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Pain in long-term adult survivors of childhood cancers and their siblings: A report from the Childhood Cancer Survivor Study

Qian Lu [a,*], Kevin R. Krull [b], Wendy Leisenring [c], Jason E. Owen [d], Toana Kawashima [c], Jennie C.I. Tsao [e], Bradley Zebrack [f], Ann Mertens [g], Gregory T. Armstrong [b], Marilyn Stovall [h], Leslie L. Robison [b], Lonnie K. Zeltzer [e]

[a] Department of Psychology, University of Houston, Houston, TX, USA
[b] Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, TN, USA
[c] Cancer Prevention Program, Fred Hutchinson Cancer Research Center, Seattle, WA, USA
[d] Department of Psychology, Loma Linda University, Loma Linda, CA, USA
[e] Pediatric Pain Program, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
[f] University of Michigan, School of Social Work, Ann Arbor, MI, USA
[g] Division of Epidemiology, Emory University, Atlanta, GA, USA
[h] Department of Radiation Physics, MD Anderson Cancer Center, Houston, TX, USA

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ABSTRACT

Little is known about pain among long-term adult survivors of childhood cancers. The study investigated pain prevalence in this population compared with sibling controls and examined pain-related risk factors. Three self-reported pain outcomes including pain conditions, prescription analgesics used, and pain attributed to cancer and treatment were assessed among 10,397 cancer survivors and 3034 sibling controls from the Childhood Cancer Survivor Study. Pain conditions (pain/abnormal sensation, migraines, and other headaches) were reported by 12.3%, 15.5%, and 20.5% of survivors, respectively; 16.7% of survivors reported use of prescription analgesics, and 21% attributed pain to cancer and treatment. Risks of reporting pain conditions and using prescription analgesics were higher among survivors than siblings, adjusting for sociodemographic factors. Younger age at diagnosis and a history of non-Hodgkin lymphoma, Wilms tumor, or neuroblastoma (compared to leukemia) were associated with greater risk of reporting pain conditions. A history of bone cancer or soft tissue sarcoma (compared to leukemia) was associated with greater risks of using prescription analgesics and cancer-related pain attribution. Non-brain-directed scatter irradiation was associated with elevated risk for migraines and cancer-related pain attribution. Female gender and lower educational attainment were associated with increased reports of all 3 pain outcomes; minority status, unemployment, and being single were associated with greater risks for reporting pain conditions. These findings contribute to the understanding of pain and associated risk factors among adult survivors of childhood cancer and suggest areas of focus for pain intervention.

1. Introduction

Approximately 80% of children with cancer survive more than 5 years from diagnosis of their disease [31]. The significant improvements in survival rates for childhood cancers [31] have led to an increased focus on identification of late effects of treatment among long-term survivors. A wide array of medical and psychosocial late effects has been documented among adult survivors of childhood cancer, such as poor physical health behaviors [25], risk for chronic illness [8], fatigue [22], cognitive and psychological impairment [23,43], and negative social outcomes [17]. However, little is known about the prevalence of pain and associated risk factors in this population.

Several studies have estimated the prevalence of pain to range from 9%–26% for outpatients and 39%–54% for inpatients among children during treatment or follow-up for a variety of cancer diagnoses [12,14,24]. These estimates suggest a frequent symptom occurrence for these patients; however, the prevalence of pain among long-term childhood cancer survivors is unclear. Studies with adult survivors of childhood cancer at 10 years [35] and 14 years postdiagnosis [22] revealed that 20%–30% of survivors

* Corresponding author. Address: Department of Psychology, University of Houston, 126 Heyne Building, Houston, TX 77204-5022, USA. Tel.: +1 713 743 8515; fax: +1 713 743 8588.
E-mail address: qlu.ucla@gmail.com (Q. Lu).

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reported pain. However, it is difficult to place the prevalence in perspective because of the limited sample size (numbers <200). In addition, because point prevalence of pain in the general adult population varies widely [6,7,15,30,36], appropriate comparison groups are needed in order to understand whether having cancer as a child places individuals at greater risk of experiencing pain during adulthood. Furthermore, risk factors associated with pain are largely unexamined for this population.

Among adult cancer survivors, the estimated prevalence of pain is 50%–75% during cancer treatment [5] and 21%–41% at 1–2 years posttreatment [18]. Although pain prevalence data exist in adult cancer survivors who have recently completed treatment, only a few large-scale studies investigated pain in long-term cancer survivors, and these studies mostly focused on breast cancer survivors [26].

The Childhood Cancer Survivor Study (CCSS) provides a unique opportunity to contribute to our understanding of pain outcomes among long-term survivors of childhood cancer because of its large sample size, comprehensive characterization of the cohort, and the availability of a sibling comparison group. By utilizing existing data obtained from the CCSS, we aimed (1) to investigate the prevalence of pain among survivors compared with that among sibling controls, and (2) to understand how sociodemographic and treatment-related risk factors were associated with pain outcomes. We expected that survivors would have higher rates of pain compared with sibling controls. Studies among adult populations suggest that risk factors for chronic pain include gender [13,40], lower socioeconomic status [9], minority status [2], and unemployment [4]. Accordingly, we hypothesized that female gender, ethnic minority, lower socioeconomic status, younger age at diagnosis, and treatments (surgery, radiotherapy, chemotherapy) would be associated with higher risk of reporting pain.

2. Methods

2.1. Participants and procedures

The CCSS was established in 1993 through funding from the National Cancer Institute as a large cohort of survivors of childhood cancer for use as a research resource. The CCSS represents the largest and most comprehensively characterized cohort of childhood cancer survivors ever assembled in North America. A detailed description of the CCSS study design, methods, and cohort characteristics is provided elsewhere [32,33].

All survivors included in CCSS fulfilled the following eligibility criteria: (1) diagnosis of leukemia, central nervous system (CNS) malignancies (all histologies), Hodgkin lymphoma, non-Hodgkin lymphoma, Wilms tumor, neuroblastoma, soft tissue sarcoma, or malignant bone tumor; (2) diagnosis and initial treatment at 1 of the 26 collaborating CCSS institutions; (3) diagnosis date between January 1, 1970 and December 31, 1986; (4) age <21 years at the time of diagnosis; and (e) survival of at least 5 years from the time of diagnosis. The CCSS was approved by the Institutional Review Boards of all participating institutions. All participants provided informed consent for their participation and medical record abstraction.

The participating sample in the current study was derived from a group of 20,720 individuals meeting the eligibility criteria above. Of these individuals identified by the collaborating institutions, 3017 (14.6%) could not be located and were considered lost for follow-up. Among the 17,703 subjects located, 14,372 (81.1%) consented to participate and completed a self-report questionnaire. A randomly selected subset of 5000 survivors was asked to nominate their closest-age sibling [33]. The random selection of such a large number of siblings should adequately represent the larger population of siblings and create a control group of non-cancer survivors with similar demographic and socioeconomic characteristics. Survivors nominated 4782 siblings who were invited for participation, of which 3846 (80%) completed the survey. To minimize recall biases, the current analysis focuses on those survivors (n = 10,397) and siblings (n = 3034) who were 18 years or older at the time of the survey.

2.2. Measures

2.2.1. Demographic and medical characteristics

Medical record abstraction, according to a structured protocol [33], was conducted at each CCSS center and included detailed information about cancer type, treatments received, and clinical characteristics of the survivor. Data on cancer therapy were abstracted from medical records and did not require patient recall of the experience. A 24-page questionnaire, completed by the survivors and siblings, provided information on demographics, personal and family medical history, functional limitations, psychological status, work history, and living circumstances. Study questionnaires can be viewed at http://www.ccss.stjude.org/. The demographic variables analyzed in the study were gender, minority status, annual household income, educational attainment, marital status, and work status. Treatment and cancer-related variables examined were treatment type (surgery, chemotherapy, and radiotherapy), diagnostic category, and age at diagnosis.

2.2.2. Specific pain conditions

On the questionnaire, participants were asked whether they had "ever been told by a doctor or other health care professional" that they "have or have had" any of the following pain conditions: "prolonged pain or abnormal sensation in arms, legs, or back," "migraine," or "other frequent headaches." Participants were given response options of "yes," "no," or "not sure." To minimize potential recall bias and to be conservative in pain estimations, "not sure" responses on these items were considered as a lack of pain and were collapsed together with the "no" responses. Participants who responded "yes" to having been diagnosed with 1 of these 3 pain conditions were then asked to indicate the age at which the pain condition first occurred, and these ages were utilized in time-to-event analyses for pain outcomes.

2.2.3. Use of prescription medications for pain

All participants were asked whether they used specific types of prescription pain medications either consistently for more than 1 month or for at least 30 days in 1 year during the 2-year period preceding the administration of the questionnaire. Examples of types of prescription pain medications were provided. Response options included "yes," "no," and "not sure." To minimize potential recall biases and to be conservative in pain estimations, responses of "not sure" were combined with "no" responses.

2.2.4. Current pain attributed to cancer or its treatment

Survivors were also asked whether they "*currently* have pain *as a result* of [their] cancer, leukemia, tumor or similar illness, or its treatment?" Participants were given the option to rate current pain on a continuum of "no pain," "small amount of pain," "medium amount of pain," "a lot of pain," or "very bad excruciating pain."

2.3. Data analysis

Survivor/sibling comparisons in the overall risk of being diagnosed with 1 of the 3 pain conditions were evaluated using Cox proportional hazards models, where age was used as the time scale, adjusting for gender, race/ethnicity, marital status, highest level of education, and annual household income. Hazard ratios (HR), 95% confidence intervals (CI), and *P*-values are reported. These analyses accounted for within-family correlations using

generalized estimating equations with sandwich SE estimates [39]. Two types of within-survivor models were employed, one adjusted for primary diagnosis and another for treatment with cranial radiation, both of which adjusted for the same demographic covariates listed for the Cox model above as well as age at diagnosis. For the 3 pain conditions – pain/abnormal sensation, migraines, and other frequent headaches – multiple imputation procedures were employed to impute missing values for age of onset for those participants who reported the presence of a pain condition but did not report the age at which the condition was first diagnosed. The method of multiple imputation was based on that described by Taylor et al. [38] and used an expectation–maximization algorithm to generate 10 imputed missing values for each missing age at first occurrence value. The final reported HR, 95% CI, and *P*-values were estimated based on the model for each pain condition and the standard formula of the multiple-imputation inference [34]. Of the 10,397 survivors who completed a survey when they were age 18 years or older, a total of 8905 had complete treatment data and were included in the Cox regression analyses. Among these survivors, age at first occurrence was imputed for 7.6% (43 of 563), 7.4% (53 of 721), and 3.7% (29 of 780) for pain/abnormal sensation, migraines, and other frequent headaches, respectively. As for the siblings age 18 years or older, the imputation models were created from the whole cohort of 3034. Among the siblings, age at first occurrence was imputed for 9.5% (18 of 190), 9.3% (43 of 461), and 16.5% (76 of 461) for pain/abnormal sensation, migraines, and other frequent headaches, respectively.

Within-survivor analyses of the binary variable "use of prescribed pain medications" were conducted using logistic regression analyses. Within-survivor analyses of pain attributed to cancer or its treatment were conducted using a partial proportional odds model where each possible dichotomization of the outcome was considered so that odds ratios could be simply interpreted as odds of being lower or higher across the entire range of the outcome. Specific comparisons were made between (1) those reporting a small amount of pain and above vs no pain, (2) a medium amount of pain and above vs a small amount of pain and no pain, and (3) a lot of pain or very bad pain vs a medium amount of pain and below. Both of these within-survivor analyses controlled for the same demographic and cancer-related covariates used in the previous Cox proportional hazards models. Two-sided *P*-values are reported and statistical significance for all models was set at $P < 0.05$. All analyses were completed using SAS version 9.1.3 (SAS Institute, Cary, NC).

3. Results

3.1. Characteristics of the sample

Survivors were largely Caucasian (84.0%), middle-income (52.0% reported annual household incomes between $20,000 and $59,999), and well educated (65.8% reported having attended at least some college). On average, survivors were 16.5 years post diagnosis (SD = 4.9, and range = 5-31). Important demographic differences between the survivors and siblings were noted (Table 1). Relative to the sibling controls, a significantly higher proportion of survivors were male and younger. Additionally, survivors were less likely than siblings to describe their ethnic identity as Caucasian, to report having an annual total household income in the highest income ranges, to be married, to have graduated from college, to have ever had a job, or to have worked within the past year.

3.2. Pain conditions

The cumulative incidence of pain/abnormal sensation, migraine headaches, and other frequent headaches were 12.3%, 15.5%, and 20.5% among survivors, and 6.3%, 15.2%, and 15.3% among siblings, respectively. Occurrence of ever having pain was compared between survivors and siblings. After adjusting for gender, ethnicity, household income, marital status, and education, survivors reported significantly higher rates of all 3 pain conditions: pain/abnormal sensation (HR 3.9, 95% CI 3.3–4.7), migraines (HR 1.9, 95% CI 1.7–2.1), and other frequent headaches (HR 1.9, 95% CI 1.7–2.1),with all *P*-values <0.001.

Table 2 summarizes risk factors for each of the pain conditions among long-term survivors of childhood cancer. As expected, demographic factors were significantly associated with each of the 3 pain conditions. Females were more likely than males to report migraines and other frequent headaches. Compared with Caucasian survivors, Hispanic survivors had a significantly elevated risk of reporting abnormal sensation and other frequent headaches, and African American survivors were at a significantly increased risk of reporting all 3 pain conditions. Being single was significantly associated with increased risk of reporting all 3 pain conditions compared with not being single. Survivors who did not complete high school reported higher rates of all 3 pain conditions compared to those who completed high school. Survivors who had never worked reported higher rates of abnormal sensation and headache in comparison to those who worked in the past year.

Age at diagnosis $\leqslant$3 years was associated with a higher risk of reporting all 3 pain conditions as compared with ages at diagnosis of 4–20 in years. Differences in risk for the 3 pain conditions across cancer diagnoses were examined using the leukemia survivors as a comparison group. Survivors with a history of non-Hodgkin lymphoma and those who survived neuroblastoma had a higher risk of reporting migraines. Survivors with a history of Wilms tumor were at a higher risk of reporting migraines and other frequent headaches. Survivors with a history of CNS tumor had a lower risk of reporting abnormal sensation and migraines. Survivors with a history of Hodgkin lymphoma were at lower risk of reporting migraines. Survivors with a history of soft tissue sarcoma were at lower risk of reporting other frequent headaches.

No significant associations between pain conditions and treatment with chemotherapy or surgery were found (data not shown). As shown in Table 2, from a model without diagnosis included, survivors who received scatter radiation (ie, indirect exposure to brain due to scatter from noncranial radiation treatment) had elevated risk of migraines compared with those who received no radiation. Survivors who received direct cranial radiation doses in the range of 1.5–50 Gy had a lower risk of reporting migraines and other frequent headaches compared with those who received no irradiation.

3.3. Use of prescribed pain medication

Among survivors, 17.9% reported using prescribed analgesics, compared to only 12.6% of the siblings. The survivors were 1.4 times more likely to have used prescribed analgesics relative to the siblings (95% CI 1.2–1.6), adjusted for gender, race, household income, age at study, marital status, education, and work status.

As shown in Table 3, female survivors were 1.8 times more likely to use prescribed analgesics than were male survivors. Survivors who had <$20,000 total household income were more likely to use prescribed analgesics relative to those with income $\geqslant$$60,000. Survivors who did not complete high school were more likely to use prescribed analgesics than were high school graduates. Those who had been employed before, but not in the last 12 months, were more likely to have used prescribed analgesics compared to those who had never been employed. Survivors who were separated, divorced, or widowed were more likely to use prescribed pain medication relative to those who were never married/partnered. No effect of ethnicity on use of pain medication was observed among survivors.

Table 1
Demographic characteristics of participating childhood cancer survivors and siblings ⩾18 years of age.

Variable	Value	Survivors n (%)	Siblings n (%)	*P*-value
Sex	Male	5593 (53.8%)	1429 (47.1%)	<0.001
	Female	4804 (46.2%)	1605 (52.9%)	
Ethnicity	Caucasian	8708 (84.0%)	2692 (91.9%)	<0.001
	African American	452 (4.4%)	68 (2.3%)	
	Hispanic	207 (2.0%)	38 (1.3%)	
	American Indian/Alaskan Native	64 (0.6%)	11 (0.4%)	
	Asian or Pacific Islander	99 (1.0%)	28 (1.0%)	
	Other	832 (8.0%)	93 (3.2%)	
Age at study (years)	18–29	7165 (68.9%)	1634 (53.9%)	<0.001
	30–39	2901 (27.9%)	1093 (36.0%)	
	>39	331 (3.2%)	307 (10.1%)	
Annual household income	⩽ $19,999	2063 (22.9%)	353 (12.8%)	<0.001
	$20,000–$59,999	4679 (52.0%)	1368 (49.7%)	
	⩾ $60,000	2255 (25.1%)	1029 (37.4%)	
Marital status	Never married	5286 (53.0%)	1001 (35.0%)	<0.001
	Divorced/separated/widowed	814 (8.2%)	262 (9.2%)	
	Married/living as married	3874 (38.8%)	1596 (55.8%)	
Highest level of schooling	Did not complete high school	1099 (11.2%)	189 (6.5%)	<0.001
	High school grad	2257 (23.0%)	535 (18.4%)	
	High school + some college	3682 (37.4%)	1059 (36.4%)	
	College grad and post grad	2795 (28.4%)	1123 (38.6%)	
Work status	Never worked	543 (5.2%)	38 (1.3%)	<0.001
	Worked, but not in last 12 months	1540 (14.9%)	221 (7.3%)	
	Worked last 12 months	8279 (79.9%)	2766 (91.4%)	
Age at primary diagnosis (years)	0–3	1899 (18.3%)		
	4–10	3607 (34.7%)		
	11–14	2398 (23.1%)		
	15–20	2493 (24.0%)		
Diagnosis	Bone cancer	1133 (10.9%)		
	CNS tumors	1322 (12.7%)		
	Hodgkin lymphoma	1876 (18.0%)		
	Wilms tumor	670 (6.4%)		
	Leukemia	3061 (29.4%)		
	Non-Hodgkin lymphoma	928 (8.9%)		
	Neuroblastoma	416 (4.0%)		
	Soft tissue sarcoma	991 (9.5%)		

CNS, central nervous system.

Survivors who were diagnosed with cancer between the ages of 15 and 20 years were more likely to use prescribed analgesics compared with those diagnosed at <3 years of age. Survivors with a history of bone cancer or soft tissue sarcoma were more likely to use prescribed analgesics compared with leukemia survivors. None of the other types of cancer diagnoses was significantly associated with use of pain medication compared to leukemia. Cranial radiation was not significantly associated with use of pain medication.

3.4. Current pain attributed to cancer or its treatment

Among survivors, 21.0% reported having pain in the past week that they attributed to their history of cancer or its treatment. Specifically, 10.8% reported having only a "small amount" of cancer-related pain; 6.7% reported having a "medium amount" of cancer-related pain; and 3.4% reported having "a lot, or very bad excruciating" cancer-related pain.

As shown in Table 4, survivors with annual household incomes of <$20,000 or $20,000–59,000 were more likely to report pain attributed to cancer or its treatment than those with incomes ⩾$60,000. Survivors who did not complete high school were more likely to report pain attributed to cancer or its treatment compared with high school graduates. Survivors who had ever been married/partnered were more likely to report pain attributed to cancer or its treatment than those who were never married/partnered. Survivors with a history of bone cancer and soft tissue sarcoma were more likely to report pain attributed to cancer or its treatment compared to those with a history of leukemia, while Hodgkin lymphoma survivors were less likely to report pain attributed to cancer or its treatment compared to leukemia survivors.

The lower section of Table 4 displays the factors for which odds ratios differed across different cut-points for the cancer pain attribution outcome. These results illustrate that although females were more likely to attribute a "small amount" or greater of pain to their cancer and treatment than were males, they were less likely to attribute "a lot or very bad excruciating" pain to cancer and its treatment compared with males. Those who had worked before, but not in the last 12 months were more likely to attribute a higher level of pain to cancer or its treatment compared to survivors who never worked. Compared to survivors diagnosed at or before 3 years of age, survivors diagnosed at 11–20 years of age were more likely to attribute a "small amount" or greater of pain to cancer and its treatment.

In a separate model with all factors except diagnosis, survivors who received scatter radiation were more likely to report pain attributed to cancer or its treatment compared to those who did not receive any radiation (Table 4).

4. Discussion

Current findings indicate that adult survivors of childhood cancer experience increased risk of reporting a pain condition and for using prescription analgesics compared to a sibling control group. We observed elevated prevalence estimates in survivors for self-reported pain/abnormal sensation (12.3%), migraines (15.5%), and other headaches (20.5%). The pain prevalence estimates correspond with the proportion of survivors who reported recently using prescription analgesics (16.7%) and who reported current pain attributed to their cancer or its treatment (21%). Moreover,

Table 2
Relative risk ratios and 95% confidence intervals for predictors of pain in childhood cancer survivors by pain condition.

	Pain or abnormal sensation			Migraine			Other frequent headaches		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Sex									
Male	1.0			1.0			1.0		
Female	0.94	(0.84–1.04)	0.23	1.48	(1.33–1.64)	<0.001	1.40	(1.26–1.54)	<0.001
Ethnicity									
Caucasian	1.0			1.0			1.0		
Hispanic	1.74	(1.27–2.39)	0.001	1.35	(0.97–1.86)	0.08	1.44	(1.06–1.96)	0.02
African American	1.91	(1.58–2.30)	<0.001	1.85	(1.54–2.22)	<0.001	1.68	(1.40–2.02)	<0.001
American Indian/Alaskan Native	1.44	(0.85–2.46)	0.18	1.18	(0.66–2.09)	0.58	1.3	(0.75–2.26)	0.35
Asian or Pacific Islander	0.41	(0.16–1.11)	0.08	0.97	(0.52–1.81)	0.92	0.88	(0.45–1.69)	0.69
Other	0.97	(0.79–1.17)	0.73	0.99	(0.83–1.19)	0.94	1.05	(0.88–1.25)	0.61
Annual household income ($)									
⩽19,999	1.17	(0.99–1.38)	0.08	1.04	(0.89–1.22)	0.59	1.08	(0.92–1.26)	0.34
20,000–59,999	1.07	(0.93–1.23)	0.34	0.99	(0.87–1.13)	0.91	1.0	(0.88–1.14)	0.95
⩾60,000	1.0			1.0			1.0		
Marital status									
Single (never married)	1.0			1.0			1.0		
Married/living as married	0.65	(0.57–0.73)	<0.001	0.74	(0.66–0.83)	<0.001	0.72	(0.64–0.80)	<0.001
Divorced/separated/widowed	0.66	(0.54–0.80)	<0.001	0.74	(0.61–0.88)	0.001	0.74	(0.61–0.88)	0.001
Highest level of schooling									
Did not complete high school	1.0			1.0			1.0		
High school grad	0.73	(0.61–0.87)	<0.001	0.75	(0.64–0.89)	0.001	0.76	(0.65–0.90)	0.001
High school + some college	0.68	(0.57–0.80)	<0.001	0.7	(0.59–0.82)	<0.001	0.68	(0.58–0.80)	<0.001
College grad and post grad	0.32	(0.26–0.39)	<0.001	0.38	(0.31–0.45)	<0.001	0.33	(0.27–0.40)	<0.001
Work status									
Never worked	1.0			1.0			1.0		
Worked last 12 months	0.7	(0.55–0.89)	0.004	0.82	(0.65–1.05)	0.12	0.76	(0.60–0.96)	0.02
Worked, but not in last 12 months	0.95	(0.73–1.24)	0.72	0.99	(0.76–1.29)	0.94	0.86	(0.67–1.11)	0.25
Age at diagnosis (years)									
0–3	1.0			1.0			1.0		
4–10	0.66	(0.56–0.77)	<0.001	0.7	(0.60–0.82)	<0.001	0.70	(0.60–0.81)	<0.001
11–14	0.33	(0.27–0.40)	<0.001	0.34	(0.28–0.41)	<0.001	0.35	(0.29–0.42)	<0.001
15–20	0.19	(0.15–0.24)	<0.001	0.19	(0.15–0.24)	<0.001	0.20	(0.16–0.25)	<0.001
Primary diagnosis									
Leukemia	1.0			1.0			1.0		
CNS tumors	0.70	(0.57–0.85)	<0.001	0.74	(0.61–0.90)	0.003	0.88	(0.73–1.06)	0.18
Hodgkin lymphoma	0.79	(0.66–0.94)	0.01	1.06	(0.90–1.25)	0.48	0.88	(0.75–1.04)	0.14
Non-Hodgkin lymphoma	1.08	(0.89–1.32)	0.44	1.31	(1.09–1.59)	0.01	1.15	(0.95–1.39)	0.14
Wilms tumor	1.22	(0.98–1.50)	0.07	1.34	(1.10–1.62)	0.003	1.22	(1.01–1.48)	0.04
Neuroblastoma	1.29	(0.98–1.68)	0.07	1.32	(1.03–1.69)	0.03	1.07	(0.83–1.37)	0.61
Soft tissue sarcoma	0.87	(0.72–1.06)	0.18	0.94	(0.78–1.14)	0.54	0.82	(0.68–0.99)	0.04
Bone cancer	1.03	(0.84–1.25)	0.79	1.01	(0.83–1.23)	0.89	0.94	(0.77–1.14)	0.51
Cranial radiation (Gy)[a] (RR, 95% CI, *P*-value)									
No radiation	1.0			1.0			1.0		
1.5–50	0.78	(0.59–1.04)	0.09	0.70	(0.55–0.89)	0.004	0.79	(0.64–0.99)	0.04
50–110	0.76	(0.47–1.22)	0.26	0.81	(0.52–1.27)	0.35	0.65	(0.41–1.03)	0.07
Scatter[b]	1.15	(0.91–1.45)	0.24	1.25	(1.03–1.52)	0.02	0.86	(0.71–1.05)	0.14

HR, hazard ratio; CI, confidence interval; RR, relative risk; CNS, central nervous system.
[a] A separate regression model where cranial radiation substituted for primary diagnosis in above model adjusted for same covariates.
[b] Scatter, that is, indirect exposure to brain due to scatter from noncranial radiation treatment.

moderate and severe levels of current pain attributed to cancer or treatment were reported by 6.7% and 3.4% of survivors, respectively. Although participants were not asked to report current pain attributable to other sources, it is reasonable to assume that the overall prevalence of pain, disregarding attribution source, is >21%.

Survivors reported significantly higher rates of all types of pain conditions assessed as well as higher use of prescription analgesics, even after controlling for observed demographic differences in income, employment, educational attainment, and marital status. These findings suggest a greater risk of being diagnosed with a pain condition among long-term childhood cancer survivors, consistent with data from studies with survivors of adult-onset cancer [29]. Despite previous reports that pain prevalence increases with age [4,36], rates among our young cohort of childhood cancer survivors (with the majority younger than 39 years) are similar to rates in the general population of older adults [7,30,36]. The findings are consistent with the known risk for health-related complications in childhood cancer survivors [8].

Hypotheses regarding demographic risk factors were largely confirmed. Female gender and lower educational attainment were associated with greater risks for all 3 pain outcomes. Minority status, unemployment, and being single were associated with greater risks for reporting all 3 pain conditions. Lower income was associated with great risk of using prescription pain medication and attributing pain to cancer. These risk factors correspond with known risk factors for pain in childhood cancer survivors and clinical and general adult populations. For instance, previous studies have found risk factors for pain, such as gender [13,40], lower socioeconomic status [9], minority status [2,27], and unemployment [4]. These factors may each relate to the availability of health insurance and access to health care [10,16]. These risk factors are also similar to known risk factors for poor health status [19,20]

Table 3
Odds ratios for using pain medication among childhood cancer survivors.

Covariates	Odds ratio	95% CI	*P*-value
Sex			
Male	1.0		
Female	1.77	(1.56–2.00)	<0.001
Race/ethnicity			
Caucasian	1.0		
Hispanic	1.12	(0.75–1.67)	0.59
African American	0.84	(0.61–1.14)	0.26
American Indian/Alaskan Native	1.21	(0.58–2.52)	0.61
Asian/Pacific Islander	0.65	(0.30–1.37)	0.25
Other	1.02	(0.82–1.27)	0.85
Age at baseline (years)			
18–29	1.0		
30–39	0.90	(0.76–1.07)	0.22
⩾39	1.0	(0.70–1.43)	0.99
Annual household income ($)			
⩽19,999	1.38	(1.15–1.66)	<0.001
20,000–59,999	1.16	(0.99–1.35)	0.06
⩾60,000	1.0		
Marital status			
Single (never married)	1.0		
Divorced/separated/widowed	1.32	(1.05–1.65)	0.02
Living as married	1.25	(1.00–1.57)	0.05
Married	1.09	(0.93–1.27)	0.28
Education			
Did not complete high school	1.0		
High school grad	0.80	(0.65–0.99)	0.04
High school + some college	0.79	(0.64–0.96)	0.02
College grad and post grad	0.57	(0.46–0.72)	<0.001
Work status			
Never worked	1.0		
Worked, but not in past 12 months	1.55	(1.13–2.13)	0.01
Worked in past 12 months	0.94	(0.70–1.27)	0.68
Age at diagnosis (years)			
0–3	1.0		
4–10	1.04	(0.86–1.26)	0.67
11–14	1.22	(0.97–1.53)	0.08
15–20	1.31	(1.02–1.68)	0.03
Primary diagnosis			
Leukemia	1.0		
Bone cancer	1.29	(1.04–1.60)	0.02
CNS tumor	0.89	(0.71–1.10)	0.29
Hodgkin lymphoma	0.91	(0.74–1.11)	0.35
Wilms tumor	1.03	(0.79–1.34)	0.82
Non-Hodgkin lymphoma	0.91	(0.72–1.17)	0.47
Neuroblastoma	1.33	(0.97–1.82)	0.08
Soft tissue sarcoma	1.32	(1.07–1.64)	0.01
Cranial radiation (Gy)[a]			
No radiation	1.0		
1.5–<50	1.0	(0.84–1.19)	0.99
50–110	0.93	(0.70–1.23)	0.60
Scatter	0.93	(0.80–1.10)	0.40

CNS, central nervous system.
[a] A separate regression model where cranial radiation substituted for primary diagnosis in above model adjusted for same covariates.

and poor psychological functioning [43] in childhood cancer survivors.

The observed pattern of differences in pain outcomes across cancer treatments, diagnoses, and age at diagnosis adds to what has previously been reported in smaller studies [3,41]. Compared with those who received no irradiation, survivors who received indirect (scatter) radiation to the brain had elevated risk for migraines. They were also more likely to attribute pain to cancer or its treatment. The finding provides indirect evidence for the argument that radiation-induced pain might sustain decades after treatment completion [5]. On the other hand, unexpectedly, compared with those who received no radiation, survivors who received cranial radiation doses in the range of 1.5–50 Gy to the brain reported lower risk for migraines and headaches. Results for direct brain irradiation in the range of 50–110 Gy, although not significant, also followed similar patterns. One possible explanation is that cognitive dysfunction associated with whole brain doses of ⩾18 Gy may have impacted the reporting of pain on the questionnaire [21]. A previous study found that brain tumor survivors who received the highest doses of cranial irradiation had the greatest severity of cognitive late effects, and were less likely to report pain/abnormal sensation and migraines [11]. It is plausible that the impact of brain irradiation on cognition may lead to both underreporting of pain and lack of attribution of current pain to cancer or its treatment. The differential finding of pain between survivors who received direct brain irradiation and those who only received indirect brain irradiation suggests the need for screening for cognitive dysfunction among the former group of survivors. Alternatively, perhaps those survivors exposed to direct cranial radiation differed in some other aspect of their treatment. We examined contributions in risk for pain from common systemic chemotherapy agents and found no clear effect. Further research may be warranted to confirm and explore this unexpected inverse pattern between cranial radiation and pain.

Our hypotheses regarding surgery and chemotherapy were not supported, as no significant associations with pain were detected (data not shown). Perhaps the impact of surgery and chemotherapy on pain decreases as survival time increases. Future studies should examine the impact of treatment within specific diagnostic groups as well as its trajectory longitudinally.

We observed increased risks for migraines and other headaches among survivors of non-Hodgkin lymphoma, Wilms tumors, and neuroblastoma in comparison to leukemia survivors, consistent with findings from a previous study [3] that survivors of Wilms tumor or advanced neuroblastoma exhibited high levels of pain during childhood. Tumors that potentially invade peripheral sensory afferents or paraspinal ganglia may produce peripheral sensitization followed by central sensitization [28]. This finding might relate to disruption of pain-inhibiting mechanisms or development of pathological pain pathways [37]. Although survivors of bone cancer or soft tissue sarcoma did not report higher levels of the specific pain conditions assessed, they were at increased risk of attributing pain to their cancer or treatment and of using prescription analgesia. The higher risk in these 2 diagnostic groups may relate to current ongoing pain in areas associated with their original tumor rather than in the specific pain locations included on the questionnaire. CNS cancer survivors reported lower rates of pain conditions compared with leukemia survivors. These findings were possibly related to cognitive dysfunction differences in the 2 diagnostic groups or to other yet unexplored reasons.

Consistent with our hypothesis and a previous study [1], we found that survivors diagnosed at a very young age (⩽3 years of age) had higher risk of reporting all 3 pain conditions compared with those diagnosed at an older age (3–20 years). In contrast, survivors diagnosed at an older age (15–20 years) were more likely to attribute pain to cancer and report prescription pain medication use compared to those diagnosed at a very young age (⩽3 years of age). One possible explanation is that knowledge of pain assessment and management in infants and toddlers was likely to be lower during the dates when these young children were diagnosed, which may have resulted in less adequate pain management. Also, survivors who were diagnosed at an older age might take "cancer diagnosis" as a more salient cue and thus be more likely to attribute current pain to their original cancer or treatment and be more likely to use analgesics. Survivors diagnosed at a very young age might not have remembered their cancer treatment and thus not associate any current pain with their original cancer.

Several limitations of the current study are worth noting. First, the study was cross-sectional in design, and thus causal relationships could not be determined. Furthermore, neither a standard-

Table 4
Odds ratios for predictors of recent pain attributed to cancer or its treatment in childhood cancer survivors.

	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value
Factors meeting proportional odds assumption									
Race/ethnicity[a]									
Non-Caucasian	1.0								
Caucasian	1.01	(0.86–1.19)	0.87						
Age at study (years)									
18–29	1.0								
30–39	1.11	(0.95–1.29)	0.19						
>39	1.22		0.26						
Annual household income ($)		(0.86–1.72)							
<$19,999	1.64	(1.37–1.95)	<0.001						
$20,000–$59,999	1.17	(1.01–1.35)	0.03						
>$60,000	1.0								
Marital status									
Single (never married)	1.0								
Divorced/separated/widowed	1.40	(1.12–1.74)	0.003						
Living as married	1.34	(1.08–1.67)	0.01						
Married	1.11	(0.96–1.29)	0.17						
Education									
Did not complete high school	1.0								
High school grad	0.67	(0.54–0.84)	<0.001						
High school + some college	0.77	(0.63–0.94)	0.01						
College grad and post grad	0.67	(0.54–0.83)	<0.001						
Primary diagnosis									
Leukemia	1.0								
Bone cancer	3.29	(2.73–3.98)	<0.001						
CNS tumor	0.96	(0.77–1.19)	0.69						
Hodgkin lymphoma	0.59	(0.48–0.73)	<0.001						
Wilms tumor	1.13	(0.86–1.47)	0.38						
Non-Hodgkin lymphoma	0.89	(0.70–1.13)	0.34						
Neuroblastoma	1.18	(0.84–1.66)	0.35						
Soft tissue sarcoma	1.93	(1.58–2.36)	<0.001						
Factors not meeting proportional odds assumption	⩾"A lot or very bad excruciating"			⩾"Medium amount"			⩾"Small amount"		
	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value
Sex									
Male	1.0			1.0			1.0		
Female	0.69	(0.52–0.91)	0.01	0.98	(0.84–1.16)	0.84	1.15	(1.02–1.30)	0.03
Work status									
Never worked	1.0			1.0			1.0		
Worked, but not in the previous 12 months	2.57	(1.19–5.54)	0.02	2.15	(1.36–3.39)	0.001	2.00	(1.36–2.94)	<0.001
Worked in the previous 12 months	0.93	(0.45–1.93)	0.84	0.92	(0.60–1.41)	0.69	1.28	(0.90–1.84)	0.17
Age at diagnosis (years)									
0–3	1.0			1.0			1.0		
4–10	0.92	(0.61–1.39)	0.70	0.92	(0.71–1.19)	0.52	1.17	(0.96–1.42)	0.12
11–14	0.89	(0.57–1.38)	0.59	1.18	(0.89–1.57)	0.25	1.65	(1.31–2.08)	<0.001
15–20	1.21	(0.79–1.87)	0.39	1.31	(0.98–1.75)	0.07	1.69	(1.32–2.16)	<0.001
Cranial radiation (Gy)[b]	1.0								
No radiation	1.0								
1.5–<50	0.95	(0.80–1.13)	0.57						
50–110	0.99	(0.75–1.31)	0.97						
Scatter	1.20	(1.04–1.40)	0.02						

CNS, central nervous system.
[a] This covariate was simplified to 2 levels due to sparse number.
[b] Adjusted for same covariates as diagnosis model in Table 3, with the exception of primary diagnosis.

ized pain measure was used nor were queries about pain in all parts of the body made (such as chest, back, abdomen, or leg). Participants were not asked to report on their use of over-the-counter analgesics, such as nonsteroidal antiinflammatory drugs. Thus, the limited choice of locations of pain and exclusion of over-the-counter pain medication may have led to the under-reporting of pain and use of analgesics in this population. To be conservative, we treated "not sure" response to the pain condition and prescription medication questions as a "no" response, a categorizing that might also have led to underestimated pain rates. Finally, the sample primarily comprised Caucasians. The limited ethnic diversity of the sample may have underestimated the overall pain rates, weakened the ability to detect ethnic differences, and reduced the generalizability of the findings. Lower percentage of minorities among siblings compared with survivors may also have overestimated differences between survivors and siblings; although this likelihood was reduced by the adjustment for race/ethnicity in all analyses. There may have also been differences between survivors and siblings in medical visits. Siblings, however, represent a better control group compared with population norms because of genetic and family-of-origin similarities [42]. It is possible, however, that siblings, due to the experience of having a sibling with cancer, are at elevated risk of pain outcomes themselves. If this is the case, then the relative risk results shown here would underestimate the

differences between survivors and a nonsibling control group. Despite these deficiencies in the questionnaire and possible underestimate of pain prevalence, the study did show differences in the pain outcomes assessed between survivors and siblings.

Importantly, risk factors for developing pain (ie, female gender, minority status, lower socioeconomic status, unemployment, and being single) identified in this study overlap considerably with known risk factors for other complications. Health-care providers should be mindful that adult survivors of childhood cancer who present with risk factors for developing poor health status are also likely to be at risk for pain. By identifying those at risk for poor outcomes, it may be possible to develop targeted, multi-faceted treatments to prevent adverse outcomes such as pain and high levels of analgesic use. Evaluating the psychological, social, environmental, and medical factors associated with pain in this population is an important direction for future research.

Conflict of interest statement

There is no conflict of interests among the authors.

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