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Stroke Impact on Mortality and Psychologic Morbidity Within the Childhood Cancer Survivor Study

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BACKGROUND: Poor socioeconomic and health-related quality of life (HRQOL) outcomes in survivors of childhood cancer can lead to distress and overall negatively impact the lives of these individuals. The current report has highlighted the impact of stroke and stroke recurrence on mortality, psychological HRQOL, and socioeconomic outcomes within the Childhood Cancer Survivor Study (CCSS). **METHODS:** The CCSS is a retrospective cohort study with longitudinal follow-up concerning survivors of pediatric cancer who were diagnosed between 1970 and 1986. Mortality rates per 100 person-years were calculated across 3 periods: 1) prior to stroke; 2) after first stroke and before recurrent stroke; and 3) after recurrent stroke. Socioeconomic outcomes, the standardized Brief Symptoms Inventory–18, the Medical Outcomes Study 36-Item Short Form Health Survey, and the CCSS–Neurocognitive Questionnaire also were assessed. **RESULTS:** Among 14,358 participants (median age, 39.7 years), 224 had a stroke after their cancer diagnosis (single stroke in 161 patients and recurrent stroke in 63 patients). Based on 2636 deaths, all-cause late mortality rates were 0.70 (95% CI, 0.68-0.73) prior to stroke, 1.03 (95% CI, 0.73-1.46) after the first stroke, and 2.42 (95% CI, 1.48-3.94) after the recurrent stroke. Among 7304 survivors, those with stroke were more likely to live with a caregiver (single stroke odds ratio [OR], 2.3 [95% CI, 1.4-3.8]; and recurrent stroke OR, 5.3 [95% CI, 1.7-16.8]) compared with stroke-free survivors. Stroke negatively impacted task efficiency (single stroke OR, 2.4 [95% CI, 1.4-4.1] and recurrent stroke OR, 3.3 [95% CI, 1.1-10.3]) and memory (single stroke OR, 2.1 [95% CI, 1.2-3.7]; and recurrent stroke OR, 3.5 [95% CI, 1.1-10.5]). **CONCLUSIONS:** Stroke and stroke recurrence are associated with increased mortality and negatively impact HRQOL measures in survivors of pediatric cancer. ***Cancer* 2019;0:1-9**. © *2019 American Cancer Society*.

KEYWORDS: health-related quality of life outcomes, mortality, pediatric cancer survivors, stroke, stroke recurrence.

INTRODUCTION

Given the improvements in survival in patients diagnosed with childhood cancer observed over the last 50 years, there are now almost 430,000 survivors in the United States.[1] However, survival comes at a cost, including an increased risk of late (>5 years from the time of diagnosis) mortality and chronic health conditions.[2,3] It is well established that survivors have an elevated risk of first-time and recurrent stroke compared with the general population, and this can be particularly heightened in patients previously exposed to radiation, such as those individuals diagnosed with brain tumors, lymphoma, and leukemia.[4-9] Previous analyses of the Childhood Cancer Survivor Study (CCSS) cohort demonstrated that age-adjusted stroke rates were elevated in cancer survivors (77 per 100,000 person-years [95% CI, 62-96 per 100,000 person-years]) compared with sibling controls (9 per 100,000 person-years [95% CI, 4-23 per 100,000 person-years]), with cranial radiotherapy (CRT) being a significant risk factor.[7,10,11] Despite this well-documented increased stroke risk in survivors of pediatric cancer, to the best of our knowledge there is a paucity of data regarding how stroke and stroke recurrence impact mortality, psychological morbidity, and overall health-related quality of life (HRQOL) outcomes.

Multiple studies have assessed predictors of poor HRQOL in adult stroke survivors. These studies have indicated that initial stroke volume and location, as well as initial neurological deficits, are key determinants for poor HRQOL.[12,13] Within the general pediatric population, young age at the time of stroke appears to have a strong influence on poor HRQOL, with the most negative impact correlating with certain periods of growth and development.[14]

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In the current study, we assessed the impact of stroke and stroke recurrence on all-cause late mortality (>5 years from cancer diagnosis), as well as on multiple aspects of psychological and socioeconomic outcomes within the CCSS.

MATERIALS AND METHODS

Sample Characteristics

The CCSS is a retrospective cohort with longitudinal follow-up of 5-year survivors of common pediatric cancers including leukemia, brain tumors, Hodgkin lymphoma, non-Hodgkin lymphoma, bone tumors, soft-tissue sarcomas, kidney tumors, and neuroblastoma who were diagnosed between January 1, 1970, and December 31, 1999, and were aged <21 years at the time of diagnosis. A detailed description of the cohort has been published previously,[15] and also is available online (www.ccss.stjude.org). Herein, we focused analyses on the original cohort of survivors who were diagnosed between 1970 and 1986 and who completed a comprehensive stroke survey that included questions regarding stroke recurrence. Appropriate institutional approval was received, and all participants consented prior to participation.

Data Collection

Cancer diagnosis and treatment exposures were collected by medical record abstraction at each participating institution. CCSS participants (or their proxy) periodically completed comprehensive questionnaires including information regarding demographics, medical conditions, and psychological outcomes (available at www.ccss.stjude.org/documents/original-cohort-questionnaires). Data were used from the baseline and multiple follow-up surveys over a 13-year interval, with outcomes for HRQOL, emotional distress, neurocognitive impairment, and social attainment taken from the follow-up surveys. A detailed stroke-specific questionnaire assessing stroke symptoms, treatment, and recurrence was conducted for participants who responded positively to a general stroke question.[9] Strokes were self-reported and dependent on the survivor definition of a stroke diagnosis. Neither brain imaging nor medical records were available for central review. Participants who had missing data regarding first stroke and recurrent stroke were not included in the final analyses (47 participants).

Outcome Measures

Vital status, date of death, and cause of death were ascertained by the National Death Index through the end of 2013. The underlying causes of death were classified using the *International Classification of Diseases, Ninth Revision* (ICD-9) and ICD-10. Deaths were grouped into 3 mutually exclusive categories using ICD-9 and ICD-10 coding: 1) recurrence or progression of primary cancer; 2) external causes (accidents, suicides, poisonings, and other external causes; ICD-9 codes 800-999 and ICD-10 codes V00-V99, Y00-Y89, X00-X99, and W00-W99); and 3) health-related causes including subsequent neoplasms (ICD-9 codes 140-239 and ICD-10 codes C00-C97 and D10-D36) and cardiac (ICD-9 codes 390-398, 402, 404, and 410-429 and ICD-10 codes I00-I02, I05-I09, I11, I13, I14, I20-I28, and I30-I52), pulmonary (ICD-9 codes 460-519 and ICD-10 codes J00-J99), and all other medical causes. Social attainment was assessed through self-report of marital status, living status, and educational level. Marital status was dichotomized into "ever married" or "never married," with "married" defined as either legal marriage or living as married. Survivors aged <30 years were excluded from the analysis of marital status. The decision to exclude patients aged <30 years was based on the goal to accommodate societal trends toward older age at the time of marriage. We hoped to avoid an inaccurate assessment of single survivors who were aged <30 years and assumed to be unmarried due to the impact of stroke versus societal norms (https://www.census.gov/data/tables/timeseries/demo/families/marital.html). Living status was dichotomized as living independently or not. Survivors aged <21 years were excluded from the analysis regarding living status. Educational attainment was categorized as "less than high school," "high school graduate," or "college graduate or higher." Survivors aged <25 years were excluded from the analysis of educational attainment. The decision to exclude patients aged <25 years was based on the goal to accommodate societal trends toward older age at the time of completion of educational attainment. We hoped to avoid an inaccurate assessment of lower educational attainment due to the impact of stroke versus societal norms (https://nces.ed.gov/fastfacts/display.asp?xml:id=27). Employment status was categorized into "employed," "unemployed, but seeking work," or "unable to work."

The Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) assessed HRQOL and comprises 8 domains: 1) physical functioning; 2) role limitations resulting from physical health problems; 3) bodily pain; 4) general health perceptions; 5) vitality; 6) social functioning; 7) role limitations resulting from emotional problems; and 8) mental health.[16] Domain scores were converted to T scores (mean, 50; SD, 10), with T scores ≤40 classified as impaired, consistent with the scoring manual.

The CCSS–Neurocognitive Questionnaire (NCQ) is a 25-item questionnaire that assessed 4 neurocognitive domains: 1) task efficiency; 2) emotional regulation; 3) organization; and 4) memory.[17] Domain scores for each participant

are calculated using a 3-point Likert scale with a range of 1 ("never a problem") to 3 ("often a problem"). These scores were compared with normative data to generate T scores, with participants with scores ≥63 classified as impaired.

The Brief Symptom Inventory 18 (BSI-18) measured emotional distress and has been validated previously in cancer survivors.[18] The BSI-18 classifies distress into 3 symptom scales: 1) anxiety (6 items); 2) depression (6 items); and 3) somatization (6 items). For each item, a 5-point Likert scale with a range of 1 ("not at all") to 5 ("extremely") is used to identify the degree to which symptoms were bothersome during the 7 days prior to test administration. The scale scores were compared with normative data to generate T scores, with participants with scores ≥63 classified as impaired. Survivors aged <18 years were excluded from BSI-18 analysis.

Statistical Analysis

Demographic and treatment characteristics of the survivors were tabulated and compared between CNS cancer and non-CNS cancer using chi-square tests. Mortality rates per 100 person-years starting from 5 years after the cancer diagnosis were estimated across 3 time periods: 1) prior to stroke (stroke free); 2) after the first stroke but before the recurrent stroke (after stroke); and (3) after the recurrent stroke. The follow-up period ended at the date of death or December 31, 2013, whichever came first. Cox regression analysis was used to assess the association between stroke and all-cause mortality hazard rates and health-related cause-specific mortality hazard rates, using age as the time scale, comparing the periods after stroke and after recurrent stroke with the stroke-free period, adjusting for sex, age at the time of diagnosis, and cardiovascular risk factors including hypertension and diabetes as well as hypercholesteremia (if reported to be >grade 1) (National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 Grade>1).

Associations between stroke and neurocognitive impairment, HRQOL, emotional distress, and social attainment were assessed using multivariable logistic regression, adjusting for sex, age at the time of diagnosis, age at the time of the survey, maximum cumulative CRT dose, and cumulative intrathecal (IT) and cumulative intravenous (iv) dose of methotrexate. Multivariable polytomous logistic regression was used for educational attainment and employment outcomes, stratified by survivors of CNS cancer and survivors of non-CNS cancer. The same adjustment variables were used for each group of survivors, with the exception of cumulative IT dose and cumulative iv dose of methotrexate for the cohort of survivors of CNS cancer.

RESULTS

Association Between Stroke and All-Cause and Health-Related Mortality

There were 14,358 survivors diagnosed with cancer between 1970 and 1986 and who completed the CCSS baseline questionnaire (Table 1). At a median follow-up of 32 years (range, 5-44 years) from diagnosis, there were 2664 deaths reported from all causes (Supporting Table 1 lists cause-specific deaths). Occurrence of stroke was reported among a total of 224 survivors (161 with a single stroke and 63 with a recurrent stroke), 48 of whom were deceased (32 after a single stroke and 16 after a recurrent stroke) at the time of follow-up. No patient reported a history of stroke prior to their cancer diagnosis. The corresponding late mortality rate (MR) per 100 person-years was 0.70 (95% CI, 0.68-0.73) in the stroke-free time period, 1.03 (95% CI, 0.73-1.46) in the post-stroke period, and 2.42 (95% CI, 1.48-3.94) in the post–recurrent stroke period (Tables 2 and 3). A history of single and recurrent stroke was associated with an increase in the late mortality hazard ratio (HR) compared with the stroke-free period (single stroke HR, 1.46 [95% CI, 1.03-2.07; $P = .04$] and recurrent stroke HR, 3.45 [95% CI, 2.11-5.65; $P < .001$]).

Among 1844 survivors of CNS tumors, 467 died prior to any reported stroke, whereas 87 survivors reported at least 1 stroke (Tables 2 and 3). The late MR per 100 person-years was 1.07 (95% CI, 0.98-1.17) in the prestroke period, 1.32 (95% CI, 0.78-2.23) in the post–single stroke period, and 1.44 (95% CI, 0.60-3.45) in the post–recurrent stroke period.

Among 12,467 survivors of non-CNS tumors, a total of 2121 died prior to any reported stroke, whereas 137 reported at least 1 stroke (Tables 2 and 3). There was a significantly increased MR noted in the post–recurrent stroke period of 3.50 per 100 person-years (95% CI, 1.94-6.33). Survivors of non-CNS tumors with a history of stroke recurrence had an increased HR for all-cause late mortality (HR, 4.77; 95% CI, 2.64-8.65 [$P < .001$]). This increase appeared to be driven by survivors of leukemia, in whom the all-cause late mortality HR increased by >10-fold in the recurrent stroke setting (HR, 10.90; 95% CI, 4.87-24.42 [$P < .001$]) (Table 2).

When specifically assessing health-related late mortality among survivors of childhood cancer, stroke was found to have a similar impact compared with all-cause mortality (Table 3). Survivors with a history of stroke demonstrated an increased cause-specific hazard rate for health-related late mortality (HR, 2.11; 95% CI, 1.40-3.20 [$P \leq .001$]), which was further increased by the presence of recurrent stroke (HR, 4.98; 95% CI, 2.87-8.63 [$P < .001$]).

TABLE 1. Demographic And Treatment Characteristics and Vital Status of Survivors of Childhood Cancer

Characteristic	All Diagnoses N = 14,358 N = 14,358 (%)	With Stroke[a] N = 224 (%)	No Stroke N = 14,087 (%)	*P*
Vital status				.24
Alive	11,694 (81.4%)	176 (78.60%)	11,499 (81.6%)	
Dead	2664 (18.6%)	48 (21.4%)	2588 (18.4%)	
Sex				.75
Male	7713 (53.7%)	118 (52.7%)	7573 (53.8%)	
Female	6645 (46.3%)	106 (47.3%)	6514 (46.2%)	
Race				.37
White, non-Hispanic	12,397 (86.3%)	194 (86.6%)	12,162 (86.3%)	
Black, non-Hispanic	694 (4.8%)	12 (5.4%)	678 (4.8%)	
Hispanic/Latino	750 (5.2%)	7 (3.1%)	741 (5.3%)	
Other	517 (3.6%)	11 (4.9%)	506 (3.6%)	
Mean age at baseline survey (SD), y	24 (7.8)	24 (7.8)	24 (7.8)	.63
Mean age at cancer diagnosis (SD), y	8 (5.8)	9 (5.7)	8 (5.8)	.23
Age at end of follow-up period (SD), y	39 (9.7)	40 (10.2)	39 (9.7)	.69
Mean y from diagnosis to death (SD)	31 (8.2)	31 (8.0)	31 (8.2)	.69
Mean age at confirmed first stroke (SD), y		21.3 (13.7)		
Mean age at second stroke (SD), y		29.0 (13.8)		
Maximum cranial radiation, Gy[b]				<.001
No CRT	4135 (33.6%)	40 (19.6%)	4090 (33.9%)	
<20	5200 (42.2%)	52 (25.5%)	5142 (42.6%)	
20 to <30	1464 (11.9%)	27 (13.2%)	1436 (11.9%)	
30 to <40	158 (1.3%)	3 (1.5%)	154 (1.3%)	
40 to <50	341 (2.8%)	10 (4.9%)	327 (2.7%)	
≥50	1026 (8.3%)	72 (35.3%)	933 (7.7%)	
Cumulative IT dose[b]				.81
None	7872 (65.3%)	139 (67.1%)	7694 (65.2%)	
<200 mg/m^2	2318 (19.2%)	39 (18.8%)	2277 (19.3%)	
≥200 mg/m^2	1859 (15.4%)	29 (14.0%)	1829 (15.5%)	
Cumulative iv methotrexate dose[b]				.05
None	9947 (81.0%)	180 (87.4%)	9727 (80.8%)	
<5000 mg/m^2	1454 (11.8%)	18 (8.7%)	1433 (11.9%)	
≥5000 mg/m^2	886 (7.2%)	8 (3.9%)	878 (7.3%)	
Smoking status at baseline[b]				.27
Current smoker	1817 (12.9%)	23 (10.4%)	1791 (13.0%)	
Former smoker	1080 (7.7%)	13 (5.9%)	1064 (7.7%)	
Never smoker	11,197 (79.5%)	186 (83.8%)	10,972 (79.4%)	
Hypertension				<.001
Yes	2171 (15.1%)	74 (33.0%)	2086 (14.8%)	
No	12,186 (84.9%)	150 (67.0%)	12,001 (85.2%)	
Diabetes				.26
Yes	726 (5.1%)	15 (6.7%)	707 (5.0%)	
No	13,631 (94.9%)	209 (93.3%)	13,380 (95.0%)	
Hypercholesteremia				<.001
Yes	1606 (11.2%)	64 (28.6%)	1533 (10.9%)	
No	12,751 (88.8%)	160 (71.4%)	12,554 (89.1%)	

Abbreviations: CRT, cranial radiotherapy; Gy, Gray; IT, intrathecal; iv, intravenous.
[a]A total of 47 survivors with missing stroke dates were excluded.
[b]Percentages for individual characteristics were calculated based on the total number of participants for whom information was available.

Association Between Stroke and Psychological Morbidity and Social Attainment

Of the overall cohort, a total of 7304 survivors of childhood cancer completed psychological and social questionnaires during follow-up. Occurrence of stroke was reported in a total of 122 of the survivors who completed psychological and social questionnaires (103 with a single stroke and 19 with a recurrent stroke). The median time between the most recently reported stroke and the psychosocial assessments was 16.2 years (range, 0-36.2 years). Respondents included 900 survivors of CNS cancer and 6404 survivors of non-CNS cancer. The CRT dose was higher in survivors of CNS cancer compared with survivors of non-CNS cancer ($P < .001$) (see Supporting Table 2). Survivors of childhood cancer with history of stroke also were more likely to report a history of hypertension ($P < .001$) (see Supporting Table 2) and hypercholesterolemia ($P = .003$) (see Supporting Table 2).

A total of 3095 survivors for whom information regarding stroke was available, including no stroke history, were excluded from the analysis of marriage outcomes

TABLE 2. Stroke and All-Cause Mortality in Survivors of Childhood Cancer Overall and by Primary Cancer Diagnosis[a]

					Late MR[b]			Late Mortality HR[b,c]	
Cancer Type	No. of Strokes	No. of Deaths	Population[a]	Person-Years	MR	95% CI	HR	95% CI	*P*
Any	No stroke	2588	14,087	368,720	0.70	0.68-0.73	Referent		
	Single stroke	32	161	3095	1.03	0.73-1.46	**1.46**	**1.03-2.07**	**.04**
	Recurrent stroke	16	63	662	**2.42**	**1.48-3.94**	**3.45**	**2.11-5.65**	**<.001**
CNS	No stroke	467	1757	43,526	1.07	0.98-1.17	Referent		
	Single stroke	14	54	1062	1.32	0.78-2.23	1.31	0.77-2.23	.32
	Recurrent stroke	5	33	348	1.44	0.60-3.45	1.42	0.58-3.47	.44
Other than CNS	No stroke	2121	12,330	325,194	0.65	0.63-0.68	Referent		
	Single stroke	18	107	2033	0.89	0.56-1.41	1.24	0.78-1.97	.37
	Recurrent stroke	11	30	314	**3.50**	**1.94-6.33**	**4.77**	**2.64-8.65**	**<.001**
Leukemia	No stroke	683	4753	122,832	0.56	0.52-0.60	Referent		
	Single stroke	7	60	1224	0.57	0.27-1.20	0.99	0.47-2.10	.98
	Recurrent stroke	6	12	125	**4.81**	**2.16-10.70**	**10.90**	**4.87-24.42**	**<.001**
HL	No stroke	607	1903	49,634	1.22	1.13-1.32	Referent		
	Single stroke	4	16	222	1.80	0.68-4.80	1.01	0.38-2.74	.98
	Recurrent stroke	1	5	32	3.08	0.43-21.89	1.33	0.18-9.60	.78

Abbreviations: CNS, central nervous system; HL, Hodgkin lymphoma; HR, hazard ratio; MR, mortality rate.
[a]The sum of the population was not 14,358 because of missing information regarding stroke in 47 patients.
[b]Bold type indicates statistical significance.
[c]Model was adjusted for sex, age at the time of diagnosis, and cardiovascular risk factor >grade 1 including hypertension, diabetes, and hypercholesterolemia.

TABLE 3. Stroke and Health-Related Mortality in Survivors of Childhood Cancer Overall and by Primary Cancer Diagnosis

					Late MR[b]			Late Mortality HR[b,c]	
Cancer Type	No. of Strokes	No. of Deaths	Population[a]	Person-Years	MR	95% CI	HR	95% CI	*P*
Any	No stroke	1159	14,087	368,720	0.31	0.30-0.33	Referent		
	Single stroke	23	161	3095	0.74	0.49-1.12	**2.11**	**1.40-3.20**	**<.001**
	Recurrent stroke	13	63	**662**	**1.96**	**1.14-3.38**	**4.98**	**2.87-8.63**	**<.001**
CNS	No stroke	204	1757	43,526	0.47	0.41-0.54	Referent		
	Single stroke	2	54	1062	1.04	0.57-1.87	**2.10**	**1.14-3.87**	**.02**
Other than CNS	No stroke	955	12,330	325,194	0.29	0.28-0.31	Referent		
	Single stroke	12	107	2033	0.59	0.34-1.04	1.62	0.92-2.88	.10
	Recurrent stroke	8	30	**314**	**2.55**	**1.27-5.09**	**6.06**	**3.01-12.20**	**<.001**
Leukemia	No stroke	224	4753	122,832	0.18	0.16-0.21	Referent		
	Single stroke	2	60	1224	0.16	0.04-0.65	0.77	**0.19-3.10**	.71
	Recurrent stroke	4	12	**125**	**3.20**	**1.20-8.54**	**16.14**	**5.94-43.84**	**<.001**
HL	No stroke	347	1903	49,634	0.70	0.63-0.78	Referent		
	Single stroke	4	16	222	1.80	0.68-4.80	1.77	0.65-4.83	.26
	Recurrent stroke	1	5	32	3.08	0.43-21.89	2.57	0.35-18.64	.35

Abbreviations: CNS, central nervous system; HL, Hodgkin lymphoma; HR, hazard ratio; MR, mortality rate.
[a]The sum of the population was not 14,358 because of missing information regarding stroke in 47 patients.
[b]Bold type indicates statistical significance.
[c]Model was adjusted for sex, age at the time of diagnosis, and cardiovascular risk factor >grade 1 (National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 Grade>1) including hypertension, diabetes, and hypercholesterolemia.

based on an age of <30 years at the time of analysis. The remaining survivors with a history of a single stroke were less likely to be married (odds ratio [OR], 0.5; 95% CI, 0.3-0.95 [$P = .04$]) compared with survivors with no stroke history (Table 4).

Survivors with a history of a single stroke (95 survivors; OR, 2.3 [95% CI, 1.4-3.8; $P = .002$]) or recurrent stroke (18 survivors; OR, 5.3 [95% CI, 1.7-16.8; $P = .005$]) were more likely to be living with a caregiver compared with stroke-free survivors. Stroke history was found to be associated with an elevated risk of an inability to work rather than being employed, and this risk tripled between survivors with single and recurrent strokes (OR for single stroke, 3.2 [95% CI, 1.8-5.7; $P < .001$]; and OR for recurrent stroke, 9.5 [95% CI, 3.2-27.9; $P < .001$]) (Table 5). It is important to note that survivors who experienced a second stroke were much more likely to report "no recovery" from the stroke (first stroke

TABLE 4. Association Between Stroke and Social Attainment in Survivors of Childhood Cancer[a]

	Stroke	Total	Yes No. (%)	No No. (%)	OR[b] (95% CI) (Yes Vs No)[c]	P[c]
Ever married	None	4080	3008 (73.7)	1072 (26.3)		
	Single	67	37 (55.2)	30 (44.8)	**0.5 (0.3-1.0)**	**.04**
	Recurrent	8	6 (75.0)	2 (25.0)	1.3 (0.2-7.0)	.75
Living with a caregiver	None	6707	1530 (22.8)	5177 (77.1)		
	Single	95	40 (42.1)	55 (57.9)	**2.3 (1.4-3.8)**	**.002**
	Recurrent	18	11 (61.1)	7 (38.9)	**5.3 (1.7-16.8)**	**.005**

Abbreviation: OR, odds ratio.
[a]Excluding survivors who were aged <30 years for outcome regarding ever married and survivors who were aged <21 years for outcome regarding independent living.
[b]The OR was adjusted for sex, age at the time of diagnosis, age at the time of the survey, maximum cranial radiotherapy dose, cumulative intrathecal dose, and cumulative intravenous methotrexate dose.
[c]Bold type indicates statistical significance.

TABLE 5. Association Between Stroke and Employment Status, Overall and by Cancer Type in Survivors of Childhood Cancer

						Unemployed Vs Employed		Unable to Work Vs Employed	
Diagnosis	Stroke	Total	Employed No. (%)	Unemployed No. (%)	Unable to Work No. (%)	OR[a] (95% CI)[b]	P[b]	OR[a] (95% CI)[b]	P[b]
Any cancer type	None	7077	6314 (89.2)	341 (4.8)	422 (6.0)	1.0		1.0	
	Single	100	72 (72.0)	5 (5.00)	23 (23.0)	1.2 (0.5-3.1)	.67	**3.2 (1.8-5.7)**	**<.001**
	Recurrent	19	10 (52.6)	1 (5.26)	8 (42.1)	1.5 (0.2-12.1)	.72	**9.5 (3.2-27.9)**	**<.001**
CNS	None	822	632 (76.9)	67 (8.2)	123 (15.0)	1.0		1.0	
	Single	32	17 (53.1)	3 (9.4)	12 (37.5)	1.6 (0.4-5.7)	.49	**4.1 (1.8-9.3)**	**<.001**
	Recurrent	10	3 (30.0)	1 (10.0)	6 (60.0)	3.2 (0.3-33)	.33	**12.7 (2.7-59.4)**	**.001**
Other than CNS	None	6255	5682 (90.8)	274 (4.4)	299 (4.8)	1.0		1.0	
	Single	68	55 (80.9)	2 (2.9)	11 (16.2)	0.9 (0.2-3.9)	.91	**2.6 (1.1-6.3)**	**.03**
	Recurrent	9	7 (77.8)	0 (0.0)	2 (22.2)	0.0 (0.0->999)	.97	**8.0 (1.6-40.5)**	**.01**

Abbreviations: CNS, central nervous system; OR, odds ratio.
[a]The OR was adjusted for sex, age at the time of diagnosis, age at the time of the survey, maximum cranial radiotherapy dose, cumulative intrathecal dose, and cumulative intravenous methotrexate dose for survivors of non-CNS tumors; for survivors of CNS tumors, the OR was adjusted for sex, age at the time of diagnosis, age at the time of the survey, and maximum cranial radiation dose.
[b]Bold type indicates statistical significance.

rate of no recovery of 8.86% vs second stroke rate of no recovery of 26.3%). A total of 1580 survivors for whom information regarding stroke was available, including no stroke history, were excluded from the analysis of educational outcomes based on an age <25 years at the time of analysis. For survivors of CNS tumors, a history of stroke was associated with increased odds of having attained less than a high school education compared with achieving a college education or higher (OR, 4.0; 95% CI, 1.2-13.7 [$P = .03$]) (see Supporting Table 3).

Adjusting for relevant treatment exposures, survivors who reported a history of strokes had more problems with task efficiency (OR for a single stroke, 2.4 [95% CI, 1.4-4.1; $P < .001$]; and OR for recurrent stroke, 3.3 [95% CI, 1.1-10.3; $P = .04$]), emotional regulation (OR for recurrent stroke, 3.6 [95% CI, 1.2-11.2; $P = .03$]), and memory (OR for a single stroke, 2.1 [95% CI, 1.2-3.7; $P = .009$]; and OR for a recurrent stroke, 3.5 [95% CI, 1.1-10.5; $P = .03$]) compared with those without a history of stroke (Table 6). Survivors with a stroke history reported reduced HRQOL in terms of physical functioning compared with those without a stroke history (OR for a single stroke, 3.1 [95% CI, 1.8-5.3; $P < .001$]; and OR for recurrent stroke, 11.0 [95% CI, 3.7-32.5; $P < .001$]). An increased prevalence of depressive symptoms was observed in survivors with recurrent stroke compared with those with a single stroke (43.8% vs 11.3%; OR, 4.9 [95% CI, 1.7-13.9; $P = .003$]).

DISCUSSION

Survivors of pediatric cancer are at an increased risk of stroke. The results of the current study demonstrated to the best of our knowledge for the first time that, when stroke does occur, survivors are at an increased risk of both all-cause and health-related mortality and are negatively impacted across the domains of social attainment, HRQOL, neurocognitive function, and emotional distress. Overall, all-cause mortality as well as health-related

TABLE 6. Association Between Stroke and Neurocognitive Function and HRQOL in Survivors of Pediatric Cancer (N = 7304)

	Variable	Stroke	Total	Yes No. (%)	No No. (%)	OR[a] (95% CI)[b]	P[b]
NCQ	Task efficiency	None	5917	1399 (23.6)	4518 (76.4)	1.0	
		Single	81	42 (51.9)	39 (48.2)	**2.4 (1.4-4.1)**	**<.001**
		Recurrent	15	9 (60.0)	6 (40.0)	**3.3 (1.1-10.3)**	**.04**
	Emotional regulation	None	5921	746 (12.6)	5175 (87.4)	1.0	
		Single	82	13 (15.9)	69 (84.2)	1.1 (0.6-2.3)	.70
		Recurrent	15	6 (40.0)	9 (60.0)	**3.6 (1.2-11.2)**	**.03**
	Organization	None	5923	777 (13.1)	5146 (86.9)	1.0	
		Single	81	15 (18.5)	66 (81.5)	1.0 (0.5-2.0)	.92
		Recurrent	15	4 (26.7)	11 (73.3)	2.2 (0.7-7.3)	.19
	Memory	None	5923	840 (14.2)	5083 (85.8)	1.0	
		Single	82	21 (25.6)	61 (74.4)	**2.1 (1.2-3.7)**	**.009**
		Recurrent	15	6 (40. 0)	9 (60.0)	**3.5 (1.1-10.5)**	**.03**
SF-36	Physical function	None	6141	712 (11.6)	5429 (88.4)	**1.0**	
		Single	89	27 (30.3)	62 (69.7)	**3.1 (1.8-5.3)**	**<.001**
		Recurrent	16	9 (56.3)	7 (43.8)	**11.0 (3.7-32.5)**	**<.001**
	Role limitations–physical	None	6120	806 (13.2)	5314 (86.8)	1.0	
		Single	87	21 (24.1)	66 (75.9)	**1.9 (1.1-3.3)**	**.03**
		Recurrent	16	7 (43.8)	9 (56.3)	**3.9 (1.4-11.3)**	**.01**
	Bodily pain	None	6134	1125 (18.3)	5009 (81.7)	1.0	
		Single	88	29 (33.0)	59 (67.1)	**2.0 (1.2-3.4)**	**.008**
		Recurrent	16	6 (37.5)	10 (62.5)	**3.1 (1.1-8.9)**	**.04**
	General health	None	5986	1366 (22.8)	4620 (77.2)	1.0	
		Single	86	30 (34.9)	56 (65.1)	1.4 (0.9-2.4)	.17
		Recurrent	16	9 (56.3)	7 (43.6)	**3.9 (1.4-11.0)**	**.01**
	Vitality	None	5998	1465 (24.4)	4533 (75.6)	1.0	
		Single	84	24 (28.6)	60 (71.4)	1.3 (0.8-2.3)	.32
		Recurrent	16	6 (37.5)	10 (62.5)	1.5 (0.5-4.6)	.43
	Role limitations–emotional	None	6106	1092 (17.9)	5014 (82.1)	1.0	
		Single	87	16 (18.4)	71 (81.6)	0.9 (0.5-1.8)	.84
		Recurrent	16	4 (25.0)	12 (75.0)	1.1 (0.3-4.1)	.85
	Social function	None	6150	820 (13.3)	5330 (86.7)		
		Single	88	12 (13.6)	76 (86.4)	1.1 (0.6-2.1)	.77
		Recurrent	16	7 (43.8)	9 (56.3)	**4.1 (1.4-11.6)**	**.009**
	Mental health	None	5998	1082 (18.0)	4916 (82.0)		
		Single	84	17 (20.2)	67 (79.8)	1.2 (0.6-2.1)	.60
		Recurrent	16	3 (18.8)	13 (81.3)	0.7 (0.1-2.9)	.59
BSI-18[c]	Depression	None	6153	692 (11.3)	5461 (88.8)		
		Single	86	8 (9.3)	78 (90.7)	0.9 (0.4-1.9)	.69
		Recurrent	16	7 (43.8)	9 (56.3)	**4.9 (1.7-13.9)**	**.003**
	Anxiety	None	6153	440 (7.2)	5713 (92.9)		
		Single	86	7 (8.1)	79 (91.9)	1.3 (0.5-2.9)	.60
		Recurrent	16	3 (18.8)	13 (81.3)	1.9 (0.4-8.6)	.40
	Somatization	None	6151	801 (13.0)	5350 (87.0)		
		Single	86	14 (16.3)	72 (83.7)	1.1 (0.5-2.2)	.85
		Recurrent	16	3 (18.8)	13 (81.3)	1.8 (0.5-6.5)	.37

Abbreviations: BSI-18, Brief Symptom Inventory-18; HRQOL, health-related quality of life; NCQ, Childhood Cancer Survivor Study–Neurocognitive Questionnaire; OR, odds ratio; SF-36, Medical Outcomes Study 36-Item Short Form Health Survey.

[a]The OR was adjusted for sex, age at the time of diagnosis, age at the time of the survey, maximum cranial radiotherapy dose, cumulative intrathecal dose, and cumulative intravenous methotrexate dose.

[b]Bold type indicates statistical significance.

[c]Survivors who were aged <18 years were excluded.

mortality increased by >3-fold in cancer survivors who experienced repeated strokes compared with those with no stroke history. Conversely, overall stroke-related mortality in the average adult population has appeared to be decreasing in recent decades, which appears to be divergent to stroke-related mortality in survivors of pediatric cancer.[19] Stroke risk in survivors of pediatric cancer has been associated previously with dose-dependent exposure to CRT.[10] It is interesting to note that the majority of the patient population in the current study did not receive CRT or received only low-dose exposure (<20 grays) as may be expected in survivors of leukemia or non-CNS solid tumors. Survivors of CNS tumors did not have a significantly greater risk of all-cause mortality after stroke or recurrent stroke. This may be attributable to the fact that the reference group, survivors of CNS tumors without a history of stroke, already have an elevated risk of mortality.[2] Regardless, recommendations to screen and

potentially intervene with regard to stroke risk in survivors of pediatric cancer might need to be implemented more aggressively. The data from the current study support close screening and potential aggressive interventions when possible.[10] We have highlighted the negative impact stroke has on HRQOL, neurocognition, emotional well-being, and socioeconomic achievement beyond the risk associated with CRT exposure and neurotoxic chemotherapies. This was magnified further within the setting of recurrent stroke. Specifically, the odds of reporting poorer physical function in HRQOL more than tripled when survivors experienced a recurrent stroke compared with those with a single stroke. The odds of reporting lower scores on HRQOL related to social function also quadrupled when comparing those with a history of recurrent strokes with those with a history of a single stroke. Survivors with a stroke history were less likely to be married and to progress to postsecondary education, and were more likely to be unemployed or unable to work and more likely to fail to achieve independent living compared with their counterparts without a stroke history. Previous studies have shown that survivors of childhood cancer who demonstrated lower neurocognitive outcomes also demonstrated worse HRQOL,[20,21] and were more likely to be economically dependent and to demonstrate lower earning ability, and stroke appears to contribute to these risks.[22-24] These previously established risks combined with the newly demonstrated overall increased negative impact of stroke and stroke recurrence on HRQOL and long-term morbidity in survivors of pediatric cancer[25] identify a high-risk population. Presumably, the link between stroke and these long-term outcomes is a combined effect of stroke-related neurocognitive injury, ongoing medical management in the poststroke period, and the burden of a new life-threatening event in a patient who already has experienced one life-threatening diagnosis, among other stressors. The former explanations also would be in line with reports of lower QOL measures among adults with a history of stroke, unrelated to a prior history of cancer.[26,27] However, larger prospective studies are needed to more completely isolate the etiology of why such a high percentage of survivors of pediatric cancer who experience stroke go on to develop negative HRQOL and psychosocial outcomes.

One key limitation of the current study was the self-reported nature of patient medical history, including stroke history and cancer recurrence. Patient self-report could be derived from self-perceived symptoms, physician-derived diagnoses, and/or imaging reports. Self-reported outcomes may introduce bias by including both false-positive results, such as focal neurologic stroke-like events (as in transient ischemic attack, nonconvulsive seizure, or hemiplegic migraine) that are unconfirmed by a physician, and false-negative findings, such as subclinical strokes that are undetected by patients or not evident to their clinicians. The standard outcome measure of stroke-related morbidity is the modified Rankin Scale, which is not captured within the CCSS survey. The self-reported HRQOL variables of "physical function" and "physical limitations" were not corroborated by neurological or clinical examinations. Thus, stroke-related morbidity outcomes can be concluded from CCSS data, but we were unable to precisely attribute a clinically meaningful severity to self-reported physical limitations. In addition, the reporting of the occurrence of a recurrent or second stroke also may include recrudescence of incident stroke symptoms rather than a new, separate event. It also is conceivable that symptoms of a stroke mimic recurrent cancer; given the nature of the self-reported data collection, we were unable to assess a reliable association between stroke and cancer recurrence. As is true in other self-reported questionnaire-based studies, there is the possibility of participation and recall biases, degrading data from both the survivor population and sibling control cohort population.[2]

Because incident stroke correlates with poorer HRQOL measures, there may be an indication to intervene sooner and more aggressively to prevent stroke in these survivors. Tighter control of modifiable stroke risk factors (eg, hyperlipidemia and hypertension) and antithrombotic therapies for primary and secondary stroke prevention may be warranted in this population.[10] Survivors who have experienced stroke may require additional support services to allay the negative impact of stroke on physical, neurocognitive, and emotional health to help these patients achieve higher rates of employment and independent living. As we continue to improve therapy for pediatric cancer patients and increase survivorship, it will be paramount for both pediatric and adult practitioners to identify those tumor survivors at greatest risk of poor long-term outcomes and low HRQOL.

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AUTHOR CONTRIBUTIONS

Sabine Mueller: Design and interpretation of the data and drafting of the article. **Cassie N. Kline:** Analysis and interpretation of the data and drafting of the article. **Robin A. Buerki:** Analysis and interpretation of the data and drafting of the article. **Yan Chen:** Design and interpretation of the data and drafting of the article. **Yutaka Yasui:** Design and interpretation of the data and drafting of the article. **Rebecca Howell:** Design and interpretation of the data and drafting of the article. **Kevin C. Oeffinger:** Design and interpretation of the data and drafting of the article. **Wendy M. Leisenring:** Design and interpretation of the data and drafting of the article. **Leslie L. Robison:** Design and interpretation of the data and drafting of the article. **Gregory T. Armstrong:** Design and interpretation of the data and drafting of the article. **Heather J. Fullerton:** Design and interpretation of the data and drafting of the article. **Kevin R. Krull:** Design and interpretation of the data and drafting of the article.

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