Hospitalization and mortality outcomes in the first five years after a childhood cancer diagnosis: a population-based study

Angela Steineck

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Beth A. Mueller

Eric Chow

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Abstract

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Angela Steineck, MD

Chair of the Supervisory Committee:

Beth Mueller, DrPH

Department of Epidemiology

Background: Children with cancer are frequently hospitalized. However, hospitalization and death by disease category are not well defined <5 years from diagnosis compared with the general population.

Methods: We conducted a retrospective cohort study using linked cancer-hospital discharge-vital registry records to identify cancer cases <20 years at diagnosis during 1987-2012 (n = 4,567) and comparison children without cancer, matched on birth year and sex (n = 45,582). Further data linkage identified serious morbidities resulting in hospitalizations or deaths <5 years from diagnosis. These outcomes were categorized as cancer- vs. non-cancer-related. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated to compare relative hospitalization and mortality <5 years from diagnosis by disease category and after excluding cancer-related outcomes. Among cancer cases, relative risks (RRs) of these outcomes for children with CNS/solid tumor cases compared with children with leukemia/lymphoma were also estimated.

Results: Greater rates of all-cause hospitalization (281.5/1,000 vs. 6.2/1,000 person-years) and death (40.7/1,000 vs. 0.15/1,000 person-years) were observed in childhood cancer cases than comparators and across all diagnosis categories. Increased rates of hospitalization (31.0/1,000

vs. 6.2/1,000 person-years; HR 5.0, 95% CI 4.5-5.5) and death (1.0/1,000 vs. 0.15/1,000 person-years; HR 10.4, 95% CI 5.6-19.1) remained when cancer-related outcomes were excluded. Although HRs for hospitalization and death did not differ greatly by treatment era, absolute rates of hospitalization were greater (1987-1999: 233.3/1,000; 2000-2012: 320.0/1,000 person-years) and death was lesser (1987-1999: 46.3/1,000; 2000-2012: 36.8/1,000 person-years) in the later treatment era among cases. Among cancer cases, children with CNS/solid tumors were less likely to have a cancer-related hospitalization (RR 0.91, 95% CI 0.87-0.97) than were those with leukemia/lymphoma.

Conclusion: Children with cancer experience greater rates of hospitalization and death in all disease categories, even when cancer-related diagnoses are excluded. Results may guide future toxicity mitigation initiatives and anticipatory guidance provided to families of children with cancer.

Introduction

Cancer is the leading cause of disease-related death of children in the United States.[1] Children with cancer are frequently hospitalized to receive cancer-related treatment and for the management of disease and treatment-related complications.[2] They may also experience other health conditions (e.g., asthma, mental health disorders, injury, etc.) that result in hospitalization among children without cancer.[3-5] Serious morbidities resulting in hospitalization, especially those that are not treatment-related, are not well described in children with cancer within the first five years of diagnosis.

Current understanding of hospitalization and mortality outcomes in children with cancer is largely based on clinical trial data.[2] However, these studies have limitations. Fewer than 50% of all children with cancer are treated on a clinical trial at time of diagnosis.[6, 7] Additionally, there are systematic gaps in the inclusion on consortium-wide cancer clinical trials based on race, age, cancer diagnosis, and presence of comorbidities.[6-9] Other non-population based studies in pediatric patients with cancer have examined emergency department utilization [10-12] or early hospital resource utilization following a diagnosis of childhood cancer.[13] Population-based studies primarily focus on individuals who have survived at least five years.[14-18] Among 5+ year childhood cancer survivors, greater rates of hospitalization and all-cause mortality have been reported compared with those without a history of cancer.[15, 17-19] Population-based studies that include individuals <5 years from diagnosis are primarily limited to a single health outcome, for example infection-related mortality or early death, a specific cancer type, or a single-institution.[13, 20-29]

Many hospitalizations following a childhood cancer diagnosis are treatment-related.[2] However, a better understanding of the spectrum of all hospital outcomes and mortality across cancer diagnoses is needed to guide clinicians in determining risk for adverse health conditions, treatment-related and otherwise, and provide insight regarding the overall burden experienced by families. We used population-based linked cancer-hospital discharge-vital registry data from

Washington State to compare the levels of hospitalization and mortality among childhood cancer cases <5 years from a childhood cancer diagnosis to those of healthy comparators and across cancer diagnoses. We hypothesized that children <5 years from a cancer diagnosis would have greater rates of hospitalization and mortality relative to similarly aged children without cancer and that patterns in morbidity and mortality would be different for childhood cancer cases versus comparators, even after excluding cancer treatment-related hospitalizations. We also explored variation in hospitalization indication among children with different types of cancer.

Methods

Subject Identification

Institutional Review Board approvals, including waiver of consent, were granted by the Washington State Department of Health and the Fred Hutchinson Cancer Research Center. In this retrospective cohort study, we used population-based cancer registry data linked to birth (1974-2012), hospital discharge (1987-2013), and death (1987-2013) records from Washington State.

All cancer cases <20 years old at diagnosis were identified from two Washington State population-based cancer registries: 1) National Cancer Institute's Surveillance, Epidemiology and End Results Program-funded Cancer Surveillance System (limited to 13 counties surrounding Puget Sound), starting in 1974; and 2) Centers for Disease Control and Prevention's National Program of Central Cancer Registries-funded Washington State Cancer Registry covering the entire state, starting in 1995. Cancer registry data include cancer type classified per the International Classification of Childhood Cancer (ICCC), third edition.[30] Using this categorization, cancer diagnosis was categorized into the following groups: leukemia, lymphoma, central nervous system (CNS), neuroblastoma, retinoblastoma, Wilms' tumor, hepatoblastoma, bone tumors, soft-tissue sarcomas, germ cell tumors, other malignant

epithelial tumor, and other unspecified. Cancer registry data additionally include International Classification for Oncology (ICD-O) morphology and topography codes; histology; diagnosis age, diagnosis date, initial therapy (chemotherapy, radiotherapy, surgery, etc.), and vital status at quarterly follow-up. Both cancer registries undergo comprehensive quality control assessment of completeness and accuracy.[31-33]

Cancer registry data for these children and adolescents were then linked to Washington State birth records to identify all cases of cancer diagnosed <20 years of age between 1974-2015 among individuals born in-state (N=6,320 eligible cases). Birth record data include maternal age, maternal health conditions and pregnancy outcomes, race/ethnicity, maternal education, maternal prenatal smoking history, insurance payer, and infant sex. Subjects with unknown sex information were excluded (n = 16; N = 6,304 eligible cases remaining). Since 1987, birth records are routinely linked to hospital discharge data for the delivery hospitalizations of both mother and infant, further enriching subject records with additional information about possible morbidities and conditions during a child's infancy. We additionally linked the children's records to subsequent hospital discharge records and to death records to identify all non-pregnancy-related hospitalizations and deaths between 1987-2013. Because hospital records were only available from 1987-2013, subjects diagnosed before 1987 were excluded from our analysis (n = 416; N = 5,888 eligible cases remaining). To allow at least one year of follow-up, cases diagnosed after December 2012 were excluded (n = 716; N = 5,172 eligible cases remaining).

A "reference date" was assigned as the date of diagnosis. Cases with a non-malignant disease (the majority being nonmalignant brain tumors, cervical carcinoma *in situ*, or skin cancers) were excluded (n = 605; N = 4,567 eligible cases remaining). For each case, 10 comparison subjects were selected from birth records, matched on birth year and sex. In total, 4,567 childhood cancer cases diagnosed between 1987-2012 were identified and included in the analyses along with 45,582 child comparators. Comparison children were assigned a

reference date equal to the date of their cases' diagnosis. We excluded comparison children if they were known to have died before the paired case's reference date, based on linkage to death certificates.

Assessment of Outcomes

The primary outcomes of interest for this study were hospitalization and death within 5 years of the reference date. Hospital discharge data included all inpatient and observation discharges in non-Federal facilities. Multiple International Classification of Disease codes, version 9 (ICD9) and version 10 (ICD10) were available for each discharge, using Medicare-Medicaid billing standards. Up to 25 discharge diagnosis codes and up to 10 contributing causes of death were screened for each hospital discharge. Data quality was ensured by the Washington State Department of Health and includes tracking and verifying records monthly and follow-up on delinquent reports. Hospital discharge records in the 5 years after the reference date were linked to subjects' records to identify the occurrence of all subsequent hospitalizations. Hospitalizations for pregnancy-related conditions were excluded. Subjects' records were also linked to the State's death registry (maintained in partnership with the National Center for Health Statistics and the State Department of Health) in order to identify underlying primary and contributing causes of death, based on ICD9 and ICD10 codes. A diagnosis code within the applicable range for any field indicated presence of the outcome. Hospitalization (first hospitalization on record) and death outcomes were evaluated overall and by ICD9/ICD10 diagnosis category, as we have done previously.[19]

To examine whether levels of hospitalizations and deaths were expected to be secondary to a case's cancer diagnosis, ICD diagnoses were further sub-categorized. The Clinical Classification Software (CCS) program was created by the Healthcare Quality and Utilization Project (HCUP) as a tool for distilling diagnostic and procedure billing codes into mutually exclusive and clinically meaningful groups to streamline the use of administrative datasets in research analysis.[34] Hospitalization and death diagnoses were dichotomized as

"cancer-related" (defined as CCS diagnostic groups 11 to 43) or "non-cancer-related" (defined as all other CCS diagnostic groups).[2, 35]

Adapting the algorithm created by Russell et al,[2] to incorporate both ICD9 and equivalent ICD10 codes, "cancer-related" diagnoses were further categorized into mutually-exclusive hospitalization indication groups identified using the following hierarchy: chemotherapy, procedure, infection, toxicity, or other. Because we did not have information regarding timing of chemotherapy within our dataset, we required both the primary and diagnosis and primary procedure field to be coded as chemotherapy. Because we did not have information regarding timing of procedures within our dataset, we used only cancer-related procedures listed in the primary or secondary procedure fields to calculate "procedure" diagnoses.

Statistical Analyses

The distributions of demographic and pregnancy/birth characteristics were compared between individuals with and without cancer. Proportions of those with missing data were also compared. No data were missing for diagnosis or birth years. Race/ethnicity data were missing for 2% of subjects in each group. Levels of missing data were similar in cases and comparison children.

Follow-up for both cancer cases and comparison children accrued from diagnosis/reference date through whichever of the following came first: December 2013, death, or reference date plus five years minus one day.[19, 36] Incidence rates for outcomes were estimated per 1,000 person-years using survival functions. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using Cox regression overall and by ICD9/ICD10 diagnosis category. HRs accounted for matching variables (birth year, sex). We examined possible effect modification of selected variables previously described as risk factors for death and hospitalization, using stratification. Gestational length (preterm <37 weeks/full-term 37+ weeks) was selected because prematurity is a known risk factor for poor health outcomes.[37]

Age at diagnosis (<1 year/1+ year) was selected for ease of comparison with similar cohort studies and because it is a risk factor for early treatment-related mortality.[16, 23] Treatment era (1987-1999/2000-2012) was selected based on previously reported trends in mortality.[38] Maternal prenatal smoking was evaluated as a potential confounder using the change in estimate approach (>10%). Sensitivity analyses were also conducted using only comparators with a history of hospitalization, due to possible differential loss to follow-up between cases and comparators, and again using only subjects ≥1 year old at the time of the reference date, for comparison with prior studies.[16] Results based on cell sizes less than five were suppressed.

To assess outcomes beyond what would be directly expected from a case's cancer diagnosis, "cancer-related" diagnoses were excluded using the CCS diagnostic groups, as detailed above. Among "non-cancer-related" hospitalizations and deaths, incidence rates per 1,000 person-years and HRs with 95% CIs were estimated overall and by ICD9/ICD10 diagnosis category.

In case-only analyses, we described the morbidity and mortality outcomes by cancer type, based on ICCC group: leukemia/lymphoma (ICCC I or II) and CNS/solid tumor (all others). All-cause hospitalization and death were described using numbers and proportions. Non-cancer-related diagnoses were then excluded and hospitalizations were categorized by indication (chemotherapy, procedure, infection, toxicity, other).[2] Number of hospitalizations, elapsed time to first hospitalization, and length of first hospitalization by indication were described using numbers and proportions. Poisson regression with robust standard errors was used to estimate relative risk (RR) and 95% CIs for each outcome, using leukemia/lymphoma as the reference group. Median time to hospitalization and interquartile ranges (IQRs) were calculated using median survival time among hospitalized cases. Median length of hospital stay and IQRs were also described among hospitalized cases. Analyses were conducted using Stata version 16 (StataCorp., College Station, TX).

Results

Description of childhood cancer cases and comparison children

A slight majority (52%) of cases were male and the majority of both case and comparator children were Caucasian (80%) (**Table 1**). Leukemia (26%), CNS tumor (21%), and lymphoma (13%) were the most common cancer diagnoses. Most cases were treated initially with chemotherapy (69%), 52% underwent surgery as part of their treatment, and 27% received radiation therapy. Most cases were diagnosed in 2000 or later (61%). Median age at follow-up or death for cases was 11.0 years (range: 0 days – 24.0 years) and for comparators was 12.0 years (range: 3 days – 24.0 years). During the follow-up period, 55% of cases and 3% of comparators were hospitalized; 16% of cases and 0.1% of comparators died. Maternal age, gravidity, parity, and education at birth were similar between cases and comparator children (**Table 2**). A greater proportion of cases weighed >4000 grams at birth (16% versus 13%) and had congenital malformations (8% versus 5%). Premature birth was similar between cases and comparators (8% versus 7%).

Hospitalization and death among cases and comparators

We observed no confounding of results by maternal prenatal smoking. Childhood cancer cases had a hospitalization rate of 281.5/1,000 person-years (versus 6.2/1,000 person-years in comparators), and a death rate of 40.7/1,000 person-years (versus 0.15/1,000 person-years in comparators) (**Table 3**). Relative to comparison children, childhood cancer cases were nearly 50 times more likely to be hospitalized (HR 49.5, 95% CI: 45.0-54.5) and >300 times more likely to die (HR 372.9, 95% CI: 239.2-581.3). Regarding cause-specific hospitalization and death, childhood cancer cases had increased HRs across all diagnosis categories. Childhood cancer cases were nearly 10 times more likely to have a hospitalization or death with a mental health disorder than comparator children (HR 9.7, 95% CI: 7.1-13.1) and >40 times more likely to have a hospitalization or death due to injury/poisoning (HR 46.1, 95% CI: 39.8-53.5). Childhood cancer cases were also >20 times more likely to have a hospitalization or death due to a

congenital disorder (HR 21.7, 95% CI: 16.9-28.0). When “cancer-related” diagnoses were excluded, childhood cancer cases were still 5 times more likely to have hospitalizations (HR 5.0, 95% CI: 4.5-5.5) and 10 times more likely to die (HR 10.4, 95% CI: 5.6-19.1) than comparison children (**Table 4**). Childhood cancer cases had increased HRs across all cause-specific hospitalization and death diagnosis categories except fractures, which was equivalent in cases and comparators.

Sub-analyses

Similar results were seen when we restricted analyses to children aged one year or older at diagnosis/reference date (**Table S1**). When comparators were restricted to children with at least one hospitalization, cancer cases were still much more likely to be hospitalized (HR 2.8, 95% CI: 2.5-3.2) and to die (HR 128.3, 95% CI: 47.8-344.4) than comparison children (**Table S2**). Regarding cause-specific hospitalization and death, childhood cancer cases had increased HRs across all diagnosis categories except mental health and fracture and no difference in risk for congenitally-related diagnoses. HRs remained greatly increased for all outcomes regardless of children’s gestational age (**Table S3**) or age at diagnosis (**Table S4**). We observed no differences in HRs by treatment era (**Table S5**). However, the absolute hospitalization rate was greater for cases in the later treatment era (1987-1999: 233.3/1,000 person-years; 2000-2012: 320.0/1,000 person-years), whereas the death rate was lesser for cases in the later treatment era (1987-1999: 46.3/1,000 person-years; 2000-2012: 36.8/1,000 person-years). Absolute rates of many cause-specific outcomes were greater in the later treatment era, including infectious, endocrine, circulatory, nervous, and musculoskeletal diagnosis categories.

Cause-specific hospitalizations among children with cancer

Among children with cancer, those with CNS/solid tumors were slightly less likely than those with leukemia/lymphoma to be hospitalized (RR 0.94, 95% CI: 0.87-1.0) but were slightly more likely to die (RR 1.15, 95% CI: 1.1-1.2) (**Table 5**). These results were similar when hospitalizations were restricted to cancer-related diagnoses. A slight majority of cases with any

cancer type had a hospitalization for a cancer-related diagnosis (52%); 25% of cases had at least one hospitalization with a primary indication for chemotherapy, 47% for procedure, 23% for infection, 26% for toxicity, and 18% for other cancer-related diagnoses. Relative to cases with leukemia/lymphoma diagnoses, cases with a CNS/solid tumor were less likely to be hospitalized for procedure, infection, or toxicity indications. For the vast majority of patients who were hospitalized, the elapsed time to first hospitalization was <1 year from diagnosis for infection, toxicity, and other cancer-related diagnoses. Patients with a leukemia/lymphoma diagnoses were more likely to have a later first hospitalization (3 - <5 years after diagnosis) for infections, toxicity, and other cancer-related diagnoses. For patients who were hospitalized, most hospitalizations were <1-week duration. Hospitalizations for other cancer-related diagnoses tended to be the longest and hospitalizations for the indication of chemotherapy tended to be the shortest. Patients with leukemia/lymphoma diagnoses were more likely to have hospitalizations lasting ≥1 week across all hospitalization indication categories.

Discussion

This retrospective cohort study used cancer registry data linked to birth, hospital discharge, and death certificate records to compare hospitalization and death occurrence between childhood cancer cases and comparison children born in Washington State. We observed greater rates of hospitalization and death across all diagnosis categories among childhood cancer cases. This remained true when cancer-related hospitalizations and deaths were excluded. This was most pronounced for hematologic and circulatory diagnosis categories, and least pronounced for mental health and fracture diagnoses, although these risks remained significantly increased. Among cancer cases, a slight majority had a cancer-related hospitalization. The vast majority of first hospitalizations occurred within a year of diagnosis and lasted <7 days. Cases with leukemia/lymphoma were more likely to be hospitalized, especially

later after diagnosis, and were more likely to have a hospitalization lasting longer than one week.

Hospitalization to receive cancer-directed therapies or manage subsequent adverse events of therapy is an expected consequence of a childhood cancer diagnosis. Population-based studies more thoroughly reflect the risk of morbidity and mortality than single-institution or trial-based studies because they include all cancer types and socio-demographic groups. For example, one population-based study described early mortality rates greater than those reported in cooperative clinical trials, suggesting certain outcomes may be under-reported in the medical literature.[22] Age <1 year at diagnosis has been described to be a risk factor for both hospitalization and death;[10, 12, 22] we observed greatly increased HRs regardless of age at diagnosis. Although a decrease in cancer-related mortality has been described from the 1950s-1990s,[23, 38-40] mortality outcomes have not substantially changed in recent decades.[39, 41] Consistent with this in our data from 1987-2013, the absolute mortality rate is somewhat lesser in the more recent treatment era. Hospitalization rates for any reason among children with cancer appear to be increasing with time;[2, 35, 42] the absolute rates of hospitalization for both cases and comparison children were somewhat greater in the more recent treatment era. This in turn has led to increased resource utilization in a time when cost-effectiveness in health care is increasingly important.[35] Although resource utilization in the Childhood Cancer Survivor Study is well documented,[15, 43] the greatest hospitalization burden typically occurs within 5 years of diagnosis.[13, 20] Evaluating hospital outcomes by diagnosis or indication in the context of population-based studies can provide insight regarding risk beyond what is expected from a diagnosis of cancer and may help identify patterns in potentially avoidable morbidity and mortality outcomes.

Chronic disease in long-term survivors of childhood cancer is well documented.[19, 43-46] However, it is likely that many of these chronic diseases develop earlier than five years post-therapy. Higher incidence rates of respiratory illnesses have been reported in childhood cancer

cases <5 years of diagnosis compared to age and sex-matched comparators.[27] Similarly, childhood cancer cases have been documented to have greater proportions of admissions for a range of chronic conditions, including asthma and mental health disorders, as early as 2 years post-therapy; this is compounded by multi-morbidity.[47, 48] A greater risk of cardiovascular disease, gastrointestinal and liver disease, renal and urinary tract disease, and endocrine disease, with associated increased rates of hospitalization compared to the general population has also been described among 1-year childhood cancer survivors.[49-54] Our results also support the development of chronic disease in children <5 years from their cancer diagnosis. Altogether, this highlights the need for further investigation to pinpoint the timing of chronic disease development, facilitating early intervention. Evaluation that is separate from therapeutic clinical trials is necessary to ensure generalizability across cancer diagnoses and demographic groups.

Skeletal morbidity in children with cancer is also a well-known consequence of selected malignancies and chemotherapy regimens.[24, 55-57] In children receiving therapy for acute lymphoblastic leukemia, the RR of fracture compared to the general population was approximately 2, with age <5 years as a risk factor.[25] Decreased bone mineral density in children receiving chemotherapy for bone sarcomas has also been described.[58] We observed a >4-fold increased risk of fracture-related outcomes in our study. When cancer-related diagnoses were excluded, however, a difference in risk was not seen. We also saw a >45-fold increased risk of injury/poisoning-related outcomes. It is possible that a greater risk for hospitalization may be partially attributed to the increased risk of complications from injury in childhood cancer cases or that cases are more likely to be hospitalized for observation following an injury. However, the injury/poisoning category included a range of diagnoses, some of which do not reflect unintentional injuries, producing misclassification and likely over-estimating true risk of injury. Regardless, chronic illness is a well-defined risk factor for non-accidental trauma.[59] Moreover, adolescents and young adults with cancer continue to participate in risky-

behaviors.[60, 61] This comes at a high-stress time when most children are not routinely seen by a primary care provider and highlights the importance of ongoing attention to health care maintenance screening measures during cancer treatment.[62, 63] Considering the potential benefit of prevention interventions, further investigation is needed to evaluate the occurrence of specific unintentional injury-outcomes and fully define this possible risk.

This study has several limitations. ICD9/10 diagnosis codes have the potential for misclassification. Small sub-sample sizes limit our ability to detect differences in some analyses. There is a possibility for loss to follow-up for hospitalization information due to emigration out of state. Childhood cancer cases may be expected to emigrate at lower rates compared with healthy children in the general population, resulting in an over-estimation of comparison children with no hospitalization data. If this is true, we would expect our estimates to be biased away from the null. However, significantly increased HRs were observed even when estimates were restricted to comparison children with at least one prior hospitalization. We would not expect similar bias with death data, as death records are shared between states due to interstate agreements. Hospital discharge records have limited detail regarding treatments, and cancer registry data only include initial treatment information. Although we may be able to speculate based on cancer type, this reduced our ability to draw conclusions on treatment-specific associations with outcomes. Additionally, it limited our ability to analyze outcomes among individuals with refractory or relapsed disease.

In this population-based analysis, we compared the overall levels of hospitalization and death outcomes experienced by children with cancer compared with children in the general population. This gives us insight into which types of complications and non-cancer-related outcomes children with cancer are at greatest risk of encountering during the early years after diagnosis, compared with rates in the general population. This information may guide clinicians in providing anticipatory guidance for families when their child is diagnosed with cancer and may help to identify specific areas that may benefit most from further mitigation of toxicity.

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Tables and Figures

Table 1. Characteristics of childhood cancer patients diagnosed in 1987-2012 and comparison children.

Characteristic	Cases[a] n = 4,567		Comparison children[a] n = 45,582	
	n	%	n	%
Sex				
Female	2,198	48.1	21,973	48.2
Male	2,369	51.9	23,609	51.8
Missing	0		0	
Race/ethnicity				
White	3,720	82.7	35,848	80.1
Black	137	3.0	1,666	3.7
Hispanic	304	6.7	3,378	7.6
Asian	254	5.6	2,656	5.9
Native American	72	1.6	975	2.2
Pacific Islander	8	0.18	184	0.4
Other	2	0.04	40	0.09
Missing	70	(1.5)	835	(1.8)
Age (years) at diagnosis/reference date				
0-3	1,526	33.4	15,247	33.4
4-9	1,075	23.5	10,734	23.5
10-14	790	17.3	7,885	17.3
15-19	1,176	25.8	11,716	25.7
Missing	0		0	
Age (years) at end of follow-up				
0-4	363	7.9	1,577	3.5
5-9	1,606	35.2	17,178	37.7
10-14	754	16.5	7,687	16.9
15-19	902	19.7	8,485	18.6
20-24	944	20.6	10,665	23.4
Missing	0		0	
Hospitalized during follow-up				
Yes	2,503	54.8	1,282	2.8
No	2,064	45.2	44,300	97.2
Missing	0		0	

Died				
Yes	754	16.5	32	0.1
No	3,812	83.5	45,550	99.9
Missing	0		0	
Cancer type				
Leukemia	1,208	26.4		
Lymphoma	600	13.1		
CNS	961	21.0		
Neuroblastoma	312	6.8		
Retinoblastoma	101	2.2		
Renal tumor	213	6.7		
Hepatic tumor	62	1.4		
Bone sarcoma	194	4.2		
Soft tissue sarcoma	316	6.9		
Germ cell tumors	207	4.5		
Other malignant epithelial	372	8.1		
Other unspecified	21	0.5		
Missing	0			
Initial course of therapy[b]				
Chemotherapy	2,667	68.7		
Missing	683	(15.0)		
Radiation	1,228	27.1		
Missing	45	(1.0)		
Surgery	2,092	52.3		
Missing	565	(12.4)		
No therapy	950	24.6		
Missing	713	(15.6)		
Treatment era				
1987-1999	1,778	38.9		
2000-2012	2,789	61.1		

a Numbers may not sum to totals due to missing

b As indicated in cancer registry. Children may have received > 1 therapy

Table 2. Parental, delivery, and infant characteristics of childhood cancer patients diagnosed in 1987-2012 and comparison children.

Characteristic	Cases n = 4,567		Comparison children n = 45,582	
	n	%	n	%
Maternal (years) age at birth				
12-19	381	8.4	4,771	10.5
20-24	1,163	25.5	12,166	26.8
25-29	1,392	30.5	13,717	30.2
30-34	1,034	22.7	9,970	21.9
35-39	503	11.0	4,031	8.9
40+	85	1.9	789	1.7
Missing	9	(0.2)	138	(0.3)
Maternal education[a]				
Less than High School	379	16.5	4,036	17.7
High School graduate	674	29.4	6,912	30.3
At least some college	1,239	54.0	11,884	52.0
Missing	159	(6.5)	1,671	(6.8)
Marital status				
Married	3,528	77.8	34,404	76.0
Single	1,008	22.2	10,882	24.0
Missing	31	(0.7)	296	(0.6)
Paternal (years) age at birth				
12-19	150	3.5	1,451	3.4
20-24	670	15.7	8,145	19.3
25-29	1,253	29.3	12,458	29.5
30-34	1,218	28.5	10,907	25.9
35-39	636	14.9	6,101	14.5
40+	346	8.1	3,091	7.3
Missing	294	(6.4)	3,429	(7.5)
Type of delivery				
Vaginal	3,269	77.6	33,157	78.9
Cesarean section	946	22.4	8,887	21.1
Missing	352	(7.7)	3,538	(7.8)
Number of prior pregnancies				
0	1,354	32.6	13,139	31.7
1	1,180	28.4	11,949	28.8
2	780	18.8	7,736	18.6
3+	836	20.1	8,644	20.8
Missing	417	(9.1)	4,114	(9.0)

Number of prior births				
0	1,936	42.4	18,993	42.2
1	1,468	32.1	14,525	32.3
2	709	15.5	6,889	15.3
3+	392	8.7	4,546	10.1
Missing	62	(1.4)	629	(1.4)
Prenatal smoking[b]				
No	3,109	84.6	30,484	83.1
Yes	564	15.4	6,183	16.9
Missing	157	(4.1)	1,548	(4.0)
Child birthweight (grams)				
250-2499	243	5.3	2,377	5.2
2500-3999	3,584	78.7	37,000	81.5
4000+	728	16.0	6,000	13.2
Missing	12	(0.3)	205	(0.4)
Gestational length (weeks)				
20-36	366	8.3	3,275	7.5
37-41	3,767	85.2	37,658	85.8
42-45	290	6.6	2,978	6.8
Missing	144	(3.1)	1,671	(3.7)
Child congenital malformation[b]				
No	3,464	92.4	35,475	94.7
Yes	283	7.6	1,979	5.3
Missing	83	(2.2)	761	(2.0)

a Data only available for children born 1992 and later
b Data only available for children born 1984 and later

Table 3. Hospitalization, mortality, and hospitalization/death for selected conditions in childhood cancer cases and comparison children.

	Person-years at risk	n	Rate per 1,000	HR (95% CI)[a]
Any Hospitalization				
Comparison	205,189	1,282	6.2	1.0 (ref)
Case	8,892	2,503	281.5	49.5 (45.0-54.5)
Death (any cause)				
Comparison	208,850	32	0.15	1.0 (ref)
Case	18,525	754	40.7	372.9 (239.2-581.3)
Cause-specific hospitalization/death				
Infectious				
Comparison	208,141	230	1.1	1.0 (ref)
Case	14,414	1,241	86.1	77.8 (65.9-91.7)
Cancer				
Comparison	208,842	7	0.03	1.0 (ref)
Case	18,388	97	5.3	159.6 (70.0-364.0)
Endocrine/metabolic				
Comparison	207,955	313	1.5	1.0 (ref)
Case	15,600	969	62.1	40.7 (35.3-46.9)
Hematological				
Comparison	208,589	96	0.5	1.0 (ref)
Case	13,212	1,496	113.2	244.8 (189.5-316.2)
Mental health disorder				
Comparison	208,661	98	0.5	1.0 (ref)
Case	18,298	81	4.4	9.7 (7.1-13.1)
Nervous system				
Comparison	208,236	217	1.0	1.0 (ref)
Case	15,365	989	64.4	63.2 (53.4-74.8)
Circulatory system				
Comparison	208,759	47	0.2	1.0 (ref)
Case	16,692	692	41.4	186.4 (133.9-259.5)
Respiratory system				
Comparison	207,547	427	2.0	1.0 (ref)
Case	15,148	1,127	74.4	36.7 (32.3-41.7)
Digestive system				
Comparison	208,066	293	1.4	1.0 (ref)
Case	14,627	1,172	80.1	54.8 (47.4-63.4)
Genitourinary system				
Comparison	208,503	126	0.6	1.0 (ref)
Case	17,106	482	28.2	47.5 (38.3-58.8)
Congenital				
Comparison	208,560	99	0.5	1.0 (ref)
Case	17,879	194	10.8	21.7 (16.9-28.0)
Skin				
Comparison	208,589	96	0.5	1.0 (ref)
Case	16,807	539	32.1	74.6 (58.3-95.4)

Musculoskeletal				
Comparison	208,497	191	0.9	1.0 (ref)
Case	17,184	447	26.0	29.5 (24.5-35.5)
Injuries				
Comparison	208,117	297	1.4	1.0 (ref)
Case	15,399	987	64.1	46.1 (39.8-53.5)
Fracture				
Comparison	208,591	104	0.5	1.0 (ref)
Case	18,425	40	2.2	4.6 (3.1-6.6)

a Accounting for matching (sex and birth year)

Table 4. Hospitalization, mortality, and hospitalization/death for selected conditions in childhood cancer cases, among non-cancer-related diagnoses.

	Person-years at risk	n	Rate per 1,000	HR (95% CI)[a]
Any Hospitalization				
Comparison	205,197	1,277	6.2	1.0 (ref)
Case	16,715	519	31.0	5.0 (4.5-5.5)
Death (any cause)				
Comparison	208,450	32	0.15	1.0 (ref)
Case	18,525	21	1.0	10.4 (5.6-19.1)
Cause-specific hospitalization/death				
Infectious				
Comparison	208,141	230	1.1	1.0 (ref)
Case	18,263	86	4.7	4.2 (3.3-5.4)
Cancer				
Comparison	208,846	4	0.02	1.0 (ref)
Case	18,515	5	0.3	12.5 (3.3-46.5)
Endocrine/metabolic				
Comparison	207,958	311	1.5	1.0 (ref)
Case	18,228	113	6.2	4.1 (3.3-5.1)
Hematological				
Comparison	208,590	95	0.5	1.0 (ref)
Case	18,117	123	6.8	14.1 (10.7-18.6)
Mental health disorder				
Comparison	208,662	97	0.5	1.0 (ref)
Case	18,489	17	0.9	2.0 (1.2-3.4)
Nervous system				
Comparison	208,236	216	1.0	1.0 (ref)
Case	18,044	148	8.2	8.0 (6.4-9.9)
Circulatory system				
Comparison	208,760	47	0.2	1.0 (ref)
Case	18,358	62	3.4	15.1 (10.2-22.4)
Respiratory system				
Comparison	207,547	426	2.0	1.0 (ref)
Case	18,250	96	5.2	2.5 (2.0-3.1)
Digestive system				
Comparison	208,069	292	1.4	1.0 (ref)
Case	18,226	93	5.1	3.6 (2.8-4.5)
Genitourinary system				
Comparison	208,503	125	0.6	1.0 (ref)
Case	18,390	46	2.5	4.3 (3.1-6.1)
Congenital				
Comparison	208,560	99	0.5	1.0 (ref)
Case	18,378	46	2.5	5.1 (3.6-7.3)
Skin				
Comparison	208,589	96	0.5	1.0 (ref)
Case	18,462	27	1.5	3.4 (2.2-5.2)

Musculoskeletal				
Comparison	208,397	191	0.9	1.0 (ref)
Case	18,353	55	3.0	3.4 (2.5-4.6)
Injuries				
Comparison	208,117	297	1.3	1.0 (ref)
Case	18,254	95	5.2	3.7 (3.0-4.8)
Fracture				
Comparison	208,591	104	0.5	1.0 (ref)
Case	18,499	8	0.43	0.9 (0.4-1.9)

a accounting for matching (sex and birth year)

Table 5. Cause-specific hospitalizations overall and by indication among children with solid and liquid tumors.

Outcome	All cases N= 4,567		Leukemia/Lymphoma N= 1,808		CNS/Solid tumor N= 2,759		RR[a] (95% CI)
	n	%	n	%	n	%	
Any hospitalization							
Yes	2,503	54.8	1,035	57.3	1,468	53.2	0.94 (0.87-1.0)
No	2,064	45.2	773	42.7	1,291	46.8	1.0 (ref)
Death (any cause)							
Yes	754	16.5	250	13.8	504	18.3	1.15 (1.1-1.2)
No	3,813	83.5	1,558	86.2	2,255	81.7	1.0 (ref)
Cancer-related hospitalization							
Yes	2,346	51.4	994	55.0	1,352	49.9	0.91 (0.84-0.98)
No	2,221	48.6	814	45.0	1,407	50.1	1.0 (ref)
Cancer-related death							
Yes	733	16.1	237	13.1	496	18.0	1.16 (1.10-1.22)
No	3,834	83.9	1,571	86.9	2,263	82.0	1.0 (ref)
Number of hospitalizations by intent							
Chemotherapy							
0	3,411	74.7	1,203	66.5	2,208	80.0	1.0 (ref)
1-4	721	15.8	466	25.8	255	9.2	0.35 (0.31-0.41)
5+	435	9.5	139	7.7	296	10.7	1.4 (1.1-1.7)
Procedure							
0	2,421	53.0	905	50.1	1,516	54.9	1.0 (ref)
1-4	1,969	43.1	822	45.4	1,147	41.6	0.91 (0.85-0.98)
5+	177	3.9	81	5.5	96	3.5	0.78 (0.58-1.0)
Infection							
0	3,520	77.1	1,260	69.7	2,260	81.9	1.0 (ref)
1-4	954	20.9	498	27.5	456	16.5	0.60 (0.53-0.67)
5+	93	2.0	50	2.8	43	1.6	0.56 (0.38-0.84)
Toxicity							
0	3,381	74.0	1,231	68.1	2,150	77.9	1.0 (ref)
1-4	1,052	23.0	522	28.9	530	19.2	0.66 (0.60-0.74)
5+	134	3.0	55	3.0	79	2.9	0.94 (0.67-1.3)
Other							
0	3,747	82.0	1,483	82.0	2,264	82.1	1.0 (ref)
1-4	756	16.6	309	17.1	447	16.2	0.95 (0.83-1.1)
5+	64	1.4	16	0.9	48	1.7	2.0 (1.1-3.4)
Elapsed time to first hospitalization (years)							
Infection							

No hospitalization	3,520	77.1	1,260	69.7	2,260	81.9	1.0 (ref)
< 1	888	19.4	445	24.6	443	16.0	0.65 (0.58-0.73)
1 - <3	129	2.8	82	4.5	47	1.7	0.37 (0.26-0.53)
3 - <5	30	0.7	21	1.2	9	0.4	0.28 (0.13-0.61)
Toxicity							
No hospitalization	3,381	74.0	1,231	68.1	2,150	77.9	1.0 (ref)
< 1	1,008	22.0	481	26.6	527	19.1	0.72 (0.64-0.80)
1 - <3	138	3.0	73	4.0	65	2.3	0.58 (0.42-0.81)
3 - <5	40	1.0	23	1.3	17	0.7	0.48 (0.26-0.90)
Other							
No hospitalization	3,747	82.0	1,483	82.0	2,264	82.1	1.0 (ref)
< 1	681	15.0	263	14.5	418	15.1	1.0 (0.90-1.2)
1 - <3	109	2.4	43	2.4	66	2.4	1.0 (0.69-1.5)
3 - <5	30	0.6	19	1.1	11	0.4	0.38 (0.18-0.79)
Length of first hospitalization (days) by intent							
Chemotherapy							
No hospitalization	3,411	74.7	1,203	66.5	2,208	80.0	1.0 (ref)
< 7	867	19.0	415	23.0	452	16.4	0.71 (0.63-0.80)
7+	289	6.3	190	10.5	99	3.6	0.34 (0.27-0.43)
Procedure							
No hospitalization	2,421	53.0	905	50.1	1,516	54.9	1.0 (ref)
< 7	1,493	32.7	570	31.5	923	33.5	1.06 (0.97-1.1)
7+	653	14.3	333	18.4	320	11.6	0.63 (0.55-0.72)
Infection							
No hospitalization	3,520	77.1	1,260	69.7	2,260	81.9	1.0 (ref)
< 7	764	16.7	363	20.0	401	14.5	0.72 (0.63-0.82)
7+	283	6.2	185	10.3	98	3.6	0.35 (0.27-0.44)
Toxicity							
No hospitalization	3,381	74.0	1,231	68.1	2,150	77.9	1.0 (ref)
< 7	886	19.4	402	22.2	484	17.5	0.79 (0.70-0.89)
7+	300	6.6	175	9.7	125	4.6	0.47 (0.37-0.58)
Other							
No hospitalization	3,747	82.0	1,483	82.0	2,264	82.1	1.0 (ref)
< 7	548	12.0	178	9.8	370	13.4	1.4 (1.1-1.6)
7+	272	6.0	147	8.2	125	4.6	0.56 (0.44-0.70)
Median (IQR) time to hospitalization (days) by intent among those who were hospitalized							
Infection	128 (64-259)		156 (73-308)		105 (58-223)		-
Toxicity	100 (48-247)		120 (55-251)		88 (44-234)		-
Other	133 (54-331)		146 (62-425)		120 (46-278)		-
Median (IQR) length of hospital stay (days)							
Chemotherapy	4.7 (3.3-7.0)		4.9 (3.4-8.2)		4.3 (3.3-6.1)		-
Procedure	5.0 (3.3-7.8)		5.2 (3.5-9.1)		4.6 (3.1-7.0)		-
Infection	5.0 (3.5-7.2)		5.1 (3.6-8.3)		4.7 (3.5-6.3)		-
Toxicity	4.8 (3.4-7.0)		5.0 (3.5-8.0)		4.6 (3.4-6.4)		-
Other	5.3 (3.3-8.4)		6.3 (3.9-10.8)		4.8 (3.0-7.0)		-

a Leukemia/lymphoma = reference group

Supplementary Tables.

Table S1. Hospitalization, mortality, and hospitalization/death for selected conditions in childhood cancer cases diagnosed after age 1 year.

	Person-years at risk	n	Rate per 1,000	HR (95% CI)[a]
Any Hospitalization				
Comparison	186,223	1,012	5.4	1.0 (ref)
Case	8,292	2,224	268.2	53.6 (48.2-59.5)
Death (any cause)				
Comparison	188,904	16	0.08	1.0 (ref)
Case	16,857	669	39.7	660.9 (353.9-1,234.0)
Cause-specific hospitalization/death				
Infectious				
Comparison	188,500	148	0.78	1.0 (ref)
Case	13,270	1,084	81.7	106.0 (86.5-129.8)
Cancer				
Comparison	188,896	7	0.04	1.0 (ref)
Case	16,720	97	5.8	159.6 (70.0-364.0)
Endocrine/metabolic				
Comparison	188,302	228	1.2	1.0 (ref)
Case	14,284	859	60.1	48.3 (41.1-56.8)
Hematological				
Comparison	188,706	78	0.4	1.0 (ref)
Case	12,090	1,335	110.4	271.9 (204.5-361.7)
Mental health disorder				
Comparison	188,716	98	0.5	1.0 (ref)
Case	16,629	81	4.9	9.7 (7.1-13.1)
Nervous system				
Comparison	188,506	152	0.8	1.0 (ref)
Case	14,052	878	62.5	76.7 (63.1-93.3)
Circulatory system				
Comparison	188,828	40	0.2	1.0 (ref)
Case	15,277	607	39.7	183.3 (129.2-260.3)
Respiratory system				
Comparison	188,084	294	1.6	1.0 (ref)
Case	13,882	995	71.7	48.5 (41.7-56.4)
Digestive system				
Comparison	188,267	249	1.3	1.0 (ref)
Case	13,351	1,044	78.2	58.8 (50.1-68.9)
Genitourinary system				
Comparison	188,666	95	0.5	1.0 (ref)
Case	15,.636	413	26.4	54.8 (42.9-70.1)
Congenital				
Comparison	188,704	72	0.4	1.0 (ref)
Case	16,364	140	8.5	20.9 (15.6-28.0)
Skin				

Comparison	188,720	72	0.4	1.0 (ref)
Case	15,348	478	31.1	95.3 (71.2-127.5)
Musculoskeletal				
Comparison	188,494	174	0.9	1.0 (ref)
Case	15,557	430	27.6	31.3 (25.8-37.9)
Injuries				
Comparison	188,252	263	1.4	1.0 (ref)
Case	14,143	868	61.4	45.2 (38.7-52.9)
Fracture				
Comparison	188,659	97	0.5	1.0 (ref)
Case	16,766	37	2.2	4.5 (3.1-6.7)

a Accounting for matching (sex and birth year)

Table S2. Hospitalization, mortality, and hospitalization/death for selected conditions in childhood cancer cases, restricted to comparators with at least one hospitalization.

	Person-years at risk	n	Rate per 1,000	HR (95% CI)[a]
Any Hospitalization				
Comparison	9,941	1,282	129.0	1.0 (ref)
Case	8,892	2,503	281.5	2.8 (2.5-3.2)
Death (any cause)				
Comparison	13,601	8	0.6	1.0 (ref)
Case	18,526	755	40.7	128.3 (47.8-344.4)
Cause-specific hospitalization/death				
Infectious				
Comparison	12,897	229	17.7	1.0 (ref)
Case	14,414	1,241	86.1	4.5 (3.8-5.5)
Cancer				
Comparison	13,593	7	0.5	1.0 (ref)
Case	18,388	97	5.3	11.6 (4.9-27.5)
Endocrine/metabolic				
Comparison	12,707	313	24.6	1.0 (ref)
Case	15,600	969	62.1	2.2 (1.9-2.6)
Hematological				
Comparison	13,346	96	7.2	1.0 (ref)
Case	13,212	1,496	113.2	14.8 (11.4-19.3)
Mental health disorder				
Comparison	208,661	98	7.3	1.0 (ref)
Case	18,298	81	4.4	0.5 (0.3-0.8)
Nervous system				
Comparison	12,987	214	16.5	1.0 (ref)
Case	17,736	989	64.4	3.3 (2.7-4.0)
Circulatory system				
Comparison	13,511	46	3.4	1.0 (ref)
Case	19,332	692	41.4	9.9 (7.0-14.0)
Respiratory system				
Comparison	12,303	425	34.5	1.0 (ref)
Case	15,148	1,127	74.4	2.0 (1.7-2.3)
Digestive system				
Comparison	12,818	293	22.8	1.0 (ref)
Case	14,627	1,172	80.1	3.0 (2.5-3.5)
Genitourinary system				
Comparison	13,259	126	9.5	1.0 (ref)
Case	17,106	482	28.2	2.8 (2.2-3.6)
Congenital				
Comparison	13,311	95	7.1	1.0 (ref)
Case	17,879	194	10.8	1.1 (0.8-1.5)
Skin				
Comparison	13,341	96	7.2	1.0 (ref)
Case	16,807	539	32.1	3.8 (2.9-5.0)

Musculoskeletal				
Comparison	13,149	190	14.4	1.0 (ref)
Case	17,184	447	26.0	1.5 (1.2-1.8)
Injuries				
Comparison	12,868	286	22.2	1.0 (ref)
Case	15,399	987	64.1	2.9 (2.4-3.4)
Fracture				
Comparison	13,342	103	7.7	1.0 (ref)
Case	18,425	40	2.2	0.3 (0.2-0.5)

a Accounting for matching (sex and birth year)

Table S3. Hospitalization, mortality, and hospitalization/death for selected conditions in childhood cancer cases by gestational length.

	Full-term birth				Premature birth			
	Person-years at risk	n	Rate per 1,000	HR (95% CI)[a]	Person-years at risk	n	Rate per 1,000	HR (95% CI)[a]
Any Hospitalization								
Comparison	182,530	1,121	6.1	1.0 (ref)	14,539	123	8.4	1.0 (ref)
Case	7,863	2,236	284.4	52.9 (47.5-59.0)	639	209	327.1	38.5 (14.1-105)
Death (any cause)								
Comparison	185,728	22	0.1	1.0 (ref)	14,897	7	0.5	1.0 (ref)
Case	16,504	656	39.7	383 (230-640)	1,389	75	54.0	51.4 (7.0-376)
Cause-specific hospitalization/death								
Infectious								
Comparison	185,095	204	1.1	1.0 (ref)	14,839	21	1.4	1.0 (ref)
Case	12,751	1,117	87.6	80.9 (67.2-97.4)	1,095	99	90.4	70.4 (9.7-511)
Cancer								
Comparison	185,721	5	0.03	1.0 (ref)	14,896	1	.	.
Case	16,390	85	5.2	145 (58.7-357)	1,370	8	.	.
Endocrine/metabolic								
Comparison	184,934	274	1.5	1.0 (ref)	14,813	33	2.2	1.0 (ref)
Case	13,831	881	63.7	43.5 (37.1-51.1)	1,188	69	58.1	49.5 (6.8-362)
Hematological								
Comparison	185,516	81	0.4	1.0 (ref)	14,864	10	0.7	.
Case	11,691	1,341	114.7	261 (195-351)	990	123	124.2	.
Mental health disorder								
Comparison	185,582	81	0.4	1.0 (ref)	14,878	8	.	.
Case	16,292	73	4.5	4.4 (0.4-43.1)	1,378	4	.	.
Nervous system								
Comparison	185,239	175	0.9	1.0 (ref)	14,805	31	2.1	1.0 (ref)
Case	13,649	885	64.8	71.6 (58.8-87.2)	1,154	82	71.0	23.0 (7.1-74.1)
Circulatory system								
Comparison	185,652	39	0.2	1.0 (ref)	14,893	3	.	.
Case	14,859	608	40.9	193.2 (132-282)	1,233	68	.	.
Respiratory system								
Comparison	184,645	356	1.9	1.0 (ref)	14,725	54	3.7	1.0 (ref)
Case	13,428	1,019	75.9	41.2 (35.6-47.6)	1,134	91	80.3	10.6 (4.5-25.1)
Digestive system								

Comparison	185,073	250	1.3	1.0 (ref)	14,797	32	2.2	1.0 (ref)
Case	12,928	1,063	82.2	61.5 (52.0-72.9)	1,126	88	78.1	62.3 (8.6-454)
Genitourinary system								
Comparison	185,427	107	0.6	1.0 (ref)	14,853	18	1.2	1.0 (ref)
Case	15,219	428	28.1	48.8 (38.3-62.1)	1,269	47	37.0	38.8 (5.2-291)
Congenital								
Comparison	185,475	86	0.5	1.0 (ref)	14,865	10	0.7	1.0 (ref)
Case	15,940	163	10.2	20.7 (15.7-27.4)	1,312	29	22.1	25.1 (3.3-191.5)
Skin								
Comparison	185,485	87	0.5	1.0 (ref)	14,882	6	0.4	.
Case	14,937	485	32.5	77.5 (58.7-102.2)	1,260	45	35.7	.
Musculoskeletal								
Comparison	185,323	168	0.9	1.0 (ref)	14,864	17	1.1	1.0 (ref)
Case	1,508	399	26.1	31.9 (25.8-39.3)	1,288	34	26.4	25.3 (3.3-191.5)
Injuries								
Comparison	185,099	254	1.4	1.0 (ref)	14,827	28	1.9	1.0 (ref)
Case	13,674	892	65.5	50.0 (42.3-59.3)	1,166	74	63.5	53.3 (7.3-390)
Fracture								
Comparison	185,498	90	0.5	1.0 (ref)	14,874	11	.	.
Case	16,414	37	2.2	5.1 (3.4-7.7)	1,383	2	.	.

a Accounting for matching (sex and birth year)

Table S4. Hospitalization, mortality, and hospitalization/death for selected conditions in childhood cancer cases by age at diagnosis.

	Diagnosed before 1 year of age				Diagnosed at 1 year of age or later			
	Person-years at risk	n	Rate per 1,000	HR (95% CI)[a]	Person-years at risk	n	Rate per 1,000	HR (95% CI)[a]
Any Hospitalization								
Comparison	18,966	270	14.2	1.0 (ref)	186,223	1,012	5.4	1.0 (ref)
Case	600	279	465	30.6 (24.1-38.8)	8,292	2,224	268.2	53.6 (48.2-59.5)
Death (any cause)								
Comparison	19,945	16	0.8	1.0 (ref)	188,904	16	0.1	1.0 (ref)
Case	1,669	86	51.5	84.9 (44.1-163.4)	16,857	669	39.7	661 (354-1234)
Cause-specific hospitalization/death								
Infectious								
Comparison	19,641	82	4.2	1.0 (ref)	188,500	148	0.8	1.0 (ref)
Case	1,144	157	137.2	27.3 (20.2-37.0)	13,270	1,084	81.7	106 (86.5-130)
Cancer								
Comparison	19,945	0	.	.	188,896	7	0.03	1.0 (ref)
Case	1,669	0	.	.	16,720	97	5.8	160 (70.0-364)
Endocrine/metabolic								
Comparison	19,653	85	4.3	1.0 (ref)	188,302	228	1.2	1.0 (ref)
Case	1,316	110	83.6	18.2 (13.3-24.9)	14,284	859	60.1	48.3 (41.1-56.8)
Hematological								
Comparison	19,883	18	0.9	1.0 (ref)	188,706	78	0.4	1.0 (ref)
Case	1,121	161	143.6	133.8 (74.4-240)	12,090	1,335	110.4	272 (204-362)
Mental health disorder								
Comparison	19,945	0	.	.	188,716	98	0.5	1.0 (ref)
Case	1,669	0	.	.	16,629	81	4.9	9.7 (7.1-13.1)
Nervous system								
Comparison	19,730	65	3.3	1.0 (ref)	188,506	152	0.8	1.0 (ref)
Case	1,313	111	84.5	26.3 (18.5-37.6)	14,052	878	62.5	76.7 (63.1-93.3)
Circulatory system								
Comparison	19,932	7	0.3	1.0 (ref)	188,828	40	0.2	1.0 (ref)
Case	1,415	85	60.1	212 (77.8-578)	15,277	607	39.7	183.3 (129-260)
Respiratory system								
Comparison	19,462	133	6.8	1.0 (ref)	188,084	294	1.6	1.0 (ref)
Case	1,266	132	104.2	12.9 (9.9-16.7)	13,882	995	71.7	48.5 (41.7-56.4)
Digestive system								

Comparison	19,799	44	2.2	1.0 (ref)	188,267	249	1.3	1.0 (ref)
Case	1,276	128	100.3	35.3 (24.4-51.1)	13,352	1,044	78.2	58.8 (50.1-68.9)
Genitourinary system								
Comparison	19,836	31	1.6	1.0 (ref)	188,666	95	0.5	1.0 (ref)
Case	1,470	69	46.9	26.3 (16.7-41.3)	15,636	413	26.4	54.8 (42.9-70.1)
Congenital								
Comparison	19,855	27	1.3	1.0 (ref)	188,704	72	0.4	1.0 (ref)
Case	151	54	35.6	24.4 (14.9-40.1)	16,364	140	8.5	20.9 (15.6-27.9)
Skin								
Comparison	19,869	24	1.2	1.0 (ref)	188,720	72	0.4	1.0 (ref)
Case	1,459	61	41.8	27.6 (17.0-45.0)	15,348	478	31.1	95.3 (71.2-127.5)
Musculoskeletal								
Comparison	19,903	17	0.8	1.0 (ref)	188,484	174	0.9	1.0 (ref)
Case	1,627	17	10.4	12.1 (6.0-24.6)	15,557	430	27.6	31.3 (25.8-37.9)
Injuries								
Comparison	19,865	34	1.7	1.0 (ref)	188,252	263	1.4	1.0 (ref)
Case	1,255	119	94.8	53.8 (34.1-84.7)	14,144	868	61.4	45.2 (38.7-52.9)
Fracture								
Comparison	19,931	7	.	.	188,659	97	0.5	1.0 (ref)
Case	16,414	3	.	.	16,766	37	2.2	4.5 (3.1-6.7)

a Accounting for matching (sex and birth year)

Table S5. Hospitalization, mortality, and hospitalization/death for selected conditions in childhood cancer cases by treatment era.

	1987-1999				2000-2012			
	Person-years at risk	n	Rate per 1,000	HR (95% CI)[a]	Person-years at risk	n	Rate per 1,000	HR (95% CI)[a]
Any Hospitalization								
Comparison	87,149	511	5.9	1.0 (ref)	118,040	771	6.5	1.0 (ref)
Case	3,947	921	233.3	46.9 (40.2-54.8)	4,944	1,582	320.0	51.1 (45.2-57.7)
Death (any cause)								
Comparison	88,682	21	0.24	1.0 (ref)	120,168	11	0.1	1.0 (ref)
Case	7,680	356	46.3	293.3 (165-521)	10,845	399	36.8	492.2 (244-991)
Cause-specific hospitalization/death								
Infectious								
Comparison	88,390	94	1.1	1.0 (ref)	119,751	136	1.1	1.0 (ref)
Case	6,048	482	79.7	78.7 (60.3-102.8)	8,367	759	90.7	77.2 (62.5-95.2)
Cancer								
Comparison	88,681	1	.	.	120,160	6	0.05	1.0 (ref)
Case	7,640	28	.	.	10,748	69	6.4	135.7 (54.7-336.4)
Endocrine/metabolic								
Comparison	88,343	109	1.2	1.0 (ref)	119,612	204	1.7	1.0 (ref)
Case	6,694	332	49.6	39.3 (30.9-49.9)	8,906	637	71.5	41.5 (34.8-49.5)
Hematological								
Comparison	88,588	34	0.4	1.0 (ref)	120,001	62	0.5	1.0 (ref)
Case	5,606	573	102	286.0 (183.1-446.7)	7,605	923	121.4	244.6 (164.3-307.1)
Mental health disorder								
Comparison	88,633	23	0.2	1.0 (ref)	120,028	75	0.6	1.0 (ref)
Case	7,619	20	2.6	9.9 (5.4-18.5)	10,679	61	5.7	9.5 (6.7-13.6)
Nervous system								
Comparison	88,388	94	1.1	1.0 (ref)	119,847	123	1.0	1.0 (ref)
Case	6,570	339	51.6	58.2 (44.0-76.9)	8,795	650	73.9	66.1 (53.4-81.7)
Circulatory system								
Comparison	88,661	11	0.1	1.0 (ref)	120,098	36	0.3	1.0 (ref)
Case	7,216	206	28.5	227.5 (116.7-443.4)	9,476	486	51.3	173.3 (118.4-253.6)
Respiratory system								
Comparison	88,157	172	1.9	1.0 (ref)	119,389	255	2.1	1.0 (ref)
Case	6,503	395	60.7	30.4 (24.9-37.1)	8,646	732	84.7	41.4 (35.1-48.8)
Digestive system								

Comparison	88,372	109	1.2	1.0 (ref)	119,694	184	1.5	1.0 (ref)
Case	6,408	383	59.8	49.5 (38.8-63.3)	8,219	789	96.0	57.8 (48.2-69.3)
Genitourinary system								
Comparison	88,555	50	0.6	1.0 (ref)	119,948	76	0.6	1.0 (ref)
Case	7,204	180	25.0	45.9 (32.5-64.9)	9,902	302	30.5	48.5 (36.9-63.7)
Congenital								
Comparison	88,578	34	0.4	1.0 (ref)	119,981	65	0.5	1.0 (ref)
Case	7,526	50	6.6	17.8 (11.2-28.2)	10,353	144	13.9	23.6 (17.5-31.8)
Skin								
Comparison	88,609	27	0.3	1.0 (ref)	119,980	69	0.6	1.0 (ref)
Case	7,169	162	22.6	89.7 (55.1-146)	9,638	377	39.1	69.6 (52.3-92.5)
Musculoskeletal								
Comparison	88,524	69	0.78	1.0 (ref)	119,873	122	1.0	1.0 (ref)
Case	7,319	114	15.6	21.5 (15.5-29.8)	8,965	333	33.7	33.8 (27.0-24.4)
Injuries								
Comparison	88,395	114	1.3	1.0 (ref)	119,721	183	1.5	1.0 (ref)
Case	6,453	389	60.3	51.6 (40.3-66.1)	8,946	598	66.8	43.1 (39.8-53.5)
Fracture								
Comparison	88,614	33	0.4	1.0 (ref)	119,976	71	0.6	1.0 (ref)
Case	7,646	12	1.6	4.4 (2.2-8.7)	10,779	28	2.6	4.6 (2.9-7.2)

a Accounting for matching (sex and birth year)