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00-04

CHILDHOOD CANCER SURVIVOR STUDY
Analysis Concept Proposal

Title: Family History of Cancer Among First-Degree Relatives of Childhood Cancer Survivors: A report from the Childhood Cancer Survivor Study

Working Group and Investigators

This publication will be written within the Genetics Working Group, with input from the Epidemiology/Biostatistics Working Group. Proposed investigators include:

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Background & Rationale

Cancer in children is rare, as are familial cancer syndromes that include pediatric cancers.(1) While cancer in families is not uncommon, reproducible family cancer syndromes are rare. However, cancer sometimes clusters in families in a reproducible manner. (2) When examining families of childhood cancer patients, familial cancer syndromes may not be fully developed due to the relative young ages of the families. Some familial syndromes are well described, such as the dominantly-inherited Li-Fraumeni syndrome. This includes family members with bone and soft tissue sarcomas, breast cancer, brain tumors, leukemia and adrenocortical carcinoma. This disease exhibits about 50% penetrance by age 30. Some affected members have been found to harbor germline mutation of the tumor suppressor gene TP53. (3-8) In addition, mutations in other tumor suppressor genes involved in p53 pathways may contribute to a propensity towards SMN. The hCHK2 is a protein kinase that is activated in response to DNA damage. It is the human homolog of the yeast Rad53 and Cds1 G2 checkpoint kinase genes that are responsible for G2 checkpoint control. It appears that normal CHK2 responds to DNA damage by phosphorylating and thus activating p53. (9) Thus, mutations of CHK2 would tend to keep p53 functionally inactive. Recently, germ line mutations of CHK2 have been found in patients with the Li-Fraumeni Syndrome who do not have a p53 mutation. (10) There are other tumors that may be part of the LFS or may be part of known or previously not described cancer family syndromes.. Hartley and colleagues have hypothesized that Wilms tumor may be part of a small number of Li Fraumeni syndrome families. (11) Another study also found a small excess of cancers in family members of Wilms tumor patients, especially early onset brain and bone tumors. (12)

The classic example of an inherited cancer syndrome is retinoblastoma. Approximately 40% of children with retinoblastoma harbor a germline mutation in the tumor suppressor gene RB1. An excess of cancer deaths in relatives under the age of 55 years and in fathers of bilateral retinoblastoma probands has been shown.(13) In a small series, an overall excess of cancer incidence in relatives of retinoblastoma patients was seen.(14) Other well-described family history syndromes include neurofibromatosis, colorectal cancer (FAP and HNPCC), hereditary breast cancer and nevoid basal cell carcinoma syndrome among others. (2) It has

been postulated that patients with brain tumors may have an increased family history of hematopoietic malignancies. (15,16)

Second malignant neoplasms (SMNs) following childhood cancer may represent a component of a familial cancer syndrome. Family history of early-onset cancer was associated with SMNs in a study of childhood cancer patients. Use of radiation therapy increased this risk, suggesting a gene-environment interaction.(17) A study of breast cancer following Hodgkin's disease failed to find an association.(18)

Concordance for childhood cancer in twins differs a bit from study to study, and may be as low as 5% or as high as 17% in monozygotic twins. For solid tumors, other than retinoblastoma, concordance is lower. (19) Risk of cancer is siblings of childhood cancer patients has also been reported to be higher for leukemia (RR=2.3) than for solid tumors (RR=1.3). (20,21) Recent studies have shown that offspring of childhood cancer survivors do not appear to be at increased risk for development of cancer. (22,23)

Collecting family history information is an arduous task. Validating all reported cancers with medical records is costly both in dollars and time. Retrospective studies of family history of cancer can produce misclassification of reported cancer occurrence among relatives. Several studies have validated self and relative report and found it generally reliable. (24-27) In a case-control study, sensitivity and specificity did not differ between cases and controls, suggesting that any bias introduced by self-report would be nondifferential. (25) Report of family cancers from first degree relatives appears to be superior to that from second degree relatives. (27)

With 13,610 family questionnaires now available for analysis, the CCSS presents a large, relatively unselected population of diverse pediatric cancers from which to study reproducible family history syndromes. The analysis of first-degree relatives will provide an important foundation upon which future studies can be performed. This will include molecular genetic studies.

Specific Aims/Objectives/Research Hypotheses

Specific Aim 1: To describe the prevalence of specific cancers in first degree relatives of childhood cancer survivors and determine whether they are at increased risk compared to those in the general population.

Specific Aim 2: To identify childhood cancers that represent components of known reproducible familial cancer syndromes.

Specific Aim 3: To identify previously not described familial cancer syndromes of which childhood cancer is a component.

Specific Aim 4: To determine whether second primary neoplasms following childhood cancer are associated with specific known or unknown familial cancer syndromes.

Specific Aim 5: To determine whether specific patterns of familial cancers, currently known or not previously described, can identify those childhood cancer survivors at increased risk for second primary neoplasms.

Specific Aim 6: To identify families at greatly increased risk for cancer for further study of biomarkers of predisposition at the molecular level.

Specific Aim 7: To assess the validity of self and family member reported family history of cancer. (Details on this will be reported in a separate manuscript that will precede or serve as a companion paper to the family history analysis – see overall methodology)

Overall methodology

The overall analysis of family history of cancer among first degree relatives of CCSS participants will be preceded by a clarification study and a validation study. A mechanism for this has been carefully considered by the Genetics and the Epidemiology/Biostatistics Working Groups and a brief description follows. The results of these studies will be analyzed by the

committee and reported in the form of a manuscript that will precede or accompany the analysis of the family history. This will be referenced in the analysis of family cancer history, so it is clear that the data reported are of high quality and validity. They will also serve to add to the literature on self-reported data and propose mechanisms for future family history research that will be time and cost-effective.

- Clarification study

This study will clarify ambiguously reported cancers or tumors on 589 first degree relatives of 541 CCSS participants. By means of individualized telephone scripts and trained interviewers, respondents will be asked to clarify their original questionnaire response. The malignant character of the reported neoplasm and/or its site will be clarified. Reported multiple primary neoplasms will be confirmed. Families in this study will not be in the validation study as they have had additional intervention with respect to their self-report.

- Validation study

This study will assess the quality of the self-reported family history data by interview with the actual individual reported to have had cancer, or the appropriate next of kin. A stratified sample of 458 families were selected. Participants are stratified by nature of respondent and potential for heightened awareness of family members of cancer.

The remainder of this concept proposal outlines the planned analyses for the family history data.

Analysis Framework

(a) Outcome of interest: First-degree relatives of CCSS proband with history of cancer.

(b) Subject Population: All cases registered in CCSS

(c) Explanatory variables:

CCSS proband:

initial diagnosis, vital status, cause of death if applicable, date of birth age at diagnosis, age at last contact or at death, follow-up time since diagnosis, race, gender, recurrence. In those with SPN's (second primary neoplasms): SPN diagnosis type, age at diagnosis of SPN, latency time from primary malignancy, outcome of SPN

First degree relatives

Relationship to CCSS proband, date of birth, date of diagnosis (and age at time) of cancer, date of last follow-up or death, race, gender, type and site of all cancers, vital status, total number of first degree relatives

CCSS questionnaire data and respondent

Relationship to CCSS proband, relationship to relatives reported on, age at time of report, need for data clarification (Y/N) and if Y, result; participation in validation study (Y/N) and if Y, result

(d) Specific Tables and analyses

Table 1. Characteristics of the Cohort

	Overall Cohort (n=)	Cases without a family history of cancer (n=)	Cas canc
Mean age at dx of cancer in CCSS proband (years)			
Sex Male (n, %) Female			
Race White (n, %) Black Other Unknown			
CCSS Primary Diagnosis Leukemia (n, %) CNS Tumor Hodgkin Disease NHL Wilms' Tumor Neuroblastoma STS Bone Tumor			
Vital Status of CCSS proband (% Alive)			
Nature of respondent of questionnaire (n,%) Survivor Parent Sibling Other			
Age of Respondent at questionnaire (years) 18 - 25 26-40 41-65 66+			
Number of first-degree relatives reported (mean/median) Parents Full siblings Half siblings Offspring			
Age of first-degree relatives reported (mean) Parents Full siblings Half siblings Offspring			
Number in Clarification study Validation study			
Time from CCSS Primary Dx to questionnaire response			

Observed and Expected Numbers of Family Cancers by CCSS Primary Cancer

CCSS Proband Primary Diagnosis	Family Cancers Observed	Family Cancers Expected	O/E Ratio (95% C.I.)
All Diagnoses			
Hodgkin's Disease			
Soft Tissue Sarcoma			
Neuroblastoma			
Kidney Tumors			
Leukemia			
Bone Tumor			
CNS Tumors			
Non-Hodgkin's Lymphoma			

Same analysis but limited to family members < 45 years of age

Observed and Expected Numbers of Cancers in All First Degree Relatives

Malignancy	Cases Observed	Cases Expected	O/E Ratio (95% C.I.)	Median time to occurrence (years)
All				
Leukemia				
CNS				
NHL				
Kidney Wilms Other kidney				
Neuroblastoma				
Retinoblastoma				
Hodgkin's disease				
Thyroid cancer				
Bone Tumors				
Soft Tissue Sarcoma				
Breast Cancer				
Melanoma				
Lung cancer				
Ovarian Cancer				
Uterine Cancer				
Colorectal cancer				
Pancreatic cancer				
Liver cancer				

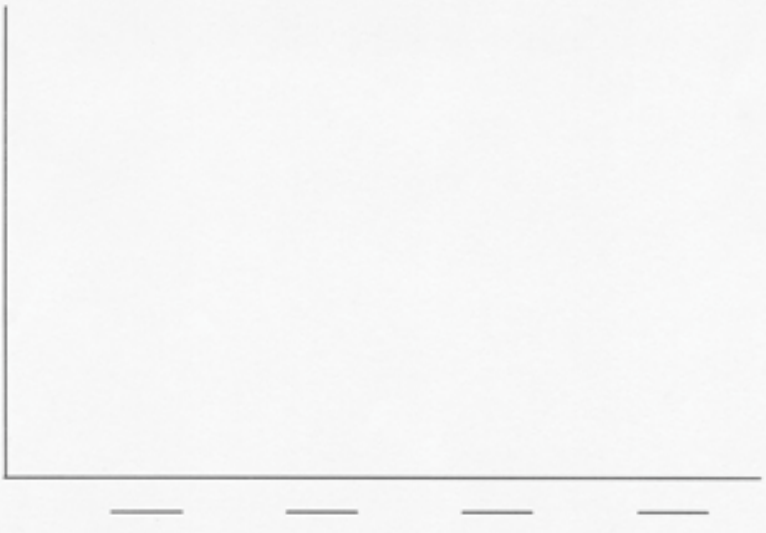
Same analysis but limited to family members < 45 years of age

Table 2. Prevalence of Obesity, Hypertension, and Diabetes Mellitus by Cancer Type Adjusted for Age and Gender*

	ALL	CNS Tumors	Bone Tumors	Hodgkin/ NHL	Kidney Tumors	Neuroblastoma
Overweight						
Obesity						
Class I						
Class II						
Class III						
All overweight/obese						
Hypertension						
Diabetes Mellitus						

* The distributions of age and gender will be assessed to determine if the above table will be illustrated as age and gender adjusted or age- and gender-specific rates.

Figure 1. Frequency Plot of Body Mass Index and Cranial Irradiation



* Categories will be determined by clustering of doses of CRT.

Risk of SMN by family history of all cancers

Cancer family history	ALL SMN	Leukemia	CNS	Thyroid	Breast	STS	Bone
Cancer in 1st degree relatives							
Parent							
Sibling							
Half-sibling							
Offspring							
Cancer in 1st degree relatives <45 years old							
Parent							
Sibling							
Half-sibling							
Offspring							

Other analyses

Pedigrees will be constructed for all families with cancer among first degree relatives. These will be reviewed by the investigators and selected pedigrees will be displayed.

Dependent on number of families identified, a table may be constructed showing types of reproducible patterns of family history and the suggested syndrome, if known. The first row of the table serves as an example

Families with apparent family history syndromes

Proband Site of Cancer	Age at onset	Affected Relatives	Site of Cancer	Age at Onset	Family history syndrome
Sarcoma	14	Father Mother Sibling Sibling	Sarcoma Breast Sarcoma CNS	40 38 12 6	LFS

Figures

Figure 1: Cumulative incidence of all cancers among first degree relatives

Figure 2: Cumulative incidence of all cancers among first degree relatives of probands with SMN and among first degree relatives of probands without SMN

REFERENCES CITED

1. Friedman DL, Meadows AT: Pediatric Tumors, in Neuget AI, Meadows AT, Robinson E (eds): Multiple Primary Cancers. Philadelphia, Lippincott Williams & Wilkins, 1999, pp 235-256.

2. Lindor NM, Greene MH. The concise handbook of family cancer syndromes (Review). J Natl Cancer Inst 90: 1039-1071, 1998.

3. Li FP, Fraumeni JF, Jr. Rhabdomyosarcoma in children: epidemiologic study and identification of a familial cancer syndrome. J Natl Cancer Inst 43: 1365-1373, 1969.

4. Li FP, Fraumeni JF, Jr. Soft-tissue sarcomas, breast cancer, and other neoplasms. A familial syndrome? Ann Intern Med 71: 747-752, 1969.

5. Garber JE, Goldstein AM, Kantor A et al. Follow-up study of twenty-four families with Li-Fraumeni syndrome. Cancer Res 51: 6094-6097, 1991.

6. Young JL, Percy CL, Asire AJ. Surveillance epidemiology and results, incidence and mortality data: 1973-1977. NCI Monogr 57: 911-981, 1981.
7. Williams WR, Strong LC. Genetic epidemiology of soft tissue sarcoma in children. In: Muller H, Weber W (eds): Familial Cancer. Basel: S. Karger, p. 151-153, 1985.
8. Malkin D, Jolly KW, Barbier N, et al. Germline mutations of the p53 tumor-suppressor gene in children and young adults with second malignant neoplasms. N Engl J Med 326: 1309-1315, 1992.
9. Hirao A, Kong YY, Matsuoka S, Wakeham A et al. DNA damage-induced activation of p53 by the checkpoint kinase Chk2. Science 287 : 1824-1827, 2000.
10. Bell DW, Varley JM, Szydlo TE, et al. Heterozygous germ line hCHK2 mutations in Li-Fraumeni syndrome. Science 286: 2528-2531, 1999.
11. Hartley AL, Birch JM, Tricker K, et al. Wilms' tumor in the Li-Fraumeni cancer family syndrome. Ca Genet Cytogenet 67:133-135, 1993.
12. Moutou C, Hochez J, Chompret A, et al. The French Wilms' tumour study: no clear evidence for cancer prone families. J Med Genet 31:429-434, 1994.
13. Strong LC, Herson J, Haas C et al. Cancer mortality in relatives of retinoblastoma patients. J Nat Cancer Inst 73:303-311,1984
14. Fedrick J, Baldwin JA. Incidence of cancer in relatives of children with retinoblastoma. Br. Med J 1:S3-S4,1978
15. Farwell J , Flannery JT: Cancer in relatives of children with central nervous system neoplasms. N Engl J Med 1984;311:749–753.
16. Kuijten R, Strom.SS, Rorke L, et al: Family history of cancer and seizures in young children with brain tumors:a report from the Childrens Cancer Group (United States and Canada).Cancer Causes and Control 1993;4:455-464
17. Kony SJ, de Vathaire F, Chompret A et al. Radiation and genetic factors in the risk of second malignant neoplasms after a first cancer in childhood. Lancet 350: 91-95, 1997.
18. Bhatia S, Meadows AT, Robison LL. Family history of patients with breast cancer after treatment of Hodgkin's disease in childhood. Late Effects Study Group Lancet 350:888-9, 1997
19. Buckley JD, Buckley CM, Breslow NE et al. Concordance for childhood cancer in twins. Med & Pediatr Oncol 26:233-229, 1996
20. Draper GJ, Heal MM, Kinnier-Wilson LM. Occurrence of childhood cancers among sibs and estimation of familal risks. J Med Genet 14:81-90, 1977
21. Li FP, Tucker MA, Fraumeni JP. Childhood cancer in sibs. J Pediatr 88:419-423, 1976
22. Blatt J. Pregnancy outcome in long-term survivors of childhood cancer. Med & Pediatr Oncol. 33(1):29-33, 1999
23. Sankila R. Olsen JH. Anderson H. et al. Risk of cancer among offspring of childhood-cancer survivors. Association of the Nordic Cancer Registries and the Nordic Society of Paediatric Haematology and Oncology N Engl J Med. 338(19):1339-44, 1998
24. Novakovic B, Goldstein AM, Tucker MA. Validation of family history of cancer in deceased family members. J Natl Cancer Inst 88: 1492-1493, 1996.
25. Aitken J, Bain C, Ward M, Siskind V, MacLennan R. How accurate is self-reported family history of colorectal cancer? Am J Epidemiol 141: 863-871, 1995.
26. Kuijten R, Bunin G, Meadows A. Validation and accuracy of cancer reporting in first degree relatives. Am J Epidemiol 136: 1019 , 1992
27. Bondy ML. Strom SS. Colopy MW. Brown BW. Strong LC. Accuracy of family history of cancer obtained through interviews with relatives of patients with childhood sarcoma. Journal of Clinical Epidemiology. 47(1):89-96, 1994