Original Article

Infections Among Long-Term Survivors of Childhood and Adolescent Cancer

A Report From the Childhood Cancer Survivor Study

Joanna L. Perkins, MD, MS[1]; Yan Chen, MMath[2]; Anne Harris, MPH[1]; Lisa Diller, MD[3]; Marilyn Stovall, MPH, PhD[4]; Gregory T. Armstrong, MD, MSCE[5]; Yutaka Yasui, PhD[2]; Leslie L. Robison, PhD[5]; and Charles A. Sklar, MD[6]; on behalf of the Childhood Cancer Survivor Study

BACKGROUND: Little is known about infections among adult survivors of childhood cancer. The authors report the occurrence of infections and risk factors for infections in a large cohort of survivors of childhood cancer. **METHODS:** The Childhood Cancer Survivor Study cohort was used to compare incidence rates of infections among 12,360 5-year survivors of childhood cancer with the rates of 4023 siblings. Infection-related mortality of survivors was compared with that of the US population. Demographic and treatment variables were analyzed using Poisson regression to determine the rate ratios (RRs) and corresponding 95% confidence intervals (CIs) for associations with infectious complications. **RESULTS:** Compared with the US population, survivors were at an increased risk of death from infectious causes (standardized mortality ratio [SMR], 4.2; 95% CI, 3.2-5.4), with the greatest risk observed among females (SMR, 3.2; 95% CI, 1.5-6.9) and among those who had been exposed to total body irradiation (SMR, 7.8; 95% CI, 1.8-33.0). Survivors also reported higher rates than siblings of overall infectious complications (RR, 1.3; 95% CI, 1.2-1.4) and higher rates of all categories of infection. **CONCLUSIONS:** Survivors of childhood cancer remain at elevated risk for developing infectious-related complications, and they have a higher risk of infection-related mortality years after therapy. Further investigation is needed to provide insight into the mechanisms for the observed excess risks. ***Cancer*** **2014;120:2514-21.** *© 2014 American Cancer Society.*

KEYWORDS: childhood cancer, adolescent cancer, late effects, infections, survivorship.

INTRODUCTION

Children with cancer have immune dysfunction as result of their underlying disease, as with lymphoid malignancies, or because of their exposure to chemotherapy.[1-4] A decreased number of T-lymphocytes is an important factor in immunodeficiency during maintenance chemotherapy.[5,6] However, which other components of the immune system are affected and to what degree and duration are unclear.

Infectious complications remain the most important cause of late morbidity and mortality in survivors after hematopoietic cell transplantation (HCT).[7] It is widely accepted that reimmunization is necessary, and many guidelines have been published.[8] However, for those children who receive treatment that does not include HCT, the risk of late infections and the potential need for reimmunization are poorly understood.

Previous studies have demonstrated that, by 6 months after therapy, most patients have recovered immune function, although some patients remain abnormal years later.[9-12] T-lymphocytes may be persistently low, with associated impaired protection against infection.[13,14] Survivors reportedly have lower numbers of lymphocyte subsets than their siblings. Patients who receive the most intensive treatments may require testing and immunizations beyond 6 months off therapy (unpublished data).[14-17]

Data from the Childhood Cancer Survivor Study (CCSS) have demonstrated that long-term survivors experience excess mortality from infectious diseases.[18] The CCSS reported that survivors were 1.6 to 2.7 times more likely to be hospitalized for infection compared with age-matched and sex-matched individuals in the general population.[19] The

Corresponding author: Joanna L. Perkins, MD, MS, Children's Hospitals and Clinics of Minnesota, 2530 Chicago Avenue S., CSC-175, Minneapolis, MN 55404; Fax: (612) 813-6325; joanna.perkins@chindrensmn.org

[1]Pediatric Hematology/Oncology, Children's Hospitals and Clinics of Minnesota, Minneapolis, Minnesota; [2]Biostatistics, University of Alberta, Calgary, Alberta, Canada; [3]Pediatrics, Dana Farber Cancer Institute/Children's Hospital, Boston, Massachusetts; [4]Radiaton Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas; [5]Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, Tennessee; [6]Department of Pediatrics, Memorial Sloan Kettering Cancer Center, New York, New York

DOI: 10.1002/cncr.28763, **Received:** December 12, 2013; **Revised:** February 21, 2014; **Accepted:** February 25, 2014, **Published online** May 13, 2014 in Wiley Online Library (wileyonlinelibrary.com)

Canadian Childhood, Adolescent, Young Adult Cancer Survivors Study (CAYACS) similarly reported infections as 1 of the most common causes of hospitalization and late morbidity.[20]

The current study was designed to investigate the incidence of and risk factors for infection-related disease and mortality in survivors of childhood cancer. To our knowledge, this represents the largest most comprehensive investigation of this issue to date.

MATERIALS AND METHODS

Inclusion Criteria

The detailed methods of the CCSS cohort have been published previously.[21-23] In brief, the CCSS is a collaborative, multi-institutional project funded by the National Cancer Institute (grant CA55727) and includes individuals who survived ≥5 years after a childhood cancer diagnosis (available at: http://ccss.stjude.org; accessed December 12, 2013). The CCSS is a retrospectively ascertained cohort of 20,346 childhood cancer survivors and a control group of approximately 4000 siblings of survivors. The study includes 26 participating clinical research centers in the United States and Canada who identified eligible patients with: 1) a diagnosis of leukemia, central nervous system (CNS) malignancy (excluding meningioma and craniopharyngioma), Hodgkin lymphoma or non-Hodgkin lymphoma, neuroblastoma, soft tissue or bone sarcoma, or kidney cancer; 2) a diagnosis date between January 1, 1970 and December 31, 1986; 3) age <21 years at diagnosis; and 4) alive 5 years from the date of diagnosis. The control group includes nearest aged siblings from a random sample of survivors.

Data Collection

The CCSS protocol was reviewed and approved by the human subjects committee at each institution. Data were collected using questionnaires administered in 1994, 2000, 2003, and 2007. A surrogate (typically a parent or spouse) was contacted for those eligible patients who died after achieving 5-year survivorship. The questionnaires addressed social and demographic information, medical conditions, health behaviors, cancer recurrences, the development of subsequent neoplasms, and family history. Data collection surveys are available for review online at http://ccss.stjude.org/documents/questionnaires (Accessed December 12, 2013).

For all CCSS participants who signed a medical release, detailed summaries of exposure to chemotherapy, radiation therapy (RT), and surgery were abstracted from medical records by trained abstracters. Information was abstracted regarding exposure to 49 specific chemotherapy agents, including the cumulative dose for 26 patients. RT data were coordinated through the Department of Radiation Physics at The University of Texas MD Anderson Cancer Center.[21]

Of the 14,358 eligible 5-year survivors who completed the baseline questionnaire, 12,360 survivors were included in the current study after the exclusion of those survivors who developed a subsequent malignant neoplasm or received any cancer-related treatment within 12 months before entering the study cohort. The sibling cohort, which consisted of 4023 siblings who completed the baseline questionnaire, was used for comparison.

Infectious complications were defined by self-report of sinopulmonary infection (bronchitis, sinusitis, tonsillitis, pleurisy, chronic cough, pneumonia), gastrointestinal (GI) infection (hepatitis, and colitis), genitourinary (GU) infection (kidney or bladder infection), and chronic gingivitis. The date of infectious complication was defined as the date of first occurrence. The infectious complication must have occurred at least 5 years after the original cancer diagnosis for incidence analysis or any time after the original cancer diagnosis for cumulative incidence analysis. All patients who had infectious complications reported in or before the 2007 follow-up questionnaire were included. Infection-related mortality was determined from reviewing International Classification of Diseases codes (9th and 10th revisions) associated with death certificates.

Statistical Analysis

Demographic and clinical characteristics (survivors and siblings: sex, race, and age; survivors only: cancer diagnosis, age at diagnosis, and treatment factors) were tabulated separately (Table 1). In analyzing the occurrence of infection-related complications, death, late relapse (5 years past diagnosis), and subsequent malignant neoplasms were treated as competing-risk events, because these would change the rates of infection-related events, and complete information on all relapses and subsequent malignant neoplasms was unavailable.

To describe infectious complications, cumulative incidences individually and combined were calculated for sinopulmonary infections, GI and GU infections, and gingivitis. Infectious complications that occurred within 5 years from cancer diagnosis were included as prevalent cases at the study-cohort entry.

Our rate analysis included: 1) an analysis at study-cohort entry of developing an infection-related complication within 5 years from the cancer diagnosis (prevalence analysis at the study-cohort entry); and 2) an analysis of

TABLE 1. Characteristics of Study Population

Characteristic	Survivors, N = 12,360		Siblings, N = 4023	
Sex	No.	%	No.	%
Male	6564	53.1	1937	48.1
Female	5796	46.9	2086	51.9
Race				
White	10634	86	3509	87.2
Black	637	5.2	112	2.8
Hispanic	650	5.3	148	3.7
Other/missing	439	3.6	254	6.3
Age at latest questionnaire, y				
<20	1058	8.6	267	6.6
20-29	3932	31.8	1134	28.2
30-39	4632	37.5	1392	34.6
≥40	2738	22.2	1230	30.6
Cancer diagnosis				
Acute lymphoblastic leukemia	3279	26.5		
Hodgkin lymphoma	1733	14		
Kidney tumors	1200	9.7		
Soft tissue sarcoma	1135	9.2		
Astrocytomas	1087	8.8		
Non-Hodgkin lymphoma	1001	8.1		
Neuroblastoma	889	7.2		
Osteosarcoma	647	5.2		
Medulloblastoma, PNET	338	2.7		
Ewing sarcoma	324	2.6		
Acute myelogenous leukemia	290	2.3		
Other CNS tumors	283	2.3		
Other leukemia	105	0.8		
Other bone tumors	49	0.4		
Age at diagnosis, y				
<1	932	7.5		
1-3	3059	24.7		
4-7	2713	21.9		
8-10	1331	10.8		
11-14	2131	17.2		
15-20	2194	17.8		
Splenectomy				
Yes	1091	8.8		
No	9482	76.7		
Not available[a]	1787	14.5		
Abdominal RT				
Yes	2685	21.7		
No	7999	64.7		
Not available[a]	1676	13.6		
Chest RT				
Yes	2781	22.5		
No	7903	63.9		
Not available[a]	1676	13.6		
Total body irradiation				
Yes	137	1.1		
No	10547	85.3		
Not available[a]	1676	13.6		
Chemotherapy				
Yes	8180	66.2		
No	2405	19.5		
Not available[a]	1775	14.4		
Steroids				
Yes	4726	38.2		
No	5859	47.4		
Not available[a]	1775	14.4		

Abbreviations: CNS, central nervous system; PNET, primitive neuroectodermal tumor; RT, radiation therapy.
[a] Either participants did not provide permission for release of treatment information or the information was missing.

developing an infection-related complication from study-cohort entry (incidence analysis after study-cohort entry). The incidence analysis was not tenable for the period from cancer diagnosis to study-cohort entry, because the survivors had to survive for 5 years to enter the cohort. For the prevalence analysis, the prevalence ratios comparing survivors with siblings were estimated individually for all of the specific infectious categories. For the incidence analysis, incidence rates were estimated by dividing the observed counts of incident cases by the person-years at risk, starting at 5 years postcancer diagnosis, to the earliest of the specific infection-related complication of interest, the end of follow-up, or any of the competing-risk events. The relative rates comparing survivors with siblings were calculated using Poisson regression, adjusting for age during follow-up (time-dependent), sex, and race. Potential within-family correlation was accounted for by using the generalized estimating equation.[24]

Among survivors, multivariable regression analyses were performed to evaluate effects of demographic and treatment variables on sinopulmonary infection, GI and GU infection, and gingivitis, both individually and combined, with covariates (sex, cancer diagnosis, age at diagnosis, splenectomy, abdominal RT, chest RT, total body irradiation [TBI], chemotherapy and steroids) included by backward selection. The analysis of prevalence was performed using log-binomial regression adjusting for age at the time of study-cohort entry. For the incidence analysis, we used Poisson regression adjusting for age during follow-up (time-dependent).

Multivariable Poisson regression also was performed to evaluate the effects of demographic and treatment variables on infection-related standardized mortality ratios (SMRs) using age-specific, sex-specific, and calendar year-specific US population rates (available at: http://www.cdc.gov/; accessed December 12, 2013) and using the method of covariate selection described above.

For missing dates of self-reported infections, we used the multiple imputation method proposed by Taylor et al[25] to impute the missing times of disease onset. For each of the 10 types of infections, we used all potential covariates in the regression analyses to impute the missing time of the onset of the reported infectious event. Ten multiply imputed data sets were analyzed and summarized using the standard method for combining multiple imputations.[26]

RESULTS

The characteristics of the study population are listed in Table 1. Approximately 53% of survivors were male (vs

TABLE 2. Incidence Rates of Infectious Complications

Infectious Complications	No. With Reported Outcome		From Cancer Diagnosis to 5 Years		≥5 Years After Cancer Diagnosis		
	Survivors, N = 12,360	Siblings, N = 4023	No.	Prevalence Ratio (95% CI)	No.	Rate (95% CI)[a]	Rate Ratio (95% CI)[b]
Sinopulmonary infection							
Bronchitis	2953	1201	1037	1.4 (1.3-1.5)	1916	14.3 (13.7-15.0)	1.4 (1.3-1.5)
Sinusitis	2509	760	836	2.0 (1.8-2.2)	1673	11.8 (11.2-12.3)	1.8 (1.6-1.9)
Tonsillitis	1789	1151	807	0.8 (0.8-0.9)	982	7.3 (6.9-7.8)	1.1 (1.0-1.2)
Pleurisy	414	119	104	2.8 (2.0-3.9)	310	1.8 (1.6-2.1)	1.4 (1.1-1.7)
Chronic cough	1327	273	436	4.0 (3.3-4.9)	891	4.3 (4.0-4.6)	2.0 (1.8-2.3)
Pneumonia	369	43	144	9.5 (5.8-15.5)	225	1.0 (0.9-1.2)	3.7 (2.6-5.3)
Any event	4804	2179	2118	1.3 (1.2-1.4)	2686	22.7 (21.8-23.6)	1.3 (1.2-1.4)
More than 1 event	2860	941	888	1.7 (1.5-1.9)	1972	11.1 (10.6-11.6)	1.5 (1.4-1.7)
Gastrointestinal infection							
Hepatitis	576	78	252	6.5 (4.8-9.0)	324	1.5 (1.3-1.7)	2.5 (2.0-3.3)
Colitis	130	53	29	1.1 (0.7-1.9)	101	0.8 (0.7-1.0)	1.2 (0.9-1.7)
Any event	696	129	277	4.6 (3.5-5.9)	419	2.0 (1.8-2.2)	1.9 (1.5-2.3)
More than 1 event	11	2	4	3.3 (0.6-17.6)	7	0.0 (0.0-0.1)	2.0 (0.4-10.6)
Genitourinary infection							
Kidney or bladder infection	1278	502	398	1.4 (1.2-1.6)	880	4.6 (4.3-4.9)	1.2 (1.1-1.4)
Chronic gingivitis	664	196	72	2.0 (1.3-3.0)	592	4.1 (3.8-4.5)	1.6 (1.4-1.9)
Any of the above infections	5578	2436	2470	1.4 (1.3-1.4)	3108	28.8 (27.7-29.8)	1.3 (1.2-1.4)

Abbreviations: CI, confidence interval.
[a] This is the rate per 1000 person-years.
[b] The rate ratio is the rate relative to the sibling cohort adjusted for sex, age, and race.

48% of siblings), 86% were Caucasian (vs 87% of siblings), and 22% were aged >40 years at time of last follow-up (vs 31% of siblings). Of the survivors, 27% had a history of acute lymphoblastic leukemia (ALL), and 65% were aged ≤10 years at diagnosis. With regard to treatment history, 66% of survivors had a history of exposure to chemotherapy, 38% had received steroid therapy, 23% had received chest radiation, 22% had received abdominal radiation, 9% had undergone splenectomy, and 1% had received TBI.

Incidence rates of infections are listed in Table 2. Compared with siblings and after adjusting for sex, age, and race, there was a statistically significantly higher rate of infections among survivors (rate ratio [RR], 1.3; 95% CI, 1.2-1.4). Survivors reported higher rates of all categories of infection, most notably pneumonia (RR, 3.7; 95% CI, 2.6-5.3), hepatitis (RR, 2.5; 95% CI, 2.0-3.3), and sinusitis (RR, 1.8; 95% CI, 1.6-1.9).

The results from multivariable analyses of demographic and cancer treatment factors associated with infectious complications are provided in Table 3. The factors associated with higher rates of overall late infectious complications included female sex (RR, 1.7; 95% CI, 1.6-1.8), a diagnosis of Hodgkin lymphoma (RR, 1.3; 95% CI, 1.2-1.6), and older age at cancer diagnosis (using ages 15-20 years as the referent group: aged <1 year [RR, 0.6; 95% CI, 0.5-0.8], ages 1-3 years [RR, 0.6; 95% CI, 0.5-0.8], and ages 4-7 years [RR, 0.8; 95% CI, 0.6-0.9]). Patients who reported being current tobacco smokers (RR, 1.4; 95% CI, 1.2-1.5) or former tobacco smokers (RR, 1.3; 95% CI, 1.1-1.5) had elevated rates of sinopulmonary infection compared with those who reported having never smoked.

A history of TBI or chemotherapy was significantly associated with increased rates of late GI infections. Survivors who had received steroids had an increased rate of chronic gingivitis (RR, 1.3; 95% CI, 1.1-1.6). No other treatment variables, including splenectomy, abdominal radiation, or chest radiation, were associated with a statistically significant increase in late infections. There was no significant difference in patterns of late infections or their associations with various risk factors when the survivors who underwent bone marrow transplantation were removed from the analysis.

Cancer diagnosis and demographic factors were independently associated with an increased incidence for many of the specific categories of late infections investigated (Table 3). By using childhood ALL as the referent population, increased risks for sinopulmonary infection were present in survivors of Hodgkin lymphoma, non-Hodgkin lymphoma, kidney tumors, and Ewing sarcoma. Increased risks of GU infections were present for survivors of non-ALL/AML leukemia, non-Hodgkin lymphoma, kidney tumors, and soft-tissue sarcomas. Conversely,

TABLE 3. Multivariable Analysis of Infection-Related Complications by Demographic and Treatment Factors

	Sinopulmonary Infection		Gastrointestinal Infection		Genitourinary Infection		Gingivitis		Any Infection	
Variable	PR (95% CI)	RR (95% CI)	PR (95% CI)	RR (95%CI)	PR (95% CI)	RR (95% CI)	PR (95% CI)	RR (95% CI)	PR (95% CI)	RR (95% CI)
Sex										
Male [Ref]										
Female	1.2 (1.1-1.4)[a]	1.8 (1.6-1.9)[a]	1.4 (1.0-1.8)[a]		4.3 (3.3-5.8)[a]	6.7 (5.5-8.1)[a]		1.2 (1.0-1.4)	1.3 (1.2-1.4)[a]	1.7 (1.6-1.8)[a]
Smoking										
Current	1.1 (0.9-1.2)	1.4 (1.2-1.5)[a]								
Former	0.9 (0.8-1.1)	1.3 (1.1-1.5)[a]								
Never										
Cancer diagnosis										
ALL [Ref]										
AML	1.1 (0.9-1.5)	1.2 (0.9-1.7)	2.4 (1.6-3.5)[a]	1.6 (0.9-2.6)	0.8 (0.2-2.4)	1.0 (0.6-1.7)	1.1 (0.2-8.2)		1.3 (1.0-1.6)[a]	1.1 (0.9-1.5)
Other leukemia	0.9 (0.5-1.4)	1.0 (0.6-1.8)	0.2 (0.0-1.7)	1.3 (0.5-3.1)	1.1 (0.3-4.1)	2.1 (1.1-4.2)[a]	5.6 (1.3-24.0)[a]		0.8 (0.5-1.3)	1.4 (1.0-2.0)
Astrocytomas	0.8 (0.7-1.1)	0.9 (0.7-1.1)	0.2 (0.1-0.6)[a]	0.4 (0.2-0.9)[a]	3.3 (1.9-5.5)[a]	1.1 (0.8-1.4)	4.7 (1.6-14.0)[a]		0.9 (0.7-1.1)	0.8 (0.7-1.0)[a]
Medulloblastoma, PNET	0.8 (0.5-1.1)	0.9 (0.6-1.2)	0.1 (0.0-0.6)[a]	0.5 (0.2-1.2)	0.9 (0.3-3.0)	0.6 (0.3-1.2)	3.1 (0.6-15.6)		0.8 (0.6-1.0)	0.9 (0.7-1.2)
Other CNS tumors	0.9 (0.6-1.3)	0.7 (0.5-1.1)	0.0 (0.0-0.2)[a]	0.9 (0.4-2.0)	2.4 (1.0-5.4)[a]	1.0 (0.6-1.8)	7.4 (1.9-28.6)[a]		0.8 (0.6-1.2)	0.8 (0.6-1.0)
Hodgkin lymphoma	1.2 (0.9-1.5)	1.6 (1.3-1.9)[a]	0.2 (0.1-0.4)[a]	0.5 (0.3-0.7)[a]	1.0 (0.6-1.8)	1.2 (0.9-1.5)	0.9 (0.3-2.5)		1.0 (0.8-1.2)	1.3 (1.2-1.6)[a]
NHL	1.2 (1.0-1.4)	1.3 (1.1-1.6)[a]	0.5 (0.3-0.8)[a]	0.5 (0.3-0.8)[a]	2.3 (1.4-4.0)[a]	1.4 (1.0-1.9)[a]	0.8 (0.2-3.8)		1.1 (0.9-1.3)	1.2 (1.0-1.4)[a]
Kidney tumors	0.9 (0.7-1.1)	1.2 (1.0-1.4)[a]	0.4 (0.2-0.7)[a]	0.6 (0.4-1.0)[a]	2.2 (1.4-3.4)[a]	1.9 (1.5-2.4)[a]	0.4 (0.1-3.1)		0.9 (0.8-1.1)	1.1 (1.0-1.3)[a]
Neuroblastoma	1.0 (0.8-1.2)	1.2 (1.0-1.5)	0.2 (0.1-0.6)[a]	0.6 (0.3-1.1)	3.1 (1.9-5.2)[a]	1.4 (1.0-1.9)	0.0 (0.0-2.5)		1.0 (0.8-1.2)	1.1 (0.9-1.3)
Soft tissue sarcoma	1.0 (0.8-1.1)	1.0 (0.8-1.2)	0.4 (0.2-0.6)[a]	0.7 (0.5-1.1)	4.1 (2.7-6.3)[a]	1.8 (1.4-2.2)[a]	3.1 (1.4-7.2)[a]		1.1 (0.9-1.2)	1.1 (0.9-1.3)
Ewing sarcoma	0.9 (0.6-1.2)	1.5 (1.1-2.0)[a]	0.3 (0.1-0.7)[a]	0.6 (0.3-1.2)	2.6 (1.3-5.0)[a]	1.1 (0.6-1.8)	1.3 (0.3-6.5)		0.9 (0.7-1.2)	1.3 (1.0-1.6)
Osteosarcoma	0.8 (0.6-1.0)	1.2 (0.9-1.6)	0.4 (0.2-0.8)[a]	0.9 (0.6-1.5)	1.6 (0.7-3.4)	1.1 (0.7-1.6)	1.0 (0.2-4.6)		0.7 (0.6-1.0)[a]	1.1 (0.9-1.4)
Other sarcoma	1.0 (0.4-2.6)	0.6 (0.2-1.9)	0.0 (0.0-1.1)	1.2 (0.3-5.3)	0.0 (0.0-3.0)	1.5 (0.5-4.2)	0.0 (0.0-12.3)		0.9 (0.4-2.1)	0.7 (0.3-1.6)
Age at diagnosis, y										
<1		0.5 (0.4-0.6)[a]		0.5 (0.2-0.9)[a]		0.7 (0.5-1.0)		1.7 (1.0-2.8)[a]		0.6 (0.5-0.8)[a]
1-3		0.5 (0.4-0.6)[a]		0.5 (0.3-0.8)[a]		0.6 (0.4-0.8)[a]		1.8 (1.3-2.6)[a]		0.6 (0.5-0.8)[a]
4-7		0.6 (0.5-0.7)[a]		0.5 (0.3-0.7)[a]		0.7 (0.5-0.9)[a]		1.6 (1.2-2.2)[a]		0.8 (0.6-0.9)[a]
8-10		0.8 (0.6-1.0)[a]		0.7 (0.5-1.1)		0.7 (0.5-1.0)[a]		1.4 (1.0-2.0)[a]		0.8 (0.7-1.0)
11-14		0.8 (0.7-1.0)		0.6 (0.4-0.9)[a]		0.9 (0.7-1.1)		1.4 (1.1-1.9)[a]		1.0 (0.8-1.1)
15-20										
Splenectomy										
Yes										
No [Ref]										
Abdominal RT										
Yes	0.8 (0.7-1.0)[a]		1.6 (1.2-2.1)[a]		1.5 (1.1-2.0)[a]					
No [Ref]										
Chest RT										
Yes	1.1 (1.0-1.3)									
No [Ref]										
Total body irradiation										
Yes	1.5 (1.1-2.2)[a]			2.1 (1.1-4.0)[a]					1.4 (1.1-1.8)[a]	
No [Ref]										
Chemotherapy										
Yes	1.2 (1.0-1.4)		1.9 (0.9-3.8)	1.7 (1.1-2.5)[a]	1.5 (1.1-2.1)[a]		2.7 (1.2-6.5)[a]		1.2 (1.1-1.4)[a]	
No [Ref]										
Steroids										
Yes								1.3 (1.1-1.6)[a]		
No [Ref]										

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; NHL, non-Hodgkin lymphoma; PR, prevalence ratio (the prevalence events that were present before cohort entry; [Ref], reference category; RR, rate ratio (the incidence of events that occurred after entry into the cohort); RT, radiation therapy.

[a] $P < .05$.

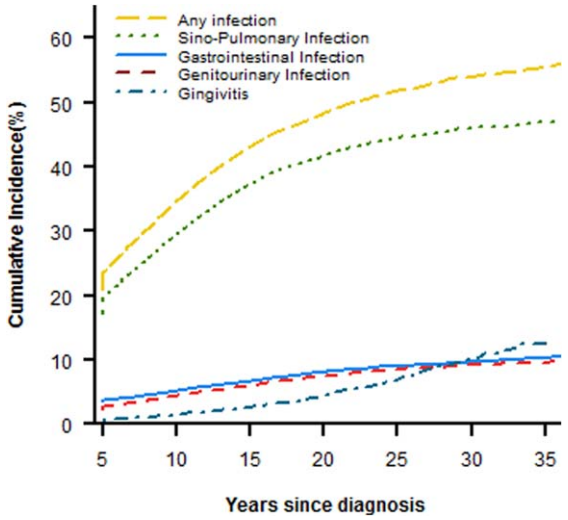

Figure 1. Cumulative incidence of infectious complications.

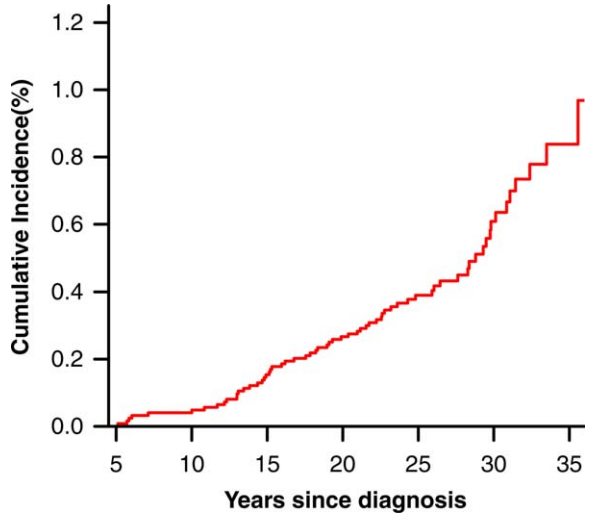

Figure 2. Cumulative incidence of infectious-related mortality.

survivors of childhood ALL had significantly higher infection rates than survivors of astrocytoma (sinopulmonary and GI infections), Hodgkin lymphoma (GI infections), non-Hodgkin lymphoma (GI infections), and kidney tumors (GI infections). Increased risks were observed for females ex (sinopulmonary infections, GU infections, and gingivitis) and for patients who were ages 15 to 20 years at cancer diagnosis (sinopulmonary, GI, and GU infections).

The cumulative incidence of infection-related complications is illustrated according to the category of infection and infectious-related mortality in Figures 1 and 2, respectively. Compared with the US population, survivors had an overall increased rate of death from infectious causes (SMR, 4.2; 95% CI, 3.2-5.4), with females (SMR, 3.2; 95% CI, 1.5-6.9) and those exposed to TBI (SMR, 7.8; 95% CI, 1.8-33.0) having the highest mortality. Among the 65 deaths that were attributed to an infectious cause, 25% were caused by pneumonia, 17% were caused by septicemia, 12% were caused by human immunodeficiency virus-associated infections, 9% were caused by bacterial endocarditis, and 37% were caused by miscellaneous other causes (eg, GI infections, encephalitis, etc).

DISCUSSION

To our knowledge, the current study is the largest to date exploring late infectious complications in childhood cancer survivors. In our cohort, nearly 33% of survivors reported infectious complications >5 years after diagnosis. Twenty-two percent of survivors reported late sinopulmonary infections, including 16% with multiple recurrences. Other types of infection were less common, although not inconsequential (GU infections, 7%; GI infections, 3%; chronic gingivitis, 5%). For all categories of late infections, survivors had a significantly higher rate compared with siblings.

In the multivariable analysis, survivors of Hodgkin and non-Hodgkin lymphoma had the highest significant risk of late overall infections. Survivors of all other disease categories, except for survivors of CNS cancer, were at a higher risk for at least 1 type of infection compared with survivors of ALL. Many of those who had CNS tumors had undergone surgery alone, which in part may explain this group's lower rates of infections.

Survivors of childhood AML are a group purported to be at greater risk for late infections because of potential long-term immune deficiencies.[27] In the current investigation, although there was suggestion of a modestly higher risk of infections in survivors of AML, these differences were not statistically significant.

With regard to the risk of infectious complications by treatment, functional (ie, radiation-induced) or anatomic (ie, surgical splenectomy) asplenia predisposes childhood cancer survivors to a lifelong risk of sepsis.[28] In our current multivariable analysis, asplenia was not associated with an increased risk of late infectious complications. This may be because of the institution of preventative measures in asplenic survivors, such as immunizations and prophylactic antibiotics. However, abdominal radiation was associated with higher risk of infection. Because the degree of functional asplenia sustained in these survivors is less defined than that in

splenectomy, they may not be receiving the same level of preventative care.

Infectious complications remain the leading cause of late morbidity and mortality in survivors of HCT.[7,8] In the current evaluation, we observed that HCT survivors who had received TBI were at higher risk for late GI infections and infectious-related mortality than those without a history of TBI. The overall numbers of TBI-exposed survivors in this cohort are relatively small, and information on graft-versus-host-disease is unknown, so it is possible that other potential differences were not evident. Other than an elevated incidence of chronic gingivitis in survivors who received steroid therapy, no other individual treatment variable was associated with an increased risk for late infectious complications.

In this investigation, female survivors had a significantly higher rate of late infections, particularly GU infections, with nearly 7 times the relative rate of that observed in males. Females also had a greater than 3-fold higher rate of death from infections. The reasons for these sex differences are unclear and require further study.

Older age at cancer diagnosis was associated with a higher incidence of late infections, except for gingivitis. It is possible that immune reconstitution after chemotherapy is more robust in younger children whose immune repertoire is still developing.

From a prevention standpoint, other than for survivors with a history of HCT, there are no standard guidelines for reimmunizing or testing titers. There are also no widely accepted guidelines for prophylactic immunizations other than encapsulated organism vaccines for asplenic patients. There is also ongoing debate regarding the use of prophylactic antibiotics for asplenic patients.[28,29] The Working Party of the British Committee for Standards in Clinic Hematology Task Force recommends lifelong antibiotics,[30] the American Academy of Pediatrics recommends antibiotics until age 5 years,[31] and the Children's Oncology Group Survivorship Guidelines recommend consideration of antibiotics.[32] Better defined guidelines for reimmunization, prophylactic immunization, and antibiotic use are needed.

The strengths of this study include the large number of survivors who were followed into adulthood, the availability of detailed treatment information, and our use of a sibling comparison group. However, several limitations need to be considered when interpreting the results. First, relying on self-reported data could result in both over-reporting and under-reporting of certain outcomes and, thus, either differential or nondifferential misclassification. Cancer survivors may have a heightened level of awareness of symptoms of illness as a result of their cancer experience, including higher rates of anxiety, depression, or somatization, which could result in reporting bias compared with siblings. However, the significantly increased risks of infections observed in the current study remained significant when we restricted the analyses to survivors without significant emotional distress (as assessed using the Behavioral Symptoms Inventory-18). Furthermore, in the current study, we relied on self-reported data; thus, we were not able to accurately ascertain the severity of infection, eg whether it was a mild illness involving sinus congestion versus severe sinusitis requiring parenteral antibiotics. However, we are unaware of data suggesting whether variability in symptom definition and/or reporting according to symptom severity would differ between patients and siblings or across subgroups of survivors.

To determine infection-related mortality, we used death certificates, which may be associated with some degree of nondifferential misclassification. Although current therapy for the majority of pediatric cancer patients includes the same agents used for the CCSS cohort,[33,34] treatment protocols change over time, using less or more intensive regimens. Thus, results from the current study may not be applicable to individuals who are treated on more contemporary protocols. The CCSS is currently undergoing expansion to include those patients diagnosed between 1987 and 1999. Future analyses will be necessary to compare the current results with more modern treatment regimens to determine whether, for example, with the elimination of routine splenectomy and decreased radiation doses, a lower incidence of infectious complications is observed.

In conclusion, long-term survivors of childhood cancer are at an increased risk of infections and infectious-related mortality, and this risk continues to increase with time from diagnosis. Females, those who receive treatment for Hodgkin and non-Hodgkin lymphoma, and aged >15 years at diagnosis appear to be at highest risk. Females and those who received TBI are at the greatest risk of infectious-related mortality. Longitudinal assessment of immunologic function of survivors of childhood cancer may provide further insight into the prevalence and pathogenesis of abnormal immunologic parameters that may place survivors at increased risk for infection. Given the observed excess risk of infection-related mortality, survivors and their clinical care providers should be aware of the need for appropriate immunizations and prompt care for suspected infection.

FUNDING SUPPORT

This work was supported by grant U24 CA55727 (to L.L.R.) from the National Cancer Institute, with additional support provided by the St. Jude Children's Research Hospital Cancer Center Support grant CA21765 and the American Lebanese Syrian Associated Charities (ALSAC).

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

REFERENCES

1. Suzuki M. Lymphocyte functions of child patients with ALL (acute lymphoblastic leukemia) in remission. *Jpn J Clin Oncol*. 1984;14:31-40.
2. Moritz B, Eder J, Meister B, Heitger A. Intact T-cell regenerative capacity in childhood acute lymphoblastic leukemia after remission induction therapy. *Med Pediatr Oncol*. 2001;36:283-289.
3. Kristinsson VH, Kristinsson JR, Jonmundsson GK, Jonsson OG, Thorsson AV, Haraldsson A. Immunoglobulin class and subclass concentrations after treatment of childhood leukemia. *Pediatr Hematol Oncol*. 2001;18:167-172.
4. Reinhardt D, Houliara K, Pekrun A, Lakomek M, Krone B. Impact of conventional chemotherapy on levels of antibodies against vaccine-preventable diseases in children treated for cancer. *Scand J Infect Dis*. 2003;35:851-857.
5. Alanko S, Salmi TT, Pelliniemi TT. Recovery of natural killer cells after chemotherapy for childhood acute lymphoblastic leukemia and solid tumors. *Med Pediatr Oncol*. 1995;24:373-378.
6. Lovat PE, Robinson JH, Windebank KP, Kernahan J, Watson JG. Serial study of T lymphocytes in childhood leukemia during remission. *Pediatr Hematol Oncol*. 1993;10:129-139.
7. Fugi S, Kapp M, Einsele H. Challenges to preventing infectious complications, decreasing re-hospitalizations, and reducing cost burden in long-term survivors after allogeneic hematopoietic stem cell transplantation. *Semin Hematol*. 2012;49:10-14.
8. Centers for Disease Control and Prevention; Infectious Disease Society of America; American Society of Blood and Marrow Transplantation. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *MMWR Recomm Rep*. 2000;49(RR-10):1-125, CE1-CE7.
9. Alanko S, Pelliniemi TT, Salmi TT. Recovery of blood B-lymphocytes and serum immunoglobulins after chemotherapy for childhood acute lymphoblastic leukemia. *Cancer*. 1992;69:1481-1486.
10. Alanko S, Pelliniemi TT, Salmi TT. Recovery of blood lymphocytes and serum immunoglobulins after treatment of solid tumors in children. *Pediatr Hematol Oncol*. 1994;11:33-45.
11. Alanko S, Pelliniemi TT, Salmi TT. Recovery of blood T-cell subsets after chemotherapy for childhood acute lymphoblastic leukemia. *Pediatr Hematol Oncol*. 1994;11:281-292.
12. Mazur B, Mertas A, Sonta-Jakimczyk D, Szczepanski T, Janik-Moszant A. Concentration of IL-2, IL-6, IL-8, IL-10 and TNF-alpha in children with acute lymphoblastic leukemia after cessation of chemotherapy. *Hematol Oncol*. 2004;22:27-34.
13. Mazur B, Szczepanski T, Karpe J, Sonta-Jakimczyk D, Bubala H, Torbus M. Decreased numbers of CD4+ T lymphocytes in peripheral blood after treatment of childhood acute lymphoblastic leukemia. *Leuk Res*. 2006;30:33-36.
14. Eckschlager T, Prusa R, Hladikova M, Radvanska J, Slaby K, Radvansky J. Lymphocyte subpopulations and immunoglobulin levels in Hodgkin's disease survivors. *Neoplasma*. 2004;51:261-264.
15. Leung W, Neale G, Behm F, Finkelstein D, Kastan MD, Pui CH. Deficient innate immunity, thymopoiesis, and gene expression response to radiation in survivors of childhood acute lymphoblastic leukemia. *Cancer Epidemiol*. 2010;34:303-308.
16. Ek T, Mellander L, Hahn-Zoric M, Abrahamsson J. Intensive treatment for childhood acute lymphoblastic leukemia reduces immune responses to diphtheria, tetanus, and Haemophilus influenzae type B. *J Pediatr Hematol Oncol*. 2004;26:727-734.
17. Ek T, Mellander L, Andersson B, Abrahamsson J. Immune reconstitution after childhood acute lymphoblastic leukemia is most severely affected in the high risk group. *Pediatr Blood Cancer*. 2005;44:461-468.
18. Yeh JM, Nekhlyudov L, Goldie S, Mertens AC, Diller L. A model-based estimate of cumulative excess mortality in survivors of childhood cancer. *Ann Intern Med*. 2010;152:409-417.
19. Kurt BA, Nolan VG, Ness KK, et al. Hospitalization rates among survivors of childhood cancer in the Childhood Cancer Survivor Study cohort. *Pediatr Blood Cancer*. 2012;59:126-132.
20. Lorenzi MF, Xie L, Rogers PC, Pritchard S, Goddard K, McBride ML. Hospital-related morbidity among childhood cancer survivors in British Columbia, Canada: report of the Childhood, Adolescent, Young Adult Cancer Survivors (CAYACS) Program. *Int J Cancer*. 2011;128:1624-1631.
21. Robison LL, Mertens AC, Boice JD, et al. Study design and cohort characteristics of the Childhood Cancer Survivor Study: a multi-institutional collaborative project. *Med Pediatr Oncol*. 2002;38:229-239.
22. Robison LL, Armstrong GT, Boice JD, et al. The Childhood Cancer Survivor Study: a National Cancer Institute-supported resource for outcome and intervention research. *J Clin Oncol*. 2009;27:2308-2318.
23. Leisenring WM, Mertens AC, Armstrong GT, et al. Pediatric cancer survivorship research: experience of the Childhood Cancer Survivor Study. *J Clin Oncol*. 2009;27:2319-2327.
24. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*. 1986;42:121-130.
25. Taylor JM, Munoz A, Bass SM, Saah AJ, Chmiel JS, Kingsley LA. Estimating the distribution of times from HIV seroconversion to AIDS using multiple imputation. Multicentre AIDS Cohort Study. *Stat Med*. 1990;9:505-514.
26. Little RJA, Rubin DB. Statistical Analysis With Missing Data. New York; John Willey & Sons, Inc.; 2002.
27. Gamis AS, Howells WB, DeSwarte-Wallace J, et al. Alpha hemolytic streptococcal infection during intensive treatment for acute myeloid leukemia: a report from the Children's Cancer Group study CCG-2891. *J Clin Oncol*. 2000;18:1845-1855.
28. Waghorn DJ. Overwhelming infection in asplenic patients: current best practice preventive measures are not being followed. *J Clin Pathol*. 2001;54:214-218.
29. Kaplinsky C, Spirer Z. Post-splenectomy antibiotic prophylaxis: unfinished story—to treat or not to treat? *Pediatr Blood Cancer*. 2006;47:740-741.
30. Working Party of the British Committee for Standards in Haematology Clinical Haematology Task Force. Guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen. *BMJ*. 1996;312:430-434.
31. American Academy of Pediatrics, Committee on Infectious Diseases. Policy statement: recommendations for the prevention of pneumococcal infections, including the use of pneumococcal conjugate vaccine (Prevnar), pneumococcal polysaccharide vaccine, and antibiotic prophylaxis. *Pediatrics*. 2000;106:362-366.
32. The Children's Oncology Group. Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers. Version 3.0. Arcadia, CA: Children's Oncology Group; 2008.
33. Green DM, Kun LE, Matthay KK, et al. Relevance of historical therapeutic approaches to the contemporary treatment of pediatric solid tumors. *Pediatr Blood Cancer*. 2013;60:1083-1094.
34. Hudson MM, Neglia JP, Woods WG, et al. Lessons from the past: opportunities to improve childhood cancer survivor care through outcomes investigations of historical therapeutic approaches for pediatric hematological malignancies. *Pediatr Blood Cancer*. 2012;58:334-343.