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Predictors of Independent Living Status in Adult Survivors of Childhood Cancer: A Report from the Childhood Cancer Survivor Study

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Abstract

Background—Adult survivors of childhood cancer and their siblings are compared on one of the most salient developmental milestones of adulthood, the ability to live independently.

Procedure—Adult survivors of childhood cancers (n=6,047) and siblings (n=2,326), all 25 years of age and older, completed a long-term follow-up questionnaire that assessed adaptive, neurocognitive, and psychological functioning, as well as demographic and health status. Multivariable logistic regression analyses and structural equation modeling (SEM) were used to identify predictors of independent living.

Results—Compared to siblings (n=206, 8.7%), survivors (n=1063; 17.7%) were more than twice as likely to live dependently (OR 2.07; 95% confidence interval [CI] 1.77–2.42). Survivors diagnosed with CNS tumors (OR 0.13, 95% CI 0.10–0.18) or leukemia (OR 0.29, 95% CI 0.23–0.27) were significantly less likely to live independently compared to those diagnosed with Hodgkin Lymphoma. Other risk factors for reduced independent living included cranial radiation (≤ 24 Gy OR 0.76, 95% CI 0.62–0.93; > 24 Gy OR 0.31, 95% CI 0.24–0.41), use of neuroleptic, anticonvulsant, or psychostimulant medication (OR 0.32, 95% CI 0.24–0.43), attention and processing speed problems (OR 0.58, 95% CI 0.47–0.71), poor physical functioning (OR 0.49, 95% CI 0.38–0.63), depression (OR 0.68, 95% CI 0.53–0.88), and racial/ethnic minority status (OR 0.39, 95% CI 0.30–0.51). SEM demonstrated that neurocognitive functioning had both direct effects on independent living status, and indirect effects through use of neurologically-directed medication, depression, and poor mental health.

Conclusion—Adult survivors of childhood cancer who experience neurocognitive, psychological or physical late effects are less likely to live independently as adults.

Keywords

Pediatric oncology; psychosocial; late effects; outcomes research

Introduction

The impact of childhood cancer continues long after treatment has ended, with many survivors facing medical challenges as adults.^{1–9} Survivors are at risk for neurocognitive late effects,^{10,11} posttraumatic stress,^{12,13} and behavioral and emotional problems.^{14,15} These late effects of treatment have the potential to impact important adaptive and social outcomes in adulthood. Physical performance limitations have also been linked to adult social outcomes,^{16,17} with neurocognitive and psychological functioning interacting with physical functioning.^{18–20}

Despite its importance in modern western societies, few studies have examined independent living as distinct from marital status in adult survivors of childhood cancer. A recent study in Norway found young adult survivors of rare childhood cancers were less likely to reside with parents than similarly aged controls.²¹ No differences were found between diagnostic or treatment groups. In contrast, adult survivors of childhood cancer in a Netherland cohort were more likely to reside with their parents than non-cancer controls.²² Male gender, younger age at diagnosis, shorter time from treatment and younger age at assessment were associated with survivor dependent living status. Diagnosis and cranial radiation therapy were not significant predictors. The role of survivors' neurocognitive, psychological and physical functioning was not assessed in either study. Given that cancer survivors experience difficulties in these domains, examination of these constructs would provide a more complete picture of the risk factors for dependent living in adulthood, and may elucidate possible avenues for intervention to support functional independence.

The Childhood Cancer Survivor Study (CCSS) cohort provides a unique opportunity to further examine independent living status, capturing detailed treatment histories from medical record abstraction, and self-report of current functional outcomes. The present study investigated independent living in adult survivors of childhood cancer who were at least 25 years of age. It was hypothesized that survivors would be less likely to live independently than sibling controls, and that demographic factors, treatment variables, physical functioning, the presence of neurocognitive and psychological late effects, and pharmacologic interventions for these late effects would influence independent living status.

Methods

Study Population: CCSS Cohort

The CCSS is a multi-site cohort study of long-term health outcomes in childhood cancer survivors. Individuals met the following eligibility criteria: 1) diagnosis of leukemia, central nervous system (CNS) tumor, Hodgkin or non-Hodgkin lymphoma, neuroblastoma, Wilms tumor, soft tissue sarcoma, or bone tumor; 2) diagnosis and initial treatment at a participating institution; 3) diagnosis between January 1, 1970, and December 31, 1986; 4) age <21 years at diagnosis; and 5) survival of at least 5 years after diagnosis.

Methodology and participants have been described in previous reports and details are available through <http://ccss.stjude.org>.^{23,24} Briefly, the institutional review board for each participating institution reviewed and approved the CCSS protocol and contact documents, and participants provided consent for the surveys and medical record abstraction. Baseline data were collected with a self-report questionnaire including information regarding medical history, living status, education, employment, marriage status, and income. A subsequent self-report survey was administered beginning in November 2002 (2003 Follow-up Survey) to obtain psychosocial outcome data. Detailed diagnosis and treatment history were obtained from survivors' treating institution through medical record abstraction.

Of the 14,363 initial participants, 9,308 completed the 2003 Follow-Up Survey. Individuals who were living in prison (n=8) and/or had a genetic condition at baseline (n=147) were excluded from analyses. For the purpose of the current analyses, cases were excluded if they were younger than 25 years of age (n=2031) at the time of the 2003 Follow-up Survey. Of the 7,122 eligible cases, 6,047 (84.9%) provided information on current living status and relevant predictor variables.

A randomly selected group of participating survivors (n=5,857) identified their closest-age sibling for participation. Of the 4,782 deemed eligible, 3,839 (80.2%) completed the baseline survey, and 2,951 (76.9% of baseline sample) completed the 2003 Follow-up. Of those who completed the 2003 Follow-up, 2,326 (78.8%) were at least 25 years of age and provided information on current living status and relevant predictor variables. Demographic information for survivors and siblings are presented in Table 1.

Outcome of Interest

The primary outcome of interest was independent living status among cancer survivors. Living status was dichotomized based on survivors' responses from the 2003 Follow-up survey. Those classified as living independently responded as "Live with spouse/partner", "Live alone" or in the "Other" category indicated they had a roommate, lived in a dorm, lived with their own children, were in the military, lived with friends, or had another non-dependent living arrangement. Living dependently included those who responded, "Live with parent", "Live with brothers and/or sisters", "Live with other relatives", or who specified that they had nursing or caregiver support under "Other" living arrangements.

Predictor Variables

Data from the Baseline survey included date of birth, sex, race/ethnicity, and history of special education services. Due to low numbers of ethnic/racial minorities, this category was dichotomized as non-Hispanic White or ethnic/racial minority. Diagnosis and treatment information was abstracted at baseline through the survivor's treating institution and included age at diagnosis (categorized <6 years of age, ≥6 and <12, and 12), use of cranial radiation therapy (none, ≤24Gy, >24Gy), and type of chemotherapy (none, chemotherapy with methotrexate/steroids, chemotherapy without methotrexate/steroids). Data from the 2003 Follow-up included personal income, education, marital status, employment status, neurocognitive functioning, psychological distress, physical functioning, and use of psychoactive medications.

Participants completed the Neurocognitive Questionnaire (NCQ), a 25-item instrument previously validated in cancer survivors.²⁵ The NCQ is comprised of four factors including task efficiency (9 items), emotional regulation (3 items), organization (3 items) and memory (4 items). Age-adjusted factor scores were dichotomized, with impairment defined as a symptom level seen in ≤10% of the standardization sample.

Psychological distress was measured by the Brief Symptom Inventory – 18 (BSI), an 18-item checklist that measures symptoms across three factors: anxiety, depression, and somatic distress.²⁶ Age-adjusted factor scores were dichotomized, with impairment defined as a symptom level seen in ≤10% of the national standardization sample.

Post-traumatic stress (PTS) was measured using a 17-item questionnaire covering diagnostic symptoms for PTS.²⁷ Items make up three factors; re-experience (5 items), avoidance (7 items) and arousal (5 items). Consistent with standardized scoring, survivors who reported at least one symptom on the re-experience factor, three symptoms on the avoidance factor, and two symptoms on the arousal factor were identified as having significant PTS symptoms.

Several measures were used to assess physical health and medication status. The Health-Related Quality of Life Short-Form (SF-36) was administered to assess the following factors: general health, bodily pain, physical functioning, role limitations due to physical functioning, and vitality.²⁸ Consistent with guidelines in the standardization manual, responses were dichotomized such that age-adjusted T-scores ≤ 40 were classified as impaired. Survivors were also asked to list medications they were taking at the time of completing the 2003 Follow-Up survey. Use of prescription medication was divided into two categories (anti-depressant/anti-anxiety and neuroleptic/psychostimulant/anticonvulsant) and dichotomized within category (yes/no).

Analyses

Frequencies of predictor variables were calculated for survivors and siblings. Generalized estimating equations (GEE) analysis was used to examine differences of predictors between groups, accounting for the intrafamily correlation between survivors and siblings (see Table 1).²⁹ Frequencies of 'living independently' were also described and compared in survivors and siblings using the GEE analysis, adjusting for age, sex, race, factors that differ significantly between survivors and siblings. Inter-correlations between living status and functional outcomes, including income, employment, educational attainment, special education and marital status examined. As a result of these comparisons, and given the acknowledged association between employment and marital status and independent living, analyses were also conducted adjusting for employment and marital status. Univariate and multivariable logistic regression models were used to evaluate associations between explanatory variables and outcome in the cancer survivor group, with the final multiple logistic regression model reduced using forward selection to determine best fit. Data were analyzed with SAS version 9.1 (SAS Institute, Cary, NC).

Structural equation models (SEM) of the observed data were analyzed using Mplus 5.2 software. SEM is a statistical technique that combines elements of factor analysis and regression/path analysis into a comprehensive methodology. SEM offers advantages over other statistical approaches in evaluating causal hypotheses because of the ability to specify models in which the putative cause is isolated from extraneous influences and measurement error. This approach permits the identification of causal pathways leading to modeled outcomes. For the SEM we chose to use a sample with complete data rather than to use data imputation in order to avoid potentially distorting coefficients of association and correlation relating variables.³¹

Two types of variables are modeled in SEM: observed and latent. In contrast to observed variables that can be directly measured (e.g. test scores), latent variables (e.g. depression) are measured indirectly by a set of observed variables. The latent variables in the SEM include depression, somatization, physical endurance, vitality, and mental health. Latent variables were used for the BSI and SF-36 given the potential for item overlap. However, since the NCQ and the PTS items are more unique and do not measure content redundant with the BSI or SF-36, these factors were treated as observed variables. Factorial validity of the latent variables was established through exploratory and confirmatory factor analyses.

Results

Table I presents demographics for survivors and siblings, and treatment characteristics for survivors. Survivors were more than twice as likely to live dependently (17.7%) compared to siblings (8.7%) after adjusting for age, sex, and race (OR 2.07, 95% CI 1.77–2.42, $p < 0.001$). Within the survivor sample, intercorrelations between independent living status and other adaptive and functional outcomes were examined. Low correlations were observed ($r < 0.3$) between independent living and personal income, employment, educational

attainment, and history of special education services. A moderate correlation was found between independent living and marital status ($r = 0.51$), likely due to the partial overlap in the operational definition of independent living. While there are clear areas of overlap between these functional outcomes, independent living represents a unique variable of interest and is not redundant with these outcomes.

Factors Associated with Independent Living for Survivors

Compared to survivors diagnosed with Hodgkin lymphoma, lower rates of independent living were demonstrated for survivors diagnosed with CNS tumors (OR 0.13, 95% CI 0.10–0.18), leukemia (OR 0.29, 95% CI 0.23–0.37), neuroblastoma (OR 0.45, 95% CI 0.30–0.68), Wilm's tumor (OR 0.49, 95% CI 0.35–0.70), and soft tissue sarcomas (OR 0.50, 95% CI 0.36–0.69), though not bone cancer (OR 0.74, 95% CI 0.53–1.04). Since medical late effects are often linked to cancer therapy, the remaining analyses used therapy as predictors in lieu of diagnosis.

Results of the multivariable model predicting independent living status within the survivor cohort are provided in Table II. Survivors who were > 12 years of age at diagnosis were more than twice as likely to live independently than those diagnosed and treated when < 6 years of age (OR 2.29; 95% CI 1.76–2.98; $p < 0.001$). Those treated with cranial radiation were less likely to live independently compared to those with no history of such therapy (≤ 24 Gy OR 0.76, 95% CI 0.62–0.93; > 24 Gy OR 0.31, 95% CI 0.24–0.41). Survivors were less likely to live independently if they reported growth hormone deficiency (OR 0.51, 95% CI 0.37–0.71) or poor physical functioning (OR 0.49, 95% CI 0.38–0.63). In addition, those survivors with neurocognitive impairment were less likely to live independently, particularly those with impaired task efficiency (OR 0.58, 95% CI 0.47–0.71). Related to this, survivors being treated with neuroleptics, stimulants, or anticonvulsant, medications prescribed for conditions associated with neurocognitive impairment, were less likely to live independently (OR 0.32, 95% CI 0.24–0.43). Survivors were less likely to be living independently if they reported current symptoms of depression (OR 0.68, 95% CI 0.53–0.88).

Figure 1 depicts the results of the SEM analyses. Important moderators of variables are identified on the left side of the figure, but their actual paths are not illustrated in order to reduce the figures complexity. A well fitting model ($N=4407$; CFI=0.997; TLI =0.998; RMSEA=0.019; probability RMSEA $\leq 0.05 = 1.000$) explained 43% of the variance in whether or not the survivor lived independently. Three latent variables and 6 directly observed variables represent the direct effects on a survivors' ability to live independently in the final model. Survivors were most likely to live independently if they: had no or less exposure to cranial radiation, had a diagnosis of solid tumor or bone cancer (as opposed to leukemia, lymphoma, or CNS tumors), were older at diagnosis; did not have growth hormone deficiency; did not use neuroleptic, stimulant or anticonvulsant medications; had greater emotional lability; were not depressed; reported lower vitality and greater physical endurance; were white; and were older at the time of study.

Indirect influences on living independently included: poor *task efficiency* through medication use ($p < 0.001$), depression ($p < 0.001$), and mental health and emotional regulation ($p < 0.001$); *medication use* through poor physical endurance ($p < 0.001$); *memory* problems through emotional regulation ($p < 0.001$); *somatization* through poor physical endurance ($p < 0.001$); *emotional regulation* through vitality ($p = 0.003$); and poor *mental health* through emotional regulation ($p < 0.001$). Important correlates (not depicted in Figure 1) included depression with mental health ($p < 0.001$) and emotional regulation ($p < 0.001$), emotional regulation with physical endurance ($p < 0.001$), and somatization with depression ($p < 0.001$) and vitality ($p < 0.001$).

Discussion

This study provides new information on the prevalence of and risk for dependent living in adult survivors of childhood cancer. Survivors in our large, multi-site cohort had a significant 2-fold increased risk of living dependently when compared to siblings, and specific treatment variables, demographic factors, and the presence of medical, neurocognitive, and psychological late effects were predictive of independent living status. Through the relatively unique approach of using SEM in this analysis, we have demonstrated causal pathways connecting these diverse predictors, which may provide insight into points of intervention.

When survivors were compared across diagnostic groups, those diagnosed with CNS tumor and leukemia displayed the greatest risk of dependent living in adulthood. This increased risk may be at least partially explained through the impact of cranial radiation therapy on neurocognitive, physical, and behavioral functioning in protocols for these diagnostic groups. Risk for dependent living status increased with greater cranial radiation exposure (>24 Gy), consistent with previous studies documenting poor adaptive functioning after radiation therapy.^{20,32} Cranial radiation therapy also had indirect influences on dependent living status through neurocognitive late effects, use of neurologically-directed medication, and mental health concerns. Neurocognitive difficulties, particularly in task efficiency, influenced dependent living through poor mental health, depression, somatization, and use of neurologically-directed medication. These findings document the expected role of neurocognitive functioning on psychological well-being and adaptive behavior of survivors. Readily available pharmacologic approaches to managing neurocognitive late effects do not appear to mitigate risk for dependent living in adulthood. Rather, use of these medications more likely represents a marker for severity of neurocognitive dysfunction, which contributes to dependence into adulthood. Similarly, growth hormone deficiency is also likely a marker of neurologic sequelae from treatment, as endocrine dysfunction is a common late effect of cranial radiation therapy.

Psychological distress influences independent living status. Depression was strongly associated with dependent living, which points to the potentially debilitating impact of mental health problems. While the literature suggests that the majority of childhood cancer survivors are coping well after treatment, previous studies have highlighted that a small but distinct subgroup of survivors experience continued emotional distress.³³ These individuals may represent a group at risk for concurrent adaptive skill deficits and dependency in adulthood. Stressors associated with dependency may also influence the likelihood of depressed mood. Given these findings, screening for mental health difficulties and intervention to address depression symptoms early on may have long-term benefit for functional independence in adulthood. While the literature suggests that use of a posttraumatic stress (PTS) model of survivorship may be beneficial in understanding the emotional sequelae of childhood cancer,^{12,13} PTS symptoms were not associated with independent living status in our analyses.

In our model, difficulties with emotional regulation were somewhat surprisingly associated with an increased likelihood of independent living. Poor emotional regulation is not necessarily associated with emotional distress, but rather implies enhanced emotional lability that may include either positive or negative emotions.³⁴ Thus, as opposed to a marker of psychological distress, this construct may represent a coping style or a personality trait that may either facilitate relationships with selected mates or make one more difficult to live with, unless that individual is in a selected and committed relationship. Alternatively, individuals who live alone or with selected loved one may be more comfortable in demonstrating emotional lability.

Physical functioning also emerged as an important predictor of independent living. Specifically, poor physical endurance appears to be a direct barrier to independent living, and is influenced by somatization (i.e., shortness of breath, numbness, and weakness), diagnosis/treatment variables, use of neurologically-directed medication, growth-hormone deficiency, and current age. Poor physical functioning has an impact on employment opportunities and income, which may also indirectly impact the ability to live independently.¹⁷ The association between endurance and independent living can also be partially explained by the increased risk for neurologic impairment in the survivor cohort. Cranial radiation therapy is associated with quantitative changes in brain integrity,³⁵ and changes in brain integrity are associated with increased symptoms of limited physical endurance.^{36–38} While survivors with better physical endurance were more likely to live independently, those who were independent were more likely to report lower vitality, which may reflect fatigue associated with the demands of caring for oneself.

Our study is not without limitations. The current cohort was treated between 1970–1986, and given changes in treatment, our findings may have limited generalizability to future outcomes of modern treatment protocols. This may be particularly true for leukemia survivors given that current treatment protocols do not typically involve cranial radiation therapy. Nonetheless, our results do reflect the range of difficulties experienced by the cohort of current adult survivors. As our sample includes only survivors who agreed to and were capable of participating in the CCSS, these findings may underestimate deficits by excluding survivors who are having greater neurocognitive or emotional difficulty. While survivors from racial/ethnic minorities were less likely to live independently than Whites/Caucasians, this may reflect the role of cultural factors in the acceptability of multi-generational households as observed in the US Census data. The CCSS is under-represented in terms of racial minority survivors, limiting the conclusions that can be drawn regarding the impact of specific racial/ethnic identity on independent living. This should be examined in more diverse populations, as understanding the influence of race and ethnicity may provide insights into how to reduce social barriers to independence.

The results of the current study permit the development of a profile of survivors who are at risk for protracted dependent living. Neurocognitive late effects, psychological difficulties, medical late effects (i.e. growth hormone deficiency), and physical functioning play important roles in the independence of survivors during adulthood. Individuals who are less than 6 years of age at time of diagnosis, and who receive cranial radiation are at increased risk for dependent living. Furthermore, those who over the course of early survivorship develop decreased physical endurance, reduced vitality, depression, and neurocognitive deficits warranting medication management are at greatest risk. From this framework, the development of interventions directed towards supporting the psychosocial, neurocognitive, and physical functioning of survivors may promote transition into independence. Monitoring and intervention for depression, evaluating the efficacy of novel approaches for addressing neurocognitive deficits (e.g., cognitive remediation), and promoting physical endurance through exercise/physical therapy programs will be important areas of study in childhood cancer survivors with potential benefit for independent living in adulthood.

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Figure 1.

Schematic representation of SEM depicting direct and indirect influences on dependent living status. Note: Psychological constructs employed in the SEM analyses reflect latent variables derived from the original factor scores. As such, not all individual items from the factors are included in the final latent values. Neuropsychological constructs reflect observed variables.

Table I

Characteristics of Survivors and Siblings

	CCSS Cohort <i>n</i> (%)	Siblings <i>n</i> (%)	p-value
Sex			
• Males	3034 (50.2)	1069 (46.0)	0.0006
• Females	3013 (49.8)	1257 (54.0)	
Current Age			
• 25–35 years	3349 (55.4)	1066 (45.8)	<0.0001
• >35 years	2698 (44.6)	1260 (54.2)	
Race/Ethnicity			
• White, non-Hispanic	5493 (91.2)	2085 (92.8)	0.0061
• Ethnic/Racial Minority	533 (8.9)	161 (7.2)	
Education			
• Some college or less	2911 (48.5)	1016 (43.8)	<0.0001
• College graduate or higher	3090 (51.5)	1302 (56.2)	
Special Education Use			
• History of special education	1078 (20.2)	151 (7.3)	<0.0001
• No special education	4249 (79.8)	1920 (92.7)	
Income			
• Less than \$19,999/year	2100 (36.0)	506 (24.8)	<0.0001
• Above \$20,000/year	3737 (64.0)	1534 (75.2)	
Employment			
• Unemployed	1226 (20.5)	308 (13.3)	<0.0001
• Employed	4756 (79.5)	2011 (86.7)	
Marital Status			
• Ever married	3981 (66.5)	1866 (80.7)	<0.0001
• Single/never married	2005 (33.5)	446 (19.3)	
Living Status			
• Living dependently	1063 (17.7)	206 (8.7)	<.0001
• Living independently	4943 (82.3)	2143 (91.2)	
Diagnosis			
• Leukemia	1823 (30.2)		
• CNS	724 (12.0)		
• HD	1098 (18.2)		
• NHL	507 (8.4)		
• Kidney(Wilms)	414 (6.9)		
• Neuroblastoma	243 (2.0)		

	CCSS Cohort <i>n</i> (%)	Siblings <i>n</i> (%)	p-value
• Soft tissue sarcoma	593 (9.8)		
• Bone cancer	645 (10.7)		
Age at Diagnosis			
• < 6 years of age	1863 (30.8)		
• 6 to <12 years	1723 (28.5)		
• ≥ 12 years of age	2461 (40.7)		
Cranial Radiation			
• None	1626 (29.4)		
• ≤ 2400 cGy	3219 (58.1)		
• > 2400 cGy	694 (12.5)		
Chemotherapy			
• Chemo with MTX/Steroids	3079 (54.7)		
• Chemo without MTX/Steroids	1304 (23.2)		
• No Chemo	1242 (22.1)		

Table II

Multivariable analysis of the association between patient characteristics, treatment factors, and late effects and independent living status

Variable	OR (95% CI)	p-value
Current Age		
25–35 years	1.00	
> 35 years	1.97 (1.57–2.49)	<0.0001
Race/Ethnicity		
White	1.00	
Black, Hispanic, and Others	0.39 (0.30–0.51)	<0.0001
Age at Diagnosis		
< 6 years	1.00	
6–11 years	1.44 (1.17–1.77)	0.001
≥12 years	2.29 (1.76–2.98)	<0.0001
Cranial Radiation Therapy		
None	1.00	
≤24 Gy	0.76 (0.62–0.93)	0.008
> 24 Gy	0.31 (0.24–0.41)	<0.0001
Chemotherapy		
None	1.00	
No Methotrexate or corticosteroids	1.48 (1.13–1.94)	0.004
Methotrexate and or corticosteroids	1.00 (0.80–1.26)	0.975
Task Efficiency		
No problem	1.00	
Impairment	0.58 (0.47–0.71)	<0.0001
Emotion Regulation		
No problem	1.00	
Impairment	1.50 (1.14–1.97)	0.004
Depression		
No problem	1.00	
Impairment	0.68 (0.53–0.88)	0.003
Physical Endurance		
No problem	1.00	
Impairment	0.49 (0.38–0.63)	<0.0001
Neuroleptic/Stimulant/Anticonvulsant Meds		
None	1.00	
Current use	0.32 (0.24–0.43)	<0.0001
Growth Hormone Deficiency		
No	1.00	
Yes	0.51 (0.37–0.71)	<0.0001