

CHILDHOOD CANCER SURVIVOR STUDY
Analysis Concept Proposal
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0. TITLE: General and risk-based health care: Comparison of the United States and Canada

0. WORKING GROUP INVESTIGATORS:

This proposed study will be within the Cancer Control Committee. Proposed investigators include:

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0. BACKGROUND AND RATIONALE:

The population of adult survivors of childhood cancer continues to grow rapidly, with a projected prevalence of as many as one survivor for every 250 young adults in the United States by the year 2010¹. Two-thirds of these survivors are likely to experience at least one late effect of their cancer or its therapy, with one-third describing a late effect that is moderate or severe in intensity². Consequently, these patients require regular and appropriately focused medical follow-up. Data from the CCSS suggests that although 90% of adult survivors of childhood cancer reported some contact with the medical system³, over half of these patients had not been seen by an MD for evaluation of a cancer related problem during the previous 2 years⁴. Furthermore, the likelihood of a cancer related visit or a physical exam decreases as patients age and their risk for modifiable late effects increases³.

Increasing knowledge about the late effects of cancer therapy have led to recommendations for periodic monitoring based on prior therapeutic exposures⁵. Although the strength of evidence for the follow-up of child cancer survivors varies between recommendations, several monitoring strategies are well supported by the available evidence. Patients exposed to anthracycline

chemotherapy are at risk for cardiac dysfunction, particularly if they have been exposed to doses greater than 300 mg/m². This group warrants regular monitoring of cardiac function^{6,7}. However, almost half of the CCSS cohort exposed to this dose of anthracycline report no such follow-up³. Similarly, females who have received radiation to the chest have been shown to be at increased risk for the development of subsequent breast cancer⁸. Recommendations for follow-up include breast self exam (BSE), clinical breast exam (CBE) and mammography (in those patients older than 27 years or more than 8 years from therapy). In a study of 90 female survivors of Hodgkin's disease who were more than 8 years off therapy and who had received mantle radiation, only 53% had received a mammogram in the previous two years⁹. In the CCSS cohort, only 56.9% of eligible survivors over 30 years old had ever had a mammogram and only 34.0% practiced regular BSE¹⁰. In this cohort, patients without health insurance were less likely to have had a CBE in the past year when compared to those with health insurance or Canadians (OR=0.58, 95% CI=0.47-0.72).

Several studies have investigated the barriers to appropriate care in childhood cancer survivors¹⁰⁻¹². In one such study, a Delphi panel of young adult survivors ranked lack of health insurance as the most important health system related barrier to care¹¹. A separate panel of American health policy experts also identified inadequate or no health insurance as an important barrier to the care of this population¹². The designation of cancer as a "pre-existing condition", insufficient coverage of preventive care, and lack of finances related to the cancer were perceived as impacting on access to adequate health insurance. These perceptions of both survivors and caregivers correspond with observations from the CCSS. Survivors without health insurance are more likely to have not had contact with a health care provider, general physical examination or a cancer related medical visit when compared to those survivors with health insurance (OR=2.34, CI=1.97-2.27)³.

The Canada Health Act and prior federal legislation adopted in Canada is intended to provide all Canadian residents universal access to health care without discrimination between clients based on age, lifestyle or health status. As a result, there are no insurance barriers to Canadian cancer survivors receiving regular and appropriate long-term care, although the availability of these resources varies by geographic location. No comparative data exist for access to long-term

follow-up care in childhood cancer survivors living in the United States compared to Canada. A study in patients with diabetes, another group that requires regular access to health care, demonstrated that Canadian patients were more likely to have contact with a physician than comparable patients living in the United States (OR=3.02, 95% CI=1.03-8.84)¹³.

0. SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES:

The purpose of the present study is to compare the prevalence of general health care and *basic* and *optimum* risk-based care in adult survivors of childhood cancer between residents of Canada and the United States. Data regarding Canadian patients will be derived from members of the CCSS cohort who were treated at The Hospital for Sick Children in Toronto, Canada. Data on US patients will be derived from the remainder of the cohort, with the analysis adjusted for sociodemographic differences between the two populations. The primary objective is to compare care between two different healthcare systems – thus all US patients (i.e. those with and without health insurance) will be combined in a single group. Secondary analyses will compare three groups: Canadian residents, US residents with health insurance and US residents without health insurance.

As a sub-analysis, we will assess whether there is an interaction between country of residence and (i) health status and/or (ii) knowledge of risks, in order to determine if patients with poorer health status or greater knowledge of their treatment-related risks are more likely/able to access care depending on their country of residence.

Hypothesis #1: Canadian residents will report higher rates of (i) general health care, (ii) basic risk-based care and (iii) optimum risk-based care than US residents.

Hypothesis #2: Differences in rates of care will be most pronounced when comparing Canadian residents to US residents without health insurance.

Hypothesis #3: Differences in rates of basic risk-based care and optimum risk-based care between Canadians and Americans will be greatest in survivors with (i) diminished health status

and (ii) greater knowledge of treatment-related risks, as these two groups are most likely to seek access to appropriate care

0. ANALYSIS FRAMEWORK:

Sample

The study sample will consist of all survivors who responded to the second follow-up questionnaire. Participants from The Hospital for Sick Children in Toronto will comprise the Canadian cohort with all remaining patients comprising the US cohort. As of May 2005, there were 1046 participants from the Hospital for Sick Children.

Outcomes of interest (all variables from 2nd f/u questionnaire where available)

General and cancer-related health care will be defined by responses to the following questions on the 2nd follow-up questionnaire:

- A1 (health care providers seen or spoken to)
- A2 (where did you receive your health care)
- A3 (how many times did you see a physician)
- A4 (reason for visit)
- A5 (how many of these visits were related to your previous cancer or similar illness)

General health care is defined as a 'yes' answer to QA1 and will be quantified by the response to QA3.

Cancer-related care is defined as 'yes' responses to QA1 and QA5 and will be reported as none, LTFU or cancer center, or other.

Basic risk-based care is defined as including each of the following components:

- a. Cancer-related care (see definition above)
- b. "Your doctor was familiar with health problems that develop after childhood cancer" (QA7)
- c. "Your doctor gave you advice about what to do to reduce risks" (QA8a)
- d. "Your doctor discussed or ordered medical screening tests" (QA8b)

Optimum risk-based care: For this outcome, we will use the subset of the study population who received either an anthracycline or chest/mantle radiation. These are the two exposures for which there has been general consensus for screening. The frequency of optimum risk-based care will be defined by:

- The proportion of males and females who received $\geq 300 \text{ mg/m}^2$ of an anthracycline or any anthracycline plus chest radiation who report an echocardiogram within the past two years (QB1).
- Proportion of females who received chest or mantle radiation and who are 27 years of age or older and report a mammogram in the past two years (QB4).

Independent (exploratory) variables

E. Sociodemographic variables:

- Country of residence
- Health insurance (Canadian, insured, not insured)
- Age at interview
- Gender
- Race/ethnicity
- Household income
- Education
- Marital status
- Employment status

E. Disease/treatment variables:

- Cancer diagnosis
- Age at diagnosis
- Chemotherapy vs. surgery vs. radiation vs. BMT vs. combination
- Anthracycline chemotherapy (yes/no; if yes \rightarrow cumulative dose)
- If “yes” to radiation \rightarrow did they receive mantle or chest radiation

E. Health status

- 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)

E. Knowledge of risks (questions T7-T11 depending on exposure)

- T7: Chest/spine radiation is risk for heart disease
- T8: Chest radiation is a risk for breast cancer
- T9: Monthly breast exam may detect tumors early
- T10: Corticosteroids increase the risk of osteoporosis
- T11: Relationship between inactivity and osteoporosis

Data Analysis Plan

Hypothesis #1: The proportions of survivors classified as receiving general health care, basic risk-based care and optimum risk-based care will be calculated overall and by residence (Canadian, US) and compared between groups with Chi-squared statistics. Results from univariate and multiple variable models will be reported as odds ratios with 95% confidence intervals. Descriptive statistics for sociodemographic, disease and treatment variables, including means and standard deviations; frequencies and proportions, will be calculated for sociodemographic, disease and treatment variables overall and by residence. In addition, sociodemographic, disease and treatment variables will be evaluated as independent predictors of the outcomes in univariate models, and as confounders or modifiers of the health care outcomes by place of residence in multiple variable logistic regression models.

Hypothesis #2: The analysis plan described in hypothesis #1 will be repeated for three groups of patients: Canadians, US with health insurance, US without health insurance

Hypothesis #3: In order to account for the possibility that either poorer health status or greater knowledge of risks influences risk-based care, we will construct regression models that include residence status, health status and knowledge of risks as predictors of receiving risk based care, and assess for interactions between these variables. In particular, we aim to determine if discrepancies in care by country of residence are greatest for those patients with poor health status (e.g. those reporting “poor” or “fair” general health, or those in lowest quartile on BSI) or greatest knowledge of risk (calculated from T7-T11).

0. SAMPLE TABLES

Table 1 – Demographic, disease and health status data

	Total		Canada		United States		P-value*
	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 insured							
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

Cardiac risk group*

Yes
No

Breast 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

Knowledge of risks

Good
Bad

* Received ≥ 300 mg/m² of an anthracycline or any anthracycline plus chest radiation

** Female, received chest or mantle radiation, ≥ 27 years of age

Table 2 – Health care received

	Total		Canada		United States		P-value*
	N	%	N	%	N	%	
General health care							
Yes							
No							
Cancer related care							
Yes							
No							
Basic risk-based care							
Yes							
No							
Optimum risk-based care							
Yes							
No							

Table 3 – Adjusted OR and 95 % CI for survivor care in Canadian and US survivors

	General health care		Basic risk-based care		Optimum risk based care	
	OR	95 % CI	OR	95 % CI	OR	95 % CI
Residence						
Canada	1.0		1.0		1.0	
US						
Gender**						
M						
F						

** Table will be constructed to include those sociodemographic and disease variables that are significant in multiple variable modeling

0. REFERENCES

1. Keene N, Hobbie W, Ruccione KS. *Childhood Cancer Survivors: A Practical Guide to Your Future*. Sebastopol, CA: O'Reilly & Associates Inc.; 2000.
2. Oeffinger KC, Eshelman DA, Tomlinson GE, Buchanan GR, Foster BM. Grading of late effects in young adult survivors of childhood cancer followed in an ambulatory adult setting. *Cancer*. 2000;88:1687-1695.
3. Oeffinger KC, Mertens AC, Hudson MM, et al. Health care of young adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Ann Fam Med*. 2004;2:61-70.
4. Oeffinger KC, Eshelman DA, Tomlinson GE, Buchanan GR. Programs for adult survivors of childhood cancer. *J Clin Oncol*. 1998;16:2864-2867.
5. Landier W, Bhatia S, Eshelman DA, et al. Development of risk-based guidelines for pediatric cancer survivors: the Children's Oncology Group Long-Term Follow-Up Guidelines from the Children's Oncology Group Late Effects Committee and Nursing Discipline. *J Clin Oncol*. 2004;22:4979-4990.
6. Lipshultz SE, Lipsitz SR, Mone SM, et al. Female sex and drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. *N Engl J Med*. 1995;332:1738-1743.
7. Lipshultz SE, Colan SD, Gelber RD, Perez-Atayde AR, Sallan SE, Sanders SP. Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. *N Engl J Med*. 1991;324:808-815.
8. Robison LL, Green DM, Hudson M, et al. Long-term outcomes of adult survivors of childhood cancer. *Cancer*. 2005;104:2557-2564.
9. Diller L, Medeiros Nancarrow C, Shaffer K, et al. Breast cancer screening in women previously treated for Hodgkin's disease: a prospective cohort study. *J Clin Oncol*. 2002;20:2085-2091.

10. 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;100:631-640.
11. Zebrack BJ, Eshelman DA, Hudson MM, et al. Health care for childhood cancer survivors: insights and perspectives from a Delphi panel of young adult survivors of childhood cancer. *Cancer*. 2004;100:843-850.
12. Mertens AC, Cotter KL, Foster BM, et al. Improving health care for adult survivors of childhood cancer: recommendations from a delphi panel of health policy experts. *Health Policy*. 2004;69:169-178.
13. Klarenbach SW, Jacobs P. International comparison of health resource utilization in subjects with diabetes: an analysis of Canadian and American national health surveys. *Diabetes Care*. 2003;26:1116-1122.