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Hospitalization Rates Among Survivors of Childhood Cancer in the Childhood Cancer Survivor Study Cohort

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Background. Chronic health conditions are common among long-term childhood cancer survivors, but hospitalization rates have not been reported. The objective of this study was to determine overall and cause-specific hospitalization rates among survivors of childhood cancer and compare rates to the U.S. population. ***Procedure.*** The Childhood Cancer Survivor Study (CCSS) is a retrospective cohort of 5+ year survivors of childhood malignancies treated at 26 participating centers. Self-reported hospitalizations from 10,366 survivors (diagnosed 1970–1986) were compared to U.S. population rates using age- and sex-stratified standardized incidence ratios (SIRs). Reasons for hospitalization were evaluated and associations between demographic, cancer and treatment-related risk factors with hospitalization were investigated. ***Results.*** Survivors were, on average, 20.9 years from cancer diagnosis (SD: 4.6, range: 13–32) and 28.6 years of age (SD: 7.7, range: 13–51). Survivor hospitalization rates were 1.6 times the U.S. population (95% CI: 1.6; 1.7). Increased hospitalization rates were noted irrespective of gender, age at follow-up and cancer diagnosis, with highest SIRs noted among male (SIR = 2.6, 95% CI: 2.2; 3.0) and female (SIR = 2.7, 95% CI: 2.4; 3.1) survivors aged 45–54. Female gender, an existing chronic health condition and/or a second neoplasm, and prior treatment with radiation were associated with an increased risk of non-obstetrical hospitalization. ***Conclusions.*** Survivors of childhood cancer demonstrate substantially higher hospitalization rates. Additional research is needed to further quantify the healthcare utilization and economic impact of treatment-related complications as this population ages. Pediatr Blood Cancer 2012; 59:126–132. © 2011 Wiley Periodicals, Inc.

Key words: cancer survivor; childhood cancer; hospitalization

INTRODUCTION

Current estimates place the number of childhood cancer survivors in the U.S. in excess of 325,000 [1]. With 5-year relative survival rates for all childhood malignancies approaching 80%, the vast majority of pediatric cancer patients will achieve long-term survival [2]. Having been exposed at an early age to radiation, chemotherapy and/or surgery, this survivor population has an elevated risk of developing treatment-related adverse health effects [3,4]. Reports from cohorts of pediatric cancer survivors describe a high burden of chronic health conditions, some of which are disabling or potentially life-threatening [5–7]. In addition, chronic health conditions predisposed by cancer therapy (e.g., second neoplasms, cardiovascular complications, etc.) may be exacerbated by organ dysfunction associated with aging and other co-morbid health conditions presenting in adulthood.

Given the high prevalence of morbidity among childhood cancer survivors and the reported decline in general and cancer-related medical visits with increased time from cancer treatment [8], the level of preventive medical care received by this at-risk population is concerning. Lack of regular outpatient follow-up for effective prevention/intervention measures among survivors may maintain a high prevalence of chronic health conditions, possibly resulting in higher rates of more serious health conditions requiring hospitalization. The magnitude of hospitalizations, as a component of the overall healthcare burden in childhood cancer survivors is unknown. Understanding rates and causes for hospitalization among childhood cancer survivors could potentially impact specific healthcare planning for these patients in terms of screening for and management of chronic health conditions. Thus, the purpose of this study was to quantify overall and cause-specific rates of reported hospitalization among a large cohort of long-term survivors of childhood cancer and compare these rates to the U.S. population. We also sought to identify risk factors for hospitalization among survivors.

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METHODS

Participants

The Childhood Cancer Survivor Study (CCSS) is a cohort of individuals who survived 5 or more years from diagnosis of

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childhood cancer [9,10]. Eligible participants were retrospectively identified from 26 collaborating institutions. The majority of subjects eligible for the CCSS cohort was recruited and completed the baseline questionnaire between 1994 and 1996, though some subjects participated as early as 1992. Of the 20,346 eligible for CCSS, 2,996 (14.8%) could not be located after extensive tracing and were considered lost to follow-up. Of the 17,633 survivors contacted, 14,358 (81%) completed the baseline questionnaire. Of those completing the baseline questionnaire, 1,174 were deceased at the time of the baseline questionnaire and were thus not eligible for continued follow-up. Twelve thousand nine hundred eighty-five survivors were eligible for the 2000 follow-up with an 80% participation rate and 12,564 were eligible for the 2005 follow-up with a 71% participation rate. Approval from the human subjects committee was obtained at all participating centers and consent was obtained from all study participants.

Data Collection

All cancer therapy information was abstracted from medical records. Socio-demographic characteristics and health-related outcomes were collected in the 1994–1996 (baseline), 2000, and 2005 questionnaires, while hospital healthcare utilization, including number and reasons for each hospitalization were collected in the 2000 and 2005 questionnaires.

Outcome

Hospitalization was the primary outcome. Participants were asked to report reason(s) for hospitalization, date, admitting hospital, and associated procedures/surgeries. Using the ninth revision of the International Classification of Diseases (ICD-9), a trained nosologist coded hospitalization reasons and grouped them into 11 organ systems/categories: infectious, neoplasm, cardiovascular, pulmonary, psychological, neurologic, gastrointestinal, genitourinary, endocrine, obstetric, and external (i.e., accidents, suicides, and poisonings).

Independent Variables

The following socio-demographic variables were considered in the analyses: sex, race/ethnicity, education, health insurance, household income, and attained age at completion of each questionnaire. Cancer-related factors included diagnosis, age at diagnosis, treatment exposures, time from diagnosis, second malignancies or relapse, and chronic health conditions. Chronic health conditions were previously graded according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAEv3.0), which characterizes clinical conditions as grade 1, mild; grade 2, moderate; grade 3, severe; grade 4, life-threatening or disabling; or grade 5, fatal [5].

Statistical Analysis

Hospitalization rates were calculated as hospitalizations per 1,000 person-years. Standardized incidence ratios (SIRs) with corresponding 95% confidence intervals (CIs) and absolute excess risks (AERs) per 1,000 person-years were calculated to compare survivor hospitalization rates to the U.S. population [11]. Each SIR was calculated as the ratio of observed hospitalization rate to expected rate. To obtain expected rates, age- and sex-specific annual U.S. population hospitalization rates were obtained for the years 1992–2005 from the National Hospital Discharge Survey (NHDS) summaries and were weighted according to the age-, sex-, and calendar year-specific person-year distributions from the CCSS cohort. Cause-specific hospitalization SIRs were adjusted for calendar year only, due to limitations in reported cause-specific NHDS hospitalization rates [12].

Sensitivity analysis was performed to assess whether the 637 participants who died during the follow-up period were more likely to have been hospitalized and contribute disproportionally to the overall hospitalization rates observed in the cohort. We assigned to those that died the mean number of hospitalizations by age and cause of death, included the amount of person-time they would have contributed had they lived through the 2005 follow-up and recalculated the SIR. The mean hospitalizations by age and cause of death were determined using data from 1,174 survivors who died before baseline, but for whom a proxy provided the number of hospitalizations in the 2 years prior to death.

To identify cancer-related and demographic risk factors for non-obstetrical hospitalization among CCSS participants, univariable associations were evaluated in generalized linear regression models, with binomial distributions and log links. Independent variables with P values ≤ 0.10 in univariate analysis were included as covariates in a multivariable model. Analyses were performed using SAS software, version 9.1 (SAS Institute, Inc., Cary, NC).

RESULTS

Demographic and cancer-related characteristics of survivors are provided in Table I. From 1992 to 2005, survivor hospitalization rates were 108.5, 177.3, and 142.1 per 1,000 person-years, respectively, for males, females, and combined (Table II). Overall, the survivor hospitalization rate was 1.6 times (95% CI: 1.6; 1.7) that of the general population with an AER of 54.9 hospitalizations per 1,000 person-years. Hodgkin disease survivors had the highest hospitalization rate (188.6 per 1,000 person-years) and over twice the rate of hospitalization compared with the general population (SIR = 2.2, 95% CI: 2.1; 2.3). Increased hospitalization rates were noted irrespective of gender, attained age, cancer diagnosis, and treatment modality. Male and female survivors aged 45–54 were among those with the greatest increase in hospitalization rates and excess risk of hospitalization (Table II).

A sensitivity analysis suggested that missing hospitalization data due to death during follow-up may not be a substantial source of bias. Assuming that those who died had not been hospitalized, the associated SIR was 1.5 (95% CI: 1.5; 1.6) versus the SIR of 1.6 (95% CI: 1.6; 1.7). Assigning the mean number of hospitalizations reported among individuals who died prior to the baseline survey yielded a SIR of 1.8 (95% CI: 1.7; 1.8). Finally, when the mean hospitalizations was assigned without adding additional person-time (presumably the maximum SIR given these data), a SIR of 1.9 (95% CI: 1.8; 1.9) was obtained.

Cause-specific SIRs and hospitalization rates for 8 cancer diagnostic groups are shown in Figure 1. Hodgkin disease survivors had the highest hospitalization rates for neoplastic, endocrine, pulmonary, and cardiovascular causes. They were also

TABLE I. Demographic and Cancer-Related Characteristics of Childhood Cancer Survivors

	Survivors N (%)
Sex	N = 10,366
Male	5,386 (52)
Female	4,980 (48)
Race/ethnicity	
White, non-Hispanic	9,189 (89)
Black, non-Hispanic	378 (4)
Hispanic	479 (5)
Other	299 (3)
Age at 2000 follow-up (years)	
Mean (SD)	28.6 (7.7)
Range	13–51
Age at cancer diagnosis (years)	
Mean (SD)	7.7 (5.8)
Range	0–20
Interval from diagnosis (years)	
Mean (SD)	20.9 (4.6)
Range	13–32
Education	
Lack high school diploma	1,346 (13)
High school graduate	5,637 (55)
College graduate	3,296 (32)
Household income	
<$20,000	1,746 (19)
≥$20,000	7,649 (81)
Health insurance	
No	1,181 (11)
Yes or Canadian	9,064 (87)
Cancer diagnosis	
Leukemia	3,501 (34)
Central nervous system	1,309 (13)
Hodgkin disease	1,344 (13)
Non-Hodgkin lymphoma	792 (8)
Wilms tumor	954 (9)
Neuroblastoma	728 (7)
Soft tissue sarcoma	885 (9)
Bone cancer	854 (8)
Treatment exposure	
Surgery	
Amputation	460 (5)
Other Surgery	7,145 (76)
None	1,842 (20)
Chemotherapy	
Anthracyclines (mg/m^2)	
None	5,728 (62)
0 to <250	1,454 (16)
250+	2,015 (22)
Alkylating agent score[a]	
None	4,670 (52)
1	1,003 (11)
2	1,145 (13)
3	1,338 (15)
4	397 (4)
5	239 (3)
6+	239 (3)
Other chemotherapy	
Bleomycin	512 (5)
Platinum	454 (5)
Radiation	
CRT	3,044 (32)
Chest	1,665 (18)
Other	1,547 (16)
None	3,200 (34)

SD, standard deviation; CRT, cranial radiation therapy. [a]Alkylating agent score calculated according to method of Tucker et al. [31].

10.8 times more likely (95% CI: 9.4; 12.4) to be hospitalized for neoplasm than the U.S. population. Central nervous system (CNS) malignancy survivors had the highest hospitalization rates for neurologic causes and were 22.2 times more likely (95% CI: 19.1; 25.6) to be hospitalized for this reason when compared to the U.S. population.

To identify demographic and cancer-related risk factors among survivors, we studied their association with risk of non-obstetric hospitalization (Table III). The multivariable regression model identified the following characteristics as statistically significant independent risk factors for hospitalization: cancer diagnosis, age less than 4 years at diagnosis, female gender, medical insurance, age 35–54 at 2000 follow-up, household income less than $20,000, and having a chronic health condition, history of relapse/second malignancy, and radiation treatment. While significant in the crude analyses, educational attainment, specific chemotherapy agents, and initial surgery type were not significant predictors of hospitalization in the final multivariable model.

DISCUSSION

These studies quantify hospitalization patterns among childhood cancer survivors. We found significantly increased hospitalization rates among survivors when compared to the U.S. population. Increased hospital utilization among cancer survivors is perhaps not surprising, given the demonstrated prevalence of severe or life-threatening health conditions [6,7]. Thus, while cure is achievable for many children with cancer, the long-term costs associated with cure are becoming increasingly apparent.

Among Hodgkin disease survivors, hospitalization rates for neoplasm, pulmonary, and cardiovascular causes were highest. These findings are consistent with reports demonstrating increased risk for second cancers—particularly breast cancer after chest irradiation—and conditions such as lung fibrosis, cardiomyopathy and coronary artery disease among Hodgkin patients [13–17]. For CNS malignancy survivors, high hospitalization rates for neoplasm and neurologic conditions are, in part, due to the risk for secondary CNS tumors following radiation and elevated risk for stroke and seizures [18–21]. The high admission rates for accidents and injuries observed among this group may be explained by sensorimotor and/or neurocognitive deficits that predisposed these survivors to injury [22–24].

Several socio-demographic factors were associated with increased hospitalization risk. Middle-aged adults had higher risk of hospitalization, reflecting a longer elapsed time since diagnosis, and increased time for late treatment toxicities and age-related disease to occur. Children diagnosed with cancer at less than

TABLE II. Hospitalization Rates by Sex, Attained Age, Diagnosis, and Treatment Type, Compared With U.S. Population[a]

	PY	Hospitalizations	Rate per 1,000 PY	SIR	95% CI	AER per 1,000 PY
All survivors (15–54 years)	65,072	9,249	142.1	1.6	1.6; 1.7	54.9
Men (15–54 years)	33,262	3,610	108.5	2.5	2.4; 2.6	65.5
15–19	5,079	390	76.8	2.5	2.2; 2.7	45.5
20–24	6,895	583	84.6	2.6	2.4; 2.8	52.2
25–34	14,105	1518	107.6	2.6	2.5; 2.7	66.2
35–44	6,399	927	144.9	2.4	2.2; 2.5	83.7
45–54	785	192	244.6	2.6	2.2; 3.0	149.8
Women[b] (15–54 years)	31,810	5,639	177.3	1.3	1.3; 1.4	43.4
15–19	4,926	540	109.6	1.2	1.1; 1.3	16.8
20–24	6,599	955	144.7	0.9	0.9; 1.0	−9.5
25–34	13,052	2,557	195.9	1.2	1.2; 1.3	36.8
35–44	6,385	1,358	212.7	2.2	2.1; 2.3	115.0
45–54	848	229	270.1	2.7	2.4; 3.1	170.8
Cancer diagnosis						
Leukemia	22,313	2,675	119.9	1.4	1.3; 1.4	31.1
CNS	8,069	1,250	154.9	1.8	1.7; 1.9	68.3
Hodgkin disease	8,763	1,653	188.6	2.2	2.1; 2.3	103.0
Non-Hodgkin lymphoma	4,998	626	125.3	1.7	1.6; 1.9	52.1
Wilms tumor	5,688	743	130.6	1.4	1.3; 1.5	37.9
Neuroblastoma	3,992	609	152.6	1.7	1.6; 1.8	63.2
Soft tissue sarcoma	5,525	840	152.0	1.7	1.6; 1.9	64.4
Bone cancer	5,725	853	149.0	1.6	1.5; 1.7	57.1
Treatment exposure						
Surgery						
None	11,764	1,491	126.7	1.2	1.1; 1.3	20.3
Amputation	3,035	411	135.4	1.5	1.4; 1.7	46.0
Other surgery	45,247	6,657	147.1	1.8	1.7; 1.8	64.0
Chemotherapy						
Anthracyclines (mg/m^2)						
None	36,634	5,283	144.2	1.6	1.6; 1.7	55.3
0 to <250	8,912	1,211	135.9	1.6	1.5; 1.7	50.5
250+	12,946	1,848	142.8	1.6	1.6; 1.7	56.1
Alkylator score[c]						
0	29,770	4,083	137.2	1.5	1.5; 1.6	47.0
1	6,297	855	135.8	1.6	1.5; 1.7	50.2
2	7,276	1,017	139.8	1.6	1.5; 1.7	53.6
3	8,581	1,261	146.9	1.7	1.6; 1.8	60.8
4	2,472	356	144.0	1.7	1.6; 1.9	61.4
5	1,532	262	171.0	1.9	1.7; 2.1	80.4
6+	1,543	286	185.3	2.3	2.1; 2.6	105.8
Bleomycin	3,389	600	177.0	2.0	1.8; 2.1	87.8
Platinum	2,660	479	180.1	2.1	1.9; 2.3	93.3
Radiation						
CRT	19,831	2,514	126.8	1.4	1.4; 1.5	38.0
Chest	10,939	1,980	181.0	2.0	1.9; 2.1	92.2
Other	9,855	1,481	150.3	1.7	1.6; 1.8	62.5
None	19,483	2,600	133.5	1.5	1.5; 1.6	46.5

PY, person-years; SIR, standardized incidence ratio; 95% CI, 95% confidence interval; AER, absolute excess risk; CNS, central nervous system; CRT, cranial radiation therapy. [a]Hospitalizations occurring between baseline and 2005 follow-up questionnaire; [b]Includes hospitalizations for obstetric reasons; [c]Alkylating agent score calculated according to method of Tucker et al. [31].

4 years of age had higher risk of hospitalization, perhaps due to greater sensitivity of developing organs to chemotherapy and radiation. For example, very young children have increased risk for cardiomyopathy after anthracycline exposure, and adverse neurocognitive outcomes, obesity and endocrine dysfunction following cranial irradiation [25–28].

Hospitalization risk for survivors with a household income less than $20,000 was 30% greater than for those with incomes $20,000 or above. At both baseline and 2002 follow-up, individuals reporting a household income of less than $20,000 were less likely to have sought medical care within the previous 2 years (86% vs. 91%; $P < 0.0001$). Therefore, less contact with the

TABLE III. Demographic and Treatment-Related Risk Factors for Non-Obstetrical Hospitalization After Childhood Cancer

	RR[a]	95% CI	*P*-value
Sex			
Male	1.0	—	—
Female	1.1	1.0; 1.2	0.09
Cancer diagnosis			
Leukemia	1.0	—	—
Central nervous system	1.4	1.2; 1.7	<0.001
Hodgkin disease	1.7	1.3; 2.1	<0.001
Non-Hodgkin lymphoma	1.1	0.9; 1.5	0.28
Wilms tumor	1.2	0.9; 1.5	0.23
Neuroblastoma	1.2	0.8; 1.6	0.39
Soft tissue sarcoma	1.4	1.1; 1.8	0.003
Bone cancer	1.4	1.1; 1.7	0.01
Age at diagnosis (years)			
0–3	1.0	—	—
4–9	0.7	0.6; 0.9	0.01
10–14	0.9	0.7; 1.0	0.04
15–20	0.7	0.6; 0.8	<0.001
Age at 2000 follow-up (years)			
<20	1.0	—	—
20–24	1.0	0.8; 1.3	0.81
25–34	1.0	0.8; 1.2	0.99
35–44	1.4	1.1; 1.8	0.01
45–54	1.7	1.1; 2.4	0.01
Household income			
≥$20,000	1.0	—	—
<$20,000	1.3	1.1; 1.4	0.001
Health insurance			
No	1.0	—	—
Yes or Canadian	1.4	1.2; 1.7	<0.001
Radiation			
CRT	1.2	1.0; 1.4	0.02
Chest	1.3	1.1; 1.6	0.009
Other	1.3	1.1; 1.5	0.008
None	1.0	—	—
Chronic health condition			
None	1.0	—	—
Any grade 1–2 condition	1.5	1.3; 1.7	<0.001
Any grade 3–4 condition	1.3	1.1; 1.7	0.008
Both grade 1–2 and 3–4 conditions	2.1	1.8; 2.4	<0.001
Second malignancy or relapse			
No	1.0	—	—
Yes	1.7	1.5; 2.0	<0.001

RR, risk ratio; 95% CI, 95% confidence interval; CRT, cranial radiation therapy. [a]RR = 1.0 indicates reference group.

medical system for regular visits or limited financial resources to treat chronic medical conditions may be contributing factors. Similar findings were described in the United Kingdom, where unemployed or low-income survivors were less likely to visit an oncology aftercare clinic for follow-up [29]. Finally, survivors with health insurance were more likely to be hospitalized when compared to those without insurance. Increased hospitalization risk among the insured is not necessarily in conflict with the finding that lower income survivors were more likely to be hospitalized. While lower income individuals may have government-sponsored insurance, they may not have adequate coverage for routine office visits and preventative health measures. Furthermore, despite insurance coverage, they may lack resources (transportation, ability to leave family or workplace) necessary to seek care.

Results from this study should be interpreted keeping in mind several limitations. Medical history and hospitalization information, with the exception of second malignancies, was not validated with medical records. In a study evaluating the validity of self-reported, specific diagnoses resulting in hospitalization, Bergmann et al. [30] reported that true-positive rates varied from 32% for colon polyps to 100% for breast cancer. Therefore, the accuracy of the specific reason(s) for hospitalization and associated procedures in our study may vary with outcome. However, in the same study, Bergmann et al., demonstrated that of the false positive self-reports, 7–20% indicated diagnoses in ''close anatomic proximity'' (i.e., within the same organ system). Thus, the categorization of hospitalization reasons into broad ICD-9 organ systems may potentially improve the accuracy of the reported data.

Participation in both follow-up surveys was high; 80% and 71%, respectively, of all eligible survivors, with 1,811 survivors deceased in the interval following the baseline survey and therefore not eligible for the 2005 survey. However, if survivors' health status influenced the likelihood of participation in CCSS or continued participation beyond the baseline questionnaire, then results may be biased. If survivors with ongoing medical issues were more likely to complete questionnaires, then hospitalization rates might be inflated, while lower estimates might result if participants were healthier than non-participants. If low income survivors were less likely to continue participation, then hospitalization rates may be influenced, though the magnitude and direction of the resulting SIR is unclear, since it is not known whether low income non-participants were more or less likely to have been hospitalized than those who participated. Incomplete participation due to death is also a potential limitation; however our sensitivity analyses suggest that survival bias is small. Cause-specific hospitalization rate comparisons were unadjusted for any differences between the CCSS cohort and the NHDS population with regard to age or sex. As the CCSS cohort is composed of mainly younger individuals as compared to the NHDS population, cause-specific SIRs may represent low estimates.

Finally, these results reflect outcomes for individuals treated for childhood cancer in the 1970s and 1980s. Evolving treatment strategies may not only increase the number of childhood cancer survivors, but may also change the spectrum and incidence of treatment toxicities. However, a sizable proportion of the estimated 325,000 childhood cancer survivors in the U.S. were treated two or more decades ago [1]. This analysis provides a first look at what the potential excess rate of hospitalization may be as this population ages.

In summary, findings of this study indicate that the significant morbidity experienced by many childhood cancer survivors is reflected in higher hospitalization rates. Measures aimed at primary prevention, and those targeting aggressive management of medical issues to prevent development or progression of disease, are critical to reducing hospitalization risk. Further research is needed to fully describe heath care utilization and the economic impact of treatment-related complications in this population.

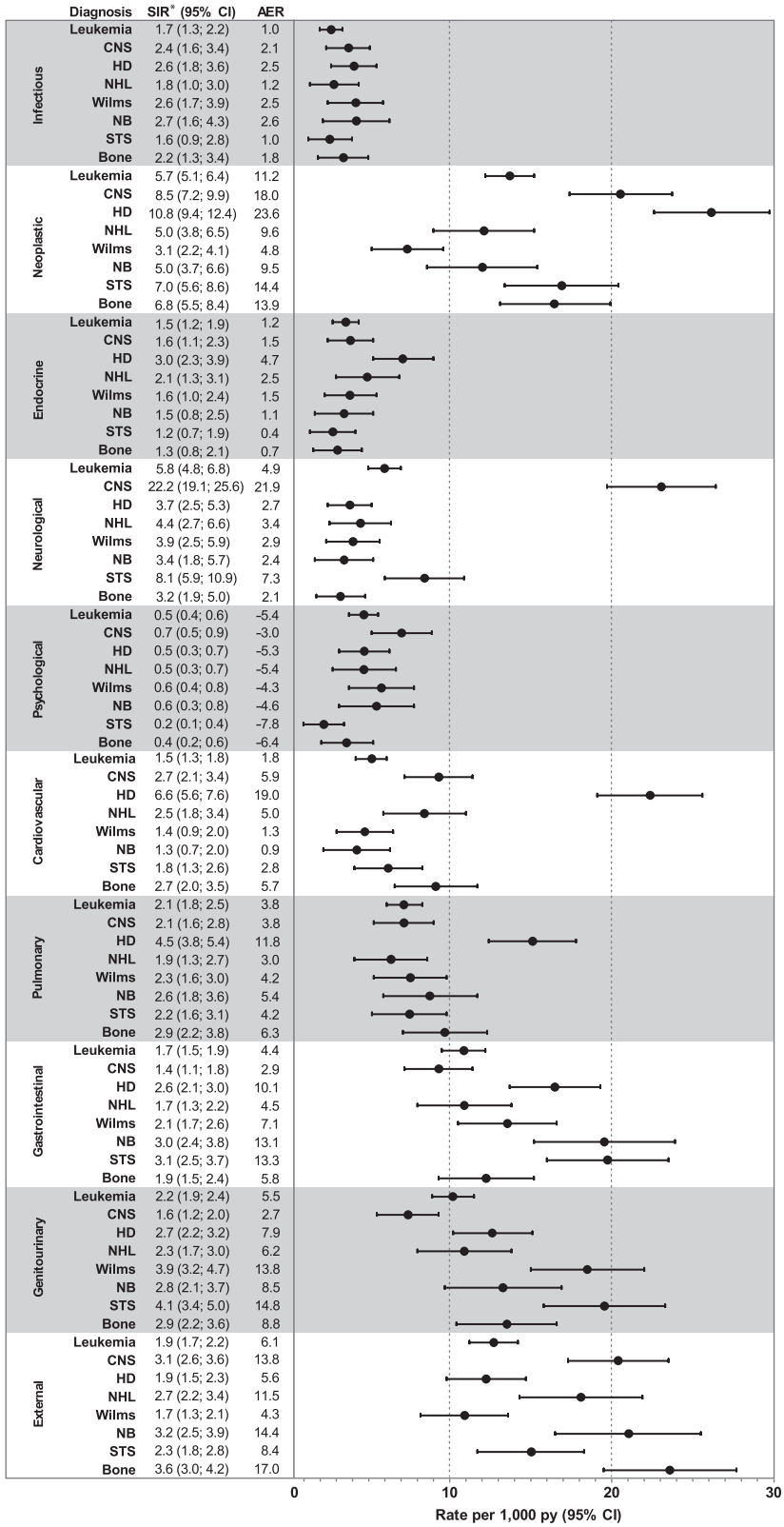

Fig. 1. Cause-specific SIRs, AERs and hospitalization rates by organ system and cancer diagnosis[a]. SIR, standardized incidence ratio; 95% CI, 95% confidence interval; AER, absolute excess risk; CNS, central nervous system tumor; HD, Hodgkin disease; NHL, non-Hodgkin lymphoma; NB, neuroblastoma; STS, soft tissue sarcoma. [a]Compared with U.S. cause-specific rate. Obstetric hospitalizations are not included. Rates are presented as hospitalizations per 1,000 person-years with error bars representing the 95% confidence interval.

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