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Fatigue in Adolescents With Cancer Compared to Healthy Adolescents

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Abstract

Background—Cancer-related fatigue is one of the most pervasive and debilitating side-effects of cancer treatment and adolescents consistently rate cancer-related fatigue as one of the most distressing aspects of treatment. Because fatigue is also high in adolescents without cancer, the current study aims to describe fatigue in adolescents with cancer relative to a control group and to identify associates of such fatigue. Knowing this is important for understanding the extent of the problem in adolescents with cancer relative to healthy adolescents and for understanding who is most at risk for fatigue and related distress.

Procedure—Adolescents with cancer and their caregivers (n =102) and adolescents without a history of chronic health conditions and their caregivers (n =97) completed the Multidimensional Fatigue Scale and measures of depression, quality of life (QoL), affect, coping, and family functioning.

Results—Adolescents with cancer and their caregivers reported significantly more adolescent fatigue across all domains (with the exception of adolescent reports of cognitive fatigue) relative to adolescents without chronic health conditions. Higher fatigue was significantly related to adolescent report of more symptoms of depression, poorer QoL, higher negative affect, less positive affect, and behavioral disengagement coping style. Fatigue was not related to active coping or family functioning.

Conclusions—Adolescents with cancer experience significantly more fatigue than peers without chronic health conditions. Reports of fatigue are closely related to multiple indicators of psychosocial well-being, suggesting that fatigue may be an important cancer-related symptom to assess and manage to improve adolescent QoL.

Keywords

adolescent; fatigue; health-related quality of life; pediatric oncology

INTRODUCTION

Cancer-related fatigue is one of the most pervasive and debilitating side-effects of cancer treatment [1–3]. Adolescents are particularly affected by fatigue as they consistently rate cancer-related fatigue as one of the most distressing aspects of treatment [4,5]. Adolescents with cancer have described fatigue as “a complex changing state of exhaustion that at times seems to be a physical condition, at other times a mental state, and at other times a combination of physical and mental tiredness [6]. Despite a focus on fatigue in adult oncology, less is known about the occurrence, impact, and risk factors for fatigue in pediatric oncology. Similar to other cancer-related morbidities that are worse for adolescents relative to younger patients, adolescents report more fatigue than younger children with cancer [4,7,8]. This developmental increase in fatigue is also found in healthy adolescents [9,10], with as many as 38% reporting clinically significant fatigue [9,11,12]. Because of the high frequency of fatigue in adolescents without cancer, the current study aimed to describe fatigue in adolescents with cancer relative to a control group and to identify associates of such fatigue. Understanding the occurrence and impact of fatigue in adolescents with cancer relative to healthy adolescents is important to describe limitations faced by adolescents with cancer and for identifying patients at greatest risk for fatigue and related distress.

Fatigue is conceptualized as a subjective experience of sustained exhaustion that is unique from sleepiness, and persists despite adequate rest [13]. Cancer-related fatigue is likely a combination of multiple factors including disease processes, treatment side-effects, and psychosocial responses to cancer. In adults, cancer-related fatigue results in significant disruption to daily activities [14], increased caregiver burden [14], and reduced psychosocial functioning [15,16]. Fatigue at diagnosis has even been shown to predict time until recurrence and overall survival rates [17]. Thus, fatigue is a critical marker of cancer morbidity worthy of further investigation.

Adolescents, in general, are particularly vulnerable to fatigue related to inadequate sleep due to unique developmental sleep needs of this age group. For example, adolescents demonstrate a need for longer sleep times, more daytime sleepiness, and shifts in circadian rhythm resulting in later bedtimes and rise times [18]. Furthermore, healthy adolescents commonly exhibit less than ideal sleep habits (e.g., short sleep times, later bedtimes on weekends), in part due to school schedules, homework, and social commitments. Disease and treatment factors (i.e., pain, nausea, clinic schedules, interrupted sleep during hospitalization) may also result in disrupted sleep during cancer treatment. Poor sleep habits and interrupted sleep is related to higher daytime sleepiness and more symptoms of depression [18], potentially putting adolescents at greater risk for fatigue relative to younger children. For adolescents with cancer, fatigue may further exacerbate the impact of cancer on pursuing normal developmental tasks of adolescence (e.g., engaging with peers, attending school, or maintaining school-related activities). Indeed, adolescents with cancer identify fatigue as a major barrier to accomplishing their goals more often than adolescents without cancer [19]. The impact of fatigue can also be long lasting as it affects between 18% [20] and 33% [21] of childhood cancer survivors and is related to lower quality of life (QoL) in survivors [22].

Although research examining the relationship of cancer and adolescent fatigue continues to grow, few studies have examined correlates of such fatigue in pediatric [23] or adult oncology [3]. Only two studies have quantitatively examined associates of fatigue in adolescents with cancer, and they found that receiving chemotherapy [24] and depression [7] were associated with fatigue. Correlates found in pediatric samples include female gender [25], depression [26], corticosteroid treatment [27,28], hospitalization [8], and brain tumor diagnosis [21]. None of these studies focus on adolescents with comparisons to healthy peers. Psychosocial correlates of fatigue such as depression and anxiety have also been found in healthy adolescents [29] and adults with cancer [30].

Given the paucity of empirical studies focusing on adolescent fatigue in pediatric oncology and the fact that adolescents with cancer are extremely vulnerable to fatigue and related negative outcomes, there is a need to better understand the contribution of cancer above and beyond typical experiences of adolescent fatigue. Thus, the current study aimed to: (1) compare adolescent and parent reports of adolescent fatigue between adolescents with and without cancer; and (2) identify demographic, psychosocial, and disease/treatment-related associates of fatigue in adolescents with cancer. For the first aim, it was hypothesized that adolescents with cancer and their caregivers would report higher levels of fatigue than peers without chronic health conditions. Caregiver and adolescent reports were included in the current study to further understand concordance between these reporters given caregivers often serve as proxy reporters for adolescents in clinical settings. Consistent with prior research, caregiver and adolescent reports were hypothesized to be moderately correlated [31]. For the second aim, fatigue among adolescents with cancer was expected to be higher in females, older adolescents, and those with brain tumors; to relate to worse treatment burden (more time since diagnosis, higher total days spent inpatient, higher treatment intensity, relapsed cancer); and to relate to psychological well-being (more depressive symptoms, lower QoL, lower positive affect, higher negative affect). The potential relationship between fatigue with income, minority status, coping (lower active coping, lower behavioral disengagement), and poorer family functioning was also explored.

METHODS

Participants

Adolescents with cancer and their caregivers (n =102) and adolescents without a history of chronic health conditions and their caregivers (n =97) completed the study. English-speaking adolescents 13–19 years old and their caregivers were eligible. For the cancer group, adolescents undergoing active cancer treatment (not palliative care), at least 1 month since initial diagnosis, and physically and cognitively able to complete questionnaires according to parent-or oncology provider-report were eligible. Control participants with a history of chronic/life-threatening health condition, acute health problem requiring hospitalization, or an immediate family member with a history of a chronic health condition were ineligible.

Of 133 eligible adolescents with cancer approached, 123 agreed to participate and 102 completed the study. Reasons for refusal included: perceptions that the study was too much work (n =2), the patient reported not feeling well (n =1), the caregiver did not want the

adolescent to participate (n =4), adolescent cognitive limitations (n =1), or no reason given (n =2). For the control group, 128 healthy adolescents contacted the principal investigator to participate, 114 were eligible and agreed to participate, and 97 completed the main study.

Procedure

Outpatient clinic and inpatient rosters were checked daily to identify potential participants with cancer and potential participants were approached in clinic or on the inpatient floor. There was no difference in fatigue reports between participants with cancer recruited in clinic (n =38) or the inpatient floor (n =64). Additionally, the control group was recruited from the community using fliers posted in an office building associated with the hospital and referrals from other participants in the study. A snowball recruitment strategy [32] was also employed, whereby participants with and without cancer were encouraged to distribute fliers with investigator contact information to potential control participants. Control participants that completed the study were referred by adolescents with cancer (n =32; 33%), referred by other control participants (n =33; 34%), or contacted the investigator after seeing a flier (n =32; 33%). Scores on dependent variables did not differ by recruitment method.

Caregivers and adolescents 18 or 19 years old completed written informed consent and adolescents under 18 completed written informed assent. After providing consent/assent, adolescents and caregivers were given questionnaires to complete at the hospital or home. Adolescents were compensated \$25 upon completion.

Measures

Demographic information—Caregivers completed a basic demographic information form regarding the child's age, gender, ethnicity and race, and family income.

Disease variables—Through review of electronic medical records, the Intensity of Treatment Rating Form (ITR-2) was completed independently by two oncology providers [33]. A third pediatric oncologist reviewed ratings and identified 10 patients with discrepant ratings. The ITR-2 is a widely used and validated system for rating cancer treatment intensity via ratings on a 1–4 scale, with higher values indicating more intense cancer treatment. Patients' medical charts were also used to identify diagnosis, time since diagnosis, number of days spent inpatient, and whether patients were being treated for an initial cancer diagnosis or relapse. Diagnoses were categorized by leukemia/lymphomas, solid tumors, or central nervous system tumors.

Multidimensional fatigue scale (MFS)—The MFS is an 18-item questionnaire that yields a total score and three subscale scores: General Fatigue, Sleep/Rest Fatigue, and Cognitive Fatigue. Items are answered on a 5-point Likert-type scale indicating how problematic each element of fatigue was over the past month on parallel forms by adolescents and caregivers. This measure was validated in pediatric cancer and healthy children (ages 5–18), demonstrating adequate reliability and validity [31]. Lower scores indicate more fatigue. Internal consistency was adequate in this sample for adolescent ($\alpha =0.81$ – 0.93) and caregiver reports of fatigue ($\alpha =0.92$ – 0.96).

Pediatric quality of life inventory (PedsQL)—Adolescents with cancer rated QoL on a 5-point Likert-type scale indicating how problematic each element of QoL has been over the past month. The measure yields scores for psychosocial QoL and physical health QoL. This measure was validated in pediatric cancer demonstrating adequate reliability and validity [31]. Higher scores indicate better QoL. Internal consistency was adequate in this sample for physical health QoL ($\alpha = 0.93$) and psychosocial QoL ($\alpha = 0.86$).

Child depression inventory (CDI)—Depression was measured using the short form (10 items) of the CDI [34]. Adolescents with cancer report their experience with symptoms of depression over the past 2 weeks. Total scores were converted into T-scores based on age- and gender-norms. This sample demonstrated adequate internal consistency ($\alpha = 0.69$).

Positive and negative affect scale (PANAS)—Affect was measured with the PANAS, which has been widely used in adolescents and demonstrates strong reliability and validity [35]. Adolescents with cancer rated their experience of 20 emotions in the past week on a 5-point scale (with higher scores indicating greater agreement with the emotion). Internal consistency was adequate in this sample for positive affect ($\alpha = 0.88$) and negative affect ($\alpha = 0.87$).

Brief COPE—Adolescents with cancer responded to items reflective of coping style on a 4-point scale, with higher scores indicating greater agreement [36]. The active coping ($\alpha = 0.60$) and behavioral disengagement ($\alpha = 0.60$) subscales were selected to reflect common fatigue coping mechanisms: active strategies (i.e., having visitors, enjoyable activities) and more disengaged strategies (i.e., sleep/rest, being alone) [26,37].

Family assessment device (FAD)—Adolescents with cancer completed the 12-item FAD general functioning scale to measure family functioning [38,39]. Items were answered on a 4-point scale, with higher scores indicating better family functioning. Internal consistency was adequate in this sample ($\alpha = 0.84$).

Data Analysis

To understand differences in fatigue between adolescents with cancer and adolescents without a history of chronic health conditions, adolescent and caregiver reports of fatigue (total fatigue and MFS subscales) were compared between groups using one-way ANOVAs. To understand agreement between adolescent and caregiver reports of fatigue, intra-class correlations were computed for MFS total score for both the cancer group and the control group [40]. Associates of fatigue were examined using ANOVAs for categorical variables and Pearson correlations for continuous variables. Variables significantly related to fatigue were entered into a single entry regression to understand the relative contribution of significant psychosocial and medical variables to fatigue.

RESULTS

Sample characteristics are described in Table I. Data were examined for skew and kurtosis and all variables, with the exception of months since diagnosis and days spent hospitalized, were evenly distributed. Months since diagnosis and days spent inpatient were both

transformed using log transformations to correct for positive skew [41]. The cancer group and the healthy control group did not differ by gender, age, or ethnicity. Income was higher in the control group [$\chi^2(3) = 8.67, P = 0.034$]. Analyses comparing the groups were run with and without income as a covariate.

Comparison of fatigue between adolescents with cancer and adolescents without chronic health conditions

Adolescents with cancer reported significantly more total fatigue than adolescents without chronic health conditions (Table II). All subscales were significantly higher among adolescents with cancer with the exception of cognitive fatigue, which was similar between groups. Likewise, caregivers of adolescents with cancer reported higher total fatigue and higher fatigue across all fatigue subscales compared to caregivers of adolescents without chronic health conditions. Results did not differ when controlling for income. Intra-class correlations between caregiver and adolescent reports of fatigue were small for adolescents without cancer (ICC = 0.18, $P = 0.039$) and large for the adolescents with cancer (ICC = 0.50, $P < 0.001$).

Demographic Correlates of Fatigue in Adolescents With Cancer

Contrary to hypotheses, older age ($r = -0.11, P = 0.291$) and female gender [$F(1, 196) = 1.48, P = 0.255$] were not related to increased fatigue. Fatigue did not differ between White and non-White adolescents [$F(1, 99) = 0.46, P = 0.500$] or by income group [$F(3, 89) = 1.70, P = 0.173$].

Psychosocial correlates of fatigue in adolescents with cancer

Total adolescent fatigue was significantly correlated with PedsQL physical functioning, PedsQL psychosocial functioning, CDI total score, PANAS positive and negative affect, brief COPE behavioral disengagement. Fatigue was not related to brief COPE active coping or FAD general family functioning (Table III).

Treatment Correlates of Fatigue in Adolescents With Cancer

Contrary to hypotheses, fatigue was not related to diagnostic category [$F(3, 97) = 0.36, P = 0.783$], treatment intensity ratings [$F(2, 98) = 0.39, P = 0.677$], time since diagnosis ($r = 0.11, P = 0.254$), relapse status [$F(1, 98) = 0.01, P = 0.942$], or days spent hospitalized ($r = -0.18, P = 0.076$).

Regression Predicting Fatigue in Adolescents With Cancer

CDI total score, PANAS positive affect, and brief COPE behavioral disengagement were entered into a single entry regression. Due to the close relationship between depression and negative affect, the PANAS negative affect was not included in this regression. The regression model significantly predicted 34.4% of the variance in fatigue (Table IV).

DISCUSSION

The current study offers the first comparison of fatigue in adolescents with cancer compared to adolescents without chronic health conditions and an examination of associates of fatigue

in adolescents with cancer. This study fills a gap in understanding the magnitude of the problem of fatigue in adolescents with cancer and factors related to such fatigue. That adolescents with cancer and parents reported significantly more fatigue than healthy adolescents across all domains (i.e., total fatigue score, general fatigue, sleep/rest fatigue) except cognitive fatigue, is a testimony to the significant problem of fatigue in adolescents with cancer above and beyond what is experienced by adolescents in general. The fatigue of adolescents with cancer in the current sample was also higher than a prior combined sample of children and adolescents with cancer using the same measure (both child and caregiver report) [31], providing support that fatigue may be more severe for adolescents relative to younger patients with cancer [4,7,8,21]. Reports of fatigue in the current study were also higher than another sample of weekly adolescent reports for 1 month postchemotherapy [42], indicating that fatigue may be relatively high across the cancer trajectory rather than just after chemotherapy.

Similar to previous reports [42], adolescents and caregivers perceived relatively fewer concerns with the cognitive aspects of fatigue. Although caregivers of adolescents with cancer reported significantly more cognitive fatigue than the control group, the level of fatigue was lower than other fatigue domains. It is possible that adolescents with cancer have fewer cognitive demands given reduced school attendance and overall expectations for productivity, resulting in a lack of awareness about levels of cognitive fatigue. Alternatively, adolescents with cancer may be motivated and/or are able to maintain cognitive functioning despite reduced physical functioning.

Fatigue ratings were more consistent for adolescents with cancer and their caregivers relative to healthy adolescents, which may be due in part to caregivers of adolescents with cancer being more attuned to their child's physical functioning and hypervigilant to cancer and treatment symptoms. Caregivers of healthy adolescents tended to underestimate their adolescent's experience with fatigue while caregivers of adolescents with cancer may overestimate the impairment caused by fatigue. Effect sizes were larger for caregiver reports relative to adolescent reports of fatigue, suggesting that caregivers may notice a larger impact of fatigue relative to healthy adolescents than adolescents report. These discrepancies across reporters highlight the importance of better understanding fatigue and the validity of proxy reports for this age group.

The lack of a relationship between fatigue with demographic and treatment factors may indicate that fatigue is not isolated to a specific sub-group of adolescents with cancer, and is a relatively universal symptom among adolescents with cancer. Fatigue was, however, closely related to several areas of psychosocial well-being including QoL, depression, positive and negative affect, and behavioral disengagement coping style. Thus, fatigue is associated with psychosocial morbidity, further exacerbating the negative experience of cancer for adolescents.

Such poor psychosocial functioning may be more relevant than demographic and treatment factors for understanding who is most at risk for fatigue.

The relationship of fatigue with psychosocial functioning is consistent with previous research in child and adult oncology and adolescents. For example, fatigue is related to depressive symptoms in children [7,26], adults with cancer [30,43], and adolescents without chronic health conditions [12]. The relationship between fatigue and depression also continues into survivorship [44,45], suggesting a persisting impact on functioning and QoL for these adolescents even after treatment. In healthy adolescents, higher levels of sedentary activities longitudinally predict fatigue [29], which may be similar to the relationship between behavioral disengagement and fatigue found in the current sample of adolescents with cancer. Research describing symptom clusters in adolescents with cancer suggests that when examined together with sleep disturbance, fatigue significantly predicts symptoms of depression [46]. Furthermore, negative affect has been related to perceiving cancer as a burden and reporting higher cancer-related distress while positive affect was strongly related to benefit finding in children and adolescents with cancer [47]. Coping strategies and negative affect may be risk factors for poor adjustment to cancer, leading to more fatigue and depression. Regression results suggest that depression is one of the strongest predictors of adolescent fatigue over positive affect and disengaged coping style. Future longitudinal study will be important to confirm the directionality between fatigue, depression, and coping and identify the most effective intervention targets for improving psychosocial well-being.

In adult oncology, psychosocial interventions targeting fatigue (e.g., psychoeducation, activity management, and fatigue coping strategies) have demonstrated a small but significant effect in reducing fatigue [48–50]. However, given the heterogeneity of these interventions, there is no consensus on whether reducing fatigue can improve other domains of psychosocial functioning or vice versa. The large correlations in the current sample between QoL and fatigue indicate the relevance of fatigue for overall psychosocial functioning in adolescents with cancer. It is possible that reducing the impact of fatigue on daily functioning could improve QoL.

There are some limitations of the study to consider. The cross sectional between-subjects nature of the current study makes it difficult to determine the directionality of relationships between psychosocial variables in adolescents with cancer. Although the sample size is large for pediatric oncology, it remains a relatively small and a heterogeneous convenience sample, thus limiting the ability to detect differences in treatment factors (e.g., chemotherapy drugs). Differences in recruitment strategies between the cancer group and controls may have impacted the results unknowingly. Fatigue and QoL were measured using the same measurement system [31], introducing the possibility that the correlation between these two constructs is inflated. Additionally, the MFS has psychometric data to support its use in children and adolescents with cancer; however, the measure is not adolescent specific. As research seeking to understand symptom experiences in adolescents with cancer expands, normative values for adolescents should be developed.

The findings have important implications for clinical practice and research in adolescent oncology. Given the significant amount of fatigue experienced by adolescents with cancer and its relationship to psychosocial well-being and QoL, it is important for providers to assess fatigue along with other cancer-related side effects. In time-limited encounters, providers should assess daytime sleepiness and energy level to engage in activities of daily

living and pleasurable activities to gauge the impact on typical adolescent functioning. Screening should especially target adolescents exhibiting symptoms of depression. Results suggest that parent proxy report can provide an accurate if not slightly inflated (i.e., indicating somewhat more fatigue) assessment of fatigue when adolescents are unable to provide self-report. Clinical interventions to manage fatigue may include exercise and cognitive behavioral interventions which have been shown to improve fatigue in adult oncology samples [2]. However, despite many interventions aimed at reducing fatigue and improving QoL in adult oncology, the literature base on psychosocial intervention in adolescent oncology is small. More research specific to adolescents with cancer investigating the directionality between fatigue and psychosocial functioning, and testing associated interventions, will be essential to improve QoL and health outcomes for this vulnerable population.

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TABLE I

Sample Demographics and Descriptives

	Cancer group (n =102)	Healthy group (n =97)
Gender (male)	58 (56.86%)	51 (52.57%)
Age, M (SD; range)	15.75 (1.76; 13–19)	15.55 (1.74; 13–19)
Ethnicity/race		
White/Caucasian	69 (67.65%)	57 (58.76%)
Black/African-American	15 (14.71%)	21 (21.65%)
Asian	3 (2.94%)	13 (13.40%)
More than one race	3 (2.94%)	3 (3.09%)
Hispanic	12 (11.76%)	3 (3.09%)
Income*		
<\$40,000	23 (22.55%)	13 (13.40%)
40,000–79,999	31 (30.39%)	23 (23.71%)
80,000–99,999	9 (8.82%)	19 (19.58%)
100,000+	31 (30.39%)	40 (41.23%)
Diagnosis		
Leukemia/lymphoma	50 (25.10%)	
Brain tumors	11 (10.78%)	
Solid tumors	41 (40.19%)	
Months since diagnosis, M (SD; range)	20.44 (38.59; 1–193)	
Number of days inpatient, M (SD; range)	37.94 (38.85; 0–200)	
Relapsed	27 (27.00%)	
Treatment intensity		
Moderate intensive (2)	21 (20.58%)	
Very intensive (3)	45 (44.12%)	
Most intensive (4)	36 (35.29%)	

** $P < 0.05$; Percentages in income may not equal 100% because of missing data or participants who endorsed multiple options.

TABLE II
 Comparison of Fatigue Between Adolescents With Cancer and Adolescents Without Chronic Health Conditions

	Group	Mean	SD	F-Value	P	Cohen's d
Adolescent report						
Total fatigue	Cancer	58.54	19.47	28.42	<0.001	0.76
	Control	71.72	14.92			
General fatigue	Cancer	55.88	22.83	46.67	<0.001	0.97
	Control	75.34	16.71			
Sleep rest fatigue	Cancer	51.06	21.42	24.78	<0.001	0.71
	Control	65.29	18.74			
Cognitive fatigue	Cancer	69.20	23.20	3.26	0.072	0.26
	Control	74.52	17.94			
Caregiver report						
Total fatigue	Cancer	53.51	19.65	156.84	<0.001	1.79
	Control	83.43	13.06			
General fatigue	Cancer	44.40	24.11	191.44	<0.001	1.97
	Control	83.46	14.19			
Sleep rest fatigue	Cancer	48.28	22.56	147.06	<0.001	1.73
	Control	81.83	15.66			
Cognitive fatigue	Cancer	67.16	22.77	38.42	<0.001	0.88
	Control	84.80	16.78			

Results did not differ when controlling for income.

TABLE III

Psychosocial Correlates of Fatigue Total Score in Adolescents With Cancer

Psychosocial measures	r
CDI T-score	-0.58**
PedsQL physical health	0.71**
PedsQL psychosocial health	0.74**
PANAS positive affect	0.24*
PANAS negative affect	-0.41**
Brief COPE active coping	0.19
Brief COPE behavioral disengagement	-0.30*
FAD general family functioning	-0.14

* $P < 0.05$;** $P < 0.001$.

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TABLE IV

Regression Predicting Total Adolescent Reported Fatigue

Predictor	β	<i>P</i>
CDI total score	-0.55	<0.001
PANAS positive affect	0.06	0.515
Brief COPE behavioral disengagement	-0.04	0.676

F (3, 97) = 16.98; *P* < 0.001.

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