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Psychosocial and Neurocognitive Outcomes in Adult Survivors of Adolescent and Early Young Adult Cancer: A Report From the Childhood Cancer Survivor Study

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ABSTRACT

Purpose

To characterize psychological and neurocognitive function in long-term cancer survivors diagnosed during adolescence and early young adulthood (AeYA).

Methods

Six thousand one hundred ninety-two survivors and 390 siblings in the Childhood Cancer Survivor Study completed the Brief Symptom Inventory-18 and a Neurocognitive Questionnaire. Treatment and demographic predictors were examined, and associations with social attainment (employment, education, and living independently) were evaluated. Logistic regression models were used to compute odds ratios (ORs) and corresponding 95% CIs.

Results

Among survivors, 2,589 were diagnosed when AeYA (11 to 21 years old). Adjusted for current age and sex, these survivors, compared with siblings, self-reported higher rates of depression (11.7% v 8.0%, respectively; OR, 1.55; 95% CI, 1.04 to 2.30) and anxiety (7.4% v 4.4%, respectively; OR, 2.00; 95% CI, 1.17 to 3.43) and more problems with task efficiency (17.2% v 10.8%, respectively; OR, 1.72; 95% CI, 1.21 to 2.43), emotional regulation (19.1% v 14.1%, respectively; OR, 1.74; 95% CI, 1.26 to 2.40), and memory (25.9% v 19.0%, respectively; OR, 1.44; 95% CI, 1.09 to 1.89). Few differences were noted between survivors diagnosed with leukemia or CNS tumor before 11 years old versus during later adolescence, although those diagnosed with lymphoma or sarcoma during AeYA were at reduced risk for self-reported psychosocial and neurocognitive problems. Unemployment was associated with self-reports of impaired task efficiency (OR, 2.93; 95% CI, 2.28 to 3.77), somatization (OR, 2.29; 95% CI, 1.77 to 2.98), and depression (OR, 1.94; 95% CI, 1.43 to 2.63).

Conclusion

We demonstrated that risk for poor functional outcome is not limited to survivors' diagnoses in early childhood. AeYA is a critical period of development, and cancer during this period can impact neurocognitive and emotional function and disrupt vocational attainment.

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INTRODUCTION

Currently, there are estimated to be more than 400,000 survivors of childhood and early young adult cancer in the United States.[1,2] These survivors are at risk for significant disease- and treatment-related morbidity. Two thirds of survivors face at least one chronic health condition, including mental health and cognitive problems.[3-6] Neurocognitive dysfunction has been demonstrated in more than 40% of survivors, with relatively higher rates of problems in processing speed, attention, memory, and executive function.[5,7] Childhood cancer survivors treated when less than 6 years of age are re-

ported to be at greater risk for neurocognitive problems compared with siblings.[8] Although many studies have examined outcomes associated with survivors of childhood cancer, few have focused on survivors diagnosed during their adolescence or early young adulthood.

The adolescent and young adult (AYA) cancer population is typically defined as encompassing the ages of 15 to 39 years. The early years of AYA, ages 11 to 21 years, are a period of rapid development of advanced neurocognitive functions related to brain maturation; this period encompasses a developmental phase when behavioral patterns are established and engrained.[9] The brain continues to grow

throughout adolescence and into early young adulthood, with accelerated development of higher-order skills such as executive functions.[9,10] The full extent of executive dysfunction may only become evident in adolescence and adulthood, with the onset of expectations to act more independently and use advanced planning and reasoning abilities.[11] Literature from traumatic brain injury patients demonstrates that mild injury during early adolescence can result in executive dysfunction that is not typically associated with similar injury during younger childhood.[12] Studies using magnetic resonance imaging of brains during early adolescence (ie, 11 to 14 years of age) have shown periods of rapid development in the dorsolateral prefrontal cortex, which is important for executive functions like abstract reasoning and problem solving.[13] This early phase of adolescent development may be more vulnerable to disruption of executive functions compared with the later phase (ie, 15 to 21 years of age) or even preadolescence (ie, 6 to 10 years of age).

The aim of this study was to characterize self-reported psychological symptoms and subjective complaints of cognitive and behavioral function in long-term survivors of cancer diagnosed during the time of adolescence and early young adulthood (AeYA; ages 11 to 21 years) and to identify risk factors within this group that may guide the development of targeted interventions to reduce adverse behavioral and social outcomes.

METHODS

Childhood Cancer Survivor Study

The Childhood Cancer Survivor Study (CCSS) is a multi-institutional, retrospective cohort study of individuals diagnosed between January 1, 1970, and December 31, 1986; individuals were younger than age 21 years of age and 5 or more years from diagnosis at the time of recruitment. Diagnoses included leukemia, CNS malignancies (all histologies), Hodgkin lymphoma, non-Hodgkin lymphoma, malignant kidney tumor, neuroblastoma, soft tissue sarcoma, and malignant bone tumor diagnosed and initially treated at one of 26 participating institutions. In addition, the study recruited the nearest-age sibling of a random sample of participating survivors to serve as a comparison group. The study procedure, cohort design, and characteristics have been described in detail elsewhere.[14,15]

The human subjects committee at each of the 26 participating institutions approved the CCSS protocol and contact documents. All study participants provided informed consent for participation in the study and for release of information from medical records. Cancer diagnosis and treatment information were obtained from the treating institution for all eligible survivors. Baseline questionnaires were collected to capture a wide variety of demographic and medical information. A follow-up questionnaire (FU2) was completed that contained self-reported assessments of neurocognitive and emotional functioning. Because of the length of this questionnaire, only a selected subset of siblings were asked to complete the neurocognitive/emotional functioning portion of the follow-up survey. The baseline and FU2 surveys and medical record abstraction form used for data collection are available at http://ccss.stjude.org. Within the context of the CCSS cohort, AeYA is defined as survivors diagnosed with cancer after 10 years but before 21 years of age. The lower limit of age 11 years was chosen because this has recently been identified as the mean age at which girls achieve Tanner stage II breast development, signaling the onset of puberty.[16] Similarly, onset of secondary sex characteristics in boys has also been shown to begin by a mean age of 10 years.[17] Given our aim to characterize neurocognitive and psychosocial outcomes that may be related to experiencing cancer within the neurobiological and socioemotional context of adolescence, we felt that it was prudent to capture participants within the entire peripubertal age range.

Of the 20,691 eligible 5-year childhood cancer survivors, 3,058 were lost to follow-up; 17,633 were contacted, and 14,357 participated in the baseline survey. Eleven thousand five hundred seventy-six survivors were contacted for the FU2 survey that contained the measures of interest for this study. Of these, 9,308 survivors (80.4%) participated in the FU2 survey, and 7,345 completed all questions on the measures of interest for the current analysis. Of these 7,345 survivors, survivors who had a diagnosis of kidney cancers and neuroblastoma were excluded as a result of small numbers, because these cancers are not typically seen during the AeYA time frame. Thus, 6,192 survivors were included in the final analysis. Three-hundred ninety siblings also completed the FU2 survey.

Outcome Measures

The Brief Symptom Inventory-18 (BSI-18) is an 18-item checklist that measures symptoms of emotional distress[18] and has been validated in cancer survivors.[19] An index score is generated for Anxiety, Depression, and Somatic Complaints; survivors with a standardized T score ≥ 63 ($\geq$ 90th percentile) were classified as having emotional distress.[18,20]

The CCSS Neurocognitive Questionnaire (CCSS-NCQ) was designed to assess self-reported neurocognitive symptoms often affected by cancer therapy.[21] The CCSS-NCQ contains four factors—task efficiency, emotional regulation, plan/organization, and working memory—derived from a 25-item questionnaire that asks participants to report the degree to which they experienced specific problems in these areas over the past 6 months. Raw scores were used and referenced to the sibling cohort, with scores $\geq$ 90th percentile of siblings classified as impaired. This threshold was used because it is also the recommended threshold in the standardization manual for the BSI-18, and this threshold was used in the validation studies of the CCSS-NCQ.

Data Analysis

Descriptive statistics for demographic and treatment variables for adolescent survivors, nonadolescent survivors, and siblings are listed in Table 1. Differences between adolescent survivors and sibling controls were evaluated using logistic regression or generalized logistic regression within a generalized estimating equation framework with compound symmetry assumption to account for within-family correlation. The impairments in emotional and neurocognitive functions between survivors diagnosed with cancer during adolescent and sibling controls were compared using logistic regression and implemented using generalized estimating equation with compound symmetry correlation structure to account for within-family correlation. Because a larger percentage of survivors of Hodgkin lymphoma, non-Hodgkin lymphoma, soft tissue sarcomas, or bone cancers were diagnosed during adolescence (n = 1,835, 70.9%), compared with survivors of leukemia or CNS tumors (n = 753, 29.1%; Table 1), the results were stratified by grouping CNS tumors with leukemias and grouping lymphomas with sarcomas/bone tumors.

The comparison between survivors diagnosed during childhood when less than 11 years of age and those diagnosed at age 11 to 21 years with respect to emotional distress and neurocognitive impairment was done using multiple logistic regression, and the results were stratified by diagnosis groups. The covariates considered in the models included current age, sex, and treatment exposures, which are typically associated with neurocognitive impairment. Although age at diagnosis is corrected with current age ($r = 0.79$), the variables are not confounded, and both have potential to offer unique predictive ability to the models. A comparison of all possible combinations of predictors was done, and the best model based on minimum Akaike Information Criterion (AIC) was selected. Current age and sex were forced into all models because they are known to be associated with outcomes. Among the other variables, for those that were not significant at the $P = .05$ level in this model, the least significant predictor was removed and the new model was considered acceptable if the increase in AIC value was less than 10 units.[22] This procedure was continued until the final model, with all insignificant factors (change in AIC value of < 10) removed, was obtained. The same approach for model selection, described earlier, was used to compare survivors diagnosed during ages 11 to 14 years to those diagnosed during the ages of 15 to 21 years, and the results, stratified by diagnosis groups, are reported in Appendix Table A1 (online only). In a similar manner, the impact of emotional and neurocognitive function on current employment, educational attainment, and living

Characteristic	AeYA Survivors (n = 2,589)		Non-AeYA Survivors (n = 3,603)		Siblings (n = 390)		P*	P†
	No.	%	No.	%	No.	%		
Sex							.5591	.4832
Female	1,305	50.4	1,789	49.7	204	52.3		
Male	1,284	49.6	1,814	50.4	186	47.7		
Current age, years							< .001	< .001
15-19	0	0.0	124	3.4	10	2.6		
20-24	0	0.0	913	25.3	51	13.1		
25-29	62	2.4	1,129	31.3	79	20.3		
30-34	568	21.9	898	24.9	77	19.7		
≥ 35	1,959	75.7	539	15.0	173	44.4		
Age at diagnosis, years					NA			< .001
< 6	0	0.0	2,237	62.1				
6-10	0	0.0	1,366	37.9				
11-14	1,255	48.5	0	0.0				
15-21	1,334	51.5	0	0.0				
Diagnosis					NA			< .001
Leukemia	461	17.8	1,997	55.4				
CNS tumor	292	11.3	610	16.9				
Hodgkin lymphoma	798	30.8	182	5.1				
Non-Hodgkin lymphoma	278	10.7	275	7.6				
Soft tissue sarcoma	279	10.8	377	10.5				
Osteosarcoma/Ewing	481	18.6	162	4.5				
Overall treatment					NA			< .001
Surgery only	204	7.9	211	5.9				
Chemotherapy	540	20.9	903	25.1				
Radiotherapy	494	19.1	332	9.2				
Chemotherapy and radiotherapy	540	20.9	1,920	53.3				
Chemotherapy					NA			< .001
Antimetabolites	959	37.0	2,249	62.4				
Corticosteroids	1,055	40.8	2,232	62.0				
CNS irradiation					NA			< .001
None	825	31.9	1,226	34.0				
Indirect‡	966	37.3	424	11.8				
Direct < 20 Gy	274	10.6	648	18.0				
Direct ≥ 20 Gy	405	15.6	1,108	30.8				
SMN or recurrence	205	7.9	95	2.6			< .001	
Education							< .001	.0894
< 12 years	74	2.9	163	4.5	9	2.3		
High school graduate	282	10.9	587	16.3	51	13.1		
Post–high school training	796	30.8	1,359	37.7	132	33.9		
College	906	35.0	1,138	31.6	135	34.6		
Postgraduate	512	19.8	323	9.0	61	15.6		
Employment							< .001	< .001
Unable to work	202	7.8	249	6.9	6	1.5		
Unemployed	275	10.6	391	10.9	44	11.3		
Student	25	1.0	248	6.9	15	3.9		
Working part time	244	9.4	500	13.9	51	13.1		
Working full time	1,815	70.1	2,168	60.2	273	70		
Household income							< .001	.2457
< $20,000	213	8.2	481	13.4	25	6.4		
$20,000-$39,999	433	16.7	795	22.1	58	14.9		
$40,000-$59,999	486	18.8	628	17.4	79	20.3		
$60,000-$79,999	443	17.1	484	13.4	65	16.7		
$80,000-$99,999	320	12.4	269	7.5	48	12.3		
> $100,000	549	21.2	367	10.2	88	22.6		
Marital status							< .001	.0022
Single	537	20.7	2,036	56.5	109	28		
Married/living as married	1,751	67.6	1,325	36.8	229	58.7		
Divorced/separated	272	10.5	218	6.1	48	12.3		

(continued on following page)

Table 1. Characteristics of Cancer Survivors and Siblings

Table 1. Characteristics of Cancer Survivors and Siblings (continued)

Characteristic	AeYA Survivors (n = 2,589)		Non-AeYA Survivors (n = 3,603)		Siblings (n = 390)		P*	P†
	No.	%	No.	%	No.	%		
Health insurance status							< .001	.7464
Yes	2,391	92.4	3,093	85.9	360	92.3		
No	181	7.0	478	13.3	29	7.4		
Live independently							< .001	.073
Yes	2,291	88.5	2,328	64.6	335	85.9		
No	272	10.5	1,242	34.5	54	13.9		
Medications								
Antidepressants	375	14.5	432	12.0	45	11.5	.004	.0785
Anxiolytics	136	5.3	114	3.2	9	2.3	< .001	< .001

Abbreviations: AeYA, adolescent and early young adult; NA, not applicable; SMN, second malignant neoplasm.
*Comparing AeYA survivors with non-AeYA survivors.
†Comparing AeYA survivors with siblings.
‡Indirect CNS irradiation indicates scatter from direct radiation to a noncranial site.

independently was examined. Odd ratios (ORs) and 95% CIs were calculated for variables retained in the final models. All statistical analyses were performed using SAS Version 9.3 (SAS Institute, Cary, NC), and two-sided statistical inferences were used throughout the analyses.

RESULTS

Characteristics of the adolescent and nonadolescent survivors and sibling controls are listed in Table 1. AeYA survivors were similar to siblings in sex and current age, although they were significantly less likely to be married (P = .02) or employed (P < .001). When AeYA survivors were compared with non-AeYA cancer survivors, non-AeYA survivors were less likely to be married (P < .001), employed (P < .001), or live independently (P < .001).

Rates of impairment in self-reported emotional and neurocognitive outcomes are listed for AeYA survivor and sibling cohorts in Table 2. After adjusting for current age and sex, survivors diagnosed as adolescents self-reported greater emotional distress, including anxiety (OR, 2.00; 95% CI, 1.17 to 3.43), somatization (OR, 2.36; 95% CI, 1.55 to 3.60), and depression (OR, 1.55; 95% CI, 1.04 to 2.30), compared with siblings. AeYA survivors also self-reported higher rates of neurocognitive problems than siblings in task efficiency (OR, 1.72; 95% CI, 1.21 to 2.43), emotional regulation (OR, 1.74; 95% CI, 1.26 to 2.40), and memory (OR, 1.44; 95% CI, 1.09 to 1.89).

The frequencies of self-reported impairment among survivors by age at diagnosis are listed in Table 3. Historically, children and adolescents diagnosed with leukemia received antimetabolite therapy and cranial radiation therapy (CRT), whereas adolescents diagnosed with lymphomas, sarcomas, or bone tumors did not receive CRT. This, combined with the difference in frequency by age, justified the stratification by groups to account for differences in both age at diagnosis and in the prevalence of CNS-directed therapies. In multivariable models, survivors diagnosed with CNS tumors/leukemia during AeYA did not differ from survivors diagnosed when less than 11 years of age in self-reported emotional distress or neurocognitive function (Table 4). For lymphoma/sarcoma survivors, diagnosis during AeYA was associated with a lower risk for self-reported emotional distress and neurocognitive dysfunction.

Stratified analyses were also conducted within AeYA subgroups (ie, those diagnosed during the first part of AeYA [11 to 14 years] v those diagnosed during the later part of AeYA [15 to 21 years]). Within the CNS tumor/leukemia group, multivariable models revealed no differences between early and late AeYA diagnosis (Appendix Table A1). However, in the lymphoma/sarcoma group, those diagnosed during early adolescence demonstrated significantly higher risk for self-reported memory (OR, 1.42; 95% CI, 1.09 to 1.86) and emotional

Table 2. Emotional and Neurocognitive Function for Survivors Diagnosed Between 11 and 21 Years of Age and Siblings

Outcome	Impairment*		Odds Ratio† (95% CI)
	No.	%	
Emotional outcomes			
Somatization			
Survivor	405	15.64	2.36 (1.55 to 3.60)
Sibling	26	6.67	1.0
Depression			
Survivor	302	11.66	1.55 (1.04 to 2.30)
Sibling	31	7.95	1.0
Anxiety			
Survivor	192	7.42	2.00 (1.17 to 3.43)
Sibling	17	4.36	1.0
Neurocognitive outcomes			
Task efficiency			
Survivor	446	17.23	1.72 (1.21 to 2.43)
Sibling	42	10.77	1.0
Emotional regulation			
Survivor	495	19.12	1.74 (1.26 to 2.40)
Sibling	55	14.1	1.0
Organization			
Survivor	346	13.36	1.18 (0.84 to 1.65)
Sibling	47	12.05	1.0
Memory			
Survivor	671	25.92	1.44 (1.09 to 1.89)
Sibling	74	18.97	1.0

*Impairment is defined as score falling in top 10% of normative sample.
†Odds ratio adjusted for age and sex.

Table 3. Survivor Emotional and Neurocognitive Function by Age at Diagnosis, Stratified by Diagnostic Groups

Emotional and Neurocognitive Function	Age < 6 Years at Diagnosis		Age 6 to 10 Years at Diagnosis		Age 11 to 14 Years at Diagnosis		Age 15 to 21 Years at Diagnosis	
	Mean (SD)	% of Group With Impaired Outcome*	Mean (SD)	% of Group With Impaired Outcome*	Mean (SD)	% of Group With Impaired Outcome*	Mean (SD)	% of Group With Impaired Outcome*
CNS tumors and leukemia								
No. of survivors	1,819		788		473		280	
Emotional outcomes								
Somatization	50.1 (8.81)	12.7	50.2 (8.91)	13.3	51.1 (9.36)	15.9	50.3 (8.94)	12.1
Depression	49.9 (9.77)	13.4	49.4 (9.60)	12.1	49.9 (10.15)	13.7	49.3 (10.07)	14.6
Anxiety	48.0 (9.32)	8.1	47.1 (8.78)	6.3	47.7 (9.49)	8.7	46.9 (9.37)	7.9
Neurocognitive outcomes								
Task efficiency	14.5 (4.66)	29.6	13.7 (4.51)	24.4	13.7 (4.44)	26.0	13.3 (4.30)	22.1
Emotional regulation	5.6 (1.80)	27.2	5.3 (1.69)	20.2	5.3 (1.76)	22.0	5.2 (1.67)	18.6
Organization	4.6 (1.69)	15.0	4.6 (1.65)	14.0	4.7 (1.66)	14.2	4.7 (1.62)	13.6
Memory	6.5 (2.25)	31.4	6.4 (2.33)	29.4	6.8 (2.39)	33.8	6.7 (2.39)	36.8
Lymphomas and sarcomas								
No. of survivors	418		578		782		1,054	
Emotional outcomes								
Somatization	51.0 (9.40)	16.3	50.2 (8.87)	13.5	51.3 (9.23)	16.1	51.3 (9.22)	16.1
Depression	49.9 (9.70)	12.4	49.7 (9.81)	13.3	49.0 (9.31)	10.4	48.5 (9.23)	10.9
Anxiety	49.0 (9.55)	9.8	48.2 (8.96)	8.7	48.1 (9.09)	7.7	47.8 (8.88)	6.5
Neurocognitive outcomes								
Task efficiency	12.5 (3.81)	15.1	12.4 (3.73)	13.1	12.5 (3.63)	14.6	12.3 (3.58)	13.9
Emotional regulation	5.4 (1.79)	23.7	5.2 (1.71)	20.1	5.2 (1.72)	20.7	5.1 (1.71)	16.8
Organization	4.4 (1.52)	7.9	4.6 (1.61)	13.1	4.7 (1.62)	13.7	4.6 (1.60)	12.7
Memory	5.8 (2.03)	18.2	5.9 (2.00)	20.2	6.1 (2.02)	23.0	6.0 (1.98)	21.6

Abbreviation: SD, standard deviation.
*Impairment is defined as symptoms falling ≥ 90th percentile of normative sample.

regulation (OR, 1.30; 95% CI, 1.01 to 1.67) problems compared with those diagnosed during late AeYA.

Finally, multivariable models were generated to investigate associations between social attainment and CCSS-NCQ and BSI-18 predictors (Table 5). Self-reported problems with task efficiency increased risk for unemployment (OR, 2.93; 95% CI, 2.28 to 3.77), attaining less than a college education (OR, 1.31; 95% CI, 1.02 to 1.69), and dependent living (OR, 2.82; 95% CI, 2.05 to 3.87) compared with survivors without problems. Self-reported problems with memory increased risk for achieving less than a college education (OR, 1.45; 95% CI, 1.17 to 1.79).

DISCUSSION

Survivors of childhood cancers are at known risk for impaired neurocognitive functioning, leading to poor attainment of adult social milestones. Although previous studies have focused on early childhood as a period of susceptibility,[23] the current study is the first to examine self-reported emotional distress and neurocognitive function in adults diagnosed with cancer during AeYA (age 11 to 21 years at diagnosis). Results demonstrate that survivors diagnosed during adolescence exhibit increased rates of self-reported emotional distress and neurocognitive dysfunction when compared with their sibling counterparts. Survivors diagnosed during AeYA were also significantly less likely than sibling controls to have attained post–high school education, to be working full time, to be married, or to be living independently, and social outcomes were related to neurocognitive symptoms.

Treatment of adolescents can be longer and more challenging than that of younger children as a result of unique developmental and psychosocial aspects of adolescence.[24] Previous studies have demonstrated that a diagnosis of cancer during this critical time can be disruptive to the growth process necessary for adulthood.[25] Cancer treatment during this time has the potential to interfere with adolescents' separation from caregivers, autonomy with regard to planning social and academic schedules, participation in social activities, and maintaining privacy, particularly of their bodies. The long-term impact of disrupted development in these important areas of social, emotional, and functional autonomy is unknown, but it is reasonable to infer that protracted or delayed maturation in these areas nay be associated with persistent distress. In addition, important brain structural and functional maturation processes continue well into adolescence and early adulthood. Areas such as the prefrontal cortex, which coordinate executive functions, mature later than areas that are associated with sensory and motor tasks.[26]

The risk for self-reported distress and neurocognitive problems among adolescent survivors was diagnosis dependent. Survivors of lymphoma or sarcoma demonstrated lower risk for self-reported distress and neurocognitive problems when diagnosed during adolescence compared with those diagnosed earlier, whereas no such differences were apparent among survivors diagnosed with CNS tumors or leukemia. Because the leukemia/CNS tumor group was more likely to receive CRT, which is well established as a significant predictor of neurocognitive late effects, it may be that the contribution of CRT to self-reported distress and neurocognitive dysfunction is apparent in adulthood, regardless of age at which CRT is administered.

Because survivor of lymphoma and sarcoma are not treated with CRT, detection of differences related to chemotherapies may be possible. In our sample, treatment with corticosteroids was associated

Table 4. Multivariable Model for the Prediction of Emotional and Neurocognitive Function in Adolescents and Young Adults Versus Younger Cancer Survivors, Stratified by Diagnostic Groups

	OR (95% CI)						
Variable	Somatization	Depression	Anxiety	Task Efficiency	Memory	Emotional Regulation	Organization
CNS tumors and leukemia							
Age at diagnosis, years							
≤ 10	1.0	1.0	1.0	1.0	1.0	1.0	1.0
11-21	1.18 (0.93 to 1.51)	1.11 (0.87 to 1.42)	1.44 (0.97 to 2.13)	1.09 (0.84 to 1.41)	1.26 (0.99 to 1.59)	1.21 (0.93 to 1.57)	0.87 (0.68 to 1.11)
Current age (per year)	—*	—	0.98 (0.95 to 1.00)	0.95 (0.94 to 0.97)	0.99 (0.97 to 1.00)	0.96 (0.94 to 0.97)	—
Chemotherapy							
Antimetabolites	—	0.72 (0.58 to 0.90)	—	0.41 (0.33 to 0.49)	0.57 (0.47 to 0.68)	0.8 (0.65 to 0.98)	0.68 (0.54 to 0.85)
Corticosteroids	—	—	—	—	—	—	—
Cranial irradiation							
None	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Indirect scatter	—	—	—	0.42 (0.15 to 1.2)	0.85 (0.40 to 1.81)	1.26 (0.60 to 2.61)	0.28 (0.07 to 1.18)
< 20 Gy	—	—	—	1.81 (1.42 to 2.30)	1.85 (1.48 to 2.31)	1.35 (1.07 to 1.70)	1.05 (0.79 to 1.40)
≥ 20 Gy	—	—	—	2.86 (2.33 to 3.50)	2.26 (1.87 to 2.73)	1.44 (1.18 to 1.77)	1.27 (1.01 to 1.60)
SMN or recurrence	—	—	—	—	—	—	—
Sex							
Male	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Female	1.74 (1.41 to 2.16)	—	—	1.59 (1.35 to 1.88)	1.47 (1.25 to 1.71)	2.13 (1.79 to 2.53)	—
Lymphomas and sarcomas							
Age at diagnosis, years							
≤ 10	1.0	1.0	1.0	1.0	1.0	1.0	1.0
11-21	0.97 (0.77 to 1.22)	0.75 (0.59 to 0.97)	0.73 (0.54 to 0.98)	0.73 (0.54 to 0.98)	0.74 (0.57 to 0.96)	0.74 (0.61 to 0.91)	1.22 (0.95 to 1.58)
Current age (per year)	—	—	—	1.03 (1.01 to 1.05)	1.05 (1.03 to 1.06)	—	—
Chemotherapy							
Antimetabolites	0.74 (0.57 to 0.95)	—	—	—	—	—	—
Corticosteroids	1.32 (1.16 to 2.48)	—	1.48 (1.11 to 1.99)	1.32 (1.06 to 1.66)	1.3 (1.07 to 1.59)	—	—
SMN or recurrence	1.70 (1.16 to 2.48)	—	—	—	—	—	—
Sex							
Male	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Female	1.47 (1.18 to 1.84)	—	—	—	1.49 (1.23 to 1.8)	1.61 (1.32 to 1.96)	—

Abbreviations: OR, odds ratio; SMN, second malignant neoplasm.
*— = variable that were not selected to contribute to the models using Akaike Information Criterion.

with greater risk of self-reported difficulties with somatization, anxiety, task efficiency, and memory for those diagnosed with lymphomas or sarcomas during adolescence. In addition, we found that those treated with steroids in younger adolescence (age 11 to 14 years) were significantly more likely than those treated in older adolescence (age 15 to 21 years) to report problems with anxiety and memory. Although the vast majority of literature examining neuropsychological late effects has focused on survivors of CNS-impacting cancers, recent findings have provided evidence that non–CNS-directed therapies may be associated with neurocognitive difficulties. For example, survivors of Hodgkin lymphoma treated with thoracic irradiation have been demonstrated to display decreased performance on measures of attention and memory function.[27] Deficits were associated with indices of cardiopulmonary health. Current findings support this previous work and contribute to the notion of multiple sources of risk for neurocognitive impairment in long-term survivors of childhood cancer.

Results should be considered in light of several limitations. It is important to note that self-reports of psychological distress and neurocognitive dysfunction are likely to be intercorrelated. This can make it difficult to discern whether emotional distress is contributing to actual or perceived neurocognitive impairment (or vice versa) or if one or more additional variables underlie the emergence of difficulties in both emotional and cognitive domains. Direct assessment of neurocognitive functioning is often conducted in smaller studies, although this was not feasible in the current study. We have, however, recently demonstrated correspondence between self-reported neurocognitive functioning on the CCSS-NCQ and performance-based measures in a sample of more than 800 adult survivors of childhood cancer.[28] Results indicated that the CCSS-NCQ demonstrates acceptable discriminant validity against widely used measures of neuropsychological functioning, particularly for the Memory and Task Efficiency domains.

An additional limitation was our choice to stratify results by grouping diagnoses with similar treatment and ages at diagnosis. Further stratification by disease would have limited the ability to use specific treatment as predictors as a result of reduced variance and/or confounding of treatment with diagnosis variables. Finally, we recognize that the treatment protocols that were used in the CCSS cohort are now more than 20 years old. Although previous studies have shown that the intensity of treatment has been reduced for many diagnoses, the pattern of cognitive impairment remains quite similar.[7] Previous treatment protocols continue to inform about current risk of late effects. For example, patient strategies for treatment of low-risk

Table 5. Multivariable Model for the Prediction of Social Attainment by Emotional and Neurocognitive Function Among Adolescents and Young Adult Survivors Age 11 to 21 Years at Diagnosis

Emotional and Neurocognitive Function	OR (95% CI)		
	Unemployed	< College Graduate	Living Dependently
Neurocognitive			
Task efficiency			
Not impaired	1.0	1.0	1.0
Impaired	2.93 (2.28 to 3.77)	1.31 (1.02 to 1.69)	2.82 (2.05 to 3.87)
Memory			
Not impaired	1.0	1.0	1.0
Impaired	—	10.45 (1.17 to 1.79)	—
Emotional regulation			
Not impaired	1.0	1.0	1.0
Impaired	—	—	0.69 (0.48 to 0.99)
Organization			
Not impaired	1.0	1.0	1.0
Impaired	—	0.73 (0.56 to 0.95)	—
Emotional			
Somatization			
Not impaired	1.0	1.0	1.0
Impaired	2.29 (1.77 to 2.98)	1.48 (1.18 to 1.85)	—
Depression			
Not impaired	1.0	1.0	1.0
Impaired	1.94 (1.43 to 2.63)	—	1.66 (1.13 to 2.41)
Anxiety			
Not impaired	1.0	1.0	1.0
Impaired	—	—	—
Sex			
Male	1.0	1.0	1.0
Female	0.41 (0.33 to 0.52)	1.04 (0.89 to 1.22)	1.33 (1.02 to 1.72)
Current age (per year)	0.98 (0.97 to 1.00)	0.98 (0.97 to 0.99)	1.05 (1.02 to 1.07)

Abbreviation: OR, odds ratio.

leukemia in the 1980s are similar to strategies for standard- and high-risk leukemia, and neurocognitive deficits were still self-reported in 34% of leukemia survivors surveyed upward of 18 years after diagnosis.[29] Also, CCSS participants and thousands of adult survivors of childhood cancer who were treated decades ago remain at risk for late effects, and it is critical to document cancer-related late effects in this group over time. Also, we recognize that we are unable to examine young adults in a more thorough manner because our inclusion criteria only included AeYAs diagnosed before the age of 21 years. As such, we recognize that generalization of treatment and late effects of young adult patients treated at nonpediatric tertiary cancer centers may be limited.

Limitations notwithstanding, the current study is the first, to our knowledge, to focus on self-reported neurocognitive function and psychological distress in survivors diagnosed during adolescence. The AeYA population is a group that is not well represented in outcome studies, although there is a need to identify emotional and behavioral issues that are specific to them. This study demonstrated that there are high rates of self-reported impairment in neurocognitive function and psychological distress that are associated with limitation in development of adult social milestones. Accordingly, further follow-up with AeYA survivors is necessary. The National Comprehensive Cancer Network published guidelines in 2012 specific to the AYA population and a neuropsychological evaluation stating that, although severe neurocognitive deficits were uncommon in the survivors of AYA cancer,

including CNS tumors, subtle deficits in executive function, sustained memory, and processing speed were noted in patients treated with CRT.[30] The National Comprehensive Cancer Network recommended that in patients with evidence of impaired educational or vocational progress, formal neuropsychological evaluation should be completed.[30] Our results suggest that these guidelines may need to be expanded to include additional diagnoses.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Psychosocial and Neurocognitive Outcomes in Adult Survivors of Adolescent and Early Young Adult Cancer: A Report From the Childhood Cancer Survivor Study

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Appendix

Table A1. Multivariable Model for the Prediction of Emotional and Neurocognitive Function in Young Versus Old Adolescents, Stratified by Diagnostic Groups

Variable	OR (95% CI)						
	Somatization	Depression	Anxiety	Task Efficiency	Memory	Emotional Regulation	Organization
CNS tumors and leukemia							
Age at diagnosis, years							
11-14	1.37 (0.87 to 2.15)	0.86 (0.56 to 1.33)	1.08 (0.62 to 1.89)	1.16 (0.80 to 1.68)	0.83 (0.59 to 1.15)	0.99 (0.65 to 1.50)	1.05 (0.67 to 1.64)
15-21	1	1	1	1	1	1	1
Current age (per year)	—	—	—	—	—	0.93 (0.90 to 0.97)	—
Chemotherapy							
Antimetabolites	—	0.65 (0.43 to 0.99)	—	0.48 (0.34 to 0.68)	0.54 (0.38 to 0.78)	—	—
Corticosteroids	—	—	—	—	—	—	—
Cranial irradiation							
None	1	1	1	1	1	1	1
Indirect scatter	—	—	—	—	1.32 (0.37 to 4.68)	—	—
< 20 Gy	—	—	—	—	1.70 (1.04 to 2.79)	—	—
≥ 20 Gy	—	—	—	—	1.84 (1.25 to 2.70)	—	—
SMN or recurrence	—	—	—	—	—	—	—
Sex							
Male	1	1	1	1	1	1	1
Female	—	—	—	1.49 (1.05 to 2.12)	1.40 (1.02 to 1.93)	2.10 (1.44 to 3.06)	—
Lymphomas and sarcomas							
Age at diagnosis, years							
11-14	1.25 (0.93 to 1.69)	0.91 (0.66 to 1.26)	1.13 (0.77 to 1.65)	1.25 (0.91 to 1.70)	1.42 (1.09 to 1.86)	1.30 (1.01 to 1.67)	1.13 (0.85 to 1.51)
15-21	1	1	1	1	1	1	1
Current age (per year)	1.04 (1.01 to 1.07)	—	—	1.05 (1.02 to 1.08)	1.06 (1.04 to 1.09)	—	—
Chemotherapy							
Antimetabolites	—	—	—	—	—	—	—
Corticosteroids	—	—	1.52 (1.03 to 2.23)	—	1.32 (1.03 to 1.68)	—	—
SMN or recurrence	1.83 (1.21 to 2.77)	—	—	—	—	—	—
Sex							
Male	1	1	1	1	1	1	1
Female	1.67 (1.26 to 2.20)	—	—	—	1.80 (1.42 to 2.29)	1.58 (1.22 to 2.03)	—

Abbreviations: OR, odds ratio; SMN, second malignant neoplasm.