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Childhood Cancer Survivor Study
Concept Proposal

1. **Study Title:**
   Frailty in childhood cancer survivors

2. **Primary working group:** Cancer Control
   Secondary working group: Epidemiology/Biostatistics, Chronic disease, Psychology/Neuropsychology

3. **Investigators:**

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4. **Background and Rational:**

Data from the United States Surveillance, Epidemiology and End Results Program (SEER) indicate that as of 2014, the 5- year survival rate for children diagnosed with cancer surpassed 85%.[1,2] Improved early survival is accompanied by improvements in late mortality Among 5-year survivors that treated in the 1990s, the 15 year survival rate was 77.1% compared to 57.2% among those treated in the 1970s.[3]

Nevertheless, while advances in treatment and supportive care have enhanced survival, survivors of childhood cancer continue to report problems with health status. Survivors are more likely than siblings to report poor general health (13.0% vs. 4.3%), poor mental health (16.3% vs. 10.5%), functional impairments (16.3% vs. 2.9%) and activity limitations (13.7% vs. 4.6%).[4] Survivors also continue to experience chronic health conditions at high frequencies, accumulating an average of 17.1 (95% confidence interval (CI); 16.2-18.1) CTCAE grade 1-5 events and 4.7 (95% CI; 4.6-4.9) grade 3-5 events by age 50 years.[5] This compares to rates among healthy peers of 9.2 (95% CI; 7.9-10.6) for grade 1-5 and 2.3 (95% CI;1.9-2.7) for grade 3-5 chronic conditions.[5] Consequently, current research and clinical care are focused not only on improving the

life-span of survivors but also on improving their long-term health. To achieve this goal, important risk factors and intermediate markers of health, need to be identified. Intermediate markers of health may signal early disease and provide opportunities for intervention. For example, among persons at risk for Type II diabetes, early identification of insulin resistance may trigger either lifestyle or medication interventions. As frailty has been identified as a marker of future morbidity and mortality in aging populations and among childhood cancer survivors,[6,7] and because there are some interventions that remediate frail health in aging populations,[8] this study will provide preliminary information to design interventions among those who have early indicators of future chronic disease onset . It will also provide information about who in this vulnerable population is most at risk for frailty.

Recent data from the St. Jude Lifetime Cohort Study (mean age 33.6 years, SD 8.1) indicate that chronic disease onset among survivors of childhood cancer may be preceded by frailty, a loss of physiologic reserve similar to that typically seen in older adults.[7] Frailty, described by Fried in the Cardiovascular Health Study, is characterized by three or more of the following: 1) low lean muscle mass, 2) self-reported exhaustion, 3) muscle weakness, 4) slow walking speed, and 5) low energy expenditure.[6] Frailty is prevalent among 9.0% of older adults,[9] 7.8% of young adult childhood cancer survivors,[7] and 8.0% of young adults treated for cancer with hematopoietic stem cell transplant,[10] and is predictive of chronic disease onset and mortality.[11]Among childhood cancer survivors, the prevalence of frailty increases with age, is higher among females, and is associated with radiation exposure and smoking.[7]

Although the St. Jude Lifetime Cohort Study analysis evaluates frailty among childhood cancer survivors, and provides important preliminary information about the prevalence of and risk factors for this phenotype, the small sample sizes among specific disease groups make it difficult to identify treatment-related risk factors.[7] The Childhood Cancer Survivor Study has a larger sample size, well characterized treatment exposures and ascertainment of chronic health conditions, providing the opportunity to estimate the direct and indirect effects of treatment-related risk factors (overall and by disease group), baseline sociodemographic risk factors and time varying risky health behaviors on frailty. The availability of the sibling cohort allows us to compare the prevalence of frailty in survivors to that in siblings by strata of age and sex, verifying/extending our findings from the St. Jude Lifetime Cohort to a broader population of childhood cancer survivors, enriched for persons in older age strata. Although the CCSS criteria are completely based on questionnaire data, the questions we have selected closely parallel to Fried[6] and SJLIFE[7] criteria. Appendix 1 describes the specific criteria used to define frailty in the Cardiovascular Health Study, the St Jude Lifetime Cohort Study, and the Childhood Cancer Cohort Survivor Study.

5. Specific aims:

Specific Aim 1:
To estimate the prevalence of the frailty phenotype among childhood cancer survivors (overall and by disease group) compared to siblings (with additional comparison by age group and sex).

Hypothesis 1:
The prevalence of frailty will be higher among childhood cancer survivors than among siblings.

Specific Aim 2:
To identify associations between sociodemographic factors, chronic conditions, and risky health behaviors and frailty among childhood cancer survivors and siblings.

Hypothesis 2:

Age, female sex, lower educational attainment and lower personal income, chronic condition severity and duration, obesity, smoking, lower physical activity and a combination of heavy alcohol intake are associated with higher risk of frailty.

Specific Aim 3:
To identify the direct and indirect effects of treatment exposures on frailty in childhood cancer survivors.

Hypothesis 3:
Treatment exposures will have a direct effect on frailty. Sociodemographic risk factors, chronic conditions and risky health behaviors will mediate the association between treatment exposures and frailty.

6. Methods:

6.1 Population:
Survivor and sibling members of the CCSS cohort who completed the baseline and follow-up 5 surveys.

6.2 Outcome of interest (Dependent variable):
The primary outcome in this study will be the **frailty phenotype**: we propose to look at the outcome in three mutually exclusive categories (1) Frail; (2) Pre-Frail (3) Non-Frail, using a modification of the Fried frailty criteria.[6] Those with three or more components will be classified as frail, those with two components will be considered pre-frail and those with none or one component, will be considered as not frail. If the number of cases of frailty and pre-frailty are small in subset analyses and/or if associations are similar for these outcomes, we will consider combining pre-frail and frail into one category in the analyses.

Five criteria of frailty phenotype based on FU5 questionnaire:

1. Low lean muscle mass will be defined as either a body mass index (BMI) <18.5 kg/m^2 (LTFU5, item: A1 and A2) or unintentional weight loss of ≥ 10 pounds in past year (LTFU5, item: A3).
2. Self-reported exhaustion: will be defined as a score of ≤40 on the vitality subscale of the short form-36 (SF-36).[12] Specifically, the questions are: How much of the time during the past four weeks (1) did you feel full of life? (LTFU5, ITEM: P1-a) (2) Did you have a lot of energy? (LTFU5, item:P1-e) (3) Did you feel worn out? (LTFU5, item:P1-g) (4) Did you feel tired? (LTFU5, item: P1-i).
3. Low energy expenditure: will be defined for males as < 383 kilocalories (kcal) per week and for females as <270 kcal per week, estimated by converting reported frequency and duration of low, moderate and vigorous activities into kilocalories using guidelines provided by the Compendium of Physical Activities[13] (http://sites.google.com/site/compendiumofphysicalactivites).[14] ((LTFU5, items: N15, N16, N17, N18). (LTFU5, items: N15, N19, N20, N21) (LTFU5, items: N22, N23, N24), (LTFU5, ITEM A1)). If the individual reports being physically active, the follow-up questions ask them to report the type of physical activity (vigorous, moderate or light), and duration of physical activity as hours per week (hours/ per week). The compendium of Physical Activities provides estimated (MET) intensity level equivalents for each respective activity performed in various settings noted in the 2013-2014 NHANES.[15] For example, individuals that reported vigorous physical activity for leisure time will have a MET score of 8.0, and those that reported moderate leisure –time physical activity will have a MET score of 4.0. Energy expenditure will be calculated by multiplying the METS (kcal/kg/hour)*weight (kg)*time (hours).

4. Slowness: will be defined as an answer of "Limited for more than three months" to either of two questions: (1) over the last two years, how long has your health limited you in walking uphill or climbing a few flights of stairs; or (2) over the last two years, how long has your health limited you in walking one block. (LTFU5, item: N29- c or e).
5. Weakness: will be defined as an answer of "yes and the condition is still present" to the question: "Have you ever been told by a doctor or other health care professional that you have, or have had weakness or inability to move arms"? (LTFU5, item: K11).

6.3 Covariates (independent variables)

6.3.1. Sociodemographic characteristics:

- Age at baseline: Date of survey completion at baseline (Baseline questionnaire) - Date of birth (Baseline questionnaire, item A1).
- Age at assessment: it will be defined as Date at the questionnaire interview - Date of birth (Baseline questionnaire, item: A1)).
- Sex: Females, Males (Baseline questionnaire. item: A2)
- Race: (1) Non-Hispanic white, (2) Non-Hispanic Black, (3) Asian, (4) Hispanic, (5) other (original cohort baseline. Item: A4) or (Expansion cohort baseline item: A5).
- Education: categorical variable (1) less than high school, (2) high school graduate (3) college graduate (LTFU5, item: A4).
- Employment: categorical variable: (1) Employed or caring for home (2) looking for work or unable to work (3) Student (LTFU5, item: A5).
- Annual household income: dichotomous variable: (1) ≥$40,000 per years, (2) <$40,000 per years (LTFU5, item: A9).
- Health insurance. (1) Yes /Canadian (2) No (LTFU5, Item: A10).

6.3.2. Health behavior:

- Smoking status: will be defined by number of pack years smoked based on answers to these questions: LTFU5 (2014) items N7–N12. Participants may also be classified for analysis as a never, ever or current smoker depending on the number of missing variables and on the data distribution.
- Alcohol use: will be defined as a heavy/risky drinker if the number of drinks for men was five or more drinks per day or 14 drinks per week, and for women four or more drinks per day or seven drinks per week, and categorized as never a heavy drinker, formerly a heavy drinker, or currently a heavy drinker. (Baseline questionnaire, item: N7, expansion questionnaire items: Q11 & O14, LTFU4 (2007) item: N3&N6, LTFU5 (2014) items: N3&N6). Patterns of risky/heavy drinking will be examined for participants and categories created based on the identified patterns and distribution of the data.
- Sedentary behavior: respondents were asked about participation in physical activity; those who report no activity in the past month on all of their questionnaires will be categorized as sedentary. Patterns of reporting sedentary behavior (or not) will be examined for participants and categories created based on the identified patterns and distribution of the data. (Baseline questionnaire item, N9, expansion O15, LTFU (2003), items D1, LTFU4 (2007), item N15).
- Obesity: Persons with BMI≥30 will be classified as obese (Baseline questionnaire items A10 &A11 , expansion questionnaire, item A3 and A4 , LTFU(2003), items q7 &q8, LTFU4 (2007), items:A1 and A2). Patterns of obesity will be examined for participants and categories created based on the identified patterns and distribution of the data.

6.3.3. Clinical variables at the first primary neoplasm:

- Age at diagnosis: Date at diagnosis –date of birth.
- Histology: Leukemia, CNS tumor, Hodgkin lymphoma, Non-Hodgkin lymphoma, Neuroblastoma, Wilms tumor, Rhabdomyosarcoma, Bone tumor.
- Treatment within 5 years of cancer diagnosis:
  Any chemotherapy:
  - Alkylating agent - Cyclophosphamide equivalent dose (CED). (Categorical: 0, 1-3999, 4000-7999, =>8000 mg/m2)
  - Anthracycline - Doxorubicin equivalent dose (mg/m2)
  - Platinum agent - Cisplatin (dose)
  - Platinum agent - Carboplatin (dose)
  - Antimetabolites - 6-Mercaptopurine
  - Antimetabolites - 6-Thioguanine
  - Antimetabolites - Methotrexate (Dose) (IT/IV)
  - Antimetabolites - Oral methotrexate
  - Microtubule targeting drugs - Vinca alkaloids (vincristine, vinblastine, vinorelbine)

  Radiation: maximum tumor dose (max TD) to the following body regions in cGY:
  - Cranial
  - Chest
  - Abdomen/Pelvis
  - Any other region

  Surgery:
  - Nephrectomy (yes/no)
  - Cystectomy (yes/no)
  - Thoracotomy (yes/no)
  - Craniotomy (yes/no)
  - Amputation(yes/no)

  Hematopoietic stem cell transplantation: (yes/no)

6.3.4. Clinical variables at the time of follow-up:

- Time since diagnosis: Current date (LTFU5)-(date at initial diagnosis) (baseline questionnaire).
- To characterize chronic conditions we will use the Common Terminology Criteria for Adverse Events version 5 (CTCAE,v5.0) where none is grade 0; mild or asymptomatic conditions are grade 1; moderate conditions are grade 2; severe, medically significant, or disabling are grade 3; and life-threatening grade 4.[16] Conditions will be considered overall and by individual (or combinations of individual) organ system(s).[17] We will include seven categories: cardiac, respiratory, endocrine, subsequent neoplasm, renal, musculoskeletal, neurologic disease. This variable will be continuous, as duration (in years) of having any grade 3-4 chronic condition, and in analyses of specific organ system the duration of a grade 3-4 organ–system specific chronic condition (in years) (LTFU5 (2014), items D1-K15). The most recent chronic condition data will be used for these analyses if the CTCAE data from LTFU5 is not available and the analysis updated when the data are available.

7. Statistical analysis

Descriptive statistics will be used to characterize the study population for all variables of interest. Table 1 will show frequencies and percentages for categorical variables, and mean and SD for continuous variables. To compare characteristics between survivors and their siblings, t-tests and chi-square tests will be used as appropriate. For all analyses, sampling weights will be used to account for under-sampling of ALL survivors in the expansion cohort.

For Aim 1, we will calculate the prevalence of each frailty phenotype: 1) pre-frailty (two-components of frailty) 2) and frailty (three-components of frailty) for the overall groups of survivors and siblings and by age group, by sex and, for survivors, by original diagnosis (Tables 2, 3a and 3b). Prevalence comparisons between survivors and siblings, within each group, and across sex-specific age categories (trend) will be conducted using generalized linear models with a log-link function and binomial (or Poisson) error structure and robust variance estimates to account for intra-family correlation. All models will be adjusted or stratified by sex and age.

Aim 2, will explore associations between sociodemographic characteristics (age at each assessment, sex, race/ethnicity, income, employment), risky health behaviors (years of smoking, patterns of heavy drinking, patterns of sedentary behavior), chronic conditions (grade and duration prior to assessment) and frailty phenotype. To accomplish this, we will employ the same model structure utilized in Aim 1. *A priori,* models will be adjusted for age and sex and the remaining factors examined for inclusion in a final multivariable model depending on their significance and the degree to which they impact other factors in the model. Results will be presented as prevalence ratios with 95% Confidence Intervals.[18,19] Chronic conditions will be evaluated overall and by organ-system (Tables 4a, 4b and 5).

For Aim 3, Structural equation modelling (SEM)[20] will be used to examine *a priori* hypothesized associations between cancer treatment, subsequent chronic conditions (grade 3-4) and frailty/pre-frailty) . We will evaluate direct and indirect associations between treatment and frailty (via chronic conditions), accounting for both sociodemographic characteristics and risky health behaviors identified in the models above, assuming no-unmeasured confounders.[21] We will present the goodness of fit indices for various models. Chi-square statistics is reported to enable comparisons between the baseline or null model and subsequent revised models. Additionally, the standardized Root Mean Square Residual (SRMR), the Comparative Fit Index (CFI), the Root Mean Square Error of Approximation (RMSEA) and 90% confidence limits. Values for the CFI greater than 0.95 suggest good fit between data and path models, whereas SRMR and RMSEA values less than 0.08 and less than 0.06 respectively suggest good model fit. [22] Figure 1 illustrates our hypothesized causal pathway. Table 6 will inform the SEM, Table 7 will present the final model.

References:

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Examples of Tables:

Tables 1: Demographic characteristics, disease and health status for study population

	CCSS members+		Siblings		P value
	No. of participants	%	No. of participants	%	
Sex					
Females					
Males					
Race/Ethnicity					
Non-Hispanic white					
Non-Hispanic Black					
Hispanic					
Asian					
Other					
Age at cancer diagnosis (Mean SD range)					
0-4			-	-	
5-9			-	-	
10-14			-	-	
15-19			-	-	
Age at assessment (Mean SD range)					
18-29					
30-39					
40-49					
50 and above					
Time since diagnosis (Mean SD range)					
5-9			-	-	
10-14			-	-	
15-19			-	-	
20 and above			-	-	
Age at baseline questionnaire (Mean SD range)					
Employment					
Employed or caring for home					
Looking for work or unable to work					
Student					
Education					
Less than high school					
High school graduate					
College graduate					
Unknown					
Household Income (USD)					
≤ $40,000					
> $40,000					
Number of smoking years					

Never					
Mean(SD)[1]					
Range(years)					
Heavy drinking ¥					
Never					
Former					
Current					
Sedentary behavior $$					
Never					
Former					
Current					
Obesity (BMI>30)					
Never					
Former					
Current					
Health insurance					
No					
Yes/Canadian					
Histology					
Leukemia			-	-	
CNS tumor			-	-	
Hodgkin lymphoma			-	-	
Non-Hodgkin lymphoma			-	-	
Neuroblastoma			-	-	
Wilms tumor			-	-	
Soft tissue sarcoma			-	-	
Bone tumor			-	-	
Treatment type					
Surgery			-	-	
Radiation			-	-	
Chemotherapy			-	-	
Combination			-	-	
Radiation					
Cranial (yes)			-	-	
Cranial (maxTD, cGY)					
Chest (yes)			-	-	
Chest (maxTD, cGY)					
Abdomen/Pelvis (yes)			-	-	
Abdomen/Pelvis (max TD, cGY)					
Other region (yes)			-	-	
Other region (max TD, cGY)					
Chemotherapy					
Alkylating agents (yes)			-	-	
Alkylating agents – (Cyclophosphamide equivalent dose) Dose mg/m^2)					
Anthracyclines (yes)					

Doxorubicin equivalent dose (Dose mg/m^2)					
Cisplatin (yes)			-	-	
Cisplatin (dose mg/m^2)					
Carboplatin (yes)			-	-	
Carboplatin (dose mg)					
6-Mercaptopurine (yes)			-	-	
6-Mercaptopurine (dose mg/ml)					
6-Thiogaunine (yes)			-	-	
6-Thiogaunine(dose mg)					
Methotrexate (yea)			-	-	
Methotrexate (dose IT/IV)					
Oral Methotrexate (yes)			-	-	
Vinca-alkaloids (yes)			-	-	
Surgery					
Nephrectomy			-	-	
Cystectomy			-	-	
Thoracotomy			-	-	
Craniotomy			-	-	
Amputation					
Any chronic condition grade 3-4					
Yes					
Duration of any chronic condition (years)					
Organ system for chronic conditions grade 3-4					
Any endocrine	(yes)				
Duration of any endocrine(years)	Mean (SD) Range				
Any respiratory	(yes)				
Duration of any respiratory (years)	Mean(SD) Range				
Any cardiac	(yes)				
Duration of any cardiac (years)	Mean(SD) Range				
Any renal	(yes)				
Duration of any renal (years)	Mean(SD) Range				
Any subsequent malignancy	(yes)				
Duration of any subsequent malignancy (years)	Mean(SD) Range				
Any neurologic	(yes)				
Duration of any neurologic (years)	Mean(SD) Range				
Any musculoskeletal	(yes)				
Duration of any musculoskeletal (years)	Mean(SD) Range				

[+] Sampling weights will be applied for all the percentages in this column.
[1] The mean of years of smoking will be calculated for individuals that reported that they are current or former smokers, and the standard deviation (SD) of the mean will be reported.
[¥] Men: five or more drinks per day or 14 drinks per week; women: four or more drinks per day or seven drinks per week.
[$$] Sedentary behavior: where no physical activity reported or irregular physical activity (i.e. fewer than three times per week and or/less than 20 minutes per sessions).

Table 2: Percentage of frailty phenotype among cancer survivors and their siblings by sex and age group

	Women Age (years)						**Men Age (years)**					
	Overall	18-29	30-39	40-49	50^{+}	P for trend	Overall	18-29	30-39	40-49	50^{+}	P for trend
	N (%) 95% Cl	N (%) 95% Cl	N (%) 95% Cl	N (%) 95% Cl	N (%) 95% Cl		N (%) 95%Cl	N (%) 95%Cl	N (%) 95%Cl	N (%) 95%Cl	N (%) 95%Cl	
Cancer survivor												
Low lean muscle mass (yes)												
Low energy expenditure (yes)												
Exhaustion(yes)												
Weakness(yes)												
Slowness(yes)												
Two component (pre-frail)												
Three component (frail)												
Siblings –comparison group												
Low lean muscle mass												
Low energy expenditure												
Exhaustion												
Weakness												
Slowness												
Two component (pre-frail)												
Three component (frail)												

Note: Prevalence % of frailty by age group, with 95% confidence limits

Table 3a: Percentage of frailty phenotype among childhood cancer survivors based on histology

Histology	Overall					
	Frail		Pre-frail		Non-frail	
	Unadjusted N (%)	Adjusted[1] N (%)	Unadjusted N (%)	Adjusted[1] N (%)	Unadjusted N (%)	Adjusted[1] N (%)
Leukemia						
CNS tumor						
Hodgkin lymphoma						
Non-Hodgkin lymphoma						
Neuroblastoma						
Wilms tumor						
Soft tissue sarcoma						
Bone tumor						

Note: n (%) the prevalence of frailty phenotype by histology.
[1]Adjusted: adjusted percentage for age at assessment

Table 3b: Percentage of frailty phenotype among childhood cancer survivors based on histology by sex

Histology	Females						Males					
	Frail		Pre-frail		Non-frail		Frail		Pre-frail		Non-frail	
	Unadjusted N (%)	Adjusted[1] N (%)	Unadjusted N (%)	Adjusted[1] N (%)	Unadjusted N (%)	Adjusted[1] N (%)	Unadjusted N (%)	Adjusted[1] N (%)	Unadjusted N (%)	Adjusted[1] N (%)	Unadjusted N (%)	Adjusted[1] N (%)
Leukemia												
CNS tumor												
Hodgkin lymphoma												
Non-Hodgkin lymphoma												
Neuroblastoma												
Wilms tumor												
Soft tissue sarcoma												
Bone tumor												

Note: n (%) the prevalence of frailty phenotype by histology.
[1] Adjusted: adjusted percentage for age.

Table 4a: Association between sociodemographic characteristics, chronic conditions and risky health behaviors and frailty among study participants (survivors and siblings)

	Overall N	Frail	Adjusted PRR[1]	Pre-frail	Adjusted PRR[2]
	N (%)	Row %	PRR (95%CI)	Row %	PRR (95%CI)
Sex					
Females					
Males					
Race/ethnicity					
Non-Hispanic white					
Non-Hispanic black					
Hispanic					
Asian					
Other					
Age at assessment (years) Mean (SD)					
18-29					
30-39					
40-49					
50 and above					
Age at baseline questionnaire Mean (SD) Range (years)					
Employment					
Employed/ caring for home					
Looking for work or unable to work					
Student					
Household Income (USD)					
≤ $40,000					
> $40,000					
Number of smoking years					
Heavy drinking ¥					
Never					
Former					
Current					
Sedentary behavior $$					
Never					
Former					
Current					
Obesity(BMI≥30)					
Never					

Former					
Current					
Health Insurance					
No					
Yes/Canadian					
Any chronic condition[++]	Duration of having any chronic condition				
Organ system for chronic conditions with grade 3-4[++]					
Duration of any cardiac					
Duration of any respiratory					
Duration of endocrine					
Duration of any renal					
Duration of subsequent malignancy					
Duration of any respiratory					
Duration of neurologic					
Duration of any musculoskeletal					

[1] Adjusted PRR: Adjusted Prevalence Rate Ratio where the reference category is non-frail (frail vs. non-frail).
[2] Adjusted PRR: Adjusted Prevalence Rate Ratio where the reference category is non-frail (pre-frail vs. non-frail).
[+] Sampling weights will be applied for all the percentages in this column.
[¥] Men: five or more drinks per day or 14 drinks per week; women: four or more drinks per day or seven drinks per week.
[$$] Sedentary behavior: where no physical activity reported or irregular physical activity (i.e. fewer than three times per week and or/less than 20 minutes per sessions).
[++] For the Duration of chronic condition, we will conduct any chronic condition, in separate models than organ system specific chronic condition.

Table 4b: Association between sociodemographic characteristics, chronic conditions and risky health behaviors and frailty among childhood cancer survivors

	Overall	Frail			Pre-frail		
	N (%)	Row %	Adjusted PRR (95% CI)	P value	Row %	Adjusted PRR (95% CI)	P value
Sex							
Females							
Males							
Race/ethnicity							
Non-Hispanic white							
Non-Hispanic Black							
Hispanic							
Asian							
Other							
Age at diagnosis Mean (SD) Range							
0-4							
5-9							
10-14							
15-19							
Age at assessment Mean (SD) Range							
18-29							
30-39							
40-49							
50 and above							
Time since diagnosis (years) Mean (SD) Range							
5-9							
10-14							
15-19							
20 and above							
Age at baseline questionnaire Mean (SD) Range							
Employment							
Employed or caring for home							
Looking for work or unable to work							
Student							
Education							
Less than high school							

High school graduate							
College graduate							
Unknown							
Household Income (USD)							
< = $40,000							
> $40,000							
Number of smoking years							
Heavy drinking ¥							
Never							
Former							
Current							
Sedentary behavior							
Never							
Former							
Current							
Obesity (BMI≥30)							
Never							
Former							
Current							
Health Insurance							
No							
Yes/Canadian							
Any chronic condition ++							
Organ system specific for chronic conditions grade 3-4++							
Duration of any cardiac (years)							
Duration of any respiratory							
Duration of any endocrine							
Duration of any renal							
Duration of any subsequent malignancy							
Duration of any respiratory							
Duration of any neurologic							
Duration of any musculoskeletal							

[1] Adjusted PRR: Adjusted Prevalence Rate Ratio where the reference category is non-frail (frail vs. non-frail).
[2] Adjusted PRR: Adjusted Prevalence Rate Ratio where the reference category is non-frail (pre-frail vs. non-frail).
[+] Sampling weights will be applied for all the percentages in this column.
[¥] Men: five or more drinks per day or 14 drinks per week; women: four or more drinks per day or seven drinks per week.
[$$] Sedentary behavior: where no physical activity reported or irregular physical activity (i.e. fewer than three times per week and or/less than 20 minutes per sessions).
[++] For the Duration of chronic condition, we will conduct any chronic condition, separate than organ system specific chronic condition.

Table 5: Association between treatment and frailty among childhood cancer survivors

	Overall N	Frail			Pre-frail		
	N (%)	Row %	Adjusted PRR PRR (95% CI)	P value	Row %	Adjusted PRR PRR (95% CI)	P value
Radiation							
Cranial (Dose cGY)							
Chest (Dose cGY)							
Abdominal /Pelvis (Dose cGY)							
Other region (Dose cGY)							
Chemotherapy							
Alkylating agents – (Cyclophosphamide equivalent dose) (Dose mg/m^2)							
Doxorubicin equivalent dose (Dose mg/m^2)							
Cisplatin							
Carboplatin							
6-Mercaptopurine							
6-Thiogaunine							
Methotrexate (Dose IT/IV)							
Oral Methotrexate							
Vinca-alkaloids							
Surgery							
Nephrectomy							
Cystectomy							
Thoracotomy							
Craniotomy							
Amputation							

[1] Adjusted PRR: Adjusted Prevalence Rate Ratio for sociodemographic characteristics and healthy risk behavior, where the reference category is non-frail (frail vs. non-frail).
[2] Adjusted PRR: Adjusted Prevalence Rate Ratio for sociodemographic characteristics and healthy risk behavior, where the reference category is non-frail (pre-frail vs. non-frail).

Table 6: Association between treatment and chronic conditions among childhood cancer survivors*

	Any chronic condition[1]		**Endocrine[2]**		**Respiratory[3]**		**Cardiac[4]**		**Renal[5]**		**SMN[6]**		**Neurology[7]**		**Musculoskel etal[8]**	
	B (SE)	P *value*	B(SE)	P *value*	B(SE)	P *value*	B(SE)	P *value*	B(SE)	P *value*	B(SE)	P *value*	B(SE)	P *value*	B(SE)	P *value*
Radiation Dose cGY)																
Cranial																
Chest																
Abdomen/Pelvis																
Other region																
Chemotherapy																
Alkylating agents – (Cyclophospham ide equivalent dose) (Dose mg/m^2)																
Doxorubicin equivalent dose (Dose mg/m^2)																
Cisplatin																
Carboplatin																
6-Mercaptopurine																
6-Thiogaunine																
Methotrexate (Dose IT/IV)																
Oral Methotrexate																
Vinca alkaloids																
Surgery																
Nephrectomy																

Cystectomy																
Thoracotomy																
Craniotomy																
Amputation																

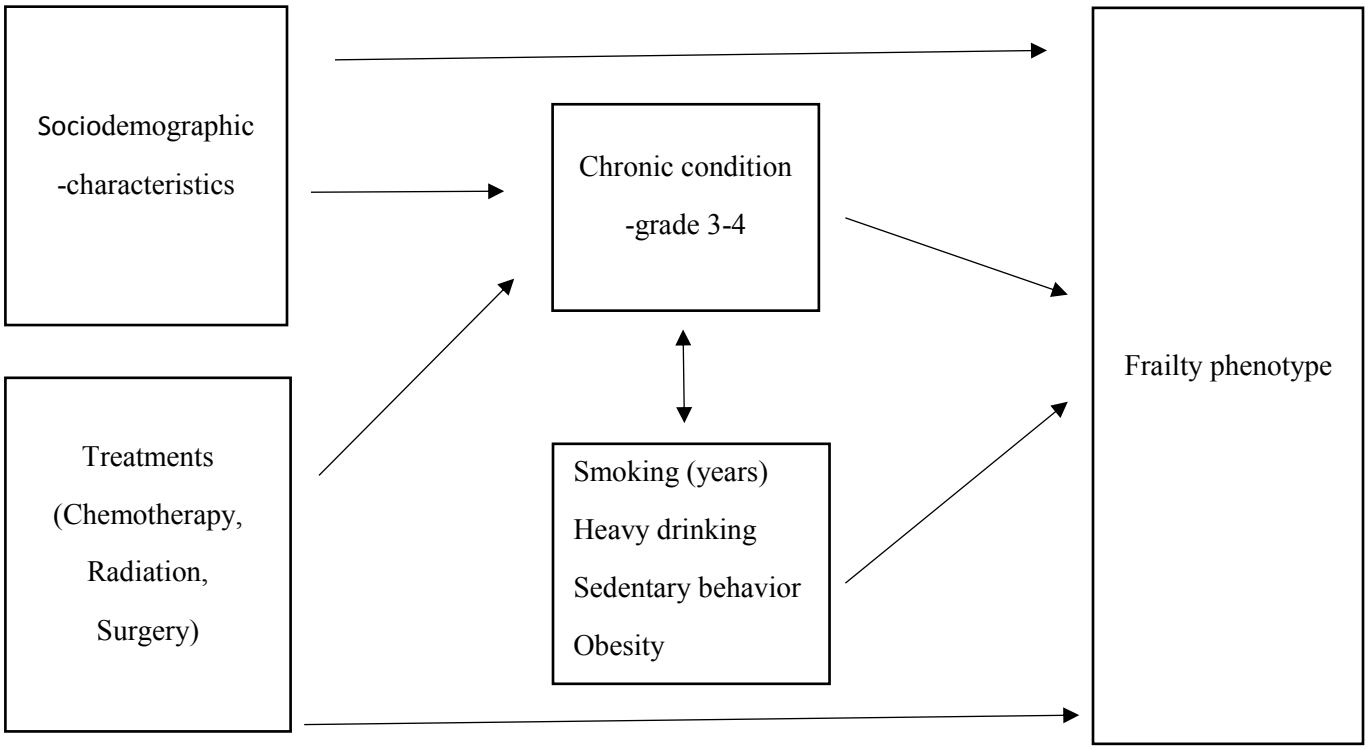
* This table is to inform structural equation model.
[1] Any chronic condition: duration of having any chronic conditions in grade (3-4)
[2] Endocrine: duration of having any endocrine chronic condition in grade (3-4)
[3] Respiratory: duration of having any respiratory chronic condition in grade (3-4)
[4] Cardiac: duration of having any cardiac chronic condition in grade (3-4)
[5] Renal: duration of having any renal chronic condition in grade (3-4)
[6] Subsequent malignancy: duration of subsequent malignancy in grade (3-4)
[7] Neurologic: duration of neurologic disease in grade (3-4)
[8] Musculoskeletal: duration of having any musculoskeletal disease in grade (3-4)
** GLM model will be conducted separately on each chronic condition, and will be adjusted for sociodemographic characteristics and risky healthy behavior.

Table 7: Goodness-of-fit Indices for various Models

Models	X^2	*df*	ΔX^2	Δdf	**CFI**	**RSMR**	**RSMREA**	**(RSMEA CL_{90})**
Null model								
No effect								
Indirect effects								
Direct/indirect effects								

Note: X^2 = chi-square; df =degrees of freedom; SRMR=Standardized Root Mean Square Residual; CFI=Comparative Fit Index; RMSEA=Root Mean Square Error of Approximation; RMSEA $CL_{90=}$ RSMEA 90% confident limits

Figure 1: Hypothesized model



Appendix 1: Specific criteria used to Define Frailty in the Cardiovascular Health Study and the St. Jude Lifetime Cohort Study

Frailty component	Cardiovascular Health Study Measure Criteria	St. Jude Lifetime Cohort Criteria	Childhood Cancer Cohort study Criteria	Comments
Low lean muscle mass	Unintentional weight loss of ≥10 pounds in past years	Lean muscle mass by DEXA ≤1.5 age and sex-specific SDS when compared with data from a national sample (NHANES)	Unintentional weight loss of ≥10 pounds in past years or BMI <18.5 kg/m^2	Because obesity is prevalent among cancer survivors, lean mass was chosen over unintentional weight loss as a measure of muscle wasting, as well being underweight (BMI<18.5) which is not typical for cancer survivor, thus can be used as a loss muscle mass
Self-reported exhaustion	Answered either a moderate amount of time or all of the time on either of the CEDS questions: I felt that everything I did was effort; and I could not get going	Score ≤40 (1SDS, based on a standard normal distribution, this represents approximately the lowest 6.7% of the general population) on the vitality subscale of the SF-36	Score ≤40 on the vitality subscale of the short form-36 (SF-36).[12] Specifically, the questions are: How much of the time during the past four weeks (1) did you feel full of life? (2) Did you have a lot of energy? (3) Did you feel worn out? Did you feel tired?	The vitality subscale of the SF-36 is specifically designed to measure vigor. The mental health subscale of the SF-36 and the CEDS depression scale are significantly correlated in adult cancer patients.
Low-energy expenditure	Expended<383 Kcal/week (men) or <270 kcal/week (women) during leisure time physical activity based on the short version of the Minnesota Leisure Time Activity questionnaire	Expended <383 kcal/week (men) or <270 kcal/week (women) during leisure time physical activity based on NHANES Physical activity questionnaire	For males, expended < 383 kilocalories (kcal) per week and for females as <270 kcal per week, estimated by converting reported frequency and duration of low, moderate and vigorous	Cut points are the same between studies. Type, duration, and frequency of physical activity from both questionnaires were converted to kcal/week based

			activities into kilocalories using guidelines provided by the Compendium of Physical Activities	on the Compendium for physical activity
Slowness	Women <159 cm tall and men <173 were classified as slow if they took ≥7 seconds to walk 15 feet at their usual pace; and women ≥159 cm tall and men ≥ 173 cm tall were classified as slow if they took ≥6 seconds to walk 15 feet at their usual pace		"Limited for more than 3 months" to either of two questions: (1) over the last 2 years, how long has your health limited you in walking uphill or climbing a few flights of stairs; or (2) over the last 2 years, how long has your health limited you in walking one block	
Weakness	Hand-grip strength stratified by body mass index and sex		Weakness or inability to move arms	
Men			Women	
BMI(kg/m^2)	Cut point (kg)		BMI(kg/m^2)	Cut point (kg)
≤24	≤29		≤23	≤17
24.1 to 26	≤30		23.1 to 26	≤17.3
26.1 to 28	≤30		26.1 to 29	≤18
>28	≤32		>29	≤21

Abbreviation: BMI; body mass index; CEDS, Centers for Epidemiology Depression Scale; DEXA, dual x-ray absorptiometry; NHANES, National Health and Nutrition Examination Survey; SDS, standard deviation score; SF-36, Medical outcomes Survey Short Form 36.