Hospitalization after Adolescent and Young Adult (AYA) Cancer: A Population-Based Study in Utah

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ABSTRACT

Background: Adolescents and young adults (AYA, age 15–39 years) with cancer may be at elevated risk for late morbidity following their cancer treatment, but few studies have quantified the excess burden of severe disease in this population. Using population-based data from Utah, we examined the risk of inpatient hospitalizations among AYA cancer survivors compared with their siblings and the general population.

Methods: Survivors of AYA cancer who were ≥2 years from diagnosis and diagnosed from 1994 to 2015 (N = 6,330), their siblings (N = 12,924), and an age- and sex-matched comparison cohort (N = 18,171) were identified using the Utah Population Database (UPDB). Hospitalizations from 1996 to 2017 were identified from statewide discharge records in the UPDB. We estimated multivariable-adjusted hazard ratios (HR) for first hospitalization and rate ratios (RR) for total hospitalizations for survivors relative to the matched comparison cohort and siblings.

Results: Overall, the risk of a first hospitalization was higher among AYA cancer survivors than the matched population-based cohort [HR = 1.93; 95% confidence interval (CI), 1.81–2.06]. Risk was most elevated for survivors of leukemia (HR = 4.76), central nervous system tumors (HR = 3.45), colorectal cancers (HR = 2.83), non-Hodgkin lymphoma (HR = 2.76), and breast cancer (HR = 2.37). The rate of total hospitalizations was also increased among survivors relative to the comparison cohort (RR = 2.05; 95% CI, 1.95–2.14). Patterns were generally similar in analyses comparing survivors to their siblings.

Conclusions: AYA cancer survivors have a higher burden of inpatient hospitalization than their siblings and the general population.

Impact: Results indicate the importance of long-term, risk-based follow-up care to prevent and treat severe morbidities after cancer treatment.

Introduction

Each year in the United States, approximately 70,000 adolescents and young adults (AYA, ages 15–39) are diagnosed with cancer (1). With advances in cancer treatments, 5-year relative survival among AYAs with cancer has steadily increased over the past few decades, and is currently over 80% for all cancer types combined (2). Long-term cancer survivors, however, may be at increased risk for a number of adverse health outcomes as a result of late effects of their curative cancer therapy.

Numerous reports from the Childhood Cancer Survivor Study and other cohorts have examined late morbidity and hospitalization among survivors of childhood cancers (3–5). However, these studies have generally only included survivors diagnosed at ages 0 to 20 years with selected cancer types common among children [e.g., leukemia, central nervous system (CNS) tumors]. Patterns of excess hospitalization among AYA cancer survivors, particularly those diagnosed with cancer types more predominant in the older end of the AYA age range (e.g., breast cancer, colorectal cancer), have not been as well-characterized (6–8). A better understanding of the burden of hospitalizations after cancer treatment among AYA survivors may help to anticipate future healthcare utilization in more recently diagnosed patients.

Using population-based data from the state of Utah, the objective of this study was to describe hospitalizations among 2-year AYA cancer survivors, and to compare these with hospitalizations among siblings and a sex- and age-matched general population cohort.

Materials and Methods

Data source

The Utah Population Database (UPDB) is a unique resource which links statewide administrative records for the entire Utah population (vital records, drivers' licenses, voter registration, marriage, and divorce records) to cancer diagnosis and treatment information available from the Utah Cancer Registry (UCR). The UCR has been part of the NCI's Surveillance Epidemiology and End Results (SEER) program since 1973 and maintains records for patients diagnosed in Utah beginning in 1966. Patient information available from the UCR includes basic demographic, tumor, and treatment information. UPDB also links administrative records and cancer diagnosis information to statewide hospital discharge data from the Utah Department of Health. The hospital discharge data include a record for each inpatient discharged from any acute care hospital in Utah and has been available in the UPDB since 1996. UPDB can also determine the date at which each person was last known to be residing in Utah from UPDB-linked records such as drivers' licenses and voter registration records. UPDB can follow

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the entire cancer and health care utilization history of the Utah population, irrespective of disease status, during their residence in the state because of these record linkages. Demographic information (sex, birth year, race/ethnicity) in the UPDB comes from multiple record sources, including Utah birth certificates, death certificates, and other administrative records. This study was approved by the Institutional Review Boards of the University of North Carolina, the University of Utah, and the Utah Resource for Genetic and Epidemiologic Research.

Study population

UPDB data were used to identify a cohort of patients who were diagnosed with a first malignant primary cancer at ages 15 to 39 years from 1994 to 2015 and survived at least 2 years after their initial cancer diagnosis. We selected 2-year survivors under the assumption that most AYA patients would have completed active treatment within 2 years of diagnosis. We excluded those without a Utah birth certificate and those who either died or were no longer known to be residing in Utah as of January 1, 1996, the date when hospitalization data became available. We also excluded those who died or were no longer known to be in Utah as of 2 years after cancer diagnosis.

Population-based comparisons were randomly selected from Utah birth certificates within the UPDB, and were matched to cancer cases on birth year and sex using a 3:1 ratio. Individuals were eligible to be selected as comparisons if they had survived and lived in Utah up until the date of diagnosis of the matched case. Selection criteria also required that population-based comparisons had not been diagnosed with cancer before age 40. All siblings of included AYA cancer cases who had a Utah birth certificate and did not have a cancer diagnosis before age 40 were also identified in the UPDB. For our analyses, we excluded matched comparisons and siblings who had died or were no longer living in Utah as of January 1, 1996, or 2 years after the corresponding cancer case's diagnosis date, whichever came later. We also excluded siblings born before 1955, the earliest birth year among cancer cases and matched comparisons.

Hospitalization outcomes

Hospital discharge records from the UPDB were used to identify hospitalization events among AYA cancer survivors, siblings, and the matched comparison group. The primary diagnosis associated with each hospitalization event was determined from International Classification of Disease (ICD) version 9 or 10 codes. Codes were categorized into meaningful diagnostic groups for analysis based on ICD chapters (9, 10). Primary diagnosis codes related to pregnancy and delivery were not included as hospitalization events.

Statistical analysis

Person-time of follow-up was accrued from 2 years after the date of cancer diagnosis among AYA cancer survivors (and the same date for their siblings and matched population comparisons) until death, last date known to be in Utah, or end of follow-up on December 31, 2017, whichever occurred first. Time to first hospitalization was evaluated for all ICD diagnostic groups combined and for each individual diagnostic group using Cox proportional hazards regression models to estimate hazard ratios (HR). For analyses comparing AYA cancer survivors to their siblings, we used marginal Cox models with robust sandwich estimators (11) to account for clustering within families. We also estimated the cumulative incidence of first hospitalization from 2 years postdiagnosis to 5, 10, and 20 years postdiagnosis using nonparametric methods to account for death as a competing risk (12).

Hospitalization rate ratios (RR) for the total number of hospitalizations of any diagnostic group were estimated using zero-inflated Poisson (ZIP) regression models, which are robust for modeling count variables with a large number of zeros (13); person-time of follow-up was used as the offset. In analyses comparing survivors to their siblings, we accounted for clustering using mixed ZIP models with random effects (14). Multivariable regression models were adjusted for sex, birth year, and diagnosis year. In sensitivity analyses, we excluded AYA survivors diagnosed with distant stage disease or leukemia, who we considered most likely to still be in active treatment after 2 years postdiagnosis. As a secondary analysis, we also estimated HRs and RRs among 5-year survivors relative to matched comparisons and siblings, with follow-up beginning at 5 years after cancer diagnosis.

Results

A total of 6,330 AYA cancer survivors, 12,924 siblings, and 18,171 matched comparison subjects were identified and included in these analyses. The majority of AYA cancer survivors were female, non-Hispanic White, and diagnosed at ages 30 to 39 years (**Table 1**). The most common cancer diagnoses overall included thyroid cancer, melanoma, breast cancer, and testicular cancer.

Among AYA cancer survivors, there were 1,523 first hospitalization events over a median follow-up of 4.9 years (IQR = 1.8–9.8 years). The cumulative incidence of a first hospitalization by 10 years postdiagnosis (with follow-up beginning at 2 years postdiagnosis) was 25.5% for all cancer types combined (Supplementary Table S1). In multivariable-adjusted models, the risk of a first hospitalization among AYA cancer survivors was 1.93 [95% confidence interval (CI), 1.81–2.06] times that among the matched comparison group (**Table 2**). The elevation in risk was greater for male survivors (HR = 2.32; 95% CI, 2.08–2.60) than for female survivors (HR = 1.78; 95% CI, 1.65–1.92) and for those with distant stage disease (HR = 3.85; 95% CI, 3.39–4.38) and regional stage disease (HR = 2.22; 95% CI, 1.99–2.48) than those with localized stage disease (HR = 1.59; 95% CI, 1.47–1.72). HRs were significantly increased relative to matched comparisons for every cancer type, but were highest for leukemia, CNS tumors, colorectal cancers, non-Hodgkin lymphoma, and breast cancer, and lowest for cervical/uterine cancers and melanoma. Patterns were generally similar in analyses comparing survivors to their siblings, although HRs tended to be slightly attenuated (**Table 2**).

In analyses of first hospitalization within individual diagnostic groups, the HR for survivors relative to matched comparisons was highest for neoplasms (HR = 11.55; 95% CI, 9.24–14.44), followed by blood diseases (HR = 3.54; 95% CI, 2.77–4.52; **Table 3**). The risk among survivors was also more than double that of comparisons for supplementary factors, infectious and parasitic diseases, nervous system diseases, circulatory diseases, skin diseases, endocrine and metabolic diseases, symptoms, signs, and ill-defined conditions, respiratory diseases, and injury and poisoning. Smaller, though significant, elevations in risk among survivors were observed for digestive diseases, mental diseases, musculoskeletal diseases, and genitourinary diseases. Rate ratios for the total count of all hospitalizations of all diagnostic groups were also elevated among AYA cancer survivors relative to matched comparisons (RR = 2.05; 95% CI, 1.95–2.14) and siblings (RR = 1.56; 95% CI, 1.45–1.68; Supplementary Table S2).

Table 1. Characteristics of 2-year AYA cancer survivors, matched population comparisons, and siblings.

	Survivors *N* (%)	Matched comparisons *N* (%)	Siblings *N* (%)
Total	6,330 (100%)	18,171 (100%)	12,924 (100%)
Median follow-up for first hospitalization, years (range)	4.9 (0.0–21.9)	6.8 (0.0–22.0)	6.8 (0.0–22.0)
Sex			
Male	2,581 (41%)	7,394 (41%)	6,518 (50%)
Female	3,749 (59%)	10,777 (59%)	6,406 (50%)
Year of birth			
1955–1969	1,430 (23%)	4,290 (24%)	3,250 (25%)
1970–1979	2,745 (43%)	7,961 (44%)	4,813 (37%)
1980–2000	2,155 (34%)	5,920 (33%)	4,861 (38%)
Race/ethnicity			
Non-Hispanic White	6,186 (98%)	17,538 (97%)	12,565 (98%)
Other	144 (2%)	520 (3%)	233 (2%)
Missing	0	113	126
Age at diagnosis			
15–19 years	651 (10%)		
20–24 years	1,014 (16%)		
25–29 years	1,353 (21%)		
30–34 years	1,632 (26%)		
35–39 years	1,680 (27%)		
Year of diagnosis			
1994–1999	1,319 (21%)		
2000–2009	2,952 (47%)		
2010–2015	2,059 (33%)		
Cancer type			
Thyroid	1,175 (19%)		
Melanoma	1,147 (18%)		
Testicular	640 (10%)		
Breast	603 (10%)		
Hodgkin lymphoma	442 (7%)		
CNS tumors	334 (5%)		
Cervix/uterus	273 (4%)		
Colon/rectum	263 (4%)		
Non-Hodgkin lymphoma	257 (4%)		
Leukemia	231 (4%)		
Other	965 (15%)		
Summary stage			
Localized	3,664 (58%)		
Regional	1,420 (22%)		
Distant	733 (12%)		
Unstaged	505 (8%)		
Missing	8		

In sensitivity analyses, HRs for first hospitalization among 2-year survivors relative to matched comparisons were 1.87 (95% CI, 1.75–2.00) and 1.77 (95% CI, 1.66–1.90) when AYAs with leukemia and distant stage disease, respectively, were excluded. Corresponding RRs for total hospitalizations were 1.98 (95% CI, 1.89–2.08) excluding leukemia, and 1.78 (95% CI, 1.69–1.87) excluding distant stage disease. In secondary analyses restricted to 5-year survivors ($N = 4{,}579$) and their matched comparisons ($N = 12{,}990$) and siblings ($N = 9{,}220$), HRs for first hospitalization were 1.62 (95% CI, 1.50–1.76) and 1.47 (95% CI, 1.34–1.61) for survivors versus matched comparisons and siblings, respectively (Supplementary Table S3). Across cancer types, HRs for survivors versus matched comparisons ranged from 1.25 for cervical/uterine cancers to 3.33 for leukemia. RRs for all hospitalizations were 1.77 (95% CI, 1.67–1.88) and 1.48 (95% CI, 1.33–1.64) for survivors relative to matched comparisons and siblings, respectively (Supplementary Table S4).

Discussion

Many AYA cancer survivors have unique healthcare needs in the years following their cancer diagnosis and treatment. Using population-based hospitalization discharge data from Utah, we found that the risk of a first hospitalization among 2-year AYA cancer survivors was nearly twice that of a sex- and age-matched comparison cohort. The elevation in risk was greatest for AYAs survivors of leukemia, lymphomas, CNS tumors, breast cancer, and colorectal cancer. Results were generally similar in analyses comparing AYA cancer survivors to their siblings, further reinforcing the robustness of our conclusions. Our findings thus highlight the importance of risk-based survivorship care in this population.

Although the need for AYA-focused survivorship research has been increasingly recognized, AYAs cancer survivors continue to represent an understudied population, with current recommendations for follow-up care in this age group based largely on studies of patients diagnosed as children. Indeed, the most recent guidelines for AYA Oncology from the National Comprehensive Cancer Network specifically acknowledge the lack of large cohort studies to address survivorship issues among AYAs who exceed the upper age limit of most childhood cancer survivor studies (20 years; ref. 1). AYAs with cancer are distinct from childhood and adult cancer patients in their cancer type distribution, disease and host biology, patterns of treatment, and psychosocial issues (15), all of which may contribute to a unique risk profile for late effects of cancer treatment and other health outcomes and support the need for research specific to survivors diagnosed as AYAs.

The highly elevated risk of hospitalization for neoplasms among AYA cancer survivors in our cohort is expected, given the potential for recurrence of the primary cancer combined with the excess risk of a second malignancy among survivors (16). However, the risk of hospitalization among survivors was also significantly increased for nearly every other diagnostic group, with risk more than double that of the matched comparison group for, among others, infectious and parasitic diseases, endocrine and metabolic diseases, blood diseases, nervous system diseases, circulatory diseases, respiratory diseases, and skin diseases. These findings are generally consistent with studies of AYA survivors in Europe and Canada (6–8).

Given the potential for several cancer therapies to cause acute and/or late adverse effects on the heart and vascular system (17), it is critical to document morbidity from circulatory diseases among cancer survivors to identify high-risk patient groups. To our knowledge, only one prior U.S.-based study has examined hospitalization from circulatory diseases among AYAs with various cancer types. Though lacking general population rates for comparison, Keegan and colleagues reported rates of cardiovascular disease (CVD), defined as hospitalization or death from coronary artery disease, congestive heart failure, and stroke, among 2-year AYA cancer survivors in California (18). In their study, cancer types with the highest incidence of CVD included CNS tumors, acute lymphoid leukemia, acute myeloid leukemia, and non-Hodgkin lymphoma. Our smaller sample size in Utah did not allow for extensive cancer type-specific analyses of hospitalization for CVD

Table 2. First hospitalization of any diagnostic group among 2-year AYA cancer survivors, matched population comparisons, and siblings.

	Survivors vs. matched comparisons[a]				Survivors vs. siblings[b]			
	N events	Person-time (years)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[c]	*N* events	Person-time (years)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[c]
Full sample								
Matched comparisons/ siblings (ref)	2,753	144,363	1	1	1,939	101,805	1	1
Survivors	1,523	40,552	1.93 (1.81–2.06)	1.93 (1.81–2.06)	1,205	32,875	1.89 (1.76–2.03)	1.78 (1.65–1.91)
Females								
Matched comparisons/ siblings (ref)	2,001	81,229	1	1	1,193	48,761	1	1
Survivors	1,025	22,897	1.78 (1.65–1.92)	1.78 (1.65–1.92)	608	14,118	1.74 (1.57–1.92)	1.70 (1.54–1.88)
Males								
Matched comparisons/ siblings (ref)	752	63,134	1	1	746	53,043	1	1
Survivors	498	17,655	2.33 (2.08–2.61)	2.32 (2.08–2.60)	283	10,806	1.84 (1.61–2.11)	1.87 (1.63–2.14)
Leukemia								
Matched comparisons/ siblings (ref)	2,753	144,363	1	1	64	3,881	1	1
Survivors	94	1,138	4.24 (3.45–5.20)	4.76 (3.87–5.85)	69	925	4.29 (3.02–6.12)	4.45 (3.12–6.34)
Non-Hodgkin lymphoma								
Matched comparisons/ siblings (ref)	2753	144,363	1	1	64	4,282	1	1
Survivors	75	1,581	2.45 (1.95–3.08)	2.76 (2.19–3.47)	68	1,370	3.21 (2.28–4.51)	3.38 (2.37–4.82)
Hodgkin lymphoma								
Matched comparisons/ siblings (ref)	2,753	144,363	1	1	132	7,892	1	1
Survivors	96	3,189	1.57 (1.28–1.93)	1.77 (1.45–2.18)	74	2,613	1.66 (1.25–2.20)	1.66 (1.25–2.21)
CNS tumors								
Matched comparisons/ siblings (ref)	2,753	144,363	1	1	119	5,697	1	1
Survivors	107	1,817	3.04 (2.51–3.69)	3.45 (2.84–4.19)	84	1,447	2.69 (2.06–3.51)	2.80 (2.14–3.68)
Testicular[d]								
Matched comparisons/ siblings (ref)	752	63,134	1	1	67	5,956	1	1
Survivors	91	5,188	1.48 (1.19–1.84)	1.50 (1.21–1.87)	49	3,211	1.36 (0.95–1.95)	1.33 (0.94–1.90)
Melanoma								
Matched comparisons/ siblings (ref)	2,753	144,363	1	1	348	18,792	1	1
Survivors	214	7,892	1.41 (1.23–1.62)	1.39 (1.21–1.60)	178	6,466	1.47 (1.23–1.76)	1.34 (1.12–1.61)
Thyroid								
Matched comparisons/ siblings (ref)	2,753	144,363	1	1	331	17,075	1	1
Survivors	246	7,169	1.78 (1.56–2.03)	1.52 (1.33–1.73)	199	5,923	1.71 (1.45–2.02)	1.44 (1.21–1.72)
Breast[e]								
Matched comparisons/ siblings (ref)	2,001	81,229	1	1	118	4,247	1	1
Survivors	197	3,224	2.42 (2.09–2.81)	2.37 (2.04–2.75)	114	1,896	2.07 (1.60–2.68)	2.02 (1.56–2.61)
Cervix/uterus[e]								
Matched comparisons/ siblings (ref)	2,001	81,229	1	1	58	2,186	1	1
Survivors	69	2,173	1.30 (1.03–1.66)	1.28 (1.01–1.63)	40	1,302	1.16 (0.77–1.74)	1.13 (0.75–1.70)
Colon/rectum								
Matched comparisons/ siblings (ref)	2,753	144,363	1	1	82	3,717	1	1
Survivors	70	1,244	2.88 (2.27–3.65)	2.83 (2.23–3.59)	59	1,022	2.51 (1.79–3.52)	2.39 (1.70–3.36)
Localized stage								
Matched comparisons/ siblings (ref)	2,753	144,363	1	1	1,167	59,831	1	1
Survivors	784	25,584	1.60 (1.48–1.73)	1.59 (1.47–1.72)	614	20,651	1.52 (1.38–1.67)	1.41 (1.28–1.55)

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Table 2. First hospitalization of any diagnostic group among 2-year AYA cancer survivors, matched population comparisons, and siblings. (Cont'd)

	Survivors vs. matched comparisons[a]				Survivors vs. siblings[b]			
	N events	Person-time (years)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[c]	*N* events	Person-time (years)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[c]
Regional stage								
Matched comparisons/ siblings (ref)	2,753	144,363	1	1	435	23,147	1	1
Survivors	373	8,444	2.28 (2.05–2.54)	2.22 (1.99–2.48)	299	6,912	2.23 (1.92–2.58)	2.05 (1.76–2.38)
Distant stage								
Matched comparisons/ siblings (ref)	2,753	144,363	1	1	225	12,104	1	1
Survivors	258	3,817	3.45 (3.03–3.92)	3.85 (3.39–4.38)	204	3,126	3.27 (2.71–3.95)	3.34 (2.77–4.03)
Unstaged								
Matched comparisons/ siblings (ref)	2,753	144,363	1	1	109	6,544	1	1
Survivors	105	2,663	2.01 (1.65–2.45)	2.04 (1.67–2.48)	87	2,158	2.37 (1.76–3.21)	2.32 (1.71–3.14)

[a]Analysis compares full survivor cohort to full matched comparison cohort.
[b]Analysis compares survivors with siblings to their siblings.
[c]Adjusted for sex, birth year, and diagnosis year.
[d]Males only.
[e]Females only.

defined as in analyses by Keegan and colleagues. However, our results indicate that hospitalization for circulatory diseases is significantly increased among AYA cancer survivors compared with the general population, underscoring the importance of long-term follow-up for prevention, detection, and management of circulatory diseases among patients with a history of AYA cancer.

In our analyses, some of the most elevated risks of hospitalization were observed among AYAs with leukemias, lymphomas, and CNS tumors, cancer types more predominant among younger AYAs and often associated with intensive and protracted cancer treatment regimens. Other studies of AYA and childhood patients with these cancer types have also reported a high risk of severe morbidity in the years following cancer diagnosis and treatment. In a study of 5-year AYA cancer survivors in Denmark, relative risks for first hospitalization were 2.21, 1.93, 1.87, and 1.64 for survivors of leukemia, brain cancer, Hodgkin lymphoma, and non-Hodgkin lymphoma, respectively, versus matched comparison subjects (6). For leukemia, the exceptionally high relative risk of a first hospitalization in our study probably reflects, in part, the greater likelihood for these patients to still be in active cancer treatment beyond 2 years postdiagnosis than AYAs with other malignancies. However, late effects of treatment or other conditions among long-term survivors are also likely important contributors to the high rates of hospitalization in this group.

Few AYA-specific studies have examined hospitalizations for AYAs with cancers more typically diagnosed in older adults, such as breast cancer and colorectal cancer. In our analyses, the risk of a first inpatient hospitalization among AYAs with breast and colorectal cancer was more than double that of both the matched comparison group and siblings, indicating a high burden of severe morbidity among survivors of these cancer types. In addition, the rate of total hospitalizations over the follow-up period among colorectal cancer survivors was more than three times that of matched comparisons, a finding which may be informative for anticipating the healthcare needs of individuals with a history of AYA colorectal cancer. Our results, considered in the context of recently reported increases in colorectal cancer incidence among young adults (19), emphasize the need for future research in larger samples to better understand the specific diagnoses that contribute to high rates of hospitalization among survivors.

Our study has several strengths. The unique data resources available in the UPDB allowed us to estimate the cumulative incidence of hospitalization among AYA cancer survivors, and to compare hospitalizations in the AYA survivor cohort to those among a sex- and age-matched population comparison group. We were also able to compare survivors to their siblings, an analysis which may provide some control for confounding due to unmeasured genetic, socioeconomic, and cultural factors. However, there are also certain limitations to our analyses. The number of hospitalizations was too small to perform cancer type-specific analyses of individual diagnostic groups or to conduct analyses focused on more specific diagnosis codes within diagnostic groups. Furthermore, we could only account for hospitalizations that occurred in Utah; information on care received out of state was not available. We were also unable to identify patients who were undergoing active cancer treatment during our follow-up period. Thus, for some conditions, such as blood disorders, hospitalizations among AYA cancer survivors could reflect toxicities associated with recent receipt of certain cancer therapies. Nevertheless, our findings provide information on the burden of hospitalization among AYAs who have survived at least 2 years from their cancer diagnosis.

In conclusion, our analyses using population-based data from Utah suggest that AYA cancer survivors have a higher risk of first hospitalization and higher rates of total hospitalizations than the general population and siblings. Cancer types at high risk included not only hematologic cancer and brain tumors, but also cancers nearly exclusive to older AYAs such as breast and colorectal cancer, indicating the importance of long-term, risk-based follow-up care to prevent and treat severe morbidities among survivors of these cancers. Future studies may be warranted to investigate associations between specific cancer therapies or lifestyle factors and

Table 3. First hospitalization within individual diagnostic groups among 2-year AYA cancer survivors, matched population comparisons, and siblings.

	Survivors vs. matched comparisons[a]				Survivors vs. siblings[b]			
	N events	Person-time (years)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[c]	*N* events	Person-time (years)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[c]
Infectious and parasitic								
Matched comparisons/siblings (ref)	97	161,497	1	1	58	112,902	1	1
Survivors	81	48,217	2.77 (2.06–3.72)	2.75 (2.05–3.69)	64	39,054	2.60 (1.83–3.70)	2.60 (1.82–3.71)
Neoplasm								
Matched comparisons/siblings (ref)	99	161,300	1	1	92	112,636	1	1
Survivors	345	47,189	11.42 (9.13–14.28)	11.55 (9.24–14.44)	270	38,204	8.39 (6.63–10.60)	8.08 (6.35–10.28)
Endocrine/metabolic								
Matched comparisons/siblings (ref)	397	160,146	1	1	278	112,011	1	1
Survivors	286	47,419	2.46 (2.12–2.87)	2.45 (2.11–2.86)	229	38,378	2.41 (2.02–2.86)	2.21 (1.86–2.64)
Blood								
Matched comparisons/siblings (ref)	124	161,285	1	1	77	112,757	1	1
Survivors	133	48,073	3.56 (2.79–4.55)	3.54 (2.77–4.52)	107	38,921	4.00 (2.98–5.37)	3.84 (2.83–5.21)
Mental								
Matched comparisons/siblings (ref)	561	159,016	1	1	376	111,401	1	1
Survivors	249	47,530	1.47 (1.27–1.71)	1.46 (1.26–1.69)	173	38,594	1.32 (1.10–1.58)	1.29 (1.07–1.55)
Nervous system								
Matched comparisons/siblings (ref)	184	161,150	1	1	129	112,758	1	1
Survivors	150	48,081	2.75 (2.21–3.41)	2.72 (2.19–3.38)	111	38,965	2.50 (1.94–3.24)	2.43 (1.87–3.15)
Circulatory								
Matched comparisons/siblings (ref)	223	160,715	1	1	186	112,293	1	1
Survivors	166	47,887	2.54 (2.08–3.11)	2.58 (2.11–3.15)	132	38,802	2.08 (1.66–2.59)	2.14 (1.72–2.68)
Respiratory								
Matched comparisons/siblings (ref)	171	160,931	1	1	109	112,729	1	1
Survivors	123	48,146	2.40 (1.90–3.03)	2.40 (1.90–3.03)	97	38,990	2.55 (1.94–3.36)	2.50 (1.89–3.31)
Digestive								
Matched comparisons/siblings (ref)	405	159,517	1	1	293	111,407	1	1
Survivors	235	47,526	1.95 (1.66–2.29)	1.95 (1.66–2.29)	182	38,508	1.79 (1.50–2.14)	1.75 (1.46–2.10)
Genitourinary								
Matched comparisons/siblings (ref)	499	158,146	1	1	274	111,300	1	1
Survivors	194	47,405	1.29 (1.10–1.53)	1.30 (1.10–1.54)	152	38,401	1.60 (1.32–1.95)	1.37 (1.12–1.66)
Skin								
Matched comparisons/siblings (ref)	51	161,707	1	1	37	113,059	1	1
Survivors	40	48,384	2.58 (1.71–3.91)	2.57 (1.70–3.89)	33	39,180	2.56 (1.61–4.09)	2.56 (1.58–4.14)
Musculoskeletal								
Matched comparisons/siblings (ref)	297	160,349	1	1	230	112,118	1	1
Survivors	117	47,995	1.35 (1.09–1.68)	1.37 (1.11–1.70)	96	38,874	1.22 (0.97–1.54)	1.19 (0.94–1.50)
Congenital								
Matched comparisons/siblings (ref)	26	161,707	1	1	27	113,059	1	1
Survivors	13	48,384	1.69 (0.87–3.29)	1.67 (0.86–3.26)	11	39,180	1.17 (0.58–2.36)	1.17 (0.57–2.41)
Symptoms, signs, and ill-defined conditions								
Matched comparisons/siblings (ref)	335	160,156	1	1	265	111,986	1	1
Survivors	246	47,701	2.45 (2.08–2.89)	2.44 (2.07–2.88)	193	38,624	2.11 (1.75–2.54)	2.02 (1.66–2.44)

(Continued on the following page)

Table 3. First hospitalization within individual diagnostic groups among 2-year AYA cancer survivors, matched population comparisons, and siblings. (Cont'd)

			Survivors vs. matched comparisons[a]				Survivors vs. siblings[b]	
	N events	Person-time (years)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[c]	*N* events	Person-time (years)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[c]
Injury and poisoning								
Matched comparisons/ siblings (ref)	403	159,382	1	1	272	111,614	1	1
Survivors	257	47,358	2.14 (1.83–2.50)	2.14 (1.83–2.51)	181	38,410	1.93 (1.59–2.33)	1.93 (1.59–2.33)
Supplementary factors influencing health status and contact with health system								
Matched comparisons/ siblings (ref)	656	159,104	1	1	446	111,458	1	1
Survivors	613	45,905	3.23 (2.89–3.61)	3.20 (2.86–3.57)	480	37,187	3.21 (2.83–3.64)	3.00 (2.63–3.41)

[a]Analysis compares full survivor cohort to full matched comparison cohort.
[b]Analysis compares survivors with siblings to their siblings.
[c]Adjusted for sex, birth year, diagnosis year.

hospitalization outcomes, and to identify strategies to reduce the burden of hospitalization among AYA cancer survivors.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Coccia PF, Pappo AS, Beaupin L, Borges VF, Borinstein SC, Chugh R, et al. Adolescent and young adult oncology, version 2.2018. NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Cancer Net 2018;16:66–97.
2. Barr RD, Ferrari A, Ries L, Whelan J, Bleyer WA. Cancer in adolescents and young adults: a narrative review of the current status and a view of the future. JAMA Pediatr 2016;170:495–501.
3. Goldsby R, Chen Y, Raber S, Li L, Diefenbach K, Shnorhavorian M, et al. Survivors of childhood cancer have increased risk of gastrointestinal complications later in life. Gastroenterology 2011;140:1464–71.
4. Perkins JL, Chen Y, Harris A, Diller L, Stovall M, Armstrong GT, et al. Infections among long-term survivors of childhood and adolescent cancer: a report from the Childhood Cancer Survivor Study. Cancer 2014;120:2514–21.
5. Kurt BA, Nolan VG, Ness KK, Neglia JP, Tersak JM, Hudson MM, et al. Hospitalization rates among survivors of childhood cancer in the Childhood Cancer Survivor Study cohort. Pediatr Blood Cancer 2012;59:126–32.
6. Rugbjerg K, Olsen JH. Long-term risk of hospitalization for somatic diseases in survivors of adolescent or young adult cancer. JAMA Oncol 2016;2:193–200.
7. Richardson DP, Daly C, Sutradhar R, Paszat LF, Wilton AS, Rabeneck L, et al. Hospitalization rates among survivors of young adult malignancies. J Clin Oncol 2015;33:2655–9.
8. Zhang Y, Lorenzi MF, Goddard K, Spinelli JJ, Gotay C, McBride ML. Late morbidity leading to hospitalization among 5-year survivors of young adult cancer: a report of the childhood, adolescent and young adult cancer survivors research program. Int J Cancer 2014;134:1174–82.
9. World Health Organization. International classification of diseases, 9th revision (ICD-9). Available from: cdc.gov/nchs/icd/icd9cm.htm.
10. World Health Organization. International classification of diseases, 10th revision (ICD-10). Available from: https://www.cdc.gov/nchs/icd/icd10cm.htm.
11. Lin DY. Cox regression analysis of multivariate failure time data: the marginal approach. Stat Med 1994;13:2233–47.
12. Lin G, So Y, Johnston G. Analyzing survival data with competing risks using SAS software. SAS Global Forum 2012; Paper 344–2012. Available from: support.sas.com/resources/papers/proceedings12/344-2012.pdf.
13. Long JS. Regression models for categorical and limited dependent variables. Thousand Oaks (CA): Sage Publications; 1997.
14. Hall DB. Zero-inflated Poisson and binomial regression with random effects: a case study. Biometrics 2000;56:1030–9.
15. Sender L, Zabokrtsky KB. Adolescent and young adult patients with cancer: a milieu of unique features. Nat Rev Clin Oncol 2015;12:465–80.
16. Lee JS, DuBois SG, Coccia PF, Bleyer A, Olin RL, Goldsby RE. Increased risk of second malignant neoplasms in adolescents and young adults with cancer. Cancer 2016;122:116–23.
17. Curigliano G, Cardinale D, Dent S, Criscitiello C, Aseyev O, Lenihan D, et al. Cardiotoxicity of anticancer treatments: epidemiology, detection, and management. CA Cancer J Clin 2016;66:309–25.
18. Keegan THM, Kushi LH, Li Q, Brunson A, Chawla X, Chew HK, et al. Cardiovascular disease incidence in adolescent and young adult cancer survivors: a retrospective cohort study. J Cancer Surviv 2018;12:388–97.
19. Lui RN, Tsoi KK, Ho JM, Lo CM, Chan FC, Kyaw MH, et al. Global increasing incidence of young-onset colorectal cancer across 5 continents: a joinpoint regression analysis of 1,922,167 cases. Cancer Epidemiol Biomarkers Prev 2019;28:1275–82.