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

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Abstract

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

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Methods: We conducted a retrospective cohort study using linked cancer registry-hospital discharge-vital 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). Data linkage identified serious morbidities resulting in cancer- and non-cancer-related hospitalizations or deaths <5 years from diagnosis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated to compare relative hospitalization and mortality by disease category and after excluding cancer-related outcomes. Among cancer cases, relative risks (RRs) of these outcomes for children with solid tumors 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 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) rates 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 were lesser (1987-1999: 46.3/1,000; 2000-2012: 36.8/1,000 person-years) in the later treatment era among cases. Children with solid tumors were less likely to have a cancer-related hospitalization than were those with leukemia/lymphoma (RR 0.91, 95% CI 0.84-0.98).

Conclusion: Even after excluding cancer-related diagnoses, children with cancer experience greater rates of hospitalization and death in all disease categories. Results may guide future toxicity mitigation initiatives and inform anticipatory guidance for families of children with cancer.

Keywords

Population-based study; cohort study; pediatric; cancer; hospitalization; mortality

Introduction

Cancer is the leading cause of disease-related death among children in the United States.[1] Children with cancer are frequently hospitalized for cancer-related treatment and management of treatment-related complications.[2] They may also experience health conditions (e.g., asthma, mental health disorders, injury, etc.) that cause hospitalizations 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 <5 years after diagnosis.

Hospitalization and mortality outcome data in children with cancer are largely informed by clinical trials.[2] However, <50% of children with cancer are treated on a clinical trial at time of diagnosis.[6, 7] Additionally, there are systematic gaps in inclusion on consortium-wide cancer clinical trials based on race, age, cancer diagnosis, and presence of comorbidities.[6-9] Among 5+ year childhood cancer survivors, population-based studies report greater rates of hospitalization and all-cause mortality compared to those without a history of cancer.[10-13] Population-based studies that include individuals <5 years from diagnosis are primarily limited to a single health outcome (i.e. infection-related mortality, early death), a specific malignancy, or a single-institution.[14-24]

Many hospitalizations following a childhood cancer diagnosis are treatment-related.[2] Improved knowledge of morbidity and mortality outcomes across cancer diagnoses may better guide clinicians in determining risk for adverse outcomes, 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 levels of hospitalization and mortality among childhood cancer cases <5 years from diagnosis to healthy children. We hypothesized that children <5 years from a cancer diagnosis have greater rates of hospitalization and mortality relative to similarly-aged children without cancer and that patterns in morbidity and mortality differ between 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 with waiver of consent were granted by the Washington State Department of Health and the Fred Hutchinson Cancer Research Center. This retrospective cohort study used population-based cancer registry data linked to birth (1974-2012), hospital discharge (1987-2013), and death (1987-2013) records from Washington State.

As part of a larger study of long term effects of cancer treatment,[10] all cancer cases <20 years old at diagnosis during 1974-2015 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 (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.[25] Cancer registry data additionally include International Classification for Oncology (ICD-O) morphology and topography codes; histology; stage (when applicable); 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.[26-28]

Cancer registry data were linked to Washington State birth records to identify all cancer cases <20 years at diagnosis between 1974-2015, and who were born in-state (N=6,320). This not only provided additional information about the cases but allowed identification of appropriate population-based comparison children for analyses. Birth records include date of birth, race/ethnicity, and sex as well as maternal (age, health conditions, education, prenatal smoking) and infant variables (birthweight, gestational age, malformations) that may be associated with childhood cancer risk and outcomes. Cases with unknown sex information were excluded (n = 16).

Cases were assigned a "reference date" defined as the date of cancer diagnosis. Cases with a non-malignant disease (primarily nonmalignant brain tumors, cervical carcinoma *in situ*, or skin cancers) were excluded (n = 605). For each case, 10 comparison subjects were selected from birth records, matched on birth year and sex. Comparators were assigned a reference date equal to their cases' diagnosis date and those who were known to have died before that date (n = 88) were excluded, based on linkage to death certificates.

Since 1987, birth records have been routinely linked to hospital discharge data for the delivery hospitalizations of mother and infant, enriching subject records with information about possible co-morbidities and infant health conditions (i.e. congenital malformations were identified if indicated by birth record and/or presence of relevant ICD9 codes 740-759 in the hospital discharge record for the delivery hospitalization, as screening both sources has been shown to improve identification of many conditions).[29] We then linked the children's records to subsequent hospital discharge records from 1987-2013 to identify all non-pregnancy-related outcomes (i.e. discharge diagnosis, hospitalization duration). Because hospital discharge data were only available from 1987-2013, cases diagnosed before 1987 were excluded (n = 416). To allow at least one year of follow-up, 716 cases diagnosed after December 2012 were excluded. Finally, data were linked to death records from 1987-2013 to identify deaths occurring in both groups. In total, 4,567 childhood cancer cases were identified and included in the analyses with 45,582 comparators.

Assessment of Outcomes

Our primary outcomes were hospitalization and death within 5 years after the diagnosis/ reference date. Washington State hospital discharge data included all inpatient and observation discharges in non-Federal facilities. Multiple International Classification of Disease codes, version 9 (ICD9) were available for each discharge, using Medicare-Medicaid billing standards. Up to 25 discharge diagnoses were screened for each hospital discharge. Data quality activities by the Washington State Department of Health include tracking and verifying records monthly and follow-up on delinquent reports. Hospital discharge records for 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 (ICD9 630-679, 760-779). Subjects' records were also linked to State death records (maintained in partnership with the National Center for Health Statistics and the State Department of Health) to identify one underlying primary and up to 10 contributing causes of death, based on ICD9 and ICD10 codes. A diagnosis code within the applicable range for any field for any hospitalization indicated presence of the outcome. First hospitalization on record and death outcomes were evaluated overall and by ICD9/ ICD10 diagnosis category, as previously described.[10, 30]

The Clinical Classification Software (CCS) program (adapted to incorporate ICD10 codes for deaths) was used to dichotomize outcomes as "cancer-related" (CCS diagnostic groups 11-43) or "non-cancer-related" (all other CCS diagnostic groups).[2, 31, 32] "Cancer-related" hospitalizations were further categorized into hierarchical mutually exclusive hospitalization indication groups: chemotherapy, procedure, infection, toxicity, or other (Table S1) using the algorithm developed by Russell et al.[2] Information regarding timing of chemotherapy and procedures within our dataset was not available: If the primary diagnosis and primary procedure fields were coded chemotherapy, then the hospitalization indication was coded "chemotherapy." If both the primary diagnosis and procedure field did not indicate chemotherapy, and a cancer-related procedure code was used in the primary diagnosis or primary procedure fields, then the hospitalization indication was coded as a cancer-related "procedure."

Statistical Analyses

Follow-up for both cancer cases and comparators accrued from diagnosis/reference date through whichever of the following came first: December 2013, death, or reference date plus five years minus one day.[10, 33] Race/ethnicity data were missing for 2% of subjects in each group. Levels of missing data for other variables were similar in cases and comparators. Incidence rates for outcomes were estimated per 1,000 person-years. 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) via baseline hazard stratification. Results were examined separately by gestational length (<37/37+ weeks), since prematurity is associated with childhood mortality,[34] by diagnosis age (<1 year/1+ year), to compare with prior studies,[17, 35], and time since reference date (<1 year, 1 - <3 years, 3 - <5 years), to review patterns over time. We also stratified by treatment era (1987-1999/2000-2012), based on mortality trends,[36] and by race (white/non-white) based on racial health outcome disparities in pediatric oncology; [37-39] further refinement was not possible due to small numbers. Important differences in risk estimates between strata were determined using the likelihood ratio test. Sensitivity analyses were conducted using only comparators with a history of hospitalization, due to possible differential loss to follow-up between cases and comparators. Because the Russell algorithm classified injuries as non-cancer-related, ICD9/10 injury/poisoning codes were manually reviewed and further dichotomized: probably/possibly cancer-related (e.g. complication of bone marrow transplant; transfusion reaction) vs. unlikely cancer-related. (Table S1). Relative risk for "treatment-related injuries/poisonings" and "non-treatment-related injuries/poisonings" was estimated in cases versus comparators. Results based on cell sizes <5 were suppressed and cells with <5 subjects masked. Analyses were conducted overall and repeated after exclusion of cancer-related outcomes as detailed above.

In case-only analyses, we described malignancy-specific morbidity and mortality outcomes, based on ICCC group: leukemia/lymphoma (ICCC I/II) and CNS/solid tumor (all others). 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 summarized. Poisson regression with robust standard errors was used to estimate relative risk (RR) and 95% CIs for each outcome (reference = leukemia/lymphoma). Median time to hospitalization and length of hospital stay (and interquartile ranges [IQRs]) were calculated among hospitalized cases. Analyses were conducted using Stata version 16 (StataCorp., College Station, TX).

Results

Cases and comparison children

A slight majority (52%) of cases were male and 80% of cases and comparators were White (Table 1). Leukemia (26%), CNS tumor (21%), and lymphoma (13%) were the most common malignancies. Most cases were treated initially with chemotherapy (69%), 52% underwent surgery, and 27% received radiation therapy. Median age at end of follow-up 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 were similar between cases and comparators (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

Cases had a hospitalization rate of 281.5/1,000 person-years (comparators: 6.2/1,000 person-years) and a death rate of 40.7/1,000 person-years (comparators: 0.15/1,000 person-years) (Table 3). Relative to comparators, 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). Cases had increased HRs across all cause-specific outcome categories. Cases were nearly 10 times more likely to have a mental health disorder-related outcome than comparators (HR 9.7, 95% CI: 7.1-13.1) and >40 times more likely to have an injury/poisoning-related outcome (HR 46.1, 95% CI: 39.8-53.5).

When cancer-related hospitalizations/deaths were excluded, cases were still 5 times more likely to have any 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) (Table 4), and had increased HRs across all cause-specific outcomes except fracture. The RRs for cancer treatment-related and non-treatment-related injuries were 13.5 (95% CI 11.9-15.4) and 1.19 (95% CI 1.05-1.35) respectively (Table S2). When non-cancer-related hospitalizations/deaths were examined, cases had increased HRs across all cause-specific outcomes (Table 5). Differences in hospitalization and death outcomes were greatest in the year after the reference date and decreased over time. However, by 3 - <5 years from the reference date, cases remained more likely to be hospitalized or die with infection, endocrine, hematologic, nervous, circulatory, or injury diagnoses.

Sensitivity analyses

Results were similar when we restricted analyses to children one year or older at diagnosis/reference date (Table S3). When comparators were restricted to children with at least one hospitalization, cancer cases remained more likely to be hospitalized (HR 2.8, 95% CI: 2.5-3.2) or to die (HR 128.3, 95% CI: 47.8-344.4) (Table S4). Regarding cause-specific hospitalization and death, cases had increased HRs across all diagnosis categories except mental health and fracture and no difference in risk for congenitally-related outcomes. HRs remained greatly increased for all outcomes regardless of gestational age (Table S5) or age at diagnosis (Table S6). We observed no large differences in HRs by treatment era (Table S7) or race (data not shown). 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 outcomes.

Cause-specific hospitalizations among cancer cases

A slight majority of cases were hospitalized for a cancer-related diagnosis (51%); 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 (Table 6). For the vast majority of hospitalized cases, the elapsed time to first hospitalization was <1 year from diagnosis for infection, toxicity, and other cancer-related diagnoses; most hospitalizations were <1-week duration. Hospitalizations for other cancer-related diagnoses were relatively longer than hospitalizations for chemotherapy. Relative to children with solid tumors, patients with leukemia/lymphoma were more likely to have hospitalizations lasting ≥1 week, slightly more likely to be hospitalized (RR 0.94, 95% CI: 0.87-1.0), and slightly less likely to die (RR 1.15, 95% CI: 1.1-1.2). These results were similar when restricted to cancer-related diagnoses. Cases with leukemia/lymphoma were more likely to be hospitalized for procedure, infection, or toxicity indications and were more likely to have a later first hospitalization (3 - <5 years after diagnosis).

Discussion

We observed increased rates of hospitalization and death across all diagnosis categories during the 5 years after diagnosis among childhood cancer cases compared with children without cancer, even after excluding cancer-related outcomes. The risk was greatest in the year following diagnosis. Although the overall hospitalization rate for cases approached that of comparators by 3-5 years post-diagnosis, it was still increased and cases remained more likely to be hospitalized for specific diagnoses, including infections, circulatory diseases, endocrine disorders, nervous system diseases, and injuries.

Hospitalization is not unexpected after a childhood cancer diagnosis. Certain outcomes may be under-reported in many studies. For example, one population-based study described greater early mortality rates than those reported in cooperative clinical trials.[16] Population-based studies reflect the risk of morbidity and mortality more completely than single-institution or trial-based studies by better representing all socio-demographic groups and cancer types. Diagnosis age <1 year reportedly increases risk of hospitalization and death;[16, 40, 41] we observed greatly increased HRs regardless of age at diagnosis. Although a decrease in cancer-related mortality has been described from the 1950s-1990s,[17, 36, 42, 43] mortality outcomes have not substantially changed in recent decades.[42, 44] Our data suggest absolute mortality is decreased in the more recent treatment era. Hospitalization rates among children with cancer appear to be increasing. This may be due to increased treatment intensity for some malignancies (e.g. autologous transplant and chemoimmunotherapy for high risk neuroblastoma), as well as more conservative supportive care practices for selected treatment regimens (e.g. prolonged hospitalization following myelosuppressive regimens for acute myelogenous leukemias).[2, 31, 45] Similarly, we observed greater absolute rates of hospitalization for all children in the more recent treatment era. This causes greater resource utilization when cost-effectiveness in health care is increasingly important.[31] Although resource utilization in childhood cancer survivors is well documented,[11, 46] the greatest hospitalization burden occurs within 5 years after diagnosis.[14, 18] Our results suggest an additional risk beyond what is expected from a child's cancer diagnosis, which persists beyond the first year following diagnosis for many diagnoses. This may help identify patterns in potentially avoidable outcomes.

Chronic disease in long-term survivors of childhood cancer is well documented.[10, 46-49] However, many chronic diseases likely develop earlier than five years post-therapy. Higher rates of respiratory illnesses have been reported in childhood cancer cases <5 years from diagnosis compared with children without cancer.[22] Similarly, childhood cancer cases have greater proportions of admissions for a range of chronic conditions, including asthma and mental health disorders, as early as 2-years post-therapy.[50, 51] A greater risk of hospitalization for various organ system diseases compared with the general population is also reported among 1-year childhood cancer survivors.[52-57] Our results support the development of chronic disease in children <5 years post-therapy, even after excluding cancer-related diagnoses. Altogether, this highlights the need to identify the timing of chronic disease development, facilitating early intervention.

Skeletal morbidity is also a well-known consequence of selected malignancies and chemotherapy regimens in pediatrics.[19, 58-60] Children with acute lymphoblastic leukemia are reported to be twice as likely to experience fracture compared to the general population.[20] Decreased bone mineral density post-therapy for bone sarcomas has also been described.[61] We observed a >4-fold increased risk of fracture; however no increased risk remained when cancer-related diagnoses were excluded. Small numbers precluded risk estimation beyond the first year. We found a >45-fold increased risk of injury-related outcomes overall. This may be due to the increased risk of complications from injury in childhood cancer cases or because cases are more likely to be closely monitored following an injury. When we further refined injuries to non-treatment-related diagnoses, a 20% increased risk remained, suggesting a child's cancer diagnosis produces some difference in risk of injury that persists after the first year. Our findings are supported by a recent report examining mortality due to unintentional injury in cancer patients of all ages.[62] Notably, chronic illness is a well-defined risk factor for non-accidental trauma.[63] Moreover, adolescents with cancer continue to participate in risky-behaviors.[64, 65] This comes at a time when many children are not routinely seen by a primary care provider and highlights the importance of ongoing health care maintenance screening during and after cancer treatment.[66, 67]

This study has several limitations. ICD9/10 diagnosis codes have the potential for misclassification. Because all discharge diagnoses were evaluated with similar weight (except the hierarchical assessment of cancer related outcomes, as described), cases may be more likely to have a diagnosis captured because they are under closer surveillance, which would bias estimates away from the null. It is difficult to assess the possible bias due to exclusion of hospitalizations in federal facilities, which were not included in the state hospital discharge database, although it is likely to be quite small as children are much less likely than adults to be hospitalized at a federal facility, which includes only military and veteran's institutions. Small sub-sample sizes limited our ability to detect differences in some analyses. It is likely that we were unable to link all state-born cases to their birth records. Although we have no way to assess the linkage accuracy, birth records were located for a majority (>70%) of cases identified in the registry and the age- and sex-distributions of linked cases is similar to that of all registry cases. There is a possibility for loss to follow-up for hospitalization due to emigration out of state. Childhood cancer cases may emigrate at lower rates compared with healthy children, over-estimating the number of comparators without hospitalization. If this is true, our estimates would be biased away from the null. However, significantly increased HRs were observed even when restricted to comparators with at least one prior hospitalization. Similar bias for mortality measures may be less likely due to cross-jurisdictional sharing of death record information for state residents, although it is likely some deaths were missed. Hospital discharge records have limited treatment information and cancer registry data only include initial treatment details. Although we may speculate based on cancer type, we were unable to draw conclusions on treatment-specific associations and to analyze outcomes with relapsed disease.

In this population-based analysis, we compared the overall hospitalization and death outcomes experienced by children within 5 years of a cancer diagnosis compared with children in the general population and found increased risks of hospitalization and death, even after excluding cancer-related diagnoses. This may provide insight into which types of complications and non-cancer-related outcomes childhood cancer cases have greatest risk of encountering early after diagnosis, inform anticipatory guidance, and help identify opportunities to prevent toxicity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

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

Characteristic	Cases n = 4,567		Comparison children n = 45,582	
	n	%	n	%
Sex				
Female	2,198	48.1	21,973	48.2
Male	2,369	51.9	23,609	51.8
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/Other	10	0.22	224	0.5
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
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
Hospitalized during follow-up				
Yes	2,503	54.8	1,282	2.8
No	2,064	45.2	44,300	97.2
Died				
Yes	754	16.5	32	0.1
No	3,812	83.5	45,550	99.9
Cancer type				
Leukemia	1,208	26.4		
Lymphoma	600	13.1		
CNS	961	21.0		
Neuroblastoma	312	6.8		
Retinoblastoma	101	2.2		

Characteristic	Cases n = 4,567		Comparison children n = 45,582	
	n	%	n	%
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		
Initial course of therapy[a]				
Chemotherapy	2,667	68.7		
Radiation	1,228	27.1		
Surgery	2,092	52.3		
None indicated	950	24.6		
Treatment era				
1987-1999	1,778	38.9		
2000-2012	2,789	61.1		

[a]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
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
Marital status				
Married	3,528	77.8	34,404	76.0
Single	1,008	22.2	10,882	24.0
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
Type of delivery				
Vaginal	3,269	77.6	33,157	78.9
Cesarean section	946	22.4	8,887	21.1
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
Number of prior births				
0	1,936	42.4	18,993	42.2
1	1,468	32.1	14,525	32.3

Characteristic	Cases n = 4,567		Comparison children n = 45,582	
	n	%	n	%
2	709	15.5	6,889	15.3
3+	392	8.7	4,546	10.1
Prenatal smoking[b]				
No	3,109	84.6	30,484	83.1
Yes	564	15.4	6,183	16.9
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
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
Child congenital malformation[b]				
No	3,464	92.4	35,475	94.7
Yes	283	7.6	1,979	5.3

[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)
Hematologica				
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				

	Person-years at risk	n	Rate per 1,000	HR (95% CI)[a]
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[b]				
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 sex and birth year.

[b]Includes fractures.

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)
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				

	Person-years at risk	n	Rate per 1,000	HR (95% CI)[a]
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[b]				
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 sex and birth year.

[b]Includes fractures.

Table 5.

Hazard ratios for non-pregnancy hospitalizations/death in childhood cancer cases relative to children without cancer, by post-diagnosis period, among non-cancer-related diagnoses.

	First year				1 to < 3 years				3 to < 5 years			
	Person-years at risk	**N**	**Rate/ 1,000**	**HR (95% CI)[a]**	**Person-years at risk**	**N**	**Rate/ 1,000**	**HR (95% CI)[a]**	**Person-years at risk**	**N**	**Rate/ 1,000**	**HR (95% CI)[a]**
Any hospitalization												
Comparison	45206	453	9.98	1.0 (ref)	85681	522	6.08	1.0 (ref)	76386	406	5.29	1.0 (ref)
Case	4033	451	109.59	10.7 (9.4-12.2)	7578	75	9.90	1.6 (1.3-2.1)	6376	44	6.90	1.3 (1.0-1.8)
Death (any cause)												
Comparison	45447	19	0.42	1.0 (ref)	86259	>5	.	.	76810	<5	.	.
Case	4410	9	2.04	4.8 (2.2-10.7)	7663	<5	.	.	6427	>5	.	.
Cause-specific hospitalization/death												
Infection												
Comparison	45389	102	2.23	1.0 (ref)	86180	78	0.89	1.0 (ref)	76749	57	0.74	1.0 (ref)
Case	4367	64	14.66	6.5 (4.8-8.9)	7643	18	2.36	2.6 (1.6-4.4)	6415	17	2.65	3.6 (2.1-6.1)
Endocrine/metabolic												
Comparison	45388	110	2.42	1.0 (ref)	86126	127	1.46	1.0 (ref)	76709	91	1.17	1.0 (ref)
Case	4346	89	20.48	8.4 (6.3-11.1)	7646	18	2.35	1.6 (1.0-2.6)	6407	17	2.65	2.3 (1.3-3.8)
Hematological												
Comparison	45429	40	0.86	1.0 (ref)	86222	33	0.38	1.0 (ref)	76783	29	0.38	1.0 (ref)
Case	4322	114	25.22	28.8 (20.0-41.6)	7654	12	1.57	4.1 (2.1-7.9)	6422	7	1.09	2.9 (1.3-6.6)
Mental health												
Comparison	45440	15	0.31	1.0 (ref)	86222	35	0.41	1.0 (ref)	76753	60	0.78	1.0 (ref)
Case	4405	6	1.36	4.4 (1.7-11.5)	7660	6	0.78	1.9 (0.8-4.6)	6423	5	0.78	1.0 (0.4-2.5)
Nervous system												
Comparison	45403	82	1.81	1.0 (ref)	86171	84	0.97	1.0 (ref)	76744	65	0.82	1.0 (ref)
Case	4306	126	29.03	15.7 (11.9-20.8)	7642	22	2.88	2.9 (1.8-4.7)	6411	15	2.34	2.9 (1.6-5.0)
Circulatory system												
Comparison	45442	15	0.33	1.0 (ref)	86240	17	0.20	1.0 (ref)	76795	18	0.23	1.0 (ref)
Case	4378	46	10.28	30.7 (17.1-55.1)	7651	13	1.70	8.5 (4.1-17.6)	6422	7	1.09	4.7 (2.0-11.2)
												Respiratory system
Comparison	45355	175	3.84	1.0 (ref)	86068	166	1.93	1.0 (ref)	76696	105	1.34	1.0 (ref)
Case	4354	73	16.76	4.3 (3.3-5.7)	7649	17	2.22	1.1 (0.7-1.9)	6416	13	2.03	1.5 (0.8-2.7)
Digestive system												

	First year				1 to < 3 years				3 to < 5 years			
	Person-years at risk	N	Rate/ 1,000	HR (95% CI)[a]	Person-years at risk	N	Rate/ 1,000	HR (95% CI)[a]	Person-years at risk	N	Rate/ 1,000	HR (95% CI)[a]
Comparison	45400	84	1.85	1.0 (ref)	86125	118	1.37	1.0 (ref)	76715	96	1.25	1.0 (ref)
Case	4353	74	16.31	8.7 (6.3-11.9)	7642	16	2.09	1.5 (0.9-2.6)	6419	9	1.40	1.1 (0.6-2.2)
Genitourinary system												
Comparison	45425	41	0.88	1.0 (ref)	86203	54	0.63	1.0 (ref)	76769	37	0.48	1.0 (ref)
Case	4384	34	7.76	8.7 (5.5-13.8)	7656	8	1.04	1.7 (0.8-3.5)	6422	5	0.78	1.6 (0.6-4.1)
Congenital												
Comparison	45422	45	0.99	1.0 (ref)	86212	42	0.49	1.0 (ref)	76780	28	0.36	1.0 (ref)
Case	4381	39	8.67	8.7 (5.6-13.3)	7652	8	1.05	2.1 (1.0-4.5)	6422	5	0.78	2.1 (0.8-5.5)
Skin												
Comparison	45432	33	0.73	1.0 (ref)	86223	36	0.42	1.0 (ref)	76779	29	0.36	1.0 (ref)
Case	4398	17	3.87	5.3 (3.0-9.5)	7658	5	0.65	1.6 (0.6-4.0)	6425	5	0.78	2.1 (0.8-5.5)
Musculoskeletal												
Comparison	45428	38	0.84	1.0 (ref)	86172	87	1.01	1.0 (ref)	76736	70	0.91	1.0 (ref)
Case	4373	44	10.06	11.9 (7.7-18.3)	7660	7	0.91	0.9 (0.4-2.0)	6421	7	1.09	1.2 (0.6-2.6)
Injuries[b]												
Comparison	45410	77	1.70	1.0 (ref)	86123	131	1.52	1.0 (ref)	76718	93	1.21	1.0 (ref)
Case	4369	56	12.82	7.5 (5.3-10.6)	7642	26	3.40	2.2 (1.5-3.4)	6407	20	3.12	2.6 (1.6-4.2)
Fracture												
Comparison	45436	21	0.46	1.0 (ref)	86209	>25	.	.	76773	>25	.	.
Case	4406	6	1.36	2.9 (1.2-7.3)	7663	<5	.	.	6427	<5	.	.

[a]Accounting for sex and birth year.

[b]Includes fractures.

Table 6.

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 (0.87-1.01)
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 (1.09-1.21)
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	1.39 (1.15-1.69)
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 (0.58-1.04)
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 (0.67-1.32)
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 (0.83-1.08)

Outcome	All cases N= 4,567		Leukemia/Lymphoma N= 1,808		CNS/Solid tumor N= 2,759		RR[a] (95% CI)
	n	%	n	%	n	%	
5+	64	1.4	16	0.9	48	1.7	1.96 (1.11-3.45)
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	1.04 (0.90-1.20)
1 - <3	109	2.4	43	2.4	66	2.4	1.00 (0.69-1.47)
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 (0.97-1.16)
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	1.36 (1.15-1.61)

Outcome	All cases N= 4,567		Leukemia/Lymphoma N= 1,808		CNS/Solid tumor N= 2,759		RR[a] (95% CI)
	n	%	n	%	n	%	
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

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