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Prevalence, Predictors, and Characteristics of Off-Treatment Fatigue in Breast Cancer Survivors

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Abstract

BACKGROUND—Lack of consensus regarding how to identify cancer patients with significant fatigue has hampered research regarding cancer-related fatigue (CRF).

METHODS—Specific criteria were used to identify CRF cases in women with stage 0-II breast cancer (BC group, n = 304). Women completed assessments before adjuvant therapy (baseline), end of adjuvant therapy (Post-Tx), and 6 and 42 months after end of adjuvant therapy (6 and 42 Month Post-Tx). At each, women completed a clinical interview and questionnaires assessing physical and mental health. A healthy control (HC) group with no history of BC (n = 337) completed 2 similar assessments 36 months apart.

RESULTS—Off-treatment CRF prevalence was 9% and 13% at the 6 and 42 Month Post-Tx assessments, respectively. Thus, 15% of the sample evidenced off-treatment CRF with 7% evidencing delayed onset CRF. CRF at the 6 Month Post-Tx assessment was associated only with CRF at baseline (OR = 3.2) and Post-Tx assessments (OR = 3.9). CRF at the 42 Month Post-Tx assessment was associated with CRF at the Post-Tx assessment (OR = 6.1), obesity at baseline, and several baseline measures of coping in response to fatigue. Off-treatment CRF cases differed markedly from CRF noncases and healthy controls on a spectrum of health status indices (mean effect size >1.0 SD).

CONCLUSIONS—Results document the prevalence of off-treatment and delayed onset CRF, suggest the utility of a cognitive-behavioral model of CRF, and support NCCN guidelines recommending monitoring fatigue across the cancer trajectory.

Keywords

fatigue; survivorship; assessment; outcomes; late effects

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CONFLICT OF INTEREST DISCLOSURES

Fatigue is a distressing symptom often reported during adjuvant cancer treatment (on-treatment fatigue). Fatigue is also reported by cancer survivors after completion of adjuvant treatment, in some instances several years afterward (off-treatment fatigue).[1,2] Epidemiology, etiology, and management of fatigue have been the focus of considerable research in the oncology setting, apropos quality of life (QOL).[3,4]

Although progress has been made in advancing scientific knowledge and understanding of fatigue in the oncology setting, significant issues remain. Critically important is the lack of consensus regarding how to define and measure fatigue for both research and clinical purposes. In some studies, fatigue "cases" are defined simply by acknowledging fatigue on a symptom checklist. This approach fails to take into account the magnitude of fatigue experienced. In other studies a cutoff score translates data on single or multi-item fatigue measures into a dichotomous index of fatigue "caseness". While accounting for fatigue severity, this approach does not consider fatigue characteristics that bear on clinical significance (eg, extent of interference with functioning or presence of comorbid conditions).

In response to this lack of consensus, criteria for identifying cases of cancer-related fatigue (CRF) have been proposed.[5] These criteria were designed to identify "cases" of fatigue characterized by clinically significant severity and duration, a broad set of specific symptoms, significant interference with everyday functioning, and no other apparent comorbidities. This case-definition approach defines CRF by 4 criteria. Criterion A requires at least a 2-week period within the last month when significant fatigue or diminished energy was experienced each day, or almost every day, along with at least 5 of 10 additional fatigue-related symptoms. For criterion B, fatigue results in significant distress or impairment of functioning. Criterion C requires clinical evidence suggesting fatigue is a consequence of cancer or cancer therapy. Criterion D requires fatigue is not primarily a consequence of a concurrent psychiatric condition (eg, major depressive disorder).

The full set of CRF criteria have been used in 2 studies.[6,7] Most studies have used a subset of CRF criteria using Criteria A and B only,[8,9] and others excluding individuals with concurrent psychiatric disorders.[10–13] Obviously, these modifications limit comparison of prevalence rates across studies. Research using CRF criteria has also compared CRF cases and noncases on physical and mental health status.[7,9–12] CRF criteria reveal cases that differ markedly from noncases re physical and mental health status. These differences are statistically and clinically significant with effect sizes (ES) between CRF cases and noncases of about 1.0 standard deviation (SD).[7] In sum, research using CRF criteria has enabled identification of patients and survivors that differ in physical and mental health status from those not meeting CRF criteria. Also, it is now known that CRF occurs in nontrivial numbers across the cancer trajectory; prevalence rates have ranged from 12.5% in advanced cancer patients[13] to 56% in female inpatients.[12]

What remains to be examined is the course of CRF across the cancer trajectory. To date, most research has obtained a snapshot of CRF at 1 point in the cancer trajectory. The lone exception examined CRF before and at conclusion of an initial course of adjuvant therapy.[7] ("Off-treatment" CRF was not assessed.) Whereas research has identified CRF in survivors

≥2 years after completion of cancer therapy, neither the proportion of persistent CRF cases that emerged during cancer therapy, nor those that emerged after conclusion of cancer therapy (so-called delayed-onset CRF) is known. Resolving this question has implications for CRF clinical management, as it may indicate whether CRF screening can be discontinued after treatment conclusion for patients who do not evidence on-treatment CRF.

The functional status of CRF cases and noncases relative to healthy individuals without a cancer diagnosis also remains to be examined. Only a single study using CRF criteria has included a healthy control group,[12] and this study was limited by both a small sample size (n = 50) and an absence of comparisons among CRF cases, noncases, and healthy controls. As some fatigue is a normal concomitant of everyday life, comparison of the functional status of CRF cases and noncases to healthy controls places CRF in its full context.

Finally, while research has characterized differences between CRF cases and noncases on a variety of functional status measures, little is known about factors that might predict development of CRF. CRF at end of an initial course of adjuvant therapy was associated with receipt of chemotherapy, a catastrophizing style of coping with fatigue, a history of depressive disorder, and tendencies to focus on symptoms and accommodate unfavorably to illness.[7] Thus, the ability to identify risk for CRF has clear importance for clinical management of this syndrome.

This study extends prior research in 2 ways: 1) full CRF criteria are used to identify CRF cases at 3 points in the cancer trajectory, enabling identification of on-treatment and off-treatment CRF, and 2) a healthy control group is included, enabling identification of differences among CRF cases and noncases, and controls in physical and mental health status. Study aims include identification of the course of CRF after adjuvant therapy, variables that predict off-treatment CRF, and differences in physical and mental health status among off-treatment CRF cases, noncases, and healthy controls. We hypothesize CRF cases will evince poorer health relative to noncases, with noncases not differing from healthy controls. We also hypothesize receipt of chemotherapy, a catastrophizing coping style, and a history of depressive disorder will predict development of CRF. Within the study cohort, some patients will evidence delayed onset CRF.

MATERIALS AND METHODS

Participants

Participants were female breast cancer (BC) patients or healthy controls (HC) recruited at 2 study sites: the Moffitt Cancer Center at the University of South Florida (USF) or the Markey Cancer Center at the University of Kentucky (UK). Eligibility criteria for the BC and HC groups were: 1) age≥18 years, 2) speak, read, and understand English, 3) no cancer history other than basal cell skin carcinoma, and 4) no chronic disease in which fatigue is a potentially prominent symptom. Additional eligibility criteria for the BC group included 1) stage 0-II BC, and 2) scheduled to receive chemotherapy (CT), radiotherapy (RT), or both (CT + RT). Additional eligibility criteria for the HC group included matching a BC participant on age (±5 years) and zip code.

Procedure

All procedures were approved by institutional review boards at both study sites. BC participants were recruited and informed consent obtained after breast surgery, but before starting adjuvant therapy. BC participants completed assessments before adjuvant therapy (baseline), at conclusion of adjuvant therapy (Post-Tx), and 6 and 42 months after conclusion of adjuvant therapy (6-Months Post-TX, 42-Months Post-Tx). Each assessment consisted of a clinical interview and a set of questionnaires. Because of variability in patient scheduling the questionnaire for each assessment was completed in-person, by telephone, or by mail, as necessary. The clinical interview was completed either in-person or via telephone. Information regarding disease stage, surgery, breast reconstruction, body mass index (BMI), and adjuvant therapy was obtained from medical records. Obesity was defined as BMI≥30 kg/m^2.

Healthy controls were identified using a database maintained by Marketing Systems Group (Fort Washington, PA) that draws from all listed telephone households in the USA. Details regarding recruitment procedures for the HC group have been described previously.[14,15] The HC group completed an Initial HC Assessment and a Follow- up HC assessment 36 months later. Both assessments were conducted on-site and consisted of a clinical interview and a set of questionnaires.

Study Measures

Demographic information (age, race, partner status, education, annual household income), physical comorbidity, and menopausal status were evaluated at the Baseline BC and Initial HC assessments. Physical comorbidity was assessed by the Charlson Medical Index[16] —18 medical conditions or procedures to which respondents indicate whether they currently have or have undergone. Menopausal status was assessed by questions developed for epidemiologic research.[17]

The BC group completed the Fatigue Catastrophizing Scale (FCS)[18] and Illness Management Questionnaire (IMQ)[19] at the baseline and 6 and 42 Month Post-Tx BC assessments. The FCS measures the tendency to engage in negative self-statements and thoughts regarding fatigue. A total score is calculated. The IMQ assesses cognitive and behavioral coping with fatigue. Only the Accommodating to Illness (IMQ-AI) and Focusing on Symptoms (IMQFS) subscales were used. The IMQ-AI subscale assesses the tendency to organize one's life to avoid overexertion and control stress. The IMQ-FS subscale assesses preoccupation with symptoms.

The Medical Outcome Study SF-36 Health Survey (SF-36),[20] Center for Epidemiological Studies Depression Scale (CESD),[21] Fatigue Symptom Inventory (FSI),[22] and the Fatigue subscale from the Profile of Mood States (POMS)[23] were completed at the 6 and 42 Month Post-Tx BC assessments and Initial and Follow-up HC assessments. The FSI assesses fatigue frequency, severity, and interference with QOL. Frequency is indexed by the number of days in the past week respondents felt fatigued and the proportion of each day they felt fatigued in the past week (0–10 rating). Fatigue severity is indexed by ratings of most, least,

and average fatigue in the past week (0–10 ratings). The extent to which fatigue interferes with QOL is indexed by 7 items (0–10 ratings) summed to create an FSI-Interference score.

Clinical Interview

The clinical interview consisted of Mood, Anxiety, and Adjustment Disorders modules from the Structured Clinical Interview for DSM-IV[24] and the Diagnostic Interview Guide for CRF.[5] The latter is a structured interview for determining whether a person meets CRF criteria.[5] Criterion A requires acknowledgment of a 2-week period of significant fatigue and lack of energy in the preceding month. If present, the occurrence of 10 fatigue-related symptoms every day or nearly every day during this 2-week period is assessed. Five or more symptoms must be present to meet criterion A. Criterion B requires fatigue symptoms causing clinically significant distress or functional impairment. Criterion C is defined by fatigue symptoms that arise from cancer or cancer therapy. Criterion D is met when fatigue symptoms are distinct and apart from a comorbid psychiatric disorder. All interviews were conducted by doctoral students in clinical psychology trained in administration and scoring of patient assessments. Training involved review of diagnostic criteria, practice interviews, and listening to audiotaped interviews. Research using similarly trained interviewers demonstrated high interrater agreement in CRF diagnosis.[6]

Statistical Analysis

To identify CRF predictors at the 6 and 42 Month Post-Tx BC assessments, cases and noncases of CRF were compared (chi-square test, *t* test) with variables available at the baseline assessment. Clinical variables included type of adjuvant therapy and surgery, immediate breast reconstruction (yes vs no), study site, disease stage, number of physical comorbidities, menopausal status, history of major depressive disorder, and BMI/obesity status (ie, BMI ≥30). Demographic variables included age, education, partner status, and racial/ethnic minority status. Coping variables included FCS, IMQ-AI, and IMQ-FS scores. Risk for CRF at the 6 and 42 month Post-Tx BC assessments was examined as a function of CRF presence at the baseline and Post-Tx BC assessments using logistic regression analyses. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

To identify characteristics associated with CRF at the 6 and 42 month Post-Tx BC assessments, comparisons of CRF cases with noncases and healthy controls were conducted using ANOVA. In conducting these 3-group ANOVAs, data from the Initial HC assessment was compared with data from the 6 month Post-Tx BC assessment for CRF cases and noncases. Similarly, data from the Follow- up HC assessment was compared with data from the 42 month Post-Tx BC assessment for CRF cases and noncases. Dependent variables included SF-36 and FSI indices and CESD and POMS-F scores. Posthoc analyses using the Least Significant Difference (LSD) test were conducted. Effect sizes (ES) for the difference between means for CRF cases and noncases were calculated as the difference between group means divided by the standard deviation (SD) in the combined sample of BC survivors.

The criterion for statistical significance was $P<.05$, except for post hoc LSD tests where $P<.01$.

RESULTS

Three hundred ninety-one women with BC were enrolled and completed the Baseline BC assessment. (The proportion of study-eligible women who declined participation was <5%.) Of these, 304 (78%) completed the Post-Tx BC assessment and at least 1 of the 2 off-treatment assessments. These 304 women constituted the final BC sample. Comparison of these 304 women to the 87 women not included in the final BC sample (study dropouts) is shown in Table 1. Study dropouts had less advanced disease at diagnosis, were less likely to have undergone mastectomy, and were less likely to have received adjuvant therapy including CT.

In the HC group, 337 women were enrolled and completed the Initial HC assessment. Comparison of these 337 women with 304 women in the final BC sample on age, education, number of physical comorbidities, and partner, obesity, menopausal, and minority status, found no differences between these groups (P>.05). The Follow- up HC assessment was completed by 194 women (58% of initial HC group).

The number of prevalent and incident CRF cases at each assessment is shown in Table 2. The prevalence of CRF at the baseline and Post-Tx BC assessments (on-treatment CRF) was 9.9% and 22%, respectively. The prevalence of off-treatment CRF at the 6 month and 42 month Post-Tx follow-up assessments was 9.2% and 13.1%, respectively. One hundred one women (33.2%) met CRF criteria at ≥1 assessments. Forty-five women met CRF criteria at 1 (n = 36) or both (n = 9) off-treatment assessments. Thus, 15% of the BC sample displayed “off-treatment” CRF. The incidence of CRF cases at the 6 and 42 month Post-Tx assessments was 11 and 10, respectively. Thus, 21 women, or 7% of the BC sample, evidenced delayed-onset CRF.

Comparison of CRF cases and noncases at the 6-Month Post-Tx BC assessment on 16 baseline variables (Table 3) revealed no differences. Similar comparison of CRF cases and CRF noncases at the 42 Month Post-Tx BC assessment (Table 3) revealed CRF cases had a higher BMI, were more likely to be obese at baseline and enrolled at the UK study site, and evidenced greater fatigue cata-strophizing and IMQ-FI and IMQ-AI scores.

Finally, CRF cases at the 6 Month Post-Tx assessment were more likely than noncases to have evidenced CRF at the baseline (23% vs 9%; OR, 3.2; 95% CI, 1.2–8.8; P = .025) and Post-Tx BC assessments (50% vs 20%; OR, 3.9; 95% CI, 1.7–9.0; P = .001). Similarly, CRF cases at the 42 month Post-Tx assessment were more likely to have evidenced CRF at the Post-Tx assessment (52% vs 15%; OR, 6.1; 95% CI, 2.6–13.9; P = .001), but were *not* more likely to have CRF at the baseline assessment (17% vs 8%; P = .153).

Cases and noncases of CRF at the 6-month Post-Tx BC assessment and healthy controls at the Initial HC assessment were compared on 17 physical and mental health indices (Table 4). A significant main effect was obtained for all indices. Post hoc analyses revealed CRF cases differed from *both* CRF noncases and healthy controls for all indices with CRF cases evidencing *poorer* health status than noncases and healthy controls. No differences were found between CRF noncases and healthy controls for any of the 17 indices except for FSI

ratings of most fatigue. The magnitude of differences between CRF cases and noncases was very large. All ESs exceeded 1.0 SD (range, 1.07–1.86 SD), with a mean of 1.39 SD.

Identical comparisons of CRF cases and noncases at the 42 Month Post-Tx BC assessment and healthy controls at the Follow-up HC assessment yielded highly similar results (Table 5). Post hoc analyses revealed CRF cases differed from noncases and healthy controls on all 17 indices with CRF cases evidencing *poorer* health status on indices. No differences were found between CRF noncases and healthy controls for 16 of 17 indices. All ESs between CRF cases and noncases exceeded 1.0 SD (range 1.14–1.84 SD), with a mean of 1.42 SD.

DISCUSSION

As anticipated, CRF was evidenced well after completion of adjuvant therapy. CRF prevalence at the 6 and 42 Month Follow-up BC assessments was 9% and 13%, respectively. While less than the 19%–30% prevalence rates in off-treatment cancer survivors previously reported,[6,8–11] differences in application of CRF criteria, timing of assessment, and types of diagnoses and treatments in the case mixture make comparison difficult. Forty-five women (15% of BC sample) met full CRF criteria at either the 6 or 42 Month Follow-up BC assessments. Thus, 1 in 6 women evidenced off-treatment CRF, suggesting the need for serious clinical attention.

As we used multiple assessments of CRF spanning the cancer trajectory, we had a unique opportunity to observe emergence of delayed-onset CRF. Of 45 women evidencing off-treatment CRF, 21 represented incident cases of CRF at the 6 or 42 Month Follow-up BC assessments. Thus, about 7% of women in our BC sample evidenced delayed-onset CRF, first meeting CRF criteria at some point *after* conclusion of adjuvant therapy. This suggests CRF clinical management should include screening for CRF after completion of adjuvant treatment, even in women not evincing on-treatment CRF.

What variables predicted off-treatment CRF? Our longitudinal design provided a unique opportunity to address this question. The only predictors of CRF at the 6 Month Post-Tx assessment were CRF at the baseline (OR, 3.2) or Post-Tx assessment (OR, 3.9). Prediction of CRF at the 42 Month Post-Tx assessment was better. Here, higher BMI and obesity status, greater tendencies to catastrophize about fatigue and focus upon and amplify physical symptoms, and a lesser tendency to accommodate to illness symptoms were predictive of CRF at the 42 Month Post-Tx assessment. (CRF cases were more likely to be from the UK study site, probably because of differences in BMI and obesity status between the 2 sites.) CRF at the Post-Tx assessment was also a predictor of CRF at the 42 Month Post-Tx assessment (OR, 6.1).

Our results provided mixed support for our hypotheses regarding factors associated with off-treatment CRF. We hypothesized a catastrophizing coping style would predict subsequent off-treatment CRF. Indeed, fatigue catastrophizing score was a significant predictor of CRF at the 42 Month Post-Tx assessment, with results for the 6 Month Post-Tx assessment trending in the anticipated direction ($P = .09$). Coupled with prior evidence linking fatigue catastrophizing with on-treatment CRF[7] and the current data linking coping tendencies

(measured by the IMQ) with CRF presence at the 42 Month Post-Tx assessment, it seems fair to conclude coping tendencies and cognitive factors play a role in CRF. On the basis of prior research with on-treatment CRF,[7] we hypothesized off-treatment CRF would be linked to receipt of CT and a history of major depressive disorder. Although our data did not support these hypotheses, the data did fall in the anticipated direction (Table 3) and, for history of depressive disorder, narrowly missed our criterion for significance at both the 6 and 42 Month Post-Tx assessments (both $P<.10$).

Application of the full set of CRF criteria[5] resulted in identification of off-treatment CRF cases that differed from CRF noncases on a spectrum of physical and mental health indices. As in our prior research examining on-treatment CRF,[7] these differences were statistically *and* clinically significant[25] with the mean ES across our 17 indices exceeding 1.0 SD at both the 6 and 42 Month Post-Tx assessments. Similar findings have been obtained using modified CRF criteria.[9–12] Unlike previous research, however, inclusion of a HC group enabled our findings for CRF cases and noncases to be placed in a broader context. Our findings demonstrate use of CRF criteria enables identification of CRF noncases with physical and mental health status similar to healthy controls (Table 4 and Table 5). Future research might examine the relationship between CRF and more behaviorally oriented outcomes such as likelihood of maintaining employment status or returning to work after cancer diagnosis and treatment.

Our findings have theoretical and clinical import. Theoretically, our findings support an emerging cognitive- behavioral model of CRF.[26] Given earlier cognitive-behavioral models of chronic fatigue syndrome[27] and chronic pain,[28] this model suggests a distinction might be drawn between factors that precipitate the initial experience of fatigue and those that perpetuate or maintain fatigue in the longterm. In the case of CRF, biological insults like CT may precipitate fatigue symptoms (hence CT's stronger association with on-treatment CRF), whereas behavioral and cognitive variables may potentially prolong the fatigue experience (hence the prominence of coping tendencies in the prediction of off-treatment CRF). Our observed link between obesity and risk for off-treatment CRF also fits this model. Physical activity during treatment has been linked to less fatigue.[29,30] As obese individuals are less likely to be physically active they would be at increased risk for CRF.

Our findings have clinical importance in at least 2 ways. First, they suggest strategies for ameliorating target thoughts (fatigue catastrophisizing) and behaviors (low activity level) associated with CRF. Indeed, cognitive behavioral interventions are effective in managing fatigue in several clinical populations, including cancer patients and survivors,[31,32] and exercise interventions are effective in managing fatigue in cancer survivors.[33] Second, our findings support current NCCN guidelines for managing fatigue in the oncology setting.[34] Current NCCN guidelines recommend periodic screening for fatigue in cancer patients both during and after cancer treatment. As we found on-treatment CRF was a significant predictor of off-treatment CRF, individuals evidencing on-treatment CRF should be monitored particularly closely. In addition, our findings suggest the presence of delayed-onset CRF. Thus, even off-treatment cancer survivors with no history of on-treatment CRF merit monitoring.

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Table 1

Baseline Characteristics of Breast Cancer Enrollees and Final Breast Cancer Sample

Variable	Study BC Enrollees n5391	Final BC Sample n5304	*p*[a]
Age,[b] y	54.8 (10.3) [25–88]	54.8 (9.8) [25–88]	ns
Disease stage			.047
0	39 (10%)	34 (11%)	
1	196 (50%)	158 (52%)	
2	156 (40%)	112 (37%)	
Mastectomy[c]	60 (15%)	39 (13%)	.017
Immediate reconstruction	16 (4%)	11 (4%)	ns
Adjuvant treatment			.001
RT only	184 (42%)	157 (52%)	
CT only	43 (11%)	27 (9%)	
CT+RT	164 (47%)	120 (39%)	
Education			ns
≤High school graduate	106 (27%)	79 (26%)	
Some college	118 (30%)	94 (31%)	
≥College graduate	157 (40%)	131 (43%)	
Annual household income			ns
<$20,000	32 (8%)	25 (8%)	
$20,000–$59,999	140 (36%)	112 (37%)	
$60,000–$99,999	112 (29%)	93 (31%)	
≥$100,000	71 (18%)	50 (16%)	
Missing	36 (9%)	24 (8%)	
Obese[d]	109 (29%)	85 (27%)	ns
Postmenopausal	236 (63%)	186 (61%)	ns
Study site			ns
University of Kentucky	134 (34%)	112 (37%)	
Moffitt Cancer Center	257 (66%)	192 (63%)	
Married/Partnered	277 (73%)	224 (74%)	ns
Minority	34 (9%)	27 (9%)	ns
No. of physical comorbidities			ns
0	265 (68%)	203 (66%)	
1	96 (24%)	78 (26%)	
≥2	30 (8%)	23 (8%)	

BC indicates breast cancer; ns, not significant; RT, radiotherapy; CT, chemotherapy.

[a] omparing study dropouts (n=87) and final sample (n=310).

[b] Mean (SD, standard deviation from the mean) [Range].

[c] Includes bilateral mastectomy or lumpectomy plus mastectomy.

[d] Defined as ≥30 kg/m^2

Table 2

Prevalence and Incidence of Cancer-Related Fatigue

Assessment	Prevalence		Incidence	
	Frequency	%	Frequency	%
Baseline	30/304	9.9	30/304	9.9
Post-Tx	67/304	22.0	50/304	16.4
6-Months Post-Tx	26/282	9.2	11/304	3.6
42-Months Post-Tx	29/222	13.1	10/304	3.3

Tx indicates treatment.

Table 3

Comparison of Baseline Characteristics of Cancer-Related Fatigue Cases and Non-Cases at 6 and 42 Months Post-Treatment Assessments

	6 Month Post-Tx			42 Month Post-Tx		
Variable	**CRF Cases n526**	**CRF Noncases n5256**	**P**	**CRF Cases n529**	**CRF Noncases n5193**	**P**
Age,[a] y	54.8 [8.1] {43–70}	55.1 [9.9] {29–82}	.863	52.1 [8.0] {38–67}	54.3 [9.5] {29–78}	.236
BMI[a]	28.0 [6.7] {18–46}	27.2 [6.1] {13–63}	.536	29.8 [7.0] {20–46}	26.8 [5.2] {17–43}	.008
No. of physical comorbidities[a]	0.7 [0.7] {0–2}	0.4 [0.8] {0–4}	.154	0.7 [0.8] {0–3}	0.4 [0.7] {0–3}	.053
FCS-fatigue catastrophizing[a]	16.5 [4.1] {11–25}	14.8 [5.1] {10–35}	.091	18.0 [6.6] {10–35}	14.4 [4.6] {10–32}	.000
IMQ accommodating to illness[a]	47.6 [9.8] {36–77}	49.0 [9.9] {26–78}	.500	44.7 [9.1] {29–62}	48.7 [9.4] {23–77}	.034
IMQ focusing on illness[a]	26.6 [6.6] {19–44}	25.5 [7.4] {12–52}	.455	28.4 [7.6] {19–52}	25.2 [7.0] {12–42}	.021
Disease stage			.567			.585
0	4 (16%)	27 (11%)		3 (10%)	20 (10%)	
I	11 (42%)	134 (52%)		13 (45%)	105 (55%)	
II	11 (42%)	95 (37%)		13 (45%)	68 (35%)	
Mastectomy[b]	6 (23%)	30 (12%	.119	7 (24%)	22 (11%)	.074
Adjuvant treatment			.154			.216
RT only	10 (38%)	136 (53%)		11 (38%)	97 (50%)	
CT only or CT1RT	16 (62%)	120 (47%)		18 (62%)	96 (50%)	
≤High school graduate	8 (31%)	61 (24%)	.474	7 (24%)	42 (22%)	.811
Obese[c]	9 (35%)	74 (29%)	.653	13 (45%)	50 (26%)	.048
Postmenopausal	15 (63%)	159 (63%)	.999	17 (59%)	118 (62%)	.838
UK study site	8 (31%)	99 (39%)	.527	16 (55%)	13 (45%)	.021
Married/Partnered	19 (73%)	186 (73%)	.999	20 (69%)	147 (76%)	.489
Minority	4 (15%)	21 (8%)	.266	4 (14%)	18 (9%)	.502
History of major depression	8 (31%)	41 (16%)	.098	9 (31%)	29 (15%)	.060

Tx indicates treatment; CRF, cancer-related fatigue; BMI, body mass index; FCS, Fatigue Catastrophizing Scale; IMQ, Illness Management Questionnaire; RT, radiotherapy; CT, chemotherapy; UK, United Kingdom.

[a] Mean [SD, standard deviation from the mean] {Range}

[b] Includes bilateral mastectomy or lumpectomy plus mastectomy

[c] Defined as ≥30 kg/m2

Table 4

Comparison of Cancer-Related Fatigue Cases, Noncases, and Healthy Controls at the 6 Month Post-Tx Assessment

Variable	CRF Cases n526	CRF Noncases n5256	Healthy Controls n5337	*p*[a]	Group Differences[b]	ES[c]
	Mean (SD) [Range]	Mean (SD) [Range]	Mean (SD) [Range]			
SF-36 indices[d]						
General health	53.8 (19.5) [20–87]	75.4 (19.1) [25–100]	74.7 (17.9) [15–100]	≤.001	C vs NC, HC	1.07
Physical functioning	52.7 (23.7) [10–100]	81.9 (20.5) [0–100]	81.3 (20.5) [0–100]	≤.001	C vs NC, HC	1.30
Social functioning	57.7 (26.0) [12–100]	89.6 (19.5) [0–100]	89.4 (19.3) [0–100]	≤.001	C vs NC, HC	1.35
Mental health	63.5 (20.9) [24–96]	83.5 (14.3) [12–100]	81.0 (15.4) [16–100]	≤.001	C vs NC, HC	1.25
Vitality	32.3 (20.3) [0–90]	64.0 (20.6) [0–100]	62.6 (19.9) [0–100]	≤.001	C vs NC, HC	1.41
Role-physical function	25.0 (36.1) [0–100]	80.2 (32.7) [0–100]	82.3 (31.8) [0–100]	≤.001	C vs NC, HC	1.51
Role-emotional function	41.3 (43.3) [0–100]	86.6 (29.1) [0–100]	88.7 (26.7) [0–100]	≤.001	C vs NC, HC	1.36
Physical health composite	36.6 (8.6) [23–54]	48.8 (9.5) [15–66]	48.6 (9.2) (16–63]	≤.001	C vs NC, HC	1.21
Mental health composite	41.8 (12.4) [22–69]	54.2 (8.3) [8–62]	53.7 (8.5) [13–72]	≤.001	C vs NC, HC	1.32
FSI indices[e]						
Least fatigue	4.1 (1.9) [0–8]	1.1 (1.8) [0–10]	1.2 (1.6) [0–8]	≤.001	C vs NC, HC	1.52
Most fatigue	7.1 (2.0) [0–10]	3.0 (2.7) [0–10]	3.9 (2.6) [0–10]	≤.001	C vs NC vs HC	1.43
Average fatigue	5.3 (1.9) [0–9]	2.0 (2.0) [0–10]	2.4 (2.0) [0–10]	≤.001	C vs NC, HC	1.48
Fatigue interference	30.8 (14.7) [0–67]	7.0 (10.5) [0–61]	7.7 (10.5) [0–58]	≤.001	C vs NC, HC	1.86
No. of days fatigued	6.2 (1.7) [0–7]	2.8 (2.5) [0–7]	2.6 (2.2) [0–7]	≤.001	C vs NC, HC	1.29
Portion day fatigued	5.8 (2.6) [0–10]	2.1 (2.1) [0–10]	2.3 (2.0) [0–10]	≤.001	C vs NC, HC	1.53
Other indices[e]						
POMS-fatigue	12.1 (6.1) [2–28]	4.5 (5.1) [0–25]	4.8 (5.3) [11–11]	≤.001	C vs NC, HC	1.35
CES-D	18.2 (9.7) [6–41]	7.0 (7.4) [0–46]	8.0 (7.8) [11–11]	≤.001	C vs NC, HC	1.36

CRF indicates cancer-related fatigue; ES, effect size; SD, standard deviation from the mean; SF-36, The Medical Outcome Study Health Survey; FSI, Fatigue Symptom Inventory; C, cases; NC, noncases; HC, healthy controls; POMS, Profile of Mood States; CES-D, Center for Epidemiologic Studies Depression Scale.

[a] *P*-value for ANOVA.

[b] Groups different by LSD test at $P<.01$.

[c] Effect size, in SD (standard deviation from the mean) units, for comparison of CRF cases and noncases.

[d] Higher values represent better status.

[e] Higher values represent poorer status.

Table 5

Comparison of CRF Cases, Noncases, and Healthy Controls at the 42-Month Post-Treatment Assessment

Variable	CRF Cases n529	CRF Non-Cases n5193	Healthy Controls n5194	*p*[a]	Group Differences[b]	ES[c]
	Mean (SD) [Range]	Mean (SD) [Range]	Mean (SD) [Range]			
SF-36 indices[d]						
General health	47.9 (19.1) [10–82]	74.3 (20.1) [15–100]	74.7 (19.8) [5–100]	≤.001	C vs NC, HC	1.21
Physical functioning	51.6 (23.1) [15–95]	81.0 (21.1) [0–100]	81.7 (22.1) [5–100]	≤.001	C vs NC, HC	1.25
Social functioning	62.9 (21.0) [0–100]	89.4 (17.7) [12–100]	89.3 (20.2) [25–100]	≤.001	C vs NC, HC	1.31
Mental health	63.3 (20.2) [24–96]	83.4 (13.5) [12–100]	80.4 (16.4) [12–100]	≤.001	C vs NC, HC	1.26
Vitality	27.8 (21.1) [0–75]	62.7 (20.0) [10–100]	61.0 (21.0) [0–100]	≤.001	C vs NC, HC	1.50
Role: physical function	35.3 (35.0) [0–100]	77.9 (33.7) [0–100]	86.2 (27.5) [0–100]	≤.001	C vs NC vs HC	1.16
Role: emotional function	46.0 (42.2) [0–100]	89.2 (25.3) [0–100]	85.6 (30.5) [0–100]	≤.001	C vs NC, HC	1.37
Physical health composite	35.8 (9.1) [21–55]	47.8 (9.8) [14–66]	49.2 (9.1) [20–63]	≤.001	C vs NC, HC	1.14
Mental health composite	42.2 (12.6) [18–67]	54.6 (7.9) [24–69]	52.9 (9.3) [16–66]	≤.001	C vs NC, HC	1.30
FSI indices[e]						
Least fatigue	4.0 (2.4) [0–9]	1.1 (1.6) [0–8]	1.3 (1.8) [0–9]	≤.001	C vs NC, HC	1.49
Most fatigue	7.5 (1.8) [4–10]	3.4 (2.7) [0–10]	3.6 (2.8) [0–10]	≤.001	C vs NC, HC	1.38
Average fatigue	5.9 (1.8) [2–9]	2.1 (1.9) [0–8]	2.3 (2.1) [0–9]	≤.001	C vs NC, HC	1.67
Fatigue interference	31.5 (15.4) [4–65]	7.0 (9.8) [0–60]	8.4 (12.6) [0–62]	≤.001	C vs NC, HC	1.83
No. of days fatigued	6.0 (1.7) [2–7]	2.6 (2.5) [0–7]	2.3 (2.1) [0–7]	≤.001	C vs NC, HC	1.31
Portion day fatigued	6.2 (2.8) [1–10]	2.3 (2.2) [0–10]	2.3 (2.3) [0–10]	≤.001	C vs NC, HC	1.49
Other indices[e]						
POMS-fatigue	15.8 (6.6) [3–28]	4.6 (4.6) [0–23]	4.6 (5.5) [0–28]	≤.001	C vs NC, HC	1.84
CES-D	19.4 (8.9) [4–40]	6.8 (6.4) [0–45]	8.5 (8.9) [0–42]	≤.001	C vs NC, HC	1.31

CRF indicates cancer-related fatigue; ES, effect size; SD, standard deviation from the mean; C, cases; NC, noncases; HC, healthy controls; SF-36, The Medical Outcome Study Health Survey; FSI, Fatigue Symptom Inventory; POMS, Profile of Mood States; CES-D, Center for Epidemiologic Studies Depression Scale.

[a] *P*-value for ANOVA.

[b] Groups different by least significant difference (LSD test at $P<.01$.

[c] Effect size for comparison of CRF cases and non-cases.

[d] Higher values represent better status.

[e] Higher values represent poorer status.