03-02

CHILDHOOD CANCER SURVIVOR STUDY
Analysis Concept Proposal

Draft: January 31, 2003

1. **Title:** Risk of cancer among twins of long-term childhood cancer survivors

2. **Working Group and Investigators:** The proposed publication will be within the Genetics Working Group. Proposed investigators will include:

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3. **Background and Rationale:**

The etiology of most childhood cancer is still largely unknown. Family studies are helpful in understanding the role of genetic factors in the development of these conditions. However, the presence of familial aggregation for a cancer does not exclude the possibility of confounding by the simultaneous clustering of environmental and cultural influences. Close examination of twins is one tool to separate genetic from environmental factors. Increased concordance rates of cancers among monozygotic twins compared to dizygotic twins are suggestive of the presence of genetic influences.

Previous twin studies have supported the contribution of genetic factors to the risk of melanoma, acute lymphoblastic leukemia, prostate cancer, Hodgkin disease, colon cancer, breast cancer, and cervical cancer. Twin studies in the childhood cancer population are particularly compelling because, generally, increased family recurrence rates of cancer are associated with younger age at diagnosis. Concordance for cancer among twins may lead to ancillary biology studies within the CCSS cohort which further examine the pathophysiology of these cancers. Successful examples of this approach include linkage analysis for breast cancer as well as molecular studies among twins with infant leukemia thought to have acquired genetic changes through the in utero event of twin-twin transfusion.

The goals of this analysis is to (1) describe the concordance patterns of cancer among twins in the CCSS cohort, overall and for same-site occurrences, by zygosity and (2) calculate the excess risk of cancer among twins of CCSS cases by zygosity. Such an analysis will help determine the role of genetic influences in the development of cancers observed among CCSS cases and their relatives.

4. Specific Aims/Hypotheses

To describe the concordance patterns of cancers and the risk of cancers among twins of childhood cancer survivors.

Hypotheses:

1. The twins of childhood cancer survivor have a higher risk of malignancy than individuals in the general population.
2. Monozygotic twins of childhood cancer survivors have a higher risk of malignancy than dizygotic twins who in turn have a higher risk than non-twin siblings.
3. Twins have a higher risk of same-site occurrence (as twin) of cancer than other sites.

5. Analysis Framework:

a. **Outcome of interest**: self-reported cancer in twin or sibling of CCSS case

b. **Subject population**: All CCSS cases. Adopted cases will be excluded. There are 229 twins of CCSS cases in the cohort (77 monozygotic, 140 dizygotic, 12 same-sex unknown zygosity). Nine of these cases' twins have a history of a cancer condition, all occurring before the age of 20 years.

c. **Variables**:

i. Case's primary cancer diagnosis
ii. Case's age at diagnosis
iii. Case's current age
iv. Case's history of secondary malignancy
v. Case's gender
vi. Twin's zygosity status
vii. Twin's history of cancer as reported by case or case's proxy
viii. Twin's gender

d. Analyses

i. Identify and describe concordance of cancers (overall and by site) of cases to their monozygotic twins, dizygotic twins, non-twin full siblings, and half-siblings.
ii. Calculate pairwise and probandwise concordance rates of cancer among twins of CCSS cases, by zygosity. These measures do not adjust for the age of the patients to provide estimates of overall cancer risk. However, these measures are useful to compare to each other, as described above.
iii. Calculate standardized incidence ratio of cancer in the monozygotic twins, dizygotic twins, non-twin full siblings, and half-siblings of the cases, overall and by zygosity (used in lieu of calculation of traditional pairwise and probandwise concordance rates which do not adjust for age) as compared to age- and gender-matched SEER data.
iv. Calculate the SIR of cancer in twins of cases with a second malignancy compared to twins of cases without a second malignancy.

v. When twin pairs are concordant for a cancer type, the survival outcomes of the two twins will be compared.

6. Specific Tables

a) Table 1 Characteristics of twins concordant for cancer

			Cancer		Age at diagnosis		Histologic Subtype	
Pair #	Zygosity	Sex	CCSS case	Twin	CCSS case	Twin	CCSS case	Twin
1								
2								
3								
Etc.								

b) Concordance rates

	Pairwise concordance rate	Probandwise concordance rate
Monozygotic twins: Any cancer Same-site cancer		
Dizygotic twins: Any cancer Same-site cancer		
Full siblings (non-twin): Any cancer Same-site cancer		
Half-siblings: Any cancer Same-site cancer		

c) Occurrence of cancers in twins of CCSS cases

Cancer		Zygosity	No. at risk	Expected Cases	Observed cases	SIR (95% CI)	SIR MZ/ SIR DZ
CCSS case	Twin						
NHL	NHL	MZ					
NHL	NHL	DZ					
NHL	Other Ca	MZ					
NHL	Other Ca	DZ					
H.D.	H.D.	MZ					
H.D.	H.D.	DZ					
H.D.	Other Ca	MZ					
H.D.	Other Ca	DZ					
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