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Relationship of Fatigue with Cognitive Performance in Women with Early-Stage Breast Cancer over Two Years:

Fatigue and Cognition in Chemotherapy

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Abstract

Objective—Fatigue and cognitive dysfunction are major concerns for women with early-stage breast cancer during treatment and into survivorship. However, interrelationships of these phenomena and their temporal patterns over time are not well documented, thus limiting the strategies for symptom management interventions. In this study, changes in fatigue across treatment phases, and the relationship among fatigue severity and its functional impact with objective cognitive performance were examined.

Methods—Participants (N=75) were assessed at five time points beginning prior to chemotherapy to 24 months after initial chemotherapy. Fatigue severity and impact were measured on the Brief Fatigue Inventory. CNS Vital Signs was used to measure performance based cognitive testing. Temporal changes in fatigue were examined as well as the relationship between fatigue and cognitive performance at each time point using linear mixed effect models.

Results—Severity of fatigue varied as a function of phase of treatment. Fatigue severity and its functional impact were moderate at baseline, increased significantly during chemotherapy, and returned to near baseline levels by two-years. At each time point, fatigue severity and impact were significantly associated with diminished processing speed and complex attention performance.

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Conclusions—A strong association between fatigue and objective cognitive performance suggests that they are likely functionally related. That cognitive deficits were evident at baseline, whereas fatigue was more chemotherapy-dependent, implicates that two symptoms share some common bases, but may differ in underlying mechanisms and severity over time. This knowledge provides a basis for introducing strategies for tailored symptom management that varies over time.

Keywords

Cancer; Oncology; Breast cancer; Fatigue; Cognition; Chemotherapy; Longitudinal; Chemobrain

BACKGROUND

While early detection and advances in treatment for breast cancer has improved the five-year survival rate for breast cancer survivors (BCSs),¹ treatment administration is often coupled with distressing symptoms that persist across the treatment trajectory.² Previous studies have suggested that cancer-related fatigue and cancer-related cognitive impairment are commonly reported by BCSs.^{3–6} According to the National Comprehensive Cancer Network guidelines, cancer-related fatigue is defined as “a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning”^{7(p.46)} and cognitive impairment as problems with memory, executive functioning and/or attention due to cancer itself or treatments.⁷ Overall, 27% of BCSs receiving chemotherapy experience severe fatigue,³ and up to 75% of BCSs report persistent cognitive impairment during treatment.⁶ These symptoms are particularly a burden to BCSs because they have been associated with occupational and social functioning difficulties, as well as decreased daily activities and quality of life.^{8–10}

It is well documented that an immune dysfunction (e.g., increased circulating cytokines) plays an important role in both cognitive impairment and fatigue,^{11,12} which has led researchers to examine potential associations of cognitive impairment with fatigue in BCSs.^{13,14} Few studies, however, have focused on the temporal relationship of these variables longitudinally, from pre- to post -cancer treatment to long-term follow-up; a research strategy that may provide important insights relative to optimizing overall cancer treatment. Additionally, the ability to better understand the prevalence, course, and persistence of adverse cognitive side effects in BCSs is currently limited by the use of multiple definitions of cognitive functioning across research studies accompanied by (a) a predominant focus on self-report cognitive measures rather than objective data collection measures and (b) a lack of consideration for potential impact of tumor-related cognitive impairment. Most self-report measures have not been tested and validated in cancer populations.⁶ However, valid and reliable computer-based testing modules such as the central nervous system (CNS) Vital Signs™ (CNSVS) or the NIH Toolbox Cognition Battery can support findings obtained from self-report measures when evaluating neuropsychological conditions in patients.^{15,16} Although cognitive impairment has been suspected to be causally related to chemotherapy, recent studies have found that objective cognitive deficits may be present prior to cancer treatment.^{17,18} Rodent animal models of cancer have also provided some support that the systemic inflammatory response to the tumor itself may be a contributing factor in the

development of affective and cognitive symptoms.¹⁹ We suggest that additional research is needed to enable healthcare providers to understand the trajectories of fatigue and cognitive impairment, so that therapeutic strategies can be tailored to mitigate both the short-term and long-term consequences of cancer and its treatment. Therefore, the purpose of this study was to delineate the relationship between the subjective experience of cancer-related fatigue and its impact and objectively measured performance-based cognitive status in women with early-stage breast cancer during active treatment through two years survivorship.

METHODS

Study Cohort

Details regarding the EPIGEN study cohort and methods have been described in our previous work.^{16,20} Participants were recruited from a designated National Cancer Center affiliated with the Medical Center of the Virginia Commonwealth University and four regional collaborative sites in Central Virginia. A total of 77 women with early-stage breast cancer, who ranged from 23 to 71 years of age, were ascertained and screened for eligibility. Inclusion criteria were as follows: (1) age of 21 years or older; and (2) a diagnosis of early-stage breast cancer (Stage I to IIIA) with a scheduled visit to receive chemotherapy. Exclusion criteria were as follows: (1) a previous history of cancer or chemotherapy; (2) a diagnosis of dementia; (3) active psychosis; or (4) a diagnosis of immune system disorders (e.g., multiple sclerosis, systemic lupus erythematosus). After providing informed consent (VCU IRB #HM 13194), participants were evaluated at five time points prior to chemotherapy through 2 years survivorship: before the start of chemotherapy (T1), at the midpoint chemotherapy (4th chemotherapy treatment; T2), 6 months after the initial chemotherapy (T3), 1 year after the initial chemotherapy (T4), and approximately 2 years following the initiation of chemotherapy (T5). The initial assessment (T1) was conducted after surgery, but prior to commencing chemotherapy in women receiving adjuvant therapy. All procedures performed in this study were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Measures

Demographic and Oncological Variables—Demographic and disease profile information were collected by participant interview and medical record review. Demographic variables included age, race, marital status and educational level. Cancer-related variables included breast cancer stage (TNM) and hormone receptor status. Treatment-related variables included type of surgery, treatment regimen (adjuvant or neoadjuvant), chemotherapeutic regimen, radiation status, and hormonal agent status.

Fatigue—The Brief Fatigue Inventory (BFI) was used to assess fatigue severity in physical, affective, cognitive, and social domains.²¹ This inventory consists of nine items and each item is rated on an eleven-point scale (0 – 10): mild fatigue (1 – 3), moderate fatigue (4 – 6), and severe fatigue (7 – 10).²¹ It has been shown to have strong reliability and validity (Cronbach's alpha = 0.95 – 0.96, internal consistency = 0.96),²¹ as well as correlations with severity ratings on other fatigue assessment inventories.^{21–24}

Anxiety and Depression—The Hospital Anxiety and Depression Scale (HADS) was developed to measure the presence and severity of anxiety and depressive symptoms, which has been widely used in multiple population, including women with breast cancer.^{25,26} The inventory consists of 14 items, and each item is rated from 0 (no symptoms) to 3 (severe symptoms). A sum score of 0 to 7 indicates a normal range, a score of 8 to 10 is suggestive of the condition, and a score 11 or greater indicates the presence of an anxiety and/or depression condition.²⁵ Its Cronbach's alphas were 0.90 for depression and 0.93 for anxiety.²⁶

Cognitive Performance—A performance-based computerized neurocognitive testing system, CNSVS (<https://www.cnsvs.com>)²⁷ was used to measure multiple neurocognitive domains, such as memory, psychomotor speed, reaction time, complex attention, and cognitive flexibility. Raw scores, age-matched standard scores, and percentile ranks are provided, with higher scores indicating better neurocognitive performance.²⁷ The subscales of the CNSVS were reported to have good test-retest reliability: attention ($r = 0.65$), memory ($r = 0.66$), psychomotor speed ($r = 0.88$), cognitive flexibility ($r = 0.71$), and reaction time ($r = 0.75$).²⁷ This instrument has been used in women with breast cancer.^{28,29}

Statistical Analysis

All analyses were conducted using SPSS v24. Descriptive statistics were obtained in the form of means, medians, and ranges for the continuous variables, and frequencies and percentages for the categorical variables. Linear mixed effects models were used to examine the temporal changes in cognitive performance domains, while adjusting for demographic covariates (age, education, race). The clinical, demographic, and oncological variables were also used in regression analyses of factors associated with fatigue. A random intercept was included in the models to account for the within-subject correlation. The temporal changes in the composite fatigue severity and functional interference ratings across the five visits were tested and compared to our previous findings¹⁶ on the temporal characteristics of cognitive performance using F-tests. These relationships were then examined for each of the five visits by hierarchical backwards stepwise linear regression analyses, which was used to simplify these complex analyses. In the next series of analyses, the relationships among demographic, clinical, oncological variables, and fatigue were examined.

RESULTS

Out of 154 women approached about study participation, 77 met study inclusion criteria and were consented for participation. Of the 77, three women (all Caucasians; ages 48, 62, and 66) failed to complete the multiple visits required for this longitudinal investigation, which resulted in a 96% retention rate. Two of the three women who did not complete the study elected to withdraw after T1 due to feeling “overwhelmed.” The third woman, who developed osteomyelitis after T2, no longer met eligibility criteria and was excluded from further follow-up. A total of 75 women who had at least two measurement points were included in the analysis.

Sample Characteristics

The demographic data, and clinical, cancer-related, and treatment-related variables are displayed in online supplemental Table 1.

Cognitive Performance Over Time

Pairwise comparisons of longitudinal performance are described in detail in our prior work.

¹⁶ There were significant improvements in all domains over time with the exception of memory performance, which remained relatively stable (Online Supplemental Table 2; Online Supplemental Figure 1).

Fatigue Severity Over Time

Since overall mean severity ratings do not reflect the temporal dynamics of fatigue across treatment phases or its functional impact over the two-year course of the study, the changes in fatigue indices were examined across the five visits. Fatigue severity varied significantly across the five assessments relative to the phase of chemotherapy intervention and subsequent follow-up ($F(4, 306) = 28.0, P < 0.001$). Participants reported lowest fatigue severity in the mild to moderate range during the baseline assessment prior to chemotherapy, with an increase to its greatest severity at T2, and remained constant through the chemotherapy period. Following chemotherapy, fatigue had decreased by the 12- and 24-month follow-up visits. Pairwise comparisons across visits using a sequential Sidak procedure indicated that significant worsening of fatigue occurred between baseline and T2 ($P = 0.02$), but significant differences in fatigue severity did not exist between T2 and T3, or between T3 or T4 relative to T1. The same temporal pattern was evident for ratings of worse fatigue over the prior 24-hours ($F(4, 306) = 12.1, P = 0.02$) and also for functional interference attributed to fatigue ($F(4, 306) = 12.4, P = 0.01$). Figure 1 shows ratings of fatigue severity and functional interference at each assessment over the two-year study period.

Relationships between Cognitive Performance and Fatigue

As reported previously,¹⁶ cognitive performance did not worsen during or after chemotherapy relative to the participants' pre-chemotherapy baseline, and performance improved in most cognitive domains over the 24-month study period. Cognitive performance across the entire two-year study period was significantly associated with fatigue severity ($R = .31; F(3, 358) = 13.1, P < 0.001$). Deficits in the domains of psychomotor speed and complex attention accounted for the relationship between cognition and fatigue severity. Cognitive performance was also associated with functional interference attributed to fatigue during the two-year study period ($R = .31; F(2, 359) = 19.9, P < 0.001$). Deficits in the domains of executive functioning ($\beta = -.12$) and psychomotor speed ($\beta = -.24$) accounted for this relationship. Group means and standard errors by cognitive domains are presented for each visit in supplemental Table 2.

Next, regression analyses were conducted to test the hypothesis that cognitive deficits in the domains of attention-executive functioning and cognitive-psychomotor speed would correspond with fatigue severity and functional interference at each assessment. Subsequent regression analyses were conducted to examine the relationship between fatigue and

cognitive performance at each visit (Table 1). Cognitive performance was associated with both fatigue severity and interference at each of the visits, though the specific domains most strongly associated with these fatigue indices varied by visit. Poorer cognitive performance was associated with greater fatigue severity and interference in all regression analyses.

T1 was significantly associated with both fatigue severity ($R = .25$; $F(1, 73) = 4.13.1$, $P = 0.03$) and functional interference ($R = .29$; $F(1, 73) = 6.4$, $P = 0.01$). Performance in the cognitive domain of complex attention was associated with both fatigue severity and functional interference, with attention deficits corresponding with more severe symptoms and impact from fatigue.

Cognitive performance was associated with fatigue severity ($R = .40$; $F(1, 72) = 14.0$, $P < 0.001$) and interference ($R = .29$; $F(1, 72) = 7.4$, $P = 0.01$) at T2, and also with fatigue severity ($R = .34$; $F(1, 71) = 13.1$, $P < 0.001$) and interference at T3 ($R = .31$; $F(1, 71) = 7.4$, $P = 0.01$). T2 and T3 corresponded with the chemotherapy treatment phase of the study. At T2, complex attention performance was associated with fatigue severity ($\beta = -.40$), where cognitive flexibility performance was associated with functional interference ($\beta = -.31$). At T3, psychomotor speed was most strongly associated with fatigue severity ($\beta = -.34$) and fatigue interference ($\beta = -.43$). Complex attention and psychomotor speed were associated with fatigue severity at T4, and psychomotor speed was significantly associated with fatigue severity and fatigue interference at T4 and T5. Overall cognitive performance was associated with fatigue at T4 assessment (Severity: $R = .40$; $F(2, 68) = 6.8$, $P < 0.01$; Functional interference: $R = .39$; $F(1, 69) = 12.0$, $P < 0.001$), and at T5 assessment (Severity: $R = .37$; $F(1, 67) = 13.1$, $P < 0.001$; Functional Interference: $R = .46$; $F(1, 67) = 18.1$, $P < 0.001$). Neither radiation treatment nor hormonal replacement therapy survived as significant predictors of fatigue, fatigue interference, or cognitive function.

Depression

HADS depression scores were highly correlated with fatigue severity ($r = .54$), and fatigue interference ($r = .61$), suggesting that the depression score may have been influenced by a specific, related symptom. Item 8 (Slowed down) was retained in the first step of the regression analysis, accounting for 25% of the total variance associated with fatigue severity. Three other items were retained in subsequent steps of the regression analysis, with total variance accounted for by their sum being approximately 9%. In other words, 73.5% of observed effect was accounted for by the symptoms of feeling slowed down, a symptom that is a major component of fatigue. While a relatively wide range of depression scores were reported by participants, symptom severity (3.5 ± 3.2) was well below the clinical threshold of 7 for depression on this screening measure.

CONCLUSIONS

In this prospective longitudinal study, we observed that cancer-related fatigue severity and impact were significantly associated with lower processing speed and complex attention performance. This strong association between subjective fatigue and cognitive performance suggests that they are likely functionally related. To the best of our knowledge, this is one of the first studies to examine the relationship between fatigue and cognitive performance

occurring over time, as well as the relationships between specific demographic, clinical, and oncological factors.

In this study, mild fatigue was present at baseline in most of the participants in the current study. This suggests that fatigue is quite common and other clinical factors, including the neurophysiological effects of the breast cancer itself, likely contribute to the experience of fatigue rather than the effects of chemotherapy alone. We found that an increase in fatigue was reported during the chemotherapy treatment period, which supported the study hypotheses and was consistent with prior reports of fatigue in the context of chemotherapy.^{30,31} A decrease in fatigue severity which occurred for most women by one year post-chemotherapy indicates that chemotherapy did not produce long-term exacerbation of fatigue beyond the levels experienced prior to chemotherapy. Van Dyk and colleagues³² similarly found that fatigue as well as sleep quality and pain correlated with neurocognitive function regardless of treatment exposure in early-stage BCSs.

Slight baseline cognitive deficits existed but did not worsen for most women during chemotherapy, suggesting that breast cancer itself along with clinical symptoms that are present at the time of diagnosis may have a greater impact on cognition than chemotherapy. Previous studies indicated that approximately 30% of BCSs are reported to show declined cognitive performance in areas of verbal learning and memory, reaction time, and global cognitive function at pre-chemotherapy period.^{6,17,18,33} One explanation for baseline cognitive impairment is that tumor-related inflammatory response (e.g., neurotoxic cytokine), oxidative stress, DNA damage, and/or cell senescence may contribute to the lower cognitive performance in patients with non-central nervous system (CNS) cancer.⁶ Genetic factors (e.g., apolipoprotein E [*APOE*], catechol-O-methyltransferase [*COMT*]) also may increase a risk for increased susceptibility to cognitive changes.^{34,35} A recent report has suggested that cancer-related post-traumatic stress may have a mediation effect on pretreatment cognitive impairment in BCSs.³⁶

Fatigue severity and impact tends to increase during the period of chemotherapy, which likely corresponds with the symptoms of “chemobrain” commonly reported by BCSs given that cognitive performance did not worsen over the chemotherapy period. Overall attention-executive and processing speed performance were most strongly associated with fatigue severity and functional interference at each study time point in this sample, even though fatigue and cognitive performance had different longitudinal trajectories. The association between cognitive performance and fatigue may have clinical significance. For many women undergoing chemotherapy, perceived alterations in mental status and reductions in functional capacity reflect transient neurophysiological effects, which may be aversive and debilitating but do not cause significant cognitive disturbances. Aligned with this result, in an analysis of the Health and Retirement Study data (n = 9,814), Porter (2013)³⁷ found that cognitive function in later life of the overall group is not associated with cancer survivorship, although individual variation certainly exists. In addition, the improvement of fatigue symptoms and cognitive performance over the two-year period of the current study indicates that chemotherapy did not cause persistent fatigue and that cognitive performance improved at rates consistent with what would be expected due to practice effects. Thus, it is unlikely that

permanent chemotherapy-associated structural or functional brain disturbances occurred, though neuroimaging studies are needed to confirm this hypothesis.

The relationship between symptoms of fatigue and depression is informative and potentially clinically significant, as it was accounted for by a single item on the HADS for which participants reported feeling “slowed down”. While study findings did not demonstrate that the study participants in this sample were experiencing major depression or clinically significant depressive symptoms, because “slowing” is a major component of fatigue, it may be that elevated depression scores on the HADS were a manifestation of fatigue, rather than vice versa. Future studies addressing a directional relationship between depression and fatigue are warranted.

Study Limitations

Despite its strengths of longitudinal data with a low attrition rate and cognitive performance assessed with reliable and validated computerized objective testing, this study does have several limitations. This includes (a) lack of age- and gender-matched BCSs not receiving cancer treatment (i.e. comparative controls); (b) absence of pre-cancer diagnosis/surgery cognitive function assessment; (c) practice effects associated with repeated administration of the CNSVS; (d) relatively mild levels of mean fatigue for the group as a whole; and (e) lack of two within-chemotherapy time-points to dissociate the full fatigue effects of chemotherapy. Inclusion of a control group did not seem feasible in the current study as it would have been difficult to discern correlations among specific cancer treatment modalities with cognitive status and fatigue findings.¹⁶ Future studies involving both age- and gender-matched BCSs not receiving chemotherapy as well as control group of non-cancer patients would improve on this limitation. In the current study, participants demonstrated lower cognitive performance than expected pre-chemotherapy. Our prior work suggests that this finding may be linked to pro-inflammatory cytokine effects,³⁸ though more work is needed in this regard. The challenge of obtaining pre-cancer diagnosis/surgery cognitive status seems insurmountable as healthcare visits generally do not include such data collection. Thus, in future studies, more precise and reliable statistical models adjusting for covariates are needed to estimate the differences in expected versus actual cognitive performance at baseline.^{16,39} With regard to the cognitive performance assessment, it is possible that practice effects of multiple administrations of the CNSVS occurred. If cognitive deficits were indeed associated with chemotherapy, one would expect that the typical test-retest improvements due to practice effects would not occur with repeated administrations. However, this is not the case, as online Supplemental Figure 1 and Table 2 demonstrate that cognitive performance improves with each repeated administration.

Clinical Implications

The findings of this study may provide healthcare providers with insight into how fatigue and cognitive impairment progress from pre-chemotherapy through 2-year survivorship and how these relationship changes over time. As a result, providers have an opportunity to use study findings as part of patient education when engaged in provider-patient discussion for preventively and collaboratively strategizing with the patient for effective symptom management and improved quality of life. To optimize treatment consequences and daily

activities during chemotherapy, we suggest that patients would benefit from interventions targeted towards fatigue and its potential effect on perceived cognitive function in routine clinical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Mean cognitive performance and Brief Fatigue Inventory ratings at each assessment over the two-year study period with sample-based standard error bars included.

Table 1.

Relationship of cognitive performance with fatigue

Cognitive Performance	Fatigue severity		Functional interference	
	β	R	β	R
Overall performance		0.32 **		0.31 **
Psychomotor speed	-.19 *		-.24 *	
Complex attention	-.15 *			
Memory	-.10 #			
Executive functioning			-.12 *	
Pre-chemotherapy (T1)		0.25 **		0.29 **
Complex attention	-.25 *		-.29 *	
During Chemotherapy (T2)		0.40 **		0.34 **
Complex attention	-.40 *			
Cognitive flexibility			-.34 *	
End of chemotherapy (T3)		0.34 **		0.31 **
Psychomotor speed	-.34 *		-.31 *	
12-month follow-up (T4)		0.40 **		0.39 **
Complex attention	-.23 *			
Psychomotor speed	-.26 *		-.39 *	
24-month follow-up (T5)		0.37 **		
Psychomotor speed	-.37 *		-.46 *	

Note. Fatigue Severity and Functional Interference based on the Brief Fatigue Inventory (BFI); a measure of cancer-related fatigue. Cognitive performance based on CNS Vital Signs performance at each time point.

0.05 < P < 0.10

* P < 0.05

** P < 0.01.