

## **CCSS Analysis Concept Proposal: Health status among adult survivors of childhood cancer by treatment era**

**Working Group:** Cancer Control

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### **Background**

Improvements in treatment and hospital care have led to an increasing number of adult survivors of childhood cancer, a substantial number of whom report medical late effects that alter health status and interfere with daily life.<sup>1,2</sup> A report from the Childhood Cancer Survivor Study (CCSS) in 2003 summarized the prevalence of adverse health status outcomes among 9535 five or more year adult survivors of childhood cancer who were treated between 1970 and 1986, compared the prevalence of these outcomes among survivors and a sibling comparison group, and evaluated associations between diagnosis and treatment related variables and adverse health status.<sup>3</sup> At a mean age of 26.8 (SD 6.2) years and a mean time from diagnosis of 17.4 (SD 4.6) years, 10.9% percent of CCS reported poor general health, 17.2% poor mental health, 12.0% functional impairments, 12.5% activity limitations, 13.2% cancer related anxiety, and 10.2% cancer related pain. Survivors were more likely than siblings to report adverse health outcomes with relative risks ranging from 1.8 (95% CI 1.6-2.1) for poor mental health to 5.2 (95% CI 4.1-6.6) for functional impairments. Survivors of CNS tumor were at the greatest risk for poor health status outcomes in all categories. Bone tumor survivors were at high risk for activity limitations and functional impairment. Demographic factors associated with adverse health outcomes included female sex, older age at interview, lower educational attainment, lower household income, and lack of health insurance. Exposure to surgery, radiation to the brain and or chest and treatment with both anthracyclines and alkylating agents were also associated with adverse health status outcomes.<sup>3</sup> Recent analysis of these data in the baseline cohort across three time points indicates age related increases in the prevalence of poor general health, functional impairments, activity limitations, and adverse health status in more than one domain.<sup>4</sup>

Data describing late effects has, in some cases, been used to modify front line clinical trials with the intention of minimizing the toxic effects of cancer therapy and improving overall health status. Specific changes in treatment are speculated to result in fewer long-term adverse outcomes even though many chemotherapy agents used in current therapeutic protocols for childhood cancer have been used for decades.<sup>5,6</sup> In addition, new agents (e.g. monoclonal antibodies) or delivery methods (e.g. conformal radiation) may yield unexpected health outcomes long after therapy ends. The Childhood Cancer Survivor Study (CCSS) has provided a wealth of information on the prevalence and predictors of adverse health status outcomes that directly apply to survivors treated in North America between 1970 and 1986.<sup>7,8</sup> These rates may be lower among survivors treated on more contemporary protocols. However, the

prevalence of adverse health status in a more contemporary cohort of the size of CCSS is not yet known. The expansion cohort of the CCSS includes individuals diagnosed between 1987 and 1999, and offers an opportunity to explore the prevalence of adverse health status outcomes across treatment eras and to determine if there are interactions between treatment era and diagnosis group or treatment exposure.

### Specific aims

1. Enumerate the prevalence of adverse health status outcomes in the adult survivors of childhood cancer (combined cohort) as reported on their baseline questionnaires and compare rates (by treatment era: 1970-1979, 1980-1989, 1990-1999) to rates reported by sibling participants in the original CCSS cohort on their baseline questionnaire.
2. Evaluate the differential effects of diagnosis or treatment on adverse health status as a function of treatment era, while taking into account demographic characteristics and health habits in the combined CCSS cohort.

### Hypotheses

1. In multivariable models adjusted for age, sex, race/ethnicity, insurance status, educational attainment and annual household income, treatment era among survivors will be associated with prevalence of adverse health status outcomes. Survivors in every treatment era will have a higher prevalence of adverse health status outcomes when compared to siblings.
2. In models adjusted for demographic characteristics and health behaviors, there will be a differential effect of diagnosis (and in a separate model, treatment modality) on adverse health status outcomes among survivors by era of treatment.

### Outcomes

1. Poor general health - answers fair or poor vs. good, very good or excellent
  - a. Expansion O21
  - b. Original J35
2. Poor mental health - score of 63 or higher on the brief symptom inventory on any of the three subscales vs. no score of 63 or higher on any of the three subscales of the Brief Symptom Inventory (BSI)<sup>9</sup>
  - a. Expansion K1-K18
  - b. Original J16-35
3. Activity limitations - answers limited for more than three months over the past two years to any of the three questions
  - a. Expansion O20 b, c, e
  - b. Original N14 b, c, e
4. Functional impairment - answers yes to any of the three questions vs. answers no to all three questions
  - a. Expansion O16-18
  - b. Original N10-N12
5. Cancer related Pain - answers a lot, very bad excruciating pain, medium amount of pain vs. no or small amount of pain
  - a. Expansion K20
  - b. Original J36
6. Cancer related Anxiety - answers a lot, very many/extreme, medium amount of anxiety/fears vs. no or small amount of anxiety/fears
  - a. Expansion K20
  - b. Original J37

## Independent variables

1. Case status (original cohort, expansion cohort, siblings)
2. Demographics
  - a. Attained age at questionnaire
    - i. Expansion cover page and A1
    - ii. Original cover page and A1
  - b. Sex
    - i. Expansion A2
    - ii. Original A2
  - c. Race/Ethnicity (Non-Hispanic Black, Non-Hispanic White, Hispanic, Asian, Other)
    - i. Expansion A5, A5a
    - ii. Original A4, A4a
  - d. Educational attainment (High school or less vs. some college)
    - i. Expansion R1-R4
    - ii. Original O1-O4
  - e. Insurance status (Yes or Canadian (original cohort only) vs. No)
    - i. Expansion U2
    - ii. Original Q2
3. Health habits
  - a. Smoking (never, past, current)
    - i. Expansion O1-O3
    - ii. Original N1a-d
  - b. Heavy Drinking (7+/week female, 14+/week male)
    - i. Expansion O9, O11-O14
    - ii. Original N3, N6, N7
  - c. Body mass index (underweight < 18.5 kg/m<sup>2</sup>, normal 18.5-24.9 kg/m<sup>2</sup>, overweight 25.0-29.9 kg/m<sup>2</sup>, obese 30+ kg/m<sup>2</sup>)
    - i. Expansion A3, A4
    - ii. Original A10, A11
4. Diagnosis
  - a. Cancer diagnosis
  - b. Age at diagnosis
  - c. Years from diagnosis
5. Treatment
  - a. Chemotherapy
    - i. Anthracycline
    - ii. Alkylating agent dose
    - iii. Glucocorticoids
      1. Dexamethasone
      2. Prednisone
    - iv. Vincristine
    - v. Methotrexate
    - vi. Bleomycin
  - b. Radiation
    - i. Brain
    - ii. Chest

- iii. Abdomen
- iv. Pelvis
- c. Surgery
  - i. Amputation lower extremity
  - ii. Amputation upper extremity
  - iii. Craniotomy
  - iv. Thoracotomy
  - v. Nephrectomy
  - vi. Cystectomy

### **Analysis**

**Aim 1.** The prevalence of each health status outcome in the combined expansion and original cohort and will be calculated and reported as number and percent among siblings and then by treatment era for survivors (1970-1979, 1980-1989, 1990-1999). Prevalence will be compared between siblings and survivors by treatment era in multivariable log binomial regression models adjusting for age, sex, and race/ethnicity. Intra-family correlation will be accounted for in these generalized estimating equations with robust variance estimates.

**Aim 2.** The potential differential effects of diagnosis or treatment on adverse health status outcomes will be evaluated in separate (diagnosis in one model, treatment in the other model) log-binomial models with interaction terms for diagnosis and era or interaction terms for treatment modality and era. Models will be adjusted for demographic characteristics, second malignant neoplasms (as a surrogate for additional treatment) and health habit variables (smoking, heavy drinking, body mass index) with p-values < 0.10 in univariate analysis. Intra-family correlation will be accounted for in these generalized estimating equations with robust variance estimates.

Table 1. Characteristics of the study population

	Siblings	1970-1979	1980-1989	1990-1999
Attained age at questionnaire				
Mean (SD)				
Median (Range)				
Age at diagnosis				
Mean (SD)				
Median (Range)				
Time since diagnosis				
Mean (SD)				
Median (Range)				
	N (%)	N (%)	N (%)	N (%)
Sex				
Female				
Male				
Race				
Asian				
Black (Non-Hispanic)				
Hispanic				
White (Non-Hispanic)				
Other				
Educational attainment				
High School or less				
High School, some college				
Insurance Status				
No				
Yes/Canadian				
Body mass index				
Underweight				
Normal				
Overweight				
Obese				
Smoking				
Current				
Past				
Never				
Heavy Drinking				
Yes				
No				

Table 2. Percentage of those with adverse health status by diagnosis and treatment era

		N	Poor general health N (row%)	Poor mental health N (row%)	Activity limitation N (row%)	Functional impairment N (row%)	Any adverse outcome N (row%)	Cancer related pain N (row%)	Cancer related anxiety N (row%)
Siblings	1970-79								
	1980-89								
	1990-99								
All diagnoses	1970-79								
	1980-89								
	1990-99								
Leukemia	1970-79								
	1980-89								
	1990-99								
CNS malignancy	1970-79								
	1980-89								
	1990-99								
Hodgkin lymphoma	1970-79								
	1980-89								
	1990-99								
Non-Hodgkin lymphoma	1970-79								
	1980-89								
	1990-99								
Wilms tumor	1970-79								
	1980-89								
	1990-99								
Neuroblastoma	1970-79								
	1980-89								
	1990-99								
Bone tumor	1970-79								
	1980-89								
	1990-99								
Soft tissue sarcoma	1970-79								
	1980-89								
	1990-99								

Table 3. Percentage of those with adverse health status by therapeutic modality and treatment era

		N	Poor general health N (row%)	Poor mental health N (row%)	Activity limitation N (row%)	Functional impairment N (row%)	Any adverse outcome N (row%)	Cancer related pain N (row%)	Cancer related anxiety N (row%)
Anthracyclines	1970-79								
	1980-89								
	1990-99								
Alkylating agents	1970-79								
	1980-89								
	1990-99								
Prednisone	1970-79								
	1980-89								
	1990-99								
Dexamethasone	1970-79								
	1980-89								
	1990-99								
Bleomycin	1970-79								

	1980-89								
	1990-99								
Vincristine	1970-79								
	1980-89								
	1990-99								
Methotrexate	1970-79								
	1980-89								
	1990-99								
Cranial radiation	1970-79								
	1980-89								
	1990-99								
Chest radiation	1970-79								
	1980-89								
	1990-99								
Abdominal radiation	1970-79								
	1980-89								
	1990-99								
Pelvic radiation	1970-79								
	1980-89								
	1990-99								
Amputation (lower)	1970-79								
	1980-89								
	1990-99								
Amputation (upper)	1970-79								
	1980-89								
	1990-99								
Craniotomy	1970-79								
	1980-89								
	1990-99								
Thoracotomy	1970-79								
	1980-89								
	1990-99								
Nephrectomy	1970-79								
	1980-89								
	1990-99								
Cystectomy	1970-79								
	1980-89								
	1990-99								

Table/Figure 4. Relative odds of adverse health status by diagnosis and treatment era

Table/Figure 5. Relative odds of adverse health status by treatment modality and treatment era

## References

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