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Suicide Ideation and Associated Mortality in Adult Survivors of Childhood Cancer

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Abstract

Background—Adult survivors of childhood cancer are at-risk for suicide ideation, though longitudinal patterns and rates of recurrent suicide ideation are unknown. We investigated the prevalence of late report (i.e. post-initial assessment) and recurrent suicide ideation in adult survivors of childhood cancer, identified predictors of suicide ideation, and examined associations among suicide ideation and mortality.

Methods—Participants included 9,128 adult survivors of childhood cancer and 3,082 sibling controls enrolled in the Childhood Cancer Survivor Study who completed a survey question assessing suicide ideation on one or more occasions between 1994 and 2010. Suicide ideation was assessed using the Brief Symptom Inventory-18. Mortality data was ascertained from the National Death Index.

Results—Survivors were more likely to report late (Odds Ratio (OR) =1.9; 95% Confidence Interval (CI) =1.5–2.5) and recurrent suicide ideation (OR=2.6, 95% CI=1.8–3.8) compared to siblings. Poor physical health status was associated with increased risk of suicide ideation in survivors (late report: OR=1.9, 95% CI=1.3–2.7; recurrent: OR=1.9, 95% CI=1.2–2.9). Suicide

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ideation was associated with increased risk for all-cause mortality (Hazard Ratio (HR) =1.3, 95% CI=1.03–1.6) and death by external causes (HR=2.4, 95% CI=1.4–4.1).

Conclusion—Adult survivors of childhood cancer are at-risk for late report and recurrent suicide ideation, which is associated with increased risk of mortality. Routine screening for psychological distress in adult survivors appears warranted, especially for survivors who develop chronic physical health conditions.

Keywords

childhood cancer; survivorship; suicide; mortality; late effects

INTRODUCTION

Adult survivors of childhood cancer are at risk for late occurring morbidities associated with their cancer and its treatment. Cardiopulmonary, musculoskeletal, endocrine, and neurologic complications are frequently reported^{1–4}, and three-fourths of survivors will develop a chronic health condition within 30 years of diagnosis⁵. In addition, subgroups of survivors are at risk for psychological late effects including symptoms of depression, anxiety, and post-traumatic stress^{6, 7}.

Suicidal behavior is a potential consequence of psychological distress. Suicide is a significant public health concern and its relevance is underscored by national mortality statistics indicating a 15% increased rate of suicide from 2000 to 2009, with suicide representing the leading cause of injury mortality in the United States⁸. Epidemiologic studies have reported increased risk for suicide associated with a variety of adult onset cancers^{9–12}, with elevated relative risk observed as many as 15 years after diagnosis¹³. While past reports have not indicated increased risk of suicide mortality in long-term adult survivors of childhood cancer compared to rates observed in the general population^{14, 15}, increased risk of suicide ideation (SI; i.e. thoughts associated with ending one's life) has been reported in adult survivors of childhood cancer compared to sibling controls¹⁶.

Little is known about suicidality in aging adult survivors of childhood cancer. The extent to which late SI emerges, recurs, or is associated with mortality in this population has important implications for screening guidelines and long-term care for survivors. The purposes of this study were to: 1) estimate and compare the prevalence of late report and recurrent SI in a large cohort of adult survivors of childhood cancer and a sibling control group; 2) identify predictors of late report and recurrent SI in survivors; and, 3) investigate the associations among SI and mortality in survivors.

PATIENTS AND METHODS

Childhood Cancer Survivor Study (CCSS)

The CCSS cohort consists of survivors of one of eight childhood cancers diagnosed 21 years of age and treated at one of 26 institutions between 1970 and 1986. All survivors were 5 years from their original cancer diagnosis upon study enrollment. Sibling controls were recruited from a randomly selected subset of survivors. Study participants completed questionnaires including information on suicide ideation at baseline (beginning in 1992) and subsequent follow-up questionnaires initiated in 2003 (follow-up 2003) and 2007 (follow-up 2007). Additional descriptions of the CCSS methodology and participants have been published elsewhere^{17, 18}. The study was approved by the institutional review board at each collaborating institution and informed consent was obtained from each participant.

Study Specific Samples

Prevalence of Suicide Ideation—At each study time point survivors and siblings 18 years of age who completed a survey item inquiring about SI were included in prevalence estimates of SI. Participants with surveys completed by proxy report were excluded. 9,128 survivors and 3,082 siblings were included in the baseline analysis (1992–2002), 7,251 survivors and 2,764 siblings in the 2003 analysis, and 7,124 survivors and 2,296 siblings in the 2007 analysis of SI.

Late Report Suicide Ideation—The study population for late report SI included survivors and siblings 18 years of age who reported no SI at baseline, and completed at least one follow-up survey. 7,230 survivors and 2,672 siblings were included in analysis of this outcome.

Recurrent Suicide Ideation—The study population for recurrent SI included survivors and siblings 18 years of age at baseline who completed the SI survey item at two or more study time points. 7,708 survivors and 2,776 siblings were included in analysis of this outcome.

Mortality—The study population for mortality included survivors 18 years of age who completed the SI survey item at any survey time point (i.e., baseline, follow-up 2003, or follow-up 2007) prior to the National Death Index search, December 31, 2007. 10,072 survivors were included in analysis of this outcome.

Primary Outcome

Each CCSS survey included items from the Brief Symptom Inventory-18 (BSI-18), a psychological screening inventory designed to assess symptoms of acute emotional distress¹⁹. Suicide ideation was assessed through a single item: “thoughts of ending your life”. Participants responded to this item on a 5-point Likert scale ranging from “not at all” to “extremely”. Consistent with previous CCSS methods, participants who endorsed any suicidal ideation on the item were considered to have SI¹⁶. Late report SI was defined as report of SI at follow-up 2003 or follow-up 2007 without endorsement of SI at baseline. Recurrent SI was defined as report of SI at >1 survey.

Individuals eligible for participation in the CCSS cohort were included in a search of the National Death Index (NDI) for deaths that occurred between January 1, 1979 and December 31, 2007. For individuals who died in the United States, the NDI provides cause of death information using the International Classification of Diseases (ICD). Additional information regarding ascertainment of cause of death for the CCSS cohort has been described elsewhere^{14, 15}. A previously developed classification schema was used to classify death as attributable to: 1) recurrence (or progression) of primary disease, 2) external causes (i.e. suicide, falls, motor vehicle accidents), or 3) nonrecurrence, nonexternal causes^{14, 15}.

Predictors and Covariates

All predictors and covariates were measured at baseline. Demographic and socioeconomic variables considered in the analyses included sex, age diagnosis, age at the time of survey completion, educational attainment (high school or >high school), marital status (single, never married; married, living as married; divorced, separated, widowed), health insurance status, and household income (<\$20,000 or \$20,000). Neurologic variables included headache, bodily pain, and history of seizure. Survivor’s self-reported physical health status was categorized as fair or poor vs. good, very good, or excellent. Treatment variables

included radiation therapy which was categorized as none, non-cranial radiation, <20Gy cranial radiation, and ≥20Gy cranial radiation. Chemotherapy was categorized as yes or no. Because the SI item from the BSI-18 is part of the depression subscale, depressive scores were calculated with the SI item treated as a missing value using published missing data rules¹⁹. Sex-specific scores were calculated based on standardized normative values and scores falling ≥90th percentile (T-score ≥63) were considered to represent a clinical level of depressive symptoms. The BSI-18 has previously been validated in adult survivors of childhood cancer²⁰. Severity of chronic medical conditions was coded using survivor self-report regarding their physical health conditions including age of onset of the condition. The Common Terminology Criteria for Adverse events (version 3) was used to grade conditions as mild (Grade 1) or moderate (Grade 2) vs. severe (Grade 3) or life-threatening/disabling (Grade 4)⁵.

Statistical Analysis

Descriptive statistics were calculated for all outcomes, predictors and covariates used in the analyses. Survivor and sibling SI was examined through logistic regression modeling with robust variance estimates to account for within family correlation using SAS version 9.2 PROC Genmod with binomial distribution and logit link (SAS Institute, Cary, NC). To investigate predictors of late and recurrent SI in survivors, multivariable models were constructed using a backward selection procedure based on minimum Akaike Information Criterion (AIC). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for predictors and covariates retained in the final models. Fine and Gray's competing risk regression model was used to investigate the difference in cumulative incidence of a specific death cause (e.g., suicide) between survivors with and without history of SI, treating other causes of death as competing risks²¹. The time scale was set from time of completion of the baseline questionnaire to time of death (or time of last contact) and December 31, 2007 (date of NDI search) was used as the cutoff date for censoring. Hazard ratios and 95% CIs for history of SI were calculated. The cumulative incidences of the 15 year follow-up for cause of death were estimated using Gray's method²².

RESULTS

Table 1 provides characteristics of survivors with late report and recurrent SI and survivors with no history of SI. Survivors were 1.8 to 2.0-times more likely than siblings to endorse SI at baseline and at each follow-up survey (see Table 2).

Late Report Suicide Ideation

Among survivors who did not endorse SI at baseline, 8% reported SI at a subsequent follow-up survey compared to 4% of siblings (OR=1.9; 95% CI=1.5–2.5) (Table 2). Survivors were, on average, 26 years from diagnosis and 34 years of age at the time of reporting late SI. After adjusting for the significant effects of depression at baseline on SI (OR=3.0; 95% CI=2.1–4.1), survivors who reported poor physical health status and headache at baseline were significantly more likely to report late SI compared to those with good health status and no pain (OR=1.9; 95% CI=1.3–2.7; OR=1.4; 95% CI=1.1–1.8, respectively). Chronic medical conditions at baseline were significantly associated with late report SI (Grade 1 or 2: OR=1.5, 95% CI=1.1–2.1; Grade 3 or 4: OR=1.6, 95% CI=1.2–2.3). History of seizures was associated with a 2-fold increased likelihood of late report SI (OR=2.0; 95% CI=1.3–3.2) (Table 3).

Recurrent Suicide Ideation

Survivors were 2.6 times more likely to report recurrent SI compared to siblings (OR=2.6, 95% CI=1.8–3.8) (Table 2). Among survivors who endorsed suicide ideation once, 22%

reported SI at a subsequent follow-up survey. Survivors were, on average, 29 years of age (20 years from diagnosis) at their first report of SI and 37 years of age (28 years from diagnosis) at time of recurrent SI. After adjusting for depressive symptoms (OR=9.1; 95% CI=6.3–13.2), poor physical health status (OR=1.9; 95% CI=1.2–2.9), headache (OR=1.6; 95% CI=1.1–2.4), and seizures (OR=2.3; 95% CI=1.3–3.9) were significantly associated with recurrent SI. Survivors with health insurance and who were married were less likely to experience recurrent SI (OR=0.5, 95% CI=0.3–0.8; OR=0.6; 95% CI=0.4–0.95, respectively) (Table 3).

Mortality

Of the 10,072 survivors who completed the suicide item at any survey, 644 were found to have died, with 10 of these deaths (1.6%) listed as suicides (Table 4). Of these, 3 (30%) reported SI prior to their death. Risk of all-cause mortality was greater in survivors with a history of SI compared to survivors without a history of SI (HR=1.29, 95% CI=1.03–1.61). Death by suicide did not differ statistically between survivors with and without a history of SI (HR=3.49, 95% CI=0.90–13.5), though survivors with a history of SI had 2.4-times the risk of death by external cause than survivors without a history of SI (HR=2.37, 95% CI=1.36–4.12). Table 5 shows external cause of death for survivors with and without SI.

DISCUSSION

This is the first study to examine longitudinal patterns of suicide ideation in a large cohort of adult survivors of childhood cancer. Suicide is a serious consequence of psychological distress and is a leading cause of death among adults in the general population. Our results indicate that adult survivors of childhood cancer are at increased risk for experiencing recurrent and late suicide ideation decades following their initial cancer diagnosis and treatment. Moreover, suicide ideation appears to be associated with increased risk of mortality in survivors.

Compared to siblings, we found that adult survivors of childhood cancer were 1.9 and 2.6 times more likely to report late and recurrent suicide ideation, respectively. Survivors with late report of SI reflect a group of survivors who did not report suicide ideation until, on average, more than 26 years post-diagnosis. Chronic medical conditions emerged as a unique predictor of late report SI, suggesting that the persistence and/or worsening of poor physical health may be associated with the onset of suicidal thoughts. These findings are consistent with data from the general population^{23, 24}; however, they have important implications in the survivor population as adult survivors of childhood cancer are at heightened risk for developing serious chronic medical conditions as they age⁵. Therefore, routine screening of psychological morbidities, including suicide ideation, may be warranted as aging survivors experience the burden of chronic medical conditions.

Fewer than 2% of survivors in our study were reported to have died by suicide. This is consistent with past reports indicating no statistically significant elevated rates of suicide in adult survivors of childhood cancer compared to the general population^{14, 15}. However, our data suggest that adult survivors with a history of suicide ideation are at greater risk for mortality compared to survivors without a history of suicide ideation. This risk appears to be driven largely by external causes of death. Though we had limited power to detect statistical significance, survivors with a history of suicide ideation had over a 3.5-fold increased risk of death by suicide. It is important to consider the potential for misclassification, especially for suicide, when relying on death certificates to determine cause of death^{25, 26}. Specifically, other external causes of death (e.g. accidental poisoning, falls) may be the result of behavior with suicidal intent.

Importantly, 30% of survivors in our study who died by suicide previously reported suicide ideation. Although the actual number of observed events is small, this finding highlights the need for close monitoring and follow-up for patients who endorse suicide ideation. While the pathway leading from suicide ideation to completed suicide is unclear, in the general population, one-third of individuals with suicide ideation make a plan, 72% of those with a plan make an attempt, and 26% move directly from ideation to an unplanned attempt ²⁷.

In addition to potential death misclassification, there are other limitations of our study that warrant discussion. We used a single item to assess distress associated with suicide ideation. Symptoms of suicide ideation can vary over short periods of time, thus reliance on a single time point with a 7-day recall period precludes measurement of SI events that precede or follow this window. Ideally, assessing for psychological morbidities would incorporate the use of a screening measure followed by a more thorough assessment of suicidal thoughts as well as plan and intent in survivors who screen positive. Recklitis et al ²⁸ have demonstrated the utility of psychological screenings for childhood cancer survivors within the context of a late effects clinic. Because survivors and siblings were required to complete an item reporting on suicide ideation to be included in our analyses, it is possible that the survivors in our study do not represent the larger population of childhood cancer survivors.

In summary, we found increased risk for late report of and recurrent suicide ideation in adult survivors of childhood cancer. These findings are consistent with the growing literature that subgroups of adult survivors of childhood cancer are at risk for psychological distress, including suicide ideation ^{16, 20}. Our data further indicate that suicide ideation may not emerge until several decades following original cancer diagnosis, underscoring the need to screen survivors who may not have reported distress previously, particularly those who develop chronic medical conditions in adulthood. Importantly, we found increased risk of mortality associated with suicide ideation in this large cohort of adult survivors of childhood cancer.

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Table 1Characteristics of survivors with and without suicide ideation^a

	None				Recurrent			
	M	SD	M	SD	M	SD	M	SD
Age at Baseline	25.1	7.4	23.8	7.7	<0.001	26.3	7.3	0.02
Age at Diagnosis	8.7	5.9	7.8	5.7	<0.001	9.5	5.9	0.04
	N	%	N	%		N	%	
Sex					0.03			0.80
Female	3272	49.2	320	55.7		117	50.0	
Male	3383	50.8	255	44.3		117	50.0	
Educational Attainment					<0.001			0.05
High School	2374	35.7	256	44.5		67	28.6	
>High School	4007	60.2	295	51.3		152	65.0	
Health Insurance					0.72			<0.001
Yes	5817	87.4	499	86.8		180	77.0	
No	755	11.3	68	11.8		49	21.0	
Household Income					0.02			<0.001
<\$ 20,000	1001	15.0	105	18.3		56	23.9	
\$ 20,000	5074	76.2	409	71.1		150	64.1	
Marital Status					<0.001			0.07
Single, never married	3584	53.9	345	60.0		139	59.4	
Married, living as married	2478	37.2	166	28.9		68	29.1	
Divorced, separated, widowed	404	6.1	39	6.8		14	6.0	
Physical Health Status					<0.001			<0.001
Fair, poor	397	6.0	75	13.0		48	20.5	
Good	6201	93.2	193	85.7		186	79.5	
Pain					<0.001			<0.001

	None			Late Report ^b			Recurrent		
	M	SD	M	M	SD	M	M	SD	P ^d
Headache	1573	23.6	191	33.2		95	40.6		
Other bodily pain	346	5.2	27	4.7		19	8.1		
No pain	4725	71.0	354	61.6		119	50.9		
Seizure									<0.001
Yes	319	4.8	48	8.4		28	12.0		
No	6144	92.3	503	87.5		194	82.9		
Chronic Health Conditions									<0.001
None	2776	41.7	192	33.4		58	24.8		
Grade 1 or 2	2305	34.6	233	40.5		105	44.9		
Grade 3 or 4	1572	23.6	150	26.1		71	30.3		
Depression									<0.001
Yes	346	5.2	75	13.0		112	47.9		
No	5110	76.8	332	57.7		97	41.5		
Diagnosis									<0.001
Leukemia	2151	32.3	211	36.7		67	28.6		
CNS Tumor	684	10.3	76	13.2		43	18.4		
Hodgkin Disease	1061	15.9	67	11.7		35	15.0		
Non-Hodgkin Lymphoma	531	8.0	44	7.7		18	7.8		
Wilms Tumor	562	8.4	44	7.7		7	3.0		
Neuroblastoma	383	5.8	33	5.7		7	3.0		
Soft tissue sarcoma	630	9.5	46	8.0		27	11.5		
Osteosarcoma	653	9.8	54	9.4		30	12.8		
Chemotherapy									0.73
Yes	4838	72.7	434	75.5		180	76.9		
No	1283	19.3	100	17.4		45	19.2		
Radiation									0.03

	None			Late Report ^b			Recurrent		
	M	SD		M	SD		M	SD	<i>P</i> ^d
None	2002	30.1		163	28.4		64	27.4	
Non-Cranial	1960	29.5		140	24.3		68	29.1	
<20Gy CRT	824	12.4		76	13.2		24	10.3	
20Gy CRT	1257	18.9		147	25.6		64	27.4	

^a covariates ascertained as of baseline unless otherwise noted

^b post-baseline assessment

^c p-value for comparison of late report SI vs. none

^d p-value for comparison of recurrent SI vs. none

Table 2
Comparison of suicide ideation in survivors and siblings

	Survivors				Siblings			
	N ^a	n ^b	%	N ^a	n ^b	%	OR (95% CI)	Adjusted OR (95% CI) ^c
Baseline	9128	713	7.81	3082	136	4.41	1.8 (1.5–2.2)	1.8 (1.5–2.1)
2003	7251	504	6.95	2764	102	3.69	1.9 (1.6–2.4)	1.9 (1.5–2.4)
2007	7124	424	5.95	2296	72	3.14	2.0 (1.5–2.5)	2.0 (1.5–2.5)
Late Report	7230	575	7.95	2672	116	4.34	1.9 (1.6–2.3)	1.9 (1.5–2.5)
Recurrent	7708	234	3.04	2776	37	1.33	2.3 (1.6–3.3)	2.6 (1.8–3.8)

^a N=number of participants eligible for evaluation

^b n=number of participants reporting suicide ideation

^c Adjusted for age, sex, race/ethnicity

Table 3Multivariable models predicting late and recurrent SI^a in survivors^b

	Late Report SI	Recurrent
	OR (95% CI)	OR (95% CI)
Female Sex	----	----
Age at diagnosis	0.98 (0.96–1.00)	----
Age at baseline	----	1.04 (1.0–1.07)
Educational Attainment		
HS vs. >HS	----	----
Household Income		
<20,000 vs. 20,000	----	----
Marital Status		
Divorced vs. Single	----	0.42 (0.20–0.87)
Married vs. Single	----	0.62 (0.41–0.95)
Health Insurance		
Yes vs. No	----	0.51 (0.33–0.78)
Physical Health Status		
Fair, poor vs. Good	1.88 (1.29–2.74)	1.87 (1.20–2.91)
Seizure		
Yes vs. No	2.04 (1.32–3.16)	2.25 (1.29–3.93)
Pain		
Headache vs. None	1.38 (1.05–1.82)	1.62 (1.11–2.36)
Other vs. None	1.00 (0.57–1.73)	1.30 (0.66–2.53)
Chronic Health Conditions		
Grade 1 or 2 vs. none	1.51(1.10–2.09)	----
Grade 3 or 4 vs. none	1.63(1.16–2.28)	----
Depression		
Yes vs. No	2.95 (2.10–4.14)	9.12 (6.32–13.2)
Chemotherapy		
Yes vs. No	----	----
Radiation		
Non-cranial vs. None	----	----
<20Gy CRT vs. None	----	----
20Gy CRT vs. None	----	----

^aSI=suicide ideation^bBest fitting multivariable models selected using minimum Akaike information criterion

Table 4Suicide ideation and mortality^a

	History of SI ^c N=1,096	No SI ^c N=8,976		
	N (% ^b)	N (% ^b)	HR (95% CI)	<i>p</i>
All-causes	89 (11.3)	555 (7.95)	1.29 (1.03–1.61)	0.02
Recurrence, progressive disease	10 (0.97)	91 (1.12)	0.89 (0.46–1.71)	0.72
Nonrecurrence, nonexternal	59 (8.2)	386 (5.87)	1.22 (0.93–1.6)	0.15
External causes	16 (1.8)	55 (0.67)	2.37 (1.36–4.12)	0.002
Suicide	3 (0.29)	7 (0.09)	3.49 (0.90–13.5)	0.07
Unknown	4 (0.37)	23 (0.28)	1.41 (0.49–4.09)	0.52

^a 1,174 eligible CCSS participants died prior to baseline and do not contribute to this analysis. 56 died by external causes, 11 were recorded as suicide.

^b Estimated 15-year follow-up cumulative incidence.

^c SI = suicide ideation

Table 5External causes of death for survivors with and without history of SI^a

	History of SI N=16	No SI N=55
Motor vehicle accident	5 (31.3%)	28 (50.1%)
Suicide	3 (18.8%)	7 (12.7%)
Accidental poisoning	3 (18.8%)	4 (7.3%)
Falls	2 (12.5%)	3 (5.5%)
Homicide, other external	2 (12.5%)	7 (12.7%)
Other	1 (6.3%)	6 (10.9%)

^aSI=suicide ideation