Original Article

Characteristics Associated With Physical Function Trajectories in Older Adults With Cancer During Chemotherapy

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Abstract

Context. Studies on physical function trajectories in older adults during chemotherapy remain limited.

Objectives. The objective of this study was to determine demographic, clinical, and symptom characteristics associated with initial levels as well as trajectories of physical function over two cycles of chemotherapy in adults aged ≥65 years with breast, gastrointestinal, gynecological, or lung cancer.

Methods. Older adults with cancer ($n = 363$) who had received chemotherapy within the preceding four weeks were assessed six times over two cycles of chemotherapy using the Short Form-12 Physical Component Summary (PCS) score. Hierarchical linear modeling was used to evaluate for interindividual variability in initial levels and trajectories of PCS scores.

Results. Mean age was 71.4 years (SD 5.5). Mean PCS score at enrollment was 40.5 (SD .45). On average, PCS scores decreased slightly (i.e., 0.21 points) at each subsequent assessment. Lower PCS scores at enrollment were associated with older age, greater comorbidity, being unemployed, lack of regular exercise, higher morning fatigue, lower evening energy, occurrence of pain, lower trait anxiety, and lower attentional function. Only higher morning fatigue and lower enrollment PCS scores were associated with decrements in physical function over time.

Conclusion. While several symptoms were associated with decrements in PCS scores at enrollment in older adults with cancer receiving chemotherapy, morning fatigue was the only symptom associated with decreases in physical function over time. Regular assessments of symptoms and implementation of evidence-based interventions should be considered to maintain physical function in older adults during chemotherapy. J Pain Symptom Manage 2018;56:678–688.

Key Words

Physical function, older adults, chemotherapy, fatigue, hierarchical linear modeling

Introduction

As the incidence of cancer among older adults in the U.S. increases to 2.3 million by 2030,[1] the impact of cancer treatment on physical function will become increasingly important. Pretreatment functional impairment and decline during treatment are associated with worse quality of life[2–4] and overall survival.[5,6] In addition, the impact of cancer treatment on

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physical function is critically important to patients. In a study of adults aged ≥60 years with limited life expectancy, more than 70% of those with cancer reported that they would not choose a treatment that results in functional impairment, even if it improved survival.[7]

Despite the importance of functional outcomes to older cancer patients, studies on the effect of treatment on physical function remain limited,[6,8–13] with only two studies focusing specifically on physical function during chemotherapy.[6,8] In these European studies, pretreatment depression, abnormal nutritional status, and dependency in instrumental activities of daily living (IADL) were associated with decrements in activities of daily living (ADL) during chemotherapy.[6,8] Chemotherapy for a new diagnosis of cancer was associated with decrements in IADL.[6] However, both of these studies examined changes in physical function between only two time points, which may miss acute within cycle, potentially nonlinear changes in physical function during treatment. Acute changes in physical function after each chemotherapy infusion may be especially important in older adults with cancer because their limited physiologic reserve may make recovering from any functional decline more challenging.[14] Furthermore, while both studies examined the association between depression and functional decline during chemotherapy, the impact of other symptoms such as morning and evening fatigue, morning and evening energy, sleep disturbance, and state and trait anxiety on physical function remains unknown.

Given the limited research on changes in and predictors of decrements in physical function in older adults during chemotherapy, the purposes of our study, in a sample of older adults with breast, gastrointestinal (GI), gynecological (GYN), and lung cancer who received chemotherapy ($n = 363$), were to evaluate for interindividual differences in physical function and to determine which demographic, clinical, and symptom characteristics were associated with initial levels as well as with trajectories of physical function over six time points during two cycles of chemotherapy.

Patients and Methods

Patients and Settings

The procedures for the parent cohort study are described in detail elsewhere.[15,16] The objective of the parent study was to characterize symptom clusters in patients with cancer receiving chemotherapy.[16–19] Eligible patients in the parent study were ≥18 years of age; had a diagnosis of breast, GI, GYN, or lung cancer; had received chemotherapy within the preceding four weeks; were scheduled to receive at least two additional cycles; and were able to read, write, and understand English. We chose to enroll patients who had received at least one prior cycle of chemotherapy to better understand their ongoing risk of decrements in physical function during subsequent cycles of chemotherapy. Patients were recruited from two Comprehensive Cancer Centers, one Veteran's Affairs hospital, and four community-based oncology programs. A total of 2234 patients were approached and 1343 consented to participate (60.1% response rate). For this analysis, patients who were ≥65 years of age ($n = 363$) were included.

Instruments

Demographic and Clinical Characteristics. Patients completed a demographics questionnaire, the Karnofsky Performance Status scale,[20–22] and Self-Administered Comorbidity Questionnaire.[23] Medical records were reviewed for disease and treatment characteristics. The MAX2 index[24,25] estimated the average risk for Grade 3 to 4 toxicity for each chemotherapy regimen.

Assessment of Physical Function. Changes in physical function over two cycles of chemotherapy were assessed using the Physical Component Summary (PCS) score from the Medical Outcomes Study–Short Form-12 (SF-12),[26–40] which assesses various aspects of physical and mental health. The PCS score consists of six items: health limitations with moderate activities, climbing several flights of stairs, accomplishing less than you would like, limitations in work or other activities, pain interference with normal work, and overall health rating. PCS scores can range from 0 to 100, with higher scores indicating better physical functioning. PCS results are scored using a norm-based algorithm with a standardized mean of 50 and an SD of 10 in the general U.S. adult population.[41] The SF-12 and PCS scores have well-established validity and reliability[26] and have been used in other studies of patients with cancer.[42,43]

Assessment of Symptoms. To evaluate common symptoms, patients completed separate Lee Fatigue Scale questionnaires[44] that evaluated diurnal variations (i.e., morning and evening) in fatigue severity and decrements in energy. Morning and evening fatigue and morning and evening energy are distinct symptoms both from phenotypic and genotypic perspectives.[45–50] In addition, patients completed the General Sleep Disturbance Scale,[51] Center for Epidemiological Studies–Depression Scale,[52] Brief Pain Inventory,[53] Attentional Function Index,[54] and Spielberger State-Trait Anxiety Inventories.[55] State

anxiety measures a person's temporary anxiety response to a specific situation while trait anxiety measures a person's predisposition to anxiety as part of one's personality.

Study Procedures

The study was approved by the institutional review board at each study site. Written informed consent was obtained from all participants. Depending on the length of their chemotherapy cycles (i.e., 14 days, 21 days, 28 days), patients completed study questionnaires in their homes a total of six times over two cycles of chemotherapy: before chemotherapy administration (i.e., recovery from previous chemotherapy cycle; Assessments 1 and 4), approximately one week after chemotherapy administration (i.e., acute symptoms in the week after infusion; Assessments 2 and 5), and approximately two weeks after chemotherapy administration (i.e., potential nadir; Assessments 3 and 6).

Statistical Analyses

Descriptive statistics and frequency distributions were generated on the sample characteristics and symptom severity scores at enrollment using the Statistical Package for the Social Sciences (SPSS, Version 24, IBM Corporation, Armonk, NY).

Hierarchical linear modeling (HLM) based on full maximum likelihood estimation was performed in two stages using software developed by Raudenbush and Bryk.[56] The HLM methods are described in detail elsewhere.[15] In brief, the HLM analysis evaluated for changes over time in PCS scores. During Stage 1, intra-individual variability in PCS scores over time was examined. Three Level 1 models were compared to determine whether the patients' level of physical function did not change over time (i.e., no time effect), changed at a constant rate (i.e., linear time effect), or changed at a rate that accelerated or decelerated over time (i.e., quadratic effect). Then, the Level 2 model was constrained to be unconditional (i.e., no predictors), and likelihood ratio tests were used to determine the best model.

The second stage of the HLM analysis examined interindividual differences in the trajectories of PCS scores by modeling individual change parameters (i.e., intercept, linear slope) as a function of proposed predictors at Level 2. Supplementary Table 1 presents a list of demographic, clinical, and symptom characteristics that were evaluated as potential predictors based on a literature review of physical function in cancer patients.[6,8–10,12,13] To improve estimation efficiency and construct a parsimonious model, bivariable exploratory Level 2 analyses were performed in which each characteristic was added as a predictor to determine whether it improved the model. Characteristics with an absolute t-value <2.0 were dropped from subsequent models. All potential significant predictors from the exploratory analyses were entered into the HLM models to predict each change parameter. Only those characteristics that maintained a statistically significant contribution in conjunction with other characteristics were retained in the final HLM model. A *P*-value of <0.05 indicates statistical significance.

One advantage of HLM is that patients with some missing data on the dependent variable (i.e., PCS score) are not eliminated from the analysis. They contribute as many assessments as were possible for them to provide. By contrast, missing data are not allowed for predictor variables so patients with any missing predictor variables were not included in the HLM analyses.

Results

Sample Characteristics

Demographic, clinical, and symptom characteristics of the sample ($N = 363$) are presented in Table 1. The sample was predominately female (68.3%) with a mean age of 71.4 (SD 5.5) years. Patients had an average of 16.5 (SD 3.1) years of education, BMI of 26.1 (SD 5.3), and Karnofsky Performance Status score of 82.6 (SD 12.6). Patients were 2.9 (SD 5.2) years from their cancer diagnosis (median 0.49 years) and primarily being treated with 21-day chemotherapy cycles (55.1%) for metastatic disease (73.6%). At enrollment, the mean morning energy score on the Lee Fatigue Scale was below the clinically meaningful cutoff. Over 67% of patients reported experiencing pain and 25.1% had a depression score of ≥ 16 suggesting depressive symptoms that warrant a clinical evaluation. In addition, the mean sleep disturbance and trait anxiety scores were above the cutoff scores for clinically meaningful levels of sleep disturbance and trait anxiety, respectively.

Changes in Physical Function Over Time

The first HLM analysis examined how physical function (i.e., PCS scores) changed over two cycles of chemotherapy. As shown in Fig. 1a, a linear model fits the data best. As shown in Table 2, the intercept in the unconditional model represents the estimated level of physical function (i.e., PCS score of 40.719 on a 0–100 scale) before the initiation of the next cycle of chemotherapy (i.e., Assessment 1). The estimated linear rate of change in physical function for each additional assessment was -0.212 ($P < .01$). As illustrated in Fig. 1a, physical function decreased slightly over the two cycles of chemotherapy.

Table 1
Demographic, Clinical, and Symptom Characteristics of Older Adults With Cancer Receiving Chemotherapy ($N = 363$)

Characteristics	*n* (%) or Mean (SD)
Demographic characteristics	
Age, yrs; mean (SD)	71.4 (5.5)
Age, yrs; median (range)	69 (65–90)
Female gender	248 (68.3)
Ethnicity	
White	289 (80.1)
Black	24 (6.6)
Asian/Pacific Islander	23 (6.4)
Hispanic/mixed/other	25 (6.9)
Education, yrs; mean (SD)	16.5 (3.1)
Married or partnered	211 (59.1)
Lives alone	106 (29.8)
Currently employed	78 (21.7)
Child care responsibilities	17 (4.8)
Income	
Less than $30,000	75 (23.9)
$30,000 to <$70,000	79 (25.2)
$70,000 to <$100,000	55 (17.5)
More than $100,000	105 (33.4)
Clinical characteristics	
Number of comorbidities, mean (SD)	2.8 (1.5)
Self-Administered Comorbidity Questionnaire score, mean (SD)	6.2 (3.4)
Specific comorbidities reported	
Hypertension	167 (46.0)
Back pain	95 (26.2)
Osteoarthritis	85 (23.4)
Lung disease	73 (20.1)
Depression	64 (17.6)
Diabetes	52 (14.3)
Heart disease	42 (11.6)
Anemia	33 (9.1)
Liver disease	26 (7.2)
Ulcer or stomach disease	16 (4.4)
Rheumatoid arthritis	13 (3.6)
Kidney disease	7 (1.9)
Body mass index, kg/m^2; mean (SD)	26.1 (5.3)
Hemoglobin, gm/dL; mean (SD)	11.5 (1.4)
Karnofsky Performance Status score, mean (SD)	82.6 (12.6)
Karnofsky Performance Status score, median (range)	90 (40–100)
Current or former smoker	169 (47.5)
Exercise on a regular basis	235 (66.2)
Cancer diagnosis	
Breast	84 (23.1)
Gastrointestinal	119 (32.8)
Gynecological	79 (21.8)
Lung	81 (22.3)
Time since cancer diagnosis, yrs; mean (SD)	2.9 (5.2)
Time since cancer diagnosis, yrs; median (range)	0.49 (0.06–38.3)
Any prior cancer treatments	269 (76.2)
Number of prior cancer treatments, mean (SD)	1.7 (1.5)
Chemotherapy MAX2 index, mean (SD)	0.152 (0.1)
Chemotherapy cycle length	
14 days	124 (34.2)
21 days	200 (55.1)
28 days	39 (10.7)
Metastatic disease at the time of study	265 (73.6)
Number of metastatic sites including lymph node involvement, mean (SD)	1.4 (1.2)
Number of metastatic sites excluding lymph node involvement, mean (SD)	0.9 (1.1)
Symptom characteristics at enrollment[a]	
Lee Fatigue Scale: morning fatigue score, mean (SD)	2.6 (2.1)
Lee Fatigue Scale: evening fatigue score, mean (SD)	4.8 (2.2)
Lee Fatigue Scale: morning energy score, mean (SD)	4.3 (2.5)
Lee Fatigue Scale: evening energy score, mean (SD)	3.8 (2.1)
General Sleep Disturbance Scale score, mean (SD)	48.7 (18.5)
Center for Epidemiological Studies–Depression Scale score, mean (SD)	10.9 (9.1)
Pain present	242 (67.2)
State Anxiety score, mean (SD)	32.0 (12.0)
Trait Anxiety score, mean (SD)	33.8 (10.5)
Attentional Function Index score, mean (SD)	6.5 (1.8)

[a]Clinically meaningful symptom cut-point scores: Lee Fatigue Scale score ≥3.2 for morning fatigue, ≥5.6 for evening fatigue, ≤6.2 for morning energy, ≤3.5 for evening energy[25]; General Sleep Disturbance Scale score ≥43[26]; Center for Epidemiological Studies–Depression Scale score ≥16[27]; State Anxiety score ≥32.2; Trait Anxiety score ≥31.8[30]; Attentional Function Index score ≤5.[29] Higher scores for Lee Fatigue Scale, General Sleep Disturbance Scale, Center for Epidemiological Studies-Depression Scale, State Anxiety Scale, and Trait Anxiety Scale indicate higher levels of symptoms. Lower scores on the Attentional Function Index and Lee Energy Scale indicate worse attentional function and lower levels of energy, respectively.

While a small sample-wide decline in PCS scores was found over time, there was a considerable interindividual variability in the intercept for physical function and moderate interindividual variability in the slope (Table 2). A spaghetti plot of a random 10% of the sample demonstrates the interindividual variability in PCS scores over the two cycles of chemotherapy (Fig. 1b). These results supported additional analyses of predictors of interindividual differences in initial levels as well as in the trajectories of PCS scores.

Characteristics Associated With Interindividual Differences in Functional Status

The second stage of the HLM analysis evaluated how the pattern of change over time in physical function varied based on demographic, clinical, and symptom characteristics. While 18 characteristics were associated with PCS score at enrollment in exploratory analyses (Supplementary Table 1), only nine characteristics were associated with PCS score at enrollment in the final HLM model (Table 2). Lower PCS scores at enrollment were associated with older age, greater comorbidity, being unemployed, lack of regular exercise, higher morning fatigue, lower evening energy, occurrence of pain, lower trait anxiety, and lower attentional function. Only higher morning fatigue ($P = 0.04$) and lower enrollment PCS score ($P = 0.01$) were associated with decrements in PCS score over time. Of note, neither the MAX2 index

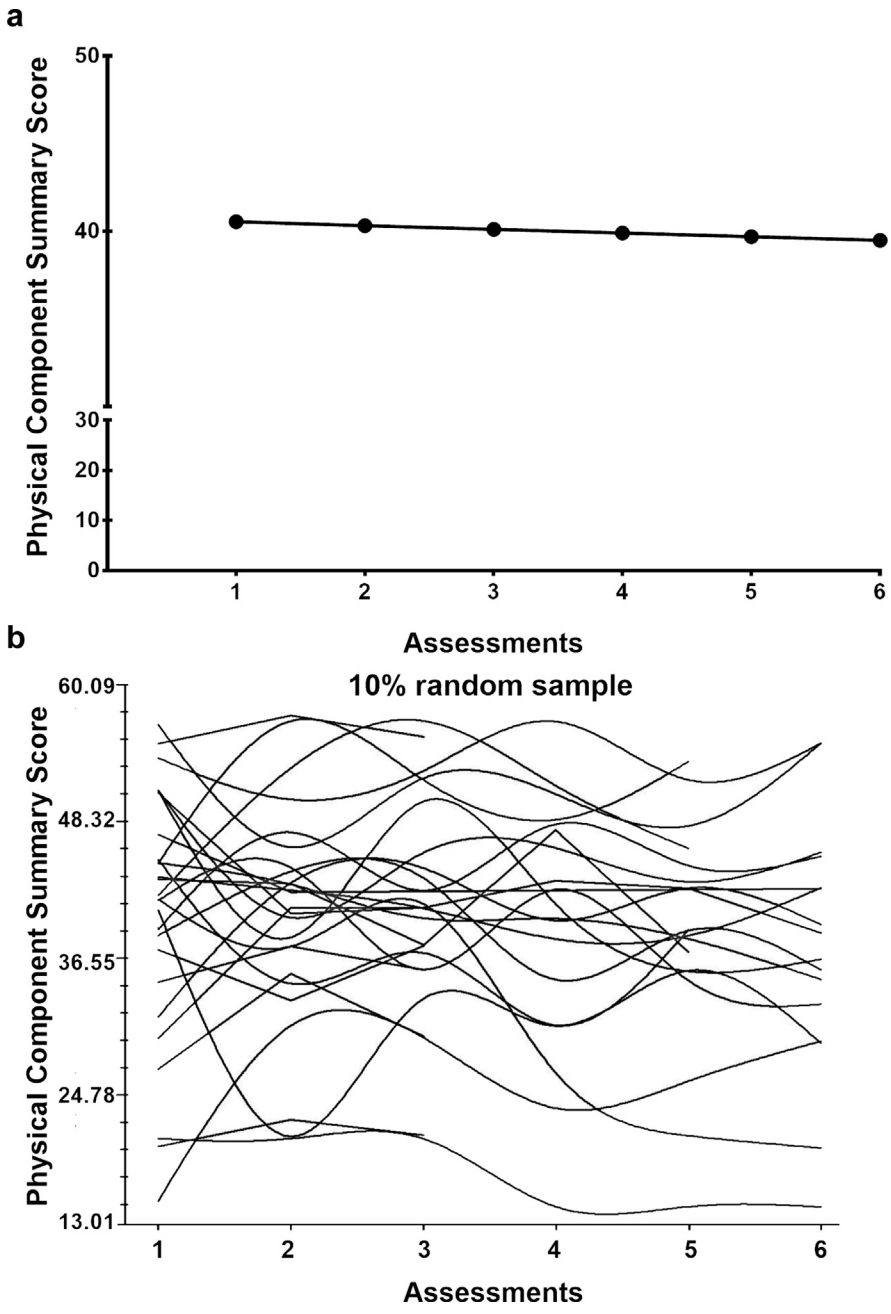

Fig. 1. a) Model of mean Physical Component Summary scores for six assessment points over two cycles of chemotherapy: before chemotherapy administration (i.e., recovery from previous chemotherapy cycle; Assessments 1 and 4), approximately one week after chemotherapy administration (i.e., acute symptoms in the week after infusion; Assessments 2 and 5), and approximately two weeks after chemotherapy administration (i.e., potential nadir; Assessments 3 and 6). b) Spaghetti plot of individual Physical Component Summary score trajectories for a 10% random sample of patients over two cycles of chemotherapy.

nor chemotherapy cycle length was associated with PCS scores at enrollment or with decrements in PCS scores over time.

To illustrate the effects of each of these characteristics on patients' enrollment levels and trajectories of physical function, Fig. 2a–d display the adjusted change curves for PCS scores estimated based on differences in age (i.e., younger/older calculated based on one SD below and above the mean age), employment status, comorbidity score (i.e., lower/higher calculated based on one SD below and above the mean comorbidity score), and exercise status, respectively. Fig. 3a–e display the adjusted change curves for PCS scores based on differences in symptoms at enrollment: morning fatigue, evening energy, occurrence of pain, trait anxiety, and attentional function

Table 2
Hierarchical Linear Model of Physical Function

Physical Function Model Characteristics	Coefficient (SE)	
	Unconditional Model	Final Model
Fixed effects		
Intercept	40.719 (0.544)[a]	40.536 (0.450)[a]
Linear rate of change per assessment	−0.212 (.079)[b]	−0.212 (0.077)[b]
Time-invariant covariates		
Intercept		
Age		−0.176 (0.082)[c]
Employed		2.479 (1.107)[c]
SCQ score		−0.577 (0.147)[a]
Exercise on a regular basis		4.141 (0.980)[a]
Morning fatigue score at enrollment		−0.871 (0.278)[b]
Evening energy score at enrollment		0.576 (0.223)[c]
Pain present at enrollment		−3.821 (1.029)[a]
Trait Anxiety score at enrollment		0.120 (0.057)[c]
Attentional Function Index score at enrollment		0.754 (0.341)[c]
Linear slope		
Morning fatigue score at enrollment		−0.080 (0.038)[c]
PCS score at enrollment		−0.020 (0.007)[b]
Variance components		
In intercept	96.256[a]	62.198[a]
In linear slope	0.753[a]	0.625[a]
Goodness-of-fit deviance (parameters estimated)	11,768.510 (6)	11,613.847 (17)
Model comparison (x^2)		154.663 (11)[a]

SE = standard error; SCQ = Self-Administered Comorbidity Questionnaire; PCS = Physical Component Summary.
[a]$P < 0.001$.
[b]$P < 0.01$.
[c]$P < 0.05$.

(i.e., lower/higher calculated based on one SD below and above the mean score for each symptom). Fig. 3f displays the adjusted change curve for physical function based on differences in PCS score at enrollment. All mean PCS scores for the various characteristics depicted in the figures are estimated or predicted means based on the HLM analyses.

Discussion

In a large sample of older adults with cancer who were entering a second or subsequent cycle of chemotherapy, we identified numerous demographic (i.e., older age, not working), clinical (i.e., higher comorbidity, lack of regular exercise), and symptom characteristics (i.e., higher morning fatigue, lower evening energy, occurrence of pain, higher trait anxiety, lower attentional function) associated with lower levels of physical function at enrollment. By contrast, only morning fatigue and PCS scores at enrollment were associated with modest decrements in physical function over time. This study is the first to identify that higher level of morning fatigue was the only symptom associated with functional decline during chemotherapy. In addition, this study is the first to assess physical function at multiple time points over two cycles of chemotherapy in older adults and to analyze changes in physical function as a trajectory, rather than as a dichotomous outcome of functional decline between two time points. It should be noted that at enrollment, the mean PCS score for our sample was 4.2 points lower than the age-based normative score of 44.9 (adults aged 65 to 74 years) based on the 2001 Utah Health Status Survey.[57]

Fatigue is one of the most common and distressing symptoms reported by patients with cancer and can result in decreased quality of life.[58–60] In this study, we identified that higher levels of morning fatigue was associated with modest decreases in physical function during chemotherapy. Specifically, as illustrated in Fig. 3a, the predicted mean PCS score for Assessment 1 (intercept) was 42.4 for patients with higher morning fatigue (one SD above the mean morning fatigue score) and 38.7 for patients with lower morning fatigue (one SD below the mean evening fatigue score). At Assessment 6, the predicted mean PCS score was 42.2 for patients with higher morning fatigue and 36.8 for patients with lower morning fatigue.

In comparison, evening fatigue, morning energy, and evening energy were not associated with changes in physical function over time. Of note, both higher morning fatigue and lower evening energy were associated with lower levels of physical function at enrollment. This finding highlights the importance of assessing for diurnal variations in fatigue severity[61] as well as decrements in energy.[62,63] In addition, research from our group demonstrated distinct characteristics associated with the trajectories of morning and evening fatigue and energy in patients with cancer,[15,45,48,50] supporting the need for comprehensive assessment of fatigue both in research and clinical care. Furthermore, management strategies for cancer-related fatigue, such as energy conservation and exercise,[64,65] may impact morning and evening fatigue differently. Therefore, morning and evening fatigue should be evaluated as distinct outcomes in addition to overall fatigue to determine how interventions modify each symptom.

In a prior study of physical function among older adults with cancer receiving chemotherapy,[6] no association was found between fatigue and functional decline. The lack of association between fatigue and functional decline in the prior study may be related to differences in the measurement of fatigue (single global measure using the Mobility-Tiredness Test vs. morning and evening fatigue and energy

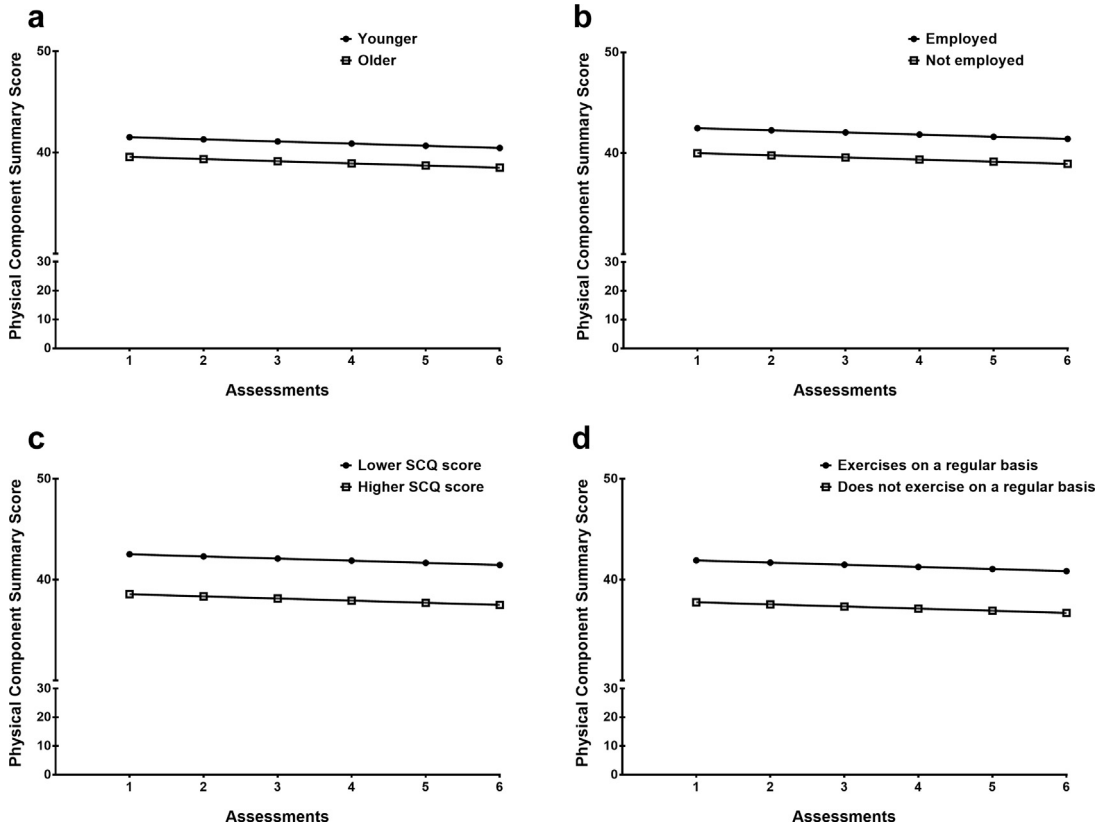

Fig. 2. Influence of a) age, b) employment status, c) Self-Administered Comorbidity Questionnaire score, and d) exercise on a regular basis at enrollment on interindividual differences in the intercept for physical function. In (a) and (c), values for one SD below and above the mean are plotted as examples. Patients were assessed six times over two cycles of chemotherapy: before chemotherapy administration (i.e., recovery from previous chemotherapy cycle; Assessments 1 and 4), approximately one week after chemotherapy administration (i.e., acute symptoms in the week after infusion; Assessments 2 and 5), and approximately two weeks after chemotherapy administration (i.e., potential nadir; Assessments 3 and 6).

levels using the Lee Fatigue Scale in our study), measurement of physical function (change in ADL and IADL vs. PCS score in our study), and the timing of the assessments (two time points before treatment and at two to three months vs. six time points over two cycles of chemotherapy in our study). In another study of functional decline during first-line chemotherapy in older adults,[8] its association with fatigue was not evaluated. Therefore, our result warrants confirmation in future research to determine if improvements in morning fatigue may mitigate decrements in physical function.

In addition, we found that lower physical function at enrollment (i.e., before next dose of chemotherapy) was associated with older age, greater comorbidity, being unemployed, lack of regular exercise, presence of pain, lower trait anxiety, and lower attentional function. While older age, greater comorbidity, and pain are risk factors for decrements in physical function,[9,10,66] unemployment and lack of regular exercise may reflect risk factors for and/or outcomes of poorer physical function. Interestingly, in our sample, higher trait anxiety, a disposition toward experiencing anxiety,[67] was associated with higher physical function scores at enrollment. Higher trait anxiety was associated with moderate intensity physical activity in a study of community-dwelling older adults,[68] which supports our finding. While the association between lower attentional function and lower physical function suggests that both processes are interrelated,[69] further research is needed to understand how the two processes interact in older adults during cancer treatment.

Consistent with a previous report,[6] we did not identify an association between depression at enrollment and initial levels or trajectories of physical function in our sample of older adults with cancer. The proportion of patients reporting depressive symptoms in the previous report (20.6%)[6] was similar to 25.1% in our study. These findings contrast with another study, where 44.5% of patients reported depressive symptoms and a positive association was found between depression and increased risk of functional decline after one cycle of first-line chemotherapy.[8] Additional research is needed to better characterize the association between depression and functional decline in older adults with cancer.

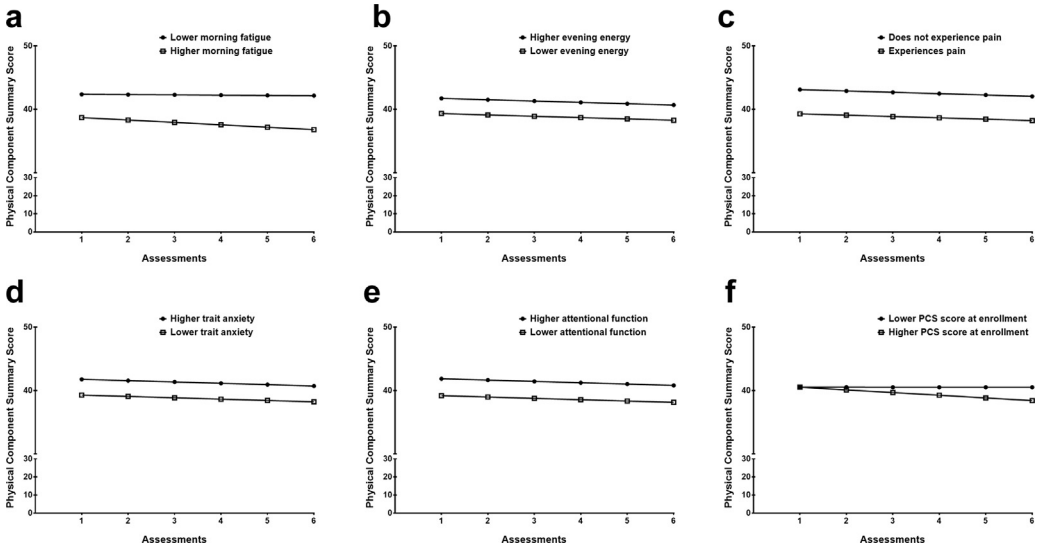

Fig. 3. Influence of symptoms including a) morning fatigue, b) evening energy, c) pain, d) trait anxiety, e) attentional function, and f) Physical Component Summary (PCS) score at enrollment on interindividual differences in the intercept for physical function. For morning fatigue and PCS score at enrollment, interindividual differences in the slope parameters for physical function are shown. In (f), values for one SD below and above the mean PCS score at enrollment are plotted as examples. Patients were assessed six times over two cycles of chemotherapy: before chemotherapy administration (i.e., recovery from previous chemotherapy cycle; Assessments 1 and 4), approximately one week after chemotherapy administration (i.e., acute symptoms in the week after infusion; Assessments 2 and 5), and approximately two weeks after chemotherapy administration (i.e., potential nadir; Assessments 3 and 6).

While a previous study found that older adults receiving first-line chemotherapy for a new diagnosis of cancer were more likely to experience decline in IADL than those treated for progression/relapse,[6] we did not detect any associations between time since cancer diagnosis or the number of prior cancer treatments and decrements in physical function in our sample. Because all our patients had received at least one cycle of chemotherapy within the four weeks before enrollment, patients treated for a new diagnosis may have already experienced some decrements in physical function before our assessments.

Strengths of our study include the focused appraisal of physical function at multiple points over two cycles of chemotherapy, which allows for the examination of acute within-cycle changes in function that may occur as a result of toxicities immediately after chemotherapy infusion into nadir and recovery. While prior studies of physical function in older adults during chemotherapy have focused on changes after one cycle[8] or several months after the initiation of chemotherapy,[6] our study design allowed us to evaluate for acute changes in physical function within a chemotherapy cycle. In addition, we analyzed physical function over time as a trajectory, rather than a dichotomous outcome of functional decline between two time points. This approach allowed us to examine more subtle changes in physical function and evaluate for different possible trajectories (e.g., linear, quadratic).

Our study has several limitations. First, while patients were uniformly assessed at three specific points (i.e., before chemotherapy administration and at approximately one and two weeks after administration) across two cycles of chemotherapy, they were recruited at various cycles in their chemotherapy treatment. As a result, changes in physical function from the initiation of chemotherapy cannot be evaluated in this study. In addition, because our study design may have excluded older adults who discontinued chemotherapy after their initial cycle(s) due to functional decline, our results may underestimate the true degree of functional decline in this population. Furthermore, additional common geriatric assessment domains such as nutrition[70,71] and frailty[72,73] that could contribute to decrements in physical function were not assessed. Finally, physical function was not assessed using objective measures (e.g., gait speed) or assessments of ADL or IADL. However, the SF-12 PCS score is a valid and reliable measure of physical function that includes assessments of ability to perform moderate activities, climb stairs, and accomplish work and other activities.[27–40] Although the number of studies of serial comprehensive geriatric assessment during cancer treatment is increasing, the large number of studies that measure

quality of life using instruments that include physical function subscales such as the SF-12, SF-36, and European Organization for Research and Treatment of Cancer QLQ-C30[74] provides additional opportunities to understand changes in physical function during cancer treatment.

It is important to note that within the geriatric oncology literature, it is crucial to highlight analyses that include function as an outcome because functional outcomes are extremely important to older adults with cancer and are not assessed in many studies. Given the numerous studies that have used the SF-12 or SF-36, which closely overlaps other measures of physical function such as the Patient-Reported Outcomes Measurement Information System Physical Function item bank,[75,76] secondary analyses of cancer studies with SF-12 or SF-36 data are important to suggest future directions for research.

Conclusions

This study is the first to identify morning fatigue as a potentially modifiable characteristic associated with decrements in physical function in older adults with cancer who were entering a second or subsequent cycle of chemotherapy. Interventions focused on improving morning fatigue may prevent functional decline in older adults receiving chemotherapy and should be studied. Because our study enrolled older adults who had already started their chemotherapy treatment, the current findings should be confirmed in patients who are assessed at the initiation of chemotherapy and followed through to treatment completion or discontinuation. Future studies need to investigate the impact of multiple co-occurring symptoms and symptom clusters on the trajectories of physical function during chemotherapy.

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Supplementary Table 1

Characteristics Evaluated as Potential Predictors of Intercept and Linear Slope for Physical Function

Characteristics	Intercept	Linear Slope
Demographic characteristics		
Age	■	
Sex		
Ethnicity (white vs. nonwhite)		
Education		
Marital status		
Live alone		
Employment status	■	
Child care responsibilities		
Clinical characteristics		
Body mass index		
Current or former smoker		
Hemoglobin	■	
Karnofsky Performance Status score	■	
Self-Administered Comorbidity Questionnaire score	■	
Exercise on a regular basis	■	
Cancer type	■	
Time since cancer diagnosis		
Any prior cancer treatments		
Number of prior cancer treatments		
Presence of metastatic disease		
Number of metastatic sites including lymph node involvement		
Number of metastatic sites excluding lymph node involvement	■	
Chemotherapy MAX2 index		
Chemotherapy cycle length		
Symptom characteristics at enrollment		
Lee Fatigue Scale: morning fatigue score	■	■
Lee Fatigue Scale: evening fatigue score	■	
Lee Fatigue Scale: morning energy score	■	
Lee Fatigue Scale: evening energy score	■	
General Sleep Disturbance Scale score	■	
Center for Epidemiological Studies—Depression Scale score	■	
Pain present	■	
State Anxiety score	■	
Trait Anxiety score	■	
Attentional Function Index score	■	
Physical Component Summary score	N/A	■

N/A = not applicable.

■ = Characteristics with an absolute t-value ≥2.0 in bivariable exploratory analyses that advanced to testing in multivariable models.