CHILDHOOD CANCER SURVIVOR STUDY
Analysis Concept Proposal

1. STUDY TITLE: Longitudinal Assessment of Chronic Health Conditions: The Aging of Childhood Cancer Survivors

2. WORKING GROUP AND INVESTIGATORS: This proposed publication will be within the Chronic Disease Working Group. Proposed Investigators will include:

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3. BACKGROUND AND RATIONALE

While numerous research studies have identified, defined and investigated risk factors for individual adverse chronic health conditions, summarizing the full spectrum of health outcomes among survivors of childhood cancer has been difficult. The Childhood Cancer Survivor Study, with its large population completing a self-report of health outcomes provided an ideal population for such and endeavor. Using the Common Terminology Criteria for Adverse Events by the NCI, in 2006 Oeffinger et. al. published the most comprehensive assessment of chronic health outcomes to date.[1-2] They identified that at a mean age of 26 years 62% of the 10,397 survivors had at least on adverse health condition and that 27% had a severe or life-threatening condition. Compared to siblings the relative risk of a severe, disabling, or life-threatening medical condition was 8.2. The cumulative incidence of these conditions was 73.4% and 42.4% respectively.

Data from the follow-up 1 (2000) questionnaire and now the Follow-Up 2007 questionnaire, with an average of 10 years additional of prospective follow-up from baseline, provides the opportunity to advance our understating of aging among adulthood among survivors of childhood cancer. This analysis proposes to update cumulative incidence of these events, while identifying longitudinal change in severity and incidence over time. In addition, this analysis will attempt to identify key outcomes that may have marked increase in incidence during the fourth decade of life (i.e. joint replacement, heart attack, stroke, renal failure, carcinomas, etc) and will quantify the occurrence of multiple chronic health conditions acknowledging that survivors may have a growing burden of multiple conditions with time.

As this concept proposes novel analysis of longitudinal data, the authors (Armstrong, Oeffinger, Robison, Leisenring and Yasui) met in February 2010 to discuss statistical strategies for evaluations of the proposed outcomes. This concept represents the final approaches put forward as a result of that meeting.

4. SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES:

Aim 1 Determine how the cumulative incidence (vs. siblings) of chronic health conditions has changed with the aging of the CCSS population through middle adulthood.

Hypothesis: Survivors will demonstrate a steeper increase in the cumulative incidence of health conditions (any, grade 3-5, and multiple conditions) with increasing age as compared to siblings.

Aim 2 Assess the impact of primary cancer diagnosis and treatment factors on risk of chronic health conditions as compared to siblings.

Hypothesis: Children with CNS tumors and Bone tumors, as well as those who received RT (CNS, chest, or abdominal/pelvic) or Chemotherapy (anthracyclines or alkylating agents) will be at increased risk for chronic health conditions compared to siblings.

Aim 3 Identify specific health conditions (e.g. joint replacement, stroke, renal failure, etc.) with significant increase in incidence during middle adulthood (i.e., 40 - 59 years) as compared to siblings.

Hypothesis: Certain conditions, such as joint replacement, stroke, renal failure, congestive heart failure, and myocardial infarction, will demonstrate significant increase in cumulative incidence during the age 40-59 years as compared to siblings.

Aim 4 Quantify the occurrence of multiple chronic health conditions as these conditions accumulate with increasing age.

Hypothesis: With increasing age, survivors will continue to accumulate increasing numbers of new health conditions (multiple chronic health conditions) compared to siblings.

5. ANALYSIS FRAMEWORK:

a. Subject population: All survivors (including those <18 at baseline) in the CCSS cohort who participated in the baseline evaluation.

b. Comparison group: Siblings who completed the baseline study.

c. Outcomes of interest: Self-report of chronic medical conditions from the baseline, FU #1 (2000) and FU2007 questionnaires (prevalence) as well as age of onset of conditions necessary for calculation of cumulative incidence. For severity, the Common Terminology for Adverse Events (version 4.0) will be applied to grade conditions as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening or disabling (grade 4), or death (grade 5). New conditions since baseline will require scoring by the study PI who, when information is not sufficient to accurately classify a condition will default to the lesser of two scores in question. In addition, the PI with the statistical team will review all questionnaires and reconcile questions that may have been modified from the baseline to the follow-up surveys to assure continuity of data collection. Maximum grade and minimum age at first occurrence will be utilized for each unique condition.

d. Exploratory variables of interest:

Socio-demographics (For Table 1)
- Gender
- Race/ethnicity
- Age at interview
- Inactive lifestyle (defined as no leisure-time physical activity in the month preceding the completion of the 2007 questionnaire).

Cancer diagnosis
Cancer treatment
Radiation
- Any
- Brain
- Chest
- Abdominal
- Pelvic
- TBI
- None

Chemotherapy
- Any
- Alkylating Agents (yes/no and by alkylating agent score)
- Anthracyclines (yes/no and by cumulative dose category)
- Cisplatin

Surgery
- Splenectomy
- Nephrectomy

Specific Combinations
- No Chemo or RT
- Chest RT + Bleomycin
- Chest RT + Anthracycline
- Chest RT + Abd or pelvic RT
- Anthracyline + alkylating agent
- Abd or pelvic RT + alkylating agent

e. Statistical analysis

Aim 1.

We will examine three primary outcomes, for survivors and siblings, as utilized in the original manuscript: any condition (grades 1-5), severe or life-threatening, including death (grades 3-5), and multiple conditions (≥2).

Cumulative incidence for these three major outcomes will be evaluated. One emphasis of this manuscript will be on impact of aging on this cohort, so we plan calculate cumulative incidence curves using age as the time scale. For this to work in our cohort, we will need to begin the curves at age 26 (the oldest age at which any subject enters the CCSS cohort – 5 years after diagnosis), among subjects who survived to age 26. The curves will utilize age at first occurrence of the outcome of interest, after age 26, and treat death as a competing risk event. Irreversible conditions that occurred before age 26 will be included as prevalent at age 26. Descriptive information about reported conditions and cause of death will be provided about subjects who do not survive to age 26. Cumulative incidence curves will extend those in the original manuscript by utilizing information from the most recent follow-up survey (2000 or 2007) completed. We will also calculate more traditional cumulative incidence curves using time since diagnosis as the time scale, beginning at 5 years post diagnosis, for comparative purposes, but expect to focus our report on age-dependent probabilities of events.

We will also examine a graphical comparison of health conditions from the baseline data vs. 2007 (original curves from NEJM and then updated with 2007) simply to see how much change has occurred with follow-up utilizing the original methods of the NEJM paper.

Comparisons between survivors and siblings will be carried out using Cox regression analyses with age as the time scale, entry into analysis at age at 5 years after diagnosis entry to cohort (Table 2). We will also examine time from diagnosis as time scale to assure this is the best approach. Hazard ratios with 95% confidence intervals for the comparison of survivor vs. sibling risks of each type of outcome will be evaluated, looking specifically at the time-dependence of the Hazard Ratio in models to determine how the comparison to siblings is evolving with either advancing age or increasing time since diagnosis. Cox regression analyses will include only subjects who have not yet had the outcome of interest at 5 years post-diagnosis. In order to describe the events occurring prior to 5 years post-diagnosis, we will also examine age and gender adjusted prevalence ratios comparing survivors to siblings.

Aim 2.

Cox regression models will be utilized to evaluate adjusted hazard ratios for subgroups of the survivor population defined by primary diagnosis and treatment factors as compared to siblings. (Table 3).

Aim 3.

Similar cumulative incidence and Cox regression age-dependent analyses will be carried out to evaluate whether there is a marked increase in the risks of specific health conditions (joint replacement, stroke, renal failure, myocardial infarction and congestive heart failure) with age, as compared to siblings. We hypothesize those listed above will be most elevated, but will examine tabulations of all conditions graded to identify any other surprisingly elevated event rates.

If such conditions are identified, we would plan to develop conditional cumulative incidence curves, illustrating new onset of chronic conditions (among those who did not have the specified condition) by decade of life, which would provide insight into development of new chronic conditions that are occurring with advancing age.

Aim 4.

Within each organ system, specific classes of conditions are defined (see rows of Appendix E of original NEJM article). Multiple chronic health conditions within each of these categories, as well as across all categories, will be assessed by looking at onset of multiple (≥2, ≥3 and ≥4 etc) health conditions. Similar to analyses described for Aims 1 and 2, age will be utilized as the time-scale to evaluate impact of increasing age on cumulative incidence and hazard ratios, compared to siblings.

Special considerations:

If a subject died between the baseline and the FU2007 evaluation there will be a gap between the death and the last questionnaire completed, during which we will not have information about whether chronic conditions occurred, since proxies did not answer the FU2007 questionnaire for deceased subjects (they did for baseline, however). We have discussed utilizing death certificate data to ascertain grade 5 conditions, but would not have similar information available for grades 1-4 conditions. As a result, we propose to take the most conservative approach,

assuming no chronic conditions occur in this time gap, and allowing follow-up time to terminate with the competing risk event of death. The alternative, censoring at last questionnaire would assume chronic condition could still occur at a later time, and inflate future incidence estimates.

6. TABLES/FIGURES:

Table 1. Demographic and cancer-related characteristics of participants

	Survivors At Follow-up (n=)	Siblings At Follow-up (n=)
Characteristic		
Deceased		
Sex		
Male		
Female		
Race/ethnicity		
Non-Hispanic white		
Other		
Education		
Did not complete High School		
High School graduate only		
High School graduate + some college		
Household income		
<$20,000		
≥$20,000		
Health Insurance		
Yes		
No		
Cancer diagnosis		
Leukemia		
CNS tumor		
Hodgkin lymphoma		
Non-Hodgkin lymphoma		
Wilms tumor		
Neuroblastoma		
Sarcoma (soft tissue)		
Bone Tumor		
Cancer treatment		
No Chemo or RT		
Chemo		
Any		
Alkylating agent		
Anthracycline		
Other		
RT		
Any		
Brain		
Chest		
Abd or pelvic		
Missing		
Age at interview (years)		
Mean		
Range		
Interval between Cancer diagnosis and study		
Mean		

Range		

Table 2. Adjusted Age-specific hazard ratios for chronic health conditions as compared to same age siblings

	Grade 1-5	Grade 3-5	≥2 conditions
Siblings	1.0	1.0	1.0
Current Age*			
5-20			
21-30			
31-40			
41-50			
50+			

* Each column represents a separate model for the outcome specified, evaluating time-dependent , age-specific hazard ratios for the comparison to siblings. Models adjusted for sex, race or ethnic group.
Note: Age categories may vary in actual analyses depending on frequency of specific outcomes and patterns observed.

Table 3. Adjusted Hazard Ratios for chronic health conditions according to type of malignancy and treatment, compared to siblings.

	Grade 1-5	Grade 3-5	≥2 conditions
Siblings	1.0	1.0	1.0
Cancer diagnosis			
Leukemia			
CNS tumor			
Hodgkin lymphoma			
Non-Hodgkin lymphoma			
Wilms tumor			
Neuroblastoma			
Sarcoma (soft tissue)			
Bone Tumor			
Cancer treatment			
No Chemo or RT			
Chemo			
Any			
Alkylating agent			
Anthracycline			
Other			
RT			
Any			
Brain			
Chest			
Abd or pelvic			

- Each cell of the table represents a separate model for the column specific outcome and for the specified group of survivors (row) compared to siblings, adjusted for sex, race or ethnic group and using age in the time scale for the model.

Other Potential Tables: Similar as Tables 2 and 3 for specific conditions and/or higher numbers of multiple conditions.

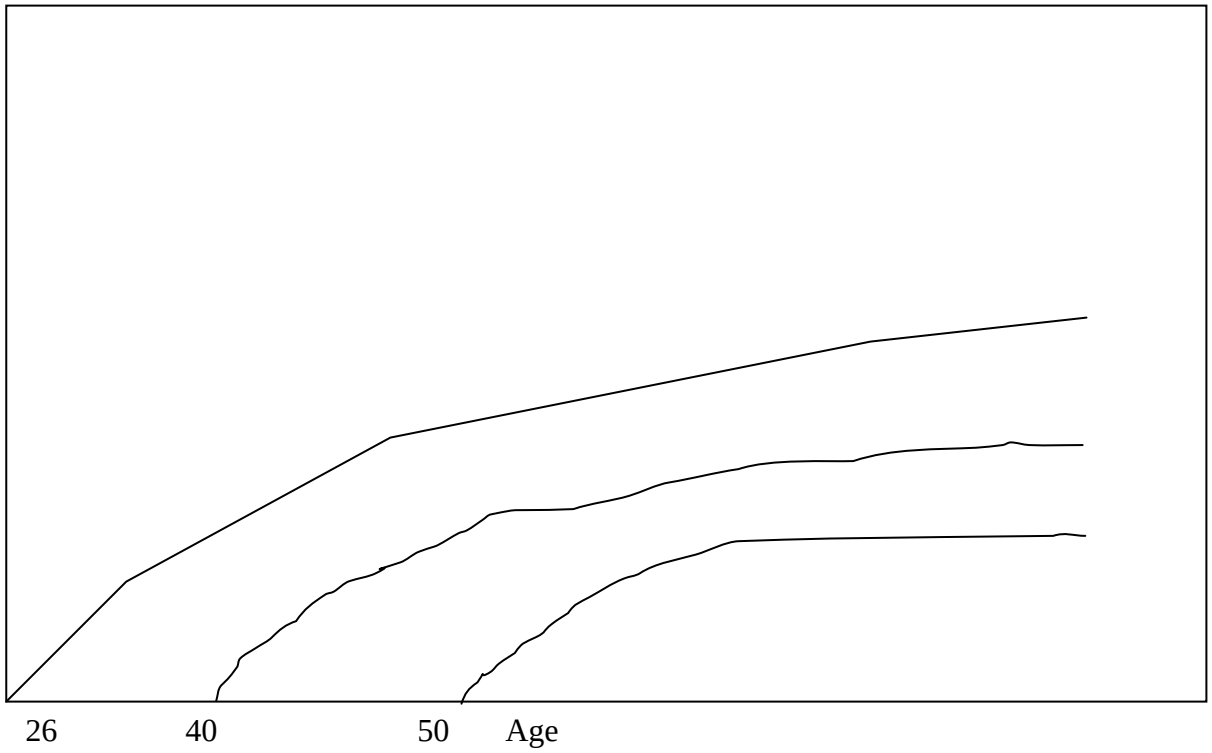
Figures:

-Cumulative incidence curves for grades 1-5, 3-5 and >2 conditions for survivors and siblings (3 figures, 2 lines per Figure)

Additional Figures, depending on results:

-Cumulative incidence of specific Conditions (Aim 2).
-Conditional cumulative incidence curves illustrating onset of specific conditions with age, and/or onset of multiple conditions with advancing age.

Example Conditional cumulative incidence curve for probability of events among subjects not having event yet at specific ages (e.g. 26, 40, 50).



-Scatter plot of the number of grade 3-5 conditions (y-axis) by age at diagnosis (x-axis, Aim 4)

REFERENCES

1. Oeffinger KC, Mertens AC, Sklar CA, et al: Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 355:1572-82, 2006

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3. Zucchi R, Danesi R: Cardiac toxicity of antineoplastic anthracyclines. Curr Med Chem Anticancer Agents 3:151-71, 2003