Childhood Cancer Survivor Study
Concept Proposal and Analytic Plan

Title: Prevalence and predictors of loneliness in young adult survivors of childhood cancer

Working groups: Psychology (primary), Chronic Disease (secondary)

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Background and Rational:

Advances in cancer therapies and supportive care have considerably increased the number of childhood and adolescent cancer survivors. The overall 5-year survival rate after diagnosis has increased over the past 4 decades from 61.5% (for the period 1975-1977) to 83.5% (for the period 2004-2010).[1] Based on recent statistics, the probability of long-term survival of childhood and adolescent cancer is very high; the estimated probability of 15-year survival among children and adolescents with cancer who survived 5 years for all cancer types is 95%.[2] This means that the majority of childhood and adolescent cancer survivors will survive into adulthood. As of January 1, 2010 there was an estimated 379,112 survivors of childhood and adolescent cancer in the United States; seventy percent of those survivors are 20 years of age or older.[2]

Young adulthood, defined by the National Cancer Institute as between 19 and 39 years of age, is a unique developmental period. It is marked by many transitions and social changes, including increasing expectation of independence. Young adults are expected to choose a career, develop intimate relationships, and establish close friendships. Meeting the developmental tasks of this stage provides a sense of satisfaction to young adults. According to Erikson's developmental psychosocial theory, a successful young adulthood encompasses the resolution of intimacy vs. isolation crises. Young adults in this developmental stage are expected to be engaged in a loving intimate relationship and have close friendships. As young adults fulfill their social roles, they become more independent, competent, have high self-esteem and can relate well to others.[3] On the other hand, young adults who experience difficulties during this stage are likely to be lonely, isolated, and fearful of relationships with others.[3]

During young adulthood, survivors of childhood and adolescent cancer experience a wide range of treatment-related late effects. Importantly, survivors experience both physical[4-7] and psychological late effects that may impede their ability to meet the demands of young adulthood.[8-14] For example, survivors face challenges related to achieving expected educational attainment,[15-17] acquiring employment,[13,16-19] developing friendships,[20] social interactions,[18,21] and establishing intimate relationships and marriage.[16,20]

Social relationships are a commonly reported area of concern for young adult survivors of childhood and adolescent cancer.[21-23] Studies have indicated that survivors experience social isolation and loneliness during adulthood,[21-24] with concerns about being unable to fit in, feeling

lonely, and being misunderstood by peers. Loneliness is a subjective state that is unpleasant and distressing.[25,26] Feelings of loneliness take their toll on the human body; the distress and agony that lonely individuals experience is reflected in both their physical and mental health.[27,28] Research on loneliness in non-cancer populations has shown increased risk for early mortality,[29] greater depressive symptomatology,[30] poor sleep efficiency,[31] increased peripheral vascular resistance and low cardiac output,[32] alcohol abuse,[33] suicide,[34] and increased hypothalamic pituitary adrenocortical activity.[35] In a study of young adults, lonely participants reported higher anxiety, anger, negative mood, and fear of negative evaluation, compared to non-lonely young adults.[30]

Despite the potential adverse effects of loneliness on psychological and physical health, loneliness is an understudied phenomenon among young adult survivors of childhood cancer. Better understanding of this phenomenon may facilitate identification of groups of survivors who are at risk for loneliness. Detecting and alleviating symptoms of loneliness in young adult survivors may help them reintegrate into society, achieve their expected social roles, and reduce psychological and physical morbidities associated with loneliness.

Specific aims:

1. To estimate the prevalence and persistence of loneliness in young adult survivors of childhood cancer and compare with a sibling comparison group.

   Hypothesis 1: We hypothesize that survivors will have a higher prevalence of loneliness and will be more likely to report persistent loneliness compared with siblings.

2. To examine demographic (age, gender, marital status, living status) socioeconomic factors (household income, educational attainment, employment in the past year), cancer diagnosis and treatment exposures (intense treatment, cranial radiation, younger age at diagnosis) associated with loneliness in young adult survivors of childhood cancer.

   Hypothesis 2: We hypothesize that female sex, unmarried status, dependent living status, lower household income, lower educational attainment, unemployment, CNS tumor diagnosis, treatment with cranial radiation, and younger age at diagnosis will be associated with loneliness.

3. To examine associations between loneliness and physical health status, health-related quality of life, and psychological distress.

   Hypothesis 3: We hypothesize that larger proportion of lonely survivors will report adverse physical health status, chronic health conditions, reduced health related quality of life, and psychological distress than non-lonely survivors.

4. To explore associations between loneliness and health behaviors (e.g., tobacco use, alcohol use, and physical activity) in young adult survivors of childhood cancer.

   Hypothesis 4: We hypothesize that a larger proportion of lonely survivors will report tobacco use, risky/heavy drinking, and will be less likely to meet physical activity guidelines than non-lonely survivors.

5. To examine associations between physical and/or cognitive limitations and loneliness, and if physical and/or cognitive limitations mediates the associations between treatment exposures and loneliness.

Hypothesis 5: We hypothesize that physical and cognitive limitations will mediate the association between treatment exposure and loneliness.

Analysis framework:

Study population: Our study sample will be comprised of young adult survivors of childhood cancer between the ages of 19-39 years at the time of completing the CCSS baseline questionnaire. We will utilize the original and expansion cohorts and siblings for each cohort. We will require that participants self-completed questionnaires because loneliness is a subjective state for which proxy report may not be reliable. Survivors/siblings in the original cohort will be required to complete the baseline questionnaire and FU 2. Survivors/siblings in the expansion cohort will be required to complete the expansion baseline questionnaire and FU 5.

	Original BL	FU 2	Expansion BL	FU 5
Loneliness	x	x	x	x
BSI-18	x	x	x	x
SF-36 physical	activity limitations only	x	activity limitations only	x
SF-36 mental	n/a	x	n/a	x
Perceived health status	x	x	x	x
Chronic health conditions	x	n/a*	x	x
Smoking	x	x	x	x
Alcohol	x	n/a*	x	x
Physical activity	one question	x	one question	x

*Available for baseline cohort at FU 4

Primary Outcome:

The primary outcome of interest is loneliness. This will be assessed using a single item from the BSI-18 related to how much survivors have been distressed or bothered by "feeling lonely" during the past 7 days. Because loneliness has not previously been evaluated in CCSS we will examine the distribution of loneliness symptoms considering multiple definitions (e.g. none vs. >a little bit; none or a little bit vs. >moderately). We will examine the prevalence of loneliness in survivors and siblings separately at two time points: Original cohort: Baseline and FU 2; Expansion cohort: Baseline and FU 5. We will consider loneliness persistent if endorsed on two consecutive surveys (i.e., baseline & follow-up).

Preliminary review of the data suggests the following prevalence of loneliness within the original CCSS cohort (not restricted to 19-39 years).

Survivors

	Not at all	A little bit	Moderately	Quite a bit	Extremely
	n (%)	n (%)	n (%)	n (%)	n (%)
Baseline	5880 (64.3)	1909 (20.9)	775 (8.5)	406 (4.4)	176 (1.9)
FU 2	4553 (59.0)	1913 (24.8)	666 (8.6)	423 (5.5)	165 (2.1)
FU 4	5676 (71.8)	1392 (17.6)	479 (6.1)	256 (3.2)	104 (1.3)

Siblings

	Not at all	A little bit	Moderately	Quite a bit	Extremely
	n (%)	n (%)	n (%)	n (%)	n (%)
Baseline	2222 (72.2)	558 (18.1)	181 (5.9)	89 (2.9)	28 (0.98)
FU 2	1966 (69.3)	568 (20.0)	192 (6.8)	85 (3.0)	25 (0.88)

FU 4	1893 (80.7)	319 (13.6)	89 (3.8)	27 (1.2)	29 (1.2)

Secondary Outcomes:

- Physical health status
  - Perceived physical health status
    - Perceived physical health status will be assessed using a single item on which survivors report their health status (poor, fair, good, very good, excellent). We will dichotomize this variable as poor, fair vs. good, very good, excellent.
  - Chronic health conditions
    - We also will consider health status using chronic health conditions coded using the common Terminology Criteria for Adverse Events version 4 (CTCAE v.4.0). According to the CTCAE v.4.0 health conditions are graded as mild (grade 1), moderate (grade 2), severe (grade 3), or life-threatening/disabling (grade 4). We will consider both the highest CTCAE v.4.0 grade for multiple organ systems (e.g. cardiac, endocrine, pulmonary) (grade 1 or 2, grade 3 or 4), as well as the number of chronic health conditions (at least 2, ≥3).[7]

- Health related quality of life
  - Health-related quality of life will be measured using the SF-36. T-scores <40 will be considered to represent impaired quality of life across the eight available domains (4 physical; 4 mental).

- Psychological distress
  - Psychological distress (anxiety, depression and somatization) will be measured with the BSI-18. Because the loneliness item contributes to the depression scale we will treat the loneliness item as missing and use recommended imputation approaches to derive a depression scale score. This is consistent with past approaches used when examining suicide ideation in CCSS.[36] T-scores ≥63 will be considered to represent significant psychological distress symptoms.

- Health behaviors
  - Tobacco use
    - Cigarettes smoking: We will examine self-reported smoking status. Participants responses to two items regarding smoking cigarettes will be used to categorize them as never smokers (smoked less than 100 cigarettes in their lifetime), former smokers (smoked at least 100 cigarettes in their lifetime but do not currently smoke), current smokers (smoked at least 100 cigarettes in their lifetime and smoke now).[37]
    - Tobacco products use: We will categorize participants based on their self-reported responses regarding the use of tobacco products (pipes, cigars, snuff, or chewing tobacco) in the past year as never users vs. users (no longer user, occasional users, or regular users).[38]
  - Alcohol use
    - We will examine risky drinking and heavy drinking as defined by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the Substance Abuse and Mental Health Services Administration (SAMHSA).

        - Risky drinking is defined by the NIAAA for men as more than 4 standard drinks in a day (or more than 14 per week) and for women as more than 3 in a day (or more than 7 per week).
        - Binge drinking is defined by the SAMHSA for men as 5 or more drinks per day (i.e. on the same occasion) and for women as 4 or more drinks per day at least once in the past month.
        - SAMHSA defines heavy alcohol use as binge drinking on 5 or more days in the past month.

    - Physical activity
        - According to CDC guidelines for physical activity, adults aged 18 to 64 years need to be engaged in a moderate intensity physical activity for 150 minute each week or 75 minute of vigorous physical activity each week. Based on the participants' responses to 6 items regarding participation in physical activity during the past month, individuals will be classified as those who meet the Center for Disease Control and Prevention (CDC) guidelines for physical activity and those who do not.[39]

Treatment exposures:

Primary treatment exposures for inclusion in multivariable models will include:

- Chemotherapy (we will examine dose distribution to determine appropriate groupings or continuous use of doses)
    - Anthracyclines (cumulative dose)
    - Alkylating agents (cumulative dose)
    - Corticosteroids (yes, no)
    - Intrathecal methotrexate (cumulative dose)
    - Intrathecal cytarabine (cumulative dose)
    - Platinum-based agents (cumulative dose)
- Radiation (CRT defined as maximum tumor dose [maxTD] to any region of the brain)
    - None
    - Non-cranial
    - <20 Gy CRT
    - ≥20Gy to <30 Gy CRT
    - ≥30 Gy CRT
- Surgery (amputation)
    - Yes
    - No

We will also examine separate models including primary cancer diagnosis [e.g., CNS tumors, ALL, HL, NHL, non-CNS solid tumors, other] in place of treatment exposures.

Covariates:

Covariates will include:

- Age at baseline or FU (years, continuous)
- Sex (female; male)
- Race/ethnicity (white, black, other)
- Age at diagnosis (years, continuous)
- Marital status (single, never married; married/living as married; divorced/separated, widowed)
- Independent living status (independent; dependent)

- Education level (≤high school; some college/training after high school; ≥college graduate)
- Employed in past year (yes; no)

Statistical Analysis

Because participants are required to complete baseline and a subsequent follow-up survey, there is the potential for selection bias. We will compare demographic, psychosocial, and treatment characteristics of survivors who completed both surveys with survivors who only completed the baseline survey. Depending on the results of these comparisons, we will consider modifications to the proposed analyses, including the use of statistical imputation.

We will calculate descriptive statistics for primary exposures, outcomes, and covariates. We will examine multicollinearity among potential exposures and covariates. Analyses for Aims 2-5 will be dependent upon the frequency of loneliness symptoms. However, based on preliminary review of the data we believe we will have sufficient observations to complete multivariable analyses.

Aim 1: To estimate and compare the prevalence and persistence of loneliness in young adult survivors of childhood cancer with sibling controls.

For aim 1, we will assess the proportion of survivors and siblings reporting loneliness at two time points (Baseline and FU 2 [original cohort] or FU 5 [expansion cohort]). Because loneliness has not previously been evaluated in CCSS we will examine the distribution of loneliness symptoms considering multiple definitions (e.g. none vs. >a little bit; none or a little bit vs. >moderately). In addition, we will assess persistence and recurrence of loneliness symptoms. We will consider loneliness persistent if endorsed on two consecutive surveys (e.g., baseline & FU 2). We will calculate and compare unadjusted prevalence ratios and corresponding 95% confidence intervals (CIs) among survivors and siblings.

Aim 2: To examine demographic, socioeconomic, and treatment exposures associated with loneliness in young adult survivors of childhood and adolescent cancer.

For aim 2, we will use multivariable logistic regression modeling to investigate predictors of loneliness in survivors. We will calculate odd ratios and corresponding 95% confidence intervals for all exposures and covariates. We will run separate models for primary treatment exposures and diagnosis. For this analysis all exposure, covariate, and outcome data will be obtained from the baseline surveys.

Aim 3: To examine the association between loneliness and physical health status, health-related quality of life, and psychological distress.

For aim 3 we will compare the unadjusted prevalence of impairment in health related quality of life, psychological distress and physical health status among survivors with and without loneliness. We will report odds ratios and corresponding 95% CIs. We will utilize multivariable logistic regression models to examine associations between loneliness and specific outcomes with models adjusted for relevant demographic and treatment exposures to reduce confounding bias. We will examine both cross-sectional associations (i.e. baseline loneliness and baseline health outcomes) as well as longitudinal associations (i.e. baseline loneliness and outcomes at FU 2 or FU 5).

Aim 4: To explore the association between loneliness and health behaviors (e.g., tobacco use, alcohol use, and physical activity) in young adult survivors of childhood and adolescent cancer.

For aim 5 we will examine the associations between loneliness feelings in survivors and different health behaviors (tobacco use, alcohol use, physical activity). We will compare the unadjusted prevalence of outcomes among survivors with and without loneliness. We will report odds ratios and corresponding 95% CIs. We will utilize multivariable logistic regression models to examine associations between loneliness and specific outcomes with models adjusted for relevant demographic and treatment exposures to reduce confounding bias. We will examine both cross-sectional associations (i.e. baseline loneliness and baseline health outcomes) as well as longitudinal associations (i.e. baseline loneliness and outcomes at FU 2 or FU 5).

Aim 5: To examine associations between physical and/or cognitive limitations and loneliness, and if physical and/or cognitive limitations mediates the associations between treatment exposures and loneliness.

First, we will examine direct associations between cognitive limitations and loneliness. Next, we will use multivariable logistic regression modeling to investigate the association between the presence of physical and/or cognitive limitations and loneliness in survivors. If treatment exposures in Aim 2 (i.e. higher doses of CRT and/or chemotherapy) are associated with loneliness; will explore the potential mediating effect of cognitive limitations (as measured by the CCSS-NCQ) and chronic disease (as defined by CTCEA grading) on the association between treatment exposures and loneliness using a causal mediation analysis. We will specify logistic regression models for the exposure-outcome and exposure-mediator relations. Odds ratios and corresponding 95% CIs for the marginal total effect and the controlled direct effects will be estimated. Models will be adjusted for a minimally sufficient set of covariates.

Sample Tables

Table 1. Characteristics of young adult survivors of childhood cancer

	Mean/Median	SD/IQR
Age at diagnosis (y)		
Age at baseline (y)		
Age at follow-up (y)		
	N	%
Sex		
Male		
Female		
Race		
White		
Black		
Other		
Educational attainment		
≤ High school		
Some college, training		
≥ College graduate		
Employed during the last year		
No		
Yes		
Marital status		
Single, never married		
Married living as married		
Divorced, separated, widowed		
Diagnosis		
Leukemia		
CNS tumor		
Hodgkin lymphoma		
Non-Hodgkin lymphoma		
Wilms tumor		
Neuroblastoma		
Soft tissue sarcoma		
Osteosarcoma		
Surgery (amputation)		
No		
Yes		
Chemotherapy*		
No		
Yes		
Radiation		
None		
Non-cranial		
<20 Gy CRT		
≥20Gy < 30 Gy CRT		
≥30Gy CRT		

*We will consider individual chemotherapies and dose distributions as described above.

Table 2. Prevalence & persistence of loneliness in young adult childhood cancer survivors

	Survivors			Siblings			
	N	n	%	N	n	%	PR (95%CI)
Baseline							
Follow-up							
Persistent loneliness							

Table 3. Multivariable model predicting report of loneliness feelings in young adult survivors of childhood cancer

	OR	95% CI
Age at diagnosis (y)		
Age at baseline (y)		
Sex		
Male	Reference	
Female		
Race		
White	Reference	
Black		
Other		
Educational attainment		
≤ High school	Reference	
Some college, training		
≥College graduate		
Employed during the last year		
No		
Yes	Reference	
Marital status		
Single, never married		
Married living as married	Reference	
Divorced, separated, widowed		
Surgery (amputation)		
No	Reference	
Yes		
Chemotherapy*		
No	Reference	
Yes		
Radiation		
None	Reference	
Non-cranial		
<20Gy CRT		
≥20Gy < 30 Gy CRT		
≥30Gy CRT		

Separate models will be examined replacing treatment exposures with primary cancer diagnosis.
*We will consider individual chemotherapies and dose distributions as described above.

Table 4. Association between loneliness and impairment in physical health related quality of life

	SF-36 subscales							
	Physical Function		Role Physical		Bodily Pain		General Health	
Loneliness	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
No	Reference		Reference		Reference		Reference	
Yes								

T-scores of ≤40 considered to represent impaired quality of life
Multivariable models adjusted for age, sex, race, education, employment, marital status, chronic health conditions, and treatment exposures (associated with loneliness and identified in Aim 2).

Table 5. Association between loneliness and psychological distress

	Depression		Anxiety		Somatization	
Loneliness	OR	95% CI	OR	95% CI	OR	95% CI
No	Reference		Reference		Reference	
Yes						

T-scores of ≥63 considered to represent significant psychological distress symptoms
Multivariable models adjusted for age, sex, race, education, employment, marital status, chronic health conditions, and treatment exposures (associated with loneliness and identified in Aim 2).

Table 6. Associations between loneliness and chronic health conditions

	Grade 1 or 2 vs. None		Grade 3 or 4 vs. None	
Loneliness	OR	95% CI	OR	95% CI
No	Ref		Ref	
Yes				

Multivariable models adjusted for age, sex, race, education, employment, marital status, and treatment exposures (chemotherapy, surgery, radiation therapy).

Table 7. Associations between loneliness and tobacco use

	Never smokers		Former smokers		Current smokers		Other tobacco product users	
Loneliness	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Yes								
No								

Multivariable models adjusted for age, sex, race, education, employment, marital status, and treatment exposures (chemotherapy, surgery, radiation therapy).

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