The relationship between fatigue prior to chemotherapy and subsequent depressive symptoms in women with breast cancer

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ABSTRACT

Background

Women with breast cancer commonly experience fatigue and depressive symptoms before, during, and after treatment. Many studies have found that fatigue and depression are correlated in women with breast cancer throughout treatment, but there are few studies that have investigated the temporal nature of this relationship.

Methods

As part of a larger study investigating sleep and fatigue in breast cancer, 89 women (mean age=51.9 yrs) with breast cancer were assessed for fatigue and depressive symptoms before beginning chemotherapy and in the last week of cycle 4 of chemotherapy. Fatigue was assessed using the Multidimensional Fatigue Scale – Short Form (MFSI-SF). Depressive symptoms were assessed with the Center for Epidemiological Studies-Depression (CES-D) questionnaire, and only women with a baseline CES-D score less than 16, suggestive of no depressive symptoms, were included in the study. The relationship between baseline MFSI-SF scores and the final CES-D scores was modeled with multiple regression models adjusted for demographic and disease related confounders.

Results

The MFSI-SF mental subscale was the only fatigue measure to remain significantly associated with either the final CES-D score (B=0.156, p=0.002) or final CES-D score ≥16 (O.R.=1.20, 95% C.I.=1.01-1.42) after adjustment for baseline CES-D score, antidepressant use, and ethnicity in a multiple regression model.

Conclusion

This study suggests that women with breast cancer who have higher levels of mental fatigue prior to chemotherapy are more likely to experience higher levels of depressive symptoms and progression to clinically significant depression following chemotherapy. Future studies should investigate if interventions that decrease fatigue prior to or early in cancer treatment will prevent worsening of depressive symptoms.

INTRODUCTION

Several studies have found that over 70% of women with breast cancer experience cancer related fatigue (CRF), defined as "a persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" [1]. In fact, women with breast cancer (BC) commonly experience debilitating CRF and depressive symptoms before, during, and after treatment [2-8]. Cancer patients report fatigue in multiple domains, which include physical, affective, and cognitive forms of fatigue [9]. In addition, 20-39% of BC patients report depressive symptoms, which have been associated with worse quality of life and disease outcomes [10,11].

Many studies of the general population have found that fatigue and depression are associated with each other [12, 13-17]. Fatigue is one of the most common symptoms accompanying depressed mood, and in one study was present in 96% of patients with depressive symptoms [13]. While the directionality of this relationship remains unclear, fatigue and depression are predictive of each other. Individuals with fatigue have an increased risk of a new depressive episode at follow up, and individuals with depression are at increased risk of

experiencing fatigue at follow up [14]. Christensen et al. found that fatigue had a sensitivity of 77% and specificity of 84% for diagnosing depression [15]. In another study, women with fatigue had a 2.6 times increased chance of developing depression over the next year, and at least a 4 times increased chance over the next 13 years [16,17].

Fatigue and depressive symptoms are also correlated before, during, and after treatment in many types of cancer, including breast cancer [5,10,18-20]. Roscoe et al. found that after the 2nd cycle of chemotherapy, depressive symptoms were positively correlated with fatigue in women with BC [24]. They further found that fatigue and depressive symptoms varied together during chemotherapy, suggesting that fatigue and depression may share a common etiology in cancer. Miura et al. investigated the relationship between cognitive fatigue (decreased concentration/attentiveness) and depression in women with BC [25]. In this study, women with higher cognitive fatigue scores had higher depressive symptoms at a single time point. Two recent studies have also shown that higher levels of fatigue at one time point predicted worse depressive symptoms at subsequent time points in women with BC [26,27]. Alternatively, other studies have found that depressive symptoms predicted long-term fatigue in BC survivors [28, 29]. Although there has been a substantial increase in research in this area in the last decade, the precise relationship between fatigue and depressive symptoms in breast cancer needs further elucidation in order to improve predictive capabilities and treatment strategies for these symptoms.

This study expands on previous research by examining the relationship between multiple types of fatigue in women with BC and depressive symptoms following chemotherapy. Because depression has been associated with decreased survival rates, decreased quality of life, and decreased adherence to a chemotherapy regimen [11,30], early recognition of a patient's risk for

depressive symptoms during chemotherapy will allow for an earlier and more focused intervention. This, in turn, may lead to improved outcomes. We hypothesized that women with higher levels of fatigue and no depressive symptoms prior to chemotherapy would be more likely to experience an increase in depressive symptoms following four cycles of chemotherapy.

METHODS

Participants:

Participants were from two studies of women undergoing chemotherapy treatment for newly diagnosed breast cancer. Both studies followed similar protocols, and included women with stage I-IIIa BC scheduled to receive four cycles of anthracycline based chemotherapy. The first study, conducted from 2001 to 2005, focused on circadian rhythms, fatigue, and sleep. Then second study, conducted between 2005 and 2010, focused on chemotherapy related cognitive impairment. Forty-eight women from study 1 and forty-one women from study 2 met inclusion criteria for this study (see Figure 1 for the Screening and Enrollment processes), all of whom were included in data analysis. Exclusion criteria for both studies included: pregnancy, other underlying medical illness, significant pre-existing anemia, metastatic breast cancer, bone marrow transplantation, and other significant physical or psychological impairment. For this analysis, participants with depressive symptomology (CES-D $\geq$ 16) at baseline were also excluded.

The University of California San Diego's Human Research Protections Program and the UCSD Moores Cancer Center's Protocol Review and Monitoring Committee approved both studies, and an informed consent was obtained from each participant prior to participation in the study.

Measures:

Fatigue: Fatigue was assessed with the Multidimensional Fatigue Symptom Inventory – Short Form (MFSI-SF) survey [31]. The MFSI-SF survey is a thirty-item instrument that has been found to be valid and reliable in assessing CRF in both clinical and research settings. It consists of five subscales that evaluate five areas of fatigue: general, emotional, physical, mental, and vigor. Each subscale is composed of six statements that participants rate from 0-4 based on how often they felt the statement was true in the past week (0=not at all, 4=extremely). Subscale scores range from 0-24, and are generated by adding the score for each component statement. Higher scores in all subscales besides vigor indicate greater fatigue. In the vigor subscale, higher scores indicate less fatigue. The total fatigue score is the sum of the general, emotional, physical, and mental subscale scores minus the vigor subscale score. The total score can range from -24 to 96 with higher scores indicating greater overall fatigue. While this instrument does not provide a cut-off for defining fatigue, Stein et al. found that in adults without cancer, the mean total MFSI-SF score was 0.85.

Depressive symptoms: Depressive symptoms were assessed with the Center for Epidemiological Studies Depression Scale (CES-D) [32]. This twenty-item instrument assesses cognitive and affective symptoms of depression. It is especially suited for populations with medical problems, as it does not include somatic measures of depression that could overlap with symptoms of underlying physical illness. Each statement is scored from 1-4 based on how often the participant felt that statement was true in the past week. For negative statements (those indicating depressive symptoms) one indicates rare or none of the time while four indicates most or all of the time. This scoring is reversed for positive statements (those indicating less depressive

symptoms). Scores for each statement are added to generate an overall score that can range from 0-60, with higher scores indicating greater depressive symptomology. A cut-off score for depressive symptoms and increased likelihood of clinically significant depression has been set at 16.

Procedure

Detailed procedural information for Study 1 has previously been published in Liu et al [33]. Briefly, after informed consent was obtained, medical records were abstracted for medical history and current medication use. Study 2 followed similar procedures [3]. For these analyses, data from MFSI-SF and CES-D instruments administered one week prior to the first cycle of chemotherapy (baseline), and during the last week of cycle 4 (C4LW) were used.

Data analysis

Descriptive statistics (mean, median, standard deviation) were calculated for MFSI-SF and CES-D scores at both time points. C4LW CES-D scores were square root transformed to achieve a normal distribution. Spearman rank correlations were computed to examine the relationship between MFSI-SF scores (total and subscales) at baseline and C4LW CES-D scores. MFSI-SF scores were determined to be significantly correlated with C4LW CES-D scores if $p<0.05$.

Potential demographic and disease related confounders were examined for association with C4LW CES-D scores and baseline MFSI-SF scores using either spearman rank correlation or independent samples t test. Variables with $p<0.1$ were determined to be confounders, and were adjusted for in subsequent analyses.

The relationship between each significant baseline MFSI-SF scale (predictor) and C4LW CES-D score (outcome) was then demonstrated using separate multiple linear regression models adjusted for confounding variables. Finally, MFSI-SF subscale scores that remained significant within the multiple linear regressions were included together in a final regression model in order to evaluate the overall predictive value of baseline MFSI-SF scores for C4LW CES-D score. To avoid collinearity, total MFSI-SF was not included in the same regression models as any of the MFSI-SF subscales.

Similarly, independent sample t tests were performed to evaluate the relationship between baseline MFSI-SF scores (total and subscales) and CES-D ≥ 16 at C4LW. MFSI-SF scores were determined to be significantly associated with C4LW CES-D ≥ 16 if $p<0.05$. Potential demographic and disease related confounding factors were examined for association with C4LW CES-D ≥ 16 and baseline MFSI-SF scores using either chi-squared or independent sample t tests. Variables with $p<0.1$ were determined to be confounders, and were adjusted for in subsequent analysis. The relationship between each significant baseline MFSI-SF scale (predictor) and C4LW CES-D ≥ 16 (outcome) was then modeled using multiple logistic regression adjusted for confounding variables to test if baseline MFSI-SF scores produced a good model for predicting C4LW CES-D ≥ 16, and to identify the relative effect size.

All analyses were performed using version 21 of SPSS (IBM corp. 2012). All statistical tests with p-values <0.05 are reported as statistically significant.

RESULTS

Detailed demographic and disease information of participants is provided in Table 1.

The mean age of the 89 women was 51.8 years (SD=9.4 years), 85% were Caucasian, 74% were married, and 84% had incomes over $100,000 per year. Because the recommended length of each chemotherapy cycle changed between 2005 and 2010 (the years of data collection), all participants in Study 1 had three-week cycle regimens while in Study 2, 36.5% had three-week cycles and 64.5% had two-week cycles. Study 1 and Study 2 participants also differed significantly in antidepressant use and chemotherapeutic agents used for treatment. Therefore, chemotherapy regimen and antidepressant use were tested as confounders, and antidepressant use was subsequently adjusted for as a confounder. There were no significant differences between Study 1 and Study 2 participants in age, race, body mass index, education level, marital status, household income, menopausal status, surgery type, cancer stage, fatigue, or depressive symptoms. The two samples were therefore merged.

The following demographic and disease related variables were tested as potential confounders in relation to C4LW CES-D and MFSI-SF scores: age, BMI, ethnicity, race, education, income, marital status, menopause status, Study 1 versus Study 2 participation, antidepressant use, cancer stage, chemotherapy regimen, chemotherapy length, surgery type, and CES-D score prior to chemotherapy. Confounders for MFSI-SF scores and C4LW CES-D scores were ethnicity, antidepressant use, and baseline CES-D score.

Association between baseline MFSI-SF scores and C4LW CES-D scores

Baseline total MFSI-SF scores

Baseline total MFSI-SF score was significantly associated with C4LW CES-D score ($r=0.383$, $p<0.001$). However, this relationship did not remain significant when included in a multiple regression model adjusted for confounders (ethnicity, antidepressant use, and baseline CES-D

score). Within the adjusted multiple regression model (R^2=0.229, p<0.001), baseline antidepressant use was the only significant predictor C4LW CES-D scores (B=0.805, p=0.041).

Baseline MFSI-SF subscale scores

Although the general, emotional, mental, and vigor MFSI-SF subscales were significantly associated with C4LW CES-D scores (all p<0.05), only the MFSI-SF mental subscale remained significant after adjusting for confounders. A multiple linear regression model with baseline MFSI-SF mental score as predictor, and adjusted for covariates (ethnicity, antidepressant use, baseline CES-D score) was significant and explained 28.1% of the variance in C4LW CES-D scores (p<0.001). The significant predictors within this model were antidepressant use (B=0.836, p=0.03), and baseline MFSI mental subscale (B=0.156, p=0.002) (Table 2). For every one point increase in the baseline MFSI-SF mental score (i.e., increased mental fatigue), C4LW CES-D score increased by 0.15 points on average.

Association between baseline MFSI-SF scores and progression to a score of CES-D≥16 at C4LW

Baseline total MFSI-SF score

After adjusting for ethnicity, antidepressant use, and baseline CES-D score, a logistic regression model with total baseline MFSI-SF score as the predictor and C4LW CES-D ≥ 16 as the response variable was significant (p=0.037), but no individual predictors were significant.

Baseline MFSI-SF subscale scores

Baseline MFSI-SF general and mental subscales were significantly associated with C4LW CES-D ≥16 (both p<0.04), but only the baseline MFSI-SF mental subscale remained significantly

associated after controlling for ethnicity, antidepressant use, and baseline CES-D score. A multiple logistic regression model with baseline MFSI-SF mental subscale score as predictor, and adjusted for covariates, significantly predicted C4LW CES-D ≥16 (p=0.01) (Table 3). The mental fatigue subscale was the only significant predictor of final CES-D score ≥16 in this model. For every one-point increase in initial MFSI-SF mental subscale score, there was a 20% increased likelihood of progression to clinically significant depression by cycle four of chemotherapy (CI=1.01-1.42).

DISCUSSION

This study found that women with breast cancer who have higher levels of mental fatigue prior to chemotherapy are more likely to experience increased depressive symptoms and progression to clinically significant depression following chemotherapy. While antidepressant use also predicted increased CES-D score, baseline depressive symptoms were not a significant predictor.

Other studies have also shown that fatigue can predict later depression in BC patients, and that cognitive fatigue is correlated with depressive symptoms in this population [26-28]. This study supports these findings, and expands on them by illustrating that mental fatigue specifically is predictive of subsequent depressive symptoms. Total fatigue and other subtypes of fatigue were not significant predictors in this group of BC patients.

Mental fatigue encompasses cognitive manifestations of fatigue such as feeling confused and/or forgetful, having difficulty remembering things, having trouble paying attention, and making more mistakes than usual [31]. The relationship between mental fatigue and worsening depression following chemotherapy may be related to a common pathophysiologic etiology of both these symptoms. While there are many proposed mechanisms for CRF, a shared

underpinning of these theories is that cancer or treatment induced cytokine dysregulation may cause complex neurologic, hormonal, and metabolic changes [34]. Similar theories have been proposed for cancer related depression [30]. Several studies have supported the role of cytokines in fatigue and depression in BC patients [35,36]. Alternatively, mental fatigue may directly play a role in worsening depression through alterations in activity, sleep, or other factors. More research is needed to fully elucidate this relationship, and to understand why mental fatigue specifically is associated with depressive symptoms.

This study suggests that research is needed to determine if early intervention for fatigue in women with BC may help prevent later depressive symptoms. Many studies have evaluated management strategies for CRF, and interventions such as cognitive behavioral therapy, physical activity, meditation, light therapy, yoga, and management of concurrent symptoms have shown some efficacy [37-39]. There are few trials, however, that have examined the impact of fatigue reduction on future depression. Tchekmedyian et al. found that reducing fatigue in lung cancer patients by treating anemia also resulted in improvement in depressive symptoms [40]. In breast cancer patients, cognitive behavioral therapy targeted for treatment of fatigue helped with depression as well [41]. Randomized controlled trials in BC patients would help establish if interventions that decrease fatigue prior to or early in treatment prevent worsening of depressive symptoms in this population.

There are some limitations to this study. First is the narrow subject population consisting of women with BC who have relatively high education and household income levels. Consequently, the results of this study may not apply to men, or to patients with different cancers or socioeconomic characteristics. The design of this study also does not allow establishment of a causative relationship between fatigue and depression. In addition, this study does not define an

MFSI-SF mental score at which point a clinician should be concerned about risk for depression or should consider possible interventions to address fatigue. Further research is therefore needed in order increase the clinical utility of these findings.

This study also has several strengths. First, it adjusted for socioeconomic and disease related confounders. This might explain why this study did not find a relationship between total fatigue and later depression, which has been noted in several other studies. It also expanded on current research by including total fatigue and multiple sub-types of fatigue in order to better delineate if specific types of fatigue are more predictive of subsequent depressive symptoms than others. Another strength is use of baseline fatigue, which increases clinical utility of the results by enabling very early risk assessment for depression in women with BC.

In summary, this study found that mental fatigue prior to chemotherapy in women with breast cancer is associated with increased depressive symptoms following chemotherapy. Fatigue may therefore be a potential target for intervention to help reduce depression, and its effects on quality of life and treatment outcomes, in women with breast cancer.

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Figure 1. Screening and Enrollment Flowchart

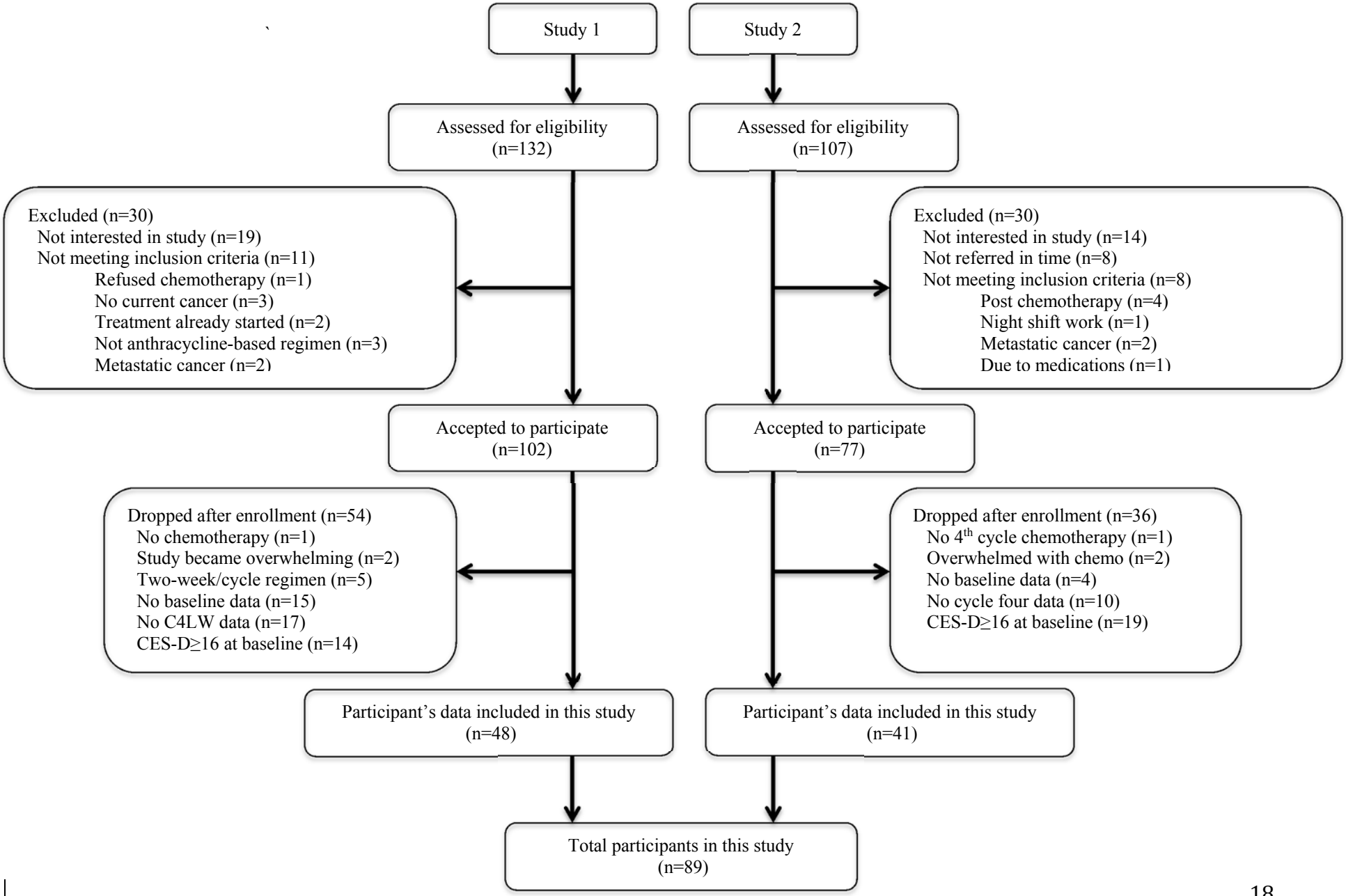

Table 1. Demographic, disease, and treatment characteristics of participants (n=89)

Variable		Value
Age (years)		
Mean (SD)		51.8 (9.4)
Range		31-79
BMI (kg/m^2)		
Mean (SD)		28.0 (6.6)
Range		19.3-51.8
Race [n (%)]		
Caucasian		74 (85.1)
Not Caucasian		13 (14.9)
Unknown		2
Education [n (%)]		
Some or completed high school		13 (14.6)
Some college		29 (32.6)
Completed college and above		47 (52.8)
Marital Status [n (%)]		
Not married		23 (25.8)
Married		66 (74.2)
Household annual income [n (%)]		
≤ $100,000		13 (16.5)
≥ $100,000		66 (83.5)
Unknown		10
Menopausal status [n (%)]		
Baseline	Pre-menopause	33 (37.9)
	Peri-menopause	9 (10.4)
	Post-menopause	32 (36.8)
	Hysterectomy	13 (14.9)
	Not available	2
Last week of Cycle 4	Pre-menopause	3 (3.4)
	Peri-menopause	18 (20.6)
	Post-menopause	53 (60.1)
	Hysterectomy	14 (15.9)
	Not available	1
Cancer stage [n (%)]		
Stage I		26 (31.3)
Stage II		34 (41.0)
Stage III		23 (27.7)
Not Available		6

Surgery type [n (%)]	
Lumpectomy	36 (42.9)
Mastectomy	37 (44.0)
Double mastectomy	6 (7.1)
No surgery before Chemotherapy	5 (6.0)
Not available	5
Chemotherapy regimen [n (%)]	
AC	24 (28.6)
AC + docetaxel	16 (19.0)
AC + paclitaxel	28 (33.3)
AC + fluorouracil	3 (3.6)
Other	13 (15.5)
Not available	5
Chemotherapy Cycle Length	
3 week	63 (70.8)
2 week	26 (29.2)
Antidepressant Use	
Yes	72 (80.9)
No	17 (19.1)

Note: AC = doxorubicin (adriamycin) + cyclophosphamide

Table 2. Multiple linear regression model with baseline MFSI-SF mental subscale as the predictor and C4LW CES-D score as the response variable

Entered Variables	**B**	**SE**	**β**	**p**
Intercept	2.700	0.594		0.000
Ethnicity	-0.729	0.415	-0.168	0.082
Antidepressant Use	0.836	0.378	0.209	**0.030**
Baseline CES-D score	0.064	0.035	0.182	0.070
Baseline MFSI-SF mental score	0.156	0.049	0.311	**0.002**

MFSI-SF, Multidimensional Fatigue Inventory-Short Form (higher score indicates more fatigue). CES-D, Center for Epidemiological Studies Depression Scale (higher score indicates more depressive symptoms). C4LW, last week of cycle 4 of chemotherapy.

Table 3. Multiple logistic regression model with baseline MFSI-SF mental subscale as the predictor and C4LW CES-D score ≥16 as the response variable

				95% C.I. for O.R.	
Entered Variables	**B**	**SE**	**O.R.**	**Lower**	**Upper**
Intercept	-0.256	1.341	0.775		
Ethnicity	-1.498	1.107	0.224	0.026	1.960
Antidepressant Use	0.999	0.604	2.714	0.831	8.866
Baseline CES-D score	0.022	0.061	1.023	0.908	1.152
Baseline MFSI-SF mental score	0.181	0.085	1.198	**1.014**	**1.416**

MFSI-SF, Multidimensional Fatigue Inventory-Short Form (higher score indicates more fatigue). CES-D, Center for Epidemiological Studies Depression Scale (higher score indicates more depressive symptoms). C4LW, last week of cycle 4 of chemotherapy.