

Social Outcomes in the Childhood Cancer Survivor Study Cohort

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A B S T R A C T

Difficulties with negotiating and achieving desired social outcomes in life may be exacerbated by the experience of childhood cancer, including adverse effects from therapies used to achieve a cure. This review of previous publications from the Childhood Cancer Survivor Study (CCSS) and other relevant literature provides insight into the prevalence of, and risk factors for, poor educational attainment, less than optimal employment status, and interpersonal relationship issues among long-term survivors of childhood cancer. The impacts of emotional health and physical disability on social outcomes are also examined. Study results suggest that childhood cancer survivors generally have similar high school graduation rates, but are more likely to require special education services than sibling comparison groups. Survivors are slightly less likely than expected to attend college, and are more likely to be unemployed and not married as young adults. Cancers and treatments that result in impairment to the CNS, particularly brain tumors, or that impact sensory functioning, such as hearing loss, are associated with greater risk for undesirable social outcomes, as are emotional health problems and physical disability. This review of relevant data from CCSS and other studies provides information on risk factors for social problems into adulthood. A greater understanding of the long-term social impacts from the diagnosis and treatment of childhood cancer is critically important for developing targeted interventions to prevent or ameliorate adverse psychosocial effects.

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INTRODUCTION

Cancer and the resulting treatment experience are potentially disruptive to the social development, emotional health, and academic progress of children and adolescents. Adverse effects in these domains are not limited to the acute treatment phase, but may surface discontinuously across the developmental life course.^{1,2} Although the majority of long-term survivors of childhood cancer are psychologically well-adapted,³ consistent scientific evidence suggests that many adult survivors of childhood cancer, particularly those with CNS impairment, are challenged in areas that reflect social dexterity. Such areas include educational achievement, friendships and social interactions, employment and financial independence, intimate relationships and marriage, and independent living.^{1,4-9}

Because of the rarity and heterogeneity of the many types of childhood cancer, and the practical difficulty in following and studying representative cohorts of survivors outside of the treatment setting, research on long-term social outcomes has been fairly limited. Primarily using results re-

ported in publications from the Childhood Cancer Survivor Study (CCSS),¹⁰ the purpose of this review article is to describe research findings related to social outcomes among long-term childhood cancer survivors.

ACADEMIC FUNCTIONING AND EDUCATIONAL ATTAINMENT

Educational achievement is known to be an important predictor of social outcome. The educational experience of the child is crucial to the optimal development of cognitive and interpersonal skills, which are important elements for social proficiency and successful transition into adulthood. The cancer experience, including the symptoms leading to the diagnosis, the family stress following diagnosis, and the toxicities and psychological distress associated with inpatient and outpatient treatment, all can contribute to significant academic disruption. The CCSS questionnaires, to date, have not included detailed items pertaining to school performance; however, questions on educational attainment and the use of special education resources have been included. Study results from the large number of

CCSS participants with available diagnosis and treatment information has provided some insight into cancer and treatment-related risk factors for poor academic achievement.

In an early CCSS manuscript, Mitby et al¹¹ reported that the use of special education services among 12,430 participating survivors was 23%. In contrast, only 8% of 3,410 siblings in the CCSS comparison group used special education services. The survivors at greatest risk for use of special education services were those diagnosed as preschoolers (5 years of age or younger), and children with a brain tumor, leukemia, or Hodgkin's disease. In particular, brain tumor survivors who were diagnosed as preschoolers had 18-fold higher odds (95% CI, 15.0 to 23.5) of a special education history than did those in the sibling group. Also, use of intrathecal methotrexate and cranial radiation exposure, alone or in combination, significantly increased the likelihood that a survivor would later use special education services. The cranial radiation effect was present with a dose response gradient. Perhaps the most important finding in the analysis was that use of special education services by childhood cancer survivors largely mitigated the increased risk for not completing high school. Just more than 12% of survivors, compared with 9% of siblings, did not complete high school, with survivors of brain tumors (adjusted odds ratio [OR], 2.7; 95% CI, 1.9 to 3.8), non-Hodgkin's lymphoma (OR, 1.8; 95% CI, 1.2 to 2.8), neuroblastoma (OR, 1.7; 95% CI, 1.1 to 2.6), and leukemia (OR, 1.6; 95% CI, 1.2 to 2.2) at the greatest risk for this outcome.

Four subsequent studies from the CCSS evaluated academic achievement among survivors of specific types of childhood cancer. Nagarajan et al¹² compared educational attainment among 694 survivors of lower-extremity malignant bone tumors. Bone tumor survivors had relative deficits in education when compared with siblings. However, the high school graduation rate in the survivors was excellent (93%), and college attendance was quite good (50%). Similarly, Punyko et al¹³ evaluated educational outcomes among 417 rhabdomyosarcoma survivors and 2,685 sibling participants. Again, high school graduation rates were high; however, survivors of childhood rhabdomyosarcoma were more likely than siblings to have failed to complete high school (9.3% v 5.3%; $P < .02$). Among a group of 25- to 49-year-old survivors of acute myeloid leukemia, 40% continued their education beyond a high school degree compared with 52% of siblings,¹⁴ and college graduation rates were also lower in 25- to 49-year-old survivors of acute lymphoblastic leukemia (ALL; 38%) than in the sibling group of comparable age (48%).¹⁵ Figure 1 summarizes the age- and sex-adjusted percentages of childhood cancer survivors in the CCSS who, in 2003, reported attending some college, by diagnosis group. Relative risks compare percentages among survivors to the sibling group. Brain tumor survivors were 11%, leukemia survivors were 7%, and non-Hodgkin's lymphoma survivors were 6% less likely than sibling cohort members to attend some college.

The results of these investigations using the CCSS cohort are similar to one large study of a Canadian cohort of childhood cancer survivors.⁴ In that multicenter study, 800 survivors age 17 years or younger were matched by age and sex with a group of 923 control participants and evaluated for social outcomes. Based on parental report, significantly more survivors than controls repeated a grade in school (21% v 9%), attended learning disability (19% v 7%) or special education programs (20% v 8%), had no close friends (19% v 8%), and did not use friends as confidants (58% v 67%). Survivors of brain tumors, followed by leukemia and neuroblastoma, were most likely to have educational problems and no close friends. As found in the CCSS

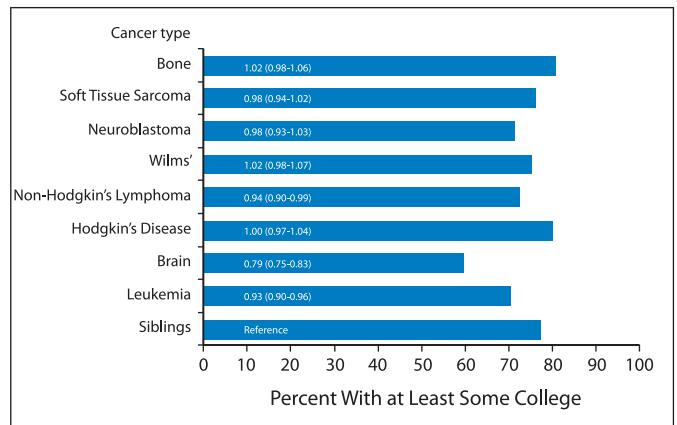


Fig 1. Age- and sex-adjusted percentages of Childhood Cancer Survivor Study participants who reported in 2003 having attended at least some college. The numbers in the blue bars show relative risk (95% CI).

cohort, survivors in this study who received cranial radiation had an increased likelihood of educational difficulties compared with survivors who did not receive cranial radiation.

Similarly, an earlier Children's Cancer Group study of 593 adult survivors of ALL and 409 sibling controls also found that ALL survivors were more likely than siblings to enter a special education (relative risk [RR], 3.4; $P < .01$) or a learning disabled program (RR, 3.6; $P < .01$) and that cranial radiotherapy of ≥ 24 Gy and young age at diagnosis (< 6 years) significantly increased educational risk.¹⁶ However, in that study, survivors generally had the same probability as their siblings of finishing high school, entering college, and earning a bachelor's degree.

Finally, in a study of 137 children (age 8 to 17 years) who were treated on Children's Oncology Group protocols,¹⁷ survivors of neuroblastoma with hearing loss, as reported by their parents, had at least twice the risk of an identified academic problem with reading skills, math skills, and/or attention, and a similarly higher risk of a general learning disability and/or special educational needs, than did neuroblastoma survivors without hearing loss. Consistent with these findings, hearing loss, presumably treatment-induced from platinum-based chemotherapy, was associated with a 10-point lower mean score in the school-functioning scale of the Pediatric Quality of Life Inventory 4.0. Also observed was a clear pattern of poorer self-reported quality-of-life scores among children with academic and psychosocial problems compared with those without such problems, particularly with school functioning.

These CCSS results and other studies demonstrate a pattern of academic risk in a subset of childhood cancer survivors, with the highest concern being children with brain tumors, those treated for cancer before 6 years of age, those treated with cranial irradiation, and those with treatment-induced hearing loss.

EMPLOYMENT

After transitioning from a school setting, an important metric for social success is adult employment. Employability and the ability to support oneself are key factors in living independently.⁵ Although quality and satisfaction of employment has yet to be evaluated in a systematic manner in CCSS or elsewhere, employment status has been

addressed recently. Pang et al¹⁸ compared employment between 9,736 CCSS survivors and 3,054 CCSS siblings (age \geq 18 years and currently living, median age 26 and 29 years, respectively) and found that 5.6% of survivors had never been employed, compared with 1.2% of the siblings (OR, 3.7; 95% CI, 2.6 to 5.1). In addition, as presented in Table 1, a greater percentage of survivors reported a lack of any employment

Characteristic	%	
	Survivor Cohort	Sibling Cohort
Attained age, years^{1*}		
< 18	26.1	21.0
18-21	17.1	13.5
22-24	13.0	10.3
25-34	34.2	34.9
\geq 35	9.6	20.3
Sex^{1*}		
Male	52.9	47.8
Female	47.1	52.2
Employed^{2†}		
In last 12 months	85.1	92.0
Not in last 12 months	9.3	6.7
Never	5.6	1.2
Rejected for job due to medical history^{2†}		
Yes	13.6	2.1
No	87.4	97.9
Annual household income, dollars^{1*}		
< 20,000	19.9	11.8
20,000-39,999	26.2	23.1
40,000-59,999	19.0	22.6
\geq 60,000	21.8	32.6
Missing	13.1	9.9
Health insurance^{1*}		
Yes	86.3	90.0
No	13.7	10.0
Educational attainment^{1*}		
< High school	9.8	5.8
High school graduate	56.1	52.8
College graduate	28.8	37.2
Missing	5.3	4.2
Marital status^{1*}		
Single	48.8	31.7
Married/living as married	40.6	54.0
Divorced/separated	10.3	10.0
Missing	0.3	4.3
Special education^{3‡}		
Yes	23.0	8.3
Missed school	3.7	0.6
Low tests	10.5	2.8
Learning/concentrating	17.5	6.0
Emotional/behavioral	2.7	1.2
No	65.6	80.6
Missing/ambiguous	11.4	11.1

*Data on age, sex, household income, and health insurance calculated on entire survivor and sibling cohort, with sample sizes of 12,358 and 3,553, respectively. Educational attainment and marital status calculated on participants \geq 18 years of age, with samples sizes of 9,128 for survivors and 2,808 for siblings.

†Employment data taken from participants \geq 18 years of age, with samples sizes of 9,736 for survivors and 3,054 for siblings.

‡Samples sizes for survivors and siblings equal 12,430 and 3410, respectively. Participants may have given more than one reason for special education.

in the past 12 months (9.3%) compared with the siblings (6.7%). Elevated risk for never having been employed was associated with not finishing high school, young age (< 4 years) at diagnosis, cranial radiation therapy of \geq 30 Gy, and female sex. All diagnostic categories were less likely to be employed in the past 12 months than members of the sibling group; however, the age- and sex-adjusted likelihood of being employed was lowest among brain tumor (RR, 0.74; 95% CI, 0.71 to 0.76) and bone tumor survivors (RR, 0.88; 95% CI, 0.85 to 0.91; Fig 2).¹⁸

In the CCSS study of rhabdomyosarcoma survivors previously mentioned,¹³ employment percentages did not differ between siblings and survivors age 18 to 24 years, but survivors between the ages of 25 and 45 years were less likely to have ever been employed than same age siblings. Survivors also were more likely than siblings to miss work due to illness. Among survivors of lower extremity malignant bone tumors, those who graduated from high school, relative to those who did not, were more likely to ever have had a job (OR, 10.5; $P < .005$), and, not surprisingly, college graduates were more likely to have been employed in the past year than were noncollege graduates (OR, 3.9; $P < .05$).¹²

Results from the CCSS indicate that chronic medical conditions after cancer therapy increase the risk for unemployment.¹⁸ The risk of having a chronic health condition increases substantially throughout adulthood.¹⁹ By 30 years after the cancer diagnosis, 73.5% of young adults survivors in the CCSS (95% CI, 69.0% to 77.0%) reported at least one chronic health condition and 42.4% had a severe, disabling or life-threatening condition (or had died from such a condition; 95% CI, 33.7% to 51.2%). Given the close dependence in the United States on having adequate health insurance through employers, the high likelihood of having a chronic health condition may be of increasing concern to adult childhood cancer survivors as they age. In the CCSS cohort, survivors were more likely than siblings (29% v 3%, respectively) to have had difficulty obtaining health coverage and were more likely to have Medicaid or Medicare (12% v 3%) as their insurance source.²⁰ Factors associated with being uninsured included lower level of educational attainment, male sex, being unmarried, or being a current smoker.

These results from CCSS build on the existing literature on employment status in childhood cancer survivors. de Boer et al⁵ recently conducted a meta-analysis of the extant literature and found that adult

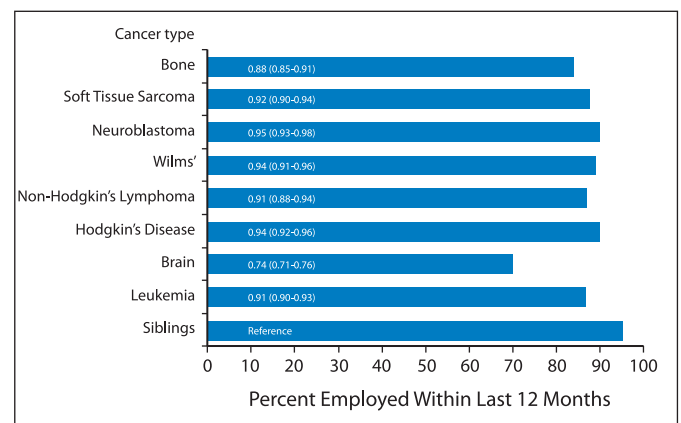


Fig 2. Age- and sex-adjusted percentages of Childhood Cancer Survivor Study participants who reported in 2003 having been employed at some time during the previous 12 months. The numbers in the blue bars show relative risk (95% CI).

survivors of childhood cancer were nearly twice as likely as healthy controls to be unemployed. Consistent with the latest CCSS analysis, the highest risk group was brain tumor survivors, for which a five-fold increased relative odds of unemployment was found in their systematic review. To summarize the CCSS findings, adult childhood cancer survivors of all diagnostic categories are at elevated risk for unemployment. Consistent with education risk, the unemployment risk is potentiated among those who were treated for brain tumors, those treated with high doses of cranial radiation, those diagnosed at a young age, females, and those with chronic medical conditions.

RELATIONSHIPS, INCLUDING FRIENDSHIPS AND MARRIAGE

Although the institution of marriage has undergone many changes in modern times, it represents a social outcome that can be used to gauge the adaptation of survivors to life after cancer. Marriage represents an aspiration for the majority of young adults in today's society.²¹ A preliminary analysis of marriage patterns in the first 10,425 patients recruited to the CCSS cohort compared frequencies of marriage among survivors with matched US Census data.²² Overall, the proportion of survivors who had ever married was slightly less than the general population within similar age groups. Females were at particular risk for lower rates of marriage. Survivors of brain tumors were at significant risk of never having married (78% of brain tumor survivors had never married *v* 62% of the whole cohort). Subsequent CCSS publications have assessed marriage patterns within specific diagnostic subgroups. Among the 694 survivors of lower extremity bone tumors analyzed by Nagarajan et al,¹² there was a reduced likelihood of ever being married compared to siblings (OR, 0.8; 95% CI, 0.62 to 0.99). In the Punyko et al¹³ analysis there were no significant differences in marital status between survivors of rhabdomyosarcoma and siblings.

Greater disparities in marital status have been observed in survivors of leukemia. An analysis of 1,206 survivors of ALL age 25 to 49 years revealed that only 55% of survivors had ever been married, compared to 69% of CCSS siblings ($P < .001$).¹⁵ Females treated with cranial radiation therapy were at increased risk of never having married. The CCSS study on acute myeloid leukemia demonstrated that survivors were less likely to marry (36% never married) than siblings (23%) or the general population (28%).¹⁴ However, because survivors had lower divorce rates, their frequency of being currently married was similar to the general population (57% for both groups), but lower than for siblings (69%).

The British Childhood Cancer Survivor Study (BCSSS), with their recently published findings describing marriage patterns of 9,954 survivors diagnosed between 1940 and 1991,²³ add to the information learned through CCSS analyses. Compared with expected rates from English and Welsh population-based statistics, fewer survivors across all age groups reported a history of ever being married. Male sex, history of a brain tumor, radiation therapy, mental retardation, and blindness were all statistically associated with a lower likelihood of marriage in the cancer survivors.

An updated analysis of marriage patterns is currently in progress for the overall CCSS cohort. This manuscript will add further insight to the recent publication from the BCCC by analyzing divorce patterns in comparison to siblings and US Census data. In an attempt to further understand the impact of late effects of cancer therapy on

marriage, this analysis will examine the association between performance on standardized instruments of psychological and neurocognitive functioning and the likelihood of ever being married or divorced.

Social and sexual relationships extend beyond the institution of marriage. These relationships are often challenging for healthy adolescents and adults, but may be especially difficult for those survivors who struggle with the burdens of past disease. van Dijk and colleagues²⁴ recently reported results from a Dutch questionnaire-based study of 60 childhood cancer survivors on psychosexual functioning. Approximately 20% of survivors had limitations in their sexual life due to their illness, and survivors who were age 25 years or older had significantly less experience with sexual intercourse than their age-matched peers.

A review of studies published between 1990 and 2005 that investigated life values, relations to others and relation to self among childhood cancer survivors demonstrated that survivors generally do not differ from their peers.²⁵ However, friendship, marriage, parenthood, and sexuality are consistent areas of concern for survivors. For example, another Dutch study administered the Course of Life questionnaire to 353 childhood cancer survivors age 18 to 30 years along with 508 peers without a history of cancer.²⁶ The survivors were less likely to have achieved milestones in psychosocial development. They tended to be older at the ages at which they had their first boyfriend or girlfriend and experienced sexual intimacy. Survivors reported fewer friends and were less likely to spend their leisure time mainly with friends. That finding is consistent with the previously mentioned Canadian educational study by Barrera et al,⁴ in which difficulties in forming close friendships and confidants were observed.

To date, the CCSS has not complemented their publications on marriage and parenthood with analyses of friendships or psychosexual functioning. However, since these important psychosocial outcomes have been shown to impact the lives of many survivors, they will be topics for future investigation within the cohort.

CORRELATES OF PSYCHOLOGICAL DISTRESS AND SOCIAL DIFFICULTIES

Psychological distress can have a negative impact on employment, financial issues, and the ability to live independently. In addition, the inability to support oneself in adulthood may increase psychological distress. In a cross-sectional analysis of CCSS data collected in 2003, Zeltzer et al²⁷ found that, compared with employed survivors, CCSS survivors seeking work or unable to work were at increased risk for symptoms of depression (OR, 2.5; 95% CI, 2.0 to 3.0), anxiety (OR, 2.5; 95% CI, 2.0 to 3.1), and somatic distress (OR, 3.4; 95% CI, 2.8 to 4.1). Similarly, those survivors who reported making less than \$20,000 per year demonstrated more symptoms of depression (OR, 1.8; 95% CI, 1.5 to 2.2), anxiety (OR, 1.6; 95% CI, 1.3 to 2.0), and somatic distress (OR, 1.7; 95% CI, 1.4 to 2.1) than did survivors at higher income levels.

The association between income and psychological distress was also demonstrated in CCSS analyses limited to specific diagnostic groups. Even though most of 2,778 CCSS solid tumor survivors did not report significant psychological distress when compared to 2,925 siblings in one study by Zebrack et al,³ psychological distress was associated with household income of less than \$20,000 and lack of

employment during the past 12 months for both survivors and controls. A similar pattern was reported in an analysis that compared 5,736 leukemia and lymphoma survivors to 2,565 siblings.²⁸ Survivors of leukemia or Hodgkin's disease reported more symptoms of depression and somatic distress when their annual income was lower than \$20,000 compared to survivors with higher household incomes. Survivors with non-Hodgkin's lymphoma also reported elevated levels of somatic distress associated with lower income levels. In a subsequent study involving 1,101 survivors of brain tumors, psychological distress was differentially related to social outcomes.⁹ In that analysis, anxiety was more evident in survivors with incomes lower than \$20,000, higher rates of depression were associated with being unmarried or not completing high school, and somatic distress was associated with being unemployed.

Household income has also been reported to be related to psychological problems in adolescent survivors. Schultz and colleagues⁸ reported on psychological functioning in 2,979 CCSS survivors and 649 CCSS siblings. Using parental report of behavioral symptoms in this group of adolescents 12 to 17 years of age at the time of survey, household income lower than \$20,000 was associated with increased symptoms of oppositional behavior (OR, 1.8; 95% CI 1.2 to 2.7), attention problems (OR, 1.7; 95% CI, 1.2 to 2.3), social withdrawal (OR, 2.1; 95% CI, 1.4 to 3.2), and antisocial behavior (OR, 1.5; 95% CI, 1.1 to 2.0).

Perceived quality of life also appears related to social attainment. In a CCSS study by Zeltzer et al,²⁷ survivors who were divorced reported significantly higher limitations in regular activities associated with emotional functioning (OR, 1.4; 95% CI, 1.1 to 1.8) and lower quality of mental health (OR, 1.5; 95% CI, 1.1 to 2.0) than did survivors who were married. A lower quality of mental health was also reported more commonly by those survivors who did not graduate from high school (OR, 1.5; 95% CI, 1.1 to 2.2). Nathan and colleagues²⁹ recently examined quality of life in 654 survivors of Wilms tumors and 432 survivors of neuroblastoma. Within that group, survivors who were actively employed reported a higher quality of mental health and fewer role restrictions associated with emotional functioning. In a recent publication from CCSS from Ness et al,³⁰ executive function and emotional health were evaluated as risk factors for social outcomes. Those results indicated that, overall, fewer cognitive and emotional problems are reported in survivors who are high school graduates, actively employed, married, and who had incomes of more than \$20,000.

CORRELATES OF PHYSICAL FUNCTIONING AND SOCIAL DIFFICULTIES

Physical disability in the general population is associated with social role difficulties. Individuals with physical performance limitations are less likely to go to college or be employed. They are also less likely to spend time with friends for social activities and less likely to participate in leisure time physical activities. Additional psychosocial stressors for survivors with physical disability include difficulties maintaining health insurance and accessing health care.^{31,32} Simply, physical ability influences the ability to perform daily tasks, and to participate fully in life roles. Among survivors participating in the CCSS cohort, those with musculoskeletal impairments, neurological deficits, or chronic pain are the most likely to have difficulties with activities necessary for participation in social roles in the home and community.³³

The association between physical performance limitations and restricted participation in expected adult social roles has been documented in the overall CCSS cohort and among specific diagnosis groups. In the overall cohort, after adjusting for age, sex, time since diagnosis, emotional health and executive function, childhood cancer survivors with physical performance limitations (evaluated by summarizing responses to six questions that asked about the participants' performance of physical activities during the past 2 years; these included vigorous activities like running or participating in strenuous sports, moderate activity like bowling or carrying groceries, walking uphill, bending, lifting, walking one block, dressing and bathing) were 43% less likely to graduate from high school, 60% less likely to be employed, 18% less likely to be married, and 38% less likely to have an annual household income of \$20,000 or more.³⁰ Neuroblastoma or Wilms tumor survivors²⁹ with reported physical performance limitations had lower rates of high school graduation, more unemployment, lower annual household incomes, and were more likely to lack health insurance than those who did not have physical performance limitations. Similarly, CCSS cohort members who were treated for rhabdomyosarcoma, and who had global physical performance limitations, were less likely to graduate from high school than those who did not have these limitations.¹³

Ness et al⁶ evaluated the impact of physical performance limitations on marriage among 157 adults (age range, 18 to 50 years) treated with hematopoietic stem cell transplantation (HCT) for their childhood onset malignancy. In this cohort, after adjusting for age at interview, time since transplantation, emotional health, and educational attainment, HCT survivors with a physical performance limitation were 80% less likely to be married than those without a physical performance limitation (95% CI, 10% to 90%). Those with a physical limitation were also less likely than those without such limitations to have graduated from high school. Joubert et al³⁴ reported an association between functional impairment and global quality of attachment to romantic partners in 97 adult (age range, 18 to 42 years) survivors of various childhood malignancies. Older age at onset of functional impairment, necessitating assistance with daily tasks from another person, was associated with poor attachment outcomes. Conversely, Nicholson et al³⁵ reported no difference in marriage rates when they compared adult survivors of childhood bone cancer to a control group. They did, however, report lower rates of employment among bone tumor survivors than controls.

These previously published data from the CCSS cohort and elsewhere demonstrate that physical performance limitations among childhood cancer survivors can have a negative impact on their participation in expected adult social roles.

CONCLUSION

Information on long-term social effects related to childhood or adolescent cancer is continuing to emerge. However, in general social outcomes data are limited and comprehensive investigations into social functioning and adaptation throughout the life course are sorely needed. Review of the literature evaluating social outcomes in childhood cancer survivors, through the CCSS cohort and from other selected studies, demonstrates the potential adverse impact of the cancer itself and the treatments required to achieve a cure. Most results to date, however, are based on cross-sectional evaluations and thus

preclude clear knowledge of the specific causes and progressive nature of psychosocial difficulties in cancer survivors. A greater understanding of this area, preferably from longitudinal designs, is critical to advancement of the field of pediatric oncology and the psychosocial well-being of cancer survivors. Using data presented here, researchers and clinicians have useful information to begin the development and implementation of targeted interventional strategies for improving social outcomes for survivors of cancer in childhood and adolescence. A next step in psychosocial research should be studies focused on incorporating existing knowledge on risk profiles directly into clinical management and into social settings, such as school and employment.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

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