

CHILDHOOD CANCER SURVIVOR STUDY
Analysis Concept Proposal
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1. TITLE: Cancer screening practices in survivors of childhood cancer

2. WORKING GROUP INVESTIGATORS:

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3. BACKGROUND AND RATIONALE:

Survivors of childhood cancer have a substantially increased risk of developing a second or subsequent malignant neoplasm (SMN).^{1,2} Prior analysis of the CCSS cohort has revealed increased rates of breast³, colon and non-melanoma skin cancer⁴ – all malignancies that can be detected by periodic surveillance tests (e.g. mammography, colonoscopy) or focused physical examination (e.g. dermatologic exam). The COG Long-Term Follow-Up Guidelines advocate periodic cancer screening in high-risk populations i.e. (1) annual dermatologic exam of all irradiated areas; (2) colonoscopy every 5-years beginning 10 years after radiation or at age 35 years (whichever is later) in survivors treated with ≥ 30 Gy radiation to the abdomen/pelvis/spine; and (3) annual mammogram in females treated with ≥ 20 Gy radiation to the breast, starting at age 25 years or 8 years off therapy, whichever is later.⁵ Additionally, the COG guidelines advocate that all survivors, regardless of risk status, comply with published ACS guidelines that advocate (1) annual mammogram beginning at age 40 years in all women; (2) annual PAP test starting 3-years after first vaginal intercourse or at age 21 (whichever occurs first) which may be reduced to every 3 years after age 30 years; and (3) colonoscopy every 10 years beginning at age

50 (or another form of colon cancer screening such as fecal occult blood yearly, flexible sigmoidoscopy or double contrast barium enema every 5 years).

CCSS has previously reported on the cancer screening practices of survivors.⁶ However, this analysis was based on data obtained in the baseline questionnaire (~1995-1996) which was administered prior to the publication of guidelines by COG and other groups,^{7,8} and increased awareness of the long-term risk of SMN in childhood cancer survivors. Overall, 78.2% of females reported a PAP test within the last 3 years, and 20.9% had had a mammogram at least once in their life. Of concern, only 56.9% of female survivors older than 30 years who had received chest or mantle radiation reported ever having received a mammogram. Survivors who were older at the time of their cancer diagnosis were more likely to report a cancer screening test, as were survivors with higher levels of future health concerns. Higher educational attainment predicted better adherence to PAP tests. Although survivors were slightly more likely than their siblings to perform cancer screening practices (except for PAP smears), compliance rates were far from ideal. As the rate of SMN's in survivors continue to rise, it is imperative that survivors receive risk-based medical care that includes appropriate screening tests that might detect new neoplasms earlier in their natural history. Data from the CCSS baseline survey suggests that this is not the case – however, it is of great interest to repeat this analysis using data from a more contemporary time period during which we hope that the publication of guidelines and increased awareness of long-term risks will have improved the screening practices of this cohort.

SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES:

The purpose of the present proposal is to:

- (1) Describe the proportion of childhood cancer survivors who reported completion of cancer screening tests (colonoscopy, mammography, PAP smears and dermatologic exam) as reported on the 2003 follow-up questionnaire, and compare rates of screening between survivors at high risk of specific SMNs (due to their prior therapy), survivors at standard risk, their siblings and the general population
- (2) Evaluate the predictors of compliance with recommended screening tests among childhood cancer survivors.

Hypothesis #1: Survivors at increased risk of specific SMNs will be more likely to undergo specific cancer screening (colonoscopy, mammogram, skin examination as appropriate) than survivors not at increased risk of specific cancers. Both groups will demonstrate higher screening rates than their siblings and population controls.

Hypothesis #2: Predictors of increased likelihood of compliance with recommended screening tests will include: older age at diagnosis, higher education attainment, insured or Canadian, greater concern about future health risks, possession of a treatment summary/copies of medical records, and knowledge of the risks arising from prior therapy.

4. ANALYSIS FRAMEWORK:

Sample

The study sample will consist of all survivors and siblings who responded to the 2003 follow-up questionnaire. Survivors who have developed one of the target cancers as a SMN (i.e. skin, colon, breast or cervical) will be excluded. Additionally, a frequency matched (age, gender, race/ethnicity) comparison group (3:1) will be randomly selected from the 2003 National Health Interview Survey (NHIS). We propose to use frequency matching rather than using the whole NHIS population as the comparison group, because even if we adjust for age, race and gender, there is likely to be residual confounding by at least age and race. The CCSS cohort is younger than the general population of adults and more likely to be white. Using the whole sample would require that our analysis techniques employ survey sampling methodology (accounting for weight, stratum and population sampling unit for each person). We do not have sampling weights for CCSS participants, although we could potentially create them. Alternatively, we could indirectly weight the NHIS sample with the CCSS age, race and gender distributions.

Survivors will be defined as high risk of developing a specific malignancy if they have received the following therapies:

- a) Skin cancer: any radiation

- b) Colon cancer: ≥ 30 Gy radiation to abdomen/pelvis/spine
- c) Breast cancer: ≥ 20 Gy radiation to chest/mantle

Outcomes of interest (all variables from FU 2003 questionnaire)

A. Screening tests, physical examination or self examination

- Colonoscopy (B2)
- Mammogram (B4)
- Pap smear (B5)
- Skin exam by health care practitioner (C12)

Independent (exploratory) variables

A. Sociodemographic variables:

- Health insurance (Canadian, private insurance, Medicaid or public assistance, not insured
FU 2003 - M1,1a,1b)
- Age at interview (From date of questionnaire completion – baseline and 2003 follow-up
and birth date)
- Gender (Baseline A2)
- Race/ethnicity (Race/ethnicity Baseline - A4, 4a)
- Household income (FU 2003 - S1)
- Education (FU2003 - 1)
- Marital status (FU2003 - 2)
- Employment status (FU2003 – 4)

B. Disease/treatment variables:

- Cancer diagnosis (Diagnosis variable, detailed diagnosis variable and ICDO codes)
- Age at diagnosis (Date of diagnosis – date of birth)
- Chemotherapy vs. surgery vs. radiation vs. BMT vs. combination
- If “yes” to radiation →
 - a. did they receive mantle or chest radiation

- b. did they receive abdominal, pelvic, and/or spinal (thoracic, lumbar, sacral) radiation

C. Health status (as a predictor of screening behavior)

- Chronic medical conditions (baseline questionnaire – classified using NCI CTCAE criteria)
- Perceived general health (E1)
- Mental health (BSI-18; G questions generate global score and depression, anxiety and somatization subdomains)
- Physical impairment /activity limitations (E3-12: Physical Function section of SF-36)
- Pain as a result of previous cancer (G19)
- Anxiety as a result of the previous cancer (G20)
- Concern about future health (F13)

D. Treatment summary or copies of medical records

- Survivor has treatment summary/medical records (A9)
- Local/primary doctor has treatment summary or medical records (A10)

E. Knowledge of risks arising from prior therapy

- Relationship between chest radiation and breast cancer (T8), need for monthly breast exam (T9)

F. Medical care

- Seen by a physician or nurse in last 2 years (A1)
- Location of care (A2)
- Visit related to prior cancer (A5)

G. Family history

- Family history of breast or colon cancer (baseline questionnaire section P)

Data Analysis Plan

Hypothesis #1: The proportion of survivors (stratified into either high risk or low risk of a particular SMN where appropriate) who reported completing cancer screening tests (colonoscopy, mammography, PAP smears and dermatologic exam) as reported on the 2003 follow-up will be calculated and reported for survivors, siblings and a randomly selected population based comparison group frequency matched (3:1) on age, gender and race/ethnicity from the National Health Interview Survey (NHIS). The proportion of those receiving cancer screening will be compared among the four groups with either age, gender and race/ethnicity adjusted generalized estimating equations (siblings and survivors), and within age, gender and race/ethnicity adjusted log-binomial or Poisson regression models (population group and survivors or siblings; high risk and low risk survivor groups). Results will be reported as risk ratios with 95% confidence intervals.

Hypothesis #2. The impact of potential personal predictors of compliance with the recommended screening guidelines (age at diagnosis, educational attainment, insurance status, concern about future health, and possession of information about previous cancer treatment) will be examined in four separate (for each outcome) multiple variable logistic regression models, adjusting for current age, gender (where appropriate) and race/ethnicity.

Special considerations: Analysis will be completed by Kirsten Ness at St Jude Children's Research Center.

5. SAMPLE TABLES

Table 1 – Demographic, disease and health status data

	Total		Siblings		Population control	
	N	%	N	%	N	%
Age group at time of questionnaire						
18-24 years						
25-34 years						
35+ years						
Gender						
Female						
Male						
Race/Ethnicity						
White						
Native American						
Asian						
Black						
Hispanic						
Other						
Insurance status						
Canadian						
US private insurance						
US private insurance						
US not insured						
Household income (annual)						
<\$20,000						
\$20-59,000						
\$60-99,999						
\$100,000+						
unknown						
Education						
<High school						
High school graduate						
College graduate						
Unknown						
Marital Status						
Married or living as married						
Single						
Divorced or separated						
Unknown						
Employment						
Employed or caring for home						
Looking for work or unable to work						
Student						
Age at diagnosis						
0-4 years						

5-9 years
10-14 years
15-19 years

Cancer diagnosis

Leukemia
CNS
Hodgkin disease
Non-Hodgkin lymphoma
Wilms' tumor
Neuroblastoma
Bone tumor
Sarcoma

Breast cancer risk group*

Yes
No

Colon cancer risk group**

Yes
No

Skin cancer risk group***

Yes
No

Health status (perceived general health)

Excellent/good/very good
Fair/poor

Health status (mental health)

Normal
Abnormal (lowest quartile on BSI)

Health status (physical impairment/activity limitation)

Yes
No (lowest quartile on SF-36 physical fn)

Health status (pain as a result of previous cancer)

Yes
No

Health status (anxiety as a result of previous cancer)

Yes
No

Treatment summary/medical records -survivor

Yes
No

Treatment summary/medical records –primary care doctor

Yes
No

* Female, received chest or mantle radiation, ≥ 25 years of age

**Received ≥ 30 Gy to abdomen/pelvis/spine (thoracic, lumbar, sacral)

***Received any radiation

Table 2a: Screening: colonoscopy

	High risk survivors*	Standard risk survivors**	Siblings**	General population**
Total number in group				
Had test within recommended period				
Had test, but not within recommended period				
Never had test				
Don't know				

* treated with ≥ 30 Gy radiation to the abdomen/pelvis/spine AND at least 10 years after radiation or ≥ 35 years (whichever is later)
 ** ≥ 50 years old

Table 2a: Screening: mammography

	High risk survivors*	Standard risk survivors**	Siblings**	General population**
Total number in group				
Had test within recommended period				
Had test, but not within recommended period				
Never				
Don't know				

* female, radiation to chest or mantle AND ≥ 25 years old and ≥ 8 years off therapy
 **female, ≥ 40 years old (US) or ≥ 50 years old (Canada)

Table 2c: PAP test

	Survivors	Siblings	General population
Total number in group			
Had test within recommended period			
Had test, but not within recommended period			
Never had test			
Don't know			

All females ≥ 21 years old

Table 2d: Dermatologic exam

	High risk survivors*	Standard risk survivors**	Siblings**	General population**
Total number in group				
Had test within recommended period				
Had test, but not within recommended period				
Never				
Don't know				

* received any radiation

**no history of receiving radiation

6. REFERENCES

1. Neglia JP, Friedman DL, Yasui Y, et al. Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study. *J Natl Cancer Inst* 2001;93(8):618-29.
2. Jenkinson HC, Hawkins MM, Stiller CA, Winter DL, Marsden HB, Stevens MC. Long-term population-based risks of second malignant neoplasms after childhood cancer in Britain. *Br J Cancer* 2004;91(11):1905-10.
3. Kenney LB, Yasui Y, Inskip PD, et al. Breast cancer after childhood cancer: a report from the Childhood Cancer Survivor Study. *Ann Intern Med* 2004;141(8):590-7.
4. Perkins JL, Liu Y, Mitby PA, et al. Nonmelanoma skin cancer in survivors of childhood and adolescent cancer: a report from the childhood cancer survivor study. *J Clin Oncol* 2005;23(16):3733-41.
5. Children's Oncology Group Late Effects Committee and Nursing Discipline. Long-term follow-up guidelines for survivors of childhood, adolescent and young adult cancers. Arcadia, CA: Children's Oncology Group; Version 2.0, March 2006; Available on-line: www-survivorshipguidelines.org.
6. Yeazel MW, Oeffinger KC, Gurney JG, et al. The cancer screening practices of adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Cancer* 2004;100(3):631-40.
7. Long term follow up of survivors of childhood cancer: A national clinical guideline. Scottish Collegiate Guidelines Network. (Accessed May 1st, 2007, at <http://www.sign.ac.uk/pdf/sign76.pdf>.)
8. Therapy based long term follow up: practice statement. In: Skinner R, Wallace WHB, Levitt GA, eds. 2nd ed: United Kingdom Children's Cancer Study Group; 2005.