, 13+ years) and medical insurance at delivery (Medicaid, Private/other) as a proxy of socio-economic status were considered for their potential effects; only those altering risk estimates by > 10% were adjusted for. HRs accounted for matching variables (sex, birth year), unless otherwise indicated. Subanalyses examined rates and HRs by cancer types when cell sizes were ≥ 5. We also stratified results by selected child/family characteristics. Likelihood ratio statistics generated interaction p values. Analyses included only subjects with known information. No data were missing for diagnosis year, birth year, or sex; 1.8% of subjects were missing race/ethnicity information. Some variables were not captured by birth records in all years: urban/rural residence and insurance were available only for 1987 or later (missing for 10.5%

and 6.2% of subjects during years available, respectively); maternal education was captured 1992 or later (missing for 7.8% of subjects during years when available).

Because earlier outcomes may relate to treatment, we separately assessed outcomes for 5–9 years after diagnosis, and 10+ years after diagnosis when complications/recurrence were less likely. Possible effects of treatment changes by diagnosis year category were also assessed. Proportional hazards assumptions were evaluated using Schoenfeld residuals. Analyses were conducted using Stata V.14 (Stata Corp., College Station, TX) and R.

Results

Leukemia (26%), central nervous system (CNS) tumors (20%), and lymphomas (14%) were the most common cancers (Table 1). Cases were 48% female, and 5% non-white. During up to 27 years of follow-up, 12% of survivors and 5% of comparison children had ≥ 1 hospitalization; 4% of survivors and 0.3% of comparison children died. Median follow-up after index date was 9.1 years (range 0.1–27.0 years) for survivors, and 9.3 years (range 0.1–27.0 years) for comparison children. Median survivor age at last follow-up was 23.8 years.

Survivors had a hospitalization rate of 13.9/1,000 person-years, and a death rate of 4.5/1,000 person-years (Table 2). Greatest rates/1,000 person-years of non-cancer hospitalization/death among survivors were for infection (6.3), injuries (6.0), endocrine/metabolic (5.8), and nervous system conditions (5.1). Relative to comparison children, survivors had more than twice the hospitalization rate (HR 2.7, 95% CI 2.4–3.0) and 14.7 times the any-cause death rate (95% CI 11.3–19.1). HRs were increased for all hospitalization/death outcomes, ranging from 1.8 (95% CI 1.4–2.2) for mental health-, to 35.1 (95% CI 23.7–51.9) for cancer-related hospitalization/death. Increased HRs were observed for diabetes (HR 3.3, 95% CI 1.9–5.9), and fracture (HR 1.6, 95% CI 1.1–2.3). Exclusion of cases with subsequent cancers resulted in HRs of 2.5 (95% CI 2.2–2.8), 29.0 (95% CI 19.3–43.6), and 12.3 (95% CI 9.3–16.3), for any hospitalization, cancer-related hospitalization, and all-cause death, respectively (data not shown). Patterns were generally similar when hospitalizations alone were examined; small numbers of cause-specific deaths precluded similar evaluation of patterns, although deaths were more common among survivors for all causes (Supplementary Table S2). Although our numbers were too small to examine cause-specific outcomes by age at diagnosis, all-cause mortality HRs ranged from 11.9 (95% CI 7.0–20.3) for children diagnosed between ages 15–19 years, to a high of 26.7 (14.7–48.6) for those diagnosed at 5–9 years; hospitalization HRs ranged from

Table 1 Childhood cancer survivors and comparison children born in Washington State, 1974–2008

Characteristic	Childhood cancer survivors ($n = 3,152$)[a]		Comparison children ($n = 31,520$)[a,b]	
	n	(%)	*n*	(%)
Female	1,516	(48.1)	15,160	(48.1)
Race/ethnicity				
White	2,617	(84.3)	25,350	(81.9)
Black	87	(2.8)	1,123	(3.6)
Hispanic	183	(5.9)	2,051	(6.6)
Asian	134	(4.3)	1,356	(4.4)
Native American	47	(1.5)	622	(2.0)
Pacific Islander	36	(1.2)	418	(1.4)
Other	2	(0.1)	32	(0.1)
Age at index date (years)[c]				
4–9	1,304	(41.4)	12,976	(41.2)
10–14	559	(17.7)	5,680	(18.0)
15–19	540	(17.1)	5,350	(17.0)
20–25	749	(23.8)	7,514	(23.8)
Age at study end/death (years)[d]				
5–9	208	(6.6)	1,930	(6.1)
10–14	418	(13.3)	3,976	(12.6)
15–19	469	(14.9)	4,597	(14.6)
20–24	700	(22.2)	6,842	(21.7)
25–29	636	(20.2)	6,503	(20.6)
30–34	505	(16.0)	5,377	(17.1)
35–39	216	(6.9)	2,295	(7.3)
Hospitalized after index date[c]	387	(12.3)	1,567	(5.0)
Died after index date[c]	137	(4.3)	95	(0.3)
Cancer type				
Leukemia	815	(25.9)		
Lymphomas	429	(13.6)		
Central nervous system	625	(19.8)		
Neuroblastoma	211	(6.7)		
Retinoblastoma	95	(3.0)		
Wilms' tumor	173	(5.5)		
Hepatoblastoma	39	(1.2)		
Bone tumors	110	(3.5)		
Soft-tissue sarcomas	203	(6.4)		
Germ cell tumors	167	(5.3)		
Other malignant epithelial	269	(8.5)		
Other unspecified	16	(0.5)		

[a]Numbers may not sum to totals due to missing values

[b]Matched on birth year and sex; restricted to those known not to have died at index date

[c]Diagnosis date 5+ years for cases diagnosed 1982–2008; same date for matched comparison children

[d]End of study participation is death, first hospitalization, or 31 December 2013

Table 2 Hospitalization, mortality, and hospitalization/death for selected conditions in 5-year childhood cancer survivors

	Person-years at risk	*n*	Rate per 1,000	HR (95% CI)[a]
Any hospitalization				
Comparison	304,419	1,567	5.2	1.0 (ref)
Survivors	27,805	387	13.9	2.7 (2.4–3.0)
Death (any cause)				
Comparison	315,233	95	0.3	1.0 (ref)
Survivors	30,396	137	4.5	14.7 (11.3–19.1)
Cause-specific hospitalization/death				
Infectious				
Comparison	311,152	606	2.0	1.0 (ref)
Survivors	29,299	183	6.3	3.2 (2.7–3.8)
Cancer[b]				
Comparison	153,910	33	0.2	1.0 (ref)
Survivors	14,296	117	8.1	14,296
Endocrine/metabolic				
Comparison	313,041	409	1.3	1.0 (ref)
Survivors	29,555	170	5.8	4.5 (3.7–5.4)
Diabetes				
Comparison	314,880	51	0.2	1.0 (ref)
Survivors	30,300	16	3.8	3.3 (1.9–5.9)
Hematological				
Comparison	314,307	185	0.6	1.0 (ref)
Survivors	29,922	117	3.8	6.7 (5.3–8.5)
Mental health disorders				
Comparison	312,482	564	1.8	1.0 (ref)
Survivors	29,938	95	3.2	1.8 (1.4–2.2)
Nervous system				
Comparison	314,004	246	0.8	1.0 (ref)
Survivors	29,691	151	5.1	6.4 (5.2–7.8)
Circulatory system				
Comparison	314,335	222	0.7	1.0 (ref)
Survivors	30,023	106	3.5	5.2 (4.1–6.5)
Respiratory system				
Comparison	313,023	354	1.1	1.0 (ref)
Survivors	29,739	133	4.5	4.0 (3.3–4.9)
Digestive system				
Comparison	312,253	497	1.6	1.0 (ref)
Survivors	29,700	137	4.6	2.9 (2.4–3.6)
Genitourinary system				
Comparison	313,722	238	0.8	1.0 (ref)
Survivors	30,024	78	2.6	3.4 (2.6–4.4)
Congenital				
Comparison	314,559	78	0.3	1.0 (ref)
Survivors	30,286	21	0.7	2.7 (1.7–4.4)
Skin				
Comparison	314,552	141	0.5	1.0 (ref)
Survivors	30,095	57	1.9	4.2 (3.1–5.8)
Musculoskeletal				
Comparison	312,528	455	1.5	1.0 (ref)
Survivors	29,677	122	4.1	2.8 (2.3–3.4)
Injuries				
Comparison	311,928	565	1.8	1.0 (ref)

Table 2 (continued)

	Person-years at risk	*n*	Rate per 1,000	HR (95% CI)[a]
Survivors	29,385	176	6.0	3.3 (2.8–3.9)
Fracture				
Comparison	313,764	221	0.7	1.0 (ref)
Survivors	30,134	34	1.1	1.6 (1.1–2.3)

[a]*HR* hazard ratio for any hospitalization, death (any cause), and cause-specific hospitalization/death (combined), accounting for birth year and sex

[b]Cancer-related hospitalizations occurring at age 20 or older

2.6 (95% CI 2.1–3.3) for children diagnosed at 15–19 years and those diagnosed at < 5 years (95% CI 2.2–3.1), to 3.1 (95% CI 2.4–4.0) for those diagnosed at 10–14 years (Supplementary Table S3).

For most conditions, absolute risks and HRs for 10+ years after diagnosis were lower than those 5–9 years after diagnosis, except for diabetes with HRs of 2.2 (95% CI 0.8–5.7) and 4.4 (95% CI 2.2–8.9) for earlier and later time periods, respectively (Table 3).

Hospitalization HRs were greater in females (HR 3.2, 95% CI 2.7–3.8) than males (HR 2.4, 95% CI 2.0–2.8; interaction $p = 0.004$), and among those who received radiation therapy (HR 3.2, 95% 2.6–3.9) than those who did not (HR 2.5, 95% CI 2.2–2.9; interaction $p = 0.04$) (Supplementary Table S4). Risks were slightly greater for children born in rural (HR = 3.5, 95% CI 2.5–4.9) than urban areas (HR 3.0, 95% CI 2.4–3.7), but this may have been due to chance. HRs did not vary by type of insurance status (HRs = 3.2 for both private and Medicaid insurance types). With the exception of Hispanic children (HR 2.7, 95% CI 1.5–4.6), HRs for all non-white race/ethnic group children were greater than that for white children (HR 2.6, 95% CI 2.3–3.0), ranging from 3.4 (95% CI 1.8–6.4) for Native Americans; 3.7 (95% CI 2.0–6.7) for African Americans; 3.8 (95% CI 2.0–7.3) for Asians; to 6.2 (95% CI 2.3–17.2) for Pacific Islanders.

When hospitalization and death were examined separately by childhood cancer type, relative to comparison children, hospitalization HRs were lowest for renal (HR 1.2, 95% CI 0.6–2.2) and greatest for bone (HR 5.7, 95% CI 3.4–9.4) tumors (Fig. 1). HRs for any-cause death ranged from 4.9 (95% CI 1.2–18.8) for renal tumors to 30.6 (95% CI 17.1–54) for CNS tumors.

To the extent possible, we also examined cause-specific outcomes (hospitalizations and/or death combined) by cancer type (Fig. 2). The greatest cancer type-specific HRs were observed for cancer-related hospitalization/death. HRs for most outcomes were increased for leukemia, lymphoma, and CNS tumors. CNS tumor survivors had the greatest HR for nervous system outcomes (HR 14.5, 95% CI 9.9–21.3). Bone tumor survivors had the greatest HR for musculoskeletal outcomes (HR 14.7, 95% CI 6.0–35.9) and injury (HR 11.4, 95% CI 5.6–23.3).

Discussion

Relatively few US studies have used population-based data to measure long-term childhood cancer outcomes [16, 17]. Population-based registries include all cancer types among all children, and avoid potential inaccuracies of self-reported outcomes [18, 19], or biases due to differential participation in research studies by demographic or other characteristics [20–22] or restriction to children at selected facilities or within clinical trial groups [10, 23]. Our analysis, enriched by additional registry data linkages, is based on an infrastructure that is potentially available to other states with similar health registries and linkage capacities. Replication of these analyses with pooled data across multiple states including those with large and diverse populations would provide more robust sub-analyses of different population-subgroups and help clarify some of the possible differences we observed across cancer types and by urban/rural location and race/ethnicity.

Our two-fold increased hospitalization risk among survivors is consistent with Utah registry data [16] and self-reported results compared to US population rates [24], but is lower than observed in Canadian registry data [25, 26]. This may have been due to our exclusion of pregnancy-related hospitalizations, and perhaps at least partly due to differences in health care systems (universal health care system vs. the private insurance/payer system in the US during a study period occurring largely prior to the Affordable Care Act in 2010). Excess hospitalizations ranged from 8 to 20 per 1,000 person-years across all subgroups, with slightly greater excesses for females, possibly some non-white groups, and children born in rural areas. The gender difference was expected [8, 17, 27] and has been suggested as due to women's relatively increased risks of obesity, poor cardiac outcome, and second malignancies such as breast cancer [28]. Modest excesses observed in some non-white groups generally reflect results of earlier studies assessing self-reported morbidity [29]. Little is known about how rurality affects morbidity among survivors, but care access may be more limited outside urban areas with cancer centers. We observed somewhat greater rate differences/1,000 person-years in rural than in urban areas, but our assessment

Table 3 Hazard ratios for non-pregnancy outcomes in childhood cancer survivors relative to children without cancer, by elapsed time since index date

	5–< 10 years post-index date[a]				Only events ≥ 10 years[b]			
	Person-years at risk	*n*	Rate/1,000	HR[c] (95% CI)	Person-years at risk	*n*	Rate/1,000	HR[c] (95% CI)
Any hospitalization								
Comparison	133,665	673	5.0	1.0 (ref)	170,755	894	5.2	1.0 (ref)
Survivors	12,699	239	18.8	3.8 (3.2–4.4)	15,106	148	9.8	1.8 (1.5–2.2)
Death (any cause)								
Comparison	135,355	32	0.2	1.0 (ref)	179,878	63	0.4	1.0 (ref)
Survivors	13,321	80	6.0	25.8 (17.0–39.1)	17,075	57	3.3	9.1 (6.4–13.1)
Cause-specific hospitalization/death								
Infection								
Comparison	134,688	262	2.00	1.0 (ref)	176,464	344	2.00	1.0 (ref)
Survivors	13,033	117	9.00	4.7 (3.8–5.9)	16,266	66	4.1	2.1 (1.6–2.7)
Cancer (age 20+)								
Comparison	41,904	9	0.2	1.0 (ref)	112,006	24	0.2	1.0 (ref)
Survivors	4,026	52	12.7	54.7 (26.9–111.1)	10,271	65	6.3	27.4 (17.0–44.2)
Endocrine/metabolic								
Comparison	134,989	148	1.1	1.0 (ref)	178,052	261	1.5	1.0 (ref)
Survivors	13,136	90	6.9	6.4 (4.9–8.3)	16,419	80	4.9	3.4 (2.6–4.3)
Diabetes								
Comparison	135,296	23	0.2	1.0 (ref)	179,585	28	0.2	1.0 (ref)
Survivors	13,306	5	0.4	2.2 (0.8–5.7)	16,994	11	0.7	4.4 (2.2–8.9)
Hematological								
Comparison	135,215	53	0.4	1.0 (ref)	179,092	132	0.7	1.0 (ref)
Survivors	13,180	62	4.5	12.5 (8.5–18.3)	16,742	55	3.3	4.4 (3.2–6.1)
Mental health								
Comparison	135,044	144	1.1	1.0 (ref)	177,439	420	2.4	1.0 (ref)
Survivors	13,242	38	2.9	2.7 (1.9–3.8)	16,697	57	3.4	1.4 (1.1–1.9)
Nervous system								
Comparison	135,152	92	0.7	1.0 (ref)	178,852	154	0.9	1.0 (ref)
Survivors	13,151	91	6.9	10.1 (7.5–13.5)	16,541	60	3.6	4.1 (3.0–5.5)
Circulatory system								
Comparison	135,220	63	0.5	1.0 (ref)	179,115	159	0.9	1.0 (ref)
Survivors	13,232	49	3.7	8.3 (5.7–12.1)	16,790	57	3.4	3.9 (2.9–5.3)
Respiratory system								
Comparison	134,984	153	1.1	1.0 (ref)	178,039	201	1.1	1.0 (ref)
Survivors	13,156	73	5.6	5.0 (3.8–6.7)	16,582	60	3.6	3.2 (2.4–4.3)
Digestive system								
Comparison	134,895	188	1.4	1.0 (ref)	177,358	309	1.7	1.0 (ref)
Survivors	13,145	84	6.4	4.8 (3.7–6.2)	16,555	53	3.2	1.8 (1.4–2.5)
Genitourinary system								
Comparison	135,112	101	0.8	1.0 (ref)	178,609	137	0.8	1.0 (ref)
Survivors	13,262	32	2.4	3.3 (2.2–4.9)	16,762	46	2.7	3.4 (2.4–4.8)
Congenital								
Comparison	135,221	50	0.4	1.0 (ref)	179,337	28	0.2	1.0 (ref)
Survivors	13,292	13	1.00	2.6 (1.4–4.9)	16,994	8	0.5	2.8 (1.3–6.3)
Skin								
Comparison	135,241	45	0.3	1.0 (ref)	179,312	96	0.5	1.0 (ref)
Survivors	13,242	32	2.4	7.3 (4.6–11.5)	16,853	25	1.5	2.8 (1.8–4.3)
Musculoskeletal								
Comparison	135,031	144	1.1	1.0 (ref)	177,497	311	1.8	1.0 (ref)

Table 3 (continued)

	5–< 10 years post-index date[a]				Only events ≥ 10 years[b]			
	Person-years at risk	*n*	Rate/1,000	HR[c] (95% CI)	Person-years at risk	*n*	Rate/1,000	HR[c] (95% CI)
Survivors	13,151	66	5.0	4.6 (3.5–6.2)	16,526	56	3.4	1.9 (1.4–2.5)
Injuries								
Comparison	134,924	204	1.5	1.0 (ref)	177,003	361	2.0	1.0 (ref)
Survivors	13,088	106	8.1	5.3 (4.2–6.7)	16,297	70	4.3	2.1 (1.6–2.7)
Fracture								
Comparison	135,187	75	0.5	1.0 (ref)	178,577	146	0.8	1.0 (ref)
Survivors	13,288	13	1.00	1.7 (1.0–3.1)	16,845	21	1.3	1.6 (1.0–2.5)

[a]Includes non-pregnancy events occurring during the time period 5–<10 years after diagnosis among 5+ year survivors and a population-based comparison group

[b]Includes non-pregnancy events occurring during the time period 10+ years after diagnosis among 5+ year survivors and a population-based comparison group

[c]*HR* hazard ratio for any hospitalization, death (any cause), and cause-specific hospitalization/death (combined), accounting for birth year and sex

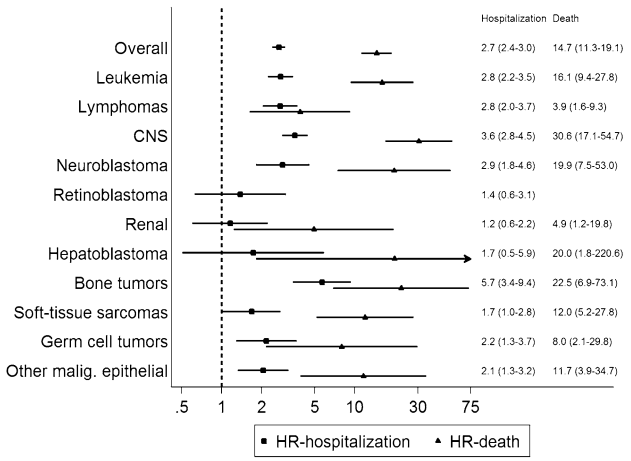

Fig. 1 Relative hazards of hospitalization and all-cause mortality among 5+ year childhood cancer survivors, compared to children without cancer, by cancer type

of this was limited to location at birth, so these results must be interpreted with caution.

Increased cardiovascular [16, 17, 25, 30, 31] and endocrine/metabolic [32, 33] morbidity is associated with selected cancer therapies. Diabetes as a specific outcome has been examined less often [34–36], and is often combined with general endocrine conditions including growth/other disorders that are more prevalent in survivors. An increased diabetes risk was expected [8, 27], but unlike most other outcomes, the risk of diabetes-related hospitalization or death that we observed increased over time since diagnosis. Small numbers precluded examination of this specific outcome by whether or not radiation was received, however, radiation damage to the pancreas during treatment may explain this result [37]. Other factors such as decreased physical activity [38–40], obesity [41], or inadequate diet [42] among survivors relative to comparison children likely also contribute.

The increased cardiovascular and cancer morbidities observed in these data were expected. Although North American registry-based studies [16, 25] suggest increased injury risk, fracture has been less studied. Decreased bone density, osteopenia, or osteoporosis have been demonstrated in children with several cancer types [43], and low bone density and fracture during treatment have been reported [44, 45]. We observed increased fracture risk consistent with some [46, 47] but not all studies [48]. Longer-term bone density may be decreased due to treatment [49], nutritional deficiencies, and reduced physical activity [49–51]. Despite decreased bone density, no increase in fracture rate was observed in a Finnish study of childhood 10+ year cancer survivors compared to controls [52] however, a twofold increased relative fracture rate by 5-years was observed in data from the UK General Practice Research Database [46], and US National Health Interview Survey data indicate increased self-reported fracture rates among adult survivors of childhood cancer [47]. Nearly 10% of adult survivors of childhood cancer (median age 32 years) with chemotherapy or radiation develop osteoporosis [53], compared to the US population prevalence of < 2% at age 50 years [54]. Fracture rates may be greater among children treated with dexamethasone [55]; as dexamethasone is increasingly used [56], it is possible that fracture risk among childhood cancer survivors may increase further in the future.

Mental health-related hospitalizations occur more often in survivors than population-based comparison groups [16, 25, 57], or siblings [58]. Most studies of self- or parent-reported mental status using sibling comparison groups [59–61] or population norms [62] generally support this. However, Danish registry data [57] demonstrated increased

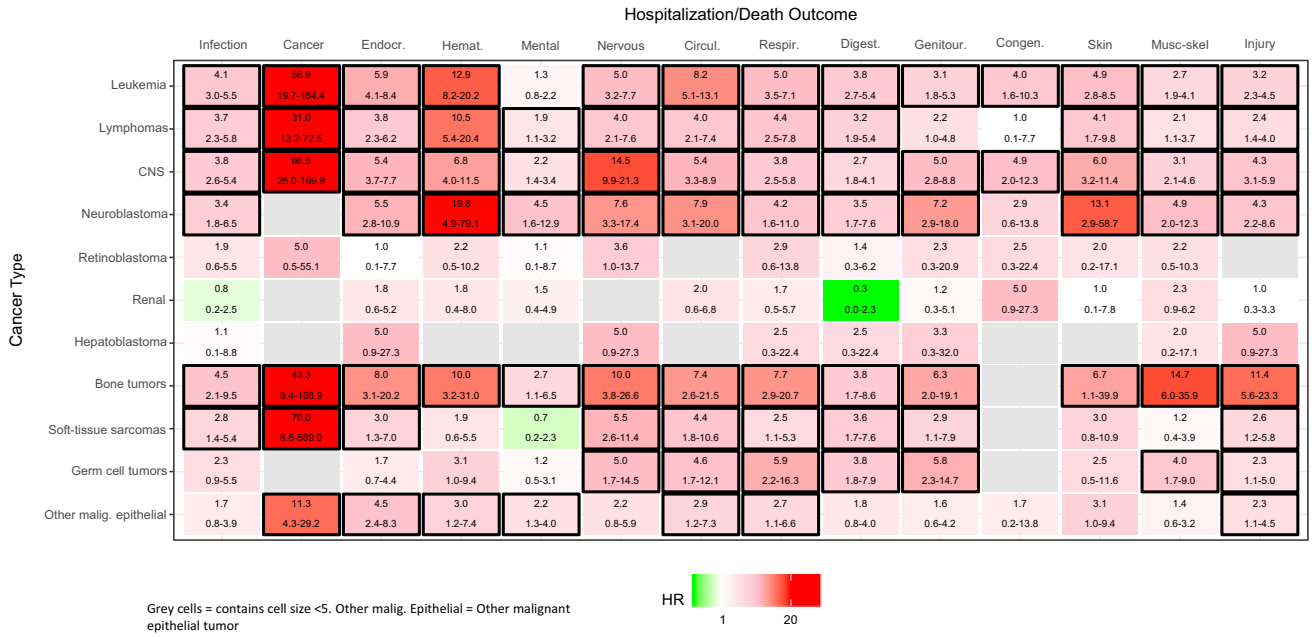

Fig. 2 Relative hazards of hospitalization/death by childhood cancer type among survivors and comparison children born in the same years

HRs vs. the general population, but not compared to siblings. Consistent with our data, risk may vary by cancer type [57, 62, 63]. The role of perceived prognosis or post-treatment disability within the relationships of different cancer types with survivors' mental health status is unclear.

We were hampered by small numbers for some sub-analyses and were restricted to the initial treatment information available in the cancer registry, the latter being a general limitation of most population-based cancer registries. Our ability to assess possible effects of some characteristics (urban/rural residence, maternal education, insurance) was limited to years for which these were present on the birth record. Although hospitalizations and death events were objectively assessed with State-mandated reporting, we relied on diagnosis codes to assess causes and could not include serious outcomes treated solely in outpatient settings. Cancer-related hospitalizations were limited to those occurring at 20 years of age or older, which may have underestimated the risk of this outcome. Some subjects may have moved out-of-State during follow-up, preventing complete outcome ascertainment among all subjects. This may have resulted in under- or over-estimation of risks if outmigration was differential (e.g., if childhood cancer survivors were more or less likely than comparison subjects to migrate elsewhere to seek care, or less likely to migrate because they wished to stay closer to their families). US Census data indicate a great majority of people who move stay within-state, $<2\%$ cite health concerns as reason for moving, and that migration rates in recent years have been decreasing and are the lowest they have been in at least 6 decades [64]. Although there is some evidence that childhood cancer survivors may more often reside with their parents [65] (which may have inflated our risk estimates), increasingly during 1975–2016 more young people in the US are living in their parents' household than in any other arrangement [66], which would attenuate any bias due to this.

Childhood cancer survivors have increased risk of serious adverse outcomes years after diagnosis, with variation by cancer type and other characteristics. Less toxic therapies may reduce subsequent morbidities [67]. Our observation of increased fracture incidence suggests an additional intervention area. Multi-state pooling of registry data would enhance elucidation of specific outcomes by cancer type, and among population-subgroups.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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