Childhood Cancer Survivor Study
Analysis Concept Proposal

Title: Health outcomes among survivors of adolescent and young adult cancer in the Childhood Cancer Survivor Study.

Working Group and Investigators: CCSS Chronic Disease Working Group

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Background and Rationale:
Each year, over 69,000 adolescent and young adults (AYA) between the ages of 15 and 39 years are diagnosed with cancer in the United States (1). Although survival rates have improved more slowly in AYAs compared to younger and older patients with cancer (2), 80% of these patients still survive at least 5 years after their cancer diagnosis (3). As a result, AYAs make up a growing population of cancer survivors who have the potential of developing serious morbidity and premature mortality from their prior cancer treatments. In order to improve outcomes for patients and survivors of AYA cancer, research priorities were identified in 2006 by a Progress Review Group (PRG) supported by the National Cancer Institute (NCI) and the Lance Armstrong Foundation (LAF) (4). One particular priority from the PRG called for research aimed at improving the knowledge of long-term health outcomes related to AYA cancers and its associated therapies.

To date, our insight into the long-term outcomes of AYA cancer survivors is limited (5) and has been largely drawn from single cancer studies (Hodgkin lymphoma and testicular cancer survivors) (6-11) or extrapolated from research of survivors of childhood cancer (12). Despite the fact that there is not a cohort that spans the age range of the AYA population (15 to 39 years), the Childhood, Adolescent, and Young Adult Cancer Survivors (CAYACS) Research Program of British Columbia assembled a cohort of all 5-year survivors of cancer diagnosed before 25 years of age with a population sample comparison to begin to improve our understanding of long-term outcomes after AYA cancer (13). Recently, the CAYACS

Research Program described the increased risk of mortality and second malignant neoplasms (SMNs) among the young adults of this cohort, those diagnosed with their cancer between the ages of 20 to 24 years (14). Although the results are informative regarding these risks among the young adult survivors from British Columbia, the limited geographic boundaries and missing data on treatment exposure in more than 25% of the cases threatens the generalizability of these outcomes. Moreover, specifically looking into the long-term outcomes of those diagnosed with cancer between 20 to 24 years of age, rather than their entire AYA-aged cohort, those 15 to 24 years, reflects one of the many inherent challenges of AYA survivorship research.

The AYA population is represented by a unique spectrum of cancer types. More so, the distribution of cancer types dramatically changes as a function of age, such that the incidence pattern of cancer types among the younger AYAs (15 to 19 year olds) does not match the older-aged individuals or even among the 20+ year olds (3). As a result, there is little homogeneity of treatment exposure among the AYA population which has resulted in grouping the AYA patients into age-specific categories to assess outcomes, especially to identify the risk associated with therapy (15). The CCSS has been instrumental in demonstrating premature mortality (16), serious morbidity (17) and diminished health status (18) among the collective group of childhood and adolescent cancer survivors, which may ultimately foreshadow the possible long-term complications of survivors of AYA cancer (19). However, a separate analysis of AYAs within the CCSS may provide a clearer and more accurate representation of outcomes among the younger AYA population. As such, the goals of this proposal are to characterize the overall and cause-specific late mortality and describe the chronic health conditions of survivors of AYA cancer in the CCSS.

Specific aims:

1. To describe the overall and cause-specific late mortality of survivors of AYA cancers within the CCSS (as compared to age and sex matched general population data) and to determine the risk of host and treatment-related factors on these outcomes (AYA cancer within the CCSS are defined as those diagnosed with primary cancer ≥ 15 year of age).

2. To determine the prevalence and cumulative incidence of morbidities via self-reported chronic health conditions based on severity (grade) in survivors of AYA cancers, to assess the impact of host and treatment-related factors on these outcomes, and to determine the risk for these outcomes in comparison to sibling controls.

Analysis Framework:

- Subject population:
    - Mortality
        - *Mortality analysis*: non-Canadian individuals within the CCSS cohort with a primary cancer diagnosis between the ages of 15 to 21 years.
        - *Mortality modeling*: individuals within the CCSS cohort with a primary cancer diagnosis between the ages of 15 to 21 years who participated in the baseline questionnaire and who have full medical record abstraction accessible.
    - Morbidity
        - Individuals within the CCSS cohort with a primary cancer diagnosis between the ages of 15 to 21 years who completed the baseline questionnaire. Morbidity data will be utilized through the last questionnaire completed.
        - Nearest-age living siblings of the AYA survivors without a history of cancer who completed at least the baseline questionnaire will be similarly included.
- Study design: Cohort design
- Outcome of interest:
    - Aim 1: Mortality rates.
        - Overall
        - Cause-specific
            - Recurrence
            - Subsequent malignancy
            - Cardiac
            - Pulmonary
            - Other causes
            - External causes
    - Aim 2: Morbidity: Health outcomes in terms of specific chronic health conditions.
        - Graded based on severity (on the Common Terminology Criteria for Adverse Events – version 4.0)
            - Any condition
            - Severe conditions
            - Multiple conditions (≥2)
- Predictor of interest: age at time of diagnosis (AYA subjects at diagnosis: 15 - 21 years)
- Variables
    - Patient sex, race/ethnicity
    - Treatment era
    - Primary diagnosis
    - Treatment
        - No chemotherapy or radiation therapy
        - Chemotherapy
            - Type
                - Alkylators
                    - Score
                - Heavy Metals (Platinum based)
                - Anti-metabolites
                - Anthracyclines
                    - Score
                    - Cumulative doses

        - Plant Alkaloids
        - Epipodophyllotoxins
            - Cumulative doses
        - Bleomycin
            - Cumulative doses
    - Radiation
        - Any (Yes/No)
        - Brain (Yes/No)
        - Chest (Yes/No)
        - Spine (Yes/No)
        - Abdominal (Yes/No)
        - Pelvic (Yes/No)
        - Total body (Yes/No)
    - Surgery
    - Specific combinations
        - Chest radiation plus anthracycline
        - Chest radiation plus bleomycin
        - Abdominal or pelvic radiation plus an alkylating agent
- Statistical methods

a) Baseline characteristics

- Descriptive statistics will be used to report baseline characteristics among the AYA CCSS cohort participants and their siblings – Table 1.

b) Analysis of Specific Aim 1: Late mortality among 5-year survivors of AYA cancer

- Among the non-Canadian CCSS subjects, the vital status and cause of death will be collected up to the date of death or the date of censoring (December 31, 2007) from the U.S. National Death Index (NDI).
- Overall mortality
    - Standardized mortality ratios (SMRs) will be calculated using the expected number of deaths based on age-, year-, and sex-specific US mortality rates and the corresponding person-years at risk observed for the cohort of interest (survivors of AYA cancer). A 95% confidence interval (CI) of each SMR will be calculated on the basis of Poisson probability models – Table 2.
    - Analysis will be undertaken to assess the impact of sex, years since diagnosis and primary diagnosis on SMR – Table 2.
    - The method of Kaplan-Meier will estimate the probabilities of overall survival of the AYA cohort. This will be compared to the age- and sex-adjusted expected survival rates for the U.S. population - Figure 1a.
    - The Kaplan-Meier method will also estimate the probabilities of overall survival of the cohort of interest stratified by original cancer diagnosis – Figure 1b.
    - Kaplan-Meier curves for overall mortality will be generated for the AYA cohort conditioned on survival of 5, 10, 15, 20 years since the original diagnosis – Figure 1c.
- Cause-specific mortality
    - Cause of death will be collected from the NDI as above. The causes of death among the AYA survivors will be grouped into six categories: recurrence/progression, subsequent malignant neoplasms, cardiac,

pulmonary, external causes (accidents, suicide, poisoning, etc.), and other causes based on International Classification of Diseases (ICD) codes – Table 2.

- Cumulative incidence will be estimated for cause-specific mortality (recurrence, nonrecurrence/nonexternal, external), treating "other" causes of death as competing risks – Figure 1d.
- SMRs will be calculated for each cause-specific death among survivors of AYA cancers in the CCSS excluding deaths attributed to recurrence or progression of the primary malignancy. The impact of sex and primary diagnosis on the SMR for each cause-specific death will also be illustrated – Table 2.
- Multivariable Poisson regression analysis will be used to assess the effects of several independent factors on cause-specific late mortality not due to recurrence. These will include the effects of treatment (radiation exposure; levels of alkylating agents, anthracyclines, epipodophyloltoxins, and bleomycin), gender, year of diagnosis, and survival since diagnosis – Table 3.

c) *Analysis of Specific Aim 2: Chronic health conditions among 5-year survivors of AYA cancer*

- Analysis will be performed on those participants who are survivors of an AYA cancer who completed at least the baseline questionnaire on self-reported health conditions.
- Morbidity will be assessed by self-reported chronic health conditions from the baseline and any subsequent follow-up questionnaires. The conditions will be scored based on severity according to the Common Terminology Criteria for Adverse Events (version 4.0), graded 1 through 5 (1: mild – 5: fatal) – as previously described (17, Armstrong-in preparation).
- Cumulative incidence of a chronic health condition will be determined for survivors of AYA cancer from the CCSS, as well as for their sibling controls. This analysis will further assess the cumulative incidence among the two groups of having any condition (grades 1 through 4); severe or life-threatening conditions (grade 3 or 4); and multiple conditions - Table 4.
- The risk associated with treatment (chemotherapy, radiation, and surgery) will be portrayed as relative risks with 95% CI among AYA survivors as compared to their sibling controls as estimated by Cox regression, using age as the time scale – Table 5. A separate regression analysis will demonstrate the risk associated with the initial diagnosis among AYA survivors as compared their sibling controls – Table 5.
- The relative risk and 95% CI of developing a specific severe (grade 3 or 4) chronic health condition will be determined for AYA survivors as compared to their sibling controls as estimated by Cox regression, using age as the time scale – Table 5.
- Calculation of cumulative incidence of a chronic health condition will be evaluated from entry into the cohort (5 years post diagnosis), treating death as a competing event. We would like to examine the total AYA survivors collectively and then according to each specific primary diagnosis – Figure 2. We will explore the utility of evaluating cumulative incidence curves as a function of age rather than time since diagnosis.
- A multivariable regression analysis will determine predictors of having a grade 3, 4, or 5 condition among survivors of AYA cancer adjusted for the type of cancer, race/ethnicity, and age at the time of study.

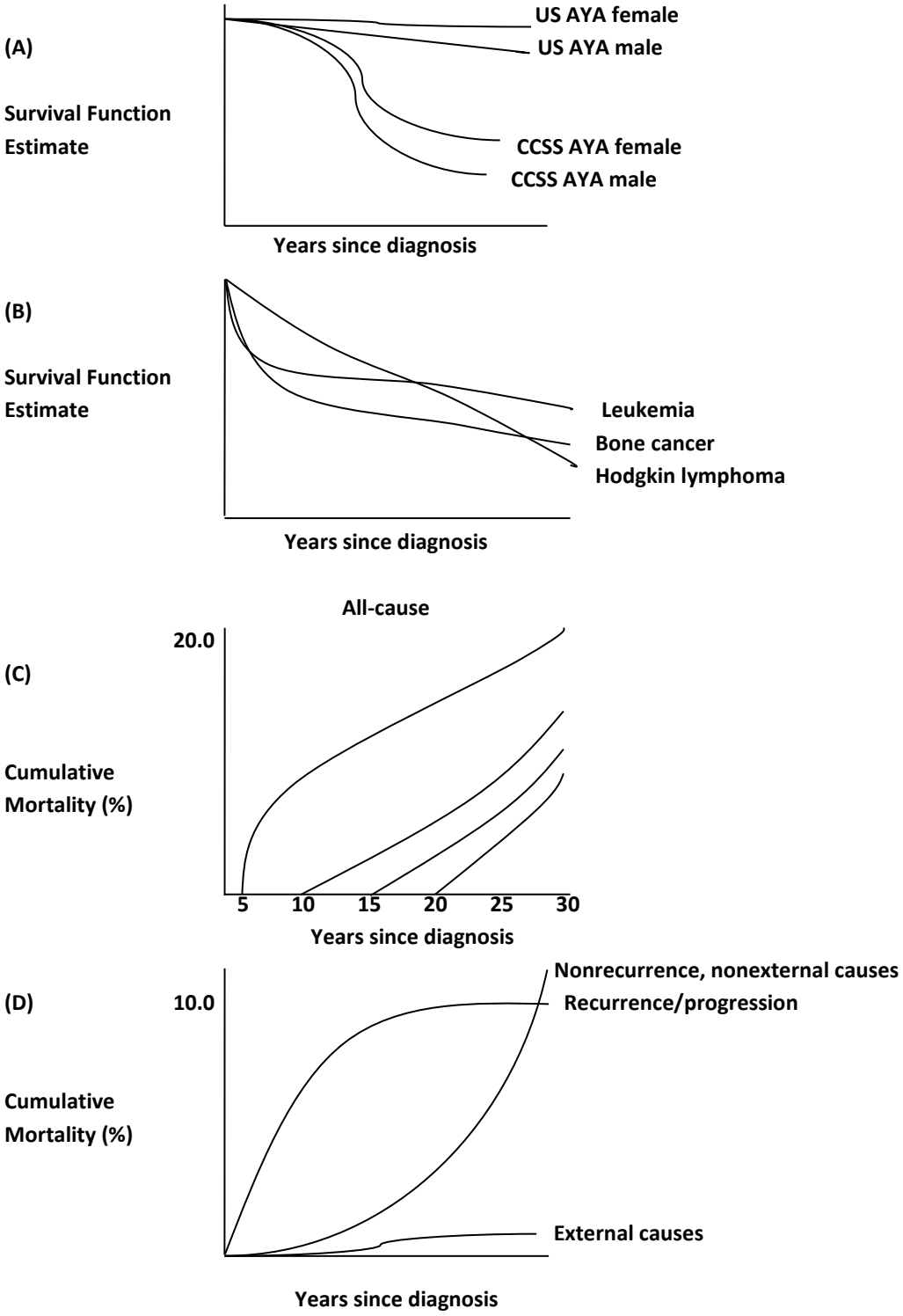
Table 1. Characteristics of adolescent and young adult survivors from the CCSS and siblings.

Characteristic	AYA Survivors	AYA Siblings	P value
Participants – No.			
Sex - No. (%)			
Male			
Female			
Race/Ethnicity - No. (%)			
White, non-Hispanic			
Other			
Treatment era			
1970 – 1979			
1980 – 1986			
Primary dx - No. (%)			
Hodgkin's disease			
Non-Hodgkin's lymphoma			
Leukemia			
-ALL			
-AML			
-Other leukemia			
Bone tumors			
-Ewing sarcoma			
-Osteosarcoma			
-Other bone tumors			
CNS tumor			
-Astrocytoma			
-Medulloblastoma, PNET			
-Other CNS malignancy			
Soft tissue sarcoma			
Kidney tumors			
Neuroblastoma			
Education – No. (%)			
Did not complete high school			
High school graduate			
Beyond high school graduate			
Household income – No. (%)			
<$20,000/year			
≥$20,000/year			
Health insurance – No. (%)			
No			
Yes or Canadian resident			
Age at interview - year			
Mean			
Range			

Table 2. Overall and Cause-Specific Standardized Mortality Ratios (SMRs) or Frequency of Deaths in 5-year Survivors of AYA cancer

Characteristic	Overall			SMN			Cardiac			Pulmonary			Other			External			Recurrence	Unknown
	# dead (%)	SMR	95% CI	# dead (%)	SMR	95% CI	# dead (%)	SMR	95% CI	# dead (%)	SMR	95% CI	# dead (%)	SMR	95% CI	# dead (%)	SMR	95% CI	# dead (%)	# dead (%)
Among all AYA patients (N=2472)																				
Sex																				
Male																				
Female																				
Survival after diagnosis, y																				
5-9																				
10-19																				
20-29																				
30+																				
Primary dx																				
Hodgkin's disease																				
Non-Hodgkin's lymphoma																				
Leukemia																				
-ALL																				
-AML																				
-Other																				
Bone tumors																				
-Ewings sarcoma																				
-Osteosarc																				
-Other																				
CNS tumor																				
-Astrocytoma																				
-Medullo-blastoma, PNET																				
-Other CNS																				
Soft tissue sarcoma																				
Kidney tumors																				
Neuro-blastoma																				

Figure 1. SURVIVAL AND MORTALITY CURVES



(A) Overall survival by sex of AYAs in the CCSS and expected survival based on age-, year-, and sex-matched US population mortality rates.
(B) Overall survival of AYA survivors based on original cancer diagnosis.
(C) Overall cumulative mortality of AYAs in the CCSS cohort, conditioned on survival of 5, 10, 15, and 20 years since the original cancer diagnosis.
(D) Cumulative cause-specific mortality.

Table 3. Relative Risk of Mortality with 95% CI due to SMN, Cardiac causes, Pulmonary causes, & Other causes.

Characteristic	SMN			Cardiac			Pulmonary			Other		
	RR	**95% CI**	***P***	**RR**	**95% CI**	***P***	**RR**	**95% CI**	***P***	**RR**	**95% CI**	***P***
Sex												
Male												
Female												
Year of diagnosis												
1970-1973												
1974-1977												
1978-1981												
1982-1986												
Survival after diagnosis, y												
5-9												
10-19												
20-29												
30+												
Radiation												
Any irradiation												
Brain irradiation												
Chest irradiation												
Spine irradiation												
Abdominal irradiation												
Pelvic irradiation												
Total body irradiation												
Alkylating agent score												
Not exposed												
1-2												
3-4												
≥5												
Anthracycline												
Not exposed												
1-100 mg/m^2												
101-250 mg/m^2												
251-400 mg/m^2												
≥401 mg/m^2												
Epipodophyllotoxin												
Not exposed												
1-982 mg/m^2												
983-4108 mg/m^2												
≥4109 mg/m^2												
Bleomycin												
Not exposed												
1-59 mg/m^2												
60-119 mg/m^2												
≥120 mg/m^2												

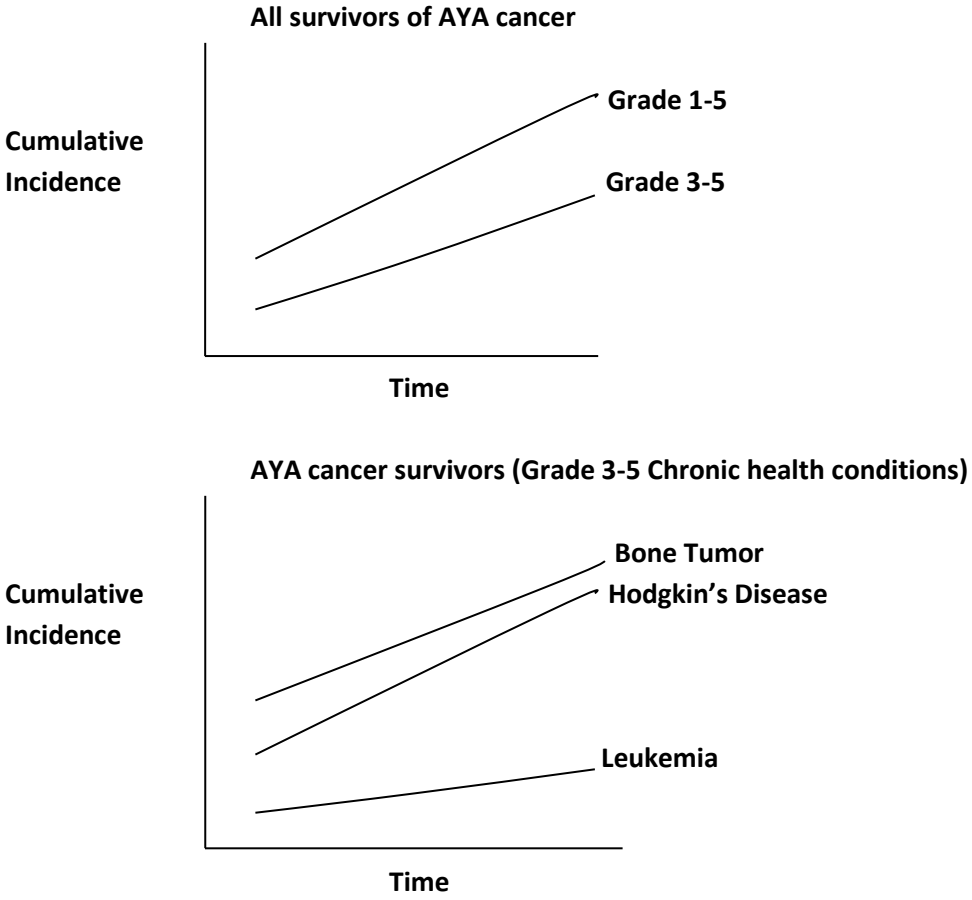
Table 4. Chronic health condition of survivors from the CCSS cohort of those treated ≥ 15 years of age (AYA) and siblings – according to severity score.

Health Condition	AYA Survivors (N = ***)	AYA Siblings (N = ***)
	No. (%)	
No condition		
Grade 1 (mild)		
Grade 2 (moderate)		
Grade 3 (severe)		
Grade 4 (life-threatening/disabling)		
Grade 5 (fatal)		
Any condition Grades 1-4 Grade 3 or 4		
Multiple health conditions ≥2 ≥3		

Table 5. Relative risk of chronic health conditions among survivors treated as an AYA, according to tumor type and treatment, as compared to their siblings.

	AYA Survivors						
Cancer diagnosis or Treatment exposure	**Any chronic health condition (Grade 1-4)**	**Severe chronic health condition (Grade 3 or 4)**	**≥2 chronic health condition**	**Cardiovascular (Grade 3 or 4)**	**Pulmonary (Grade 3 or 4)**	**Endocrine (Grade 3 or 4)**	**Subsequent Malignant Neoplasm (Grade 3 or 4)**
	Relative Risk (95% Confidence Interval)						
AYA Siblings	**1.0**	**1.0**	**1.0**	**1.0**	**1.0**	**1.0**	**1.0**
All AYA Survivors							
Primary dx							
Hodgkin's disease							
Leukemia							
Bone tumors							
Non-Hodgkin's lymphoma							
CNS tumor							
Soft tissue sarcoma							
Wilms' tumor							
Neuroblastoma							
No chemotherapy or radiation							
Chemotherapy							
Any							
Alkylating agent							
Platinum based							
Anti-metabolites							
Anthracyclines							
Plant Alkaloids							
Bleomycin							
Radiation therapy							
Any irradiation							
Brain irradiation							
Chest irradiation							
Spine irradiation							
Abdominal irrad.							
Pelvic irradiation							
Total body irrad.							
Surgery							
Any							
Specific combo							
Chest RT+anthra.							
Chest RT+bleomyc.							
Abd/pelvic RT+alk							

Figure 2. Cumulative incidence of chronic health conditions among cancer survivors treated as AYAs.



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