

Inflammation and Behavioral Symptoms After Breast Cancer Treatment: Do Fatigue, Depression, and Sleep Disturbance Share a Common Underlying Mechanism?

Julienne E. Bower, Patricia A. Ganz, Michael R. Irwin, Lorna Kwan, Elizabeth C. Breen, and Steve W. Cole

From the Cousins Center for Psychoneuroimmunology, Semel Institute; Jonsson Comprehensive Cancer Center; and Schools of Medicine and Public Health, University of California, Los Angeles, CA.

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Corresponding author: Julienne E. Bower, PhD, University of California, Los Angeles, Department of Psychology, 1285 Franz Hall, Los Angeles, CA 90095-1563; e-mail: jbower@ucla.edu.

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A B S T R A C T

Purpose

Fatigue, depression, and sleep disturbance are common adverse effects of cancer treatment and frequently co-occur. However, the possibility that inflammatory processes may underlie this constellation of symptoms has not been examined.

Patients and Methods

Women (N = 103) who had recently finished primary treatment (ie, surgery, radiation, chemotherapy) for early-stage breast cancer completed self-report scales and provided blood samples for determination of plasma levels of inflammatory markers: soluble tumor necrosis factor (TNF) receptor II (sTNF-RII), interleukin-1 receptor antagonist, and C-reactive protein.

Results

Symptoms were elevated at the end of treatment; greater than 60% of participants reported clinically significant problems with fatigue and sleep, and 25% reported elevated depressive symptoms. Women treated with chemotherapy endorsed higher levels of all symptoms and also had higher plasma levels of sTNF-RII than women who did not receive chemotherapy (all $P < .05$). Fatigue was positively associated with sTNF-RII, particularly in the chemotherapy-treated group ($P < .05$). Depressive symptoms and sleep problems were correlated with fatigue but not with inflammatory markers.

Conclusion

This study confirms high rates of behavioral symptoms in breast cancer survivors, particularly those treated with chemotherapy, and indicates a role for TNF- α signaling as a contributor to postchemotherapy fatigue. Results also suggest that fatigue, sleep disturbance, and depression may stem from distinct biologic processes in post-treatment survivors, with inflammatory signaling contributing relatively specifically to fatigue.

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INTRODUCTION

Behavioral symptoms are among the most common adverse effects of cancer diagnosis and treatment and include fatigue, depression, and sleep disturbance.¹ The prevalence of fatigue and depression have been carefully studied in patients with and survivors of breast cancer, and research suggests that approximately one third of survivors report significant symptoms of fatigue²⁻⁴ and that 20% to 30% report elevated depressive symptoms.⁵ An emerging literature on sleep disturbance also suggests a high prevalence of sleep disturbance in patients with cancer; 40% to 50% of survivors of breast cancer report problems with sleep.^{6,7} Each of these symptoms is associated with substantial impairment in quality of life and may also have relevance for disease-related outcomes,⁸ which motivates calls to include behavioral symptoms as a sixth vital sign.⁹

The mechanisms underlying behavioral symptoms in cancer survivors have not been determined. Symptoms of fatigue, depression, and sleep disturbance frequently co-occur in cancer populations,^{2,10} leading to speculation about common underlying mechanisms. In particular, there is growing interest in the possibility that these symptoms may be driven by activation of the proinflammatory cytokine network.^{9,11} Basic research on neural-immune signaling has demonstrated that proinflammatory cytokines signal the CNS to trigger a constellation of behavioral changes that include fatigue, sleep disturbance, and depressive-like symptoms in animal models.¹² Consistent with this research, administration or induction of proinflammatory cytokines in healthy humans is associated with increases in depressed mood, fatigue, and sleep problems,¹³⁻¹⁵ and inflammation is common among noncancer populations that have depression or sleep disorders.^{16,17} In

research about patients with cancer, there is growing literature that links inflammation and fatigue during¹⁸⁻²¹ and after²²⁻²⁶ cancer treatment, although little is known about mechanisms underlying fatigue immediately after treatment completion, a time when fatigue levels are typically at their peak.²⁷ There has been minimal examination of inflammatory correlates of depressive symptoms or sleep disturbance in cancer populations, and no studies have comprehensively examined fatigue, depression, and sleep and their association with inflammatory markers in patients with cancer to assess potential common underlying pathways. In addition, the role of cancer treatments as potential inducers of inflammation and behavioral symptoms has not been carefully assessed. Chemotherapy is of particular interest, because it has been associated with acute increases in inflammatory markers^{18,28-30} and fatigue,^{4,31,32} which may persist long into survivorship.^{3,33,34} Determining the mechanisms underlying these common, disabling adverse effects of cancer treatment is critical for the development of targeted interventions for prevention and treatment.

The goals of the current study were as follows: to characterize the prevalence and comorbidity of fatigue, depressive symptoms, and sleep disturbance in a sample of women with early-stage breast cancer who had recently completed treatment with surgery, radiation and/or chemotherapy; to determine the contribution of treatment-related factors to behavioral symptoms and inflammation in the aftermath of cancer treatment, focusing on chemotherapy; and to test the hypothesis that inflammatory processes would contribute to these symptoms.

PATIENTS AND METHODS

Participants and Procedures

Participants for this study were drawn from a larger study of cognitive functioning after cancer treatment conducted at the University of California, Los Angeles. Eligibility criteria for the parent trial were as follows: diagnosed with stages 0 to IIIA breast cancer; completed primary cancer treatment (ie, surgery, radiation therapy, and/or chemotherapy) within the past 3 months and not yet started endocrine therapy; age 21 to 65 years; no neurologic or immune-related medical conditions (eg, autoimmune disease); and nonsmoker.

Participants for the parent study were identified primarily through tumor registry rapid case ascertainment from hospitals where collaborating physicians practiced as well as through direct referral from surgical and medical oncology practices. Patients received a brochure describing the study and were asked to contact the research office if they were interested in participating. A phone screen was conducted to determine eligibility, after which participants were scheduled for an in-person appointment at the University of California, Los Angeles, where they provided blood samples, completed self-report questionnaires, were weighed and measured for determination of body mass index (BMI), and underwent comprehensive neuropsychologic testing. Assessments were conducted in the morning (before 11 AM) after an overnight fast. The current report focuses on self-report and immune data from 103 women who completed the baseline assessment and who had no confounding medical conditions. The research was approved by the University of California, Los Angeles, institutional review board, and informed consent was obtained from all participants.

Behavioral Measures

Demographic and clinical information were determined from self-report questionnaires. Fatigue was assessed by using the Fatigue Symptom Inventory (FSI), a valid and reliable, 14-item measure specifically designed to assess fatigue in cancer populations.³⁵⁻³⁷ Items that assessed average fatigue, most fatigue, and least fatigue in the past week were averaged to obtain a measure of fatigue severity.³⁶ Depressive symptoms were assessed by using the Beck Depression Inventory-II (BDI-II), a 21-item measure that assesses cog-

nitive, affective, and vegetative symptoms of depression during the prior 2 weeks with excellent reliability and validity.³⁸ The Pittsburgh Sleep Quality Index (PSQI) was used to assess subjective sleep quality and disturbances over the prior month. This 19-item questionnaire has high internal consistency, test-retest reliability, and diagnostic validity with polysomnography.³⁹

Inflammatory Markers

Blood samples for circulating inflammatory markers were collected by venipuncture into EDTA tubes, placed on ice, centrifuged for acquisition of plasma, and stored at -80°C for subsequent batch testing. We focused on three inflammatory markers that have been associated with cancer-related fatigue in previous research: interleukin-1 (IL-1) receptor antagonist (IL-1ra), soluble tumor necrosis factor (TNF) receptor type II (sTNF-RII), and C-reactive protein (CRP).^{20,22-25} Plasma levels of IL-1ra and sTNF-RII were determined by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN) according to the manufacturer's protocols, with a lower limit of detection of 31 and 234 pg/mL for IL-1ra and sTNF-RII, respectively. CRP levels were determined by a high-sensitivity enzyme-linked immunosorbent assay (Immundiagnostik; ALPCO Immunoassays, Salem, NH) according to the manufacturer's protocol but with an extended standard curve to a lower limit of detection of 0.2 mg/L. All samples were run in duplicate, and assays were repeated on two separate assay days for sTNF-RII and IL-1ra; intra-assay and interassay mean levels were used in all analyses. The intra- and interassay precision of all tests were less than or equal to 10%.

Statistical Analyses

t tests were used to compare demographic and clinical characteristics of women treated with chemotherapy versus not, and correlations were used to examine associations among behavioral symptoms. Chemotherapy effects on symptoms and inflammatory markers were tested by one-way analysis of covariance (ANCOVA), and predictors of behavioral symptoms were examined with ANCOVA and multiple regression analyses. Given the small numbers of women treated with chemotherapy alone, the chemotherapy group included women treated with and without radiation therapy. Hence, all multivariate analyses controlled for exposure to radiation therapy as well as age and time since treatment completion, given potential effects of these variables on fatigue^{2,27}; analyses with inflammatory markers as the outcome also controlled for BMI.⁴⁰ Because their distributions were clearly non-normal and highly skewed, all inflammatory marker measures were transformed before analyses by using a natural log transformation. Analyses of depression were conducted by using all items from the BDI-II (total score) and with items that assessed energy/fatigue and sleep quality removed to minimize overlap with these symptoms.

RESULTS

Demographic characteristics of study participants are listed in Table 1. Women treated with chemotherapy were younger at diagnosis ($49.6 \nu 52.8$ years; $t_{(101)} = 1.99$; $P = .05$) and a longer time had elapsed since their cancer diagnoses ($8.3 \nu 5.1$ months; $t_{(100)} = -9.58$; $P < .001$), consistent with a longer duration of treatment in this group. In addition, the time between treatment completion and the study visit was somewhat shorter for women treated with chemotherapy ($26.8 \nu 36.5$ days; $t_{(87)} = 1.82$; $P = .07$).

Prevalence of Behavioral Symptoms

Symptoms of fatigue, sleep disturbance, and depression were elevated at the end of primary treatment. The average fatigue severity score was 3.85, and 64% of the sample scored greater than the clinically significant cutoff of 3.³⁶ The average score on the PSQI was 8.02; 65% percent scored greater than the clinically significant cutoff of 5, and 46% scored greater than the alternative cutoff of 8 that was suggested for patients with chronic illness, including cancer.⁴¹ The

Table 1. Demographic and Clinical Characteristics of Study Participants

Characteristic	Patients	
	No.	%
Age, years		
Mean	51.2	
Range	32-66	
Ethnicity		
White	89	86
Other	14	14
Married/committed relationship*	81	79
Education status		
High school graduate/some college	20	19
College graduate	53	52
Graduate degree	30	29
Yearly income, \$*		
≤ 60,000	10	10
60,000-100,000	25	25
≥ 100,000	65	65
Cancer treatment		
No chemotherapy	53	52
Surgery only	14	
Surgery + radiation	39	
Chemotherapy	50	48
Surgery + chemotherapy	9	
Surgery + radiation + chemotherapy	41	
Time since diagnosis, months		
Mean	6.7	
Range	1.7-12.5	
Time since treatment, days		
Mean	31.8	
Range	1-112	

*Numbers were based on available data.

Table 2. Differences in Behavioral and Inflammatory Outcomes by Chemotherapy Status

Characteristic	Chemotherapy		No Chemotherapy		P
	Mean	SD	Mean	SD	
Fatigue by FSI	4.52	2.27	3.24	1.98	.003
Sleep disturbance by PSQI	8.98	3.62	7.19	4.02	.01
Depressive symptoms by BDI-II	11.10	6.55	7.34	7.58	.019
Soluble TNF receptor II, pg/mL	2454	717	2152	623	.003
IL-1 receptor antagonist, pg/mL	231	163	331	399	.61
C-reactive protein, mg/L	2.09	3.21	3.27	5.26	.89

NOTE. Unadjusted means are reported. P values are from analysis of covariance controlling for age, time since treatment completion, and radiation therapy; analyses for inflammatory outcomes also controlled for BMI. Abbreviations: BDI-II, Beck Depression Inventory-II; BMI, body mass index; FSI, Fatigue Symptom Inventory; IL, interleukin; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation; TNF, tumor necrosis factor.

Association Between Inflammatory Markers and Behavioral Symptoms

Analyses next were conducted to investigate the association between inflammatory markers and fatigue, depression, and sleep disturbance. As predicted, sTNF-RII was associated with higher levels of fatigue, controlling for age, time since treatment, and radiation therapy ($P = .025$). To additionally probe this association, we examined levels of sTNF-RII in women who scored in the clinically significant range of the FSI (FSI severity > 3) and found significant elevations in sTNF-RII in this group when analysis controlled for confounders (unadjusted mean of sTNF-RII in fatigued women = 2,400 pg/mL v 2127 pg/mL in nonfatigued women; $P = .036$). However, fatigue was not associated with IL-1ra or CRP (both $P > .9$), nor were these inflammatory markers elevated in women who had clinically significant fatigue. Neither depression nor sleep disturbance was associated with any of the inflammatory markers (all P for BDI-II > .15; all P for PSQI > .80). Similar findings were observed in analyses in which fatigue and sleep items were deleted from the BDI-II and in analyses that compared data of women who scored in the clinical range of the BDI-II or the PSQI.

Given effects of chemotherapy on fatigue and sTNF-RII, we examined the association between fatigue and sTNF-RII within the chemotherapy- and no chemotherapy-treated groups separately. Fatigue was associated with significant elevations in sTNF-RII in the chemotherapy-treated group, controlling for confounders ($P = .03$). However, there was no association between fatigue and sTNF-RII in patients not receiving chemotherapy ($P > .70$). Simple correlations between fatigue and sTNF-RII in the chemotherapy versus no-chemotherapy groups are shown in Figure 1. Of note, there was no evidence for an association between depressive symptoms or sleep disturbance and the inflammatory markers in either group.

average score on the BDI-II was 9.15, and 25% percent of women scored greater than the clinically significant cutoff of 14.³⁸

Fatigue was significantly correlated with depressive symptoms for total BDI-II ($r = 0.54$; $P < .001$) and for BDI-II without energy/fatigue or sleep items ($r = 0.43$; $P < .001$); fatigue was also significantly correlated with sleep disturbance ($r = 0.34$; $P = .001$). Depressive symptom severity and sleep disturbance were also correlated on the total BDI-II ($r = 0.55$; $P < .001$) and on the BDI-II without energy/fatigue or sleep items ($r = 0.52$; $P < .001$).

Effects of Chemotherapy on Behavioral Symptoms and Inflammatory Markers

Analyses were first conducted to determine the effect of chemotherapy exposure on behavioral symptoms and inflammatory markers. In analyses controlling for age, time since treatment completion, and radiation therapy, chemotherapy was associated with significantly higher levels of all behavioral symptoms (all $P < .02$; Table 2). None of the covariates were significantly associated with behavioral symptoms.

Chemotherapy was also associated with higher levels of sTNF-RII, controlling for age, time since treatment completion, radiation therapy, and BMI (Table 2). Older age and higher BMI were also significant predictors of higher sTNF-RII in these analyses (all $P < .05$). There was no significant association between chemotherapy exposure and plasma concentrations of IL-1ra or CRP (Table 2).

DISCUSSION

This study confirms high levels of fatigue, depressive symptoms, and sleep disturbance in patients with breast cancer who have recently completed primary treatment, particularly among those treated with

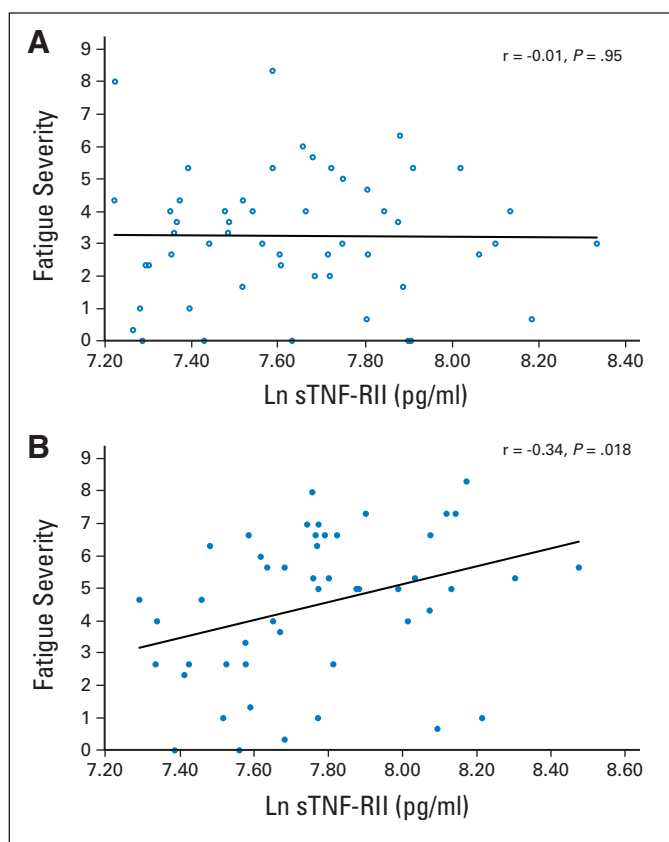


Fig 1. Correlation between fatigue severity and natural log (LN)-transformed soluble tumor necrosis factor receptor II (sTNF-RII) in (A) no chemotherapy and (B) chemotherapy-treated groups.

chemotherapy. Scores for all three symptoms were much greater than levels seen in comparison samples of healthy women,^{36,42,43} which highlights the importance of these behavioral disturbances in the immediate post-treatment period. However, despite strong correlations among symptoms, we found no evidence for a common inflammatory mechanism driving symptom expression. Instead, the only symptom associated with the inflammatory markers assessed was fatigue, which was correlated specifically with elevations in sTNF-RII. These findings are consistent with previous research linking sTNF-RII and fatigue in longer-term survivors of breast cancer,²² and they extend those results to demonstrate an association between TNF and fatigue in the immediate post-treatment period. Exposure to chemotherapy was also associated with elevations in sTNF-RII, and the strongest association between sTNF-RII and fatigue was seen in chemotherapy-treated patients.

In contrast with fatigue, neither depressive symptoms nor sleep disturbance was associated with sTNF-RII or other circulating markers of inflammation. A recent meta-analysis showed a reliable association between inflammatory markers (including CRP and IL-1ra) and self-reported depressive symptoms, although this effect was small, and studies in patients with cancer are extremely limited.¹⁶ In addition, few studies have differentiated between affective and vegetative symptoms of depression, which may have distinct biologic correlates. For example, among patients with ovarian cancer, plasma and ascites levels of IL-6 were correlated with vegetative symptoms of depression, including fatigue, but not

with affective symptoms (eg, sadness).⁴⁴ Among patients undergoing interferon alfa therapy for malignant melanoma, fatigue and other vegetative symptoms emerged earlier than depressed mood and were less responsive to paroxetine treatment,⁴⁵ which was similar to findings in other cancer populations.⁴⁶ In our previous research in patients with breast cancer, general depressive symptoms were not associated with markers of inflammation, including sTNF-RII, IL-1ra, and CRP.^{20,22} These findings suggest that fatigue and depression, though closely related, may have distinct biologic underpinnings, and that fatigue may be more closely tied to inflammatory processes in the context of breast cancer.

Inflammation is common among individuals with sleep disorders⁴⁷ and in those with objectively-assessed sleep disturbance.⁴⁸⁻⁵¹ However, evidence that self-reported sleep problems are associated with circulating markers of inflammation is mixed.⁵²⁻⁵⁵ The current findings suggest that elevations in circulating inflammatory markers, specifically sTNF-RII, IL-1ra, and CRP, may not contribute to subjective sleep disturbance at the completion of breast cancer treatment, despite high levels of sleep problems at this time. Instead, other research suggests that affective and cognitive/behavioral factors may contribute to cancer-related insomnia.⁵⁶ Future studies should probe biologic, affective, and cognitive/behavioral factors that may contribute to fatigue, depression, and sleep problems to identify unique and common mechanisms for these symptoms.

These findings suggest a role for TNF- α in chemotherapy-induced fatigue. Results showed that sTNF-RII, rather than IL-1ra or CRP, was specifically associated with fatigue. The soluble TNF receptor is shed from a cell surface after stimulation of the cell by the proinflammatory cytokine TNF- α and, therefore, serves as a marker for TNF- α activity.⁵⁷ In animal models, treatment with the chemotherapy agent adriamycin induces elevations in peripheral TNF- α , which then migrates across the blood brain barrier and causes inflammation and oxidative stress in the brain.⁵⁸ Conversely, pharmacologic blockade of TNF with etanercept led to reduced fatigue in patients with cancer who were undergoing chemotherapy.⁵⁹ In the current sample, circulating concentrations of sTNF-RII in chemotherapy-treated patients were quite high, comparable to those seen in our previous research with persistently fatigued survivors of breast cancer.²² In contrast, plasma levels of IL-1ra in this sample were much less than levels linked to cancer-related fatigue in our previous research^{20,22,23} and may have been insufficient to induce behavioral changes. Levels of CRP in this sample were high, comparable to levels associated with fatigue in previous studies.²⁰ It is possible that inflammatory cytokines, although correlated, may have distinct associations with the CNS and physical health. For example, sTNF-RII, but not IL-6, was correlated with stress-induced changes in the CNS,⁶⁰ and sTNF-RII predicted coronary heart disease independent of CRP.⁶¹

Despite growing interest in behavioral adverse effects of cancer treatment and their interrelationships, no previous studies have comprehensively examined fatigue, depressive symptoms, and sleep disturbance and their biologic underpinnings. The current findings suggest that, although these symptoms frequently co-occur in the aftermath of breast cancer treatment, they do not necessarily share a common underlying inflammatory biology at this point in the cancer trajectory. Conclusions are limited by the cross-sectional nature of the data, which particularly limits conclusions about causality; for example, women may have had elevated fatigue and

sTNF-RII before treatment. Longitudinal studies are required to additionally probe the associations among these symptoms and the mechanisms that contribute to their onset and persistence over time. In addition, we focused on three biomarkers that serve as proxies for the activity of three key proinflammatory cytokines—IL-1 β (IL-1ra), TNF- α (sTNF-RII), and IL-6 (CRP)—and have been correlated with cancer-related fatigue^{20,22-25} and with depression and sleep disturbance in noncancer populations.^{18,53,54} However, it is possible that other markers of inflammation not assessed here may contribute to these symptoms. It is also possible that elevated inflammatory markers may be more apparent in women with clinical depression and/or sleep disorders. Moreover, although women were screened for neurologic and immune-related medical conditions, other potential causes of behavioral symptoms, including anemia and thyroid dysfunction, were not assessed.

The present results implicate TNF- α signaling as one mechanism underlying the development of treatment-related fatigue and highlight the need for future studies to define other biologic mechanisms driving the emergence of sleep disturbance and depressive symptoms. Identification of unique and common mechanisms for these common

adverse effects of cancer treatment is essential for the development of targeted interventions.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Julienne E. Bower, Patricia A. Ganz, Michael R. Irwin, Steve W. Cole

Financial support: Patricia A. Ganz

Administrative support: Patricia A. Ganz

Provision of study materials or patients: Patricia A. Ganz

Collection and assembly of data: Patricia A. Ganz, Lorna Kwan, Elizabeth C. Breen

Data analysis and interpretation: Julienne E. Bower, Michael R. Irwin, Lorna Kwan, Elizabeth C. Breen, Steve W. Cole

Manuscript writing: All authors

Final approval of manuscript: All authors

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