

CHILDHOOD CANCER SURVIVOR STUDY

Analysis Concept Proposal

- I. **Title:** Marriage Patterns in Adult Survivors of Non-CNS Childhood Cancers
- II. **Working Group and Investigators:** This proposed publication will be within the Epidemiology/Biostatistics Working Group. Proposed investigators will include:

Chris Janson	christopher.m.janson@yale.edu	617-645-4281
Nina Kadan-Lottick	nina.kadan-lottick@yale.edu	203-785-4640
Amanda Termuhlen	atermuhlen@chi.osu.edu	
Ann Mertens	mertens@epi.umn.edu	
Wendy Leisenring	wleisenr@fhcrc.org	
Leslie Robison	les.robison@stjude.org	
Lonnie Zeltzer	lzeltzer@mednet.ucla.edu	
Sui Tsang	sui.tsang@yale.edu	
Dan Green	daniel.green@roswellpark.org	
Others		

III. **Background and Rationale:**

Cure rates for childhood cancer have risen considerably over the past several years, with overall five-year survival rates now above 70 percent (Ries et al., 1999). As the population of childhood cancer survivors has grown, so too has recognition that survivors face unique risks related to late effects of their malignancy and subsequent therapy. These late effects range from the physical, including organ dysfunction and second neoplasms, to the psychosocial, and can have profound effects on survivor quality of life.

Marriage represents an important measure of psychosocial functioning, and as such, can be used to assess the adaptation of childhood cancer survivors to adult life (Rauck et al., 1999). Success in marriage requires navigation from adolescence to adulthood, including development of an independent sense of self and emotional maturity. Some studies have suggested impaired psychological development in survivors that could translate to poor marriage outcomes. For example, a small study of 27 survivors by Kokkonen et al. found that up to half of subjects showed delayed psychosexual maturation, with late separation from parents (Kokkonen et al., 1996). Initial analysis of the CCSS cohort showed that survivors were less likely to have married than age-matched controls from the 1995 U.S. census (Rauck et al., 1999).

A recent CCSS study focused on survivors of pediatric CNS malignancy and found lower rates of marriage than non-CNS cancer survivors, sibling controls, and the U.S. population at large (Termuhlen et al., in preparation). Investigators found that male gender and tri-modal therapy (surgery, radiation, and chemotherapy) were the strongest predictors of non-marriage within the CNS survivors. Male survivors were less likely to be married across the entire CCSS cohort. Interestingly, late effects such as fertility problems, neurologic sequelae, and altered physical appearance were not associated with non-marriage in CNS tumor survivors. The results of this study were consistent with

prior analyses of marriage rates in CNS tumor survivors. Byrne et al. compared 2170 survivors treated from 1945-1975 with 3138 sibling controls. Byrne found that, while survivors as a whole were less likely to marry than controls, the group at highest risk for non-marriage was the subset of male CNS tumor survivors (Byrne et al., 1989). The manuscript in preparation by Termuhlen et al. does not necessarily represent the experience of non-CNS cancer survivors because of differences in cognitive and neurological effects of therapy.

Marriage patterns have not been studied in a large, representative sample of long-term survivors of non-CNS childhood cancer. The Childhood Cancer Survivor Study provides a unique opportunity for such analysis. In this proposal, we will 1) describe patterns of marriage, and 2) identify patient and treatment characteristics associated with marriage and divorce. Such an analysis is particularly timely because data available from the Follow-Up 2 survey will allow us to examine the contribution of psychosocial and neurocognitive functioning to marriage, an important indicator of the ongoing burden of previous cancer therapy.

IV. Specific Aims:

This project will characterize marriage patterns in survivors of non-CNS childhood cancer. Specifically, we propose to:

1. Describe marriage patterns, including age at first marriage, percentage ever married, and percentage ever divorced. Information from the baseline and follow-up surveys will be combined for a complete picture of survivor marriage patterns.
2. Identify patient and treatment characteristics associated with higher rates of adverse marriage outcomes, namely a.) non-marriage and b.) divorce.

V. Hypotheses:

1. Survivors of non-CNS cancers, compared to sibling and U.S. census population-based controls, will have similar rates of marriage and divorce.
2. The following patient and treatment characteristics will be associated with higher rates of non-marriage (i.e. never-married), in case-case comparisons.
 - a. Adolescent age at diagnosis (age 13-20)
 - b. History of recurrence or new cancer
 - c. Self-reported interference of health with daily life (disease burden)
 - d. Unemployment
 - e. Low personal income
 - f. Psychological distress
 - g. Impaired executive function, as assessed by neurocognitive scores
 - h. Survivor infertility
 - i. Growth abnormalities, including diminished final height and growth hormone

- deficiency
 - j. History of bone marrow transplantation
 - k. History of CNS irradiation
3. The following patient and treatment characteristics will be associated with higher rates of divorce, in case-case comparisons.
- a. Self-reported interference of health with daily life (disease burden)
 - b. Unemployment
 - c. Low personal income
 - d. Psychological distress
 - e. Impaired executive function
 - f. Survivor infertility
 - g. History of recurrence or new cancer

VI. Analysis Framework:

1. Subject population:
- a. CCSS cohort members, excluding survivors of CNS malignancy, and restricted to those subjects age 15 years and older at the time of completion of the baseline. The age restriction will ensure that all subjects are eligible for marriage and divorce for the length of the study. Self-reported information about marital status and other characteristics will be obtained from the baseline, as well as both follow-up surveys.
 - b. Sibling controls, restricted to those subjects age 15 years and older at the time of the baseline.
 - c. U.S. population, as measured by the 2002 U.S. Census Bureau
 - i. Data from the 2002 Current Population Survey (CPS) includes marital status, stratified by gender, current age (15 years and older), race, and personal earnings. Details can be found at the following website:
<http://www.census.gov/population/www/socdemo/hh-fam/cps2002.html>.
2. Outcomes of interest:
- a. Marital status
 - i. Never-married:
 - From CCSS: Defined as “single” on FU2 and “single” on FU1 and “never married” on baseline. (In theory, “single” on FU2 should equal “never married,” because selecting the “single” option meant not selecting the “separated,” “divorced,” or “widowed” options. However, cross-checking with FU1 and the baseline will ensure accuracy.)
 - From 2002 CPS: Defined as “never married.”
 - Note: The CCSS includes a “living with partner as married” option, while the U.S. Census does not. Those members of the U.S. population who may have been living

as married would be catalogued as “never married.” Therefore, for comparison with the U.S. population, “living with partner as married” will be defined as single. Living as married, however, is an important outcome and measure of social achievement, and it will be included in additional descriptive analyses. For case-case comparisons, “living with partner as married” will be defined as married, since it represents a positive outcome.

ii. Ever-divorced:

- From CCSS: Defined as “divorced” or “separated” on FU2, or “divorced” or “separated” on FU1, or “divorced” or “separated” on baseline. (Note: We acknowledge that some divorce cases will be missed in this way. For example, an individual who responded “married” on FU1 may have ended that relationship and since started a new one. On FU2, they will again respond “married.” The number of divorce cases missed in this manner, however, will be negligible.)
- From 2002 CPS: Defined as “divorced” or “separated.” (Note: This represents “currently divorced”; “ever-divorced” is not available from the census data. Thus, when comparing CCSS subjects with U.S. population, we will use “currently divorced” as the outcome. When comparing within the CCSS cohort, we will use “ever-divorced.”)

b. Age at first marriage (Baseline L#4); Type of first marriage (Baseline L#5); Number of marriages (Baseline L#3): This data is available only for those subjects married at the time of the baseline. It will be included in a descriptive analysis, with comparison made between survivors and siblings.

3. Explanatory variables:

- a. Gender
- b. Current age
- c. Age at diagnosis
 - i. Comparison: age 13-20 years vs. age <13 years
- d. Cancer diagnosis
- e. Treatment modality
 - i. Abstracted from medical records.
 - ii. Comparison: CNS irradiation vs. none
 - iii. Comparison: BMT vs. no BMT
- f. Treatment duration
 - i. Abstracted from medical records.
 - i. Comparison: Treatment >12 months vs. <12 months

- g. Infertility
 - i. Documented infertility: All females with ovarian failure have been identified based on question 19 from follow-up 1. No similar dataset exists for males.
 - ii. Perceived infertility: Defined as “yes” to Baseline E13.
 - iii. Note: Documented infertility is available for females only, while perceived infertility is available for all subjects. Pending preliminary analysis, the most appropriate use of these variables will be decided.
 - iv. Note: Some cases of infertility will be missed in this fashion, as infertility was not re-assessed on the FU2. We will therefore potentially underestimate the association of infertility history and marital outcome.
- h. Diminished height
 - i. Current height obtained from FU2 7.
 - ii. Diminished height defined as height below the tenth percentile for age, gender, and ethnicity, as reported by the CDC.
(<http://www.cdc.gov/nchs/fastats/bodymeas.htm>)
 - iii. Comparison: height below the tenth percentile vs. height above the tenth percentile
- i. History of growth hormone deficiency
 - i. Defined as “yes” to Baseline E8.
 - ii. Comparison: history of deficiency vs. none
- j. History of recurrence or secondary malignancy
 - i. Defined as “yes” to Baseline K1 or “yes” to FU1 17 or “yes” to FU2 R1.
 - ii. Comparison: History of recurrence/SMN vs. none
- k. Perceived disease burden
 - i. Defined as “low” if response to FU2 E20 “not at all” or “slightly.”
 - ii. Defined as “moderate” if response to FU2 E20 “moderately.”
 - iii. Defined as “severe” if response to FU2 E20 “quite a bit” or “extremely.”
 - iv. Comparison: severe vs. moderate vs. low
- l. Employment status
 - i. Defined as “employed/retired” if “working full-time” or “working part-time” or “caring for home / not seeking paid work” or “retired” or “student” on FU2 4.
 - ii. Defined as “unemployed, looking” if “unemployed and looking for work” on FU2 4.
 - iii. Defined as “disabled” if “unable to work due to illness or disability” on FU2 4.
 - iv. Comparison: disabled vs. unemployed/looking vs. employed/retired
- m. Personal income
 - i. Obtained from FU2 S3.
 - ii. Comparison: no income vs. income < 40,000 vs. income > 40,000
- n. Executive functioning
 - i. Measured by the BRIEF (FU2 J1-25).

- ii. Standardization of BRIEF performance is currently in progress by Dr. Zeltzer and Dr. Kadan-Lottick.
 - iii. Comparison will be preliminarily defined as severely impaired vs. moderately impaired vs. not impaired.
 - o. Psychosocial distress
 - i. Measured by the Brief Symptom Inventory (Baseline J16-35, FU2 G1-18)
 - ii. As above, standardization of these measures is in progress and will be incorporated into the current analysis when available.
 - iii. Comparison will be preliminarily defined as significant vs. moderate vs. low distress.
 - iv. For the analysis, the more severe of each subject's two BSI scores (Baseline and FU2) will be used. This variable can more accurately be defined as a history of psychosocial distress.
 - p. Race
 - q. Educational status
- 4. Statistical Analysis:
 - a. In univariate analysis, we will determine the association between each predictor (explanatory variable) and outcome. Unadjusted odds ratios with 95% confidence intervals will be calculated to compare the probability of outcomes among survivor comparison groups, as defined by explanatory variables.
 - b. Multivariate analysis will be used to determine the independent role of each variable. For the multivariate analysis, we will include gender, current age, and those variables which were significant or marginally significant in the univariate analysis. The independent explanatory value of each variable will be expressed in adjusted odds ratios with 95% confidence intervals.
 - c. We will test for effect modification and confounding variables. Potential effect modifiers include gender and executive function on never-been-married outcome.
 - d. If gender is a significant effect modifier, we will carry out separate analyses for male and females.
 - e. Sample tables are included in section IX below.

VII. **Additional Considerations:**

Chris Janson is a 4th year Yale medical student, who will be mentored by Nina Kadan-Lottick. Chris is funded by the Yale School of Medicine, Department of Student Research for a semester of full-time research. As part of this research, he will attend the annual CCSS Investigator's Meeting. The statistical analysis for this study will be done at Yale, with final review by the Statistics Center.

VIII. **References:**

Byrne J, Fears TR, Steinhorn SC, et al. Marriage and divorce after childhood and adolescent cancer. *JAMA* 1989; 262: 2693-2699.

Kokkonen J, Vainionpaa L, et al. Physical and psychosocial outcome for young adults with treated malignancy. *Pediatr Hematol Oncol* 1996; 14: 223-232.

Rauck A, Green D, Yasui Y, Mertens A, and Robison L. Marriage in the survivors of childhood cancer: A preliminary description from the Childhood Cancer Survivor Study. *Med Pediatr Onc* 1999, 33:60-63.

Ries L, Smith M, Gurney J, et al. Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995. Bethesda, MD: National Cancer Institute SEER Program; 1999. NIH publication No. 9904649.

Termuhlen A, Williamson J, Yasui Y, Green D, and Robison L. Late effects and marriage in survivors of pediatric and adolescent central nervous system malignancy: A report from the Childhood Cancer Survivor Study. In preparation.

