Title

Long-term survivors of childhood bone and soft tissue sarcomas are at risk of hospitalization

Journal

Pediatric Blood & Cancer, 64(6)

ISSN

1545-5009

Authors

Gonzalez, Cristian D

Randall, R Lor

Wright, Jennifer

et al.

Publication Date

2017-06-01

DOI

10.1002/pbc.26371

Peer reviewed

HHS Public Access

Author manuscript

Pediatr Blood Cancer. Author manuscript; available in PMC 2019 September 03.

Published in final edited form as:

Pediatr Blood Cancer. 2017 June ; 64(6): . doi:10.1002/pbc.26371.

Long-term survivors of childhood bone and soft tissue sarcomas are at risk of hospitalization

Cristian D. Gonzalez[1], **R. Lor Randall**[2,3], **Jennifer Wright**[4,5], **Holly Spraker-Perlman**[4], **Jian Ying**[5], **Carol Sweeney**[5,6,7], **Ken R. Smith**[6,8,9], **Anne C. Kirchhoff**[4,6]

[1]University of Utah School of Medicine, Salt Lake City, Utah

[2]Sarcoma Services, Huntsman Cancer Institute, Salt Lake City, Utah

[3]Department of Orthopaedics, University of Utah, Salt Lake City, Utah

[4]Department of Pediatric Hematology and Oncology, University of Utah, Salt Lake City, Utah

[5]Department of Internal Medicine, University of Utah, Salt Lake City, Utah

[6]Cancer Control and Population Sciences Research Program, Huntsman Cancer Institute, Salt Lake City, Utah

[7]Utah Cancer Registry, Salt Lake City, Utah

[8]Pedigree and Population Resource (Utah Population Database), Huntsman Cancer Institute, Salt Lake City, Utah

[9]Department of Family and Consumer Studies, University of Utah, Salt Lake City, Utah

Abstract

Background: Childhood cancer survivors can have a high burden of chronic conditions related to cancer treatment, some of which are debilitating or potentially life-threatening. Much remains to be learned about late effects in bone and soft tissue sarcoma survivors.

Procedures: The Utah Cancer Registry was used to identify survivors of bone (N = 71) and soft tissue sarcomas (N = 98) who were diagnosed at ages 0–20 years between 1973 and 2007 and were alive at least 5 years after diagnosis. We selected an age–sex-matched comparison cohort (N = 934). Hospitalizations from 1996 to 2012 were extracted from the Utah Department of Health statewide inpatient hospitalization discharge records. Cox, Poisson, and Gamma regressions were used to evaluate the risk of hospitalization, rate of admission, and length of stay for survivors versus the comparison cohort. Primary ICD-9 codes defined the most common reasons for hospitalizations.

Results: The hazard ratio (HR) of any hospitalization was higher for survivors in reference to the comparison cohort (HR = 2.12, 95% confidence interval [CI] 1.51–2.97). Survivors experienced more hospital admissions (rate ratio [RR] = 4.58, 95% CI 3.92–5.35) and longer length of stay

Correspondence: Anne C. Kirchhoff, Cancer Control and Population Sciences Research Program, Huntsman Cancer Institute, 2000 Circle of Hope, Rm 4145, Salt Lake City, UT 84112. anne.kirchhoff@hci.utah.edu.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

(RR = 1.28, 95% CI 1.12–1.46) compared with the comparison cohort. Survivors treated with any chemotherapy were at three-fold higher risk (HR = 3.37, 95% CI 1.94–5.83) of hospitalization compared with survivors who received surgery and/or radiation alone. Among hospitalized survivors, the most common reason was injury for bone tumor (26.8%) and neoplasm for soft tissue sarcoma (12.2%).

Conclusion: Childhood survivors of bone tumor and soft tissue sarcoma face ongoing risk of hospitalization for years after diagnosis.

Keywords

AYA; bone and soft tissue sarcoma; child and adolescent cancer; survivorship; Utah Population Database

1 | INTRODUCTION

From 1975 to 2010, due to advancements in chemotherapy, surgery, and radiation, the 5-year relative survival for childhood bone tumors improved from 50.4 to 75.5% and that for soft tissue sarcomas improved from 64.8 to 78.1%.[1] However, it is now well understood that the therapy used to treat these cancers can cause significant damage to organ systems that may manifest many years after the original therapy.[2] Chemotherapy, in comparison to surgery or radiation, can affect rapidly growing cells in multiple organ systems. These late effects include second cancers, cardiovascular conditions, and other acute and chronic problems and can lead to a high burden of health-care utilization among these patients.[3]

By 10 years after diagnosis, 58% of bone and 35% of soft tissue sarcoma survivors report at least one severe or life-threatening late effect.[2] Unfortunately, few survivors of these cancers receive risk-based health care to identify or manage late effects in an early, treatable stage.[4] The majority of healthcare programs designed for bone and soft tissue sarcoma patients revolve around improving physical function, while other areas such as psychological and social functioning are often poorly addressed.[5] In addition, some larger oncology programs have late effect clinics that provide cancer survivors with preventive care, close follow-up, and screening to improve the overall health. However, these services are rare, especially for patients living outside of major cities, and underutilized due to lack of insurance, lack of adequate financial resources, work and family obligations, and inability to navigate the healthcare system.[6]

As part of an earlier study, our team found that long-term survivors of bone and soft tissue sarcoma are hospitalized at a rate 2.55 and 1.82 times, respectively, than that of similar-aged comparisons without cancer[7] using data from the statewide Utah Population Database (UPDB) and Utah Cancer Registry (UCR). Here, we extend our earlier analyses to evaluate differences in hospitalization and hospital morbidity for these patients and to better understand the impact of risk factors (e.g., sex, treatment) on hospitalizations. We hypothesized that bone and soft tissue sarcoma survivors who received chemotherapy for the treatment of their original cancer were at an increased risk of hospitalization than survivors not receiving chemotherapy. Reasons for hospitalization among these patients were explored to identify potential areas for improvement in patient care.

2 | METHODS

2.1 | Data access

The UCR, a National Cancer Institute Surveillance Epidemiology and End Results (SEER) registry of statewide cancer records, was used to identify bone and soft tissue sarcoma survivors. Demographic information and vital records (birth and death certificates) were obtained from the University of Utah's Pedigree and Population Resource, which houses the UPDB.[8,9] Records from the UPDB are linked to statewide resources, including the UCR and Utah Department of Health (DOH). Statewide inpatient hospitalization claims have been collected by the DOH since 1996. The University of Utah's Institutional Review Board and the Utah Resource for Genetic and Epidemiologic Research approval was obtained for this project.

2.2 | Participants

Children and adolescents (ages <21 years at diagnosis) diagnosed with bone or soft tissue sarcoma were identified using the UCR from 1973 to 2007. Similar to one of our previous papers,[7] a comparison sample without a history of cancer and matched by sex and age was also selected from the UPDB. Bone and soft tissue sarcoma survivors were classified based on the International Classification of Childhood Cancers. Due to treatment similarities, the extra-osseous Ewing sarcoma survivors were aggregated under the bone tumor group. As our goal was to understand late effects after therapy, we defined "survivors" as patients who were alive 5 or more years from their original diagnosis date and limited analyses to this group.

2.3 | Measures

2.2.1 | Hospitalization outcomes—Hospitalization discharge data were available from 1996 to 2012. Using discharge records, the total number of inpatient hospitalizations was calculated for the bone and soft tissue sarcoma survivors and the comparison group, counting hospitalizations taking place 5 years after diagnosis and later. Hospitalizations for pregnancy or delivery based on International Classification of Disease Version 9 (ICD-9) codes were excluded. Hospital diagnoses were determined using the principal ICD-9 diagnosis code for that admission. These codes are grouped by ICD-9 chapter, generally equivalent to organ systems or disease process, to classify the type of late morbidity. The ICD-9 chapter "injury" includes complications of surgical and medical treatment (i.e., postoperative infections and mechanical complications of internal orthopedic devices).

2.2.2 | Cancer-related measures—The UCR provided diagnosis, age at diagnosis, year of diagnosis, age at last follow-up, and first course of treatment received for their original cancer (e.g., receipt of surgery, chemotherapy, or radiation). "Systemic treatment" included any receipt of chemotherapy, whether alone or in combination with other modalities. "Local treatment" was defined by any treatment modality in which chemotherapy was not utilized (i.e., radiation and/or surgery).

2.2.3 | Other variables—Demographic information such as sex, year of birth, age at last follow-up, race/ethnicity, and county of birth was obtained from birth certificate data from

the UPDB and records from the UCR. The vast majority (>85%) of Utah residents are Caucasians with European ancestry. As a result, race/ethnicity was grouped as non-Hispanic White versus Other. Rural residence at diagnosis/index date was defined as living in a county with less than 75% of the population in an urban area (population >2,500).

2.3 | Statistical analyses

Demographic differences were assessed between the cancer survivor and the comparison cohort based on the Pearson χ^2-test. Cox regression, Poisson regression, and Gamma regressions were used to evaluate of the hazard rate for hospitalization, hospitalization counts, and length of stay for survivors versus the comparison cohort, respectively. Specifically, time to first hospitalization was modeled using Cox regression model stratified by sex, year of birth, and year when follow-up started. Admission rates, that is, the number of admissions per cohort member, were modeled using Poisson regression models with survivor status and sex, year of birth, and year of first follow-up visit as covariates and logarithm follow-up time as an offset. Length of stay, that is, average number of days hospitalized, excluding those with no hospitalizations, was modeled using a Gamma regression model with survivor status and sex, year of birth, and year of first follow-up visit as covariates. Kaplan–Meier estimates of time-to-first hospitalization between the survivor and comparison group are statistically compared by using the log-rank test. Hypothesis tests were two-tailed and significance level was set at $P<0.05$. All analyses were performed using SAS 9.4.

Complete hospitalization data were available starting in 1996, so hospitalizations are not captured for those patients diagnosed from 1973 to 1990 until this date. To address this issue, two diagnosis year subgroups were created (1973–1990 and 1991–2007), which allowed for evaluation of hospitalization differences between the two groups starting at least 5 years after diagnosis. In survivor-only models, differences by demographics (age at diagnosis, sex) and by systemic treatment versus local were examined by fitting the models for these subgroups adjusting for time since diagnosis. Frequency of different primary ICD-9 codes for hospitalization were tallied to find the most common cause for hospitalization. Multivariable Cox regression models were estimated to compare the time to first hospitalization for each ICD-9 code between survivors and the comparison group.

3 | RESULTS

From 1973 to 2007, there were N = 169 patients of bone (N = 71) and soft tissue sarcomas (N = 98) who survived 5 or more years after diagnosis, along with N = 934 comparison cohort members who were alive and eligible for follow-up. The average follow-up time for survivors was 15.3 years (SD = 8.7) and 14.0 years (SD = 9.1) for the comparison group (NS). Table 1 shows that demographic characteristics were similar between the survivors and the comparison cohort.

A total of 65 survivors of 169 had at least one hospitalization. The hazard ratios (HRs) of any hospitalization (HR = 2.12, 95% confidence interval [CI] 1.51–2.97) and admission rate (rate ratio [RR] = 4.58, 95% CI 3.92–5.35) were greater for the bone and soft tissue sarcoma survivors than for the comparison cohort (Table 2). If hospitalized, length of stay on average

was longer among survivors (RR = 1.28, 95% CI 1.12–1.46) than in the comparison cohort. Approximately 40% of the survivors diagnosed from 1991 to 2007 experienced a hospitalization starting 5 years after diagnosis, while less than 15% of the comparison group experienced a hospitalization by 10 years after follow-up started (Fig. 1).

Male survivors' admission rate was three-fold higher (RR = 3.00, 95% CI 2.31–3.89) and female survivors' six-fold higher (RR = 6.40, 95% CI 5.22–7.85) than their respective comparison groups (Table 2). Both male and female survivors had lengths of stay that were approximately 35% longer than that of their comparisons. The number of admissions was significantly higher for survivors diagnosed from 1973 to 1990 than for the comparison group (RR = 2.39, 95% CI 1.88–3.03), but the contrast was stronger when we examined survivors diagnosed from 1991 to 2007 (RR = 8.49, 95% CI 6.79–10.61).

Among survivors, 46% had systemic treatment that included chemotherapy compared with 54% who received only radiation and/or surgery (data not shown). In multivariable survival analyses limited to survivors, systemic treatment for original diagnosis (HR = 3.17, 95% CI 1.77–5.68 vs. local therapy) was significantly associated with higher risk of hospitalization during follow-up. Additionally, hospitalization risk was higher among patients who were aged 5–9 years at diagnosis when compared with patients diagnosed at ages 0–4 (HR = 2.78, 95% CI 1.04–17.04). However, survivors diagnosed at ages 10–20 years did not differ compared with those diagnosed at ages 0–4 (HR = 1.72, 95% CI 0.71–4.16).

In Table 3, the primary diagnosis of the first hospitalization during follow-up showed that neoplasms were the most common admitting diagnosis with an HR of 11.9 (95% CI 4.00–35.1) compared with those without cancer, although ICD-9 grouping for neoplasm does not distinguish between a second cancer, relapse of the primary cancer, or late complications of the primary cancer. Survivors were at a threefold increased risk (HR = 3.60, 95% CI 1.30–10.40) of developing a disorder or disease of the pulmonary system. Pneumonia, acute upper respiratory illness, and acute respiratory failure were the most common causes of pulmonary-related hospitalizations among survivors (Table 4). Other common reasons for hospitalizations among survivors included diseases of the skin and subcutaneous tissue, musculoskeletal system and connective tissue, injury, and inpatient rehabilitation. When bone and soft tissue sarcoma survivors were evaluated separately, the most common reason for hospitalization among survivors was injury for bone sarcomas (26.8%) and neoplasm for soft tissue sarcoma (12.2%) (NS).

4 | DISCUSSION

This study demonstrates that long-term survivors of childhood and adolescent bone and soft tissue sarcomas are at an increased risk of hospitalization in relation to an age- and sex-matched comparison cohort who were never diagnosed with cancer. Overall, survivors of childhood bone tumors and sarcomas are hospitalized at a five-fold higher rate and have a longer hospital stay than those without cancer. These findings build on earlier work from our team and other groups demonstrating that providers caring for survivors of childhood cancers need to address health problems before they lead to acute hospitalizations.[4,7] Survivors should be informed about the increased burden of health issues during surveillance

appointments, ideally prior to the development of a condition requiring urgent action or hospital admission.[10]

Previous studies have demonstrated that adult survivors of childhood cancer treated with all three treatment modalities (chemotherapy, surgery, and radiation) for their primary cancer were at the highest risk of hospitalization compared with those survivors in other treatment groups (chemotherapy alone, chemotherapy and radiation, radiation alone, surgery and chemotherapy).[11–13] When we compared the bone and soft tissue sarcomas survivors who received systemic treatment (chemotherapy or any combination treatment with chemotherapy) with survivors who received local treatment only (radiation and/or surgery), there was a three-fold higher hospitalization risk for survivors who received systemic treatment. These results indicate that the use of chemotherapy for bone and soft tissue sarcomas is an independent risk factor for hospitalization 5 or more years after the end of therapy. Survivors who initially had higher disease burden/and or metastatic disease are far more likely to receive systemic treatment rather than local treatment only. These patients are at a high risk of cancer recurrence and/or complications from their metastatic diseases. In addition to late effects, increased hospitalization risk of survivors who received systemic therapy may also be partially due to the recurrence of their primary cancer.

In addition, our findings are consistent with those of earlier studies in which neoplasm is the most common reason for hospitalization in bone tumor survivors.[11] Since these hospitalizations occurred at least 5 years after the initial cancer diagnosis, most of these hospitalizations are likely not due to acute complications or initial treatment of the primary cancer. However, the ICD-9 category for neoplasm does not distinguish whether survivors are being hospitalized for a second cancer, relapse of the primary cancer, or late complications of the primary cancer, and we suggest future studies investigate neoplasm-related hospitalizations in more depth. Other common reasons for hospitalization among survivors included diseases of the skin and subcutaneous tissue, pulmonary system, and injury. Mechanical complication from orthopedic devices and postoperative infections were the most common codes identified for survivors who were hospitalized for injury. Two other studies demonstrated similar results in which neoplasms and injury were one of the most common reasons for hospitalizations among bone and soft tissue sarcoma survivors.[11,12]

There are some limitations to this study. The sample size was small, as bone and soft tissue sarcomas are rare cancers. However, cancer incidence data from UCR and hospitalization data from the UPDB cover the entire state, which capture a larger number of participants, a wider range of population groups, and in different geographic locations in relation to a single large institution study. For patients diagnosed between 1973 and 1990, complete hospital admission data could not be captured because hospitalizations data became available in 1996. Due to sample size limitations, we were unable to identify if racial or ethnic minority groups were at an increased risk of hospitalization. Also, we did not delineate disease extent, specific translocations, and subtypes of certain cancers. Patients with metastatic cancers are much more likely to relapse and therefore have either poorer survival overall or more complications related to therapy and/or disease relapses. In addition, we are unable to evaluate the type, dosing, and time period of chemotherapy and radiation.

Our results demonstrated that childhood survivors of bone and soft tissue sarcomas are at an increased risk of hospitalization and experience longer hospital stays when they are admitted. Systemic treatment of their original cancer and a cancer diagnosis between the ages of 5 and 9 years were independent risk factors for future hospitalization. The majority of hospitalizations in bone and soft tissue sarcoma survivors were due to neoplasm, suggesting that the survivors are frequently affected by second cancers, relapse, or complications from their primary cancer. High doses of radiation and the use of multiple chemotherapy agents in these patients can significantly increase the risk of a secondary cancer,[14] although it was not possible to evaluate the effects of specific chemotherapeutic agents with these data. Future protocols in preventative medicine that may provide early detection of late effects that may lead to long-term morbidity may significantly decrease the number of survivors developing severe, acute medical conditions that lead to hospitalization. Alleviating barriers to health-care access and educating child and adolescent survivors on the importance of close follow-up with a late-effect clinic may reduce hospitalizations.

ACKNOWLEDGMENTS

We thank the Pedigree and Population Resource of the Huntsman Cancer Institute, University of Utah (funded in part by the Huntsman Cancer Foundation) for its role in the ongoing collection, maintenance and support of the Utah Population Database (UPDB). Partial support for the Utah Population Database and this project was provided by the Huntsman Cancer Institute Cancer Center Support Grant P30CA042014 from the National Cancer Institute. Support for the Utah Cancer Registry is provided by contract #HHSN 261201000026C from the National Cancer Institute with additional support from the Utah Department of Health and the University of Utah. Huntsman Cancer Foundation/Huntsman Cancer Institute and the Primary Children's Hospital Foundation.

Abbreviations:

CI
confidence interval

HR
hazard ratio

ICD-9
International Classification of Disease Version 9

NS
not shown

RR
rate ratio

SD
standard deviation

SEER
Surveillance Epidemiology and End Results

UCR
Utah Cancer Registry

Utah Population Database

Utah Population Database

REFERENCES

1. National Cancer Institute, National Institutes of Health. Epidemiology, and End Results Program. http://seer.cancer.gov/csr/1975_2011/browse_csr.php?sectionSEL=28&pageSEL=sect_28_table.08.html. Accessed February 13, 2015.
2. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med. 2006;355(15):1572–1582. [PubMed: 17035650]
3. Rebholz CE, Reulen RC, Toogood AA, et al. Health care use of long-term survivors of childhood cancer: the British Childhood Cancer Survivor Study. J Clin Oncol. 2011;29(31):4181–4188. [PubMed: 21947833]
4. Nathan PC, Greenberg ML, Ness KK, et al. Medical care in long-term survivors of childhood cancer: a report from the childhood cancer survivor study. J Clin Oncol. 2008;26(27):4401–4409. [PubMed: 18802152]
5. Kwong TN, Furtado S, Gerrand C. What do we know about survivorship after treatment for extremity sarcoma? A systematic review. Eur J Surg Oncol. 2014;40(9):1109–1124. [PubMed: 24767804]
6. Pratt-Chapman M, Simon MA, Patterson AK, Risendal BC, Patierno S. Survivorship navigation outcome measures: a report from the ACS patient navigation working group on survivorship navigation. Cancer. 2011;117(15 Suppl):3575–3584. [PubMed: 21780092]
7. Kirchhoff AC, Fluchel MN, Wright J, et al. Risk of hospitalization for survivors of childhood and adolescent cancer. Cancer Epidemiol Biomarkers Prev. 2014;23(7):1280–1289. [PubMed: 24925676]
8. Cannon Albright LA. Utah family-based analysis: past, present and future. Hum Hered. 2008;65(4):209–220. [PubMed: 18073491]
9. Duvall SL, Fraser AM, Rowe K, Thomas A, Mineau GP. Evaluation of record linkage between a large healthcare provider and the Utah Population Database. J Am Med Inform Assoc. 2012;19(e1):e54–e59. [PubMed: 21926112]
10. Cherven B, Mertens A, Meacham LR, Williamson R, Boring C, Wasilewski-Masker K. Knowledge and risk perception of late effects among childhood cancer survivors and parents before and after visiting a childhood cancer survivor clinic. J Pediatr Oncol Nurs. 2014;31(6):339–349. [PubMed: 25013005]
11. 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(5):1174–1182. [PubMed: 24037993]
12. 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(7):1624–1631. [PubMed: 21280033]
13. Mcbride ML, Lorenzi MF, Page J, et al. Patterns of physician follow-up among young cancer survivors: report of the Childhood, Adolescent, and Young Adult Cancer Survivors (CAYACS) research program. Can Fam Phys. 2011;57(12):e482–e490.
14. Schwartz B, Benadjaoud MA, Cléro E, et al. Risk of second bone sarcoma following childhood cancer: role of radiation therapy treatment. Radiat Environ Biophys. 2014;53(2):381–390. [PubMed: 24419490]

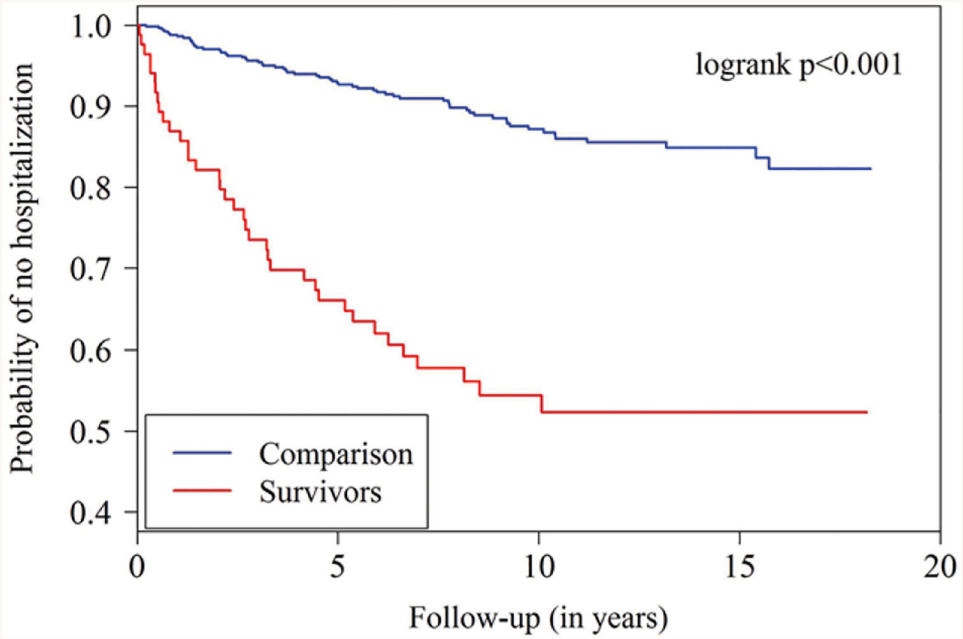

FIGURE 1.
Kaplan–Meier curve. Time-to-first hospitalization of survivors versus comparison group

TABLE 1

Demographics of malignant bone and soft tissue sarcoma survivors and comparison cohort

	Malignant bone tumor					Soft tissue sarcoma				
	Malignant bone tumor survivors, N = 71		Comparison, N = 434		*P* value[a]	Soft tissue sarcoma survivors, N = 98		Comparison, N = 500		*P* value[b]
	N	%	N	%		N	%	N	%	
Sex										
Male	37	52	252	58	0.35	47	48	256	51	0.56
Female	34	48	182	42		51	52	244	49	
Age at last follow-up, years										
5–10	0	0	0	0	0.24	1	1	2	1	0.27
11–20	5	7	13	3		5	5	27	5	
21–30	20	28	125	29		30	31	193	39	
31–40	29	41	149	34		30	31	161	32	
41–60	17	24	143	33		31	32	114	23	
> 60	0	0	4	1		1	1	3	1	
Race/ethnicity										
Non-Hispanic White	68	96	408	94	0.60	95	97	481	96	0.79
Other	3	4	26	6		3	3	19	4	
County at birth										
Urban	65	92	380	88	0.34	84	86	442	88	0.46
Rural[c]	6	8	54	12		14	14	58	12	
	Mean	SD[d]	Mean	SD[d]		Mean	SD[d]	Mean	SD[d]	
Age at last follow-up, years	33.6	9.6	36.0	10	0.07	35.7	10.9	33.1	10.2	0.02
Age at diagnosis, years	14.3	3.7	N/A	N/A	N/A	12.2	6.1	N/A	N/A	N/A

[a] *P* value comparing bone tumor survivors versus matched controls.

[b] *P* value comparing the soft tissue sarcoma survivors versus matched controls.

[c] Rural defined as living in a county with less than 75% of population in an urban area (population ≥2,500).

[d] Standard deviation.

TABLE 2

Multivariable regressions of hospitalizations, admissions, and length of stay for survivors versus comparison cohort

Subset	N	Time to first hospitalization			Number of admissions					Length of stay (days)				
		HR[a,b]	95% CI	*P*	Mean (SD[c])	Median (IQR[d])	RR[e,f]	95% CI	*P*	Mean (SD[c])	Median (IQR[d])	RR[e,f]	95% CI	*P*
Bone and soft tissue sarcomas														
Comparison (ref)	934	1			0.38 (1.48)	0 (0,0)	1			3.27 (4.37)	2 (2,3)	1		
Survivors	169	2.12	1.51–2.97	<0.001	1.83 (4.71)	0 (0,2)	4.58	3.92–5.35	<0.001	4.04 (5.21)	3 (2,4)	1.28	1.12–1.46	<0.001
Male														
Comparison (ref)	508	1			0.36 (1.64)	0 (0,0)	1			4.45 (6.61)	3 (2,5)	1		
Survivors	84	1.81	1.11–2.97	0.02	1.19 (2.72)	0 (0,1)	3.00	2.32–3.89	<0.001	3.83 (3.72)	3 (1,5)	1.39	1.14–1.69	<0.001
Female														
Comparison (ref)	426	1			0.39 (1.27)	0 (0,0)	1			2.62 (2.11)	2 (2,3)	1		
Survivors	85	2.45	1.53–3.90	<0.001	2.46 (6.03)	0 (0,2)	6.40	5.22–7.85	<0.001	4.13 (5.72)	3 (2,4)	1.35	1.18–1.54	<0.001
Diagnosis 1973–1990														
Comparison (ref)	421	1			0.51 (1.42)	0 (0,1)	1			3.49 (5.50)	2 (1,3)	1		
Survivors	85	1.30	0.81–2.09	0.27	1.19 (2.50)	0 (0,1)	2.39	1.88–3.03	<0.001	3.42 (2.72)	3 (2,4)	0.95	0.77–1.09	0.62
Diagnosis 1991–2007														
Comparison (ref)	513	1			0.26 (2.53)	0 (0,0)	1			3.00 (2.27)	2 (2,4)	1		
Survivors	84	3.87	2.31–6.49	<0.001	2.48 (6.15)	0 (0,2)	8.49	6.79–10.61	<0.001	4.35 (6.06)	3 (2,4)	1.53	1.35–1.73	<0.001

[a] Stratified by sex as relevant, birth year, and diagnosis year; excludes hospitalizations for pregnancy and delivery.

[b] Hazard ratios.

[c] Standard deviation.

[d] Interquartile range.

[e] Rate ratio.

[f] Adjusted for sex as relevant, birth year, and diagnosis year; excludes hospitalizations for pregnancy and delivery.

TABLE 3

Diagnostic codes for hospitalization and HRs for first admission among bone and soft tissue sarcoma survivors versus the comparison group

	Bone tumor and soft tissue sarcoma, N = 169		Comparison, N = 934		Multivariable analysis		
Diseases, disorders, and conditions[a]	**Number of admissions**	**%**	**Number of admissions**	**%**	**HR**[b,c]	**95% CI**	***P* value**
Neoplasms	21	12.4	13	1.4	11.9	4.0–35.1	<0.001
Endocrine, nutritional, metabolic, immune	3	1.8	14	1.5	1.0	0.3–4.0	0.97
Mental	10	5.9	44	4.7	1.7	0.7–3.7	0.23
Nervous system	5	3.0	6	0.6	3.4	0.7–16.0	0.12
Circulatory system	6	3.6	12	1.3	1.9	0.6–5.8	0.26
Respiratory system	10	5.9	14	1.5	3.6	1.3–10.4	0.02
Digestive system	10	5.9	32	3.4	1.4	0.6–3.1	0.40
Genitourinary system	7	4.1	39	4.2	0.9	0.4–2.2	0.80
Skin and subcutaneous tissue	6	3.6	3	0.3	5.6	1.1–27.8	0.04
Musculoskeletal system and connective tissue	17	10.1	21	2.2	3.8	1.7–8.4	<0.001
Congenital	2	1.2	3	0.3	2.7	0.4–19.4	0.32
Injury and poisoning	27	16	36	3.9	3.6	2.0–6.5	<0.001
Symptoms; signs; and ill-defined	9	5.3	11	1.2	6.2	1.8–20.6	0.003

[a] Infectious and parasitic, blood and blood forming organs, certain conditions originating in the perinatal period, and residual codes not shown due to insufficient sample for analysis.

[b] Hazard ratios.

[c] Multivariate model adjusted for sex, birth year, and diagnosis year.

TABLE 4

Most common reasons for hospitalizations among survivors of bone tumors and soft tissue sarcoma (by system)

	Most common code	Second most common code	Third most common code
Neoplasms	V5811 (antineoplastic chemotherapy)	V581 (maintenance chemotherapy)	1,716 (malignant neoplasms of connective and other soft tissue of pelvis)
Diseases of the respiratory system	486 (pneumonia)	4,659 (acute URI)	51,881 (acute respiratoryfailure)
Skin and subcutaneous tissue	6,826 (cellulitis of leg-cellulitis and abscess of leg)	6,820 (cellulitis of face)	6,822(cellulitis of trunk), 6,827 (cellulitis of foot), 70,703 (pressure ulcer of lower back), 70,705 (pressure ulcer of buttocks)
Symptoms; signs; and ill-defined	V5789 (rehab care involving other specified rehab procedures)	78,701 (nausea and vomiting)	78,906 (abdominal pain, epigastric)
Diseases of the musculoskeletal system and connective tissue	72,210 (lumbar disk replacement)	73,681 (unequal leg length)	7,242 (lumbar spinal stenosis)
Injury	99,859 (postoperative infection)	99,649 (mechanical complication of internal orthopedic device)	99,685 (complications of bone marrow transplantation)