Analysis Concept Proposal

1. **Study Title:** Health Outcomes in Older Survivors of Childhood Cancer

2. **Working Groups:** Chronic Disease (primary); Subsequent Malignancy, Psychology, Cancer Control (secondary)

Investigators:

Rusha Bhandari	rbhandari@coh.org
Saro Armenian	sarmenian@coh.org
F. Lennie Wong	lenniewong@coh.org
Lisa Kenney	lisa_kenney@dfci.harvard.edu
Lucie Turcotte	turc0023@umn.edu
Claire Snyder	csnyder@jhu.edu
Eric Chow	ericchow@uw.edu
Kevin Oeffinger	kevin.oeffinger@duke.edu
Joe Neglia	jneglia@umn.edu
Kevin Krull	kevin.krull@stjude.org
Paul Nathan	paul.nathan@sickkids.ca
Rebecca Howell	rhowell@mdanderson.org
Wendy Leisenring	wleisenr@fredhutch.org
Greg Armstrong	greg.armstrong@stjude.org
Kirsten Ness	kiri.ness@stjude.org

3. **Background and rationale**

It is well recognized that childhood cancer survivors experience substantial disparities in health outcomes during young adulthood compared with the general population. Recent studies suggest that survivors exhibit physiologic and molecular signs of accelerated aging, attributed in part to cancer diagnosis and treatment exposures at an early age.[1,2] The prevalence of frailty, one of the most widely-recognized phenotypes of aging, is approximately three times higher in survivors compared with sibling controls,[3] and has been associated with an increased risk of premature mortality[2]. In fact, mortality rates rise sharply over time in 5-year childhood cancer survivors, with a reported mortality rate of 6.5% at 10 years that increases to 18.1% by 30 years from cancer diagnosis.[4] By 15 years following diagnosis, the mortality rate from other (non-recurrent, non-external) causes surpasses that from primary disease.[4] In these younger survivors, aging-related health conditions such as subsequent malignant neoplasms (SMNs) and cardiopulmonary diseases are the leading causes of late mortality, with incidence rates exceeding those reported for the general population.[5] As the Childhood Cancer Survivor Study (CCSS) includes patients who were diagnosed between 1970-1999, prior studies have primarily focused on younger (<50 years old) survivors. There is a paucity of information on health outcomes, including cause-specific mortality, in the large and growing population of aging childhood cancer survivors, a knowledge gap to be addressed in the current proposal.

Recent studies from the CCSS have shown that the 15-year cumulative incidence of SMNs in survivors has steadily decreased over time (incidence rates: diagnosed in 1970s, 3%; diagnosed in 1990s, 1.5%), reflecting changes in therapeutic approaches (e.g. decreasing use or doses of radiation and chemotherapeutic agents associated with SMNs).[6] Despite these improvements, childhood cancer survivors continue to have a high burden of SMNs at a relatively young age; by age 40 years, survivors have a significantly higher standardized incidence ratio (SIR) of SMNs compared to the age- and sex-matched general population.[6] Risk factors for SMNs include female

sex, radiation exposure, and treatment with high doses of alkylating and platinum agents. The most common SMNs are breast and thyroid cancer.[6] However, these associations are largely driven by data from younger (<50 years old at survey completion) CCSS participants and, while they reflect treatment-related risk factors for SMNs, they may not reflect the long-term burden of *de novo* aging-associated risk factors. For example, in the general population, there are well-established relationships between lifestyle (e.g. tobacco smoking, alcohol consumption) and socioeconomic (e.g. income, education) factors and aging-related cancers such as breast, lung, and prostate.[7,8] Defining the patterns and incidence rates for SMNs in older survivors, as well as modifiers of cancer risk, may facilitate refinement of existing screening and prevention strategies.

With regard to other comorbidities, survivors have a nearly 6-fold higher cumulative incidence of at least one severe or life-threatening chronic health condition (CHC) compared to sibling controls.[9] Similar to trends seen with mortality and SMNs, these health conditions develop early during the survivorship period, and their incidence increases with time.[10] CCSS participants in their mid-twenties appear to have a similar incidence of severe, life-threatening, or fatal health conditions as 50-year-old siblings.[10] Amongst survivors without a severe, disabling, life-threatening, or fatal health condition by the age of 35, over 25% develop a new condition within 10 years, compared to 6% of healthy siblings.[10] The cumulative incidence is highest for cardiovascular, endocrine, and musculoskeletal conditions that, in the general population, typically develop and are screened for at later ages.[5,11,12] Survivors are also more likely to report worse health status (poor general health, adverse mental health, functional impairment, activity limitations) than sibling comparisons. Sociodemographic risk factors for adverse health status among survivors include female sex, lower annual household income, not graduating from high school, smoking, non-white race, and older age. Treatment-related risk factors for adverse health status outcomes include exposure to alkylating agents, anthracyclines, radiation (specifically cranial and chest), and surgery.[13] That said, as for SMNs, information on health outcomes of CCSS participants has been largely derived from younger (<50 years) study participants. To date, few studies have investigated whether the late effects of cancer treatment persist in very long-term survivors (i.e. ≥50 years), or whether the health outcomes and mortality rates of this older cohort of CCSS participants reflect those of the general population. Importantly, none have investigated the association between aging-related lifestyle or behavioral risk factors and long-term health outcomes in older cancer survivors.

Until recently, the relatively younger age of the baseline CCSS cohort, coupled with the limited longitudinal data on health outcomes in these survivors, has precluded such investigations. For the proposed study, we will leverage the now-older CCSS cohort and use data from follow-up questionnaires (e.g. Follow-up 4 to 6) to characterize the burden of late effects in older survivors. Moreover, the proposed study will complement the renewed emphasis on aging in cancer survivors that was articulated in the most recent CCSS competitive renewal application to the NIH. These findings may set the stage for future studies that will inform evidence-based screening and prevention strategies for aging survivors of childhood cancer.

4. Specific aims/objectives/research hypotheses

Aim 1: Estimate the cumulative incidence of overall and cause-specific mortality in CCSS participants, conditional on having survived to 50 years of age. Compare the risk of mortality (overall and cause-specific) in this survivor cohort to the age-, calendar year-, race-, and sex-matched general U.S. population using the standardized mortality ratio.
Hypothesis 1: CCSS participants will have a higher relative rate of overall and cause-specific mortality compared with the general population.

Aim 2: Determine the cumulative incidence of and risk factors (sociodemographic, diagnosis, treatment-related, behavioral [time-dependent]) for SMNs occurring at age ≥50 years in CCSS participants, conditional on having survived to 50 years of age. Compare incidence rates for SMNs in this cohort to the age-, calendar year-, race-, and sex-matched incidence rates in the general U.S. population. Evaluating risk factors for SMNs in this older cohort of survivors may identify whether lower doses of certain exposures, which may not be associated with SMNs in younger survivors, have later effects and are associated with risk for SMNs in older survivors.
Hypothesis 2a: Standardized incidence ratios (SIRs) for SMNs will be higher for CCSS participants ≥50 years of age, relative to the general population.
Hypothesis 2b: Select sociodemographic, diagnosis, treatment-related, and behavioral risk factors will be associated with an increased risk of SMNs in this cohort.

Aim 3: Compare the prevalence of any or multiple (≥2) severe or life-threatening CHCs and of frailty reported at any age between survivors and siblings who completed a health outcomes questionnaire at ≥50 years of age. Identify sociodemographic, diagnosis, treatment-related, and behavioral risk factors associated with specific CHCs and frailty in survivors.
Hypothesis 3a: Severe or life-threatening CHCs will be more prevalent in survivors than in siblings.
Hypothesis 3b: Frailty will be more prevalent in survivors than in siblings.
Hypothesis 3c: Select sociodemographic, diagnosis, treatment-related, and behavioral risk factors will be associated with CHCs and frailty in survivors.

Aim 4: Compare the prevalence of adverse health status outcomes (e.g. poor general health, adverse mental health, functional impairment, activity limitations) between survivors and siblings who completed a questionnaire at ≥50 years of age. Determine the association between CHCs and adverse health status in survivors. Identify the sociodemographic, diagnosis, treatment-related, and behavioral risk factors associated with adverse health status in survivors.
Hypothesis 4a: Adverse health status will be more prevalent in survivors than in siblings.
Hypothesis 4b: The prevalence of survivors with adverse health status will vary by severity of CHCs, as well as by sociodemographic, diagnosis, treatment-related, and behavioral risk factors.

5. Analysis Framework

Participants:

Aim 1 will include childhood cancer survivors diagnosed between 1970 and 1999, who were born before 1967 and survived to ≥50 years of age by the end of 2016. This will allow for ≥1 year of follow up after achieving 50 years of age until the time of the last U.S. National Death Index search by the CCSS (12/2017); **Figure 1**.

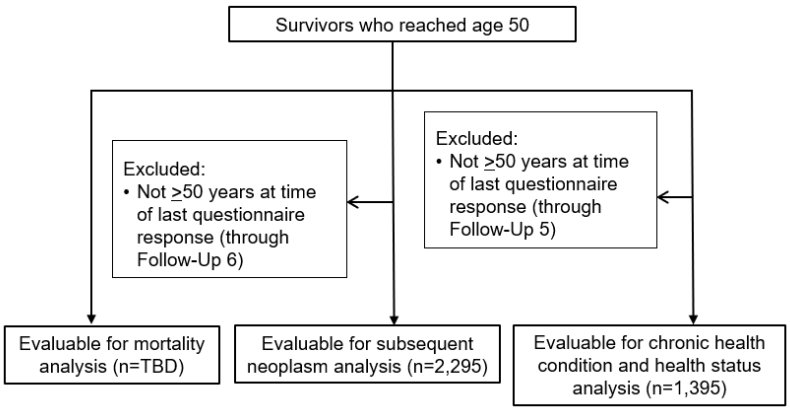

Figure 1. CONSORT diagram of evaluable participants from the Childhood Cancer Survivor Study

Aim 2 will include survivors who completed any questionnaire at ≥50 years of age that asked about SMNs (through FU6). Of 3,257 participants who completed a questionnaire through FU6, 2,295 were ≥50 years at the time of completion. Amongst these older survivors, 50% were male, 59% were age 50-54, 30% were age 55-59, 9% were age 60-64, and 1% were age 65-69 at the

time of last questionnaire completion. The majority were diagnosed between 1970-1979 (73%) and were age 15-20 at the time of diagnosis (51%). The most common diagnosis was Hodgkin disease (28%), followed by acute lymphoblastic leukemia (ALL; 18%), osteosarcoma (12%), soft tissue sarcoma (12%), and non-Hodgkin lymphoma (10%).

Aims 3 and 4 will include survivors and siblings who completed a health outcomes and health status questionnaire (FU4 or FU5) at ≥50 years of age. Of 2,054 survivors who completed FU4 or FU5, 1,395 were ≥50 years at the time of completion. Amongst them, 47% were male, 68% were age 50-54, 27% were age 55-59, 5% were age 60-64, and <1% were age 65-69 at the time of last questionnaire completion. The majority were diagnosed between 1970-1979 (85%), and were age 15-20 at diagnosis (60%). The most common diagnosis was Hodgkin disease (33%), followed by ALL (14%), osteosarcoma (13%), and soft tissue sarcoma (12%), and non-Hodgkin lymphoma (9%). Of 640 siblings who completed FU4 or FU5 at ≥50 years of age, 42% were male. Their median age was 54 (range 50-69).

Outcome Measures:

Mortality: Overall and cause-specific mortality survivor cohort will be determined through a search of the U.S. National Death Index through the end of 2017. Cause of death will be categorized as recurrence of primary cancer, subsequent malignancy, cardiac causes, pulmonary causes, external causes, other causes, or unknown.[14,15] Mortality data for the general population will be obtained through the CDC's online database.[16]

SMNs: All CCSS follow-up questionnaires assess for subsequent malignancies. SMNs will be defined as neoplasms that are histologically distinct from the primary tumor.[17,18] Specific diagnoses will be ascertained, as well as whether each was a new diagnosis or recurrence, and recurrence/diagnosis date. Cancer incidence for the general population will be obtained from the Surveillance, Epidemiology, and End Results (SEER) database[19].

Health conditions:

Severity of CHCs will be assessed per the Common Terminology Criteria for Adverse Events v5.0.[20] For the current proposal, outcomes of interest will be limited to severe or disabling (grade 3), life-threatening (grade 4), or fatal (grade 5).

Frailty will be categorized using a modified Fried frailty criteria[21]:
(1) low lean muscle mass: body mass index <18.5 kg/m^2 or unintentional weight loss of ≥10 pounds in the past year;
(2) self-reported exhaustion: score of ≤40 on the Vitality subscale of the Medical Outcomes Survey SF-36[22];
(3) low energy expenditure: $<383_{kcal/wk}$ (male) or $<270_{kcal/wk}$ (female);
(4) walking limitations: "limited for more than 3 months" in response to "Over the last 2 years, how long has your health limited you in walking uphill or climbing a few flights of stairs?" or "Over the last 2 years, how long has your health limited you in walking one block?"; and
(5) weakness: "yes and the condition is still present" in response to "Have you ever been told by a doctor or other health care professional that you have, or have had, weakness or inability to move your arms?"
Participants endorsing at least 2 of 5 criteria will be considered prefrail, and those endorsing ≥3 will be considered frail.[3]

Health status outcomes: Four domains of health status will be characterized.

General health will be assessed from the question "Would you say that your health is excellent, very good, good, fair, or poor?" A response of fair or poor will be classified as poor general health.[13]

Mental health will be assessed using the 18-item Brief Symptom Inventory (BSI-18). Responses will be scored and converted to T-scores on the Global Severity Index and the three symptom-specific subscales (depression, somatization, and anxiety). T-scores of 63 or higher will be classified as elevated and considered adverse mental health.[13,23]

Functional impairment: Functional status will be assessed from questions that ask respondents if they had an impairment or health problem that resulted in (1) needing help with personal care needs, (2) needing help handling routine needs, or (3) keeping them from holding a job or attending school.[13]

Activity limitation will be determined from questions that ask respondents if in the last 2 years their health was limited for more than 3 months in: (1) the kinds or amounts of moderate activities they could do, like moving a table, carrying groceries, or bowling; (2) walking upstairs or climbing a few flights of stairs; or (3) walking 1 block.[13]

Independent variables:

1. Sociodemographic
    - Age at diagnosis
    - Age at questionnaire
    - Sex
    - Race/Ethnicity
    - Education
    - Employment
    - Income
    - Insurance status

2. Primary diagnosis
    - Hodgkin disease
    - ALL
    - Non-Hodgkin lymphoma
    - Osteosarcoma
    - Soft tissue sarcoma
    - Other

3. Treatment-related
    - Chemotherapy exposures (agent, lifetime cumulative dose)
        - Alkylating agents
        - Anthracyclines
        - Epipodophyllotoxins
        - Platinum agents
    - Radiation (field, dose)
        - Any site
        - Brain or Spine

        - Chest
        - Abdominal
        - None
    - Hematopoietic cell transplantation
    - Surgery
        - Splenectomy
        - Nephrectomy
        - Limb amputation
        - Other
        - None

4. Behavioral
    - Smoking
        - Number of years smoked
        - Never smoker
        - Former smoker
        - Current smoker
    - Alcohol consumption[24]
        - Low-risk
        - High-risk
    - Physical activity[25]
        - Sedentary
        - Non-sedentary

Analytic approach:

Table 1 will include descriptive statistics of the sociodemographic, diagnosis, and treatment-related characteristics of CCSS participants for each of the study aims and for the sibling cohort.

Aim 1: We will calculate cumulative all-cause and cause-specific mortality by attained age in 5-year intervals (i.e. 50-54, 55-59, 60-64, 65-69) and summarize this information in Table 2. We will also calculate 5-year mortality rates among participants who survived to at least age 50 years. We will use the standardized mortality ratio (SMR) to quantify all-cause and cause-specific mortality risks for the CCSS cohort compared to the comparable general population. To calculate the expected number of deaths, we will use the age-, calendar year-, race (white/non-white)-, and sex-specific U.S. mortality rates available at the CDC (Table 3).

Aim 2: We will calculate the cumulative incidence of SMNs for cancer survivors after age 50. We will calculate SIRs for SMNs, as the number observed divided by the expected number based on age-, calendar year-, race-, and sex-specific incidence rates from SEER, stratified by attained age (Table 4). We will then use Fine-Gray sub-distribution multivariable hazard regression to evaluate the association between SMNs occurring after age 50 and sociodemographic, diagnosis, treatment-related, and behavioral risk factors, accounting for death as a competing risk (Table 5).

Aim 3: We will compare the prevalence of any or multiple (≥2) grade 3 or 4 CHCs between the cancer survivor and sibling cohorts who have attained the age of 50 using logistic regression for binomial outcomes, adjusting for sex, age at questionnaire, and statistically significant sociodemographic and behavioral risk factors. Logistic regression models will be used since survivors are required to survive to age 50 for this analysis, but events occurring prior to age 50 will be included in the analysis. Since many conditions are considered irreversible, those that

occurred prior to age of 50 are relevant as existing conditions in the population. We will use the same approach to compare the prevalence and magnitude of risk for frailty (Table 6). For cancer survivors, we will use multivariable logistic regression models to evaluate the association between the development of grade 3–5 CHCs or frailty and sociodemographic, diagnosis, treatment-related, and behavioral risk factors (Table 7).

Aim 4: We will report the prevalence of adverse health status for both the cancer survivor and sibling cohorts. We will use logistic regression for binomial outcomes to compare the prevalence of adverse health status outcomes between survivors and siblings, adjusted for sex and age at questionnaire - the rationale for using logistic regression was outlined above, for Aim 3. Of note, we will develop an additional regression model that includes severity of CHCs as covariables in the two groups, allowing us to assess the magnitude of risk that is independent of underlying CHC severity (Table 6). For cancer survivors, we will use multivariable logistic regression models to evaluate the association between adverse health status and sociodemographic, diagnosis, treatment-related, and behavioral risk factors (Table 7).

6. Special considerations

To our knowledge, this will be the first study to comprehensively characterize long-term health outcomes in older (age ≥50 years) childhood cancer survivors and sibling controls. The unique infrastructure and resources provided by the CCSS will allow us to quantify the magnitude of risk for late effects, taking into consideration the background risks associated with aging in non-oncology populations. Ultimately, this study may provide important insights into appropriate resource allocation and development of targeted screening and prevention strategies in these older survivors. The growing population of long-term childhood cancer survivors makes development of prevention strategies imperative, to ensure that they live long and healthy lives well after completion of cancer treatment. Depending on timing, we will also consider including data from the ongoing FU7 survey which may be available later in 2022, as it would likely increase both the numbers of individuals eligible for this analysis as well as extend the duration of follow-up for both survivors and siblings. If data from FU7 is available, for Aim 3 we will consider evaluating both the prevalence of CHCs by age 50 and the cumulative incidence of de novo severe or life-threatening CHCs in those ≥50 years old.

REFERENCES

1. Ness KK, Wogksch MD. Frailty and aging in cancer survivors. *Transl Res.* 2020;221:65-82.
2. Ness KK, Krull KR, Jones KE, et al. Physiologic frailty as a sign of accelerated aging among adult survivors of childhood cancer: a report from the St Jude Lifetime cohort study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2013;31(36):4496-4503.
3. Hayek S, Gibson TM, Leisenring WM, et al. Prevalence and Predictors of Frailty in Childhood Cancer Survivors and Siblings: A Report From the Childhood Cancer Survivor Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2020;38(3):232-247.
4. Armstrong GT, Liu Q, Yasui Y, et al. Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2009;27(14):2328-2338.
5. Suh E, Stratton KL, Leisenring WM, et al. Late mortality and chronic health conditions in long-term survivors of early-adolescent and young adult cancers: a retrospective cohort analysis from the Childhood Cancer Survivor Study. *Lancet Oncol.* 2020;21(3):421-435.
6. Turcotte LM, Liu Q, Yasui Y, et al. Temporal Trends in Treatment and Subsequent Neoplasm Risk Among 5-Year Survivors of Childhood Cancer, 1970-2015. *JAMA.* 2017;317(8):814-824.
7. Zhang YB, Pan XF, Chen J, et al. Combined lifestyle factors, incident cancer, and cancer mortality: a systematic review and meta-analysis of prospective cohort studies. *Br J Cancer.* 2020;122(7):1085-1093.
8. Coughlin SS. Social determinants of breast cancer risk, stage, and survival. *Breast Cancer Res Treat.* 2019;177(3):537-548.
9. Gibson TM, Mostoufi-Moab S, Stratton KL, et al. Temporal patterns in the risk of chronic health conditions in survivors of childhood cancer diagnosed 1970-99: a report from the Childhood Cancer Survivor Study cohort. *Lancet Oncol.* 2018;19(12):1590-1601.
10. Armstrong GT, Kawashima T, Leisenring W, et al. Aging and risk of severe, disabling, life-threatening, and fatal events in the childhood cancer survivor study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2014;32(12):1218-1227.
11. Bhakta N, Liu Q, Ness KK, et al. The cumulative burden of surviving childhood cancer: an initial report from the St Jude Lifetime Cohort Study (SJLIFE). *Lancet.* 2017;390(10112):2569-2582.
12. Armenian SH, Sun CL, Kawashima T, et al. Long-term health-related outcomes in survivors of childhood cancer treated with HSCT versus conventional therapy: a report from the Bone Marrow Transplant Survivor Study (BMTSS) and Childhood Cancer Survivor Study (CCSS). *Blood.* 2011;118(5):1413-1420.
13. Hudson MM, Oeffinger KC, Jones K, et al. Age-dependent changes in health status in the Childhood Cancer Survivor cohort. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2015;33(5):479-491.
14. Fidler-Benaoudia MM, Oeffinger KC, Yasui Y, et al. A Comparison of Late Mortality Among Survivors of Childhood Cancer in the United States and United Kingdom. *J Natl Cancer Inst.* 2021;113(5):562-571.
15. Mertens AC, Liu Q, Neglia JP, et al. Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *J Natl Cancer Inst.* 2008;100(19):1368-1379.
16. Compressed Mortality File 1999-2016 on CDC WONDER Online Database; 2017. https://wonder.cdc.gov/mortsql.html.

17. Bhatia S, Chen Y, Wong FL, et al. Subsequent Neoplasms After a Primary Tumor in Individuals With Neurofibromatosis Type 1. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2019;37(32):3050-3058.
18. Turcotte LM, Liu Q, Yasui Y, et al. Chemotherapy and Risk of Subsequent Malignant Neoplasms in the Childhood Cancer Survivor Study Cohort. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2019;37(34):3310-3319.
19. SEER Cancer Statistics Review (CSR) 1975-2018. National Cancer Institute (NCI). Surveillance, Epidemiology, and End Results Program (SEER) Web site. https://seer.cancer.gov/csr/1975_2018/. Accessed December 6, 2021.
20. Program CTE. Common terminology criteria for adverse events, version 5.0. In: Institute NC, ed. Bethesda, MD.
21. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci.* 2001;56(3):M146-156.
22. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care.* 1992;30(6):473-483.
23. LR D. *Brief Symptom Inventory 18: Administration, Scoring, and Procedures Manual.* Minneapolis, MN: NCS Pearson; 2001.
24. Alcohol Research: Current Reviews Editorial S. Drinking Patterns and Their Definitions. *Alcohol Res.* 2018;39(1):17-18.
25. Delaney A, Howell CR, Krull KR, et al. Progression of Frailty in Survivors of Childhood Cancer: A St. Jude Lifetime Cohort Report. *J Natl Cancer Inst.* 2021;113(10):1415-1421.

APPENDIX A

Table 1 Sociodemographic, diagnosis, and treatment-related characteristics of the cancer survivor and sibling cohorts					
	Survivors included in mortality analysis (n=TBD, but will be larger than SMN analysis)	Survivors included in SMN analysis (n=2,295)	Survivors included in health outcome analysis (n=1,395)	Sibling cohort (n=640)	*P*-value*
Age at diagnosis (or index date)					
Age at questionnaire					
Sex					
Male					
Female					
Race/Ethnicity					
Non-Hispanic White					
Non-Hispanic Black					
Hispanic					
Other					
Education					
High school or below					
Some college					
College graduate and above					
Household income					
<$40,000					
$40,000-$100,000					
>$100,000					
Insurance status					
Insured					
Uninsured					
Employment					
Employed					
Retired					
Unemployed					
Diagnosis				NA	NA
Hodgkin disease					

Acute lymphoblastic leukemia					
Non-Hodgkin lymphoma					
Osteosarcoma					
Soft tissue sarcoma					
Other					
Hematopoietic cell transplantation				NA	NA
Yes					
No					
Chemotherapy				NA	NA
Alkylating agents					
Anthracyclines					
Epipodophyllotoxins					
Platinum agents					
Radiation therapy				NA	NA
Any site					
Brain or Spine					
Chest					
Abdominal					
None					
Surgery				NA	NA
Splenectomy					
Nephrectomy					
Limb amputation					
Other					
None					
*Comparison of survivors in health outcome analysis and sibling cohort					

Table 2 Cumulative mortality by cause of death in cancer survivors by attained age										
Attained age (years)	All-cause mortality, n (%)	Primary disease recurrence, n (%)	Subsequent malignancy, n (%)	Cardiac causes, n (%)	Pulmonary causes, n (%)	External causes, n (%)	Infection/ Sepsis, n (%)	Other, n (%)	Unknown, n (%)	Total
50-54										
55-59										
60-64										
65-69										
Total										

Table 3 Standardized mortality ratios by demographic and clinical characteristics and cause of death					
		Years of follow-up after age 50			
	Overall	5 year	10 year	15 year	20 year
Entire survivor cohort					
Sex					
Male					
Female					
Race/Ethnicity					
Non-Hispanic White					
Non-Hispanic Black					
Hispanic					
Other					
Cause of death					
Primary disease recurrence					
Subsequent malignancy					
Cardiac causes					
Pulmonary causes					
External causes					
Infection/Sepsis					
Other					
Unknown					

Table 4 SIR of SMN compared to the general population		
Attained age	SIR	*P*-value
Age 50-54 years		
SMN diagnoses		
Age 55-59 years		
SMN diagnoses		
Age 60-64 years		
SMN diagnoses		
Age 65-69 years		
SMN diagnoses		

Table 5 Risk factors for SMN in cancer survivors*						
	Univariable Analysis			Multivariable Analysis[#]		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age at diagnosis						
Age at questionnaire						
Sex						
Male						
Female						
Race/Ethnicity						
Non-Hispanic White						
Non-Hispanic Black						
Hispanic						
Other						
Education						
High school or below						
Some college						
College graduate and above						
Household income						
<$40,000						
$40,000-$100,000						
>$100,000						
Insurance status						
Insured						
Uninsured						
Employment						
Employed						
Retired						
Unemployed						
Diagnosis						
Hodgkin disease						
Acute lymphoblastic leukemia						
Non-Hodgkin lymphoma						
Osteosarcoma						
Soft tissue sarcoma						
Other						
Hematopoietic cell transplantation						
Yes						
No						
Chemotherapy						
Alkylating agents						
Anthracyclines						
Epipodophyllotoxins						
Platinum agents						
Radiation therapy						
Any site						
Brain or Spine						

Chest						
Abdominal						
None						
Surgery						
Splenectomy						
Nephrectomy						
Limb amputation						
Other						
None						
Health behaviors						
Smoking						
Number of years smoked						
Current smoker						
Former smoker						
Never smoker						
Alcohol consumption						
Low-risk						
High-risk						
Physical activity						
Non-sedentary						
Sedentary						
SMN diagnoses						
*Will discuss with the statistical team which time-varying SES and lifestyle/behavior variables to use. [#]Model adjusted for significant covariables						

Table 6 Prevalence of chronic health conditions (grade 3-4), pre-frailty, frailty, and adverse health status in survivors and siblings					
	Survivors, n (%)	Siblings, n (%)	Prevalence Ratio*	95% CI	*P*-value
≥1 CHC					
≥2 CHC					
Pre-frail					
Frail					
Adverse Health Status					
General Health					
Mental Health					
Functional Impairment					
Activity Limitation					
Adverse health status[#]					
General Health[#]					
Mental Health[#]					
Functional Impairment[#]					
Activity Limitation[#]					
*Siblings as referent group, adjusted for age, sex, and statistically significant sociodemographic and behavioral risk factors [#]Adjusted for severity of chronic health conditions					

Table 7 Multivariable analysis of risk factors for chronic health conditions (grade 3-5), prefrailty, frailty, and adverse health status in survivors*																
	Chronic health condition		Pre-frail		Frail		Adverse health status		General health		Mental health		Functional impairment		Activity limitation	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age at diagnosis																
Age at questionnaire																
Sex																
Male	1.0		1.0		1.0		1.0		1.0		1.0		1.0		1.0	
Female																
Race/Ethnicity																
Non-Hispanic White	1.0		1.0		1.0		1.0		1.0		1.0		1.0		1.0	
Non-Hispanic Black																
Hispanic																
Other																
Education																
High school or below																
Some college																
College graduate and above	1.0		1.0		1.0		1.0		1.0		1.0		1.0		1.0	
Household income																
<$40,000																
$40,000-$100,000																
>$100,000	1.0		1.0		1.0		1.0		1.0		1.0		1.0		1.0	
Insurance status																
Insured	1.0		1.0		1.0		1.0		1.0		1.0		1.0		1.0	
Uninsured																
Employment																
Employed	1.0		1.0		1.0		1.0		1.0		1.0		1.0		1.0	
Retired																
Unemployed																
Diagnosis																
Hodgkin disease	1.0		1.0		1.0		1.0		1.0		1.0		1.0		1.0	

Acute lymphoblastic leukemia																
Non-Hodgkin lymphoma																
Osteosarcoma																
Soft tissue sarcoma																
Other																
Hematopoietic cell transplantation																
Yes																
No	1.0		1.0		1.0		1.0		1.0		1.0		1.0		1.0	
Chemotherapy																
No alkylator, anthracycline, epipodophyllotoxin, platinum exposure	1.0		1.0		1.0		1.0		1.0		1.0		1.0		1.0	
Alkylating agents																
Anthracyclines																
Epipodophyllotoxins																
Platinum agents																
Radiation therapy																
Any site																
Brain or Spine																
Chest																
Abdominal																
None	1.0		1.0		1.0		1.0		1.0		1.0		1.0		1.0	
Surgery																
Splenectomy																
Nephrectomy																
Limb amputation																
Other																
None	1.0		1.0		1.0		1.0		1.0		1.0		1.0		1.0	
Health behaviors																
Smoking																

Number of years smoked																
Current smoker																
Former smoker																
Never smoker	1.0		1.0		1.0		1.0		1.0		1.0		1.0		1.0	
Alcohol consumption																
Low-risk	1.0		1.0		1.0		1.0		1.0		1.0		1.0		1.0	
High-risk																
Physical activity																
Non-sedentary	1.0		1.0		1.0		1.0		1.0		1.0		1.0		1.0	
Sedentary																
*Analytic approach to be discussed with statistical team in consideration of time to event																