Original Article

Objective Physical and Mental Markers of Self-Reported Fatigue in Women Undergoing (Neo)Adjuvant Chemotherapy for Early-Stage Breast Cancer

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BACKGROUND: Objective, treatment-independent markers of cancer-related fatigue are needed to advance clinical trials. In the current study, the authors evaluated physical, neurocognitive, and serologic markers for correlation with self-reported fatigue before and after (neo)adjuvant chemotherapy for patients with early-stage breast cancer. **METHODS:** Women with AJCC TNM Stage I-III breast cancer consented to assessment before and after the completion of 4 cycles of dose-dense doxorubicin and cyclophosphamide. Assessment included self-reported fatigue (using the Brief Fatigue Inventory), depression (using the Center for Epidemiologic Studies–Depression Scale [CES-D]), Pittsburgh Sleep Quality Index, and 28 objective measures (grip strength in dominant and nondominant hands, 6-minute walk, daily total energy expenditure, 14 neurocognitive tests, and 10 serologic markers). Generalized linear regression models of fatigue were constructed (1 model per marker), and adjusted for depression, timing before/after chemotherapy, menopausal status, obesity, and educational level. P values were adjusted to control the False Discovery Rate. **RESULTS:** Of 28 subjects, 3 withdrew without completing baseline assessments. Prechemotherapy and postchemotherapy data were available for the evaluation of physical measures (25 subjects aged 50.6 ± 9.5 years), neurocognitive tests (22 subjects), and serologic markers (10 subjects). On covariate-adjusted analysis, interleukin (IL)-12 was found to be associated with fatigue at both assessments ($P<.01$). Serum eotaxin ($P<.01$), IL-1RA ($P<.01$), monocyte chemoattractant protein 1 (MCP-1) ($P<.01$), and performance on 2 neurocognitive (Trail Making) tests ($P<.01$ and $P=.02$, respectively) were found to be inversely associated with fatigue before chemotherapy but not afterward, whereas daily energy expenditure, serum MCP-1, and serum macrophage inflammatory protein 1a (MIP-1a) were found to be associated with fatigue after receipt of chemotherapy but not before ($P<.01$ for each). The association between energy expenditure and fatigue was detectable only if an actively athletic subject with outlier values of energy expenditure was excluded. **CONCLUSIONS:** Serum IL-12 merits confirmatory testing as an objective, treatment-independent measure of fatigue in patients with early-stage breast cancer. *Cancer* 2017;123:1810-6. © 2017 The Authors. *Cancer* published by Wiley Periodicals, Inc. on behalf of *American Cancer Society*. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

KEYWORDS: breast cancer, cancer-related fatigue, chemotherapy, physical function.

INTRODUCTION

Fatigue is consistently one of the most common symptoms reported by patients undergoing cancer treatment. It may develop early in the course of therapy, and may persist for months afterward.[1,2] By definition, "cancer-related fatigue (CRF) is 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."[3] In patients with cancer, several factors contribute to CRF, including the underlying disease, comorbid symptoms, and medical conditions, as well as treatment with chemotherapy and radiotherapy. Fatigue is seldom an isolated symptom, but generally is a component of a symptom complex that may include depression, anxiety, and sleep disorders.[4] The ability to study and conduct interventional trials to decrease CRF has been compromised by the complexity of the problem as well as the lack of an objective measurement of what is primarily a subjective symptom.[5]

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TABLE 1. Study Design

Assessments	Baseline	7 Days After Cycle 4 of AC
Quality of life	X	X
Brief Fatigue Inventory		
CES-D		
Pittsburgh Sleep Quality Index		
Physical measures	X	X
BMI		
Grip strength (both hands)		
6-min walk		
Total energy expenditure		
Neurocognitive testing	X	X
Grooved pegboard (both hands)		
Digit symbol coding and symbol search		
Conners' Continuous Performance Test II		
Trail Making Test parts A and B		
4 color-word interference tests		
4 verbal fluency tests		

Abbreviations: AC, dose-dense doxorubicin and cyclophosphamide; BMI, body mass index; CES-D, Center for Epidemiologic Studies–Depression Scale.

Tools such as the 6-minute walk, accelerometers, and hand grip have been used by pulmonologists and geriatricians to provide objective information that may distinguish functional age from chronologic age.[6-8] Neurocognitive tests also may provide an objective assessment of psychomotor processing time, reaction time, and executive functioning.[9,10] Women undergoing (neo) adjuvant chemotherapy for early-stage breast cancer often report fatigue, and that symptom may have both physical and cognitive components.[11]

In the current study, we undertook a clinical trial to assess and identify objective measurements of physical and cognitive fatigue. A battery of validated measures were performed before and after 4 cycles of (neo) adjuvant chemotherapy and compared with patient-reported fatigue as assessed by the Brief Fatigue Inventory (BFI). Approximately one-half of the participants had blood obtained for the assessment of cytokines. The results of that clinical trial are reported herein.

MATERIALS AND METHODS

Patients from the outpatient medical oncology clinics at the City of Hope Comprehensive Cancer Center in Duarte, California were recruited to participate in a clinical trial regarding CRF in patients with breast cancer. Women with newly diagnosed, AJCC TNM Stage I-III invasive ductal breast cancer were eligible if they had an Eastern Cooperative Oncology Group performance status of 0 to 2, were aged > 18 years, were not being treated

with daily nonsteroidal anti-inflammatory drugs, and were to receive the chemotherapy regimen of dose-dense doxorubicin and cyclophosphamide (AC). The study was approved by the Institutional Review Board of the City of Hope Comprehensive Cancer Center. Each participant provided an informed consent form before participation in the current study.

The study design is summarized in Table 1. The repeated assessments included 3 self-reported (fatigue [Brief Fatigue Inventory (BFI)], depression [Center for Epidemiologic Studies–Depression Scale (CES-D)], and Pittsburgh Sleep Quality Index [PSQI]) and 28 objective measures (4 physical markers [grip strength in dominant and nondominant hands, a 6-minute walk test, and daily total energy expenditure (averaged over 1 week)], 14 examiner-administered neurocognitive tests [grooved pegboard in dominant and nondominant hands, digit symbol coding and symbol search (Wechsler Adult Intelligence Scale [WAIS] -4th edition), 2 Trail Making tests (parts A and B), and 4 color-word interference and 4 verbal fluency tests (Delis-Kaplan Executive Function System [D-KEFS])], and 10 serologic markers [eotaxin, granulocyte colony-stimulating factor, hepatocyte growth factor, interleukin (IL)-12, IL-1RA, interferon-inducible protein 10, monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein (MIP)-1a, MIP-1b, and RANTES]).

The tools used to assess both physical and cognitive function, in addition to the patient's quality of life, are summarized below.

Quality of Life Measures
Brief Fatigue Inventory

The BFI is a 9-item questionnaire that addresses the impact of fatigue on daily function. The items are scored on a numeric rating scale from 0 to 10, with 0 indicating no fatigue or does not interfere with activity/work and 10 indicating bad fatigue or completely interferes with activity/work. The tool was developed specifically for the assessment of fatigue in patients with cancer.[12]

Pittsburgh Sleep Quality Index

The PSQI is a 19-item index that measures subjective sleep quality grouped into 7 component scores: sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. A global PSQI score also can be scored. The PSQI has demonstrated internal consistency, with an overall reliability coefficient of 0.83. The index

can be completed in <5minutes, and numerous studies have supported its high validity and reliability.[13]

Center for Epidemiologic Studies–Depression Scale

The CES-D is a 20-item, self-report scale that was originally developed to measure depressive symptoms in the general population and has been used to screen for depression in samples of medically ill individuals. Responses are rated on a 4-point scale, and the total score ranges from 0 to 60. Scores of ≥ 16 are indicators of clinical depression.[14]

Physical Assessments
Body Mass Index

The patients' body mass index was determined as weight in kg/height in m^2.

Activity Monitor BodyBugg

The BodyBugg (BodyMedia, Pittsburgh, Pennsylvania) is a monitor worn on the back of the upper right arm (the tricep) against the skin and underneath clothing. The monitor measures the wearer's caloric expenditure through information gathered by 4 sensors: a galvanic skin response sensor, heat flux sensor, thermistor-based sensor, and 3-dimensional accelerometer.[15] Women were asked to wear the BodyBugg all day in conjunction with recording daily activity logs for 7 pretreatment days (within a 2-week window before the initiation of chemotherapy with AC) and for 7 posttreatment days (within days 8-14 after cycle 4 of AC chemotherapy). The total energy expenditure was recorded as the average over 1 week. The validation of this testing has been reported elsewhere.[16]

Six-minute walk

Patients were instructed to wear comfortable shoes and were asked to walk as quickly as possible for 6 minutes. This test occurred in a marked (premeasured) hallway within the breast clinic. The distance walked during those 6 minutes was calculated.

Hand grip

Grip strength was recorded using a hand grip dynamometer in both the dominant and nondominant hand. Patients were instructed to squeeze the device as hard as they could. Each hand was tested 3 times, and the highest score was recorded in kilograms.[8]

Neurocognitive Testing

Each participant was tested by a single trained individual (S.W.). The total time for completion for the neurocognitive battery was approximately 40 minutes. Tests were completed in the following order.

Conners' Continuous Performance Test II (Version 5)

The Conners' Continuous Performance Test II (Conners' CPT II; version 5) is a neuropsychological task that has repeatedly been shown to differentiate individuals with attention deficit from normal groups. The standard protocol of the Conners' CPT II computerized test uses a short practice exercise before administration of the full test to ensure that the respondent fully understands the task before proceeding. After the practice exercise, a new administration of the Conners' CPT is initiated that is 14 minutes long. Conners' CPT II respondents are required to press the space bar or click the mouse whenever any letter except the letter "X" appears on the computer screen.

Several variables may be derived from the Conners' CPT II, including errors of omission and commission, mean hit reaction time, standard error of the mean hit reaction time, d', and beta. Overall performance on the 2 signal detection measures, d' and beta, as well as increased variability in reaction time over time, are reported to have the strongest relationship to attention symptoms. The program is commonly used as a screening tool to identify potential attention problems, and as an aid in monitoring treatment effectiveness. The Conners' CPT II has been used in prior research to determine whether there has been improvement or deterioration with changes in medication.

WAIS Digit Symbol Coding

WAIS Digit Symbol Coding is a symbol substitution task which requires the subject to copy symbols that are paired with numbers for 2 minutes. This test is a psychomotor performance test, requiring motor persistence, sustained attention, processing speed, and visuomotor coordination. The average test-retest reliability coefficient is 0.84, with an average alpha of .81. This test is one of the several cognitive subsets comprising the 4th edition of the WAIS. The standardization sample consists of 2450 individuals stratified for sex, race, and geographic region consistent with the percentages of those variables in the most recent US census.[9]

Trail Making Test Parts A and B

The Trail Making Test part A is a timed paper-and-pencil task requiring the patient to connect encircled numbers randomly arranged on a page as quickly as possible without errors. It requires both attention skills and

TABLE 2. Characteristics of 25 Subjects Prior to (Neo)adjuvant Chemotherapy

Characteristic	No. (%)
AJCC TNM Stage of disease	
IA	3 (12)
IIA-IIB	11 (44)
IIIA-IIIC	11 (44)
Chemotherapy to be initiated	
Adjuvant	13 (52)
Neoadjuvant	12 (48)
Menopausal status	
Premenopausal	9 (36)
Perimenopausal	2 (8)
Postmenopausal	14 (56)
College education	
Yes	9 (36)
No	11 (44)
Unknown	5 (20)
Characteristic	Median (Range)
Body mass index	31.0 (19.0-39.6)
Fatigue (BFI)	1.1 (0-6.7)
Depression (CES-D)	12 (1-42)
Sleep quality (PSQI)	6 (1-19)

Abbreviations: BFI, Brief Fatigue Inventory; CES-D, Center for Epidemiologic Studies–Depression Scale; PSQI, Pittsburgh Sleep Quality Index.

TABLE 3. Fatigue Index Among 25 Patients With Breast Cancer: Multivariable Associations With Covariates

	Fatigue Index (SE)	Unadjusted P
Intercept (mean fatigue level at the prechemotherapy visit in a patient with median depression [CES-D score of 12] and without obesity, college education, or perimenopausal status)	1.27 (0.26)	<.0001
Per point on depression scale (CES-D)	+0.17 (0.02)	<.0001
Timing of visit by perimenopausal status		.001[a]
Prechemotherapy, not perimenopausal	0	
Prechemotherapy, perimenopausal	-0.05 (0.45)	
Postchemotherapy, not perimenopausal	+1.47 (0.40)	
Postchemotherapy, perimenopausal	+3.92 (0.76)	
Obesity and educational level		<.0001[a]
Obese without college education[b]	+1.55 (0.34)	
Obese with college education	-0.73 (0.50)	
Nonobese without college education[b]	0	
Nonobese with college education	+0.18 (0.20)	

Abbreviations: CES-D, Center for Epidemiologic Studies–Depression Scale; SE, standard error.
[a] P value shown refers to the interaction between the 2 variables.
[b] Subjects whose educational history was unknown were grouped with the non-college-educated subjects.

information processing speed. Part B is a more challenging timed task, requiring the patient to sequentially alternate between 2 mental sets (letters and numbers). It requires set shifting, processing speed, working memory, and cognitive flexibility. On average, Part A has a test-retest reliability coefficient of 0.79 and Part B has a test-retest reliability coefficient of 0.89.[17]

Grooved Pegboard
The grooved pegboard is a widely used test with which to assess fine motor coordination and dexterity. It consists of a small board containing a set of slotted holes angled in different directions. Each peg has a ridge along one side, requiring it to be rotated into position for correct insertion. The score is time to completion. Test-retest reliability has been found to be substantial (reliability coefficient of ≥ 0.82) with no consistent practice effects.[18]

The Delis-Kaplan Executive Function System (D-KEFS)
The D-KEFS is a neurocognitive battery, consisting of several tests and sub-tests which measure a wide spectrum of verbal and nonverbal executive functions. Each test is designed to be a stand-alone instrument that can be administered individually or along with other D-KEFS tests. The D-KEFS was standardized on a stratified sample of 1,750 individuals of varying age ranges. Two D-KEFS subtests are recommended as part of the neurocognitive battery: the Color-Word Interference Test and the Verbal

Fluency Test. The Color-Word Interference Test, a test assessing inhibition, was used herein. For each section, test-retest reliability coefficients were 0.90, 0.83, and 0.91, respectively. (time: 5 minutes), The Verbal Fluency Test assesses fluent productivity in the verbal domain and evaluates the spontaneous production of words under restricted search conditions. The test-retest reliability coefficient in the current study was on average 0.70, with an α of .83.[10]

Statistical Analysis
The primary endpoint, fatigue index, and the candidate objective markers were analyzed as continuous variables. Scores on neurocognitive tests were expressed as z scores; all other measures were log-transformed as necessary to optimize the model's fit to the observed data. To take into account the repeated assessment of subjects, generalized

TABLE 4. Fatigue Index Among 25 Patients With Breast Cancer: Associations With Individual Biomarkers, Adjusted for Covariates[a]

	Before Chemotherapy Median (5th, 95th Percentile)	Association (SE)	P[b]	After Chemotherapy Median (5th, 95th Percentile)	Association (SE)	P[b]
Physical markers (N=25)						
Average daily TEE, per 100 kcal						
All subjects	2048 (1523, 2601)	-0.03 (0.04)	.60	1869 (1627, 2264)	+0.05 (0.16)	.90
All subjects except the athlete[c]	2034 (1523, 2283)	−0.02 (0.08)	.90	1864 (1627, 2091)	**+0.38 (0.10)**	**.003**
Grip strength, per kg						
Dominant hand	25 (10, 36)	0 (0.03)	.99	22 (10, 34)	+0.06 (0.03)	.16
Nondominant hand	24 (11, 33)	+0.03 (0.02)	.51	22 (10, 35)	+0.03 (0.02)	.51
6-min walk, per 100 meters	414 (312, 464)	0 (0)	.92	386 (264, 460)	0 (0)	.92
Neurocognitive markers (N=22)						
Grooved pegboard						
Dominant hand	0.34 (-1.18, 1.50)	−0.28 (0.14)	.16	0.39 (-0.84, 1.44)	−0.28 (0.14)	.16
Nondominant hand[d]	0.31 (-1.20, 2.14)	−0.02 (0.12)	.92	0.21 (-0.96, 1.44)	−0.02 (0.12)	.92
Trail Making Test 2	0.67 (-1.33, 1.33)	**-0.69 (0.22)**	**.008**	0.33 (-1.00, 1.33)	+0.35 (0.39)	.60
Trail Making Test 4	0 (-1.00, 1.00)	**-0.76 (0.22)**	**.005**	0.33 (-1.00, 1.33)	−0.08 (0.32)	.90
Digit Symbol	0.33 (-2.00, 1.67)	−0.03 (0.12)	.90	0.50 (-1.67, 2.00)	−0.03 (0.12)	.90
Symbol Search	0.67 (-1.00, 2.00)	−0.29 (0.17)	.23	0.67 (-0.33, 2.00)	−0.29 (0.17)	.23
Color Patch	0.50 (0, 1.33)	−0.35 (0.37)	.56	0.67 (-0.33, 1.33)	−0.35 (0.37)	.56
Color Word	0.67 (0, 1.33)	−0.25 (0.31)	.62	0.67 (-0.33, 1.33)	−0.25 (0.31)	.62
Color Inhibition	0.33 (-0.33, 1.33)	−0.24 (0.15)	.27	0.17 (-0.67, 1.33)	−0.24 (0.15)	.27
Inhibition Switch	0.17 (-1.33, 1.33)	−0.17 (0.15)	.51	0.50 (-1.33, 1.33)	−0.17 (0.15)	.51
Letter Fluency	0 (-0.67, 1.33)	+0.10 (0.28)	.89	0.33 (-0.67, 1.00)	−0.57 (0.30)	.18
Category Fluency	0.67 (-0.67, 1.67)	−0.06 (0.16)	.87	0.33 (-1.33, 1.33)	−0.06 (0.16)	.87
Switch Correlation	0.67 (-1.33, 2.33)	−0.25 (0.12)	.15	0.33 (-0.67, 1.67)	−0.25 (0.12)	.15
Switch Accuracy	0.67 (-0.67, 2.00)	−0.19 (0.16)	.51	0.67 (-1.00, 1.33)	−0.19 (0.16)	.51
Serologic markers (N=10)	Median (range), pg/mL			Median (range), pg/mL		
Eotaxin, per 10 pg/mL	82 (22, 159)	**-0.23 (0.07)**	**.008**	64 (26, 156)	+0.19 (0.08)	.06
G-CSF, per 100 pg/mL	96 (49, 149)	+0.46 (0.82)	.80	127 (71, 173)	+0.46 (0.82)	.80
HGF, per 100 pg/mL	483 (259, 2940)	−0.02 (0.05)	.87	562 (368, 1358)	−0.02 (0.05)	.87
IL-12, per 100 pg/mL	257 (199, 398)	**+1.00 (0.26)**	**.002**	199 (176, 404)	**+1.00 (0.26)**	**.002**
IL-1RA, per 100 pg/mL	324 (154, 479)	**-0.90 (0.28)**	**.008**	300 (132, 538)	+0.17 (0.23)	.68
IP-10, per 10 pg/mL	52 (36, 98)	+0.29 (0.17)	.22	47 (25, 72)	+0.29 (0.17)	.22
MCP-1, per 100 pg/mL	412 (246, 1579)	**-0.19 (0.06)**	**.02**	261 (129, 1493)	**+0.20 (0.06)**	**.007**
MIP-1a, per 10 pg/mL	42 (27, 50)	+0.01 (0.66)	.99	36 (26, 49)	**+1.86 (0.43)**	**.002**
MIP-1b, per 10 pg/mL	76 (52, 209)	−0.18 (0.07)	.07	63 (36, 141)	+0.20 (0.13)	.30
RANTES, per 1000 pg/mL	8534 (2382, 10845)	+0.08 (0.08)	.56	8570 (6306, 14049)	+0.08 (0.08)	.56

Abbreviations: G-CSF, granulocyte colony-stimulating factor; HGF, hepatocyte growth factor; IL, interleukin; IP-10, interferon-inducible protein 10; MCP-1, monocyte chemoattractant protein 1; MIP, macrophage inflammatory protein; SE, standard error; TEE, total energy expenditure.

[a] Covariates taken into account in each model were depression; menopausal status (perimenopausal vs premenopausal or postmenopausal), timing of assessment, and their interaction; and obesity, education (college vs less or unknown), and their interaction.

[b] P values were adjusted to control the False Discovery Rate. Values significant at False Discovery Rate-adjusted P<.05 are shown in bold type.

[c] One subject was a 36-year-old athlete who continued to train vigorously throughout the study and had outlier values for TEE both before and after chemotherapy.

[d] Before chemotherapy, a single subject exceeded the time limit for this neurocognitive test; her missing score was replaced with the lowest score possible (z score of -3.00).

linear regression models of fatigue (1 model per objective marker) were constructed using generalized estimating equations with an independent correlation matrix. All models were adjusted for the following covariates: depression score centered on the mean of all values; menopausal status, timing of assessment (prechemotherapy or postchemotherapy), and their interaction; and obesity, college education, and their interaction. Due to the large number of hypotheses (28 objective markers, each before and after chemotherapy), the False Discovery Rate was controlled using the linear step-up method of Benjamini and Hochberg.[19]

RESULTS

Of the 28 enrolled subjects, 3 were nonevaluable because they withdrew before the first week of the study. The baseline characteristics of the remaining subjects (age 50.3 ± 9.5 years) are summarized in Table 2. The median CES-D score was slightly elevated at 12 (range, 1-42), and the median PSQI of 6 is indicative of poor sleep quality.[13]

Preparatory to evaluating candidate markers for fatigue, a model of BFI was constructed to identify the covariates needing to be controlled in the main analysis. As shown in Table 3, the following covariates were identified:

depression (CES-D), status pre- or post-chemotherapy, menopausal status, obesity, and college education.

According to covariate-adjusted analysis (Table 4), serum eotaxin ($P < .01$), IL-1RA ($P < .01$), MCP-1 ($P < .01$), and performance on 2 neurocognitive (Trail Making) tests ($P < .01$ and $P = .02$, respectively) were found to be inversely associated with fatigue before chemotherapy but not afterward. Daily energy expenditure, serum MCP-1, and serum MIP-1a were found to be significantly associated with fatigue after chemotherapy but not before. The association between energy expenditure and fatigue was detectable only if the athletic subject with outlier values of energy expenditure was excluded. IL-12 was the only marker that correlated significantly with fatigue both before and after chemotherapy.

DISCUSSION

A scientific research committee within the National Comprehensive Cancer Network concluded that progress in the study of CRF is compromised by the lack of clinical measures and the consistent use of self-report questionnaires; the results of which may vary throughout the day.[5] We undertook the current prospective pilot study to identify an objective marker of self-reported CRF. Participants were tested 7 to 10 days before the initiation of chemotherapy and 7 to 10 days after the fourth cycle of chemotherapy, a time that would reflect their hematologic and functional nadir. All subjects had recently been diagnosed with breast cancer, and the impact of their diagnosis may have contributed to the relatively high CES-D scores and poor sleep quality at baseline.

Many of the assessments we performed correlated with self-reported fatigue using the BFI. It is interesting to note that none of the physical measurements (energy expenditure, hand grip, 6-minute walk) were found to be consistently associated with fatigue before and after chemotherapy. This finding raises the possibility that, at least in patients with early-stage breast cancer, CRF does not resemble common fatigue. Also worthy of comment is the lack of a consistent association between fatigue and neurocognitive tests.

Only the cytokine IL-12 correlated with fatigue both before and after chemotherapy. Changes in inflammatory markers have been reported in conjunction with CRF before, during, and after treatment.[20] The contribution of immune signaling to CRF is intriguing and complex. Several factors contribute to increases in cytokines, including treatment, obesity, and depression. In the current study, obesity was found to be associated with fatigue, except in college-educated individuals. To our

knowledge, it is unclear whether cytokine changes are a marker of other biologic processes, or contribute to the symptom of fatigue. It is of interest that we observed the greatest increase in fatigue among those participants who were perimenopausal at the time of diagnosis. Although the majority of breast cancer is diagnosed among postmenopausal women, younger women who undergo chemotherapy are at risk of experiencing premature menopause and its associated endocrine changes, which contribute to fatigue. The impact of endocrine changes on fatigue could not be assessed in this small sample.

Much of the data concerning CRF in breast cancer survivorship is derived from population-based, rather than prospective studies. A strength of the current study is that all patients were enrolled and tested prospectively. Because CRF is influenced by several factors, such as type of treatment, depression, sleep problems, hypothalamic-pituitary-adrenal function, neurotransmitters, and skeletal muscle and fitness, as well as psychological factors, well-designed prospective clinical trials should control for as many of these risk factors as possible.[4,20-23]

The current study was limited by the small number of participants (especially in the analysis of serologic markers) and the many factors that contribute to CRF. In addition, only the BFI was used to determine the patients' report of fatigue. Nonetheless, the assessment of IL-12 warrants further investigation in other populations of patients undergoing different treatment modalities and different chemotherapy regimens.

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CONFLICT OF INTEREST DISCLOSURES

Joanne E. Mortimer has acted as a paid consultant for Puma Pharmaceuticals for work performed outside of the current study. Arti Hurria has received research funding from Celgene (prior Abraxis BioScience), Novartis, and GlaxoSmithKline and has acted as a paid consultant for Boehringer Ingelheim Pharmaceuticals, Carevive Systems Inc, Sanofi, and GTx for work performed outside of the current study. Brian Tiep is an inventor of oxygen delivery devices and consults for some of those companies and reports no conflict of interest. He also acts as a paid consultant for CHAD Therapeutics Inc, Drive Medical, and Nonin Medical Inc for work performed outside of the current study.

AUTHOR CONTRIBUTIONS

Joanne E. Mortimer: Study design, study conduct, data analysis, and article preparation. **Sarah Waliany**: Conduct of neurocognitive testing, data collection, and article preparation. **Christina M. Dieli-Conwright**: Study conduct and article preparation. **Sunita K. Patel**: Study conduct and article preparation. **Arti Hurria**: Study enrollment and article preparation. **Joseph Chao**: Study enrollment and article preparation. **Brian Tiep**: Study design and article preparation. **Carolyn E. Behrendt**: Study design, data analysis, and article preparation.

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