CCSS Analysis Concept Proposal
26 April 2013

Study Title:
Longitudinal Analysis of Pulmonary Complications in Survivors of Childhood Cancer

Working Groups:
Chronic Disease – Primary
Epidemiology/Biostatistics – Secondary
Second Malignancy - Additional

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Background:

Cooperative group protocols, multi-modal and risk-based therapies, and pharmacologic advances have contributed to consistent improvements in survival rates for children diagnosed with a malignancy. While varied across diagnostic groups, overall 5-year survival rates now approach 80% and estimates have suggested over 325,000 survivors of childhood cancer alive in the United States today.[1] With these improvements, research efforts have increasingly focused on the late sequelae of cancer therapy in an effort to better characterize and understand the risks to long-term health and the need for appropriate risk-based screening and counseling of these young adults. Furthermore, psychosocial sequelae, social habits, and the overall aging process may significantly further impact the long-term health outcomes of this growing population of adults formerly treated for a pediatric cancer.

Despite improved cancer survival rates, late mortality for childhood cancer survivors exceeds the expected rate compared to the age- gender-matched U.S. population.[2] Overall cumulative mortality at 30 years from diagnosis has been estimated at 18.1% (17.3-18.9%).[3] Early CCSS data suggested recurrence or disease progression as the leading cause of death, however, subsequent analysis has shown this to plateau while deaths attributed to non-recurrence, non-external causes continue to increase.[3] Mortality from non-recurrence/non-external causes may potentially increase faster with further follow-up, having increased from 2.0 to 7.0% during the period 15-30 years from diagnosis. The leading causes of death are subsequent neoplasms

(Standardized Mortality Ratio (SMR) 15.2, 95% CI 13.9-16.6) followed by cardiac (SMR 7.0, 95% CI 5.9-8.2) and pulmonary (SMR 8.8, 95% CI 6.8-11.2) events.[2-4]

Late pulmonary toxicity following chemotherapy and/or radiation therapy has been reported by a number of investigators and appears to be highest among survivors of HL, leukemia, rhabdomyosarcoma, and stem cell transplant.[5] A recent systematic review reported significant associations with exposure to radiation, alkylating agents, bleomycin, hematopoietic stem cell transplant (HSCT), and thoracic surgery.[6] Using the CCSS cohort, Mertens et al. identified numerous late pulmonary toxicities occurring ≥ 5 years from diagnosis, such as significant associations between pulmonary fibrosis and radiation exposure (RR 4.3, 95% CI 2.9-6.6) and supplemental O_2 use and radiation (1.8, 95% CI 1.5-2.2), BCNU 1.4, 95% CI 1.0-2.0), bleomycin (1.7, 95% CI 1.2-2.3), busulfan (3.2, 95% CI 1.5-7.0), CCNU (2.1, 95% CI 1.4-2.9), and cyclophosphamide (1.5, 95% CI 1.3-1.0) exposures.[7] Additionally, an increased risk for second neoplasms of the lung and bronchus has been identified with a standardized incidence ratio of 3.4 (95% 1.9-6.1).[8] Perhaps more important is the continued increase in adverse pulmonary outcomes with time. The cumulative incidence for fibrosis, chronic cough, pleurisy, and exercise-induced dyspnea are increased at 25 years from diagnosis among survivors treated with chemotherapy alone and radiation alone (Figure 1 below) and others have reported an interaction between therapeutic modalities. The lack of any evidence of a plateau in these cumulative incidence curves suggests the need for further follow-up with advancing age and time from diagnosis.

While survivors of pulmonary toxic therapies are frequently asymptomatic, functional measures of pulmonary capacity decrease with time, potentially leading to impaired exercise capacity and contributing to a sedentary lifestyle, further impairing overall health among survivors of childhood cancer. Pulmonary function impairment has been reported in up to 44% of childhood cancer survivors that received known pulmonary toxic therapy at a median of 18 years after diagnosis.[9] Bleomycin itself has been associated with spirometry abnormalities in 41% of patients including both obstructive and restrictive defects as well as diffusion capacity abnormalities in 19% of patients who received a median dose of 60 units/m^2.[10] Radiation involving the chest has been associated with obstructive lung disease in 39%, restrictive lung disease in 15%, hyperinflation in 29%, and abnormal diffusion capacity in 14% of childhood cancer survivors.[11] Additionally, individual host factors such as genetics, smoking, and physical inactivity are known to adversely affect lung function and be associated with pulmonary disease in a non-cancer population.[12] These factors may further compound pulmonary toxicity after cancer therapy.

Understanding the specific long-term risks to respiratory health for survivors of childhood cancer will help refine guidelines for appropriate screening and surveillance, promote health counseling, and, hopefully, contribute to the design and testing of targeted interventions to decrease respiratory morbidity and mortality for these survivors.

Specific Aims:

1.) Describe the prevalence, cumulative incidence, and relative risks compared to sibling controls of adverse pulmonary outcomes (chronic cough, need for extra oxygen, emphysema, lung fibrosis, and/or bronchogenic carcinoma, etc.) and pulmonary-related mortality among childhood cancer survivors and assess longitudinal changes over time in this population with advancing age.

   Hypothesis: The prevalence and cumulative incidence of pulmonary complications and pulmonary-related mortality will be increased in survivors compared to the sibling control group.

   Hypothesis: The risk of a pulmonary-related death will be increased compared to the age-, year-, and gender-specific U.S. population.

   Hypothesis: The incidence of adverse pulmonary outcomes will increase more quickly with advancing age among cancer survivors compared to controls.

   Hypothesis: The relative risk of adverse pulmonary outcomes will be elevated among cancer survivors compared to the sibling control group.

2.) Assess the impact of cancer treatment-related factors (chemotherapy and/or chest-directed radiation therapy) on late adverse pulmonary outcomes among childhood cancer survivors.

   Hypothesis: Pulmonary complications will significantly associated with a history of chest directed radiation therapy and/or chemotherapy exposure (particularly to alkylating agents and anti-tumor antibiotics) and/or thoracic surgery.

3.) Assess the association between pulmonary outcomes and physical performance among cancer survivors exposed to pulmonary toxic therapies.

   Hypothesis: Adverse pulmonary outcomes will be significantly associated with decreased physical performance.

Methods:

Outcomes of interest –
   a. Bronchitis
   b. Pleurisy
   c. Asthma
   d. Abnormal chest wall
   e. Chronic cough
   f. Need for extra oxygen
   g. Recurrent pneumonia
   h. Emphysema
   i. Lung fibrosis

j. Breathing problems
k. Bronchoscopy
l. Lung surgery
m. Lung transplant
n. Second malignant neoplasm of the lung or bronchus

	Baseline	F/U 2000	F/U 2007
Conditions	G1, G5-G13, I19-20,24, section K	9, 11a, 11e-11m, section 17	H1-H8, J23, J26, section P

Pulmonary related mortality – NDI data.

Physical performance - N14 (baseline) and N26 (Follow-Up 2007). (Scored per Ness et al. Annals of Internal Medicine, 2005;143:639-647)

Subject population –

Inclusion Criteria:
1.) CCSS survivors or siblings reporting a pulmonary event
2.) Completed baseline questionnaire, Follow-Up 2003, and/or Follow-Up 2007
3.) Consented to medical record abstraction

Exclusion Criteria:
1.) Experienced pulmonary event prior to cohort entry (i.e. childhood asthma)

Outcome data will include responses from the baseline, Follow-Up 2000, and Follow-Up 2007 questionnaires, with data included from any questionnaires to which a subject responded. We will compare the baseline status of participants who responded to the 2003 and/or 2007 questionnaires to those who did not respond to the 2003 and/or 2007 questionnaires to assess the extent to which our results might be biased due to selective attrition or death.

Explanatory variables –

Demographics for both survivors and siblings
        Gender
        Race/ethnicity
        Age at questionnaire
        BMI

Demographics/Treatment Variables for survivors
        Age at diagnosis
        Cancer diagnosis
        Radiation – yes/no (with radiation dose and location)
                Chest (i.e. mantle, whole or partial lung), spine, and total body irradiation
                Scatter from neck or abdomen in secondary analysis

Chemotherapy – yes/no (with cumulative doses)
Busulfan, Bleomycin, BCNU, CCNU, Cyclophosphamide, Ifosfamide, Methotrexate, Cisplatin, and additional agents where sufficient numbers of cases were exposed
Surgery of spine, lung or chest wall – yes/no
BMT – yes/no

Associated factors:
Smoking/tobacco status categorized as yes, prior, or none
History of grades 2-4 congestive heart failure prior to pulmonary outcomes as categorized by the master matrix[13].

Statistics –

Descriptive statistics including means, medians, standard deviations, ranges, frequencies and proportions will be used to summarize characteristics of the study population demographics, treatments and associated measurements.

Aim 1 –

Cumulative Incidence. Self-reported information from all surveys will be accumulated so that age at first occurrence of each primary outcome will be available for each subject up to their last contact time. When age of onset is not reported, multiple-imputation methodology for event-time imputations will be utilized. Counts of incident events will be reported as raw numbers and also as rates per 1000 person-years as was done previously.[7] Incidence rates will also be shown within different age bands to demonstrate the changes as the population ages. Cumulative incidence curves will be evaluated for each condition, treating death from other causes as a competing risk event.

Excess mortality. Deaths due to pulmonary complications will be confirmed through the national death index. Standardized Mortality Ratios (SMRs) will be calculated compared to the US population using age, sex, and calendar year rates from the National Center for Health Statistics to evaluate expected numbers of deaths.

Relative Risk. Cox proportional hazards models will be used to estimate the hazard ratios and 95% confidence intervals for developing pulmonary conditions as compared between survivors and siblings. Models will be adjusted for explanatory variables listed above. Age will be utilized as the time scale for Cox proportional hazards models, to adequately adjust for the age dependence of these outcomes.   The proportional hazards assumption will be tested to evaluate whether risk of pulmonary conditions is increasing at a different rate for survivors than it is for siblings. If so, models allowing constant hazard ratios within age intervals will be fit and results reported.   Correlations between survivors and siblings of the same family will be taken into account using sandwich standard error estimates.

Aim 2 –

Associations. Among survivors, Cox proportional hazard models will also be used to evaluate the late effects of specific treatments, with adjustments for explanatory variables listed above. The data will also be reported within diagnostic groups. Full multivariable models assessing treatment effects will be built for each outcome having enough events to support this, including both treatment and adjustment factors that are either significant or which markedly modify the effects of another factor in the model.

Aim 3 –

Physical Performance. Generalized linear models will be used with the binary outcome of having physical performance limitations to evaluate relative risk (RR) estimates for the probability of having performance limitations for survivors with adverse pulmonary outcomes versus survivors without adverse pulmonary outcomes. Models will be adjusted for explanatory variables listed above. Each subject will contribute a record for the binary performance limitation outcome at baseline and/or at FU2007. Having a prior pulmonary condition would be a covariate at each time point, along with other covariates, like age, gender etc. Generalized estimating equation methodology will be used to account for intra-subject correlation due to multiple observations per person.

Sample tables and figures –

Table 1 – Demographics of Survivors and Sibling Cohorts
Table 2 – Number and Rate of Pulmonary Conditions
Table 3 – Relative Risk of Pulmonary Conditions Compared with Siblings
Table 4 – Relative Risk of Treatment Factors by Pulmonary Conditions compared by treatment.
Table 5 – Physical Performance according to Pulmonary Outcomes
Figure 1 – Cumulative Incidence Curves (similar to first report)

Table 1:

Characteristic	Number of Patients (%)	
	Survivor Cohort	Sibling Cohort
Total		
Gender		
Etc…		

Table 2:

Pulmonary Condition	Total Number (%)	Reported First Occurrence of Pulmonary Conditions		
		Age <30 number (rate)	Age 30-40 number (rate)	Age >40 number (rate)
Lung Fibrosis				
Emphysema				
Etc…				

Table 3:

Reported Pulmonary Condition	RR Survivor vs. Sibling (95% CI)
Lung Fibrosis	
Emphysema	
Etc…	

Table 4:

Pulmonary Condition	RR (95% CI)					
	Fibrosis	Emphysema	Cough	Need Oxygen	Pleurisy	Etc.
Radiation						
BCNU						
CCNU						
Bleomycin						
Busulfan						
Cyclophos.						
Etc.						

Table 5:

Physical Performance	RR (95% CI)		
	Personal Care Skills	Routine Activities	Etc.
Fibrosis			
Emphysema			
Cough			
Need Oxygen			
Pleurisy			
Etc.			

Figure 1:
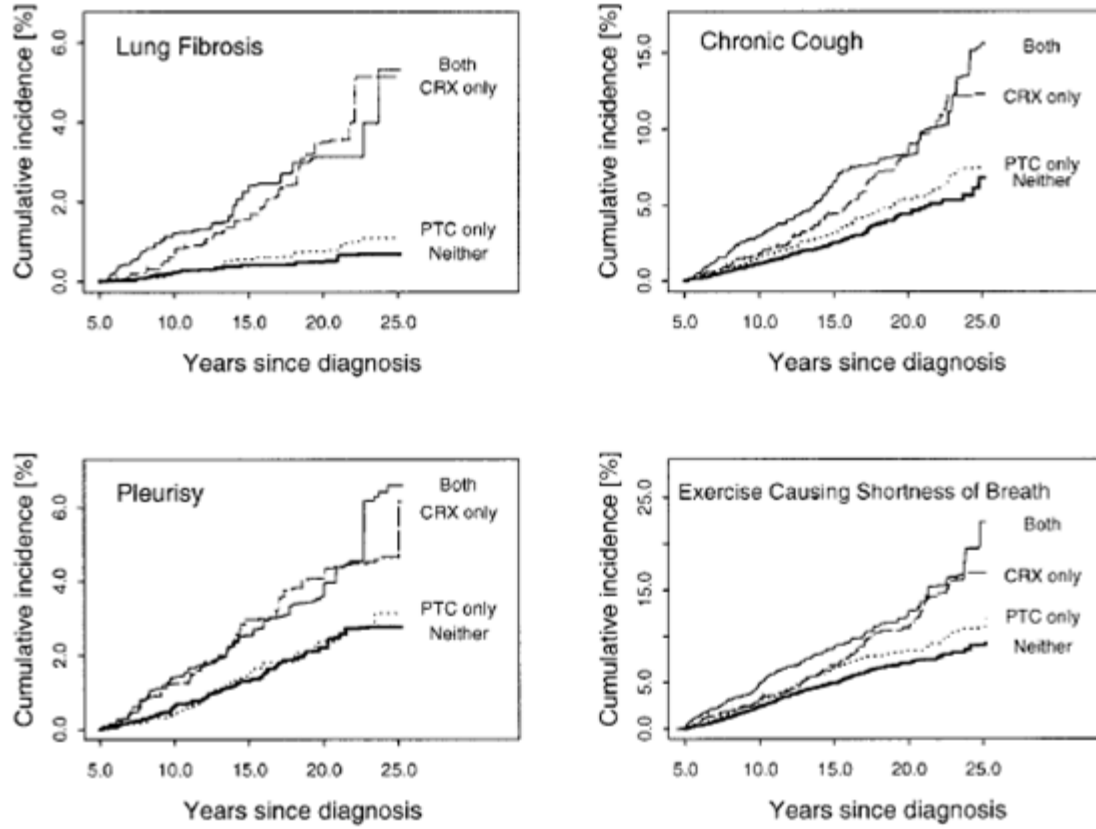
References:

1. Mariotto AB, Rowland JH, Yabroff KR, et al. Long-term survivors of childhood cancers in the United States. *Cancer Epidemiol Biomarkers Prev*. 2009;18(4):1033-1040.

2. Mertens AC, Liu Q, Neglia JP, et al. Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *J Natl Cancer Inst*. 2008;100(19):1368-1379.

3. Armstrong GT, Liu Q, Yasui Y, et al. Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. *J Clin Oncol*. 2009;27(14):2328-2338.

4. Mulrooney DA, Neglia JP, Hudson MM. Caring for adult survivors of childhood cancer. *Curr Treat Options Oncol*. 2008;9(1):51-66.

5. Hudson MM, Mulrooney DA, Bowers DC, et al. High-risk populations identified in Childhood Cancer Survivor Study investigations: implications for risk-based surveillance. *J Clin Oncol*. 2009;27(14):2405-2414.

6. Huang TT, Hudson MM, Stokes DC, Krasin MJ, Spunt SL, Ness KK. Pulmonary outcomes in survivors of childhood cancer: a systematic review. *Chest*. 2011;140(4):881-901.

7. Mertens AC, Yasui Y, Liu Y, et al. Pulmonary complications in survivors of childhood and adolescent cancer. A report from the Childhood Cancer Survivor Study. *Cancer*. 2002;95(11):2431-2441.

8. Friedman DL, Whitton J, Leisenring W, et al. Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *J Natl Cancer Inst*;102(14):1083-1095.

9. Mulder RL, Thönissen NM, van der Pal HJ, et al. Pulmonary function impairment measured by pulmonary function tests in long-term survivors of childhood cancer. *Thorax*. 2011;66(12):1065-1071.

10. Zorzi A, Yang CL, Dell S, Nathan PC. Bleomycin Associated Lung Toxicity in Childhood Cancer Survivors. 12th International Conference on Long-Term Complications of Treatment of Children and Adolescents for Cancer. Williamsburg, VA, USA; 2012:Abstract #110.

11. Venkatramani R, Kamath S, Wong K, et al. Correlation of Clinical and Dosimetric Factors with Adverse Pulmonary Outcomes in Children Receiving Lung Irradiation. 12th International Conference on Long-Term Complications of Treatment of Children and Adolescents for Cancer. Williamsburg, VA, USA; 2012:Abstract #111.

12. Torpy JM, Goodman DM, Burke AE, Livingston EH. JAMA patient page. Chronic obstructive pulmonary disease. *JAMA*. 2012;308(12):1281.

13. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med*. 2006;355(15):1572-1582.