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# Use of a Case Definition Approach to Identify Cancer-Related Fatigue in Women Undergoing Adjuvant Therapy for Breast Cancer

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## Abstract

**Purpose—**Use a proposed case-definition approach to identify the prevalence of cancer-related fatigue (CRF), demographic, clinical and psychosocial predictors of subsequent CRF, and psychosocial factors associated with concurrent CRF.

**Patients and Methods—**Women (n = 288) undergoing adjuvant therapy for early-stage breast cancer were recruited from two outpatient clinics. Women completed a baseline assessment before adjuvant therapy and a post-treatment assessment at the conclusion of an initial course of adjuvant chemotherapy or radiotherapy. At both assessments, women completed a clinical interview and measures of fatigue, distress, coping, and quality of life (QOL). The clinical interview consisted of modules from the *Diagnostic and Statistical Manual of Mental Disorders Fourth Edition* (DSM-IV) and a diagnostic interview to identify cases of CRF.

**Results—**CRF prevalence at the baseline and post-treatment assessments was 10% and 26%, respectively. Multivariate analyses identified factors prospectively associated with greater risk for CRF at the post-treatment assessment, including receipt of adjuvant chemotherapy and a tendency to catastrophize in response to fatigue. Patients with and without CRF differed on a host of concurrent measures of fatigue, depression, functioning, and QOL with mean effect sizes in the range of 1.0 standard deviation.

**Conclusion—**CRF is a clinical syndrome experienced before and during adjuvant therapy for breast cancer. Results suggest CRF has a multifactorial etiology and support use of the proposed case definition approach to defining CRF. Future research is necessary to determine the scientific value of these criteria for understanding the etiology and management of fatigue in the oncology setting.

## INTRODUCTION

Fatigue is a common and distressing symptom reported by patients with cancer during and after completion of adjuvant treatment. Because of its impact on quality of life (QOL), fatigue in patients with cancer and survivors of cancer has been the focus of a large body of research.[1–4] This research has focused on describing the prevalence and severity of fatigue, identifying

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etiological and maintaining factors, and developing evidence-based approaches to fatigue prevention and management.

Fatigue is a phenomenon that defies easy definition and measurement. As a result, no consensus exists regarding the best way to assess and define fatigue in the cancer setting. Fatigue has been assessed using single-item measures, multi-item unidimensional scales (eg, Fatigue subscale from the Profile of Mood States[5]), and multiscale, multidimensional inventories (eg, Fatigue Symptom Inventory[6,7]). Although each approach has its strengths and weaknesses, scientific progress can be impeded by this heterogeneity. Nowhere is this more evident than when one considers reports of the prevalence of fatigue in patients with cancer. A recent review identified prevalence estimates of fatigue during treatment for cancer that ranged from 25% to 99%.[3] Some of this variance is due to heterogeneity in the diagnoses and therapies represented in study samples and the timing of fatigue assessment. However, much of the variance in prevalence estimates is due to use of different instruments for measuring fatigue. Even more importantly, variance in fatigue prevalence estimates is due to lack of well-defined criteria for translating responses on continuous measures of fatigue into a categoric measure of fatigue "caseness." Stated differently, the reported prevalence of fatigue varies widely because of a lack of consensus regarding how to define the presence or absence of fatigue in general or, more specifically, the presence or absence of severe and clinically important cases of fatigue.

Why is a consensual definition of fatigue "caseness" important? Progress in understanding the etiology of fatigue and developing evidence-based approaches to managing fatigue is likely to be enhanced by a shared understanding among researchers of what constitutes fatigue. Without this, it is difficult to interpret conflicting research findings. Does the failure of an otherwise successful therapeutic approach to managing fatigue in one study suggest a weakness in the therapy or does it simply reflect application to a qualitatively or quantitatively different type of fatigue problem?

Recently, criteria for identifying cases of cancer-related fatigue (CRF) have been proposed.[8] This case-definition, or clinical syndrome, approach defines CRF in terms of four criteria.[8–10] Criterion A requires at least a 2-week period within the preceding month during which significant fatigue or diminished energy was experienced each day, or almost every day, along with the experience of at least five of 10 additional fatigue-related symptoms. Criterion B requires that the experience of fatigue result in significant distress or impairment of functioning. Criterion C requires that clinical evidence be present suggesting fatigue is a consequence of cancer or cancer therapy. Finally, Criterion D requires that fatigue not be primarily a consequence of a concurrent psychiatric condition (eg, major depressive disorder). A similar case-definition approach has been used to identify cases of chronic fatigue syndrome for purposes of research and therapy[11], and, of course, this approach is embodied in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria for the diagnosis of psychiatric disorder.[12] As with any arbitrary set of definitional criteria, research is necessary to examine its scientific utility.

Only two studies have used this case-definition approach to the study of CRF. As part of a national telephone survey, Cella et al[9] identified 379 cancer survivors who had received chemotherapy. Sixty-six (17%) met both criteria A and B for CRF (criteria C and D were not assessed). This proportion increased to 20% when considering only respondents for whom it had been less than 1 year since conclusion of adjuvant therapy. Sadler et al[10] assessed 51 recipients of a bone marrow transplant 5 to 11 months after their transplant hospitalization. Respondents completed QOL measures and an interview to identify CRF based on full criteria A through D.[8] CRF prevalence was 21%. Compared with those without CRF, patients with CRF reported fatigue that was greater in severity, frequency, pervasiveness, and interference with QOL. Patients with CRF were also characterized by poorer role functioning, less vitality,

and more depressive symptoms. Although the study by Cella et al[9] involved a large sample of cancer survivors, the full set of CRF criteria was not applied. In contrast, the study by Sadler et al[10] employed the full set of CRF criteria, but the sample size was limited. Clearly, there is a need to investigate application of the full set of proposed CRF criteria in a large sample of patients with cancer or cancer survivors.

The present study examines use of the proposed case-definition approach to identification of CRF in a large sample of women who received adjuvant therapy for early-stage breast cancer. There were several goals: (1) identify the prevalence of CRF both before and after receipt of an initial course of adjuvant chemotherapy or radiotherapy; (2) identify demographic, clinical, and psychosocial predictors of CRF experienced at the conclusion of an initial course of adjuvant therapy; and (3) characterize patients meeting criteria for CRF with regard to concurrent measures of fatigue, distress, and QOL. Based on prior research in the cancer setting, we hypothesized that CRF prevalence would be greater in women receiving adjuvant chemotherapy relative to women receiving adjuvant radiotherapy.[13–15] Furthermore, based on prior research in the cancer setting indicating that higher scores on continuous measures of fatigue are associated with a tendency to react to fatigue with negative self-statements and negative thoughts about the future regarding fatigue,[16–18] we hypothesized that CRF would be associated with a style of coping with fatigue characterized by greater catastrophizing. Finally, based on symptom perception theory[19] and prior research with chronic fatigue syndrome,[20,21] we hypothesized that patients with CRF would be characterized by coping styles reflecting less accommodation to illness and greater focusing on symptoms.[21]

## PATIENTS AND METHODS

### Patients

Participants were women receiving adjuvant therapy after diagnosis of stage 0 to II breast cancer. Participants were recruited at two sites: the H. Lee Moffitt Cancer Center and Research Institute at the University of South Florida (USF; Tampa, FL) and the Markey Cancer Center at the University of Kentucky (UK; Lexington, KY). Other study eligibility criteria were (1) age at least 18 years; (2) no psychiatric or neurologic disorder that would interfere with study participation; (3) ability to speak, read, and understand English; (d) no history of cancer other than basal cell skin carcinoma; (e) no history of surgical treatment with lumpectomy or mastectomy; (f) scheduled to receive adjuvant therapy consisting of radiotherapy (RT) alone, chemotherapy (CT) alone, or both adjuvant CT and RT; and (g) no concurrent chronic or life-threatening disease in which fatigue is a prominent symptom (eg, AIDS, multiple sclerosis).

### Procedure

After Institutional Review Board approval, potential participants were identified from daily clinic rosters followed by review of medical records and consultation with clinic staff. Participants were recruited during a clinic visit after surgery but before the start of adjuvant therapy. At this visit, project staff provided information about the study, and written informed consent for participation was obtained. Before initiation of adjuvant therapy, women completed a baseline assessment consisting of a set of questionnaires and a clinical interview. On completion of the initial course of adjuvant therapy (CT or RT), women completed a post-treatment assessment consisting of questionnaires and a clinical interview. Because of variability in patient scheduling across and within study sites, the questionnaire portion of the baseline and post-treatment assessments was completed using a combination of in-person assessments, mail-back questionnaires, and telephone interviews, as necessary. The clinical interview portion of both assessments was always completed during an in-person or telephone interview. Information regarding stage of disease, surgery, and adjuvant therapy was obtained from medical records.

## Questionnaires

**Demographic information—**Age, race, marital status, current employment status, education, and whether the woman was living with children in her home were assessed via questionnaire at the baseline assessment.

**Medical Outcome Study SF-36 Health Survey—**The Medical Outcome Study SF-36 Health Survey (SF-36)[22] is a 36-item measure of physical and mental health and QOL. The SF-36 consists of eight subscales that can be combined to create composite indices of physical and mental health.[23] The SF-36 was completed at the post-treatment assessment.

**Profile of Mood States—**Profile of mood states (POMS)[5] is a 65-item measure of current mood disturbance that yields six sub-scale scores. Only the seven-item Fatigue subscale (POMS-F) was used here. Coefficient alpha, a measure of internal consistency, for the POMS-F was .96. The POMS-F was completed at the post-treatment assessment.

**Center for Epidemiological Studies Depression Scale—**The Center for Epidemiological Studies Depression Scale (CES-D)[24] is a 20-item measure of depressive symptoms. Coefficient alpha was .91. The CES-D was completed at the post-treatment assessment.

**Fatigue Symptom Inventory—**The Fatigue Symptom Inventory (FSI)[6,7] consists of 13 items assessing the frequency and severity of fatigue and the degree to which fatigue interferes with QOL. Frequency is indexed by the number of days in the past week on which respondents felt fatigued (0 to 7 scale) and the proportion of each day they felt fatigued (0 to 10 scale). Fatigue severity is indexed by separate ratings (0 to 10 scale) for most, least, and average fatigue in the past week. The extent to which fatigue interferes with QOL is indexed by seven items (all 0 to 10 scales) summed to create an FSI-Interference subscale. Coefficient alpha for the FSI-Interference subscale was .95. The FSI was completed at the post-treatment assessment.

**Memorial Symptom Assessment Scale—**The Memorial Symptom Assessment Scale (MSAS)[25] assesses the presence, during the previous week, of 26 symptoms, including fatigue, associated with cancer and cancer treatment. If a symptom is present, ratings of severity (slight, moderate, severe) and bothersomeness (not at all, a little bit, somewhat, very much) are provided. The MSAS was completed at the post-treatment assessment.

**Fatigue Catastrophizing Scale—**The Fatigue Catastrophizing Scale (FCS)[17,18] is a 10-item measure of the tendency to engage in negative self-statements and thoughts about the future regarding fatigue. A total score is calculated and coefficient alpha for the FCS was .86. The FCS was completed at the baseline assessment.

**Illness Management Questionnaire—**The 55-item Illness Management Questionnaire (IMQ)[22] was designed to assess cognitive and behavioral coping with chronic fatigue syndrome. Although four subscale scores are calculated, only the Accommodating to Illness and Focusing on Symptoms subscales were used here. The Accommodating to Illness subscale assesses the tendency to organize and plan one's life to avoid overexertion and control stress. The Focusing on Symptoms subscale assesses the tendency to be preoccupied with symptoms, linked with an appraisal of helplessness and of one's life as dominated by the illness. Coefficient alpha values for the Accommodating to Illness and Focusing on Symptoms subscales were .86 and .79, respectively. The IMQ was completed at the baseline assessment.

**Change in Level of Activity—**A single item administered at the post-treatment assessment assessed change in physical activity level since breast cancer diagnosis. Three response alternatives were provided: increased, decreased, or has not changed.

## Clinical Interview

The clinical interview consisted of completion of the Mood, Anxiety, and Adjustment Disorders modules from the Structured Clinical Interview for the DSM-IV, Research Version (SCID-I-RV)[26] and the Diagnostic Interview Guide for Cancer-Related Fatigue (DIG-CRF).[8] The DIG-CRF is a structured interview to determine whether a respondent meets the four criteria for diagnosis of CRF. Criterion A requires acknowledgment of a 2-week period of significant fatigue and lack of energy in the preceding month. If not present, the interview is ended. If significant fatigue is present, the presence of 10 additional fatigue-related symptoms every day or nearly every day during the same 2-week period during the preceding month is assessed. A minimum of five symptoms must be present to meet criterion A. If four or fewer symptoms are present, the interview is ended. Criterion B requires that these symptoms cause clinically significant distress or functional impairment. Again, if criterion B is not met, the interview is ended. Finally, criterion C requires evidence that fatigue symptoms are a consequence of cancer or cancer therapy, and criterion D requires that the symptoms are not primarily a consequence of a comorbid psychiatric disorder (eg, major depression). Interviewers were doctoral students in clinical psychology trained in administration and scoring of both the SCID and DIG-CRF portions of the clinical interview. Training involved review of diagnostic criteria, practice interviews, and review of audiotaped interviews with study participants. Previous research using similarly trained interviewers demonstrated high inter-rater reliability in the diagnosis of CRF.[10]

## Statistical Analysis

Prevalent and incident cases of CRF at the post-treatment assessment were compared with noncases of CRF using a set of 13 clinical, demographic, and psychosocial variables from the baseline assessment. Comparisons used $\chi^2$ or *t* test, as appropriate. Clinical variables included type of adjuvant therapy (CT *v* RT), study site (UK *v* USF), surgery (mastectomy *v* lumpectomy), and history of major depressive disorder (yes *v* no). Demographic variables included age (as a continuous variable), education (at least high school *v* beyond high school), current partner status (yes *v* no), current employment status (working full/part time *v* not employed), living with a child in the home (yes *v* no), and race (minority *v* nonminority). Psychosocial variables included total FCS score and IMQ subscale scores for Focusing on Symptoms and Accommodating to Illness (all continuous variables). To identify multivariate predictors of prevalent and incident cases of CRF at the post-treatment assessment, a pair of binary logistic regression analyses was conducted. The independent variables in both analyses were the set of 13 variables used in the preceding analyses. A series of *t* tests was used to compare prevalent cases and noncases of CRF on QOL (SF-36 General Health, Physical and Social Functioning, Vitality, and Mental Health subscale scores; SF-36 Physical and Mental Health composite indices), fatigue (POMS-F total score; FSI ratings of least, most, and average fatigue; FSI Fatigue Interference subscale, number of days and typical portion of day fatigued in past week), and depression (CES-D total score) measures obtained at the post-treatment assessment. To further identify factors associated with CRF at the post-treatment assessment, a series of $\chi^2$ analyses was conducted. Dependent variables included current DSM-IV diagnosis of major depressive disorder; presence, severity, and bothersomeness of fatigue symptom reports on the MSAS; and change in activity level since cancer diagnosis.

Assuming a two-tailed test with an $\alpha$ of .05 and 25% of respondents reporting CRF at the post-treatment assessment, power analyses indicated that 280 respondents would be sufficient to detect a mean difference of 0.40 standard deviation (SD) between patients with CRF and those

without with power ≥.80 for all continuous variables. Likewise, assuming a two-tailed $\chi^2$ test, alpha equal to .05, and 50% of respondents receiving adjuvant chemotherapy, power analyses indicated that 280 respondents would be sufficient to detect a 15% difference between patients with CRF and those without with power ≥0.80. Finally, assuming a two-tailed test, $\alpha$ equal to .05, 25% of respondents reporting CRF, and 50% of respondents receiving adjuvant chemotherapy, power analyses indicated that 280 respondents would be sufficient to detect an odds ratio (OR) ≥ 2.0 with power ≥ 0.70.

## RESULTS

A total of 288 women completed the baseline and post-treatment assessments and constituted the study sample in all analyses. The proportion of eligible women who declined participation was less than 5%. Study participants were drawn from both USF (n = 184; 64%) and UK (n = 104; 36%), had a mean age of 54.5 years (SD = 10.1; range 21 to 79), and were primarily white (n = 263; 91%). The post-treatment assessment came at the conclusion of a complete course of adjuvant RT for 137 women (48%) and a complete course of adjuvant CT for 151 women (52%). A complete course of adjuvant RT consisted of receipt of 30 to 35 individual RT treatment sessions. A complete course of adjuvant CT consisted of receipt of 4 to 8 cycles of CT. Because the post-treatment assessment came at the completion of adjuvant RT or CT, no woman was undergoing treatment at the time of the post-treatment assessment. (Some women in the CT group later received adjuvant RT, but this occurred after completion of the post-treatment assessment.) The mean time between baseline and post-treatment assessments was 57.4 days for the RT group and 97.3 days for the CT group. Additional characteristics of the sample are shown in Table 1. No differences were found between the UK and USF subsamples with regard to any demographic or clinical characteristic. Data for the UK and USF sites were then combined for all analyses.

### Prevalence and Incidence of CRF

At the baseline assessment, 30 women (10.4% of entire sample) met the criteria for CRF. Of these 30 women, 15 did not meet criteria for CRF at the post-treatment assessment and thus represented “resolving” cases of CRF. Seventy-five women (26%) met criteria for CRF at the post-treatment assessment. Of these, 60 had not met CRF criteria at the Baseline Assessment and thus represented incident cases of CRF (80% of all patients with CRF at the post-treatment assessment and 21% of the entire sample). The remaining 15 women meeting CRF criteria at the post-treatment assessment also met CRF criteria at the baseline assessment and were patients with “persistent” CRF. The prevalence and incidence of CRF at each study assessment is shown in Table 2.

### Predictors of Prevalent and Incident Cases of CRF at the Post-Treatment Assessment

Relative to patients without CRF (n = 213), patients with prevalent CRF (n = 75) at the post-treatment assessment were more likely to have received adjuvant chemotherapy ($\chi^2_1$=5.44; $P$ < .05) and to have a history of major depressive disorder ($\chi^2_1$=6.78; $P$ < .05). Patients with prevalent CRF were also younger ($t_{283}$ =2.11; $P$ <.05) and reported higher Fatigue Catastrophizing ($t_{279}$ =7.525; $P$ <.001) and IMQ-Focusing on Symptom scores ($t_{277}$ =4.05; $P$ <.05) at baseline. Likewise, patients with incident CRF were more likely to have received adjuvant chemotherapy ($\chi^2_1$=5.79; $P$ <.05) and to have a history of major depressive disorder ($\chi^2_1$=7.24; $P$ <.05). They also evidenced higher Fatigue Catastrophizing ($t_{264}$ =5.06; $P$ <.001) and lower IMQ-Accommodating to Illness scores ($t_{264}$ =1.97; $P$ <.05). Results for IMQ-Focusing on Symptom scores missed our .05 criterion for statistical significance ($t_{264}$ =1.92; $P$=.056); patients with incident CRF were characterized by higher scores on this subscale. Results are shown in Table 3.

The set of 13 clinical, demographic, and psychosocial variables used in the preceding analyses yielded significant prediction of both prevalent ($\chi^2_{13}$=52.43; $P$ <.001) and incident ($\chi^2_{11}$=37.22; $P$ <.001) cases of CRF. Inspection of the ORs for CRF prevalence indicated only that higher Fatigue Catastrophizing scores at baseline were a significant predictor of prevalent CRF (OR = 1.19; $P$ <.01). Specifically, each one-point increase in Fatigue Catastrophizing scores was associated with an approximate 20% increase in the likelihood of being classified as having prevalent CRF. Inspection of the ORs for CRF incidence indicated only higher Fatigue Catastrophizing (OR = 1.14; $P$ <.01) and receipt of adjuvant chemotherapy (OR = 2.23; $P$ <.05) were significant predictors of incident CRF. More specifically, women receiving adjuvant chemotherapy were more than twice as likely as women receiving adjuvant radiotherapy to develop CRF over the course of adjuvant therapy. Likewise, each one-point increase in Fatigue Catastrophizing scores was associated with a 14% increase in the likelihood of developing CRF over the course of therapy. Results are presented in Table 4.

### Factors Associated With Prevalent CRF at the Post-Treatment Assessment

Patients with prevalent CRF at the post-treatment assessment differed from patients without CRF on all 15 psychosocial indices obtained at the post-treatment assessment (all $P$ values <. 001). Effect sizes ranged from 0.83 SD (SF-36 General Health and Mental Health subscales) to 1.36 SD (SF-36 Vitality subscale). The mean effect size was 1.06 SD. For all 15 indices, women meeting CRF criteria reported poorer status. Results are shown in Table 5.

Finally, relative to patients without CRF at the post-treatment assessment, patients with CRF were more likely to: (1) report decreases in activity level since breast cancer diagnosis (86% *v* 59%; $\chi^2_1$=13.19; $P$ <.01); (2) evidence a current diagnosis of major depression (17% *v* 2%; $\chi^2_1$=21.26; $P$ <.001); and (3) report the presence of fatigue symptoms on the MSAS (97% *v* 87%; $\chi^2_1$=5.73; $P$ <.05). Among women reporting current fatigue symptoms on the MSAS, patients with CRF were more likely to report “severe” fatigue symptoms (42% *v* 8%; $\chi^2_2$=57.99; $P$ <.001) and to report that their fatigue symptoms bothered them “very much” (42% *v* 7%; $\chi^2_3$=55.74; $P$ <.001). Results are presented in Table 6.

## DISCUSSION

This study represents the first use of the complete set of proposed criteria for identifying patients with CRF in a large sample of patients with cancer who have recently completed a course of adjuvant therapy. Prior research has used only a subset of the proposed criteria[9] or has applied the full set of criteria in a sample of limited size.[10] Of our sample, 26% met full criteria for CRF at the conclusion of the initial course of adjuvant therapy. Our CRF prevalence rate of 26% is a bit higher than the 17% to 21% rates found in prior research with cancer survivors.[9,10] However, one would expect a higher prevalence of CRF in those who have recently completed adjuvant therapy, particularly because adjuvant chemotherapy was a risk factor for developing CRF in the current study. Importantly, although only 10% and 26% of respondents met the full set of CRF criteria at the baseline and post-treatment assessments, respectively, 37% and 54%, respectively, acknowledged a 2-week period in the preceding month during which they had experienced significant fatigue or a lack of energy every day or nearly every day (first part of criterion A). Clearly, use of the full set of CRF criteria identified a much more restricted set of cases of significant fatigue.

Although 20% to 25% of our sample evidenced CRF for the first time at the conclusion of adjuvant therapy, CRF was also evidenced in the immediate postsurgical period. Approximately 10% of our sample met criteria for CRF at the baseline assessment, before adjuvant therapy. CRF in the postsurgical period could stem from tumor-related factors or the physical and psychological stresses associated with surgery and a diagnosis of malignant disease. Further study of postsurgical CRF is merited. Although half of the cases of postsurgical

CRF resolved by the post-treatment assessment, the remaining half persisted. Whether persistent CRF is associated with greater risk for subsequent "off treatment" fatigue[27] is a significant question. Further follow-up is necessary to characterize the long-term trajectory of this early-onset and persistent CRF. It is unknown whether early identification and management of CRF before adjuvant therapy might reduce risk for CRF later in the disease trajectory.

Our hypotheses regarding factors predictive of CRF development were largely supported. In both univariate and multivariate analyses, both a tendency to catastrophize in response to fatigue and receipt of adjuvant chemotherapy were associated with incident CRF at the post-treatment assessment. Relative to women who received adjuvant radiotherapy, women who received adjuvant chemotherapy were more than twice as likely to develop CRF over the course of therapy (OR = 2.23). Likewise, each one-point increment on our measure of Fatigue Catastrophizing was associated with a 14% increase in risk for developing CRF over the course of adjuvant therapy (ie, OR = 1.14). Thus, a difference of six points in Fatigue Catastrophizing scores between two women (OR = 2.19) would represent an increase in risk for developing CRF approximately equivalent to the risk conferred by receipt of adjuvant chemotherapy (OR = 2.23).

Support was weaker for our hypotheses regarding the relationship of CRF to other coping variables. Scores on the IMQ Accommodating to Illness and Focusing on Symptoms subscales were associated with CRF incidence in the univariate analyses. As hypothesized, a tendency to cope with chronic illness by accommodating to one's illness was associated with reduced risk for developing CRF. Conversely, a greater tendency to cope with chronic illness by focusing attention on one's symptoms was linked to greater risk for developing CRF in the univariate analyses, although neither variable was significantly associated with CRF incidence or prevalence in the multivariate analyses. The failure to obtain strong support for our hypotheses regarding IMQ subscale scores and risk for CRF is probably due to the generic nature of the IMQ. In contrast to our measure of catastrophizing, the IMQ assesses coping tendencies with respect to illness in general, rather than fatigue in particular. This lack of specificity of measurement with regard to how women coped with fatigue in the context of breast cancer limits the predictive power of the IMQ with regard to subsequent prevalent or incident CRF. More specific measurement of tendencies to focus on fatigue symptoms and to cope with fatigue symptoms through accommodation might have yielded stronger support for our hypotheses.

Considered together, our results suggest that development of CRF may be linked to coping behaviors. Catastrophizing in response to fatigue symptoms, evidenced by a tendency to react to fatigue with negative self-statements and negative thoughts about the future regarding fatigue, was linked to increased risk for developing CRF. In addition, the development of CRF was linked in some analyses to a tendency to accommodate to illness by organizing and planning one's life to avoid stress and overexertion (decreases risk) and a tendency to focus on symptoms, as evidenced by a preoccupation with symptoms accompanied by appraisals of helplessness and of one's life being dominated by illness (increases risk). Although some might question the credibility of a diagnosis of CRF given these links to cognitive and behavioral variables, such skepticism is unwarranted. CRF criteria define a complex of symptoms of a specific duration that have a significant impact on daily functioning. No assumptions about etiology are implied, other than that the observed fatigue is a likely consequence of cancer or cancer therapy. Furthermore, it is well recognized that cognitive and behavioral factors play a prominent role in the development and maintenance of chronic pain,[28,29] a syndrome to which CRF has been compared. Consequently, the fact that cognitive and behavioral factors may play a similar role in CRF should not impugn a diagnosis of CRF. Assuming that cognitive and

behavioral factors contribute to CRF development, our results suggest that interventions using cognitive-behavioral techniques might be effective in the management of CRF.[3,30]

We observed a significant relationship between major depressive disorder and CRF. Of patients with CRF at the post-treatment assessment, 17% also met criteria for a concurrent diagnosis of major depressive disorder. In contrast, only 2% of patients without CRF did so. It should be noted, however, that although a concurrent diagnosis of major depression was significantly more likely in women with CRF, more than 80% of patients with CRF did not meet criteria for a major depressive disorder. Although some overlap between symptoms of fatigue and depression may be the norm in the cancer setting,[31] only a minority of women with CRF also presented with a diagnosis of major depression. Thus, routine use of antidepressant therapy for managing CRF is probably inappropriate. Furthermore, whereas CRF criteria acknowledge potential comorbidity between CRF and major depression, criterion D for CRF requires determination of whether fatigue symptoms are primarily attributable to a comorbid psychiatric disorder, such as a major depression, or to cancer diagnosis and treatment. This can be difficult, but Cella et al[8] have suggested means for making this distinction. They suggest that fatigue attributable to cancer diagnosis and treatment tends to be characterized by less prominent cognitive symptoms, onset coincident with cancer diagnosis and treatment initiation, greater synchronization of symptoms with receipt of adjuvant therapy, and little diurnal fluctuation in symptoms.

The relationship between depression and CRF was further demonstrated in the significant univariate relationship between a history of major depressive disorder and prevalent and incident CRF at the post-treatment assessment. Why a prior major depressive disorder might be associated with enhanced risk for CRF is unclear, although a history of major depressive disorder is considered a predisposing factor for psychological morbidity after cancer diagnosis and treatment.[32] In some patients, major depression and CRF might share a common biologic substrate. Alternatively, major depression and CRF might both be linked to poor coping skills or an unsupportive social environment. The mechanism(s) underlying a link between history of major depressive disorder and CRF merit exploration and an individual's history of depression should be routinely considered in developing an appropriate clinical management plan.

The proposed criteria for defining CRF represent clinical criteria, developed by a panel of experts. Although these criteria can be applied reliably to identify CRF,[10] their scientific utility is still being established. The proposed criteria might even require some revision as research data accumulate. In this study, use of the proposed criteria resulted in identification of a set of cases of severe and prolonged fatigue, associated with significant functional impairment, and primarily caused by cancer diagnosis and treatment and not comorbid psychiatric disorder. Most significantly, application of these criteria resulted in identification of groups of patients with CRF and those without that differed profoundly on an array of self-report indices of current QOL and functional status often associated with fatigue. In all instances, group differences greatly exceeded the threshold of 0.5 SD often used to characterize group differences on health status measures as clinically "important" and/or "meaningful."[33–36]

Limitations of this study should be noted. Although women with certain comorbidities linked to significant fatigue symptoms (eg, AIDS, multiple sclerosis) were excluded from study, we did not assess physical comorbidity in our sample. Such comorbidities can affect the experience of fatigue and ideally should be included as control variables in future analyses comparing patients with CRF and those without. In addition, we did not assess fatigue in women with breast cancer treated with surgery alone (no adjuvant therapy) or in a comparison group of healthy women without breast cancer. Obviously, criterion C for CRF (are symptoms a consequence of cancer or cancer therapy?) would technically exclude formal diagnosis of CRF

in a healthy comparison group. However, collection of information relevant to criteria A, B, and D for CRF from a healthy comparison group or women with breast cancer treated with surgery alone would place our prevalence and incidence rates for CRF in additional, suitable contexts.

In conclusion, the present study suggests that CRF is a common clinical syndrome in women with early-stage breast cancer both before after adjuvant therapy. Approximately 25% of our sample met criteria for CRF, a much lower estimate of fatigue prevalence than the 25% to 99% estimates based on less stringent definitional criteria.[3] In contrast, the prevalence of CRF in our study seems to be comparable or even slightly higher than the prevalence of major depression in patients with cancer, noted to be in the 0% to 38% range.[37] However, less than 20% of patients with CRF in our study evidenced a concurrent major depression, suggesting the importance of distinguishing these two syndromes. Our results also suggest CRF has a multifactorial and complex etiology. Some factors might predispose a patient to develop CRF (eg, history of major depressive disorder), others might precipitate CRF (eg, adjuvant chemotherapy), and still others might exacerbate or maintain CRF (eg, Fatigue Catastrophizing). Finally, although CRF criteria identified patients reporting profound and debilitating fatigue, the ultimate scientific value of the proposed criteria for CRF remains to be demonstrated. The proposed criteria will be valuable to the extent that they are able to identify a relatively homogeneous clinical syndrome that is empirically linked to specific physical and laboratory findings, specific etiological and maintaining factors, and ultimately specific approaches to clinical prevention and treatment.

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**Table 1**

Demographic and Clinical Characteristics of Study Sample (n = 288)

| Variable | No. | % |
|---|---|---|
| Married or partnered | 217 | 75 |
| White | 263 | 91 |
| History of depressive disorder | 52 | 18 |
| Living with children in home | 87 | 26 |
| Employed full/part time | 146 | 52 |
| Education | | |
| < High school | 74 | 26 |
| Some college | 91 | 32 |
| College graduate | 73 | 26 |
| Post-baccalaureate study or degree | 47 | 16 |
| Annual household income* | | |
| < $20,000 | 23 | 8 |
| $20,000–$59,999 | 109 | 38 |
| > $60,000 | 126 | 44 |
| Stage of disease at diagnosis | | |
| Stage 0 | 25 | 9 |
| Stage I | 148 | 51 |
| Stage II | 114 | 40 |
| Surgery | | |
| Lumpectomy | 248 | 86 |
| Mastectomy† | 39 | 14 |

*26 women (10%) did not provide information regarding annual household income.

†Includes women with both mastectomy and lumpectomy (n = 4) and bilateral mastectomy (n = 6).

**Table 2**

Diagnoses of CRF at Baseline and Post-Treatment Assessments

| | No. | % |
|---|---|---|
| Baseline assessment | | |
| No CRF | 258 | 90 |
| Total CRF Cases | 30 | 10 |
| "Resolving" cases of CRF* | 15 | |
| "Persistent" cases of CRF† | 15 | |
| Post-treatment assessment | | |
| No CRF | 213 | 74 |
| Total CRF cases | 75 | 26 |
| Incident cases of CRF‡ | 60 | |
| "Persistent" cases of CRF | 15 | |

Abbreviations: CRF, cancer-related fatigue.

* Meeting criteria for CRF at the baseline assessment but not at the post-treatment assessment.

† Meeting criteria for CRF at both the baseline and post-treatment assessments.

‡ Meeting criteria for CRF at the post-treatment assessment but not at the baseline assessment.

**Table 3**

Comparison of Prevalent and Incident CRF With Absence of CRF at the Post-Treatment Assessment

| | CRF Prevalence | | | CRF Incidence | | |
|---|---|---|---|---|---|---|
| | With CRF (n = 75) | Without CRF (n = 213) | *P** | With CRF (n = 60) | Without CRF (n = 213) | *P* |
| Age in years (SD) | 52.3 | 55.2 | .036 | 52.7 | 55.1 | .116 |
| SD | 8.1 | 10.6 | | 8.3 | 10.6 | |
| Fatigue Catastrophizing | 18.3 | 13.7 | < .001 | 17.5 | 14.0 | < .001 |
| SD | 5.9 | 3.9 | | 5.8 | 4.3 | |
| IMQ-Accommodate to Illness | 47.9 | 49.4 | .266 | 46.9 | 49.8 | .050 |
| SD | 9.5 | 10.3 | | 9.1 | 10.4 | |
| IMQ-Focus on Symptoms | 26.0 | 22.7 | < .001 | 24.8 | 23.0 | .056 |
| SD | 7.0 | 5.8 | | 6.3 | 6.2 | |
| With current partner, % | 71 | 77 | .279 | 70 | 78 | .226 |
| Child living in home, % | 32 | 30 | .770 | 28 | 32 | .752 |
| Employed full/part time, % | 51 | 52 | .999 | 55 | 52 | .767 |
| UK study site, % | 41 | 34 | .328 | 45 | 33 | .127 |
| Racial minority, % | 6 | 9 | .459 | 7 | 9 | .999 |
| < High school grad, % | 28 | 25 | .756 | 30 | 25 | .497 |
| Chemotherapy, % | 64 | 48 | .022 | 65 | 47 | .019 |
| Lumpectomy, % | 87 | 86 | .999 | 90 | 86 | .520 |
| History of depressive disorder, % | 28 | 15 | .014 | 28 | 14 | .011 |

Abbreviations: CRF, cancer-related fatigue; SD, standard deviation; IMQ, Illness Management Questionnaire; UK, University of Kentucky.

* $\chi^2$ test for categorical variables and *t* test for continuous variables.

**Table 4**

Logistic Regression Analysis of Prevalent (n = 75) and Incident (n = 60) Cases of CRF at the Post-Treatment Assessment

| | CRF Prevalence | | | CRF Incidence | | |
|---|---|---|---|---|---|---|
| | **OR** | **95% CI** | ***P*** | **OR** | **95% CI** | ***P*** |
| Age | 1.00 | 0.96 to 1.04 | .997 | 0.97 | 0.96 to 1.04 | .839 |
| Fatigue Catastrophizing | 1.19 | 1.10 to 1.29 | .001 | 1.14 | 1.05 to 1.23 | .001 |
| IMQ-Accommodate Illness | 0.99 | 0.96 to 1.03 | .574 | 0.97 | 0.93 to 1.01 | .105 |
| IMQ-Focus on Symptoms | 1.02 | 0.96 to 1.09 | .566 | 0.99 | 0.93 to 1.06 | .851 |
| With current partner | 1.09 | 0.51 to 2.36 | .821 | 1.10 | 0.49 to 2.46 | .824 |
| Living with child in home | 0.76 | 0.35 to 1.64 | .487 | 0.56 | 0.25 to 1.26 | .161 |
| Employed full/part time | 1.14 | 0.59 to 2.23 | .690 | 1.17 | 0.58 to 2.37 | .657 |
| UK study site | 1.44 | 0.74 to 2.79 | .286 | 1.70 | 0.85 to 3.41 | .135 |
| Racial minority | 1.44 | 0.42 to 4.95 | .561 | 1.17 | 0.34 to 4.08 | .801 |
| < High school graduate | 1.15 | 0.56 to 2.33 | .709 | 1.17 | 0.51 to 2.34 | .682 |
| Chemotherapy | 1.84 | 0.90 to 3.77 | .097 | 2.23 | 1.06 to 4.69 | .035 |
| Lumpectomy | 0.66 | 0.23 to 1.86 | .431 | 0.55 | 0.17 to 1.78 | .316 |
| History of depressive disorder | 1.51 | 0.70 to 3.23 | .289 | 1.73 | 0.77 to 3.91 | .187 |

Abbreviations: CRF, cancer-related fatigue; OR, odds ratio; IMQ, Illness Management Questionnaire; UK, University of Kentucky.

**Table 5**

Comparison of Patients With CRF (n = 75) and Those Without (n = 213) at the Post-Treatment Assessment

| | With CRF | | Without CRF | | | |
|---|---|---|---|---|---|---|
| **Variable** | **Mean** | **SD** | **Mean** | **SD** | ***P**** | **Effect Size†** |
| SF-36 indices | | | | | | |
| General health | 59.9 | 19.6 | 76.0 | 17.4 | < .001 | 0.83 |
| Physical functioning | 47.6 | 25.3 | 77.1 | 21.0 | < .001 | 1.15 |
| Social functioning | 51.2 | 26.7 | 79.5 | 22.5 | < .001 | 1.06 |
| Mental health | 66.6 | 19.6 | 81.0 | 14.7 | < .001 | 0.83 |
| Vitality | 23.3 | 19.1 | 53.9 | 24.2 | < .001 | 1.36 |
| Physical health composite | 35.1 | 8.3 | 46.3 | 9.1 | < .001 | 1.10 |
| Mental health composite | 41.9 | 10.7 | 51.5 | 8.9 | < .001 | 0.93 |
| FSI indices | | | | | | |
| Least fatigue | 3.9 | 2.0 | 1.8 | 2.1 | < .001 | 0.93 |
| Most fatigue | 7.7 | 1.9 | 4.5 | 2.9 | < .001 | 1.05 |
| Average fatigue | 5.7 | 2.0 | 2.9 | 2.3 | < .001 | 1.12 |
| Fatigue interference‡ | 4.6 | 2.1 | 1.6 | 2.0 | < .001 | 1.26 |
| No. days fatigued | 6.4 | 1.3 | 3.8 | 2.5 | < .001 | 1.04 |
| Portion day fatigued | 6.1 | 2.5 | 3.1 | 2.5 | < .001 | 1.06 |
| POMS-fatigue | 15.4 | 7.1 | 7.1 | 5.9 | < .001 | 1.15 |
| CES-D | 19.1 | 9.1 | 9.2 | 8.1 | < .001 | 1.05 |

Abbreviations: CRF, cancer-related fatigue; SD, standard deviation; SF-36, Medical Outcome Study SF-36 Health Survey; FSI, Fatigue Interference subscale; POMS, Profile of Mood States; CES-D, Center for Epidemiological Studies Depression Scale.

* *t* Test with 286 *df*.

† Calculated as mean group difference divided by standard deviation of entire sample.

‡ Mean item score.

**Table 6**

Comparison of Patients With CRF and Those Without at the Post-Treatment Assessment

| Variable | With CRF | | Without CRF | | *P** |
|---|---|---|---|---|---|
| | No. | % | No. | % | |
| DSM-IV diagnosis of major depression | 13 of 75 | 17.3 | 5 of 213 | 2.3 | .000 |
| Decrease in activity level after diagnosis | 39 of 45 | 86.7 | 67 of 119 | 56.3 | .001 |
| Presence of fatigue symptoms (MSAS) | 69 of 71 | 97.2 | 184 of 211 | 87.2 | .017 |
| Severity of fatigue symptoms (MSAS) | | | | | |
| Slight | 5 of 67 | 7.5 | 92 of 182 | 50.5 | .000 |
| Moderate | 34 of 67 | 50.7 | 76 of 182 | 41.8 | |
| Severe | 28 of 67 | 41.8 | 14 of 182 | 7.7 | |
| Bother of fatigue symptoms (MSAS) | | | | | |
| Not at all | 2 of 67 | 3.0 | 44 of 183 | 24.0 | .000 |
| A little bit | 13 of 67 | 19.4 | 76 of 183 | 41.5 | |
| Somewhat | 24 of 67 | 35.8 | 50 of 183 | 27.3 | |
| Very much | 28 of 67 | 41.8 | 13 of 183 | 7.1 | |

Abbreviations: DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; CRF, cancer-related fatigue; MSAS, Memorial Symptom Assessment Scale.

* $\chi^2$ test.