Treatment and Lifestyle Profiles of Healthy Aging Survivors of Childhood Cancer.

Primary Working Group: Chronic Disease
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BACKGROUND & RATIONALE:

Overall survival of childhood cancer at 5 years now exceeds 85%, and over 500,000 survivors of childhood cancer reside in the United States.[1,2] However, despite improvements in overall and event-free survival, many childhood cancer survivors remain at elevated risk over their lifetime for secondary physical, neurocognitive, and psychosocial late effects.[2–4] On average, childhood cancer survivors develop more chronic health conditions (CHCs) and experience higher mortality,[5–10] and also report worse functional status compared with the non-cancer population.[11–14] Although late mortality and severe or disabling CHCs have generally decreased in more recent decades,[9,10] survivors from more recent eras have self-reported higher rates of poor general health and cancer-related anxiety compared with prior, highlighting a need to examine temporal trends as cancer treatment evolves.[13] Yet, many survivors of childhood cancer experience no or minimal late effects compared with similarly aged controls without a cancer history. Additionally, survivors who report healthy lifestyle behaviors have lower rates of health complications and mortality, suggesting that some premature deaths may be preventable with lifestyle modifications.[7] Of modifiable lifestyle factors, high-risk alcohol use patterns among survivors have been associated with worse health status.[15] Similarly, physical inactivity has been associated with early mortality and musculoskeletal CHCs.[16,17] Tobacco use is another factor potentially associated with worse health status[13] and could be another target for lifestyle modification efforts.[10]

Most research in childhood cancer survivorship to date has explored factors associated with subsequent poor health outcomes, including cardiomyopathy, endocrinopathies, neurocognitive deficits, and psychosocial functioning.[2,18–20] This work has been critical to improve recognition of toxic treatment exposures, counsel patients on risks, and devise strategies to reduce late effects. Conversely, there may be benefit in specifically examining the opposite: survivors of childhood cancer who experience minimal late effects and maintain healthy lifestyles through adulthood. So far, a primary focus on healthy survivors has been applied to survivors of childhood cancer in relatively limited settings. For

example, a recent investigation of long-term survivors of Wilms tumor focused on those who received lower intensity treatment,[21] and found that many such survivors' health status compared somewhat favorably with sibling comparison subjects. A study focused on children with acute myeloid leukemia also demonstrated that most long-term survivors, regardless of treatment regimen, reported good-to-excellent health status.[22] However, this approach has not been broadly applied to the general population of childhood cancer survivors, who, irrespective of disease type, may share types of treatment exposures and other risk factors for morbidity. Focusing on cancer survivors with healthy long-term outcomes may help to identify behaviors or factors that promote good functional status—including treatment regimens associated with minimal long-term toxicity in case future treatment de-escalation is possible—and provide stronger recommendations for lifestyle counseling during survivorship.[13,18]

To evaluate the aging profiles of healthy childhood cancer survivors over time, we will examine the cumulative burdens of CHCs and functional status among long-term childhood cancer survivors as well as their siblings. We will also examine differences by cancer diagnosis type and treatment exposures to provide insight into cancer treatment combinations associated with low long-term morbidity. Among cancer survivors, we will assess how demographic characteristics, treatment exposures, and lifestyle factors are associated with lower CHC burden and better functional status.

Careful consideration will be given to avoid or minimize overlap with the numerous prior investigations focused specifically on factors associated with adverse outcomes globally among long-term cancer survivors. Future work could focus on factors associated with better psychological well-being, to complement this proposed study, which will be limited to physical health. Together, results from this proposal will provide valuable insights into the exposures and behaviors of healthy aging cancer survivors, informing potential interventions directed toward the promotion of active and healthy lifestyles.

SPECIFIC AIMS

The overall goal of this study is to focus on *healthy aging* in cancer survivors. We will estimate the proportion of survivors with healthy aging, defined as having a *good functional status* and *low burden of CHCs* for attained age compared with sibling controls. For this analysis, we will define good functional status as not having functional impairment or activity limitations at the time of most recent follow-up (as in Ness et al).[13] We will define a low burden of CHCs as having a number of cumulative (non-fatal) CHCs at the time of most recent functional status ascertainment, that does not exceed the mean cumulative count (MCC) of CHCs in same aged, same sex siblings.[19,23] Finally, after describing prevalence, we will assess demographic, treatment, and lifestyle factors predictive of low CHC burden, good functional status, and healthy aging as a whole.

Data will be analyzed from the entire CCSS cohort of childhood cancer survivors and sibling comparison participants. Primary and secondary data requested for analysis will include CHCs, health status, and late mortality. Correlative factors will include tobacco use, alcohol use, physical activity, medical screening behaviors, insurance status, marital status, educational attainment, employment, age, sex, race, treatment era, chemotherapy exposure(s), radiation exposure(s), surgery exposure(s), and hematopoietic stem cell transplant status.

This will be a cross-sectional analysis where cancer survivors are assessed at single timepoints, rather than a longitudinal analysis examining trends in non-fatal CHCs and functional status over time. As

such, careful consideration will be given to the interplay between era of diagnosis/treatment and aging outcomes, given that participants with a higher attained age will have likely been diagnosed in earlier treatment eras and participants who were lost to follow-up may also differ from the rest of the cohort. Acknowledging these limitations, this analysis will also examine outcomes in the context of age attained and treatment era.

Aim 1a: Describe the proportion of cancer survivors by age group who have a low number of cumulative CHCs. We will examine cancer survivors at the timepoint of their most recent functional status assessment. We will stratify survivors into age groups of 20-34, 35-49, and 50+ years. If there are sufficient numbers of participants, we may consider more narrow age categories for reporting (e.g., 20-29, 30-39, 40-49, 50+). As above, for survivors, a "low" number of Grade 3-4 CHCs will be defined as having a number of cumulative CHCs not exceeding the MCC of CHCs in same age, same sex siblings.

- *Hypothesis: The proportion of cancer survivors with low CHC burden relative to siblings will be below 50% for all age groups and decrease with advancing age*.

Aim 1b: Describe the proportion of cancer survivors by age group with a good functional status. We will examine cancer survivors and siblings within age categories as defined in Aim 1a, at their time of most recent functional status assessment. "Good" functional status among cancer survivors will be defined as not having functional impairment or activity limitations (defined similarly to Ness et al)[13] at attained age.

- *Hypothesis: The proportion of cancer survivors with good functional status will be lower than that of age- and sex-matched siblings, and decrease with advancing age. Differences between cancer survivors and siblings will increase with each older age category.*

Aim 1c: Examine degrees of overlap between low CHC burden and good functional status. Across each age category defined above, we will test associations between low CHC burden for attained age with good functional status at the same timepoint, adjusting for treatment era.

- *Good functional status will be associated with having a low cumulative CHC burden for age. Associations between these outcomes will be stronger in older age groups.*

Aim 2: Estimate the prevalence of cancer survivors with healthy aging by cancer diagnosis type and treatment era. "Healthy aging" will be defined as a binary variable (yes/no) for survivors as having both a low number of CHCs and a good functional status, defined in Aim 1. We will examine cancer survivors within age categories of 20-34, 35-49, and 50+ years (or more narrow age categories if data allow, and as a total aggregate) and by treatment era, defined by decade of initial cancer diagnosis (e.g., 1970-1979, 1980-1989, etc.). Results will provide insight into how aging after therapy has evolved over time, as well as how it may differ among various cancer types.

- *Hypothesis: The proportion of cancer survivors who exhibit healthy aging relative to age- and sex-matched siblings will vary by cancer diagnosis type and treatment era. Cancer survivors will meet criteria for healthy aging in lower proportions as they age.*

Aim 3: Identify demographic, treatment, and lifestyle predictors associated with healthy aging among cancer survivors. We will apply multivariable logistic regression models at ages 20-34, 35-49, and 50+ years (or more narrow age categories if data allow), to estimate the odds of healthy aging, as defined in Aim 2. Models will be conditioned on surviving up to the minimum age of each category. Covariates will include survivor demographics, cancer diagnosis type, cancer treatment exposures, treatment era, and baseline health behaviors.

- *Hypothesis: Lower exposures to anthracycline and alkylator chemotherapy, total radiation dose, and not receiving cranial radiation will be associated with healthy aging. Low alcohol use, abstinence from tobacco, and healthy BMI at baseline will be associated with healthy aging.*

ANALYSIS FRAMEWORK:

Populations of interest:

This analysis will include all cancer survivors and sibling controls enrolled in the CCSS.

Outcomes of interest:

Aim 1: For Aim 1a, the main outcome of interest will be the total number of cumulative non-fatal Grade 3+ CHCs for each individual patient at their attained age at their most recent follow-up that included a functional status assessment. CHC grades will be defined by Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. We will also examine cumulative Grade 2+ CHCs in a sensitivity analysis. CHCs will be counted if ever reported with a Grade equal to or greater than 3 (or 2 for the sensitivity analysis), leading up to a participant's attained age at time of most recent functional status assessment. No types of CHCs will be weighted more heavily than others (i.e., a cancer CHC will be counted the same as diabetes CHC). Siblings at each attained age will have cumulative Grade 2+ and 3+ CHCs tabulated for comparison purposes, stratified by sex. The MCC[19,23] in same age/sex siblings will be used to define low versus high CHC burden among survivors (i.e., survivors with a cumulative CHC count above the sibling MCC will be considered as having "high CHCs" for their sex and attained age. If the MCC among a sibling age/sex group is below 1, the cutoff for high CHC burden applied to the relevant survivors will be set to 1.

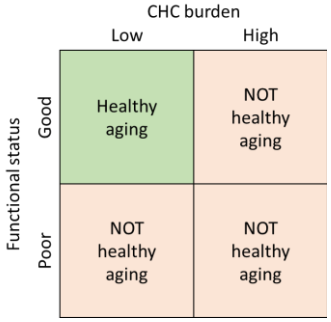
For Aim 1b, functional status will be defined as a binary variable based on participant report at follow-up surveys. Participants without functional impairment or activity limitations, defined similarly to Ness et al.,[13] will be characterized as having "Good" functional status. Slight variations from the definition of Ness et al will be implemented to allow for functional status assessment at a greater number of follow-up timepoints, rather than FU-4 and FU-5 only. For purposes of this study, functional impairment will be defined as having limitations in bathing or dressing oneself (FU-5: O3j) or reporting problems with work or regular daily activities as a result of physical health (FU-5: O4d). Activity limitations will be defined as reporting problems with moderate activities in a typical day (for example, bowling, carrying groceries, or walking one block; any of FU-5 O3b, O3c, O3i) in the past 4 weeks. Participants with either functional impairment or activity limitations will be characterized as having "Poor" functional status. As functional status measures are taken longitudinally and may be subject to missing data/non-response, only the most recent measure of functional status for survivors and siblings will be used for classification.

For Aim 1c, low CHC burden and good functional status will be characterized as described above.

In a sensitivity analysis, we will also capture functional status and cumulative CHCs from survivors who responded at a single timepoint (FU-2 [2003], FU-4 [2007], FU-5 [2014], or FU-6 long [2017]) and compare the point prevalence of these outcomes at one or more of these follow-up surveys to outcomes of the analysis incorporating the most recent follow-up of functional status only.

Aims 2 and 3: The primary outcome of interest for these two Aims will be "healthy aging" among cancer survivors by age group. Healthy aging will be defined as a binary variable, based on whether a cancer survivor is categorized as having low CHCs AND good functional status for age (Figure 1). Cancer survivors with high CHCs AND/OR poor functional status will be characterized as not having healthy aging.

Figure 1. "Healthy aging" definition



Correlative outcomes and covariates of interest:
Additional covariates to be accessed are summarized in the following Table.

Table 1: Covariate list

Variable	Data Source	CCSS Definition
Age attained	CCSS records	Age at the time of most recent questionnaire where CHC/functional status are ascertained
Age at dx	CCSS records	Age at diagnosis
Decade of dx	CCSS records	1970s; 1980s; 1990s
Sex	CCSS records	Male; Female
Race	CCSS records	White; Black; American Indian or Alaska Native; Asian or Pacific Islander; Other
Ethnicity	CCSS records	Hispanic; Non-Hispanic
Education	Baseline survey	<High school; High school-some college; College graduate or greater
Marital status	Baseline survey	Married; Single; Divorced or separated; Widowed. *At the time of most recent questionnaire where CHC/functional status ascertained.*
Health insurance coverage	Baseline survey	Yes; No
Annual household income	Baseline survey	<$19,000; $20,000-$39,000; $40,000-$59,000; $60,000-$79,999; $80,000-$99,999; >$99,999; Don't know
Neighborhood household income	Baseline survey	If census tract/block group levels or zip code are available, would report as median income in 2010 (to maintain consistency across eras)
Cancer diagnosis type	CCSS records	Acute lymphoblastic leukemia; Acute myeloid leukemia; Other leukemia; Hodgkin Lymphoma; Non-Hodgkin Lymphoma; CNS tumor; Bone cancer or sarcoma; Neuroblastoma; Wilms tumor; Other embryonal non-CNS solid tumor
Anthracycline exposure (doxorubicin equivalent mg/m2)	CCSS records	None; 1-99 mg/m2; 100-249 mg/m2; 250+ mg/m2
Alkylator exposure (cyclophosphamide equivalent dose)	CCSS records	None; 1-3999 mg/m2; 4000-7999 mg/m2, 8000+ mg/m2
Other chemotherapy exposure	CCSS records	No; Yes
Radiation exposure	CCSS records	None; Any non-cranial XRT separate from TBI; Cranial XRT separate from TBI; TBI
Surgery exposure	CCSS records	No; Cranial surgery; Spinal surgery; Any major thoracic surgery; Any major abdominal surgery; Primary amputation; Primary limb salvage; Other surgery
Stem cell transplant	CCSS records	No; Yes
History of late relapse (>5 years from original cancer diagnosis)	CCSS records	No; Yes—will also capture as potential time-varying event

BMI	Baseline survey for planned analysis; may consider follow-up survey data ad hoc	<18.5 kg/m^2, 18.5-24.9 kg/m^2, 25-29.9 kg/m^2, ≥ 30 kg/m^2
Alcohol use (baseline)	Baseline survey for planned analysis	Categorize as None; Low/moderate; Heavy or Risky ("binge" drinking) as per US Dept of Agriculture guidelines 2020-2025 and NIAAA: - Low/Moderate drinking: <7 drinks per week for females, <14 drinks per week for males <65 years, <7 drinks per week for anyone 65 years or older - Heavy drinking: >3 drinks per day or >7 per week for females; >4 drinks per day or >14 per week for males - Binge drinking: 4+ drinks on one occasion for females, 5+ drinks on one occasion for males
Tobacco use (baseline)	Baseline survey for planned analysis	Categorize as Never smoker; Former smoker; Active smoker Use questions O1 and O3 (expansion cohort baseline) or Qs N1 and N1.d (original baseline) • Never smoker, O1= No AND O3= No • Former smoker O1= Yes AND O3= No • Current Smoker, O1= Yes AND O3=Yes
Physical activity (baseline)	Baseline survey for planned analysis	Use questions O15 (expansion cohort baseline) or N9 (original cohort baseline) Categorize as per Scott et al. (JAMA Oncol 2018)[17] using MET hr/wk: 0; 3-6; 9-12; 15-21

Methods and statistical analysis (by aim):

Demographic analysis: We will gather frequencies, means/SDs, and medians/IQRs of demographic, disease, and treatment-related information to characterize childhood cancer survivors. This information will be summarized in the demographic table (Table 2).

Aim 1: Survivors will be separated by age groups of 20-34, 35-49, and 50+ years, depending on age at most recent evaluation of functional status. Alternatively, different age groupings may be considered if each subgroup contains enough participants (e.g., 20-29, 30-39, 40-49, 50+ years). The prevalence of cancer survivors for outcomes of interest (low CHCs and good functional status) will be calculated with 95% confidence intervals. Mock results are shown in Table 3. We will compare average CHCs between survivors and siblings in each age category using chi-square tests (not shown in table). To compare proportions of participants with good functional status between cancer survivors and siblings, we will use chi-square tests stratified by age category and/or decade of diagnosis (not shown in a table).

In sensitivity analysis, we will also analyze outcomes (CHCs, functional status) as above; however, rather than including all participants' most recent functional status assessments (and their corresponding cumulative CHC burden at the time of that assessment) as outcomes, we will evaluate cumulative CHCs and functional status of all participants who responded to a single survey timepoint (i.e., FU-2 only). This approach may account for potential survivor bias, where participants with healthier aging profiles may be more likely to respond to subsequent follow-up surveys.

Aim 2: Survivors will be separated by the same age groups used in Aim 1. Survivors will also be stratified separately by general cancer diagnosis type (ALL, AML, other leukemia, low-grade glioma, medulloblastoma, other CNS tumor, Hodgkin lymphoma, non-Hodgkin lymphoma, renal tumors, neuroblastoma, soft tissue sarcoma, osteosarcoma, Ewing sarcoma, other bone tumors). For

examination by treatment era, survivors will be stratified by decade of cancer diagnosis (e.g., 1970-1979, 1980-1989, etc.). Proportions of survivors meeting criteria for healthy aging (Figure 1) will be calculated, with standard errors. Mock results of stratified data are shown in Tables 3B-C, with an alternate combined age/era presentation shown in Table 3D, given the high degree of overlap between attained age group at most recent follow-up and year/decade of diagnosis. If the degree of overlap between these covariates is excessive, we will consider analyzing CHCs and functional status at cross-sectional time points as outcomes of interest (i.e., 10 years from diagnosis, 20 years from diagnosis, 30 years from diagnosis), including for participants with follow-up responses within 5 years of these timepoints. We will compare functional status proportions between survivors and siblings in each age category using chi-square tests. Mock results depicting temporal trends by cancer type are shown in Table 4.

Aim 3: Logistic regression models will be calculated by age-specific subgroups to estimate potential associations between the healthy aging and covariates of interest (see Table 5). The model will be adjusted for age at diagnosis, sex assigned at birth, race/ethnicity, baseline health insurance coverage, baseline marital status, treatment factors (anthracycline and alkylator exposure, stem cell transplant history, surgery, radiation), history of late relapse (if before period of reporting of cumulative CHCs and functional status), and baseline lifestyle factors (BMI, smoking, alcohol use, physical activity). Models will be conditioned on surviving up to the minimum age of each category. Potential associations will first be estimated with univariate regression, followed by multivariable regression with model variables determined by backward selection.

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TABLE 2 Participant characteristics

Characteristic	Cancer survivors N=	Siblings N=
Age at questionnaire (years)		
21-34		
35-49		
50+		
Age at diagnosis (years)		
0-4.99		
5-9.99		
10-14.99		
15-20		
Time elapsed from diagnosis (years)		
10-10.99		
20-29.99		
30-39.99		
>=40		
Sex		
Male		
Female		
Other/Refused		
Race and Ethnicity		
White, Non-Hispanic		
Black, Non-Hispanic		
Hispanic/Latino		
Other		
Chronic Health Conditions (Grade 3+ [or 2+])		
None		
1		
2 or more		
Health insurance coverage		
Yes		
No		
Educational attainment		
<High school		
High school - some college		
College graduate and or greater		
Marital Status		
Married		
Single		
Divorced/Separated		
Widowed		
Alcohol use (baseline)		

None		
Low or moderate		
Heavy or risky		
Smoking (baseline)		
Never smoker		
Former smoker		
Current smoker		
Physical activity (MET/week; baseline)		
0		
3-6		
9-12		
15-21		
BMI (kg/m^2; baseline)		
<18.5		
18.5-29.9		
≥30		
Cancer diagnosis type		
ALL		*
AML		*
Other leukemias		*
Low-grade glioma		*
Medulloblastoma		*
Other CNS tumors		*
Hodgkin lymphoma		*
Non-Hodgkin lymphoma		*
Kidney tumors		*
Neuroblastoma		*
Soft tissue sarcoma		*
Osteosarcoma		*
Ewing sarcoma		*
Other bone tumors		*
Chemotherapy exposure		
Anthracycline		*
Alkylator		*
Other		*
None		*
Radiation exposure		
None		*
Any non-cranial radiation		*
Radiation including cranial		*
TBI		*
Surgery exposure		
No		*

Yes; cranial		*
Yes; major thoracic		*
Yes; major abdominal		*
Yes; amputation/limb salvage		*
Yes; other		*
Stem cell transplant		
No		*
Yes		*
History of late relapse		
No		*
Yes		*

*Not applicable to siblings. Will report these characteristics for cancer survivors only.

TABLE 3A Proportions of cancer survivors with low burden of chronic health conditions and high functional status, stratified by age (could make figure if interesting trends)

Age group	Low burden of chronic health conditions, % (95% CI)	Good functional status, % (95% CI)
21-34		
35-49		
50+		

TABLE 3B Proportions of cancer survivors with low burden of chronic health conditions and high functional status, stratified by cancer type (could make figure if interesting trends)

Cancer type	Low burden of chronic health conditions, % (95% CI)	Good functional status, % (95% CI)
ALL		
AML		
Other leukemias		
Low-grade glioma		
Medulloblastoma		
Other CNS tumors		
Hodgkin lymphoma		
Non-Hodgkin lymphoma		
Kidney tumors		
Neuroblastoma		
Soft tissue sarcoma		
Osteosarcoma		
Ewing sarcoma		
Other bone tumors		

TABLE 3C Proportions of cancer survivors with low burden of chronic health conditions and high functional status, stratified by treatment era (could make figure if interesting trends)

Treatment era	Low burden of chronic health conditions, % (95% CI)	Good functional status, % (95% CI)
1970s		
1980s		
1990s		

TABLE 3D (ALTERNATIVE TABLE to 3A and 3C) Proportions of cancer survivors with low burden of chronic health conditions and high functional status, stratified by age and treatment era

Age group	Treatment era	Low burden of chronic health conditions, % (95% CI)	Good functional status, % (95% CI)
21-34	1970s		
	1980s		
	1990s		
35-49	1970s		
	1980s		
	1990s		
50+	1970s		
	1980s		
	1990s		

TABLE 4 The proportion of cancer survivors with healthy aging profiles, stratified by age and cancer disease type (may optionally turn into a figure)

Cancer type	21-34, % (SE)	35-49, % (SE)	50+, N (%)
ALL			
AML			
Other leukemias			
Low-grade glioma			
Medulloblastoma			
Other CNS tumors			
Hodgkin lymphoma			
Non-Hodgkin lymphoma			
Kidney tumors			
Neuroblastoma			
Soft tissue sarcoma			
Osteosarcoma			
Ewing sarcoma			
Other bone tumors			

TABLE 5 Predictors of healthy aging among survivors of childhood cancer

Characteristic	Univariate OR (95% CI)	Multivariable OR (95% CI)
Age at diagnosis (years)		
0-4.99		
5-9.99		
10-14.99		
15-20		
Sex		
Male		
Female		
Other/Refused		
Race and Ethnicity		
White, Non-Hispanic		
Black, Non-Hispanic		
Hispanic/Latino		
Other		
Educational attainment		
<High school		
High school - some college		
College graduate and or greater		
Health insurance coverage		
Yes		
No		
Marital Status		
Married		
Single		
Divorced/Separated		
Widowed		
Anthracycline exposure		
None		
1-199 mg/m2 doxorubicin equivalents		
200-349 mg/m2 doxorubicin equivalents		
≥350 mg/m2 doxorubicin equivalents		
Alkylator exposure		
None		
1-4000 mg/m2 cyclophosphamide equivalent dose		
4000-8000 mg/m2 cyclophosphamide equivalent dose		
≥8000 mg/m2 cyclophosphamide equivalent dose		
Radiation exposure		
None		
Any non-cranial radiation, separate from TBI		

Radiation including cranial, separate from TBI		
TBI		
Surgery exposure		
No		
Yes; cranial		
Yes; major thoracic		
Yes; major abdominal		
Yes; amputation/limb salvage		
Yes; other		
Stem cell transplant		
No		
Yes		
History of late relapse		
No		
Yes		
Tobacco use		
None		
Former smoker		
Current smoker		
Alcohol use		
None		
Low or moderate		
Heavy or binge		
Physical activity category (MET hrs/wk)		
0		
3-6		
9-12		
15-21		