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Marriage and Divorce in Survivors of Childhood Cancer: A Report from the Childhood Cancer Survivor Study

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Abstract

MARRIAGE AND DIVORCE IN SURVIVORS OF CHILDHOOD CANCER: A REPORT FROM THE CHILDHOOD CANCER SURVIVOR STUDY. Christopher M. Janson, Amanda M. Termuhlen, John A. Whitton, Leslie L. Robison, Lonnie K. Zeltzer, and Nina S. Kadan-Lottick. Section of Hematology-Oncology, Department of Pediatrics, Yale University School of Medicine, New Haven, CT.

In this report from the Childhood Cancer Survivor Study (CCSS), we described marriage and divorce rates in survivors of childhood cancer, as compared to a sibling control group and the general U.S. population. We also sought to identify patient and treatment characteristics that were associated with survivor marital status. This study included 8,930 five-year survivors of childhood malignancy and 2,855 sibling controls participating in the CCSS. Data on marital status, sociodemographic factors, and current health status were obtained from questionnaires; detailed disease and treatment histories were available from medical records. Marital status of the U.S. population was obtained from the 2002 Current Population Survey of the U.S. Census. We found that survivors were more likely to have never married than both sibling (odds ratio [OR] = 1.79; 95 % CI = 1.65-1.94; $p < 0.0001$) and population controls (OR = 2.29; 95 % CI = 2.19-2.38; $p < 0.0001$), with persistence of trends across age and gender strata. Once married, survivors divorced at rates equivalent to controls. In adjusted analysis, we found that several survivor characteristics predicted never-married status, including treatment involving cranial radiation (OR = 2.41; $p < 0.0001$), CNS tumor diagnosis (OR = 2.05; p

< 0.0001), history of growth hormone deficiency (OR = 2.02; p < 0.0001), and unemployment secondary to disability (OR = 1.78; p = 0.0001). Survivor characteristics predictive of divorce included unemployment (OR = 1.91; p < 0.0001, for unemployed or disabled), lower educational achievement (OR = 1.74; p < 0.0001, for non-college graduates), and psychological distress (OR = 1.60; p < 0.0001). This study confirms prior reports of lower marriage rates in survivors of childhood cancer, providing further evidence that this population struggles with psychosocial adjustment to adult life.

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Introduction

Advances in pediatric cancer care have achieved overall five-year survival rates of almost 80 percent, a dramatic increase from rates of less than 30 percent in 1960 [1]. As a result, the majority of children diagnosed with cancer can now expect to survive into adulthood. As one author eloquently stated, "children with cancer become adults who had cancer" [2]. The survivor population increases each year, and recent reports estimate that greater than 1 in 640 adults aged 20 to 39 is a survivor of childhood malignancy [3].

Although cure has become an achievable goal, survivorship is not without complications. Modern treatment regimens employ combinations of chemotherapy, radiation, and surgery, each of which is associated with a range of delayed toxicities. Furthermore, malignancy itself confers certain risks, relating to both host genetic predisposition and the systemic effects of illness. Recently, researchers have focused efforts on identifying these long-term effects, with hopes of minimizing morbidity and improving survivor quality of life.

The physical health consequences of cancer have been extensively characterized, and survivors are known to be at increased risk for an array of adverse outcomes. For example, survivors are at elevated risk for the development of new primary cancers [4]. These subsequent malignant neoplasms (SMNs) are the product of both genetic susceptibility and therapeutic exposures, particularly radiation, alkylating agents, and epipodophyllotoxins [4-6]. Survivors also experience high rates of cardiovascular morbidity, including the development of cardiomyopathy, arrhythmias, congestive heart failure, and even sudden cardiac death [7]. Cardiovascular late effects are associated with exposure to anthracycline drugs and mediastinal radiation [7]. Survivors have

additionally been shown to be at increased risk for pulmonary complications [8], infertility [7], impaired growth [7, 9], and endocrine dysfunction [10].

These late effects have a profound effect on survivor morbidity, mortality, and overall health status. In a recent report, Oeffinger et al. estimated that greater than 60 percent of a large survivor cohort suffered at least one chronic health condition; this condition was severe or life-threatening in more than 25 percent of survivors [11]. Survivor mortality rates exceed that of the general population by 8-fold, with persistence of this elevation for at least 25 years after diagnosis [12, 13]. Although disease recurrence accounts for greater than 50 percent of deaths, treatment-related sequelae contribute substantially to excess survivor mortality [12]. Finally, when surveyed about their health status, greater than 40 percent of former patients reported negative effects in at least one of the following domains: general health, mental health, functional status, limitations in activity, cancer-related pain, and cancer-related fear or anxiety [14].

While the physical health consequences of survivorship have been well-established, the psychosocial sequelae have been more difficult to elucidate. Many studies have concluded that survivors adjust well to life after cancer, citing rates of psychiatric morbidity that are equivalent to or less than population norms [15, 16]. On the other hand, subsets of survivors have been shown to be at particular risk for depression [17-19], anxiety [18], post-traumatic stress disorder [20-22], and even suicidal thoughts [23, 24]. In a systematic review of the literature, Eiser et al. noted that standardized measures of psychological health often failed to identify issues, where interview and other techniques revealed important concerns [15].

Chang [18], Zeltzer [25], and others have proposed an alternative approach to assessing the psychosocial well-being of survivors – namely, the consideration of survivor performance in the tasks of adulthood. These outcomes represent more sensitive and meaningful markers of adjustment, and provide insight into the ability of survivors to pursue a normal life. Along these lines, survivors have been shown to experience lower achievement in education [26], higher rates of unemployment [16, 27], and difficulty obtaining health insurance [16, 28].

Marriage represents one such social outcome that can be used to gauge the adaptation of survivors to life after cancer. Although the institution of marriage has undergone many changes in modern times, it remains a "symbol of successful self-development" and an aspiration for the majority of young adults in today's society [29]. Relationships are challenging for all adults, but may be especially difficult for survivors, who struggle with the burdens of past disease. In one study, 29 percent of childhood cancer survivors cited disability or prior illness as a barrier to marriage [30]. Uncertainty about future health may also frustrate survivor relationships. Zebrack et al. found that the more survivors worried about their health, the more negative their self-image and outlook on life [31].

Disruptions in psychological development may also interfere with the ability of survivors to form intimate relationships. As Lansky noted, these "developmental disruptions may have special significance for the adolescent, who is already struggling with unique issues of separation, changes in peer relationships, [and] emergent sexuality" [17]. Multiple studies have documented delayed psychosexual maturation in survivors, with late separation from parents [32, 33]. Stern et al. found survivors to have impaired

sexual and social self-images [34], while Madan-Swain et al. described higher rates of body image disturbances in adolescent survivors, compared to controls [35]. Survivors have reported difficulty meeting others, and, in one study, were less likely to have close friends than population controls [36, 37]. Similarly, Gray et al. reported higher rates of relationship dissatisfaction in survivors, when compared to controls [38].

The available literature on marriage outcomes after childhood cancer is limited by inconsistent results and small, non-representative samples. Early investigations, including a study of 142 former patients by Li and Stone, reported no difference in marriage rates between survivors and the general population [39]. In contrast, Byrne et al. compared 2170 survivors with 3138 sibling controls, and found a higher likelihood of non-marriage in cases [40]. This often cited study, although large and comprehensive, included patients from an older treatment era, so its results may not be generalizable to current survivors. Several recent studies have corroborated Byrne's finding of a marriage deficit in survivors, although none has approached his study in sample size. Moreover, many of these studies have focused on specific demographic or disease sub-groups, including a study of 500 Dutch cases by Langeveld et al., and an analysis of 694 lower extremity bone tumor survivors by Nagarajan et al. [41, 42].

A further limitation of the current literature has been its failure to explore the underlying causes of observed patterns. For example, survivors of central nervous system (CNS) tumors have been shown consistently to be the group at highest risk for adverse marriage outcomes [40]. In Byrne's study, male CNS tumor survivors were the least likely to be married. When they did marry, they were older, and their first

marriages were shorter, compared to other cancer diagnosis groups. The underlying mechanism of this observation has yet to be fully characterized.

The Childhood Cancer Survivor Study (CCSS) provides a unique opportunity to improve our understanding of marriage outcomes. This cohort was established in 1994 as a means of investigating long-term outcomes in survivors of childhood cancer [43]. It consists of approximately 14,000 cases, representing patients who survived at least five years after diagnosis with cancer. Subjects were diagnosed prior to age 21, between 1970 and 1986, and with a broad distribution of cancer types. For each of the cases, detailed disease and treatment data are available, as well as sociodemographic information. In addition, participants underwent standardized self-report assessment of mental health and neurocognitive status. Approximately 3000 siblings were included in the cohort to serve as a comparison group. Cohort members have been followed for several years after diagnosis and across a range of marriageable ages.

A preliminary report from the CCSS described lower marriage rates in survivors when compared to age-matched controls from the 1995 U.S. population [44]. Marriage outcomes are dynamic, and the longitudinal nature of the CCSS cohort allows for reassessment of survivor functioning in this area. This is particularly pertinent for marriage which is an age-dependent phenomenon. Furthermore, the recent availability of standardized psychosocial and neurocognitive data for cohort participants provides the opportunity to explore new explanatory factors.

Statement of Purpose

In this paper, we seek to 1) describe marriage and divorce rates in 8930 childhood cancer survivors from the Childhood Cancer Survivor Study (CCSS) cohort, with comparison to 2855 sibling controls and data from the U.S. Census; and 2) identify patient and treatment factors that affect marital status. In particular, we will examine the contribution of psychosocial distress and neurocognitive impairment to the outcomes, non-marriage and divorce.

Methods

Study Population

CCSS Cohort

The Childhood Cancer Survivor Study (CCSS) is a multi-institutional, retrospective cohort of survivors of childhood cancer designed to study the late effects of cancer therapy. Eligibility criteria for participation in the CCSS cohort were: (1) diagnosis of leukemia, CNS tumor, Hodgkin's lymphoma, non-Hodgkin's lymphoma, Wilms' tumor, neuroblastoma, soft tissue sarcoma, or bone tumor; (2) diagnosis and initial treatment at one of the 26 participating oncology centers; (3) diagnosis between January 1, 1970, and December 31, 1986; (4) age younger than 21 years at diagnosis; and (5) survival of ≥ 5 years after diagnosis. Patients with a primary diagnosis of retinoblastoma, non-CNS germ cell tumors, and hepatic tumors were not included.

Starting in August, 1994, participants completed an extensive baseline questionnaire including demographic and socioeconomic characteristics, marital status, and health history. Two subsequent surveys were administered (in May, 2000, and November, 2002, respectively) to obtain updated and new information. Participants' medical records were reviewed by trained data abstractors to establish cancer diagnosis and treatment information. The methodology has been previously described [43] and copies of study documents are available at http://www.stjude.org/epidemiology/. Each participating center's institutional review board reviewed and approved the CCSS protocol and contact documents.

Of the 20,691 patients eligible for participation, 14,363 completed the baseline questionnaire; 3,058 were lost to follow-up; and 3,205 refused participation. Of the

14,363 initial participants, 10,366 completed the first follow-up questionnaire (FU1), and 9,308 completed the second follow-up questionnaire (FU2).

For the current analysis, the cohort was restricted to those subjects age 15 years and older as of FU2. This age range is consistent with previous studies on marriage, as well as with U.S. Census data on marriage. Subjects were excluded if they were married prior to diagnosis of malignancy, or if they died or were lost to follow-up prior to completion of the third survey.

Siblings

The CCSS database includes information on siblings of survivors. A random sample of participating survivors (n= 6,005) was asked to contact their sibling closest in age for participation in the study. 3,839 siblings completed the baseline questionnaire, 2,540 completed FU1, and 2,951 completed FU2. For the current analysis, siblings were restricted to those subjects age 15 years and older as of FU2. Siblings were excluded if they died or were lost to follow-up prior to completion of the third survey.

U.S. Population

Data on marital status of the U.S. population was obtained from the 2002 Current Population Survey (CPS), as issued by the Bureau of Census. The report includes marital status, stratified by gender, current age (15 years and older), and race. Details can be found at the following website: http://www.census.gov/population/www/socdemo/hh-fam/cps2002.html.

Measures

On each CCSS questionnaire, participants categorized themselves as "single/never married," "married," "living as married," "widowed," "divorced," or

"separated/no longer living as married." Survey responses were incorporated into three outcomes: "never-married," "currently-divorced," and "ever-divorced." "Never-married" was available from the most recent survey, FU2. Subjects responding "divorced" or "separated" on FU2 were defined as "currently-divorced." Cases who reported "divorced" or "separated" on any of the three surveys were classified as "ever-divorced." We acknowledge that some divorce cases may be missed in this way. For example, an individual responding "married" on consecutive surveys may in fact be divorced and remarried. We anticipate that the number of divorce cases missed in this manner will be negligible, given a median time of 5 years between the baseline and FU1, and 2 years between FU1 and FU2.

In the 2002 Current Population Survey (CPS), marital status of the general population was catalogued as "never married," "married," "widowed," "divorced," or "separated." "Never-married" and "currently-divorced" were clearly defined in the CPS; "ever-divorced," however, was not available. Also, the CPS did not include a "living with partner as married" category; presumably, those who were living with a partner outside of legal marriage were catalogued as "never married." Therefore, when drawing comparison to the general population, cohort members in the "living with partner as married" category as of FU2 were considered "never-married."

Predictor variables were defined by responses to CCSS questionnaires and by medical record abstraction. Sociodemographic factors included gender, current age, race, employment status, and personal income. Data from the most recent survey was used for variables that change with time (e.g. personal income). Disease-related factors included primary diagnosis, age at diagnosis, treatment modality, and treatment duration. Late

effects of treatment were also investigated as risk factors. These included growth hormone deficiency defined by self-report, cancer recurrence, and development of a subsequent malignant neoplasm (SMN). Diminished height was defined as height below the tenth percentile for age, gender, and ethnicity, as reported by the Centers for Disease Control and Prevention (CDC) (http://www.cdc.gov/nchs/data/ad/ad361.pdf). Perceived infertility was defined as "yes" to the question, "Has a doctor ever told you that you might have trouble having children?" Survivors' ongoing experience of disease burden was assessed with the following question: "During the past 4 weeks, to what extent have your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?"

Psychological health was evaluated with the Brief Symptom Inventory-18 (BSI-18). The BSI-18 is an 18-item checklist that measures symptoms of anxiety, depression, and somatic distress. Its validity as a screening tool in adult survivors of childhood cancer has been previously described [45]. Responses were scored according to published BSI-18 guidelines to generate a Global Severity Index (GSI) score [46]. A GSI t-score ≥ 57 was used to identify cases, as done previously by Zabora et al. [47]. Subjects with GSI elevations ≥ 57 on either of two BSI-18 administrations were classified as having a positive history of psychological distress.

Executive functioning was evaluated with the Behavior Rating Inventory of Executive Functioning (BRIEF). Responses were scored on a Behavioral Regulation (BR) scale, a Metacognition (MC) scale, and an overall Global Executive Composite scale, according to published guidelines [48]. Raw scores were standardized based on a normative population to generate t-scores, adjusted for age and gender. Subjects with t-

scores ≥ 65 (1.5 standard deviations from the mean) were classified as having impaired functioning [49].

Analyses

Frequencies of "never-married" and "currently-divorced" were described in CCSS cases and compared to frequencies for siblings and the U.S. population (as of the 2002 CPS). "Currently-divorced" was expressed as a percentage of those eligible for divorce. In other words, the proportion "currently-divorced" was equal to the number "divorced" or "separated," divided by the total number "married," "widowed," "divorced," or "separated." Frequencies within groups were described overall and in a stratified fashion, by age, gender, and race. Likelihood ratio tests were used to determine the statistical significance of differences between groups.

Case-case comparisons were conducted with respect to the outcomes, "never-married" and "ever-divorced." Univariate logistic regression was used to estimate associations between explanatory variables and each outcome. Age-adjusted odds ratios with 95% confidence intervals were calculated to compare the probability of outcomes among survivor sub-groups. Multiple regression models, including factors marginally significant in the unadjusted analysis ($p < 0.2$), were created to determine the independent role of each variable. The analysis of "ever-divorced" was restricted to those subjects who had been married at least once, and were therefore eligible for divorce. Analysis of "ever-divorced" was also restricted to subjects who had reported marital status on all three surveys.

Results

Marital Status of CCSS Cohort at Last Contact

At the time of most recent contact, 42.4 % (n = 3,783) of survivors were currently married, 7.3 % (n = 654) were divorced or separated, 0.2 % (n = 20) were widowed, and 47.7 % (n = 4,257) had never been married. Included in the never-married category were 3,828 (42.9 %) single survivors, and 429 (4.8 %) individuals who lived with a partner outside of marriage.

In contrast, 55.7 % (n = 1,590) of siblings were currently married, 9.0 % (n = 256) were divorced or separated, 0.2 % (n = 6) were widowed, and 33.5 % (n = 957) had never married. Of those siblings who had never married, 818 (28.7 %) were single, and 139 (4.9 %) reported living with a partner outside of legal marriage.

Comparison of Survivor Marital Status with Siblings and the U.S. Population

Overall, survivors were significantly more likely to be never-married than both siblings and the U.S. population (Table 1). When compared to siblings, survivors were 1.79 times as likely to be never-married (OR = 1.79; 95 % CI = 1.65-1.94; $p < 0.0001$). This trend was apparent across all age groups greater than 25 years old; it was particularly marked for those in the 30-34 year age group, where survivors were 2.42 times more likely than siblings to be never-married (OR = 2.42; 95 % CI = 1.94-3.03; $p < 0.0001$). This trend also remained significant when subjects were stratified by gender.

When compared to the U.S. population, survivors were more than twice as likely to be never-married (OR = 2.29; 95 % CI = 2.19-2.38; $p < 0.0001$). This trend was apparent for all age groups older than 20 years, and most pronounced in those older than

40 years (OR = 2.58; 95 % CI = 2.25-2.95; p < 0.0001). In addition, the effect was slightly more potent in females (OR = 2.41; 95 % CI = 2.27-2.55; p < 0.0001) than in males (OR = 2.16; 95 % CI = 2.04-2.29; p < 0.0001).

Table 1: Never-Married Status – Comparison of Survivors with Siblings and the U.S. Population

	All Ages (15+)		
	Percent Survivors	Percent Siblings	Percent U.S.
Total	47.7	33.5†	28.5*
Male	50.5	37.4†	32*
Female	44.8	30.6†	25.2*

	Age 15-19 years			Age 20-24 years			Age 25-29 years		
	Percent Survivors	Percent Siblings	Percent U.S.	Percent Survivors	Percent Siblings	Percent U.S.	Percent Survivors	Percent Siblings	Percent U.S.
Total	96.3	95.7	97.4	84.5	81.7	79.7*	59.7	50†	47*
Male	95.5	97.4	98.3	89.4	85.9	85.4*	65.2	55.3†	53.7*
Female	96.9	94.3	96.5	79.8	77.8	74*	54.2	44.8†	40.4*

	Age 30-34 years			Age 35-39 years			Age 40+		
	Percent Survivors	Percent Siblings	Percent U.S.	Percent Survivors	Percent Siblings	Percent U.S.	Percent Survivors	Percent Siblings	Percent U.S.
Total	40.1	21.7†	28.5*	25.7	14.3†	17.9*	18.5	9.2†	8.1*
Male	43.3	26.1†	34*	27.9	15.1†	21.1*	20.6	10.1†	9.3*
Female	36.6	18.1†	23*	23.2	13.7†	14.7*	16.4	8.5†	7*

† Indicates p < 0.05, survivors vs. siblings
* Indicates p < 0.05, survivors vs. U.S.

Rates of divorce did not differ significantly among survivors, siblings, and the U.S. population (Table 2). Of those who had been married, 14.7 percent of survivors,

13.8 percent of siblings, and 16.1 percent of the U.S. population were currently-divorced. No statistically significant differences in divorce rates were observed across age or gender groups (data not shown).

Table 2: Proportion Currently-Divorced – Comparison of Survivors with Siblings and the U.S. Population

	All Ages (15+)		
	Percent Survivors	Percent Siblings	Percent U.S.
Total	14.7	13.8	16.1
Male	13.8	13.3	14.4
Female	15.5	14.2	17.6

Predictors of Never-Married Status in Survivors

We examined the effect of various survivor characteristics on the likelihood of being never-married. It is important to note that for this analysis, "living as married" was categorized as "married."

Age-adjusted analyses indicated that several sociodemographic variables were significantly associated with never-married status (Table 3). Male survivors (OR = 1.46; $p < 0.0001$) were more likely to be never-married than females. Unemployed (OR = 1.78; $p < 0.0001$) and disabled (OR = 3.49; $p < 0.0001$) survivors were more likely to be never-married than their employed counterparts. Low personal income (OR = 1.73; $p < 0.0001$) was more strongly associated with non-marriage. There was a slight trend for lower educational achievement to predict never-married status (OR = 1.31; $p = 0.03$, for high school non-graduates).

Table 3: Association of Survivor Sociodemographic Characteristics with Never-Married Status (OR estimates adjusted for age at last contact)

Survivor Characteristics		Never-married		
		%	OR (95% CI)	p
Gender	Male	44.2	1.46 (1.32-1.61)	<.0001
	Female	38.5	1	.
Education	Did not complete high school	50.4	1.31 (1.02-1.68)	0.033
	Completed high school	46.2	1.13 (1.02-1.25)	0.015
	College graduate	34.4	1	.
Employment status	Disabled	57.3	3.49 (2.91-4.2)	<.0001
	Unemployed, looking	58.1	1.78 (1.42-2.25)	<.0001
	Employed or retired	39.0	1	.
Personal income	< $40,000	48.1	1.73 (1.53-1.96)	<.0001
	≥ $40,000	21.4	1	.

We also explored the relationship between disease and treatment factors and never-married status, adjusting for current age (Table 4). Survivors diagnosed before age 13 (OR = 1.22; $p = 0.01$) were slightly more likely to be never-married than those diagnosed at a later age. When comparing survivors of different tumor types, CNS tumor survivors (OR = 3.57; $p < 0.0001$) were most likely to be never-married. Survivors of leukemia (OR = 1.36; $p = 0.005$) and neuroblastoma (OR = 1.31; $p = 0.05$) were at modest risk for non-marriage. With regard to treatment, survivors who received cranial radiation (OR = 2.16; $p < 0.0001$) were more likely to be never-married than those who had not. Bone marrow transplantation and treatment duration were not associated with never-married status.

Table 4: Association of Disease and Treatment History with Never-Married Status (OR estimates adjusted for age at last contact)

Survivor Characteristics		Never-married		
		%	OR (95% CI)	p
Age at diagnosis	<13	50.6	1.22 (1.05-1.42)	0.0097
	13-20	15.4	1	.
Diagnosis	Leukemia	49.2	1.36 (1.1-1.68)	0.0053
	CNS	62.5	3.57 (2.82-4.54)	<.0001
	HD	13.9	0.74 (0.57-0.97)	0.027
	NHL	29.6	1.04 (0.8-1.36)	0.75
	Kidney (Wilms)	46.2	0.79 (0.62-1.02)	0.074
	Neuroblastoma	59.9	1.31 (1.00-1.73)	0.054
	Soft tissue sarcoma	33.9	1.16 (0.9-1.5)	0.26
	Bone cancer	20.1	1	.
RT to brain	Received RT to brain (or TBI)	54.3	2.16 (1.91-2.45)	<.0001
	Received RT but not to brain	27.8	0.94 (0.83-1.08)	0.41
	No RT	42.5	1	.
BMT	Yes	44.0	1.03 (0.62-1.68)	0.92
	No	41.6	1	.
Treatment duration	>=1 year	42.8	1 (0.89-1.13)	0.98
	<1 year	38.1	1	.

CNS – Central nervous system tumor; HD – Hodgkin's lymphoma; NHL – Non-Hodgkin's lymphoma; RT- Radiation therapy; TBI – Total body irradiation; BMT – Bone marrow transplantation

Age-adjusted analyses also revealed a number of late disease and treatment sequelae that were associated with never-married status (Table 5). Recurrence of disease (OR = 1.32; p = 0.0006) and development of a subsequent malignant neoplasm (OR = 1.5; p = 0.0002) elevated a survivor's risk for non-marriage. Growth hormone deficiency (OR = 3.55; p < 0.0001) and short stature (OR = 1.96; p < 0.0001) predicted never-married status. Survivors with fertility concerns (OR = 1.27; p = 0.0003) were more likely to be never-married. Survivors reporting severe (OR = 1.45; p < 0.0001) and

moderate (OR = 1.25; p = 0.01) difficulty with daily activities had higher rates of non-marriage than those reporting low difficulty. Scoring positively on a standardized screen for psychological distress (OR = 1.29; p < 0.0001) placed survivors at higher risk for being never-married. Survivors with organizational and problem solving difficulties, as measured by the metacognition index of the BRIEF, were more likely to be never-married (OR = 1.87; p <0.0001). An elevated composite BRIEF score also predicted non-marriage, although the behavioral regulation profile did not.

Table 5: Association of Late Effects with Never-Married Status (OR estimates adjusted for age at last contact)

Survivor Characteristics		Never-married		
		%	OR (95% CI)	p
Perceived infertility problem	Yes	32.3	1.27 (1.12-1.45)	0.0003
	No	21.1	1	.
Diminished height	Yes	57.2	1.96 (1.74-2.21)	<.0001
	No	37.0	1	.
GH deficiency	Yes	76.3	3.55 (2.85-4.45)	<.0001
	No	39.2	1	.
SMN	Yes	35.0	1.5 (1.21-1.85)	0.0002
	No	41.8	1	.
Recurrence	Yes	45.8	1.32 (1.13-1.55)	0.0006
	No	40.9	1	.
Recurrence or SMN	Yes	41.7	1.4 (1.23-1.61)	<.0001
	No	41.4	1	.
Difficulty with normal activities	Severe	45.6	1.45 (1.21-1.74)	<.0001
	Moderate	44.7	1.25 (1.05-1.48)	0.011
	Low	40.5	1	.
GSI t-score ≥ 57	Yes	40.9	1.29 (1.16-1.44)	<.0001
	No	37.3	1	.
BRIEF BRI ≥ 65	Yes	45.1	1.02 (0.87-1.18)	0.82
	No	39.3	1	.

Survivor Characteristics		Never-married		
		%	OR (95% CI)	p
BRIEF MCI ≥ 65	Yes	51.8	1.87 (1.57-2.22)	<.0001
	No	38.7	1	.
BRIEF TotI ≥ 65	Yes	49.5	1.54 (1.3-1.82)	<.0001
	No	38.9	1	.

GH – Growth hormone; SMN – Subsequent malignant neoplasm; GSI – Global Severity Index from BSI-18; BRI – Behavior regulation index from BRIEF; MCI – Metacognition index from BRIEF; TotI – Total or composite index from BRIEF

Finally, we constructed a multivariate model for never-married status, consisting of the factors that were identified as significant in the unadjusted analysis (Table 6). In this adjusted analysis, several variables remained significant independent predictors of never-married status. CNS tumor survivors were the highest risk diagnosis group (OR = 2.05; $p < 0.0001$), followed by survivors of neuroblastoma (OR = 1.75; $p = 0.0036$), soft tissue sarcoma (OR = 1.64; $p = 0.0041$), and bone cancer (OR = 1.48; $p = 0.026$). Cranial radiation was a strong predictor of never-married status (OR = 2.41; $p < 0.0001$); interestingly, when allowing for interaction with gender, males receiving cranial radiation were protected from the outcome of never-married (OR = 0.54; $p < 0.0001$). Disability was highly predictive of being never-married (OR = 1.78; $p = 0.0001$). Low personal income was protective (OR = 0.64; $p = 0.0009$); however, when interaction with gender was taken into account, males with low personal income were significantly at risk for being never-married (OR = 3.05; $p < 0.0001$). With regard to late effects of illness, growth hormone deficiency (OR = 2.02; $p < 0.0001$), psychological distress (OR = 1.30; $p = 0.0009$), and a history of recurrence or new cancer (OR = 1.24, $p = 0.033$) were significantly associated with never-married status.

Table 6: Predictors of Never-Married Status
Multivariate Analysis

Survivor Characteristics		Never-Married		
		OR	**95% CI**	**p**
Gender	Male	0.80	0.59-1.08	0.15
	Female	1	.	.
Current age		0.87	0.86-0.88	<.0001
Race	All others	1.30	1.06-1.60	0.012
	White, non-Hispanic	1	.	.
Employment status	Unemployed, looking	1.30	0.93-1.83	0.12
	Disabled	1.78	1.33-2.37	0.0001
	Employed or retired	1	.	.
Personal income	< $40,000	0.64	0.49-0.83	0.0009
	≥ $40,000	1	.	.
Diagnosis	Leukemia	1.17	0.85-1.60	0.34
	CNS	2.05	1.45-2.92	<.0001
	NHL	1.22	0.86-1.74	0.27
	Kidney (Wilms)	1.02	0.73-1.44	0.91
	Neuroblastoma	1.75	1.20-2.55	0.0036
	Soft tissue sarcoma	1.64	1.17-2.29	0.0041
	Bone cancer	1.48	1.05-2.09	0.026
	HD	1	.	.
RT to brain	Yes	2.41	1.90-3.07	<.0001
	No	1	.	.
GH deficiency	Yes	2.02	1.48-2.79	<.0001
	No	1	.	.
Recurrence or SMN	Yes	1.24	1.02-1.51	0.033
	No	1	.	.
GSI t-score ≥ 57	Yes	1.30	1.11-1.51	0.0009
	No	1	.	.

CNS – Central nervous system tumor; HD – Hodgkin's lymphoma; NHL – Non-Hodgkin's lymphoma; RT– Radiation therapy; GH – Growth hormone; SMN – Subsequent malignant neoplasm; GSI – Global severity index from BSI-18

Predictors of Ever-Divorced Status in Survivors

We explored the association of several survivor characteristics with the outcome, ever-divorced (Table 7). There was a significant association between educational attainment and ever-divorced status. Survivors who had not completed high school (OR = 2.65; $p < 0.0001$) and those who had completed high school but not college (OR = 2.1; $p < 0.0001$) were more likely to be ever-divorced than college graduates. Unemployed (OR = 2.4; $p < 0.0001$) and disabled (OR = 3.4; $p < 0.0001$) survivors had higher rates of ever-divorced than employed subjects. Low personal income (OR = 1.59; $p < 0.0001$) was associated with a higher risk for ever-divorced.

Table 7: Association of Survivor Sociodemographic Characteristics with Ever-Divorced Status (OR estimates adjusted for age at last contact)

Survivor Characteristics		Ever-divorced		
		%	OR (95% CI)	p
Gender	Male	20.7	0.9 (0.78-1.04)	0.16
	Female	22.0	1	.
Education	Did not complete high school	31.7	2.65 (1.81-3.83)	<.0001
	Completed high school	26.8	2.1 (1.81-2.44)	<.0001
	College graduate	15.5	1	.
Employment status	Disabled	46.2	3.4 (2.59-4.44)	<.0001
	Unemployed, looking	34.7	2.4 (1.68-3.4)	<.0001
	Employed or retired	19.2	1	.
Personal income	< $40,000	23.5	1.59 (1.36-1.87)	<.0001
	≥ $40,000	17.8	1	.

Most patient characteristics related to disease and treatment history did not demonstrate statistically significant associations with ever-divorced status (Table 8). Younger age at diagnosis (OR = 1.27; $p = 0.01$) was moderately associated with ever-

divorced status. Several treatment-related late effects predicted the outcome of ever-divorced, including short stature (OR = 1.26; p = 0.02), severe difficulty with daily activities (OR = 2.36; p < 0.0001), and a history of psychological distress (OR = 1.89; p < 0.0001) (Table 9). All three parameters of executive functioning as measured by the BRIEF were associated with ever-divorced. Thus, survivors with difficulty regulating emotions (OR = 1.52; p = 0.0002), and those with organizational or planning problems (OR = 1.46; p = 0.0031) were at risk for having been ever-divorced.

Table 8: Association of Disease and Treatment History with Ever-Divorced Status (OR estimates adjusted for age at last contact)

Survivor Characteristics		Ever-divorced		
		%	OR (95% CI)	p
Age at diagnosis	<13	20.5	1.27 (1.05-1.52)	0.013
	13-20	22.7	1	.
Diagnosis	Leukemia	20.8	1.06 (0.82-1.36)	0.66
	CNS	21.5	1.02 (0.74-1.41)	0.89
	HD	24.3	1.06 (0.82-1.37)	0.67
	NHL	24.4	1.18 (0.87-1.59)	0.29
	Kidney (Wilms)	14.4	0.74 (0.51-1.07)	0.11
	Neuroblastoma	19.8	1.09 (0.71-1.66)	0.69
	Soft tissue sarcoma	19.4	0.87 (0.64-1.19)	0.39
	Bone cancer	22.6	1	.
RT to brain	Received RT to brain (or TBI)	21.1	1.1 (0.9-1.34)	0.36
	Received RT but not to brain	20.8	0.98 (0.82-1.18)	0.86
	No RT	19.8	1	.
BMT	Yes	16.7	0.79 (0.32-1.68)	0.57
	No	20.8	1	.
Treatment duration	>=1 year	20.4	0.99 (0.84-1.18)	0.95
	<1 year	21.4	1	.

CNS – Central nervous system tumor; HD – Hodgkin's lymphoma; NHL – Non-Hodgkin's lymphoma; RT- Radiation therapy; TBI – Total body irradiation; BMT – Bone marrow transplantation

Table 9: Association of Late Effects with Ever-Divorced Status (OR estimates adjusted for age at last contact)

Survivor Characteristics		Ever-divorced		
		%	OR (95% CI)	p
Perceived infertility problem	Yes	23.3	1.06 (0.92-1.24)	0.42
	No	22.2	1	.
Diminished height	Yes	23.7	1.26 (1.03-1.54)	0.024
	No	20.9	1	.
GH deficiency	Yes	25.9	1.49 (0.94-2.28)	0.077
	No	21.4	1	.
SMN	Yes	22.2	0.91 (0.69-1.2)	0.52
	No	21.3	1	.
Recurrence	Yes	21.7	0.97 (0.76-1.24)	0.84
	No	21.4	1	.
Recurrence or SMN	Yes	22.2	0.96 (0.79-1.17)	0.71
	No	21.2	1	.
Difficulty with normal activities	Severe	37.1	2.36 (1.84-3.01)	<.0001
	Moderate	24.2	1.31 (1.01-1.67)	0.036
	Low	19.7	1	.
GSI t-score ≥ 57	Yes	30.0	1.89 (1.62-2.2)	<.0001
	No	18.4	1	.
BRIEF BRI ≥ 65	Yes	25.9	1.52 (1.22-1.89)	0.0002
	No	19.5	1	.
BRIEF MCI ≥ 65	Yes	27.0	1.46 (1.13-1.88)	0.0031
	No	19.7	1	.
BRIEF TotI ≥ 65	Yes	28.9	1.69 (1.33-2.14)	<.0001
	No	19.4	1	.

GH – Growth hormone; SMN – Subsequent malignant neoplasm; GSI – Global Severity Index from BSI-18; BRI – Behavior regulation index from BRIEF; MCI – Metacognition index from BRIEF; TotI – Total or composite index from BRIEF

In a multivariate model, controlling for those factors that were significant in the unadjusted analysis, we found several independent predictors of ever-divorced status (Table 10). The strongest predictors were unemployment (OR = 1.91; $p < 0.0001$, for

unemployed or disabled) and lower educational achievement (OR = 1.74; p < 0.0001, for non-college graduates). Psychological distress was also strongly associated with ever-divorced status (OR = 1.60; p < 0.0001). Other independent predictors included age at diagnosis (OR = 1.3; p = 0.033, for age < 13) and perceived fertility problems (OR = 1.22; p = 0.038). Difficulty with normal activities was not significantly associated with ever-divorced status; however, when interaction with gender was taken into account, males reporting severe levels of difficulty were at risk for ever-divorced (OR = 2.17; p = 0.02).

Table 10: Predictors of Ever-Divorced Status
Multivariate Analysis

Survivor Characteristics		Ever-Divorced		
		OR	**95% CI**	**p**
Gender	Male	0.82	0.67-0.99	.043
	Female	1	.	.
Current age		1.04	1.02-1.06	<.0001
Employment status	Unemployed or disabled	1.91	1.40-2.58	<.0001
	Employed or retired	1	.	.
Education	Not college graduate	1.74	1.44-2.10	<.0001
	College graduate	1	.	.
Age at diagnosis	<13	1.30	1.02-1.66	0.033
	13-20	1	.	.
Difficulty with normal activities	Severe	1.15	0.77-1.71	0.49
	Moderate or low	1	.	.
GSI t-score ≥ 57	Yes	1.60	1.30-1.96	<.0001
	No	1	.	.
Perceived fertility problem	Yes	1.22	1.01-1.47	0.038
	No	1	.	

GSI – Global severity index from BSI-18

Discussion

In the current study of a large, multi-site cohort of childhood cancer survivors, we found that survivors are twice as likely not to marry compared to the general population, and 1.8 times as likely not to marry compared to a sibling comparison group, with persistence of these trends across age and gender strata. However, we did not find any differences in the likelihood of divorce among those who do marry. This is the largest study to date examining marriage outcomes in childhood cancer survivors. Our study had the additional advantage of having extensive subject profiles that included potential contributing factors, such as detailed treatment histories and standardized measures of neurocognitive and emotional status. In adjusted analysis, we identified CNS tumor diagnosis, treatment involving cranial radiation, history of growth hormone deficiency, and unemployment secondary to disability as the most important factors in determining never-married status. The strongest predictors of ever-divorced were unemployment, lower educational level, and psychological distress.

In general, our results are consistent with prior studies on marriage rates after childhood cancer. In a previous report from the Childhood Cancer Survival Study, Rauck et al. compared marriage rates of survivors with the 1995 U.S. population [44]. They found that survivors, particularly females, were more likely to be never-married than age-matched controls. However, they reported equivalent marriage rates in male survivors and controls, whereas we observed a marriage deficit across both genders. Furthermore, the overall marriage deficit reported by Rauck for each age group is modest compared to our observations (Table 11).

Table 11: Never Married Status – Comparison with findings of Rauck et al., 1999

Never-married

	Age 15-19 years		Age 20-24 years		Age 25-29 years	
	Percent Survivors	Percent U.S.	Percent Survivors	Percent U.S.	Percent Survivors	Percent U.S.
Current study	96.3	97.4	84.5	79.7	59.7	47
Rauck et al., 1999	97.9	97.4	76.5	73.7	46.9	43.2
	Age 30-34 years		Age 35-39 years		Age 40+	
	Percent Survivors	Percent U.S.	Percent Survivors	Percent U.S.	Percent Survivors	Percent U.S.
Current study	40.1	28.5	25.7	17.9	18.5	8.1
Rauck et al., 1999	26.2	23.6	16.5	16.4	10	11.3

For example, in the 25-29 year and 30-34 year age groups, Rauck observed approximately 3 percent differences between survivors and controls (46.9% vs. 43.2%, and 26.2% vs. 23.6%, respectively), compared to our finding of differences on the order of 12 percent (59.7% vs. 47%, and 40.1% vs. 28.5%). Furthermore, where Rauck observed no difference in the 35-39 year and 40+ age groups, we found significant survivor deficits of approximately 8 and 10 percent, respectively. In comparing these studies, we must take into account differences in methodology. First, we treated living with a partner outside of legal marriage as never-married, while Rauck included this outcome in the married category. A very small proportion of survivors reported living with a partner, so this variation alone cannot account for the observed differences. Second, our study includes 8,930 cohort members who completed the second follow-up

questionnaire, whereas Rauck's study included 10,425 of those who had completed the initial baseline survey. Dissimilarity in the respondent groups could account for the discrepancy. This would imply that those who had dropped out of the cohort were more likely to have been married. On the contrary, most authors feel that it is the less well-adjusted survivors who are lost to follow-up.

We have observed that as the CCSS cohort ages, the marriage deficit becomes more apparent. In Rauck's report, the median age of survivors at ascertainment of marital status was 26 years, with a maximum of 48 years; in the present paper, the median age of survivors was 31 years, with a range of up to 54 years. More cohort members have entered the marriageable range of ages, and accordingly their shortcomings have become more evident.

The current study replicates the findings of prior studies concerning an amplification of the marriage deficit in survivors of CNS tumors. In a comparison of 2170 survivors and 3138 siblings, Byrne et al. showed that CNS tumor survivors were the least likely of all diagnosis groups to have married; moreover, when they married, they did so at older averages ages than siblings [40]. Male CNS cancer survivors were half as likely as siblings to have married (adjusted rate ratio 0.48). This effect was significant but less pronounced in female CNS survivors (adjusted rate ratio 0.73). Similarly, Rauck et al. found CNS survivors to have higher rates of non-marriage than other diagnosis groups and population controls. Again, the deficit was more severe in male CNS survivors than in females.

Byrne proposed that the exaggerated deficiency in male CNS cancer survivors may relate to societal expectations about the male's role as provider. In her words, "the

general expectation that women marry men who are taller, older, and more able and intelligent could make men of short stature or impaired mental functioning worse marriage candidates than similarly affected women" [40]. This theory may not be very relevant in modern times, although it is interesting to consider. In support of this theory, Byrne found that low educational achievement was more predictive of non-marriage in male CNS survivors than in their female counterparts. Of CNS tumor survivors who had not completed eighth grade, 84% of men were unmarried, compared to 70% of women. In the current study, we observed an association between lower educational attainment and never-married status for all survivors. However, when controlling for other variables in the final analysis, educational status did not remain significantly predictive. On the other hand, we found that males earning less than $40,000 were three times as likely to be never-married as males with higher income and females of any income. Thus, some elements of Bryne's theory may have credence after all.

While CNS tumor survivors have been identified consistently as the highest-risk group, survivors of other diagnoses have also been shown to experience difficulty with marriage. In a report on 694 survivors of lower extremity bone tumors, Nagarajan et al. found that survivors were less likely to have married than siblings (OR = 0.8); males were twice as likely as females to be never-married [42]. We looked at survivors of bone cancer at all sites, and found a similarly high risk for being never-married. However, we did not observe any gender difference in outcome.

One of the advantages of the current study is that, with its large number of cases, it has the statistical power to make reliable estimates. For example, Byrne reported a marginally significant risk of non-marriage among survivors of Hodgkin's disease (n=

257). In contrast, we found that survivors of Hodgkin's (n = 1194) were the lowest risk group.

The current study has some limitations which must be acknowledged. Due to the time elapsed between surveys and the nature of the question about marital status, it is possible that some cases of divorce were missed. As a result, we may have under-estimated the risk of being ever-divorced. Another limitation concerns the fact that members of the CCSS cohort, having been diagnosed between 1970 and 1986, were treated in an older era. Their illness experience may differ from that of more recent survivors, so the outcomes observed here may not be generalizable to all survivors. Finally, although the size of the CCSS cohort is a strength, it also limits the nature of contact with participants to standardized questionnaires. Smaller studies on marriage have utilized interviews; such a method, however, would be logistically difficult in our cohort. Thus, while we can state that survivors marry less frequently than controls of similar age and gender, we do not understand the thoughts, fears, and motivations underlying this behavior.

This study highlights the fact that many survivors of childhood cancer continue to struggle with adjustment to adulthood. The formation of intimate relationships is an important developmental task, and the low marriage rate of survivors suggests impairment in this area. Although the survivor population may not exhibit overt psychiatric morbidity, their difficulties with education, employment, and marriage indicate serious psychosocial issues. Future studies should further characterize those survivor sub-groups at highest risk for non-marriage, with particular attention to the mechanisms at play. A better understanding of the barriers to marriage will enable

family members and clinicians to provide necessary support. This report emphasizes that long-term follow-up care of childhood cancer survivors must be comprehensive, with attention to both their psychosocial and medical needs.

References

1. Ries, L.A.G., et al., *SEER Cancer Statistics Review, 1975-2003.* National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2003/, based on November 2005 SEER data submission, posted to the SEER web site, 2006.
2. Schwartz, C.L., *Health status of childhood cancer survivors: cure is more than the eradication of cancer.* Jama, 2003. **290**(12): p. 1641-3.
3. Hewitt, M., S.L. Weiner, and J.V. Simone, eds., *Childhood cancer survivorship: improving care and quality of life. Washington, D.C.: National Academies Press.* 2003.
4. Neglia, J.P., et al., *Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study.* J Natl Cancer Inst, 2001. **93**(8): p. 618-29.
5. Bassal, M., et al., *Risk of selected subsequent carcinomas in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study.* J Clin Oncol, 2006. **24**(3): p. 476-83.
6. Davies, S.M., *Subsequent malignant neoplasms in survivors of childhood cancer: Childhood Cancer Survivor Study (CCSS) studies.* Pediatr Blood Cancer, 2007.
7. Schwartz, C.L., *Long-term survivors of childhood cancer: the late effects of therapy.* Oncologist, 1999. **4**(1): p. 45-54.
8. Mertens, A.C., et al., *Pulmonary complications in survivors of childhood and adolescent cancer. A report from the Childhood Cancer Survivor Study.* Cancer, 2002. **95**(11): p. 2431-41.
9. Gurney, J.G., et al., *Final height and body mass index among adult survivors of childhood brain cancer: childhood cancer survivor study.* J Clin Endocrinol Metab, 2003. **88**(10): p. 4731-9.
10. Gurney, J.G., et al., *Endocrine and cardiovascular late effects among adult survivors of childhood brain tumors: Childhood Cancer Survivor Study.* Cancer, 2003. **97**(3): p. 663-73.
11. Oeffinger, K.C., et al., *Chronic health conditions in adult survivors of childhood cancer.* N Engl J Med, 2006. **355**(15): p. 1572-82.
12. Mertens, A.C., et al., *Late mortality experience in five-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study.* J Clin Oncol, 2001. **19**(13): p. 3163-72.
13. Mertens, A.C., *Cause of mortality in 5-year survivors of childhood cancer.* Pediatr Blood Cancer, 2007.
14. Hudson, M.M., et al., *Health status of adult long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study.* Jama, 2003. **290**(12): p. 1583-92.
15. Eiser, C., J.J. Hill, and Y.H. Vance, *Examining the psychological consequences of surviving childhood cancer: systematic review as a research method in pediatric psychology.* J Pediatr Psychol, 2000. **25**(6): p. 449-60.
16. Teta, M.J., et al., *Psychosocial consequences of childhood and adolescent cancer survival.* J Chronic Dis, 1986. **39**(9): p. 751-9.
17. Lansky, S.B., M.A. List, and C. Ritter-Sterr, *Psychosocial consequences of cure.* Cancer, 1986. **58**(2 Suppl): p. 529-33.

18. Chang, P.N., *Psychosocial needs of long-term childhood cancer survivors: a review of literature.* Pediatrician, 1991. **18**(1): p. 20-4.
19. Zeltzer, L.K., et al., *Comparison of psychologic outcome in adult survivors of childhood acute lymphoblastic leukemia versus sibling controls: a cooperative Children's Cancer Group and National Institutes of Health study.* J Clin Oncol, 1997. **15**(2): p. 547-56.
20. Rourke, M.T., et al., *Posttrauamatic stress disorder (PTSD) in young adult survivors of childhood cancer.* Pediatr Blood Cancer, 2006.
21. Hobbie, W.L., et al., *Symptoms of posttraumatic stress in young adult survivors of childhood cancer.* J Clin Oncol, 2000. **18**(24): p. 4060-6.
22. Langeveld, N.E., et al., *Posttraumatic stress symptoms in adult survivors of childhood cancer.* Pediatr Blood Cancer, 2004. **42**(7): p. 604-10.
23. Recklitis, C.J., et al., *Suicidal ideation and attempts in adult survivors of childhood cancer.* J Clin Oncol, 2006. **24**(24): p. 3852-7.
24. Howard, R.A., P.D. Inskip, and L.B. Travis, *Suicide after childhood cancer.* J Clin Oncol, 2007. **25**(6): p. 731; author reply 733-4.
25. Zeltzer, L.K., *Cancer in adolescents and young adults psychosocial aspects. Long-term survivors.* Cancer, 1993. **71**(10 Suppl): p. 3463-8.
26. Mitby, P.A., et al., *Utilization of special education services and educational attainment among long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study.* Cancer, 2003. **97**(4): p. 1115-26.
27. de Boer, A.G., J.H. Verbeek, and F.J. van Dijk, *Adult survivors of childhood cancer and unemployment: A metaanalysis.* Cancer, 2006. **107**(1): p. 1-11.
28. Park, E.R., et al., *Health insurance coverage in survivors of childhood cancer: the Childhood Cancer Survivor Study.* J Clin Oncol, 2005. **23**(36): p. 9187-97.
29. Cherlin, A.J., *American marriage in the early twenty-first century.* Future Child, 2005. **15**(2): p. 33-55.
30. Holmes, H.A. and F.F. Holmes, *After ten years, what are the handicaps and life styles of children treated for cancer? An examination of the present status of 124 such survivors.* Clin Pediatr (Phila), 1975. **14**(9): p. 819-23.
31. Zebrack, B.J. and M. Chesler, *Health-related worries, self-image, and life outlooks of long-term survivors of childhood cancer.* Health Soc Work, 2001. **26**(4): p. 245-56.
32. Stam, H., M.A. Grootenhuis, and B.F. Last, *The course of life of survivors of childhood cancer.* Psychooncology, 2005. **14**(3): p. 227-38.
33. Kokkonen, J., et al., *Physical and psychosocial outcome for young adults with treated malignancy.* Pediatr Hematol Oncol, 1997. **14**(3): p. 223-32.
34. Stern, M., S.L. Norman, and M.A. Zevon, *Adolescents with cancer: Self-image and perceived social support as indexes of adaptation.* Journal of Adolescent Research, 1993. **8**: p. 124-142.
35. Madan-Swain, A., et al., *Adolescent cancer survivors. Psychosocial and familial adaptation.* Psychosomatics, 1994. **35**(5): p. 453-9.
36. Meadows, A.T., L. McKee, and A.E. Kazak, *Psychosocial status of young adult survivors of childhood cancer: a survey.* Med Pediatr Oncol, 1989. **17**(6): p. 466-70.

37. Barrera, M., et al., *Educational and social late effects of childhood cancer and related clinical, personal, and familial characteristics.* Cancer, 2005. **104**(8): p. 1751-60.
38. Gray, R.E., et al., *Psychologic adaptation of survivors of childhood cancer.* Cancer, 1992. **70**(11): p. 2713-21.
39. Li, F.P. and R. Stone, *Survivors of cancer in childhood.* Ann Intern Med, 1976. **84**(5): p. 551-3.
40. Byrne, J., et al., *Marriage and divorce after childhood and adolescent cancer.* Jama, 1989. **262**(19): p. 2693-9.
41. Langeveld, N.E., et al., *Educational achievement, employment and living situation in long-term young adult survivors of childhood cancer in the Netherlands.* Psychooncology, 2003. **12**(3): p. 213-25.
42. Nagarajan, R., et al., *Education, employment, insurance, and marital status among 694 survivors of pediatric lower extremity bone tumors: a report from the childhood cancer survivor study.* Cancer, 2003. **97**(10): p. 2554-64.
43. Robison, L.L., et al., *Study design and cohort characteristics of the Childhood Cancer Survivor Study: a multi-institutional collaborative project.* Med Pediatr Oncol, 2002. **38**(4): p. 229-39.
44. Rauck, A.M., et al., *Marriage in the survivors of childhood cancer: a preliminary description from the Childhood Cancer Survivor Study.* Med Pediatr Oncol, 1999. **33**(1): p. 60-3.
45. Recklitis, C.J. and P. Rodriguez, *Screening childhood cancer survivors with the brief symptom inventory-18: classification agreement with the symptom checklist-90-revised.* Psychooncology, 2006.
46. Derogatis, L.R., *BSI-18 Administration, Scoring, and Procedures Manual.* National Computer Systems: Minneapolis, MN, 2000.
47. Zabora, J., et al., *A new psychosocial screening instrument for use with cancer patients.* Psychosomatics, 2001. **42**(3): p. 241-6.
48. Gioia, G.A., et al., *Confirmatory factor analysis of the Behavior Rating Inventory of Executive Function (BRIEF) in a clinical sample.* Child Neuropsychol, 2002. **8**(4): p. 249-57.
49. Gioia, G.A., et al., *Profiles of everyday executive function in acquired and developmental disorders.* Child Neuropsychol, 2002. **8**(2): p. 121-37.