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Testing a biobehavioral model of fatigue before adjuvant therapy in women with breast cancer

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Abstract

Background: Fatigue is one of the most common and disabling side effects of cancer and its treatment. Although research has typically focused on fatigue that occurs during and after treatment, patients may experience fatigue even before treatment onset. The current study was designed to identify biobehavioral risk factors associated with fatigue before adjuvant therapy in women with early-stage breast cancer.

Methods: Patients with Stage 0-IIIA breast cancer (n=270) were recruited before onset of adjuvant or neoadjuvant therapy with radiation, chemotherapy, and/or endocrine therapy. Host factors were identified from an empirically-based, biobehavioral model of fatigue and assessed using self-report questionnaires, medical record review, and blood collection (for genetic data). Fatigue was also assessed by questionnaire. Linear regression analyses were used to assess the

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association between host factors and dimensions of fatigue, with general fatigue as the primary dimension of interest.

Results: Fatigue was elevated at the pre-treatment assessment relative to published controls. Bivariate analyses identified a number of demographic, cancer-related, and biobehavioral correlates of fatigue. In the multivariable model, predictors of general fatigue included younger age, lower education, lower cancer stage, and history of childhood maltreatment (all *p*s < .05), with the full model accounting for 18.4% of the variance in fatigue. Secondary analyses identified common and specific predictors of emotional, mental, and physical dimensions of fatigue.

Conclusion: Among women who have not yet started treatment for breast cancer, demographic and psychosocial factors are associated with elevated fatigue and could be used to identify at-risk patients for early intervention.

Precis:

Fatigue is one of the most common side effects of cancer treatment and may be elevated even before treatment onset, setting the stage for more severe and persistent symptoms throughout the cancer trajectory. This study examined biobehavioral risk factors for fatigue in breast cancer patients before adjuvant therapy and identified demographic and psychosocial factors associated with fatigue, including childhoodhood adversity.

Keywords

Fatigue; Breast Cancer; Host Factors; Childhood Adversity; Depression; Genetic

BACKGROUND

Fatigue is one of the most common and debilitating side effects of cancer and its treatment.[1, 2] Cancer-related fatigue has adverse emotional, social, occupational, and economic consequences for patients and their caregivers,[3] and may impact treatment adherence and survival.[4] Most studies in this area have focused on fatigue that occurs during and after treatment.[5] However, some patients experience significant fatigue even before treatment onset,[6] which may portend a more difficult treatment course and slower recovery. Indeed, evidence suggests that pre-treatment fatigue is one of the strongest predictors of persistent fatigue up to 5 years after treatment completion.[7–14] To date, there has been minimal examination of factors associated with fatigue at this critical stage of the cancer trajectory. Identifying host factors that contribute to fatigue *before* adjuvant treatment will help to identify vulnerable patients who would benefit from early, targeted intervention and elucidate underlying mechanisms.

Cancer-related fatigue is multifactorial and can be influenced by a variety of demographic, medical, psychosocial, behavioral, and biological factors.[2] An empirically-based biobehavioral model of cancer-related fatigue that identifies key factors associated with fatigue during and after treatment has been proposed.[1] However, it is not known whether this model is relevant for patients before adjuvant therapy. Research on other behavioral symptoms (e.g., insomnia) demonstrates that factors involved with symptom initiation may differ from those involved in symptom persistence.[15] Similarly, there may be unique

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predictors of fatigue experienced early in the cancer trajectory, before onset of adjuvant therapy. The few studies to examine correlates of fatigue before treatment onset have identified demographic and medical factors associated with fatigue, including younger age, children in the home, and higher body mass index.[16] Fatigue is also correlated with other symptoms before treatment onset, including depressed mood and sleep disturbance,[16–18] although it is unclear whether these are a cause or consequence of fatigue. Other host factors that have emerged as predictors of fatigue during and after treatment have rarely been evaluated before treatment onset, including history of depression,[19–22] childhood trauma,[23–26] and genetic risk factors, particularly variants in genes involved in inflammation and immune response (e.g., *IL1, TNFA, IL6*).[27] Importantly, these host factors are present before cancer diagnosis, which clarifies the temporal nature of their association with fatigue.

The multi-dimensional nature of cancer-related fatigue further complicates the identification of risk factors and development of effective interventions. The defining characteristic of cancer-related fatigue is a subjective feeling of tiredness,[28] but it may also include a sense of physical, emotional, and/or cognitive tiredness or exhaustion.[29, 30] However, many studies use unidimensional measures of fatigue that focus primarily on fatigue severity or collapse across dimensions for analyses. This limitation is striking given evidence that different dimensions of fatigue have distinct correlates and show different responses to cancer treatment and to intervention.[31–33]

The goal of the current study was to identify correlates of fatigue among women diagnosed with early-stage breast cancer who had not yet started adjuvant therapy. Drawing from a biobehavioral model of fatigue,[1] we tested key demographic, medical, psychosocial, and biological factors that have been linked with fatigue across the cancer continuum. Among the psychosocial and biological risk factors, we focused on stable host factors rather than more transient factors that could be a consequence of fatigue. We were particularly interested in history of depression, childhood adversity, and cytokine genetic polymorphisms which have been linked with fatigue during and after cancer treatment,[19–27, 34] Our primary analyses focused on general fatigue, which includes feelings of tiredness and is most comparable to unidimensional measures of fatigue used in previous research. Secondary analyses examined whether these risk factors were also associated with other dimensions of fatigue, including physical, mental, and emotional fatigue.

METHODS

Patients and Procedures:

Patients were recruited from oncology practices in Los Angeles to participate in a longitudinal, observational study of cancer-related fatigue (RISE study). Women were eligible if they had been recently diagnosed with Stage 0-IIIA breast cancer and had not yet started adjuvant or neoadjuvant therapy with radiation, chemotherapy, or endocrine therapy. Primary recruitment sites were UCLA and Cedars Sinai Medical Center (CSMC).

Participants completed assessments at baseline, end of treatment (for those who received radiation and/or chemotherapy), and at 6, 12, and 18 month post-treatment follow-ups; we

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focus here on the baseline assessment. The Institutional Review Boards at UCLA and CSMC approved the study, and all participants provided written informed consent.

Measures:

Data were collected through self-report questionnaires, interviews, blood collection, and medical chart review.

Fatigue was assessed with the Multidimensional Fatigue Symptom Inventory-Short Form, which includes four subscales assessing distinct dimensions of fatigue.[35, 36] General fatigue assesses the degree to which respondents felt tired, worn out, sluggish, and fatigued in the past week, and was the primary outcome of interest. Physical fatigue assesses feelings of weakness, heaviness, and achiness in the past week; mental fatigue assesses trouble remembering things and paying attention, difficulty concentrating, and confusion in the past week; and emotional fatigue assesses feeling upset, nervous, sad, depressed, and tense in the past week. Across subscales, higher scores indicate more fatigue.

Demographic characteristics were obtained from self-report at baseline and included age, race/ethnicity, marital status, income, education, employment status, and presence of children at home.

Disease and treatment-related information was obtained from medical record abstraction and included cancer stage, type of surgery received, and time from diagnosis to baseline assessment.

Pre-cancer medical co-morbidities were assessed with a questionnaire version of the Charlson Co-morbidity Scale, a reliable and valid measure that includes a variety of chronic diseases including heart attack, stroke, cardiovascular disease, asthma, diabetes, autoimmune disease, and dementia.[37] Height and weight were measured at baseline for determination of body mass index.

History of childhood maltreatment was assessed with the Childhood Trauma Questionnaire, [38] a 28-item measure that includes questions about physical, emotional, and sexual abuse, as well as physical and emotional neglect that occurred during childhood. Women were categorized into one of three maltreatment groups using a scoring algorithm with established sensitivity and specificity: no maltreatment; physical and/or emotional abuse or neglect but no sexual abuse; and sexual abuse with or without physical and/or emotional abuse or neglect.[39]

History of major depressive disorder (MDD) prior to cancer diagnosis was determined using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID). The SCID was administered by trained interviewers and interviews were reviewed and scored by a consensus panel, led by a psychiatrist with expertise in depression (MI).

Genomic DNA was extracted from peripheral blood leukocytes and assayed by a commercial TaqMan Genotyping Assay (Applied Biosystems, Foster City, CA) performed on a iCycler real-time polymerase chain reaction instrument (BioRad, Hercules, CA) following manufacturer's protocols, as previously described.[40] We focused on SNPs in

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genes encoding pro-inflammatory cytokines that have been linked to cancer-related fatigue, including *IL1B* −511 C>T (rs16944), *IL6* −174 G>C (rs1800795), and *TNF* −308 G>A (rs1800629).[40–42]

Data and Power Analysis:

Bivariate linear regression analyses assessed the relationship between each predictor and each dimension of fatigue, with general fatigue as the primary outcome. Given our interest in identifying predictors of different dimensions of fatigue (rather than characterizing fatigue groups or cases), fatigue was treated as a continuous variable in all analyses. Variables that were associated with an MFSI-SF scale with bivariate $p<0.10$ were included in a multivariable model for that scale. Multivariable linear regression models were fit using multiple imputation (20 imputations generated using chained equations)[43] to handle missing values, and coefficient estimates and standard errors were obtained using Rubin's rules. Multivariable models controlled for time since diagnosis. The percent of variance explained, as measured by R^2, was obtained by averaging the R^2 values from the 20 imputation analyses.[44] Analyses were conducted in Stata version 13.1.

The target sample size was based on the prevalence of key predictor variables and the magnitude of the hypothesized association with fatigue. Power analyses determined that 240–280 patients would be required to detect effect sizes of 0.35–0.45.

RESULTS

Enrollment began in 1/2013 and ended in 7/2015. Over this period, 409 women were screened, 302 of whom met initial eligibility criteria and consented for participation. Thirty-two women were later determined to be ineligible (n=5) or failed to complete the baseline questionnaire (n=27). Thus, the final sample consisted of 270 women.

Characteristics of study participants are shown in Table 1. Women were 56 years old on average and primarily White, college educated, and working full- or part-time. The majority had been diagnosed with Stage I (47%) or Stage II (24%) breast cancer and treated with lumpectomy or mastectomy prior to study enrollment. Note that 10% of study participants had *not* received surgery prior to enrollment, as they were scheduled to undergo neoadjuvant chemotherapy before surgery. The median number of days from diagnosis to study enrollment/baseline assessment was 56; 80% were enrolled within 3 months of diagnosis, though a handful (n=6) were enrolled more than 6 months post-diagnosis, typically because they waited several months before starting adjuvant treatment. Twenty-three percent had a history of major depressive disorder prior to breast cancer diagnosis, which is higher than that reported in breast cancer patients with similar clinical characteristics (17%)[21] but lower than that reported in a community sample of midlife women (32%).[45] Forty percent reported a history of emotional, physical, or sexual maltreatment as children, comparable to demographically similar samples of women.[39]

The average score on the MFSI-SF general fatigue scale was 7.8 and ranged from 0–24. In the validation study for this scale,[29] the average score among women with no cancer history was 5.06, indicating that fatigue was elevated in our sample even before adjuvant therapy

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had begun. Mean scores on each of the MFSI-SF subscales, and correlations among subscales, are reported in Table 2.

Bivariate correlates of fatigue

Bivariate analyses identified a number of significant correlates of fatigue (see Table 3). Primary analyses focusing on general fatigue showed that women of younger age, lower income and/or education, with earlier-stage disease, treated with mastectomy, and who had a history of childhood maltreatment or history of depression reported higher levels of general fatigue (all *p*s < .05). Income and childhood maltreatment were also associated with significantly higher levels of emotional, physical, and mental fatigue (*p*s < .05); individual correlates of different fatigue dimensions are reported in Table 3.

Multivariable models of fatigue

We next fit multivariable linear regression models including variables that were associated at p<0.10 in bivariate analyses. Results are shown in Table 4. For general fatigue, younger age, lower education, lower disease stage, and history of childhood maltreatment emerged as significant predictors (all *p*s < .05). These factors were also associated with other dimensions of fatigue, though childhood maltreatment was the only factor associated with all fatigue dimensions at p< or =0.05. The association between childhood maltreatment and general fatigue is depicted in Figure 1. Other risk factors were associated with specific dimensions of fatigue in the multivariable models. In particular, presence of medical co-morbidities was a significant predictor of physical and mental fatigue, and history of depression was a significant predictor of emotional and mental fatigue. Among the genetic risk factors assessed, only one showed a significant association with fatigue: high-expression variants of the *IL6* SNP were associated with significantly higher levels of physical fatigue. Together, the predictors explained 18–22% of the variance in general, physical, and mental fatigue, but only 13.9% in emotional fatigue.

CONCLUSION

This study applied a biobehavioral model of cancer-related fatigue to identify risk factors for fatigue before commencement of adjuvant therapy in a large sample of women with breast cancer. This point in the cancer trajectory has received minimal empirical attention, despite evidence that pre-treatment fatigue is one of the strongest and most consistent predictors of post-treatment fatigue and may set the stage for elevated fatigue years after treatment.[7, 8] Across general and specific sub-dimensions of fatigue, women of younger age, lower income or education, who had a history of childhood maltreatment reported elevated symptoms, suggesting a vulnerable phenotype. Also notable were those factors that were consistently *not* associated with fatigue, including partner status, race, and body mass index.

Psychosocial factors emerged as key predictors of fatigue in this sample. Women who had experienced abuse or neglect as children (40% of the sample) reported higher levels of all dimensions of fatigue, and those with a history of depression (23%) reported significantly higher levels of emotional and mental fatigue in bivariate analyses. These factors are known to increase risk for physical and behavioral symptoms in other contexts[46, 47] but have only

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recently been examined in relation to cancer-related fatigue.[19–22, 24–26] There are several mechanisms through which these factors may influence fatigue, including alterations in neural, neuroendocrine, immune, and/or behavioral processes.[48–51] In particular, both childhood adversity and depression are associated with elevated inflammation[51–53] which has linked with cancer-related fatigue,[1, 54] suggesting that inflammation may contribute to fatigue even before adjuvant treatment in vulnerable patients. Indeed, one small study found that childhood trauma was associated with elevated fatigue and inflammation before radiation therapy in women with breast cancer.[26] Interestingly, childhood adversity and history of depression showed differential associations with specific dimensions of fatigue in multivariable models. Results from these analyses suggested that history of depression and childhood adversity make unique independent contributions to mental fatigue, but that childhood adversity is more strongly associated with general fatigue and history of depression is more strongly associated with emotional fatigue in this sample. These findings highlight the importance of examining dimensions of fatigue and provide insight into their distinct associations with psychosocial vulnerability factors.

Results also demonstrate the importance of socioeconomic status in the experience of fatigue. Women with lower levels of income or education may be less prepared for the demands of diagnosis, surgery, and adjuvant treatment preparation, or may have fewer financial resources to meet those demands. Further, results highlight age as a significant risk factor for general, emotional, and mental fatigue, with younger women at higher risk. These findings are consistent with previous research[19, 55, 56] and underline the vulnerability of younger women to behavioral side effects of breast cancer.[57]

Although certain risk factors were associated with multiple dimensions of fatigue, results also revealed more specific effects. This was particularly evident for physical fatigue, which had several unique predictors in multivariable models, including receipt of mastectomy and high expression variants of the *IL6* −174 SNP. These findings suggest that medical and genetic risk factors may play a stronger role in physical fatigue, operationalized by the MFSI-SF as feelings of bodily weakness, achiness, and heaviness. Of note, previous studies have demonstrated associations with variants in the *IL6* gene and fatigue before, during, and after cancer treatment.[40, 58, 59] In addition to mastectomy, the one disease-related variable to predict fatigue in multivariate models was cancer stage; women with lower stage disease reported higher levels of general, mental, and physical fatigue. In the post-treatment period, cancer stage is typically not strongly associated with fatigue, depression, and other aspects of quality of life.[60] However, it is possible that stage may be more salient closer to the time of diagnosis, when women are learning about the treatment and survival-related implications of their cancer. Still, our finding that women with lower stage disease reported *more* fatigue is unexpected, as previous studies have typically found that lower cancer stage is associated with lower (rather than higher) fatigue, if any association is reported.[61] This unexpected finding requires examination in future research.

Factors that were not associated with fatigue in this sample also merit discussion. In particular, we found no association between partner status and fatigue, although previous work has suggested that partnered women report lower levels of fatigue, at least in the post-treatment period.[55, 61] It is possible that that the instrumental support provided by a partner

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may become more important during and after treatment as symptoms increase. Further, body mass index (BMI) was not associated with fatigue, though previous studies have shown that BMI is associated with fatigue before[16] and after treatment[62] in women with breast cancer. There was also no association between race/ethnicity and fatigue in this sample, other than elevated physical fatigue among Hispanic women. These findings are consistent with our previous research with breast cancer survivors[55] and with results from several large samples of mixed cancer survivors,[22, 63] although racial differences in fatigue have been observed during cancer treatment.[22]

Several limitations of the study should be noted. Although this study was designed to evaluate fatigue relatively early in the cancer trajectory, participants were assessed after surgical resection of the primary tumor in most cases (i.e., unless they were scheduled to receive neoadjuvant chemotherapy). Surgery can influence fatigue;[64] indeed, we found that treatment with mastectomy was associated with higher levels of physical fatigue. It would be ideal to obtain a pre-surgical measure of fatigue to better capture a true pre-treatment baseline, although there are challenges with recruitment and assessment during the interval between diagnosis and surgery. In addition, our ability to identify socioeconomic correlates of fatigue may have been limited by characteristics of the sample, which was predominantly White and well-educated, although we did find evidence of elevated fatigue among those of lower income and/or education as well as higher levels of physical fatigue among Hispanic women. Further, the majority of women had early-stage (Stage I or II) breast cancer, which limits the generalizability of the results.

There is growing evidence of substantial individual variability in the experience of fatigue during and after treatment, which may be present even before treatment onset. Indeed, a recent study of women with early-stage breast cancer assessed before surgery and at 4 and 8 month follow-ups identified two groups of patients with distinct fatigue trajectories: one with low fatigue before surgery that remained low and stable throughout the assessment period, and one with high fatigue before surgery that increased during treatment then declined by 8 months (though never to pre-surgery levels).[65] This suggests that much of the variance in cancer-related fatigue may be driven by factors that predate the cancer experience. The current study identified several of these factors, though note that the combination of medical, demographic, disease, and psychosocial risk factors included here explained roughly 20% of the variance in pre-treatment fatigue. It will be important to determine whether these factors are also associated with increased fatigue in the immediate aftermath of adjuvant treatment and in the subsequent months and years, or if different processes play a more important role at later stages of survivorship. Our findings also offer insight into different dimensions of fatigue and reveal common and unique predictors of these dimensions. From a clinical perspective, several of these risk factors may not be “on the radar” of treating physicians, including childhood maltreatment, but may aid in the identification of vulnerable patients and delivery of early interventions to those most in need.

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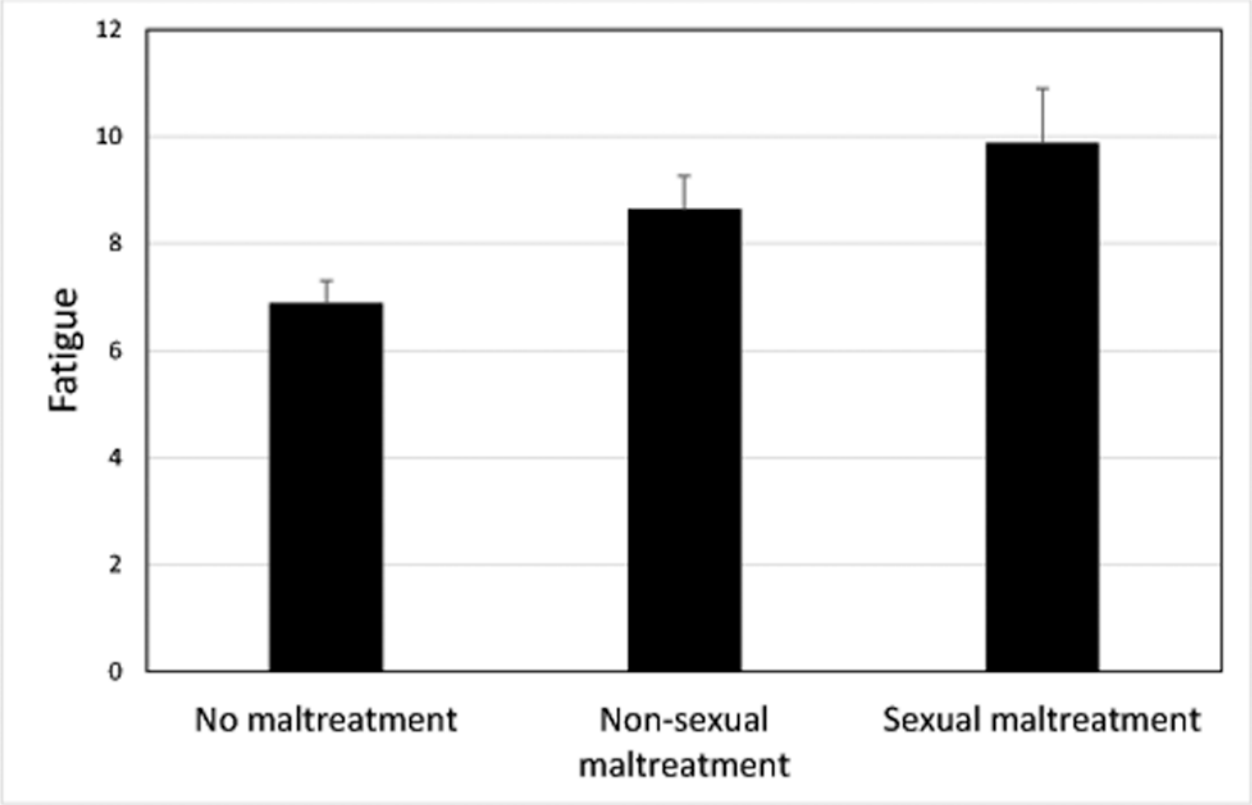

Figure 1.

Adjusted mean scores on the MFSI-SF general fatigue subscale for women at each category of childhood maltreatment. Women who had experienced non-sexual maltreatment (physical and/or emotional abuse or neglect) or who had experienced sexual maltreatment (with or without physical and/or emotional abuse or neglect) in childhood reported significantly higher levels of fatigue than women with no history of maltreatment.

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Table 1.

Summary of participant characteristics at baseline (N = 270)

	Mean (SD), min-max or N (%)
Demographic characteristics	
Age, years	56 (11), 26.8-88.5
Race	
White, non-Hispanic	193 (71)
Black	12 (4)
Hispanic	27 (10)
Asian	30 (11)
Other	8 (3)
Income (missing n = 4)	
Less than $60,000	67 (25)
$60,000 to $100,000	53 (20)
$100,000 or more	146 (55)
Educational attainment	
Less than college degree	78 (29)
College graduate	108 (40)
Post-graduate degree	84 (31)
Employed (full or part-time)	161 (60)
Married or living as married	174 (64)
Any children living at home	110 (41)
Disease and treatment-related variables	
Cancer stage at diagnosis	
0	32 (12)
1	128 (47)
2	64 (24)
3	10 (4)
Indeterminable (neoadjuvant or missing pathological information)	36 (13)
Surgery	
No surgery (neoadjuvant)	25 (10)
Lumpectomy	159 (59)
Mastectomy	86 (32)
Months since diagnosis	2.2 (1.3), 0.4-9.5
Biobehavioral risk factors	
BMI, kg/m^2	25.4 (5.8), 14.9-45.6
Charlson comorbidity index	
0	206 (76)
1	49 (18)
2 or 3	15 (6)
Childhood maltreatment	
No maltreatment	163 (60)

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	Mean (SD), min-max or N (%)
Non-sexual maltreatment (physical/emotional abuse or neglect)	75 (28)
Sexual maltreatment	32 (12)
Past history of depression (missing n = 8)	
No	202 (77)
Yes	60 (23)
TNF-308 (missing n = 33)	
GG	181 (76)
GA	49 (21)
AA	7 (3)
IL6-174 (missing n = 33)	
GG	117 (49)
GC	94 (40)
CC	26 (11)
IL1B-511 (missing n = 33)	
GG	38 (16)
AG	112 (47)
AA	87 (37)

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Table 2.

Means and correlations among MFSI scales (n=270)

	Mean (SD)	General	Emotional	Physical	Mental
General	7.72 (5.79)				
Emotional	6.68 (5.30)	0.50			
Physical	3.86 (4.40)	0.66	0.34		
Mental	4.65 (4.17)	0.63	0.56	0.47	
Cronbach's alpha		0.95	0.91	0.87	0.89

All correlations are significantly different from 0 with $p<0.0001$.

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Table 3.

Bivariate linear regression results for four MFSI-SF scales

	Primary:		Secondary:					
	General		Emotional		Physical		Mental	
	Coef	P	Coef	P	Coef	P	Coef	P
Demographic characteristics								
Age, 10-year increase	−0.63	.042	−0.80	.004	−0.04	.861	−0.39	.075
Race (intercept: non-Hispanic white)	7.99		6.76		3.66		4.65	
Black	−2.49	.151	−1.68	.286	−1.74	.182	−1.15	.356
Hispanic	−0.14	.910	1.35	.215	2.01	.026	0.64	.456
Asian	−0.95	.403	−0.49	.633	0.58	.503	−0.05	.949
Other	−1.11	.596	−2.89	.131	0.59	.708	−0.40	.790
Income (intercept: Less than $60,000)	8.86		8.30		5.43		5.43	
$60,000 to $100,000	−1.01	.340	−2.02	.037	−1.83	.021	−0.17	.825
$100,000 or more	−1.80	.035	−2.29	.003	−2.27	<.001	−1.40	.023
Education (intercept: college or less)	8.21		7.17		4.20		4.83	
Post-graduate	−1.57	.039	−1.56	.025	−1.10	.058	−0.60	.279
Education (intercept: college or less)	8.21		7.17		4.20		4.83	
Employed	0.44	.541	−0.20	.766	−0.63	.249	−0.11	.827
Partnered status (intercept: not)	7.00		6.45		4.07		4.55	
Partnered	1.13	.125	0.36	.591	−0.33	.561	0.15	.779
Children at home (intercept: absent)	7.38		6.51		3.60		4.54	
Present	0.85	.238	0.43	.513	0.65	.237	0.27	.600
Cancer and treatment-related variables								
Stage at diagnosis (intercept: 0 or 1)	8.67		6.96		4.58		5.29	
Stage 2 or 3	−2.21	.003	−0.59	.388	−1.77	.002	−1.72	.001
Surgery (intercept: none or lumpectomy)	6.99		6.50		3.19		4.40	
Mastectomy	2.32	.002	0.57	.411	2.11	<.001	0.77	.157
Biobehavioral risk factors								
BMI, 1-unit increase	0.04	.531	−0.05	.409	0.06	.169	−0.01	.939
Charlson comorbidity index, 1-point increase	0.92	.105	0.78	.136	1.18	.006	0.73	.076
Childhood maltreatment (intercept: none)	6.60		5.86		3.18		3.60	
Nonsexual maltreatment	2.42	.002	1.97	.007	1.50	.014	2.27	<.001
Sexual maltreatment	3.81	.002	2.33	.022	2.22	.008	3.52	<.001
History of major depression (intercept: no)	7.18		6.10		3.77		4.19	
Yes	2.56	.003	2.63	.001	0.67	.309	2.27	<.001
TNF, per high expression allele	−1.17	.122	0.13	.851	−0.88	.125	−0.65	.237
IL6, per high expression allele	0.41	.473	0.19	.716	0.71	.099	−0.09	.835
IL1B, per high expression allele	0.10	.862	−0.02	.962	0.29	.489	0.56	.160

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Table 4.

Multivariable linear regression model results for four MFSI-SF scales

	Primary:		Secondary:					
	General		Emotional		Physical		Mental	
Percent of variance explained (R^2)	18.4%		13.9%		22.8%		20.3%	
	Coef	P	Coef	P	Coef	P	Coef	P
Age, 10-year increase	−0.71	.016	−0.87	.001			−0.58	.005
Race (ref: white)								
Black					−2.44	.052		
Hispanic					0.38	.645		
Asian					0.43	.772		
Other					1.00	.238		
Income (ref: Less than $60,000)								
$60,000 to $100,000	−0.41	.684	−1.74	.061	−1.13	.138	0.39	.582
$100,000 or more	−0.88	.298	−1.65	.034	−1.47	.027	−0.74	.205
Education (ref: college or less)								
Post-graduate	−1.97	.009	−1.56	.025	−0.93	.097		
Stage at diagnosis of 2 or 3 (ref: 0 or 1)	−1.55	.028			−1.39	.010	−1.32	.009
Mastectomy (ref: no surgery or lumpectomy)	1.16	.145			1.37	.020		
Charlson, 1-point increase					0.92	.025	0.83	.035
Childhood maltreatment (ref: none)								
Nonsexual	1.76	.023	1.39	.051	1.01	.079	1.73	.002
Sexual	3.00	.009	1.72	.103	1.63	.050	2.21	.005
History of major depression (ref: no)	1.53	.063	2.22	.004			1.51	.010
IL6, per high expression allele					0.86	.036		

Results were obtained using multiple imputation (30 imputations) due to missing values. All models control for time since diagnosis.