ANALYSIS CONCEPT PROPOSAL

DETERMINANTS OF LONGITUDINAL HEALTH-RELATED QUALITY OF LIFE CHANGE IN ADULT SURVIVORS OF CHILDHOOD CANCER

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STUDY TITLE

Determinants of longitudinal health-related quality of life changes in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study

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BACKGROUND AND RATIONALE

Despite advancements in treatment and survival outcomes, childhood cancer survivors continue to face a significant amount of late medical effects.[1,2] As a result, a subset of childhood cancer survivors experience poorer health-related quality of life (HRQOL) in comparison to national norms and/or sibling controls.[3] However, few studies have evaluated the changes in HRQOL over survivors' lifetime, and identified the risk factors associated with HRQOL changes.

Previous studies assessing HRQOL of childhood cancer survivors are largely based on a cross-sectional design.[3-5] These studies concluded that cancer diagnosis, chronic health conditions, and treatments are significant determinants of HRQOL. However, past research has not applied a broad framework when evaluating the determinants of longitudinal HRQOL changes in childhood cancer survivors. An article published in NEJM has identified five factors contributing to health status changes in Americans:[6] health behaviors/lifestyles (40%), genetic predisposition (30%), social connection (15%), health services/care (10%), and environmental exposure (5%).[6]

Clinical Determinants of HRQOL

Survivors who received specific treatments show worse HRQOL. For example, bone tumor and cranial irradiation are important risk factors of poor health status, psychological distress, and somatization among pediatric ALL and brain tumor survivors,[3,7,8].[3] Certain chemotherapy agents (e.g., anthracyclines and alkylating agents) are also associated with significant psychological distress and physical HRQOL deficits.[7] Pediatric CNS germ cell tumor survivors treated with radiation therapy have worse HRQOL than those not treated with radiation

therapy.[9] Furthermore, children undergoing both radiation and chemotherapy have reported worse physical functioning when compared with those who have received surgery alone.[9,10]

Socio-Demographic Determinants of HRQOL

Socio-demographic factors associated with adverse health status/HRQOL are female sex, older ages, minority race/ethnicity, lower educational attainment, lack of social support and health insurance, and unmarried status.[3,7] Aging and longer time from diagnosis significantly increases the prevalence of multiple symptoms in childhood cancer survivors, which in turn negatively impacts HRQOL.[11] Aging has also been associated with poor health behavior patterns[12], which is one of the risk factors of impaired HRQOL. Lower educational attainment, lower household income, and lack of health insurance negatively impacts HRQOL in cancer survivors. [3,7] When examining race, Latino and non-Latino survivors of childhood cancer report similar HRQOL.[13]

Environmental Determinants of HRQOL

Environmental factors (such as SES and health care resources at the community level) can impact HRQOL. A survey of leukemia and lymphoma AYA survivors reveals that low neighborhood-SES is associated with poorer physical domains of HRQOL.[14] Residential location indeed is a key factor of one's overall cancer prognosis[15] since resource-limited environments lead to advanced disease at diagnosis, malnutrition, infections, and barriers to access healthcare systems.[16] Residing in a low SES community with limited healthcare resources is a key barrier of accessing preventive and ongoing medical care, leading to poor health status and HRQOL. Although neighborhood/community SES or resources can impact HRQOL of childhood cancer survivors, we will not include this variable in this study because the zip codes of study participants collected from the earlier CCSS surveys (e.g., FU2 which is the baseline of this study) were overridden by the newer surveys if participants migrated to other locations.

Health Behavior Determinants of HRQOL

The majority of childhood cancer survivors do not meet the national health behavior guidelines.[17-19] There is evidence supporting elevated incidence of risky health behavior (e.g., substance use) as childhood cancer survivors grow into adulthood.[12,17] This could potentially negatively influence HRQOL. For example, current smokers have shown lower physical HRQOL than current non-smokers, and former smokers who quit smoking have shown improvement in physical HRQOL.[20] Another health behavior that could potentially decrease HRQOL in survivors is obesity. Obesity is one of the most important risk factors that predict adverse changes in HRQOL and is strongly correlated with physically inactive lifestyles.[21] However, the effects of alcohol consumption on HRQOL are mixed, with some studies in general populations showing that excessive alcohol consumption/binge drinking are associated with worse subjective health.[22]

Health Status (Chronic Health Condition, Psychological Distress, and Neurocognitive Deficits) and HRQOL

A recent study focusing on 604 cancer survivors (including childhood cancer and adult-onset cancer) and non-cancer individuals revealed that pain and two or more chronic health conditions significantly decreased physical HRQOL, whereas depression and two or more chronic health conditions significantly decreased mental HRQOL.[11] Furthermore, a CCSS study found the indirect effect between cancer experience on HRQOL was through the influence of emotional distress.[23] Not surprisingly, a higher number of health problems that a cancer survivor has adversely impacts mental HRQOL.[24] Additionally, neurocognitive conditions, which have a direct impact on educational attainment, employability, interpersonal relationships, independent living, and emotional functioning, can be associated with HRQOL impairment. Among acute lymphoblastic leukemia (ALL) survivors who did not receive cranial-spinal irradiation, survivors reported lower psychosocial HRQOL than the population norms,[25] and neurocognitive deficits in

verbal cognitive abilities and visual-motor integration skills were specifically significantly associated with worse physical and psychosocial HRQOL.[25]

Limitations in HRQOL Studies in Childhood Cancer Survivors

From a design perspective, the majority of previous HRQOL studies in childhood cancer survivors have primarily been cross-sectional in nature. Although sparse longitudinal studies have evaluated HRQOL change in childhood cancer patients and survivors, these studies largely focused on the therapeutic phase and/or shortly thereafter.[26,27] The use of larger longitudinal cohorts (e.g., CCSS) will provide an opportunity to evaluate the changes in HRQOL over time, and identify modifiable risk factors in survivors with poor HRQOL for future clinical interventions.

SPECIFIC AIMS & RESEARCH HYPOTHESES

This study will focus on adult survivors of childhood cancer and sibling controls who enrolled in the original CCSS cohort only. The objective is to compare HRQOL and its changes over time among survivors and controls. Risk factors/determinants of HRQOL changes over time among survivors will be further evaluated. Determinants of HRQOL under consideration include socio-demographic factors, health service resources, health behaviors/lifestyles, and chronic health conditions. Determinants and HRQOL data were collected from two individual time points in the original CCSS (FU2 in 2003 and FU5 in 2014). *We are interested in predicting HRQOL at FU5 and the change of HRQOL from FU2 to FU5 using the variables being collected from FU2. The use of an earlier time point (FU2) to predict future HRQOL (FU5) in long-term childhood cancer survivors helps clinicians identify the risk factors of suboptimal HRQOL for interventions before HRQOL starts to worsen and identify the protective factors of optimal HRQOL that can facilitate improvement.* Specific aims and hypotheses are described as follows:

- Aim 1: To describe the HRQOL change status from FU2 to FU5 among survivors.

  Hypothesis 1: A higher proportion of survivors will have decreased HRQOL than those having persistent suboptimal or optimal HRQOL over time, followed by those having improved HRQOL in individual domains, PCS, and MCS.

  Note 1, for each subject we will categorize eight HRQOL domains, PCS and MCS scores at each time point (FU2 and FU5, respectively) as optimal and suboptimal status based on the 1SD criterion. That said, ≥ 40 for optimal status and <40 for suboptimal status.

  Note 2, the use of 1SD-criterion approach to establish optimal and suboptimal status may raise concern since some survivors who have worsening HRQOL may be classified as persistently optimal if HRQOL scores at FU2 and FU5 are all above 40. However, 1SD-criterion approach has been commonly used in PRO research because the results derived from this approach are clinical relevance/meaningful (1SD below the norm), which is similar to the strategy used to define hypertension (130/80 mm Hg). Basically, if the HRQOL scores are optimal (>40), the change status will not have immediate or significant health threatening. In addition to the 1SD-criterion approach, we will explore an alternative approach by examining change in HRQOL scores of at least 0.5SD.

  Note 3, for Aims 1-5, we will further stratify the subjects based on their HRQOL at FU2 (i.e., optimal and suboptimal) to identify the risk and protective factors of HRQOL changes over time. Specifically, to develop a model for elucidating the risk factors of HRQOL decrement, we will focus on subjects having optimal HRQOL at FU2; subjects in this group will be classified as having persistently optimal HRQOL and decreased HRQOL. To develop a model for elucidating the protective factors of HRQOL improvement, we will focus on subjects having

suboptimal HRQOL at FU2; subjects in this group will be classified as having persistently suboptimal HRQOL and improved HRQOL. ***See Table 1 for the definitions of the HRQOL change status.***

- Aim 2: To evaluate the effects of socio-demographic factors on HRQOL at FU5, and HRQOL change status over time *(survivors only)*.

  Hypothesis 2: Survivors who are older, widowed/separated, living not independently, have lower educational attainment or lower annual family income, and those have no health insurance coverage at FU2 will be more likely to have suboptimal HRQOL at FU5, as well as decreased HRQOL over time than their counterpart survivors.

- Aim 3: To evaluate the effects of health behaviors (cigarette smoking and physical inactivity) on HRQOL at FU5, and HRQOL change status over time *(survivors only)*.

  Hypotheses 3: Survivors who have unhealthy lifestyles (currently smoking and/or physically inactive) at FU2 will be more likely to have suboptimal HRQOL at FU5, as well as decreased HRQOL over time than those who have healthy lifestyles.

- Aim 4: To evaluate the effects of chronic health conditions (including physical, emotional, cognitive) on HRQOL at FU5 and HRQOL change status over time *(survivors only)*.

  Hypotheses 4: Survivors who have more severe chronic health conditions at or after FU2 will be more likely to have suboptimal HRQOL at FU5, as well as decreased HRQOL over time than those who have less severe conditions.

  Note 1, chronic physical health conditions include vision/eye, hearing, speech, pulmonary, cardiovascular, gastrointestinal, renal, musculoskeletal, neurologic, hematologic, endocrine disorders.[28]

  Note 2, in addition to examining chronic health conditions at FU2 (yes/no), we will also examine new onset chronic health conditions by FU5, and categorize these variables by clinical relevance and frequency, as well as pattern of occurrence (e.g. absent at both FU2 and FU5, new onset prior to FU5, and persistence from FU2 to FU5).

- Aim 5: To evaluate the cumulative effects of risk factors on HRQOL decrement over time based on the selected socio-demographic, health behaviors, and chronic health condition variables, and evaluate the cumulative effects of protective factors on HRQOL improvement over time *(survivors only)*. Based on the selected predictors, risk and protective scores of HRQOL change will be created for each survivor.

  Hypotheses 5: A parsimonious model that contains significant risk factors derived from the training sample will demonstrate acceptable predictive validity of HRQOL decrement through the validation sample. Similarly, a parsimonious model that contains significant protective factors created from the training sample will demonstrate acceptable predictive validity of HRQOL improvement through the validation sample.

- Exploratory Aim: To compare the change in HRQOL between survivors and controls from FU2 to FU5.

Note, we consider this Aim as exploratory because approximately 320 siblings completed FU2 and fewer completed both FU2 and FU5. The research team will decide whether to include the results of this Aim in the manuscript after the data analysis is completed.

METHODS

Participants

This study will evaluate HRQOL of childhood cancer survivors and their sibling controls enrolled in CCSS at two different time points. Of the eligible participants, 12,455 survivors and 3,419 sibling controls have completed the baseline survey with detailed treatment and diagnosis information abstracted from the medical records.[29] This study will focus on the original CCSS cohort by evaluating longitudinal change from FU2 (2003) to FU5 (2014) among survivors and controls, and identifying determinants associated with the changes in HRQOL over time.

1. Inclusion criteria
    a. All pediatric cancer diagnoses
    b. Age at FU2 survey completion: ≥ 18 years of age
    c. A completion of both FU2 and FU5 surveys
2. Exclusion criteria
    a. A completion of FU2 survey alone, FU5 survey alone, or none
    b. A proxy-report for either FU2 or FU5 survey

Utilization of study samples across different aims

We plan to select approximately 80% of the evaluable, random survivors for model development (as a training sample) in Aims 1-4 and the creation of the cumulative risk scores and cumulative protective scores, and use the remaining 20% of evaluable, random survivors for the model validation (as a validation sample) in Aim 5.

Outcomes of interest: HRQOL

HRQOL was evaluated by the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36).[4,23,30] This tool was designed to measure perceived health status and daily functional status.[31] Specifically, eight HRQOL domains of the SF-36 that will be used include: physical functioning (PF), role limitation due to physical health problems (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitation due to emotional health problems (RE), and mental health (MH).[32] Higher scores indicate better HRQOL

Additionally, two summary measures will be used, Physical Component Summary (PCS) and Mental Component Summary (MCS)[32]. PCS and MCS were scored on a T-metric (mean=50, SD=10) with higher scores indicating better physical and mental HRQOL. For each study participant, the calculation of eight domain scores, PCS and MCS, was age/sex-adjusted based on a national representative sample.

Predictors of HRQOL changes

***** Note, see TABLE 1 for the Categories of Individual Predictors/Variables *****

1. Socio-demographics
    a. Age at the time of survey completion
    b. Sex: male and female
    c. Race/ethnicity: white, non-Hispanic; black, non-Hispanic; Hispanic; and other

d. Education attainment: did not complete high school (HS), HS graduate/GED, training after HS or some college, and college graduate or postgraduate level
e. Employment status: working full-time, working part-time, and unemployed or other than full-time and part-time employment
f. Annual household income: <$20,000, $20,000-$79,999, and ≥$80,000
g. Marital status: married/living with partner, widowed/divorced/separated, and single (never married)
h. Living arrangement: living independently, and living not independently

2. Cancer diagnosis
   a. Primary cancer: leukemia, CNS tumor, Hodgkin lymphoma, non-Hodgkin lymphoma, Wilms tumor, neuroblastoma, soft tissue sarcoma, bone tumor, and other (medical records abstraction)
   b. Secondary cancer or recurrence: yes/no

3. Time interval
   a. Years since cancer diagnosis using two variables age at cancer diagnosis (in years) and age at survey completion (in years)
   b. Interval between FU2 and FU5 (in years)

4. Cancer treatment
   a. Chemotherapy: methotrexate, corticosteroid, anthracyclines, alkylating agents, and other chemotherapy (yes or no for each)
   b. Radiotherapy: brain irradiation, chest irradiation, abdominal irradiation, pelvic irradiation, and other radiation therapy (yes or no for each)
   c. Surgery: splenectomy, nephrectomy, amputation, and other major surgery (yes or no for each)

5. Chronic Health Conditions (CHCs)
   a. Organ system-based physical CHCs:
      i. CHCs by organ systems: vision/eye, hearing, speech, pulmonary, cardiovascular, gastrointestinal, renal, musculoskeletal, neurologic, hematologic, endocrine disorders.
      ii. Each organ system-based CHC comprises several homogenous subtypes, and each subtype was graded by the CTCAE criterion: none (grade 0), mild (grade 1), moderate (grade 2), severe (grade 3), and life-threatening or disabling (grade 4). Each subtype with an organ system will be further classified as presence (grades 2-4) and absence (grads 0-1). The presence of an organ-based physical CHC is defined as the presence of any subtype within an organ system having a CTCAE grades 2-4.
   b. Emotional distress:
      i. Brief Symptom Inventory-18 by three domains (anxiety, depression, and somatization) and global severity index (GSI).
      ii. For each domain, impairment status was defined by sex-adjusted score ≥63 (**see Table 1** for the definition and classification).
   c. Neurocognitive functioning (self-reports):
      i. Neurocognitive functioning by four domains (emotional regulation, memory, task efficiency, and organization).
      ii. For each domain, impairment status was defined by score ≥63 (**see Table 1** for the definition and classification).
6. Health behaviors/lifestyles

i. Self-reported cigarette smoking: never, past, and current cigarette smokers based on CDC guideline (**see Table 1** for the definition and classification)
ii. Self-reported physical activity: active and inactive based on CDC guideline (**see Table 1** for the definition and classification)

7. Health insurance coverage
   a. Health insurance coverage: yes (insured American/Canadian resident) and no (uninsured American)

Analytic approach

Aim 1: To describe the HRQOL change status from FU2 to FU5 among survivors. ***See Table 3.***

- Univariate analysis will be performed to report the participant numbers and frequency counts based on the HRQOL change status.

Aim 2: To evaluate the effects of socio-demographic factors on HRQOL at FU5, and HRQOL change status over time (survivors only). ***See Table 4.***

- Model 2a: Predicting suboptimal HRQOL at FU5. For each HRQOL domain, PCS, and MCS, a multiple logistic regression model will be performed to assess the effects of socio-demographic factors on suboptimal HRQOL (1SD below the norm) at FU5.
- Models 2b1/2c1 (subjects having *optimal* HRQOL at FU2 only): For each HRQOL domain, PCS, and MCS, a multiple logistic regression model will be performed to test the effects of socio-demographic factors on HRQOL improvement over time.
- Models 2b2/b2c2 (subjects having *suboptimal* HRQOL at FU2 only): For each HRQOL domain, PCS, and MCS, a multiple logistic regression model will be performed to test the effects of socio-demographic factors on HRQOL decrement over time.
- For all modeling, factors identified with P-value<0.2 will be selected for further testing under Aim 5.

Aim 3: To evaluate the effects of health behaviors (i.e., cigarette smoking and physical inactivity) on HRQOL at FU5, and HRQOL change status over time (survivors only). ***See Table 5.***

- Model 3a: Predicting suboptimal HRQOL at FU5. For each HRQOL domain, PCS, and MCS, a multiple logistic regression model will be performed to test the effects of health behavior factors on suboptimal HRQOL (1SD below the norm) at FU5.
- Models 3b1/3c1 (subjects having *optimal* HRQOL at FU2 only): For each HRQOL domain, PCS, and MCS, a multiple logistic regression model will be performed to test the effects of health behavior factors on HRQOL improvement over time.
- Models 3b2/3c2 (subjects having *suboptimal* HRQOL at FU2 only): For each HRQOL domain, PCS, and MCS, a multiple logistic regression model will be performed to test the effects of health behavior factors on HRQOL decrement over time.
- For all modeling, age, sex, time interval between FU2 and FU5, and HRQOL at FU2 will be included in the analysis. Factors identified with P-value<0.2 will be selected for further testing under Aim 5.

Aim 4: To evaluate the effects of chronic health conditions (including physical, emotional, cognitive) on HRQOL at FU5 and HRQOL change status over time (survivors only). ***See Table 6.***

- Model 4a: Predicting suboptimal HRQOL at FU5. For each HRQOL domain, PCS, and MCS, a multiple logistic regression model will be performed to test effects of health status factors on suboptimal HRQOL (1SD below the norm) at FU5.
- Models 4b1/4c1 (subjects having *optimal* HRQOL at FU2 only): For each HRQOL domain, PCS, and MCS, a multiple logistic regression model will be performed to test the effects of health status factors on HRQOL improvement over time.
- Models 4b2/4c2 (subjects having *suboptimal* HRQOL at FU2 only): For each HRQOL domain, PCS, and MCS, a multiple logistic regression model will be performed to test the effects of health status factors on HRQOL decrement over time.
- For all modeling, age, sex, time interval between FU2 and FU5, and HRQOL at FU2 will be included in the analysis. Factors identified with P-value<0.2 will be selected for further testing under Aim 5.

Aim 5: To evaluate the cumulative effects of risk factors on HRQOL decrement over time based on the selected socio-demographic, health behaviors, and chronic health condition variables, and evaluate the cumulative effects of protective factors on HRQOL improvement over time (survivors only). Based on the selective predictors, risk and protective scores of HRQOL change will be created for each survivor. ***See Table 7.***

- Model 5a: Predicting suboptimal HRQOL at FU5. For each HRQOL domain, PCS, and MCS, a multiple logistic regression model will be performed to test effects of socio-demographic, health behaviors, and chronic health condition variables selected from Aims 3-5 on the suboptimal HRQOL (1SD below the norm) at FU5.
- Models 5b1/5c1 (subjects having *optimal* HRQOL at FU2 only): For each HRQOL domain, PCS, and MCS, a multiple logistic regression model will be performed to test the effects of socio-demographic, health behaviors, and chronic health condition variables selected from Aims 3-5 on HRQOL improvement.
- Models 5b2/5c2 (subjects having *suboptimal* HRQOL at FU2 only): For each HRQOL domain, PCS, and MCS, a multiple logistic regression model will be performed to test the effects of socio-demographic, health behaviors, and chronic health condition variables selected from Aims 3-5 on HRQOL decrement.
- For all modeling, age, sex, time interval between FU2 and FU5, HRQOL at FU2, as well as significant factors selected from Aims 2-4 with P-value<0.2 will be tested. The variation inflation factor (VIF) index will be estimated and the cut-point 10 will be used to determine multicollinearity among predicators associated with HRQOL. Those variables that meet the VIF criterion <10 or are clinically meaningful/important will be selected into the final model.
- Cumulative risk and protective indices development: among subjects with suboptimal HRQOL at FU2, ORs of selected predictors be utilized to estimate the risk scores of HRQOL decrement at FU5 for each individual (i.e., a summation of ORs for each survivor to account for the weights of different predictors). Similarly, among subjects with optimal HRQOL at FU2, ORs of selected variables be utilized to estimate the protective scores for predicting optimal HRQOL at FU5 for each survivor. We will use the receiver operating characteristic (ROC) approach to determine the extent to which the risk or protective scores can optimally predict the HRQOL decrement or improvement over time. We will use the areas under the ROC curves (AUCs) to evaluate the predictive property of the models, with the AUC deemed as acceptable if between 0.7 and 0.8 and excellent if >0.8. To develop parsimonious predictive models, we will remove each predictor at a time (starting from the predictor with the largest p-value) from the modeling to assure that the predictive validity is not jeopardized (i.e., a minimal change of AUC). Finally, we will establish optimal cut-points for the risk and protective scores,

respectively, based on equal sensitivity and sensitivity. We will use the bootstrapping methods to avoid over-optimization of the scores with regarding to the classification of outcomes.

- Validation: Among the 20% of the cohort held out for validation, we will evaluate the risk/protective scores that were developed among the development data set. ROC curves will be presented, along with AUCs to illustrate the discrimination abilities of the scores in an independent data set. Further measures such as predictive values will be calculated to illustrate the clinical utility of the scores.

Methods to adjust for the p-value related to multiple comparisons

For Aims 2, 3, 4, and 5 that involve 4 multiple models, the adjusted p-value (0.05/4=0.0125) will be used to decide the statistical significance for the results.

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TABLES

Table 1: Variable identification, sources, and categorization (operational definition)

Variable	FU2	FU5	Categorization
	Section/item	Section/item	
HRQOL (MOS SF-36): 8 domain scores, PCS and MCS	E1-22, F1-14	O1-8, P1-3	Original HRQOL scores on each domain (PF, RP, BP, GH, VT, SF, RE, MH), PCS and MCS were based on T-scores. For each subject, we will categorize his/her eight HRQOL domain, PCS and MCS scores at FU2 and FU5, respectively, as *optimal and suboptimal status:* ***≥ 40 (optimal) and <40 (suboptimal)***. To develop a model for elucidating the risk factors of HRQOL decrement from FU2 to FU5, we will focus on subjects having optimal HRQOL at FU2 and create a variable containing two levels indicating a change status: 1=Persistently optimal HRQOL (FU2 to FU5) 2=Decreased HRQOL (FU2 to FU5) To develop a model for elucidating the *protective factors* of HRQOL improvement from FU2 to FU5, we will focus on subjects having suboptimal HRQOL at FU2 and create a variable containing two levels indicating a change status: 1=Persistently suboptimal HRQOL (FU2 to FU5) 2=Improved HRQOL (FU2 to FU5)
Basic demographics			
Age at survey completion			Mean (SD) Median (range)
Sex			1=Male 2=Female
Race/ethnicity			1=White, non-Hispanic 2=Black, non-Hispanic 3=Hispanic 4=Other
Personal-level SES			

Education attainment	1	A4	1=Did not complete high school (HS) 2=HS graduate/GED 3=Training after HS or some college 4=College graduate or postgraduate level
Employment status	4	A5	1=Working full-time 2=Working part-time 3=Unemployed or other than full-time and part-time employment 1=Favorable: working full or part-time 2=Unfavorable: otherwise
Annual household income	S1	A7	1=<$20,000 2=$20,000-$79,999 3=≥$80,000 1=Favorable: ≥$80,000 2=Unfavorable: <$80,000 Or using poverty line to classify
# of members in the household supported on this income	S2	A8	Continuous: 1-9
Marital status	2	M2	1=Married/living with partner 2=Widowed/divorced/separated 3=Single 1=Favorable: married/living with partner 2=Unfavorable: otherwise
Living arrangement	3	M1	1=Live with spouse/partner 2=Live with parents 3=Live with roommate 4=Live with brothers/sisters 5=Live with relatives 6=Live alone 7=Other status 1=Favorable (living independently): "Live with spouse/partner", "Live alone" or in the "Other status" category indicated they had a roommate, lived in a dorm, lived with their own children, were in the military, lived with friends, or had another nondependent living arrangement 2=Unfavorable (living not independently): "Live with parent",

			"Live with brothers and/or sisters", "Live with other relatives", or who specified that they had nursing or caregiver support under "Other status"
Health insurance and usual source of cancer care			
Health insurance coverage	A10	M1	1=Insured or Canadian resident 2=Uninsured
Usual source of cancer care	A5	B3	1=Yes (≥1 visit(s)) 2=No (no visits or missing [assume no visits given the skip pattern design])
Health behavior			
Cigarette smoking status[1]	L1-5	N7-12	1=Never smoked (smoked <100 cigarettes in entire lifetime) 2=Past smoker (smoked ≥100 cigarettes in entire lifetime, but currently do not smoke) or current smoker (smoked ≥100 cigarettes in entire lifetime and currently do smoke) 1=Healthy group 2=Unhealthy group
Physical activity[2]	D1-7	N15-21	2008 CDC Guidelines 1=Active (≥150 minutes of moderate and/or ≥75 minutes of vigorous intensity physical activity each week) 2=Inactive (otherwise) 1=Healthy group 2=Unhealthy group
Cancer diagnosis			1=Leukemia 2=Central nervous system tumor 3=Hodgkin's disease 4=Non-Hodgkin's lymphoma 5=Wilms' tumor 6=Neuroblastoma 7=Sarcoma 8=Bone tumor 9=Other
Cancer treatment			
Time since diagnosis			Mean (SD) Median (range)
Chemotherapy			Methotrexate (1=No; 2=Yes) Corticosteroid (1=No; 2=Yes) Anthracyclines (1=No; 2=Yes)

			Alkylating agents (1=No; 2=Yes) Other chemotherapy (1=No; 2=Yes)
Radiation therapy			Brain irradiation (1=No; 2=Yes) Chest irradiation (1=No; 2=Yes) Abdominal irradiation (1=No; 2=Yes) Pelvic irradiation (1=No; 2=Yes) Other radiation therapy (1=No; 2=Yes)
Surgery			Splenectomy (1=No; 2=Yes) Nephrectomy (1=No; 2=Yes) Amputation (1=No; 2=Yes) Other major surgery (1=No; 2=Yes)
Relapse/second malignant neoplasms			1=No 2=Yes
Health status			
Organ system-specific physical chronic health conditions (CHC) and grading[3]			CHCs by organ systems: 1=vision/eye disorders 2=hearing disorders 3=speech disorders 4=pulmonary disorders 5=cardiovascular disorders 6=gastrointestinal disorders 7=renal disorders 8=musculoskeletal disorders 9=neurologic disorders 10=hematologic disorders 11=endocrine disorders CTCAE grading for each subtype CHC within an organ system: 0=None or G1 (mild) 1=G2 (moderate), G3 (severe) or G4 (fatal) Presence of an organ system-specific CHC: any subtype CHC within an organ system having a CTCAE G2-4 1=Not presence 2=Presence
Psychological distress (BSI-18)	G1-20	L1-20	Continuous T-scores for each domains (anxiety, depression, somatization) and global severity index (GSI) Binary for each domains and GSI (sex-adjusted cutoff: ≥63): 1=Not impaired 2=Impaired

Neurocognitive function (NCQ)	J1-25	Q1-33	Continuous scores for each domains (memory, task efficiency, organization, emotional regulation) Binary for each domains (cutoff: ≥63): 1=Not impaired 2=Impaired

Table 2: Comparisons between FU2 participants and both FU2/FU5 participants of cancer survivors[#]

	FU2 participants (N=)	Both FU2/FU5 participants (N=)	t-statistic or X2-statistic (P-value)
	M (SD/range) or N (%)	M (SD/range) or N (%)	
Age at FU2			
Sex			
Race/ethnicity			
Education attainment at FU2			
Employment status at FU2			
Annual household income at FU2			
Marital status at FU2			
Living arrangement at FU2			
Health insurance coverage at FU2			
Usual source of cancer care at FU2			
Cigarette smoking at FU2			
Physical activity at FU2			
Chronic health conditions at FU2			
Cancer diagnosis[†]			
Chemotherapy[†]			
Radiation therapy[†]			
Surgery[†]			
Years since diagnosis (FU2)			

For the categorization of each variable, see definitions in Table 1

† See the list of categories for cancer diagnosis, chemotherapy, radiation therapy, and surgery in Table 1

Table 3 (Aim 1): HRQOL at FU2 and FU5 and the change status from FU2 to FU5 in cancer survivors

	HRQOL at FU2		HRQOL at FU5		HRQOL change status from FU2 to FU5				
	Suboptimal HRQOL	Optimal HRQOL	Suboptimal HRQOL	Optimal HRQOL	Decreased HRQOL	Persistently suboptimal HRQOL	Improved HRQOL	Persistently optimal HRQOL	X2-statistic (P-value)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
PF									
RP									
BP									
GH									
VT									
SF									
RE									
MH									
PCS									
MCS									

PF: physical functioning, RP: role limitation due to physical health problems, BP: bodily pain, GH: general health perceptions, VT: vitality, SF: social functioning, RE: role limitation due to emotional health problems, MH: mental health, PCS: Physical Component Summary, MCS: Mental Component summary

Table 4 (Aim 2): Effects of socio-demographic factors on HRQOL at FU5 and HRQOL change status in cancer survivors[#, †]

	HRQOL at FU5		HRQOL change status: from FU2 to FU5[‡]			
	PCS	MCS	PCS		MCS	
	Model 2a (Outcome = suboptimal HRQOL)		Model 2b1 (Outcome = improved HRQOL)[§]	Model 2b2 (Outcome = decreased HRQOL)[&]	Model 2c1 (Outcome = improved HRQOL)[§]	Model 2c2 (Outcome = decreased HRQOL)[&]
	OR [95%CI, P-value]	OR [95%CI, P-value]	OR [95%CI, P-value]	OR [95%CI, P-value]	OR [95%CI, P-value]	OR [95%CI, P-value]
Education attainment at FU2						
Employment status at FU2						
Annual household income at FU2						
Living arrangement at FU2						
Health insurance coverage at FU2						
Usual source of cancer care at FU2						
Age at FU2						
Sex at FU2						
Race/ethnicity at FU2						
Time interval (FU2 and FU5)						
HRQOL at FU2						
Interaction: HRQOL at FU2 and significant predictors selected from Aim 2						

* P<0.05; **P<0.01; ***P<0.001

For the categorization of each variable, see definitions in Table 1

† Eight domains of SF-36 will be estimated/reported in separate Tables with the same format (not shown)

‡ Stratify survivors by those having suboptimal and optimal HRQOL at FU2, respectively

§ Restrict to survivors having suboptimal HRQOL at FU2

& Restrict to survivors having optimal HRQOL at FU2

Table 5 (Aim 3): Effects of health behaviors on HRQOL at FU5 and HRQOL change status in cancer survivors[#, †]

	HRQOL at FU5		HRQOL change status: from FU2 to FU5[‡]			
	PCS	MCS	PCS		MCS	
	Model 3a (Outcome = suboptimal HRQOL)		Model 3b1 (Outcome = improved HRQOL)[§]	Model 3b2 (Outcome = decreased HRQOL)[&]	Model 3c1 (Outcome = improved HRQOL)[§]	Model 3c2 (Outcome = decreased HRQOL)[&]
	OR [95%CI, P-value]	OR [95%CI, P-value]	OR [95%CI, P-value]	OR [95%CI, P-value]	OR [95%CI, P-value]	OR [95%CI, P-value]
Cigarette smoking at FU2						
Physical activity at FU2						
Age at FU2						
Sex at FU2						
Time interval (FU2 and FU5)						
HRQOL at FU2						
Interaction: HRQOL at FU2 and significant predictors selected from Aim 3						

* P<0.05; **P<0.01; ***P<0.001

For the categorization of each variable, see definitions in Table 1

† Eight domains of SF-36 will be estimated/reported in separate Tables with the same format (not shown)

‡ Stratify survivors by those having suboptimal and optimal HRQOL at FU2, respectively

§ Restrict to survivors having suboptimal HRQOL at FU2

& Restrict to survivors having optimal HRQOL at FU2

Table 6 (Aim 4): Effects of chronic health conditions on HRQOL at FU5 and HRQOL change status in cancer survivors[#, †]

	HRQOL at FU5		HRQOL change status: from FU2 to FU5[‡]			
	PCS	MCS	PCS		MCS	
	Model 4a (Outcome = suboptimal HRQOL)		Model 4b1 (Outcome = improved HRQOL)[§]	Model 4b2 (Outcome = decreased HRQOL)[&]	Model 4c1 (Outcome = improved HRQOL)[§]	Model 4c2 (Outcome = decreased HRQOL)[&]
	OR [95%CI, P-value]	OR [95%CI, P-value]	OR [95%CI, P-value]	OR [95%CI, P-value]	OR [95%CI, P-value]	OR [95%CI, P-value]
Chronic physical health conditions (organ system-specific) at or after FU2[$]						
Emotional distress at or after FU2[$]						
Neurocognitive deficits at or after FU2[$]						
Age at FU2						
Sex at FU2						
Time interval (FU2 and FU5)						
HRQOL at FU2						
Interaction: HRQOL at FU2 and significant predictors selected from Aim 4						

* P<0.05; **P<0.01; ***P<0.001

For the categorization of each variable, see definitions in Table 1

† Eight domains of SF-36 will be estimated/reported in separate Tables with the same format (not shown)

‡ Stratify survivors by those having suboptimal and optimal HRQOL at FU2, respectively

§ Restrict to survivors having suboptimal HRQOL at FU2

& Restrict to survivors having optimal HRQOL at FU2

$ In addition to examining chronic health conditions at FU2 (yes/no), we will also examine new onset chronic health conditions (including physical, emotional and neurocognitive) by FU5, and categorize these variables by clinical relevance and frequency, as well as pattern of occurrence (e.g. absent at both FU2 and FU5, new onset prior to FU5, and persistence from FU2 to FU5.

Table 7 (Aim 5): Effects of cumulative risk on HRQOL at FU5 and HRQOL change status in cancer survivors[#, †]

	HRQOL at FU5		HRQOL change status: from FU2 to FU5[‡]			
	PCS	MCS	PCS		MCS	
	Model 5a (Outcome = suboptimal HRQOL)		Model 5b1 (Outcome = improved HRQOL)[§]	Model 5b2 (Outcome = decreased HRQOL)[&]	Model 5c1 (Outcome = improved HRQOL)[§]	Model 5c2 (Outcome = decreased HRQOL)[&]
	OR [95%CI, P-value]	OR [95%CI, P-value]	OR [95%CI, P-value]	OR [95%CI, P-value]	OR [95%CI, P-value]	OR [95%CI, P-value]
Socio-demographic variables selected from Aim 2						
Health services variables selected from Aim 2						
Health behavior variables selected from Aim 3						
Chronic physical health conditions, emotional distress, and neurocognitive deficit variables selected from Aim 4						
Time interval (FU2 and FU5)						
HRQOL at FU2						
Interaction: HRQOL at FU2 and significant predictors selected from Aim 5						

*P<0.05; **P<0.01; ***P<0.001

Variables from Tables 4-6 with P<0.2, meet the VIF criterion <10, and clinically meaningful/important will be used in the final model.

† Eight domains of SF-36 will be estimated/reported in separate Tables with the same format (not shown)

‡ Stratify survivors by those having suboptimal and optimal HRQOL at FU2, respectively

§ Restrict to survivors having suboptimal HRQOL at FU2

& Restrict to survivors having optimal HRQOL at FU2

References (for Table 1 only; see pages 9-11 for a complete list of references)

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