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Cognitive and Occupational Function in Survivors of Adolescent Cancer

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Purpose: Adolescents with cancer have unique developmental considerations. These include brain development, particularly in the frontal lobe, and a focus on completing education and entering the workforce. Cancer and treatment at this stage may prove to uniquely affect survivors' experience of cognitive and occupational function.
Methods: An exploratory, cross-sectional, descriptive comparative study was employed to describe cognitive and occupational function in adult survivors of adolescent cancer (diagnosed between the ages of 15 and 21 years) and explore differences in age- and gender-matched controls.
Results: In total, 23 survivors and 14 controls participated in the study. While significant differences were not found between the groups on measures of cognitive and occupational function, several small and medium effect sizes were found suggesting that survivors may have greater difficulty than controls. Two small effect sizes were found in measures of neuropsychological performance (the Digit Vigilance test [$d = 0.396$] and Stroop test [$d = 0.226$]). Small and medium effect sizes ranging from 0.269 to 0.605 were found for aspects of perceived and total cognitive function. A small effect size was also found in work output ($d = 0.367$).
Conclusions: While we did not find significant differences in cognitive or occupational function between survivors and controls, the effect sizes observed point to the need for future research. Future work using a larger sample size and longitudinal design are needed to further explore cognitive and occupational function in this vulnerable and understudied population and assist in the understanding of patterns of change over time.

Keywords: cognitive function, neuropsychological function, occupational function, employment, survivorship

Introduction

Survivorship needs after adolescent cancer is understudied.[1,2] Studying adult survivors of adolescent cancer is important, considering the developmentally vulnerable time when cancer diagnosis and treatment occur. Many adolescents are completing high school and entering college or the workforce; however, adolescents with cancer may miss or delay important milestones.[3,4] Moreover, the brain, especially the frontal lobe, matures and develops into the early 20s.[5] The frontal lobe is involved with several domains of cognitive function, including psychomotor function, planning, reasoning, judgment, impulse control, and memory.[6] Cancer and its treatment could affect the typical neurological and behavioral development and disrupt the adolescent survivor's long-term employment status. However, there is a lack of research examining the cognitive changes experienced by adolescents diagnosed with cancer during this vulnerable period of development.

Previous studies of adult survivors of adolescent and young adult (AYA) cancer have described varying rates of employment[7–9]; they generally indicate reduced employment rates among survivors of AYA cancer compared to controls. However, employment rates alone do not capture broad information on how an individual functions within an occupational role. Successful employment requires numerous functional skills, including physical, mental, and social health, basic competence, and character traits important to work.[10] Together, these skills and attributes are termed occupational function.[10] Yet, no study has explored occupational function in survivors of adolescent cancer and no study has explored differences in occupational function and cognitive function between survivors of adolescent cancer and peers without a cancer history.

The aims of this exploratory study are to (1) describe cognitive and occupational function among adult survivors of adolescent cancer and (2) explore differences in cognitive and occupational function between adult survivors of

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adolescent cancer and age- and gender-matched healthy controls. Since adolescence is a developmentally rich time, elucidating the potential disruption of a cancer diagnosis and treatment may improve understanding of cognitive and occupational outcomes associated with adolescent cancer, and provide direction for interventions to improve outcomes.

Materials and Methods

This was an exploratory, single-center, descriptive, cross-sectional comparative study of adult survivors of adolescent cancer and age- and gender-matched healthy controls. The study was approved by the University of Pittsburgh Institutional Review Board. Informed consent was obtained from all participants. Cancer survivors were recruited between February 2015 and May 2016 from an outpatient pediatric oncology clinic, which treats individuals diagnosed before the age of 22 years. Although not required for study participation, cancer survivors who enrolled were asked to refer a ''healthy friend/sibling'' of the same sex and within 2 years of their age to serve as a control for comparison.

Participants

Inclusion criteria for survivors of adolescent cancer were (1) cancer diagnosis between age of 15 and 21 years (middle or late adolescence)[11–13]; (2) currently between the age of 18 and 39 years; (3) 2 years or more since active cancer treatment; and (4) able to speak and read English. Cancer survivors were excluded if they had a diagnosis of neurological condition or mental impairment before cancer diagnosis. Controls met the same inclusion and exclusion criteria, but had no history of cancer. In addition, controls were frequency matched to the cancer survivors, being of the same gender and within 2 years of the survivor's age. Some survivors enrolled in the study stated they did not have a healthy friend or sibling to ask to participate. In this case, they were included in the study without a healthy control.

Measures

Participants were asked to complete both self-report questionnaires and a battery of neuropsychological measures administered by research personnel trained in proper administration of the tests and supervised by a neuropsychologist.

Demographic and clinical characteristics. Participants completed a demographic questionnaire, which collected information about race, marital status, education, and employment. Clinical characteristics, including medical history and current medications, were collected; these were verified through the use of medical records for the survivor group. *The Intensity of Treatment Rating (ITR-3.0) Scale*[14] was used to classify the intensity of pediatric cancer therapy according to treatment modality and stage/risk level for the patient. Based on these characteristics, the ITR assigns an intensity level from 1 (minimally intensive) to 4 (most intensive). The ITR-3.0 is a reliable and valid instrument[14] that facilitates classification of complex diagnoses and treatment regimens, and allows for comparisons across intensity groups,[15] including AYA cancer patients.[7]

Neuropsychological measures. A battery of neuropsychological measures assessing a broad range of cognitive domains was used. Measures were selected for their psychometric properties and relevance to cognitive development in adolescents and young adults.

Digit Vigilance (DV) Test[16] assesses capacity for sustained attention. Higher scores indicate poorer function.

Digit Symbol Substitution Test[17] assesses one's capacity for sustained, focused concentration and directed visual shifting. Higher scores indicate better function.

Grooved Peg Board Test[18] assesses dexterity and psychomotor functioning. Higher scores indicate poorer function.

Stroop Color and Word Test[19] assesses executive function and cognitive inhibition. The Stroop test yields an interference score, and higher scores indicate better function.

Verbal Fluency Test[20] assesses executive function and control over cognitive processes, including selective attention, mental set shifting, internal response generation, and self-monitoring. Higher scores indicate better function.

Trail Making Test A and B[21] assesses executive function, mental flexibility, and attention. Higher scores indicate poorer function.

Wechsler Memory Scale[22] assesses numerous aspects of memory. Higher scores indicate better function.

Letter Number Sequencing Test[23] assesses working memory. Higher scores indicate better function.

Rey-Osterrieth Complex Figure Test[24] assesses visual perceptual, skills, spatial organization, constructional ability, and visual memory. Higher scores indicate better function.

Wisconsin Card Sorting Test (WCST)[25] primarily assesses perseveration and abstract thinking, but also measures executive function. The WCST yields a perseveration score where higher scores indicate poorer function.

Perceived cognitive function. Patients Assessment of Own Functioning Inventory (PAOFI),[26] a self-report measure of cognitive difficulties, has shown correlation to changes in neuropsychological functioning in samples of cancer patients,[27–29] and has demonstrated reliability and validity.[30] The PAOFI assesses perceptions of performance in five domains: memory, executive function, language, orientation, and sensorimotor ability. Higher scores indicate poorer perceived function.

Anxiety, fatigue, and depression. Depressive symptoms were measured with the 20-item *Center for Epidemiological Studies-Depression Scale-Revised [CESD-R]*,[31] which has shown good reliability and validity in cancer patients.[32] A cut score of 20 has been shown to detect major depressive disorder in the general population.[33] Anxiety and fatigue were measured by the *Profile of Mood States-Short Form [POMS-SF]*[34] Tension-Anxiety subscale and Fatigue-Inertia subscale, respectively. The POMS-SF has good reliability and validity.[34] A T-score ≥ 60 on one of the subscales indicates clinically significant anxiety or fatigue.[34]

Occupational function. The *Work Limitations Questionnaire (WLQ)*[35] is a 25-item self-report measure of work functioning. It has demonstrated reliability and validity for use among several different jobs and chronic health conditions, including cancer.[36] The WLQ yields four subscale scores indicating limitations in performing a dimension of one's job (Time, Physical, Mental and Interpersonal, and

Output) and a total score. Higher scores indicate poorer function.

Missing data. In the case of missing responses on multi-item questionnaires, unless instructed otherwise by the instrument developer, if 80% or more items for each subscale and total score were completed by the participant, the mean item response was calculated from the available item responses to impute values for the missing items and obtain subscale and total scores. When less than 80% (or the developer-specified amount) of items had been answered, no score was calculated.

Data analysis

Group-specific descriptive statistics, consistent with a variable's level of measurement and observed distribution, were calculated. Group comparative analyses were used to explore differences in demographic or clinical characteristics between cancer survivors who referred a healthy control and those who did not. We also explored differences in demographic characteristics between survivors and controls. Between-group differences were examined using independent sample *t*-tests for interval/ratio variables and chi-square tests of independence or Fisher's exact tests if sparse cells for nominal variables. For interval- and ratio-scaled variables, nonparametric testing using the Mann-Whitney U-test for interval- and ratio- scaled variables was used if nonnormality or outliers were encountered. Due to the exploratory nature of the study and sample size considerations, our primary focus was parameter estimation and confidence intervals.

For aim 1, simple descriptive statistics were calculated for each subscale and total score in both the adolescent cancer survivor and healthy control groups. The confidence interval of the mean (95%) was calculated and reported for the survivor group. For aim 2, one-way multivariate analysis of variance (MANOVA) with further exploration of the individual construct-specific domains was conducted for cognitive and occupational function between survivor and control groups. Effect sizes (as Cohen's *d*) with 95% confidence intervals were calculated for each neuropsychological measure, subscale, and total score. Interpretation of Cohen's *d* was guided by ranges used in neuropsychology research (0.20–0.49 = small effect, 0.50–0.79 = medium effect, and 0.80 or above = large effect).[37] MANOVA was applied to each set of tests for each domain of cognitive function (attention, memory, and executive function), except for the domain of psychomotor speed where an independent *t*-test was used since this domain had one score. In addition, correlations between perceived cognitive function with depressive symptoms, anxiety, and fatigue were explored using Spearman's rho as previously performed in other populations of cancer survivors.[38,39] Research has shown that self-reported anxiety symptoms in the absence of clinically significant anxiety does not affect cognitive performance.[40] Thus, the level of anxiety was dichotomously recoded (clinically significant anxiety or not) based on cutoffs put forth (T-score ≥ 60).[34] Assumptions of MANOVA[41] and independent *t*-test[42] were met for each dependent variable in the model. There were no univariate outliers in our study; however, there was one multivariate outlier, a cancer survivor who demonstrated an unusual pattern in performance on neuropsychological measures of attention. Analyses were performed with and without this individual, which did not change the conclusions drawn; thus, we opted to use the entire sample in our analysis.

Results

There were no significant differences in demographic factors or disease and treatment characteristics for cancer survivors who referred a healthy control and those who did not. Thus, the entire sample (23 cancer survivors and 14 controls) was used for analysis. Demographic and clinical characteristics of the sample are shown in Table 1. Cancer survivors were $\sim$23 years of age and had some college education. Most participants were Caucasian ($n = 21$, 91.3%), male ($n = 16$, 69.6%), and were never married ($n = 20$, 87.0%). In the survivor group, the mean age at cancer diagnosis was 17.4 years; the most common diagnosis was Hodgkin Lymphoma ($n = 10$, 43.4%) and treatment lasted $\sim$1 year. There were no significant differences in demographic factors, levels of depressive symptoms, or fatigue between the survivor and control groups. Cancer survivors had significantly higher anxiety scores than the controls ($p = 0.049$); however, there was no difference in clinically significant levels of anxiety,[34] $p = 0.275$. Since research has shown that self-reported anxiety symptoms in the absence of clinically significant anxiety do not affect cognitive performance,[40] anxiety was not included as a covariate in the model.

Cognitive function scores for the cancer survivor group and comparisons between the survivor and control groups are summarized in Table 2. Mean scores for each of the tests in the survivor group were within the expected range based on population normative data. Although no significant differences between survivors and controls were found through multivariate or univariate analysis of variance, the direction of effects that were observed may suggest poorer cognitive function in cancer survivors than in controls. In addition, two cognitive domains demonstrated small effect sizes, the DV Test performance ($d = 0.396$) and the Stroop score ($d = -0.226$).

Small or medium effect sizes were found for differences in each of the perceived cognitive function (PAOFI) subscales, except the sensory perceptual domain. Differences between groups in PAOFI subscales, except the Use of Hands, suggest that survivors reported greater difficulty than controls. Differences in total perceived cognitive function scores also exhibited a small to medium effect size ($d = 0.441$), indicating that survivors (M = 32.78, SD = 23.02) reported greater difficulty with overall cognitive functioning compared to controls (M = 23.71, SD = 15.54). A follow-up analysis found that, for both cancer survivors and controls, poorer perceived cognitive function in each subscale (except Use of Hands) and total perceived cognitive function significantly correlated with increased depressive symptoms, anxiety and fatigue. Correlations between perceived cognitive function and depressive symptoms, anxiety, and fatigue are reported in Table 3.

Occupational function is summarized in Table 4. Approximately 43% of cancer survivors were employed full time, and an additional 21% were students and employed in part-time work. The greatest work difficulties for cancer survivors were found with time management, mental-interpersonal demands, and work output. Survivors reported least difficulty with meeting physical demands of their work. No significant differences between survivors and controls in work limitations were found for participants who were employed. Effect size

Table 1. Baseline Characteristics of Survivors of Adolescent Cancer and Healthy Control Groups

Characteristic	*Survivors of AYA cancer* (n = *23*) *Mean ± SD median (IQR)*	*Healthy control* (n = *14*) *Mean ± SD median (IQR)*	*Test statistic*	p
Age (years)	23.8 ± 4.0	22.9 ± 3.8	$t = 0.64$	0.526
	22.6 (5.0)	21.7 (3.1)	$U_{MW} = 133.0$	0.394
Education (years)	14.7 ± 2.4	14.7 ± 2.5	$t = 0.03$	0.976
	15.0 (5.0)	14.0 (4.0)	$U_{MW} = 152.5$	0.793
Disease and treatment factors				
Age at diagnosis (years)	17.4 ± 1.9	NA	—	—
Length of treatment (years)	1.2 ± 1.4	NA	—	—
Mood				
Depressive symptoms	11.7 ± 11.9	9.5 ± 8.9	$t = 0.62$	0.538
	7.0 (14.0)	7.1 (13.0)	$U_{MW} = 149.0$	0.722
Anxiety (T-score)	48.9 ± 11.5	41.7 ± 7.5	$t = 2.04$	0.049
	49.0 (20.0)	39.5 (9.0)	$U_{MW} = 98.0$	0.049
Fatigue (T-score)	46.3 ± 10.2	43.3 ± 6.7	$t = 0.94$	0.354
	44.0 (19.0)	42.0 (9.0)	$U_{MW} = 135.5$	0.429
	Percent (n)	*Percent* (n)		
Sex (male)	69.6 (16)	64.3 (9)	—	1.000[FE]
Marital status (never married)	87.0 (20)	85.7 (12)	—	1.000[FE]
Race (Caucasian)	91.3 (21)	85.7 (12)	—	0.625[FE]
Hispanic descent (no)	95.7 (22)	78.6 (11)	—	0.142[FE]
Identified a healthy control (yes)	60.8 (14)	NA	—	—
Cancer diagnosis				
Acute lymphoblastic leukemia	17.4 (4)	NA	—	—
Acute myelocytic leukemia	4.3 (1)	NA	—	—
Osteosarcoma	8.7 (2)	NA	—	—
Chondrosarcoma	4.3 (1)	NA	—	—
Ewing's sarcoma	8.7 (2)	NA	—	—
Germ cell tumor	8.7 (2)	NA	—	—
Hodgkin lymphoma	43.4 (10)	NA	—	—
Non-Hodgkin lymphoma	4.3 (1)	NA	—	—

AYA, adolescent and young adult; FE, Fisher's exact; IQR, interquartile range; MW, Mann–Whitney *U* test; NA, not applicable; SD, standard deviation.

estimation revealed a small to medium effect in reported work output ($d = 0.430$), indicating that working survivors of adolescent cancer (M = 21.66, SD = 29.98) reported worse work output than controls (M = 10.71, SD = 14.92).

Discussion

This study describes cognitive and occupational function in survivors of adolescent cancer and explores differences between survivors and healthy controls. While cognitive and occupational differences between survivors and controls were not statistically significant, there were interesting findings in effect sizes. Two small effect sizes were found for differences in neuropsychological performance and several small and medium effect sizes for differences in perceived cognitive function. Still, survivors generally fell within the expected range on neuropsychological measures, which may indicate that differences between the groups are not clinically meaningful. Finally, we found a small to medium effect size in differences in reported work output in the survivor group compared to controls.

Statistically significant differences between survivors and controls were not found. This may be because there were no differences between groups with regard to cognitive or occupational function. However, the lack of significant findings could also be due, in part, to a small sample size or the lack of sensitivity of the measures to detect subtler differences between groups. In addition, ~40% of the survivors had been diagnosed with Hodgkin lymphoma, requiring a treatment regimen that is considered by many to carry a lower risk for cognitive difficulties,[43] which may have affected our findings. Still, the effect sizes of differences in neuropsychological measures may indicate that survivors of adolescent cancer have trouble with aspects of memory and executive function, warranting further research. Furthermore, the DV and Stroop tests may be sensitive to between-group differences in survivors of adolescent cancer and controls. This is consistent with reports that suggest both the DV and Stroop tests demonstrate excellent sensitivity to subtle changes in cognitive function. The Stroop test sensitively detects prefrontal dysfunction[44] and the DV Test sensitively detects frontal lobe dysfunction.[16] However, it is important to emphasize that this is the first study

Table 2. Cognitive Function in Survivors of Adolescent Cancer Compared to Healthy Controls

Test	*Cancer survivors Mean ± SD [95% CI]* n = *23*	*Cancer survivors* n *(%) impaired*[a] n = *23*	*Healthy controls Mean ± SD* n = *14*	*Test statistics* p-*value*	*Cohen's d [95% CI]*
Attention				$F_{MV} = 0.671$ $p = 0.518$	
Digit Vigilance (seconds)[b]	409.13 ± 100.72 [365.58 to 452.69]	5 (21.7)	370.91 ± 88.95	$F_{UV} = 1.365$ $p = 0.251$	$d = 0.396$ [−0.28 to 1.07]
Digit symbol, 90-second total (no. correct)	80.52 ± 14.54 [74.24 to 86.81]	0 (0)	82.79 ± 15.85	$F_{UV} = 0.197$ $p = 0.660$	$d = -0.151$ [−0.82 to 0.51]
Memory				$F_{MV} = 0.343$ $p = 0.883$	
Letter number sequencing (no. correct)	11.26 ± 3.19 [9.88 to 12.64]	1 (4.3)	11.07 ± 3.22	$F_{UV} = 0.199$ $p = 0.658$	$d = 0.059$ [−0.61 to 0.72]
Rey figure, immediate (no. accurate elements)	22.48 ± 6.47 [19.68 to 25.27]	4 (17.4)	21.64 ± 6.68	$F_{UV} = 0.564$ $p = 0.564$	$d = 0.128$ [−0.54 to 0.79]
Rey figure, delayed (no. accurate elements)	22.09 ± 6.63 [19.22 to 24.95]	4 (17.4)	20.82 ± 6.50	$F_{UV} = 0.639$ $p = 0.429$	$d = 0.193$ [−0.47 to 0.86]
Stories B and C, immediate (no. correct)	25.61 ± 5.71 [23.14 to 28.08]	0 (0)	25.64 ± 5.34	$F_{UV} = 0.013$ $p = 0.909$	$d = -0.005$ [−0.670 to 0.659]
Stories B and C, delayed (no. correct)	22.70 ± 5.64 [20.25 to 25.14]	0 (0)	23.46 ± 5.09	$F_{UV} = 0.164$ $p = 0.688$	$d = -0.140$ [−0.80 to 0.53]
Executive function				$F_{MV} = 0.163$ $p = 0.956$	
Stroop interference (difference between performance and expected)	3.96 ± 8.08 [0.46 to 7.45]	0 (0)	5.86 ± 8.97	$F_{UV} = 0.443$ $p = 0.510$	$d = -0.226$ [−0.89 to 0.44]
Trail making, part B (seconds)[b]	69.21 ± 23.13 [59.21 to 79.22]	0 (0)	71.50 ± 31.81	$F_{UV} = 0.064$ $p = 0.802$	$d = -0.086$ [−0.75 to 0.58]
Verbal fluency, FAS (no. correct)	37.70 ± 11.54 [32.70 to 42.69]	0 (0)	38.50 ± 11.23	$F_{UV} = 0.043$ $p = 0.837$	$d = -0.070$ [−0.73 to 0.59]
Wisconsin card sorting test perseverative errors (no. errors)[b]	9.09 ± 5.52 [6.70–11.47]	0 (0)	9.86 ± 7.12	$F_{UV} = 0.136$ $p = 0.715$	$d = -0.125$ [−0.79 to 0.54]
Psychomotor speed					
Grooved Pegboard, dominant hand (seconds)[b]	69.93 ± 17.39 [62.41–77.45]	0 (0)	67.33 ± 14.62	$t = 0.461$ $p = 0.648$	$d = 0.158$ [−0.51 to 0.82]
Patient perception				$F_{MV} = 1.514$ $p = 0.215$	
Memory[b]	14.96 ± 9.35 [10.91–19.00]	NA	10.00 ± 6.04	$F_{UV} = 4.191$ $p = 0.048$	$d = 0.599$ [−0.08 to 1.28]
Language and communication[b]	7.91 ± 5.57 [5.51–10.32]	NA	4.85 ± 4.06	$F_{UV} = 3.020$ $p = 0.091$	$d = 0.605$ [−0.07 to 1.28]
Use of hands[b]	1.00 ± 1.31 [0.43–1.57]	NA	1.79 ± 1.53	$F_{UV} = 1.695$ $p = 0.202$	$d = -0.566$[c] [−1.24 to 0.11]
Sensory perceptual[b]	1.22 ± 1.86 [0.41–2.02]	NA	1.29 ± 2.02	$F_{UV} = 0.233$ $p = 0.632$	$d = -0.036$ [−0.70 to 0.63]
Higher level cognitive and intellectual function[b]	7.70 ± 7.42 [4.49–10.90]	NA	5.79 ± 6.55	$F_{UV} = 1.894$ $p = 0.178$	$d = 0.269$ [−0.40 to 0.94]
Total[b]	32.78 ± 23.02 [22.83–42.74]	NA	23.71 ± 15.54	$t = 1.301$ $p = 0.202$	$d = 0.441$ [−0.23 to 1.11]

Higher scores indicate better performance, except where noted. Cohen's *d*: small ($d = 0.20$–0.49), medium ($d = 0.50$–0.79), large ($d \geq 0.80$).
[a]Cognitive impairment is defined as z-score ≤ -2.0.[59]
[b]Higher scores indicate poorer performance.
[c]Please see explanation of potential cause of this unexpected finding in Discussion section.
CI, confidence interval; F_{MV}, multivariate F statistic; F_{UV}, univariate F statistic; NA, not applicable.

Table 3. Correlation Between Perceived Cognitive Function and Depressive Symptoms, Anxiety, and Fatigue

PAOFI score	*Depressive symptoms (n = 36)*	*Anxiety (n = 36)*	*Fatigue (n = 36)*
Memory			
Spearman's rho	0.528	0.378	0.339
p	0.001	0.023	0.043
Language and communication			
Spearman's rho	0.652	0.437	0.413
p	<0.001	0.008	0.012
Use of hands			
Spearman's rho	0.315	0.293	0.200
p	0.062	0.083	0.242
Sensory Perceptual			
Spearman's rho	0.574	0.510	0.384
p	<0.001	0.001	0.021
Higher level cognitive and intellectual function			
Spearman's rho	0.769	0.509	0.456
p	<0.001	0.002	0.005
Total			
Spearman's rho	0.727	0.513	0.480
p	<0.001	0.001	0.003

PAOFI, Patient Assessment of Own Functioning Inventory.

designed to explicitly measure cognitive function in survivors of adolescent cancer and, thus, we are unable to directly compare with other studies' findings in this population.

Survivors of adolescent cancer reported greater perceived cognitive difficulty, including poorer memory, language and communication skills, executive function, and total perceived cognitive function, than controls. These findings are consistent with past reports that cancer survivors experience poorer perceived cognitive function than controls even in the absence of worse neuropsychological function.[45,46] An unusual pattern was found in the perceived Use of Hands subscale, whereby controls reported greater difficulty than survivors. However, there was a surprising situation where two controls reported either nerve damage or a previous hand injury that affected use of their hands. We suspect this situation may explain the unexpected finding, but this should be explored in future studies with a larger sample. Still, total perceived difficulty on the Use of Hands subscale remained quite low on average for both groups.

Similar to research in perceived cognitive function in other cancer survivors, we found an association between perceived cognitive function and anxiety, depressive symptoms, and fatigue.[38,46] However, it is uncertain whether symptoms of anxiety, depression, and fatigue contribute to poorer perceived cognitive function or whether they may be the result of subtle cognitive difficulties that go undetected in measures of neuropsychological function.

It is theorized that greater perceived cognitive difficulty may relate to compensatory mechanisms in the brain even in the absence of impaired neuropsychological function.[47,48] For instance, research using functional magnetic resonance imaging (fMRI) in other cancer survivor populations have shown that although neuropsychological performance may not be impaired, the alterations in activation patterns in the brain suggest a compensatory mechanism, whereby greater effort and mental processes are required to perform similar to healthy controls.[49–51] Future research should investigate if perceived cognitive difficulties align with mechanisms of

Table 4. Occupational Function in Survivors of Adolescent Cancer Compared to Healthy Controls

Occupational factors	*Cancer survivors, n = 23, n (%)*	*Healthy controls, n = 14, n (%)*		
Work status				
Full-time student, not working	4 (17.4)	3 (21.4)		
Student and part-time work	5 (21.7)	4 (28.6)		
Student and full-time work	1 (4.3)	0 (0.0)		
Part-time work only	3 (13.0)	0 (0.0)		
Full-time work only	10 (43.4)	7 (50)		
	Mean ± SD [95% C.I.] n = 19	*Mean ± SD n = 11*	*Test statistic p-value*	*Cohen's d [95% CI]*
Aspects of occupational function in participants who are employed			$F_{MV} = 1.877$ $p = 0.147$	
Time	21.31 ± 31.04 [7.35–35.27]	21.36 ± 20.50	$F_{UV} = 0.240$ $p = 0.628$	$d = -0.002$ [−0.74 to 0.74]
Physical	8.03 ± 11.88[a] [2.54–13.52]	13.03 ± 20.91	$F_{UV} = 0.680$ $p = 0.417$	$d = -0.316$ [−1.07 to 0.44]
Mental-interpersonal	24.43 ± 27.93 [11.87–36.99]	22.70 ± 17.33	$F_{UV} = 0.101$ $p = 0.753$	$d = 0.070$ [−0.67 to 0.81]
Output	20.53 ± 28.91 [7.53–33.53]	11.36 ± 15.67	$F_{UV} = 0.384$ $p = 0.541$	$d = 0.367$ [−0.38 to 1.12]
Total	4.50 ± 5.28[a] [2.13–6.87]	4.67 ± 4.34	$t = -0.090$ $p = 0.929$	$d = -0.034$ [−0.78 to 0.72]

Cohen's *d*: small ($d = 0.20$–0.49), medium ($d = 0.50$–0.79), large ($d \geq 0.80$).
[a]$n = 18$.

compensation in the brain and whether deficits align with education or work outcomes.

In our sample, survivors of adolescent cancer were not less likely to be employed full or part time than healthy controls; however, survivors of adolescent cancer did report reduced work quality and quantity compared to controls.[35] While numerous studies have examined the concept of ''return to work'' following a cancer diagnosis, there is a dearth of this research in survivors of adolescent cancer since these individuals often are not employed at the time of cancer diagnosis and treatment. For survivors of adolescent cancer, there is the additional factor of pursuing higher education/training, establishing a career, and entering the workforce after cancer diagnosis and treatment. To our knowledge, interventions to assist survivors of adolescent cancer in entering the workforce have not been explored. Whether cancer survivors merely perceive reduced work output or in fact have reduced work quantity and quality should be further explored, since this may impact their ability to maintain employment and could have vast career development and financial implications. Efforts to explore factors that contribute to poorer work output with consideration to both qualitative and quantitative methods are needed. Investigation into how to best support this vulnerable population in achieving professional goals and optimal occupational functioning is especially important given their life stage.

Studies examining the relationship between occupational function and cognitive function in other populations of cancer survivors have been conducted.[52–55] A study of breast cancer survivors revealed that the strongest predictors of work limitations are difficulties in the cognitive domains of memory and executive function.[52] Similarly, a study of brain tumor survivors found that work limitations were most significantly predicted by memory, executive function, and attention deficits.[53] In addition, a study of adult survivors of childhood cancer found that impaired task efficiency, organization, memory, and behavioral regulation were significantly associated with unemployment as an adult.[56] The frontal lobe, a part of the brain under development during adolescence, is involved in numerous domains of cognitive function, including memory and executive function. Dysfunction in this part of the brain is associated with work limitations in other populations of cancer survivors.[52,53,56] However, research has not been conducted to explore these relationships specifically in those diagnosed with cancer during adolescence. Future work with a large sample may explore this relationship.

Strengths and limitations

There are several limitations to acknowledge. First, this study was cross-sectional and did not examine changes in cognitive function over time; future studies should include a longitudinal design, including pre-treatment testing. Second, limited and unequal sample sizes between groups did not provide adequate power for hypothesis testing and may have contributed to the lack of statistically significant differences observed. Small sample sizes also prevented more complex analyses, including investigation of the relationship between cognitive and occupational function. Third, the sample of cancer survivors was not balanced and representative of all survivors of adolescent cancer. The sample comprised primarily Caucasians and a large proportion had been diagnosed with Hodgkin Lymphoma. Fourth, there was no assessment of socioeconomic status, which has shown correlation to cognitive function.[57,58] Fifth, the neuropsychological measures in this study did not provide a comprehensive assessment of all domains of cognitive function and may not have been sensitive to subtle between-group differences. The neuropsychological battery was limited to 10 measures assessing four domains of cognitive function to reduce subject burden and fatigue. However, more extensive neuropsychological testing may have detected statistically significant differences between the groups.

The strengths of this study include the use of a neuropsychological battery specifically chosen to measure aspects of cognitive function developing during adolescence. The sample composed exclusively of individuals diagnosed with cancer during adolescence and included matched controls. To our knowledge, this is the first study specifically designed to explore cognitive function in survivors of adolescent cancer.

Conclusions

While we did not find significant differences between survivors and controls on objective measures of cognitive function, the effect sizes found point to the need for future research. Survivors of adolescent cancer report poorer perceived cognitive function than healthy controls. In addition, there were no significant differences in the rate or level of employment between adolescent cancer survivors and controls; however, adolescent cancer survivors reported more difficulty with work output compared to their healthy counterparts. Future, longitudinal studies are needed, which include a larger sample of survivors of AYA cancer, to elucidate who is at risk for cognitive difficulties and difficulty with work output. Clearly understanding cognitive and occupational problems associated with disease and treatment will inform development of interventions to assist survivors in achieving optimal functioning.

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