Research Article

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Risk of Hospitalization for Survivors of Childhood and Adolescent Cancer

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Abstract

Background: Childhood cancer survivors may be at increased risk of hospitalization because of cancer-related late effects.

Methods: Using data from population-based research resources in Utah, we identified childhood and adolescent cancer survivors who were diagnosed from 1973 to 2005 ($N = 2{,}571$). We selected a comparison cohort based on birth year and sex ($N = 7{,}713$). Hospitalizations from 1996 to 2010, excluding pregnancy and delivery, were determined from discharge records. Multivariable regressions were used to evaluate hospitalization admissions, length of stay, and diagnosis for survivors starting five years from diagnosis versus the comparison cohort.

Results: When follow-up began in 1996, there were $N = 1{,}499$ survivors and $N = 7{,}219$ comparisons who were alive and eligible for follow-up. Average follow-up for survivors was 13.5 years (SD = 8.5) and for the comparison 14.0 years (SD = 8.7; $P = 0.05$). Survivors were hospitalized, on average, 1.62 (SD = 3.37) times contrasted to 0.79 (SD = 1.73) for the comparison cohort. In multivariable analyses, the hazard ratio (HR) of any hospitalization since 1996 was higher for survivors than the comparison cohort [HR, 1.52, 95% confidence interval (CI), 1.31–1.66]. Survivors experienced a higher hospital admission rate [rate ratio (RR) = 1.67; 95% CI, 1.58–1.77] than the comparison cohort. The number of hospitalizations was highest for neuroblastoma (RR = 2.21; 95% CI, 1.84–2.66) and bone tumors (RR = 2.55; 95% CI, 2.14–3.02) in reference to the comparison cohort. Survivors were hospitalized because of blood disorders more often (HR, 14.2; 95% CI, 6.3–32.0).

Conclusions: The risk of hospitalization and lengths of stay are elevated among childhood cancer survivors.

Impact: Research to identify strategies to prevent and manage survivors' health problems in outpatient settings is needed. *Cancer Epidemiol Biomarkers Prev; 23(7); 1280–9. ©2014 AACR.*

Introduction

Survival from childhood cancer has increased substantially over the past 40 years and many childhood cancer survivors have medical late effects because of the chemotherapy, surgery, and radiation used to treat their cancers. By 30 years after diagnosis, approximately 73% of survivors report at least 1 chronic condition, and their risk of severe, life-threatening conditions is approximately 6 times higher than unaffected siblings (1). Unfortunately, childhood cancer survivors tend to receive less survivorship-focused health care the further they are from their diagnosis (2, 3). As health problems emerge for survivors, the lack of preventive care for identifying conditions at an early stage may lead to the development of complex health conditions that require hospitalization (4, 5). Although the Children's Oncology Group guidelines provide evidence for early identification and treatment of late effects, these guidelines may not always translate into reduced morbidity and mortality for patients. In the Childhood Cancer Survivor Study (CCSS), survivors' incidence of hospitalization was 1.6 times higher than that of the general population, with the highest risk borne by Hodgkin lymphoma survivors (4).

To our knowledge, the CCSS is the only study that has evaluated long-term survivors' risk of hospitalization in the United States (4). Although the CCSS is a large, retrospective cohort of the most common cancers in childhood, it does not include diagnoses common to adolescence such as germ cell tumors. Importantly, hospitalization information is limited to self-report by survivors in the CCSS. Thus, hospitalization discharge data provide a

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more comprehensive picture of survivors' hospitalization risk. Furthermore, other details about hospitalization—such as length of stay—are needed for understanding the magnitude of survivors' use of health care resources. In a Canadian study set in British Columbia, hospitalized childhood cancer survivors had a longer hospital stay than the comparison sample at 10.9 days on average compared with 7.8 for the unaffected sample (5). Length of hospital stay has not been evaluated in U.S. childhood cancer survivor samples.

Here we report on hospitalizations among a population-based cohort of survivors of child and adolescent cancer from the Utah Cancer Registry in relation to a comparison cohort sampled to be similar on birth year and sex from the Utah Population Database (UPDB). Using hospitalization discharge data from 1996 to 2010, we first determine whether survivors' risk of hospitalization was elevated relative to the comparison cohort and describe survivors' rate of hospitalizations and length of hospital stays. Because earlier reports demonstrate sex and cancer differences in hospitalization, we report our risk estimates both by sex and cancer diagnosis. We also evaluated hospital diagnosis, comparing survivors to the comparison cohort.

Materials and Methods

Data access

We analyzed data from the University of Utah's Pedigree and Population Resource, which houses the UPDB. The UPDB is a unique data resource that has been used by researchers in genetics, epidemiology, and public health (6, 7). This database includes linkages to the Utah Cancer Registry (UCR), statewide vital records for births and deaths, driver licenses, and voter registration records. The UCR is a Surveillance Epidemiology and End Results (SEER) registry of statewide cancer records, beginning in 1966. For over 30 years, researchers have used the UPDB and linked UCR information to identify and study individuals with cancer. Since 1996, the UPDB has included records from the Utah Department of Health statewide inpatient hospitalization claims data, which we used to determine hospitalizations for this project. Study approval was received from the University of Utah's Institutional Review Board and the Utah Resource for Genetic and Epidemiologic Research.

Subject sampling and eligibility

A cohort of childhood cancer survivors was identified from the linked UCR and UPDB. A noncancer comparison cohort, selected on birth year and sex, was sampled from Utah birth certificates through the UPDB.

Childhood cancer cohort. Individuals who were diagnosed with cancer between the ages of 0 and 20 years during January 1, 1973, and December 31, 2005, were identified by the UCR. Survivors were limited to individuals with a Utah Birth Certificate and satisfied criteria for a cancer diagnosis under the International Classification of Childhood Cancers (ICCC; ref. 8). The ICCC is the standard classification system for childhood cancers. Unlike adult cancer classification systems, it emphasizes morphology rather than the primary site of the cancer (8). We excluded nonmelanoma skin cancers and cancers *in situ*. A total of 2,571 cases met these criteria.

Comparison cohort. Noncancer participants were randomly selected from Utah birth certificates, which were accessed through UPDB. Eligible comparison cohort participants had to have survived and be living in Utah up until the date of diagnosis of the matched case. This cohort was selected on birth year and sex using a 3 to 1 ratio of the unaffected cohort to cancer cases ($N = 7{,}713$). This ratio was selected based on power calculations to detect a hazard ratio (HR) difference of 1.2 in hospitalizations using estimates from the British Columbia, Canada, hospitalizations study with >0.90 power (9).

Participant follow-up

The UPDB includes the date that each person in the database was last known to be residing in Utah via records such as driver's license, voter registration, and marriage records. Although such records may be less robust for accessing follow-up time for children, only 9% of our sample was under the age of 20 at last follow-up (and this proportion did not differ between the survivors and the comparison cohort). Thus, we had verified Utah residence for 91% of our sample (10).

For the current analyses, follow-up for hospitalizations started 5 years after the cancer diagnosis, but not before 1996, for cases and at the comparable date for comparisons. We limited our cancer cases to participants who had survived 5 or more years after their original cancer diagnosis, because the majority of treatment is completed by this time, and imposed this same timeframe on the comparison sample. In 1996, when the hospitalizations claims data became available, there were $N = 1{,}499$ survivors who met these criteria who were alive or entered into the sample when their follow-up started if that was at a later date. A total of $N = 7{,}219$ individuals were in the comparison cohort and were alive in 1996 or when their follow-up started if that was at a later date. Participants were considered censored after their last known to be residing in Utah date or they had died as confirmed by death certificates. A total of 64 cases and 51 controls died after follow-up began but before experiencing a hospitalization. By the end of follow-up there were 688 survivors and 4,702 comparisons who did not experience a hospitalization within our follow-up time or were no longer known to be in Utah.

Measures

Hospitalization outcomes. Hospitalizations were ascertained from the Utah Department of Health hospital discharge data, which includes a record for each inpatient discharged from any acute care hospital in Utah. Using discharge records, we calculated the total number of hospitalizations for each survivor and comparison cohort. Hospitalizations (including emergency/trauma, urgent

care, and elective admissions) were limited to those that occurred 5 or more years from diagnosis and were completed (discharged or in-hospital death) by the end of follow-up on December 31, 2010. Average length of stay among all hospitalizations includes either all or part of the day. We also examined the type of admission (emergency/trauma, urgent care, and elective admissions). Estimates for number of hospitalizations and length of stay exclude hospitalizations for pregnancy or delivery based on International Classification of Disease Version 9 (ICD9) codes.

Hospital diagnosis was determined by ICD9 code for the "principal diagnosis code." These codes were grouped by ICD9 chapter, generally equivalent to organ systems, to categorize the type of late morbidity. Only the first hospitalization diagnosis in a particular ICD9 chapter was counted as the indicator of the presence of that type of late morbidity (multiple diagnoses or hospitalizations with the same diagnosis were not counted again).

Cancer-related measures. The UCR's data were queried for demographics at diagnosis (e.g., age at diagnosis), diagnosis (e.g., diagnosis, year of diagnosis), and treatment factors (e.g., receipt of surgery, chemotherapy, or radiation). Because of the small number of cancers for certain ICCC diagnoses potentially affecting confidentiality, we grouped retinoblastomas, hepatic tumors, and other unspecified tumors in aggregate as "other." Diagnosis year was generated for the cancer cases. For the comparison cohort, the year of diagnosis for their case was used, allowing us to control for any time period differences that could affect hospitalizations.

Other variables. Birth certificate data from the UPDB and records from the UCR were used to ascertain sex, age at last follow-up, and race/ethnicity. We grouped race/ethnicity as non–Hispanic White versus Other because of the small number of Other race participants. Rural county at birth was determined by living in a county with less than 75% of population in an urban area (population $\geq$2,500; ref. 11).

Statistical analyses

Demographics were compared between the cancer survivor and the comparison cohort using χ^2 statistics. We compared demographic and cancer-related factors among cancer cases with no hospitalization during follow-up to those with any hospitalization during this time. The mean, median, and interquartile range of the number of admissions and length of stay were generated for the overall sample of survivors and comparison cohort and by sex.

Regression models

Hospitalizations among cancer survivors and the comparison cohort were assessed by comparing time to first hospitalization and hospitalization rate (hospitalization count per year) for our follow-up time of January 1, 1996 to December 31, 2010. Time to first hospitalization was evaluated using Cox proportional hazard models adjusted for sex, birth year, and year of diagnosis (12). HRs and 95% confidence intervals (95% CI) are reported.

Hospitalization rates were modeled using zero-inflated Poisson (zip) regression models to account for the large number of cases and the comparison reporting no hospitalizations, using follow-up time as an offset (13). Zero-inflated regression models are more robust in the face of excess zeros than other regression models for evaluating count data as it estimates a 2-part regression that tests the probability of having no hospitalizations (a binomial model) and then predicts a count of the number of visits. The zip regression models controlled for sex, birth year, and diagnosis year and estimates are reported as rate ratios (RR) and 95% CIs.

To model average length of stay as a continuous outcome, we used a γ regression model with log link function and controlled for the same factors as the other models. Our final set of regression models examined hospitalization diagnosis using Cox proportional hazard models comparing all survivors to the comparison cohort (12).

Analyses were performed with the whole cohort and then separately for female and male participants as there were significant interactions by sex for both time to first hospitalization and number of admissions. In addition, we ran models stratified by year of diagnosis (1973–1990 and 1991–2005), allowing for the 5 years after diagnosis timing for assessing hospitalization starting in 1996. As survivors and the comparison participants who were in the pre-1991 group may have experienced hospitalizations before 1996 that we were unable to capture, these estimates provide an overview of newly incident hospitalizations for the group diagnosed 1991–2005. We also ran models to examine number of hospitalizations and length of stay by cancer diagnosis in reference to the comparison cohort. Because of the small number of Other race participants, none of the models was adjusted for race. Rural/urban county at birth did not differ between the survivors and the comparison cohort and was also excluded in our models. All statistical analyses were performed in SAS version 9.3 (SAS Institute Inc.) using PHREG for time to first hospitalization, COUNTREG for count of hospitalizations, and GENMOD for length of hospital stay. All P values were 2-sided and the significance level was set at 0.05.

Results

The average follow-up time starting in 1996 for survivors was 13.5 years (SD = 8.5) and for the comparison 14.0 years (SD = 8.7; $P = 0.05$). Survivors were proportionally more female than the comparison cohort (50.6% vs. 47.1%; $P = 0.01$; Table 1). Age at last follow-up also differed significantly with fewer survivors ages 21 to 30 years (34.4%) than the comparison (38.3%), and more survivors ages 31 to 40 years (36.2% vs. comparison 32.7%; overall $P = 0.01$). The comparison cohort (4.2%) tended to be of Other races more often than survivors (2.3%; $P = 0.001$).

When we examined characteristics among survivors (Table 2), females more often than males were more likely

Table 1. Demographics of survivors and comparison cohort

	Survivors	Comparison	
	N (%)	*N* (%)	*P*-value
Sex			
Male	740 (49.4)	3,818 (52.9)	0.01
Female	759 (50.6)	3,401 (47.1)	
Year of birth			
1952–69	315 (21.0)	1,368 (19.0)	<0.001
1970–79	553 (36.9)	2,431 (33.7)	
1980–89	531 (35.4)	2,641 (36.6)	
1990–94	100 (6.7)	779 (10.8)	
Age at last follow-up, y			
5–10	12 (0.8)	30 (0.4)	0.01
11–20	129 (8.6)	612 (8.5)	
21–30	515 (34.4)	2,766 (38.3)	
31–40	543 (36.2)	2,362 (32.7)	
41–60	300 (20.0)	1,447 (20.1)	
Race/ethnicity			
Non–Hispanic White	1,464 (97.7)	6,917 (95.8)	0.001
Other	35 (2.3)	302 (4.2)	
County at birth			
Urban	1,315 (87.7)	6,235 (86.4)	0.16
Rural[a]	184 (12.3)	984 (13.6)	

[a]Rural defined as living in a county with less than 75% of population in an urban area (population ≥2,500).

to have had any hospitalizations ($P < 0.001$). Survivors who were hospitalized tended to be older at last follow-up (greater than 60% were ages 31–60 years compared with 50% with no hospitalizations, overall $P < 0.001$). Although cancer type was not significantly associated with hospitalization, leukemia, lymphoma, central nervous system (CNS), and epithelial cancers (e.g., melanomas and thyroid cancers) had the highest proportion experiencing hospitalization (approximately 17% each).

In total, among the 1,499 survivors there were 5,625 total hospitalization admissions and among the 7,219 in the comparison cohort there were 2,419 admissions. Urgent care comprised the majority of admissions for both survivors (3,012/5,625 admissions; 53%) and comparison cohort (1,264/2,419 admissions; 52%; data not shown).

In our multivariable analyses, survivors had an elevated risk of hospitalization in relation to the comparison cohort (Table 3). The hazard for any hospitalization was 52% higher for survivors than the comparison cohort (HR, 1.52; 95% CI, 1.31–1.66; $P < 0.001$), and was elevated both for female survivors (HR, 1.21; 95% CI, 1.08–1.35; $P < 0.001$) and male survivors (HR, 2.66; 95% CI, 2.25–3.13; $P < 0.001$). On average, survivors had 1.62 (SD = 3.37) hospital admissions compared with 0.79 (SD = 1.73) in the comparison cohort, although the median for both groups was zero. In γ regression analysis, this translated to a 67% higher rate of admission among survivors (RR = 1.67; 95% CI, 1.58–1.77; $P < 0.001$). Female survivors, on average, had a greater number of admissions (2.17; SD = 3.76) than the comparison cohort females (1.34; SD = 2.09; RR = 2.00; 95% CI, 1.79–2.23; $P < 0.001$). Male survivors had 1.05 (SD = 2.81) admissions on average whereas their counterparts had 0.30 (SD = 1.14; RR = 2.12; 95% CI, 1.88–2.38; $P < 0.001$).

The length of stay was longer for hospitalized survivors, with a stay of 4.55 days (SD = 8.70), on average, compared with 3.07 (SD = 4.09) for the comparison (RR = 1.35; 95% CI, 1.25–1.46; $P < 0.001$; Table 3). Male survivors had the longest average length of stay, with 5.40 (SD = 18.15) hospitalization days compared with 4.04 (SD = 6.19) for female survivors, 3.83 (SD = 4.98) for the male comparison, and 2.72 (SD = 3.44) for the female comparison. In our multivariable regressions of the male subgroup, there were no differences between survivors and the comparison cohort for length of stay. However, among females, survivors' length of stay was significantly longer (RR = 1.41; 95% CI, 1.29–1.54; $P < 0.001$) than the comparison cohort.

In addition, when we evaluated the hospitalization outcomes in models stratified by diagnosis year, survivors diagnosed before 1991 were at an elevated risk of having any hospitalization (HR, 1.21; 95% CI, 1.08–1.36; $P < 0.001$), a higher admission rate (RR = 1.35; 95% CI, 1.25–1.45; $P < 0.001$), and a longer average length of hospital stay (RR = 1.26; 95% CI, 1.14–1.39; $P < 0.001$) than the comparison cohort. Survivors diagnosed in 1991 or later also were at higher risk than the comparison cohort, with estimates of any hospitalization (HR, 2.14; 95% CI, 1.86–2.46; $P < 0.001$), admission rate (RR = 2.33; 95% CI, 2.14–2.54; $P < 0.001$), and average length of hospital stay (RR = 1.50; 95% CI, 1.34–1.68; $P < 0.001$).

More than 10% of survivors with CNS tumors, neuroblastomas, bone tumors, and other cancers had 5 or more hospitalizations (Table 4). In multivariable regressions, all diagnostic groups except renal tumors and germ cell tumors had a greater number of hospitalizations than the comparison cohort. This ranged from a 25% higher rate of admissions for epithelial cancers (RR = 1.25; 95% CI, 1.10–1.41; $P < 0.001$) to an over 2-fold higher rate for neuroblastoma (RR = 2.21; 95% CI, 1.84–2.66; $P < 0.001$) and bone tumors (RR = 2.55; 95% CI, 2.14–3.02; $P < 0.001$) in reference to the comparison cohort. Renal cancer survivors' had a 39% lower hospitalization rate than the comparison cohort (RR = 0.61; 95% CI, 0.41–0.90; $P = 0.01$). Once hospitalized, the length of stay was also longer for most cancers than the comparison cohort. The hospital stays ranged from 26% longer for both sarcoma ($P = 0.04$) and germ cell tumors ($P = 0.05$) to 58% longer for leukemias ($P < 0.001$) and 61% longer for CNS tumors ($P < 0.001$) than the comparison cohort. Renal cancer, epithelial cancer, and other cancer did not significantly differ on length of stay.

When selected hospitalization diagnoses were evaluated, survivors had a significantly elevated risk across several ICD9 conditions compared with the comparison

Table 2. Characteristics of hospitalized survivors compared with survivors with no hospitalizations

	No hospitalization $N = 752$	Any hospitalization[a] $N = 747$	
	N (%)	*N* (%)	*P* value
Sex			
Male	487 (64.8)	253 (33.9)	<0.001
Female	265 (35.2)	494 (66.1)	
Year of birth			
1952–69	165 (21.9)	150 (20.1)	0.69
1970–79	273 (36.3)	280 (37.5)	
1980–89	268 (35.6)	263 (35.2)	
1990–94	46 (6.1)	54 (7.2)	
Age at last follow-up, y			
5–10	11 (1.5)	1 (0.11)	<0.001
11–20	72 (9.6)	57 (7.6)	
21–30	294 (39.1)	221 (29.6)	
31–40	241 (32.1)	302 (40.4)	
41–60	134 (17.8)	166 (22.2)	
Original cancer diagnosis			
Leukemias	147 (19.6)	126 (16.9)	0.07
Lymphomas	132 (17.6)	131 (17.5)	
CNS/intracranial/intraspinal	99 (13.2)	131 (17.5)	
Neuroblastoma	30 (4.0)	33 (4.4)	
Renal tumors	49 (6.5)	27 (3.6)	
Malignant bone tumors	27 (3.6)	36 (4.8)	
Sarcomas	50 (6.7)	47 (6.3)	
Germ cell	68 (9.0)	57 (7.6)	
Epithelial	121 (16.1)	133 (17.8)	
Other[b]	29 (3.9)	26 (3.5)	
Age at original diagnosis, y			
0–4	219 (29.2)	171 (22.9)	0.008
5–9	115 (15.3)	107 (14.3)	
10–14	125 (16.6)	164 (22.0)	
15–20	292 (38.9)	305 (40.8)	
Year of diagnosis			
1973–1979	146 (19.7)	116 (15.5)	0.15
1980–1984	123 (16.6)	123 (16.5)	
1985–2000	419 (56.6)	444 (59.4)	
2001–2005	52 (7.0)	64 (8.6)	
Treatment for original diagnosis			
None or unknown	139 (18.5)	109 (14.6)	0.04
Chemotherapy	161 (21.4)	143 (19.1)	
Radiation	90 (12.0)	109 (14.6)	
Surgery	156 (20.7)	165 (22.1)	
Chemotherapy and surgery	110 (14.6)	92 (12.3)	
Chemotherapy and radiation	49 (6.5)	66 (8.8)	
Radiation and surgery	26 (3.5)	28 (3.8)	
Chemotherapy, radiation, and surgery	21 (2.8)	35 (4.7)	

[a]Excludes hospitalizations for pregnancy and delivery.
[b]Other includes retinoblastoma/hepatic tumors/other unspecified tumors.

cohort (Fig. 1). This ranged from an over 14-fold higher hazard of hospitalization for diseases of the blood, typically anemia (HR, 14.2; 95% CI, 6.3–32.0; $P < 0.001$) and an almost 10-fold higher hazard for neoplasms (HR, 9.5; 95% CI, 6.8–13.2) to a 1.6 higher risk for skin diseases (HR, 1.60; 95% CI, 1.1–2.3; $P = 0.02$) and mental disorders (HR, 1.60;

Table 3. Multivariable regressions of hospitalizations, admissions, and length of stay for survivors versus comparison cohort

		Any hospitalization			Number of admissions					Length of stay (days)				
	N	HR[a,b]	95% CI	*P*	Mean (SD)	Median (IRQ)	RR[a,c]	95% CI	*P*	Mean (SD)	Median (IRQ)	RR[a,c]	95% CI	*P*
Full sample														
Comparison (ref)	7,219	1			0.79 (1.73)	0 (0,1)	1			3.07 (4.09)	2 (2,3)	1		
Survivors	1,499	**1.52**	**1.31–1.66**	<**0.001**	1.62 (3.37)	0 (0,2)	**1.67**	**1.58–1.77**	<**0.001**	4.55 (8.70)	3 (2,4)	**1.35**	**1.25–1.46**	<**0.001**
Females														
Comparison (ref)	3,401	1			1.34 (2.09)	1 (0,2)	1			2.72 (3.44)	2 (2,3)	1		
Survivors	759	**1.21**	**1.08–1.35**	<**0.001**	2.17 (3.76)	1 (0,3)	**2.00**	**1.79–2.23**	<**0.001**	4.04 (6.19)	2 (2,4)	**1.41**	**1.29–1.54**	<**0.001**
Males														
Comparison (ref)	3,818	1			0.30 (1.14)	0 (0,0)	1			3.83 (4.98)	2 (1,4)	1		
Survivors	740	**2.66**	**2.25–3.13**	<**0.001**	1.05 (2.81)	0 (0,1)	**2.12**	**1.88–2.38**	<**0.001**	5.40 (18.15)	3 (2,5)	1.12	0.99–1.28	0.08
Diagnosis 1973–1990														
Comparison (ref)	3,993	1			0.98 (2.02)	0 (0,1)	1			2.72 (3.44)	2 (2,3)	1		
Survivors	897	**1.21**	**1.08–1.36**	<**0.001**	1.41 (2.74)	0 (0,2)	**1.35**	**1.25–1.45**	<**0.001**	4.04 (6.19)	2 (2,4)	**1.26**	**1.14–1.39**	<**0.001**
Diagnosis 1991–2005														
Comparison (ref)	3,226	1			0.54 (1.26)	0 (0,1)	1			3.83 (4.98)	2 (1,4)	1		
Survivors	602	**2.14**	**1.86–2.46**	<**0.001**	1.94 (4.12)	1 (0,2)	**2.33**	**2.14–2.54**	<**0.001**	5.40 (18.15)	3 (2,5)	**1.50**	**1.34–1.68**	<**0.001**

NOTE: Bold values indicate statistical significance at $P < 0.05$.

[a]Adjusted for sex as relevant, birth year, and diagnosis year; excludes hospitalizations for pregnancy and delivery.

[b]Hazard ratios.

[c]Rate ratios.

Table 4. Hospitalizations by diagnosis groups versus comparison cohort

		Number of hospitalizations (%)						Number of admissions[a]			Length of stay (days)[a]		
	N	0	1	2	3	4	≥5	RR[c]	95% CI	*P*	RR[c]	95% CI	*P*
Comparison (ref)	7,219	65.8	15.0	8.8	5.0	2.5	2.9	1			1		
Leukemias	273	53.8	15.4	12.5	6.2	4.0	8.1	**1.84**	**1.65–2.05**	**<0.001**	**1.58**	**1.28–1.95**	**<0.001**
Lymphomas	263	50.2	17.5	11.0	8.4	5.3	7.6	**1.83**	**1.65–2.04**	**<0.001**	**1.35**	**1.17–1.55**	**<0.001**
CNS/intracranial/intraspinal	230	43.0	20.0	13.0	8.3	4.4	11.3	**1.71**	**1.53–1.92**	**<0.001**	**1.61**	**1.36–1.91**	**<0.001**
Neuroblastoma	63	47.6	14.3	14.3	7.9	4.8	11.1	**2.21**	**1.84–2.66**	**<0.001**	**1.30**	**1.04–1.64**	**0.02**
Renal tumors	76	64.5	19.7	7.9	4.0	1.3	2.6	**0.61**	**0.41–0.90**	**0.01**	1.10	0.85–1.43	0.45
Malignant bone tumors	63	42.9	17.5	15.9	3.2	6.4	14.3	**2.55**	**2.14–3.02**	**<0.001**	**1.40**	**1.07–1.84**	**0.02**
Sarcomas	97	51.6	21.7	9.3	6.2	3.1	8.3	**1.82**	**1.54–2.16**	**<0.001**	**1.26**	**1.01–1.58**	**0.04**
Germ cell	125	54.4	23.2	9.6	3.2	4.0	5.6	1.15	0.93–1.42	0.20	**1.26**	**1.00–1.60**	**0.05**
Epithelial	254	47.6	21.7	12.6	7.9	2.8	7.5	**1.25**	**1.10–1.41**	**<0.001**	1.11	0.95–1.29	0.20
Other[b]	55	52.7	16.4	9.1	5.5	5.5	10.9	**2.19**	**1.79–2.68**	**<0.001**	1.03	0.78–1.36	0.85

NOTE: Bold values indicate statistical significance at $P < 0.05$.

[a]Adjusted for sex as relevant, birth year, and diagnosis year. All estimates exclude hospitalizations for pregnancy and delivery.

[b]Other includes retinoblastoma/hepatic tumors/other unspecified tumors.

[c]Rate ratios.

95% CI, 1.2–2.0; $P < 0.001$). Genitourinary, musculoskeletal, and congenital conditions did not differ. Among the most common cancer groups (not shown in figures or tables), leukemia patients were hospitalized because of blood diseases (HR, 19.8; 95% CI, 4.3–91.8; $P < 0.001$) more often, whereas patients with lymphoma and CNS tumor were hospitalized because of neoplasms (HR, 11.2; 95% CI, 3.8–33.2; $P < 0.001$ and HR, 30.9; 95% CI, 9.4–101.5; $P < 0.001$, respectively). Epithelial cancer survivors also a higher rate of hospitalization because of neoplasms (HR, 6.9; 95% CI, 2.9–16.6; $P < 0.001$) than the comparison cohort.

Discussion

Our findings support earlier studies that report an elevated risk of hospitalization for survivors of childhood and adolescent cancer (4, 5), and expand on these findings by using population-based hospitalization discharge data from Utah. We found that these cancer survivors experience hospitalization at a rate almost 1.7 times greater than an age- and sex-matched comparison cohort. In stratified analyses limited to survivors diagnosed 1991 or later, indicating survivors experiencing their first incident hospitalization at the beginning follow-up in 1996, the risk of hospitalization compared with the comparison cohort was more than 2-fold greater. The rate of hospital admissions was approximately 2 times higher for both male and female survivors than unaffected females and males from the comparison cohort. Blood disorders—primarily conditions such as anemia—and neoplasms were common reasons for hospitalization for survivors, similar to findings from the British Columbia, Canada, cohort (9).

Both female and male survivors had a higher risk of any hospitalization than the comparison cohort, with male survivors at a 2.7 times higher risk than males in the comparison and female survivors at a 21% higher risk than females in the comparison. Although we were unable to investigate other aspects of health care, such as outpatient visits, to understand what may be driving this high hospitalization rate among the males, earlier CCSS reports show that male childhood cancer survivors are somewhat less likely to have received any medical care in the past 2 years than female survivors (14). As such, male survivors may be less connected with the medical system, meaning that they may develop more severe conditions that go unmanaged and lead to hospitalization. Future studies should examine whether there is an association between delay of medical intervention and hospitalizations among male survivors.

We identified certain cancer groups that had elevated hospitalization rates, suggesting that early medical intervention is needed for high-risk cancers. Although most cancer subgroups we investigated had significantly more hospital admissions than the comparison cohort, neuroblastoma and bone tumor survivors were especially at risk, with a more than 2-fold higher rate of hospitalization in relation to the comparison cohort. Although we lacked

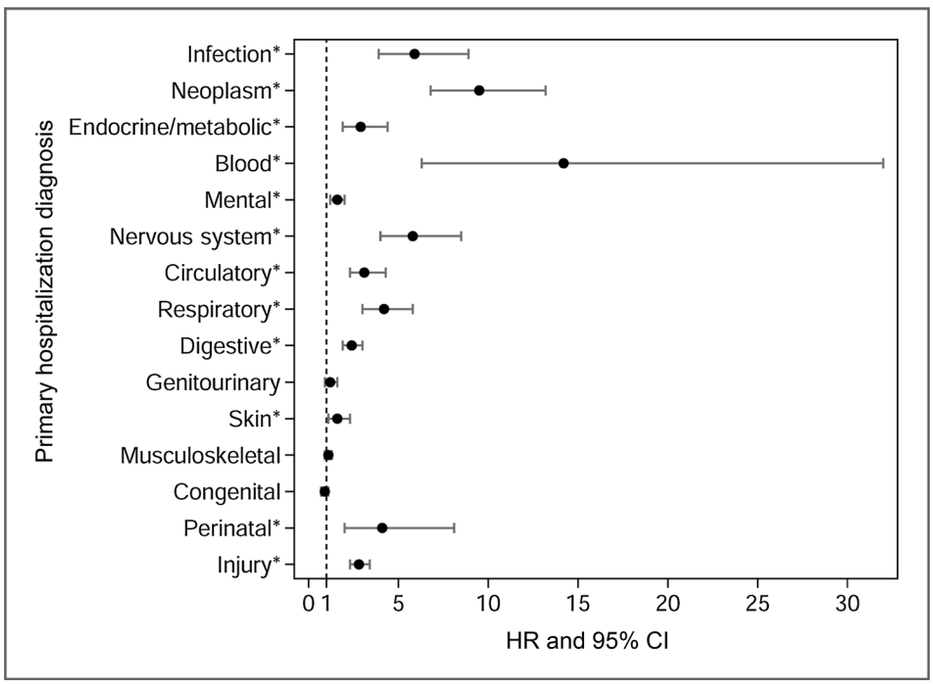

Figure 1. HRs and 95% CIs of hospital diagnosis for full survivor sample versus comparison cohort (reference). *, significant at $P < 0.05$.

the sample size to investigate hospital diagnoses specific to these cancers in detail, both neuroblastoma and bone tumor patients experience severe late effects. These effects include cardiopulmonary disease (15) and second cancers (16), and for patients with bone tumor, physical function and orthopedic complications (17, 18), with the incidence of life-threatening conditions approaching 35% for neuroblastoma and 60% for bone tumor, by 30 years after diagnosis (1). In a subanalysis not reported here, we found that the patients with neuroblastoma were hospitalized most often for respiratory and genitourinary problems, whereas the patients with bone tumor were hospitalized because of neoplasms. The impact of these conditions on hospitalization should be investigated in future studies of pediatric cancer.

Certain cancers, however, show favorable findings, in that germ cell and renal tumor survivors were not at additional risk of hospitalization. The therapies required for the lower risk germ cell and renal tumors are often shorter and less toxic than many other childhood cancers and may be associated with fewer long-term sequelae causing fewer hospitalizations. In fact, renal cancers had a lower hospitalization rate than the comparison cohort. Based on our current data, the reason behind this lower rate is unknown and warrants exploration in future studies.

We also found that cancer survivors had longer stays in the hospital than the comparison cohort. Leukemia, lymphoma, and CNS tumors, for example, are the most common cancers diagnosed during childhood (19) and all were at risk for longer hospital stays. Hospitalizations were 35% longer for lymphoma and approximately 60% longer for both leukemia and CNS survivors in reference to the comparison cohort. When we examined the hospital diagnosis, leukemia survivors experienced blood diseases more often than the comparison cohort, whereas lymphoma and CNS survivors were hospitalized for neoplasms more often. For these cancers, by 5 years after diagnosis, although the risk of relapse is still high, the risk of second cancers becomes increasingly common (16, 20). Although we were unable to evaluate specific conditions leading to this morbidity risk, both lymphoma and CNS tumor survivors may be hospitalized because of treatment for recurrences, metastatic disease, and/or second cancers, suggesting the need for better surveillance to detect second malignancies in earlier stages.

Our findings demonstrate that survivors of child and adolescent cancer require better strategies to prevent, manage, and treat conditions before they become severe enough to require hospitalization. As the numbers of child and adolescent survivors continues to grow (21), the high hospitalization rate reported here and elsewhere indicates that these survivors will have an increasing impact on the U.S. health care system. Patients with chronic conditions disproportionately impact health care costs in the United States, and the greatest health care costs for hospitalizations typically occur in the first days of hospitalization (22). Even though child and adolescent cancer survivors comprise a small proportion of cancer survivors in the United States, more than 65% of these survivors are between the ages of 20 to 65 years, indicating that there are decades of potential high medical utilization and costs as they experience late effects from treatment (21, 23). Our research team is planning future research to examine hospital-related costs among survivors and to find strategies to identify and mitigate preventable hospitalizations among high-risk survivors.

In addition, beyond the direct costs from hospitalization, information on the indirect costs, including work status and productivity because of hospitalizations (24) for this population, is needed. Also, although we did not have information on health insurance coverage, the earlier CCSS study found that insured survivors were hospitalized more often than the uninsured (4). As the Patient Protection and Affordable Care Act insurance exchanges and the Medicaid expansion in approximately half of states increase insurance coverage for uninsured survivors (25), future research is needed to address the impact of increasing access to preventive health care on childhood cancer survivors' hospitalizations.

Certain limitations are inherent when using hospital discharge data for a population-based comparison sample. Our analyses are limited to residents who were born in Utah (i.e., had a Utah birth certificate), and our estimations of hospitalizations are only available for individuals who received their health care in Utah. Differential mobility out of Utah for medical care for the cancer cases and the comparison cohort could affect our estimates. Our sample was limited to one state that has limited ethnic and racial diversity. Thus, we were unable to identify specific ethnic/racial survivor subgroups that may be at particular risk for health conditions prompting hospitalization. In addition, as our cohort is very homogeneous, studies done in more diverse populations may reflect different findings.

Because of sample size limitations, we were unable to perform detailed analyses of hospitalization diagnosis by cancer group or to examine more specific disease subgroups beyond ICD9 chapters. We were also unable to determine whether participants in our sample were currently undergoing active cancer treatment for a relapse of their primary cancer that could potentially elevate our estimates. Thus, the elevated risk of blood disorders among patients with leukemia, for example, may be due in part to anemia related to ongoing cancer therapy. However, by limiting hospitalizations to those occurring 5 or more years after diagnosis, the overwhelming majority should have completed their first course, cancer-directed therapy. Despite these limitations, our study improves on earlier reports that used self-report data on hospitalizations without validation to medical records by using a state-level hospitalization dataset from the department of health that also allowed us to evaluate length of stay and the reasons for hospitalization.

In conclusion, long-term child and adolescent cancer survivors have higher rates of hospitalizations than the general population and longer hospital stays. In particular, female survivors' hospital stays are 40% longer than females without a cancer history, and survivors of common cancers such as leukemia, CNS, and bone cancer experience stays between 40% and 60% longer. Much of the hospital-related morbidity among cancer survivors is due to blood disorders, such as anemia, which could potentially be identified and managed in outpatient settings rather than by inpatient treatments. However, many survivors are hospitalized because of neoplasms, meaning that relapse of the original cancer or second cancers may drive much of their health care utilization. Our findings suggest that the health problems faced by child and adolescent cancer survivors lead to hospitalizations that may have substantial effects on the health care burden, medical costs, and quality of life for this population.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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