

1. STUDY TITLE: Longitudinal Patterns of Psychological Distress in Adult Survivors of Childhood Cancer

2. WORKING GROUP AND INVESTIGATORS:

2.1. Working Group: Psychology

2.2. Investigators:

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3. BACKGROUND AND RATIONALE:

Long-term follow-up studies of childhood cancer survivors suggest that most adult survivors are psychologically healthy<sup>1,2</sup> but that certain subgroups are at heightened risk for psychological distress, including suicide ideation.<sup>3,4</sup> A previous report on psychological outcomes for the entire CCSS cohort indicated that although survivors reported greater global distress than siblings, their overall scores fell below population norms.<sup>2</sup> Specific risk factors for psychological distress among survivors included female sex, lower educational attainment, unmarried status, low household income, presence of a major medical condition, and treatment with cranial radiation therapy. Zebrack et al<sup>5</sup> reported that among brain tumor survivors, higher levels of psychological distress were associated with the aforementioned sociodemographic variables as well as poor physical health status, though diagnostic and treatment variables were not associated with increased distress. Recklitis et al<sup>5</sup> further reported that adult survivors in the CCSS cohort were at increased risk for suicide ideation, with 7.8% of survivors endorsing suicide ideation. Suicide ideation was associated with CNS cancer diagnosis, poor physical health status and cancer related pain.

In the general population, higher levels of psychological distress are present among females and those with lower compared to higher educational attainment.<sup>6,7</sup> Recent longitudinal data suggest that these disparities, observed throughout adulthood, are a result of psychological distress specific to a set of individuals with persistent distress rather than acute distress among continually changing sets of individuals.<sup>6</sup> However, change in psychological distress in adulthood has been reported in relation to changes in sociodemographic factors (e.g, job loss, divorce) and health status.<sup>8,9</sup> How patterns of psychological distress persist or change among adult survivors of childhood cancer is largely unknown.

We propose to conduct a longitudinal assessment of psychological distress among the CCSS cohort. While previous CCSS reports indicate that psychological distress impacts only a subgroup of adult survivors, the cross-sectional nature of these studies has precluded investigation of how psychological distress may change over the course of survivorship or in response to changes in identified risk factors. A longitudinal approach to examining psychological functioning will further allow for the identification of potential protective factors associated with decreased distress over time. Knowledge of how psychological distress persists or changes in this cohort over time is essential for targeted interventions to address distress disparities among survivors.

#### 4. SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES:

##### 4.1. Primary Aims:

- 4.1.1. To characterize patterns of change in psychological distress among survivors from Baseline through 2007.
- 4.1.2. To identify disease, treatment and demographic characteristics related to patterns of psychological distress (i.e. stable, improved, worsened).

##### 4.2. Secondary Aims:

- 4.2.1. To investigate patterns of change in suicidal ideation among survivors from Baseline through 2007.
- 4.2.2. To examine the association between changes in psychological distress and social functioning (i.e. employment, marriage).

##### 4.3. Primary Hypotheses:

- 4.3.1. There will be identifiable subgroups of survivors who demonstrate patterns of stability and change in psychological distress from Baseline through Follow-up.
- 4.3.2. Female survivors will demonstrate increased risk of persistent psychological distress in comparison to male survivors.
- 4.3.3. CNS tumor diagnosis and cranial radiation therapy will be associated with increased risk of persistent psychological distress.

##### 4.4. Secondary Hypotheses:

- 4.4.1. The prevalence of recurrent suicide ideation (reported at the time of two or more surveys) will be greater for CNS tumor survivors than survivors of other childhood cancers.
- 4.4.2. Survivors who report poor physical health status and cancer-related pain at Baseline will be more likely to report recurrent suicide ideation.
- 4.4.3. Sociodemographic variables at Baseline (e.g. low income, low educational attainment, unemployment) will be associated with increased risk of persistent psychological distress.

#### 5. ANALYSIS FRAMEWORK:

- 5.1. Population: Cancer survivors who were at least 18 years of age at Baseline and completed the BSI at Baseline, 2003 Follow-up and 2007 Follow-up.

Number of survivors who completed the Brief Symptom Inventory at each time point

	Baseline	Baseline & 2003	Baseline, 2003 & 2007	%*
Leukemia	2686	1518	1211	45.1
CNS Tumor	1137	581	403	35.4
Hodgkin's Disease	1645	1068	820	49.8
Non-Hodgkins Lymphoma	841	463	358	42.5
Wilms Tumor	584	325	253	43.3
Neuroblastoma	360	188	146	40.1
Soft tissue sarcoma	884	543	432	48.9
Bone tumors	1000	619	480	48.0

\*Percent of survivors with baseline BSI data who completed the BSI at both follow-ups

- 5.2. Outcomes of interest: The primary outcome of interest is the Brief Symptom Inventory (BSI-18). Psychological distress data were collected using the BSI at the time of each survey (Baseline [questions J.16 to J.35], 2003 Follow-up [questions G1 to G18], and 2007 Follow-up [questions L1 to L18]). Scores for Somatization, Depression, and Anxiety subscales and the composite Global Severity Index (GSI) will be examined as continuous variables to allow for the investigation of changes in psychological distress that are below the threshold of clinical impairment. Significant change in distress will be defined as a change greater than the 90% confidence interval of the standard error of the mean for each subscale and global composite. In addition, a t-score of 63 or above on the GSI will be used as a cut-off to create a binary outcome categorizing survivors as psychologically distressed or not.

Confidence Intervals of the Standard Error for BSI subscales

	Standard Error	90% C.I.
Depression	4	6.6
Anxiety	4.58	7.56
Somatization	5.66	9.34
Global Severity Index	3.16	5.21

The BSI has a single item that assesses suicidality (Baseline question J.19). Consistent with the approach used by Recklitis et al<sup>3</sup>, survivors who endorse any suicidal ideation on this item will be considered to have suicide ideation. Additionally, to allow for a measure of depression excluding suicide ideation, this item will be treated as missing for the calculation of the BSI depression scale score. Recurrent suicide ideation will be defined as positive identification of suicide ideation on more than one questionnaire. As we do not know the number of survivors who reported recurrent suicide ideation, this secondary aim will be pursued assuming sufficient observations are available.

5.3. Primary Predicators:

- Sex
  - Male
  - Female

- Age at diagnosis, years
  - 0-6
  - 7-10
  - 11-15
  - 16-20
- Age at baseline, years
  - 18-24
  - 25-29
  - 30-34
  - $\geq 35$
- Cancer Diagnosis
  - Leukemia
  - CNS tumors
  - Hodgkin's Disease
  - Non-Hodgkin's Lymphoma
  - Wilms tumor
  - Neuroblastoma
  - Soft tissue sarcoma
  - Bone tumors
- Chemotherapy Variables
  - Anthracycline
  - Alkylating Agents
  - Antimetabolites & Corticosteroids
  - Vinca Alkaloids & Heavy Metal
  - None
- Radiation Variables
  - Cranial
    - 0-29 Gy
    - 30-49 Gy
    - 50 Gy and greater
  - Other bodily (yes/no)
  - None
- Physical Health Status (Baseline question N.15)
- Cancer Related Pain (Baseline question J.36)

#### 5.4. Covariates:

- Health Insurance (Baseline question Q.2)
  - Current health insurance (yes/no)
- Marriage (Baseline question L.2)
  - Single, never married
  - Married or living as married
  - Divorced or separated or no longer living as married
- Employment (Baseline question O.6)
  - Employed during the past 12 months (yes/no)
- Education Level (Baseline question O.1)
  - Less than 12 years
  - Completed high school

- High school & some college
- College/postgraduate
- Household Income (Baseline question Q.8)
  - < \$19,999
  - \$20,000-\$39,999
  - \$40,000-\$59,999
  - > \$60,000
- Psychoactive Medication Treatment (Baseline questions 9 and 15)
  - Antidepressant
  - Anxiolytic
  - Mood Stabilizer
  - Neuroleptic
  - Analgesic

## 5.5 Statistical Modeling

- 5.5.1. Frequency distributions will be used to categorize relevant outcome variables, predictors, and covariates according to reasonable groupings and consistent with previous CCSS manuscripts.
- 5.5.2. Descriptive statistics including means, standard deviations, medians, ranges, frequencies, and percents will be calculated for the primary outcomes of interest (psychological distress) at each questionnaire as well as for the primary predictors (disease and treatment variables, physical health status, cancer-related pain) and all covariates (Table 1). Since the population of subjects who completed all 3 BSI questionnaires may differ from those who completed only one or two, we will present BSI summary statistics for survivors who responded to the BSI at every time point and for survivors who responded to the BSI at any time point (Table 2). If survivors who completed 3 BSI questionnaires differ substantially from those who completed 2 or fewer, we will complete the proposed longitudinal analysis with survivors who completed only two surveys and compare the results to those obtained from the model including survivors who completed all three surveys.
- 5.5.3. To address the first aim we will use latent profile analysis (model-based clustering procedure) to determine classes/clusters of survivors based on patterns of psychological distress over time. We will include the anxiety, depression and somatization subscales from the BSI as indicators in these analyses. LPA fit indices will include the Bayesian Information Criterion (BIC) and a likelihood difference test (VLMR) with  $p$  values reported to indicate which model provides the best fit (Table 3). We expect that several clusters will be identified. These may include survivors with (a) low distress at all three time points, (b) high, clinically significant distress at all time points, and (c) fluctuating distress levels (Figure 1). Cluster/class membership will then be used as outcome variables in subsequent analyses. To address primary hypotheses 2 and 3, regression analyses will be performed to determine whether demographic, disease and treatment variables predict group membership for each cluster (Table 4). We will also provide a figure showing the variability in patterns of individuals within each class to illustrate how well the class structure fits. This will provide evidence that the class

grouping does not simply represent an average, but is actually representative of the majority of the subjects in the class.

- 5.5.4. Comparisons of recurrent suicide ideation will be made between subgroups of survivors using logistic regression models with robust variance estimates to account for within subject correlation. A multivariable model adjusted for age will be fitted and an Odds Ratio and 95% confidence interval will be reported for the comparison between groups of survivors. Logistic regression will also be utilized to investigate the association between Baseline cancer-related pain and physical health status and recurrent suicide ideation (Table 5). This will enable us to address hypotheses 1 and 2 from the Secondary Hypotheses.
- 5.5.5. Regression analyses will be used to investigate the association between sociodemographic variables at Baseline and group membership for identified classes/clusters based on patterns of psychological distress (presented within Table 4). Separate models will be examined for each cluster. This approach will target hypothesis 3 from the Secondary Hypotheses.

Table 1. Survivor Descriptive Statistics\*

Variable	Survivors	
	N	%
Sex Male Female		
Age at Baseline 18-24 25-29 30-34 ≥ 35		
Cancer Diagnosis Leukemia CNS Tumor Hodgkin's Disease Non-Hodgkins Lymphoma Wilms tumor Neuroblastoma Soft tissue sarcoma Osteosarcoma		
Radiation Therapy Brain 0-29 Gy 30-49 Gy 50 Gy Other bodily None		
Chemotherapy (possible groupings) Alkylating Agents Anthracycline Antimetabolites & Corticosteroids Vinca Alkaloids & Heavy Metals None		
Age at diagnosis 0-6 7-10 11-15 16-20		
Education < High School Completed High School High School & Some College College/Postgraduate		
Household Income < \$19,999 \$20,000-\$39,999 \$40,000-\$59,999 > \$60,000		
Marital Status Single, never married Married/living as married Divorced/separated		
Employed Yes No		

Table 2. BSI Scores at Baseline, 2003- and 2007-Follow-Up

	Survivors who completed BSI at each time point						Survivors who completed BSI at any time point					
	Baseline (n= )		2003 FU (n= )		2007 FU (n= )		Baseline (n= )		2003 FU (n= )		2007 FU (n= )	
	M(SD)	%Imp*	M(SD)	%Imp	M(SD)	%Imp	M(SD)	%Imp	M(SD)	%Imp	M(SD)	%Imp
Anxiety												
Depression												
Somatization												
GSI Composite												

\* Impaired  $\leq$  10%ile



Table 3. Model Fit Indices for 1 to X-Class Solutions of BSI Scores

Model	BIC	Adjusted BIC	VLMR <sub>p</sub>	Adjusted VLMR <sub>p</sub>	Entropy
1-class solution			---	---	---
2-class solution					
3-class solution					
4-class solution					

Figure 1. Sample figure of classes from Colman et al<sup>10</sup>

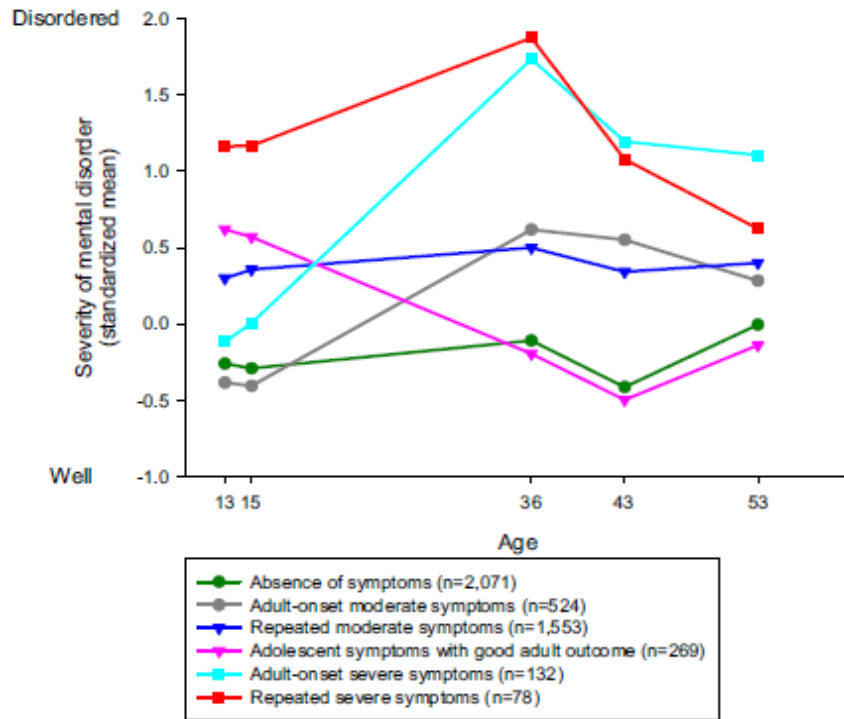


Figure 1. Six longitudinal classes of depressive and anxious symptomatology from age 13 to 53 years.

Table 4. Multivariable regression model predicting patterns of psychological distress

	Cluster 1	Cluster 2	Cluster 3	Cluster 4
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Sex Female Male				
Age at diagnosis 0-6 7-10 11-15 16-20				
Radiation Therapy Brain 0-29 Gy 30-49 Gy 50 Gy Other bodily None				
Chemotherapy Yes No				
Cancer related pain None Small amount Medium amount Very bad, excruciating				
Health status Poor Fair Good Very Good Excellent				
Psychoactive Medication Use Antidepressant Anxiolytic Analgesic None				
Education < High School High School & Some College College/Postgraduate				
Household Income < \$19,999 \$20,000-\$39,999 \$40,000-\$59,999 > \$60,000				
Employed in last year Yes No				
Ever Married Yes No				
Health Insurance Yes No				

Table 5. Recurrent suicide ideation in survivors

Variable	Survivors		Odds Ratio	95% CI
	N	%		
Sex				
Male				Ref
Female				
Diagnosis				
Leukemia				Ref
CNS Tumor				
Hodgkin's Disease				
Non-Hodgkins Lymphoma				
Wilms tumor				
Neuroblastoma				
Soft tissue sarcoma				
Osteosarcoma				
Radiation				
Brain				
0-29 Gy				
30-49 Gy				
50 Gy and greater				
Other Bodily				
None				Ref
Education				
< High School				
High School & Some College				
College/Postgraduate				Ref
Household Income				
< \$19,999				
> \$20,000				Ref
Employed in last year				
Yes				Ref
No				
Ever Married				
Yes				Ref
No				
Health status				
Poor				
Fair				
Good				
Very Good				
Excellent				Ref
Cancer related pain				
None				Ref
Small amount				
Medium amount				
Very bad, excruciating				
Psychoactive Medication Use				
Antidepressant				
Anxiolytic				
Analgesic				
None				Ref
Depression				
Depression $\geq$ 63				
No elevation				Ref

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