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CHILDHOOD CANCER SURVIVOR STUDY
Analysis Concept Proposal
February 21, 2006

1. **STUDY TITLE:** Clustering of cardiovascular risk factors in adult survivors of pediatric cancer

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

As the cohort of phase I of CCSS ages, the medical concerns of these survivors resemble those of middle aged Americans, albeit perhaps at a younger age. Included in these medical problems are increased risks for diabetes and cardiac disease both of which are major health problems in the American adult population. We are interested in determining if adult survivors of childhood cancer are developing trends suggestive of metabolic syndrome. Metabolic syndrome, also known as Syndrome X or cardiac dysmetabolic syndrome, is a cluster of risk factors that are associated with a multiplicative risk of cardiovascular disease and all-cause mortality. Two commonly used definitions include the National Cholesterol Education Program – Adult Treatment Panel III (NCEP-ATP III) and the WHO criteria [1] [2, 3]. By NCEP-ATIII criteria, 3 or more of the following criteria must be present for the diagnosis of metabolic syndrome 1) hypertension BP > 130/85, 2) waist circumference > 102 cm males or > 88 cm females, 3) HDL< 40 in males or < 50 in females 4) Triglyceride level > 150 and 5) fasting plasma glucose > 110. The WHO criteria for metabolic syndrome include impaired glucose tolerance or diabetes mellitus and/or insulin resistance plus 2 or more 1) hypertension BP > 140/90, 2) triglycerides > 150 or HDL < 35 in males or < 39 in females, 3) waist to hip ratio > 0.9 males or > 0.85 in females and/or BMI > 30 and 4) UACR (urine albumin/creatinine ratio) > 30. Individuals with metabolic syndrome double their risk for coronary heart disease and increases their risk for type 2 diabetes by 10 fold.

Several papers have alluded to the presence of one or more of the characteristics of metabolic syndrome in survivors of pediatric cancer. In a study of 50 cancer survivors compared to 50 age- and gender-matched controls and found the survivors at increased risk for fasting hyperinsulinemia (RR 3.0 ;95% CI 1.0-8.6), reduced HDL (RR 7.9 ;95% CI 2.2-29.6) and obesity (RR 4.5 ;95% CI 1.3-15.8)[4]. A study of patient who had received BMT found 52% to be hyperinsulinemic and 39% to be hyperinsulinemic and hypertriglyceridemic [5]. Link suggested that ALL survivors who were growth hormone deficient are clinically very similar to individuals with metabolic syndrome with obesity, hypertension, hyperlipidemia and increased fat mass [6]. In the GH deficient leukemia survivors, peak growth hormone response to stimulation tests inversely correlated with fat mass, insulin and waist to hip ratio.

In non-oncology patients, GH deficiency is associated with increase in visceral fat and several cardiovascular risk factors including: increase in carotid intima and media thickness, increase in clotting factors fibrinogen and plaminogen activator inhibitor-1, increase in C-reactive protein, interleukin-6 and sialic acid (inflammatory markers of vascular disease), increase in insulin resistance, decrease in cardiac function and increase in LDL and decrease in HDL [7]. A 2002 review article by Simpson et al analyze the effect of GH therapy in adults who are GH deficient. They report the normalization of body composition, improvement in quality of life, reduction of risk factors for cardiovascular disease, improvement in lipid profiles and increased muscle strength and exercise capacity [8].

Within the CCSS the presence of diabetes, although an infrequent outcome, is more common in survivors than in their siblings. Of 13,177 survivors living at the time of enrollment, 125 (0.95%) reported current medications for diabetes. In comparison, of 3,846 siblings, 23 (0.59%) reported being on a medication for diabetes. Adjusting for age, gender, and race, the odds ratio (OR) and 95% confidence intervals (95% CI) for survivors having diabetes, in comparison with siblings, was 1.8 (95% CI=1.1-2.9, P=0.02). Cancer treatment factors associated with diabetes include: abdominal radiation (OR=2.9; 95% CI= 1.8-4.8, P<0.0001) and total body irradiation (OR=2.5; 95% CI= 1.1-6.0, P=0.04). In patients with leukemia if treated with TBI the risk of developing diabetes was OR=9.2, 95% CI=3.7-23.1, p<0.0001) Cancer therapy that was not associated with diabetes included cranial radiation, treatment with corticosteroids or corticosteroids in combination with L-asparaginase.

The CCSS cohort can be queried to determine the frequency of each of the components of the metabolic syndrome via extrapolation from self-reported medication use and body mass index. The information available within the CCSS dataset will not allow for the determination of metabolic syndrome per the criteria defined by NCEP-ATP III or WHO. However, a proxy suggestive of metabolic syndrome can be used. This "clustering of cardiovascular risk factors" (clustered CVRF) would include obesity (BMI $\geq$ 30) plus at least two of three CVRF (hypertension, dyslipidemia, diabetes mellitus). Cancer treatment risk factors and history of growth hormone deficiency will be evaluated for association with components of the cluster of cardiovascular risk factors.

4. SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES:

Question Are childhood cancer survivors more likely to have a clustering of cardiovascular risk factors (diabetes, hypertension, dyslipidemia) in conjunction with obesity in comparison to siblings.

Aim 1 Determine the prevalence of obesity, diabetes, hypertension, or dyslipidemia requiring medications for management and "clustered CVRF" in cancer survivors compared to siblings.

Hypothesis 1 Adult survivors will have greater prevalence of:

1. Obesity
2. Hypertension on medication therapy
3. Dyslipidemia on medication therapy
4. Diabetes mellitus on medication therapy

Hypothesis 2 Prevalence of "clustering CVRF" will be greater in survivors than siblings.

Aim 2 Identify correlates of risk.

Hypothesis 1 Previous exposure to cranial radiotherapy or total body irradiation will be associated with an increase in risk of individual CVRF and clustering CVRF.

Hypothesis 2 Survivors previously treated who are growth hormone deficient and currently as adults not treated with growth hormone will be more likely to have metabolic syndrome.

Aim 3 (exploratory) Determine if general health care utilization modifies the likelihood of reporting CVRF in survivors in comparison with siblings.

Hypothesis 1 Because their health may be more closely monitored, survivors will have higher rates of treatment for the following in comparison with siblings:

1. Obesity

2. Hypertension requiring medications
3. Dyslipidemia requiring medications
4. Diabetes mellitus requiring medications

5. ANALYSIS FRAMEWORK:

a. Subject population: Childhood cancer survivors who are >= to 18 years of age at time of completion of the questionnaire and at least 5 years off therapy enrolled in CCSS who have completed Follow Up questionnaire #2 (FU2) .

b. Comparison group: Siblings

c. Outcomes of interest:

1. Body mass Index $\geq$ 30 kg/m^2

2. Dyslipidemia defined as treatment with medications to lower cholesterol or triglycerides.

3. Hypertension defined as treatment with medications for high blood pressure for hypertension

4. Hyperglycemia / DM defined as treatment with oral medication or insulin for diabetes.

d. Independent variables of interest:
- socio-demographics (age, gender, race/ethnicity, household income)
- cancer diagnosis
- cancer treatment
- interval from cancer diagnosis
- previous treatment with growth hormone
- visit with a physician in the last 2 years
- Tobacco/smoking

f. Statistical analysis

This cross-sectional study will calculate the prevalence of obesity, hypertension, dyslipidemia, and diabetes mellitus in the survivor and sibling participants. The prevalence of participants having two, three, or four of these CVRF will be determined. The "clustered CVRF" (2 of 3 of hypertension, dyslipidemia or diabetes mellitus plus obesity) will be calculated.

Logistic regression models will be generated to estimate odds ratios (OR) and 95% confidence intervals (95% CI) for individual CVRF and clustered CVRF, adjusted for age and gender. Treatment exposures will be assessed individually and in combination. The modifying effect of outpatient health care utilization will be assessed and included in the models as an adjuster if there is a significant difference between survivors and siblings.

Statistical analyses will be performed at Fred Hutchison Cancer Center.

6. TABLES/FIGURES:

Table 1. Demographic and cancer-related demographics of participants

Factors	Survivors	Siblings
Gender		
Females		
Males		
Race/Ethnicity		
White – non Hispanic		
Black – non Hispanic		
Hispanic		
Other- not specified		
Histology		
Acute Lymphoblastic Leukemia		
Other Leukemia		
Brain Tumors		
Hodgkin's disease		
Non-Hodgkin's Lymphoma		
Wilms' tumor		
Neuroblastoma		
Soft Tissue Sarcomas		
Bone Malignancies		
Amputation		
No amputation		
Age at Diagnosis (years)		
Age at Interview (years)		
Radiation treatment site included:		
Brain		
Spine		
Abdomen		
Pelvis		
Total body irradiation		
Chest		
Head		
Unspecified radiation site		
Radiation status unknown		
No Radiation		
Chemotherapy included:		
Anthracycline		
Alkylating agent		
Anthracycline and alkylating agents		
Other Chemotherapy		
No Chemotherapy		

Table 2. Frequencies of individual and clustered cardiovascular risk factors in participants with odds ratio in survivors compared with siblings.

	% Survivors	% Siblings age and gender matched	OR (CI)
BMI $\geq$ 30 kg/m^2			
Hypertension*			
Dyslipidemia*			
Diabetes mellitus*			
Two of the above			
Three of the above			
Four of the above			
Clustered CVRF+			

* On current medication therapy for condition.
+ Clustered CVRF: obesity plus at least two of the three CVRF.

Table 3. History of growth hormone deficiency in survivors and association with components of the metabolic syndrome cluster.

	Growth hormone deficient (off GH Rx currently)	No previous diagnosis of GHD
BMI $\geq$ 30 kg/m^2		
Hypertension*		
Dyslipidemia*		
Diabetes mellitus*		
Two of the above		
Three of the above		
Four of the above		
Clustered CVRF+		

7. REFERENCES:

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