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Predictors of Significant Worsening of Patient-Reported Fatigue over a One-Month Timeframe in Ambulatory Patients with Common Solid Tumors

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Abstract

Purpose—Understanding the determinants of fatigue worsening may help distinguish between different fatigue phenotypes and inform clinical trial designs.

Patients and Methods—Patients with invasive cancer of the breast, prostate, colon/rectum, or lung were enrolled from multiple sites. At enrollment during an outpatient visit and 4–5 weeks later patients rated their symptoms on a 0–10 numerical rating scale. A 2-point change was considered clinically significant for fatigue change. Effects of demographic and clinical factors on patient-reported fatigue were examined using logistic regression models.

Results—3123 patients were enrolled at baseline and 3032 were analyzable for fatigue change. At baseline, 23% had no fatigue, 35% mild, 25% moderate, and 17% severe. Key parameters in our model of fatigue worsening includes fatigue at baseline (OR 0.75), disease status (OR 1.99), performance status (OR 1.38), history of depression (OR 1.28), patient perception of bother due to comorbidity (OR 1.26) and treatment exposures including recent cancer treatment (OR 1.77), and use of corticosteroids (1.37). The impact of gender was examined only in colorectal and lung cancer patients, and it was a significant factor with men most likely to experience worsening of fatigue (OR=1.46).

Conclusions—Predictors of fatigue worsening include multiple factors that are difficult to modify: baseline fatigue level, gender, disease status, performance status, recent cancer treatment, bother due to comorbidity, and history of depression. Future fatigue prevention and treatment trial designs should account for key predictors of worsening fatigue.

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Keywords

cancer fatigue; symptom management; medical oncology; ambulatory care

INTRODUCTION

Fatigue is the most prevalent symptom experienced by patients and confronted by healthcare providers in the outpatient oncology setting, and it is clearly a symptom with major impact on patients. Despite the publication of dozens of original research studies and review articles every year, progress has been disappointing in terms of understanding the various biological underpinnings of cancer fatigue and establishing evidence-based standards and a strong consensus about how patients should be assessed and treated[1–5]. There are no less than 170 published interventional studies intended to improve cancer fatigue[6], and these are most often negative trials[7–14]. One of the challenges is considerable diversity in the conceptual and operational definition of fatigue in cancer, with no fewer than 24 conceptual definitions posed in the literature.[5] Most self-report scales address the sensation and the impact domains of fatigue, and some scales include additional domains.[15] The popular National Comprehensive Cancer Network (NCCN) definition refers to cancer-related fatigue as 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."[16]

Several authors have discussed the importance of the pre-existing (baseline) levels of fatigue as an important determinant of response to an intervention[12, 17–20], but data regarding the impact of baseline fatigue and other fixed and modifiable factors are limited. We sought to evaluate the determinants of worsening self-reported fatigue levels in a secondary analysis of a prospective study describing symptom expression and practice patterns in ambulatory patients with common solid tumors. In these data, much like in ordinary clinical practice, we do not have clear attributions for individual symptoms such as fatigue that are causing functional interference. Indeed, patients with various comorbidities often have multiple causes of fatigue. As such, we focused this report on the construct of patient-reported fatigue rather than cancer-related fatigue. We hypothesized that through analyses of these prospective data, we could explore a wide set of key variables, including disease type, cancer stage, cancer treatment status and type, supportive care medication exposures, and other clinical and demographic variables in order to identify key predictors of worsening fatigue. Finding such factors would clearly have implications for the design and conduct of clinical trials aimed at the treatment or prevention of fatigue in ambulatory solid tumor patients.

METHODS

Study Design and Subjects

From March 3, 2006, to May 19, 2008, we enrolled oncology outpatients at any point in the trajectory of their care for invasive breast, lung, prostate, or colorectal cancer. Patients were registered at 38 institutions, including 6 academic sites and 32 community clinics. Patients

treated in academic centers were enrolled from disease site-specific clinics. In contrast, patients treated in community clinics were enrolled from general oncology clinics. Eligible patients had to be at least 18 years of age, receiving care at an Eastern Cooperative Oncology Group-affiliated institution, willing to complete the follow-up survey, and judged by the study screener to have cognitive function adequate for completing study surveys. Patients were recruited when they checked in for their clinic appointments, and patient information was collected before their visit with a clinician. Patients and their treating clinicians were surveyed at the initial visit and at follow-up 28–35 days later. Further details about the study cohort have been published.[21] The protocol was approved by the institutional review boards at each registering institution. All patients provided written informed consent.

Study Procedures

Patients were recruited when they checked in for their clinic appointments, and patients' information was collected before their visit with a clinician. Patients and their treating clinicians were surveyed at the initial visit and at follow-up 28–35 days later.

Patients were asked to read the instructions at the beginning of each questionnaire and complete all items in terms of their experience during the preceding 24 hours. Reasons for incomplete forms were documented on the Assessment Compliance Form. Patients who could not complete the follow-up questionnaire because of acute illness were given the option to mail the forms to the treating clinic by day 42 after the initial visit.

Study Measures

The initial survey was used to collect patients' basic clinical and demographic information, including cancer treatment history and current therapies. At the initial and follow-up visits, patients reported symptom intensity and functional interference using a modification of The University of Texas MD Anderson Cancer Center Symptom Inventory (MDASI), a validated measure that is very similar to the Brief Fatigue Inventory in terms of structure and patient burden assessment.[22, 23] Patients used the MDASI to rate "fatigue (tiredness) at its worst" along with symptoms and functional interference items that they most frequently experienced in the previous 24 hours using an 11-point Likert scale ranging from 0 ("not present") to 10 ("as bad as you can imagine"). Clinicians reported patients' specific medications, including those that were newly prescribed. A clinician-specific survey was used to ascertain symptom prioritization and symptom attribution. The protocol and case report forms are accessible on the study web site[24].

Statistical Analysis

Patients were grouped into four categories based on their fatigue level at baseline measured by the fatigue item of the MDASI: no fatigue (0), mild fatigue (1–3), moderate fatigue (4–6) and severe fatigue (7–10). The association between fatigue severity at baseline and patient demographic and disease characteristics was examined using the Chi-square test.

A 2-point change in the fatigue item of the MDASI between the initial and follow up assessments was considered clinically significant.[25] This study focused on fatigue

worsening, defined as a 2-point increase in fatigue score between the two assessments. Fisher's exact tests were used for the association between fatigue change and fatigue severity at baseline. Univariate and multivariable logistic regression models were used to examine the unadjusted and adjusted effects of demographic and clinical factors on fatigue worsening in patients with baseline levels of fatigue in the range of 0–8. A total of 31 variables were included as covariates in the logistic models. These variables either have been shown to be associated with fatigue worsening in previous studies or there are possibilities for such association based on biology. For cancers affecting both men and women at similar rates (lung and colorectal cancer), sex was also evaluated as a potential predictor of fatigue worsening. The Variance Inflation Factor (VIF) was used to check multicollinearity among these variables in the multivariable regression model. The largest VIF value was 1.9. A separate category for missing data was generated for categorical covariates if the proportion of missingness was no less than 5 percent. For categorical covariates with less than 5 percent missing data and continuous covariates, patients with missing data were excluded from the logistic models. Robust standard errors of mean (i.e., clustered sandwich estimator) were used in the logistic regression models to account for the clustering effect of institutions (i.e., patients enrolled in the same institution might not be independent).

All P values were two-sided and $P < 0.05$ was considered statistically significant. STATA 11.0 software (2009; StataCorp, College Station, TX) was used for all data analysis.

Results

The study flow diagram is summarized in Figure 1. Of the 3,123 patients enrolled in this study, we found 3,032 with a self-reported fatigue item available at enrollment (97%). No fatigue (score = 0) was reported by 691 patients (23%), mild fatigue by 1,049 (35%), moderate fatigue by 765 (25%), and severe fatigue by 527 (17%).

Patient demographics and disease characteristics at the initial assessments are summarized in Table 1. Strong associations between fatigue severity and indicators of disease complexity, such as advanced stage, number of metastatic sites, and perceived degree of care difficulty, were found. Also noted are unilateral associations between worse fatigue severity and black-race- and minority-based institutions.

The proportion of patients with initial fatigue scores of 1–3, 4–6, or 7–8 whose fatigue level worsened by 2 or more points varied significantly by initial fatigue level. Changes in fatigue severity according to initial fatigue expression levels and separated by cancer treatment exposure are summarized in Table 2. The logistical regression model for fatigue worsening is summarized in Table 3. Key parameters in this model include fatigue at baseline (odds ratio [OR] 0.75), disease status (OR 1.99), performance status (OR 1.38), history of depression (OR 1.28), patient perception of bother due to comorbidity (OR 1.26), and treatment exposures, including recent cancer treatment (OR 1.77) and use of corticosteroids (1.37).

The role of sex could only be explored in lung and colorectal cancer patients, as they are diseases that affect both men and women in significant proportions. Men had higher odds of

worsening fatigue during the study period than women, after adjusting for other covariates (OR = 1.46; 95% confidence interval [CI]: 1.06–2.02, *P* value = 0.0201).

Discussion

This prospective study of patient-report fatigue in outpatient oncology in the United States provides strong point estimates concerning the prevalence of fatigue in the most common settings for cancer care and the distribution of fatigue according to levels of severity and by key clinical and demographic attributes. We found that 60% of patients have mild-to-moderate levels of fatigue and 17% of patients had severe fatigue. These data take us beyond summaries of fatigue prevalence with wide ranges (typically 50%–90%) that have been typically reported for a variety of different care settings. The existing fatigue data have been predominantly derived from breast cancer patients during their adjuvant treatment with radiation and/or chemotherapy, with some studies evaluating other patient cohorts after therapy or during treatment or groups of advanced cancer patients referred for specialized care[6]. Although these data focus on the construct of patient-reported fatigue rather than cancer-related fatigue, our findings are consistent with data related to cancer-related fatigue from other researchers who have found that approximately 30%–60% of patients have mild to moderate fatigue, approximately 20% of patients have severe levels of fatigue during or shortly after treatment for cancer, and approximately 10%–15% have fatigue as a chronic effect of treatment[26–31].

In the existing fatigue literature, from a variety of different cohorts, predictors of fatigue have included most prominently co-existing psychological symptoms and mental health factors (including the tendency toward catastrophizing)[29, 30, 32–35], co-existing pain[36, 37], duration of cancer treatment[38], primary disease site[39], comorbidity[32, 40–42], and a variety of other factors. As shown in Table 2, we found that the worsening in fatigue levels varied according to baseline levels of fatigue, and our model of fatigue worsening included baseline fatigue as a significant predictor. It is therefore important to take into account the baseline level of fatigue when trying to decipher the underlying basis for fatigue change. We also found that improvement in fatigue varied according to the baseline level, and this trend was consistent across all categories of timing in relation to cancer treatment. Overall, more than half of the patients who reported a fatigue level of 7–8 at study enrollment improved by 2 or more points, whereas less than one-third improved significantly when they reported fatigue in the 4–6 range at enrollment. There are a variety of endpoints that have been used in fatigue trials, and most of these trials define the minimal clinically meaningful change as a 0.3–0.5 effect size. In this dataset, the standard deviation for the MDASI fatigue item at study enrollment was 2.9. Thus, a 2-point change in this item represents a moderate effect size of 0.69 that is considered clinically meaningful.

It is notable that most of the significant predictors of fatigue change cannot easily be modified, although one factor, prescription of corticosteroids, is modifiable. This category of medication is often directed at symptom management and is sometimes intended specifically for the treatment of fatigue. It is most likely that the short-term prescription of corticosteroids for symptom control is not what was reflected in this logistical regression.

Rather, the model more likely reflects other uses of corticosteroids, such as prolonged treatment of pain or chronic underlying inflammatory conditions.

These findings have important implications. It is clear that interventions to intervene on the prevalent symptom of fatigue as a clinical trial outcome is of great interest, but it continues to be an evolving field[5, 43]. Fatigue interventions in patients with complex chronic illness most often target two assessments 3–4 weeks apart[44], and there are multiple examples of such trial intervals.[10, 45–47] For these studies, the trends at 4 weeks are highly correlated with the 6 and 8 week results. Moreover, there are also a number of high profile fatigue trials that are focused on shorter intervals in the 2–4 week range.[8, 9, 14, 19, 48] We believe that our data about fatigue change during this 28–35 day interval is highly relevant to clinicians and trialists. We acknowledge that further longitudinal data would also be relevant and such data will be needed in future studies to better understand the trajectory of this symptom. Future fatigue studies should account for levels of baseline fatigue, baseline and longitudinal prescription of corticosteroids as well as consideration of comorbidity (including history of depression). Data from this study should provoke clinicians to consider the possibility that some interventions may be undervalued (or overvalued), based on the existing literature, which often does not account for these key variables[20]. Furthermore, clinicians should be alert to the fact that men are especially vulnerable to fatigue worsening, and explicit discussion of fatigue risk may provide care providers opportunities to manage it proactively.

This study has several important limitations. First, these data only generalize to outpatient care settings and patients with common solid tumors over the time interval of 28–35 days. Although there is a known, high correlation between single item screening fatigue screening and multiple-item instruments,[28] the use of a single item measure of fatigue severity in this study limits the comparison with studies of cancer-related fatigue that include more detailed assessment and attribution of the symptom. Another limitation is that the prescribing data concerning corticosteroid use do not reveal details related to the underlying reason for prescribing, and the data about recent cancer treatment data were also very general. Finally, it is noteworthy that no bio-specimens were collected.

In conclusion, both the proportion of patients with worsening fatigue and the set of predictors for fatigue worsening vary depending on the category of baseline fatigue and exposure to co-prescribed medications. Among patients with solid tumors for whom there is a good gender mix (e.g., patients with lung or colorectal cancer), male gender was a strong predictor of fatigue worsening. These data draw attention to clinicians and clinical trialists to the need for comprehensive assessment of ambulatory cancer patients to include multiple symptoms and all comorbidities and concomitant medications in order to unveil modifiable factors and improve on the patient experience of fatigue. Ultimately, rigorous case definitions and correlative science will be needed to improve our understanding of mechanisms for fatigue in cancer patients and improve our ability to identify clinically useful, distinct phenotypes for fatigue in ambulatory cancer patients.

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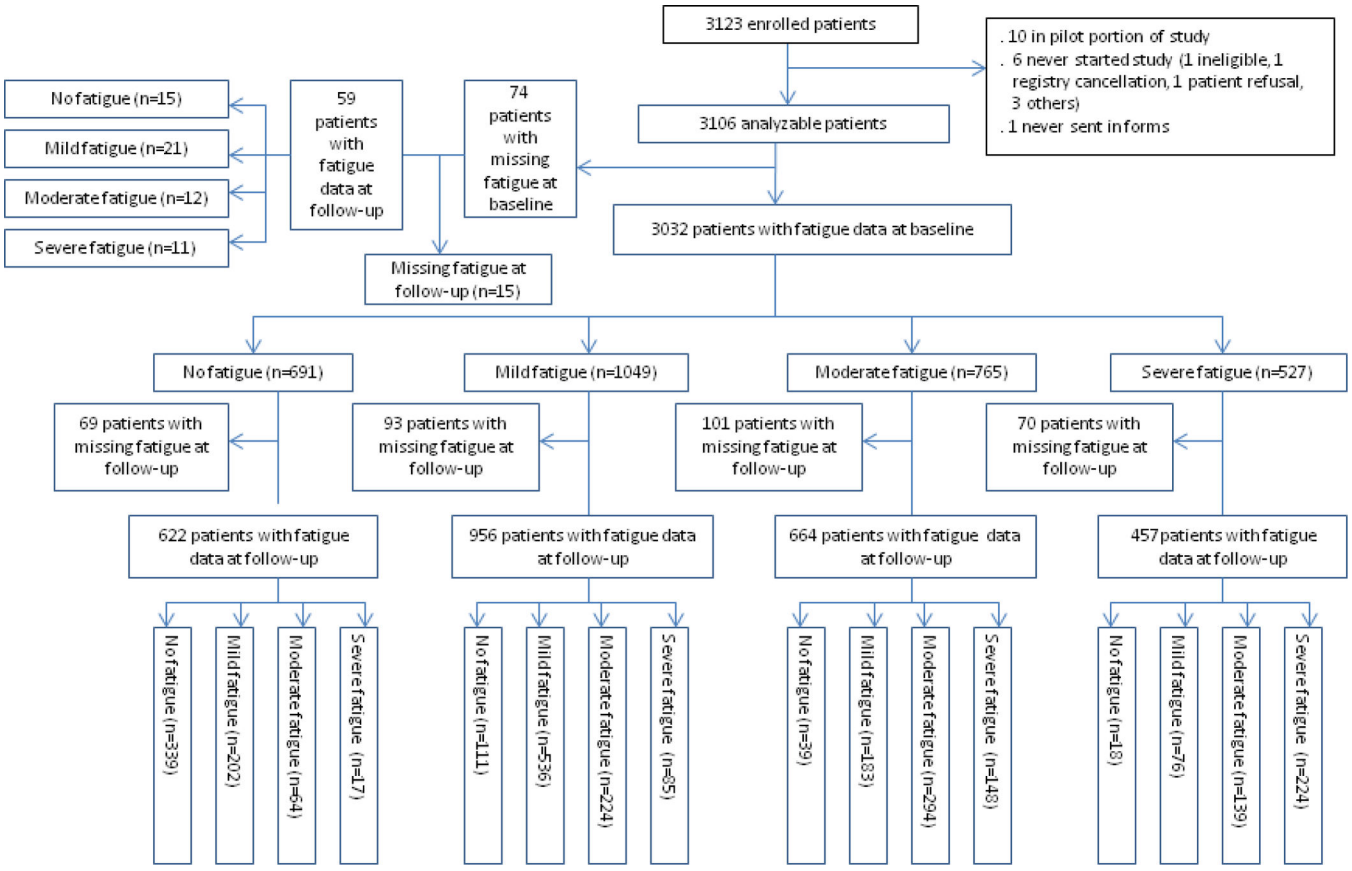

Figure 1.

Study flow diagram. Mild fatigue: fatigue scores of 1–3, moderate fatigue: fatigue scores of 4–6, and severe fatigue: fatigue scores of 7–10. A total of 2699 patients reported a fatigue score at both initial and follow-up assessments.

Table 1

Demographic and Disease Characteristics by Severity of Fatigue at Baseline

Demographic and disease characteristics		Number of patients	Fatigue score at baseline (%)				
			0	1–3	4–6	7–10	*P* value
Demographic characteristics							
Age (years)	>=55	2075	74.24	67.78	69.15	61.1	< 0.001
	<55	957	25.76	32.22	30.85	38.9	
Sex	Female	2,126	22.3	35.6	24.5	17.6	0.186
	Male	906	24.0	32.2	27.0	16.8	
Race and ethnicity	Minority	667	28.6	26.4	23.2	21.7	< 0.001
	Non-Hispanic whites	2,137	20.8	36.9	25.9	16.5	
Disease Characteristics							
Primary disease site	Breast	1,509	24.3	36.7	23.0	16.0	< 0.001
	Colon/rectum	700	24.3	34.3	25.6	15.9	
	Prostate	307	27.4	30.3	28.7	13.7	
	Lung	516	13.6	31.4	29.3	25.8	
Current status of disease	CR/PR/ SD	2,583	24.3	35.1	24.7	15.9	< 0.001
	PD	432	13.9	31.3	27.8	27.1	
Current stage of disease	Non-advanced	1,877	29.1	34.9	21.9	14.1	< 0.001
	Advanced	1,145	12.5	34.2	30.5	22.8	
ECOG performance status	0	1,718	29.9	38.7	21.0	10.5	< 0.001
	1–4	1,300	13.5	29.2	30.9	26.4	
Duration of cancer	Median	3,032	1.7	1.2	1.1	1.1	0.002
Treatment of Cancer							
Institution type	Academic	296	29.7	25.7	25.0	19.6	0.001
	Community	2,736	22.0	35.6	25.3	17.1	
Prior chemo/immuno/hormonal therapy	No	1,160	22.8	35.7	24.7	16.8	0.740
	Yes	1,871	22.7	33.9	25.6	17.7	

Demographic and disease characteristics		Number of patients	Fatigue score at baseline (%)				
			0	1–3	4–6	7–10	*P* value
Prior radiation therapy	No	1,737	24.1	34.5	24.9	16.5	0.208
	Yes	1,269	21.0	35.1	25.5	18.4	
Current therapy (any type)	No	783	32.6	32.4	21.1	13.9	< 0.001
	Yes	2,249	19.4	35.4	26.7	18.6	
Number of medications currently taking	0–4	882	28.3	37.6	20.2	13.8	< 0.001
	5–9	1,180	21.0	35.3	27.4	16.3	
	>=10	668	13.9	29.9	31.0	25.2	
Receive individual counseling	No	2,736	23.1	35.1	25.2	16.7	0.009
	Yes	291	20.3	29.6	26.1	24.1	
Participate support group	No	2,829	22.9	34.6	25.2	17.3	0.762
	Yes	199	20.1	34.2	26.6	19.1	
Quality of Life							
Clinician perception of being bothered by difficulty related to co-morbidities	Not at all/ A little bit	2,273	25.7	36.3	23.7	14.4	< 0.001
	Moderately/Quite a bit/Extremely	741	13.8	29.6	30.1	26.6	
Patient perception of being bothered by difficulty related to co-morbidities	Not at all/ A little bit	2,039	27.2	37.6	21.8	13.4	< 0.001
	Moderately/Quite a bit/Extremely	986	13.6	28.5	32.4	25.6	
Weight loss in the previous 6 months	< 5%	2,571	24.8	35.5	24.5	15.2	< 0.001
	>=5%	427	11.0	29.7	29.3	30.0	
Patient reported overall quality of life	Good/ Excellent	2126	28.9	39.8	21.1	10.2	< 0.001
	Fair /Poor/ Very poor	897	8.4	22.1	35.1	34.5	
History of depression	No	2,147	26.0	35.8	24.2	14.0	< 0.001
	Yes	881	15.0	31.6	27.8	25.7	
Overall		3,032	22.8	34.6	25.2	17.4	

Abbreviations: ECOG, Eastern Cooperative Oncology Group

Notes:
1) Significance was tested by chi-square test for binary and categorical variables, and Fisher's exact test of the equality of the medians was used for continuous variables. Significance level was set at 0.05.
2) Seventy-four patients had missing fatigue data at baseline.
3) The total number of patients did not add up to 3032 for some variables due to missing values.

Table 2

Change in Fatigue Severity by Fatigue Severity Level at Baseline

A. All patients

Fatigue score at baseline	No. of patients	Better	No change	Worse
0	622	0 (0.0)	439 (70.6)	183 (29.4)
1–3	**956**	**82 (8.6)**	**542 (56.7)**	**332 (34.7)**
1	356	0 (0.0)	224 (62.9)	132 (37.1)
2–3	600	82 (13.7)	318 (53.0)	200 (33.3)
4–6	**664**	**208 (31.3)**	**308 (46.4)**	**148 (22.3)**
7–10	**457**	**245 (53.6)**	**186 (40.7)**	**26 (5.7)**
7–8	301	151 (50.2)	124 (41.2)	26 (8.6)
9–10	156	94 (60.3)	62 (39.7)	0 (0.0)
Total	2699	535 (19.8)	1475 (54.6)	689 (25.5)

B. Patients with no current therapy

Fatigue score at baseline	No. of patients	Better	No change	Worse
0	230	0 (0.0)	182 (79.1)	48 (20.9)
1–3	**222**	**22 (9.9)**	**128 (57.7)**	**72 (32.4)**
1	86	0 (0.0)	56 (65.1)	30 (34.9)
2–3	136	22 (16.2)	72 (52.9)	42 (30.9)
4–6	**135**	**45 (33.3)**	**66 (48.9)**	**24 (17.8)**
7–10	**88**	**55 (62.5)**	**27 (30.7)**	**6 (6.8)**
7–8	55	31 (56.4)	18 (32.7)	6 (10.9)
9–10	33	24 (72.7)	9 (27.3)	0 (0.0)
Total	675	122 (18.1)	403 (59.7)	150 (22.2)

C. Patient with current therapy within 1 month

Fatigue score at baseline	No. of patients	Better	No change	Worse
0	104	0(0.0)	55 (52.9)	49 (47.2)
1–3	**195**	**16 (8.2)**	**88 (45.1)**	**91 (46.7)**
1	76	0(0.0)	37 (48.7)	39 (51.3)
2–3	119	16 (13.4)	51 (42.9)	52 (43.7)
4–6	**122**	**31 (25.4)**	**55 (45.1)**	**36 (29.5)**
7–10	**98**	**58 (59.2)**	**35 (35.7)**	**5 (5.1)**
7–8	64	34 (53.1)	25 (39.1)	5 (7.8)
9–10	34	24 (70.6)	10 (29.4)	0 (0.0)
Total	519	105 (20.2)	233 (44.9)	181 (34.9)

D. Patients with current therapy between 1 month and 1 year

Fatigue score at baseline	No. of patients	Better	No change	Worse
0	173	0(0.0)	112 (64.7)	61 (35.3)
1–3	**386**	**31 (8.0)**	**224 (58.0)**	**131 (33.9)**
1	140	0(0.0)	91 (65.0)	49 (35.0)
2–3	246	31 (12.6)	133 (54.1)	82 (33.3)
4–6	**312**	**98 (31.4)**	**139 (44.6)**	**75 (24.0)**
7–10	**207**	**94 (45.4)**	**100 (48.3)**	**13 (6.3)**
7–8	141	62 (44.0)	66 (46.8)	13 (9.2)
9–10	66	32 (48.5)	34 (51.5)	0(0.0)
Total	1,078	223 (20.7)	575 (53.3)	280 (26.0)

E. Patients with current therapy beyond 1 year

Fatigue score at baseline	No. of patients	Better	No change	Worse
0	112	0(0.0)	87 (77.7)	25 (22.3)
1–3	**151**	**13 (8.6)**	**101 (66.9)**	**37 (24.5)**
1	52	0(0.0)	39 (75.0)	13 (25.0)
2–3	99	12 (13.1)	62 (62.6)	24 (26.2)
4–6	**92**	**32 (34.8)**	**47 (51.1)**	**13 (14.1)**
7–10	**62**	**37 (59.7)**	**23 (37.1)**	**2 (3.2)**
7–8	39	23 (59.0)	14 (35.9)	2 (5.1)
9–10	23	14 (60.9)	9 (39.1)	0(0.0)
Total	417	82 (19.7)	258 (61.9)	77 (18.5)

Note: Change in fatigue severity: worse was defined as >=2 point increase; better was defined as >=2 point decrease; no change was defined as <2 points change (either increase or decrease)

Table 3

Logistic Regression Modeling Fatigue Worsening for Patients with Baseline Fatigue Level of 0–8 (n=2,367)

Variable		Univariate regression				Multivariable regression			
		OR	95% CI		P value	OR	95% CI		P value
Demographics									
Age	< 55 v > = 55	0.98	0.81	1.19	0.858	1.10	0.86	1.41	0.448
Race	Non-Hispanic white v other	0.95	0.80	1.13	0.564	0.96	0.79	1.16	0.673
Disease Characteristics									
Duration of cancer	Continuous (years)	0.96	0.94	0.98	0.001	0.97	0.94	1.00	0.032
Disease status	PD v other	1.60	1.27	2.03	<0.001	1.99	1.53	2.58	<0.001
Disease site	Colorectal v breast	0.89	0.68	1.17	0.424	0.77	0.57	1.04	0.090
	Prostate v breast	0.91	0.62	1.33	0.633	0.93	0.59	1.45	0.744
	Lung v breast	1.36	1.10	1.67	0.004	1.18	0.90	1.55	0.222
Advanced disease	Yes v no	1.04	0.84	1.29	0.704	0.92	0.69	1.22	0.564
Treatment of Cancer									
Exposure to corticosteroids	Yes v no	1.55	1.21	1.98	0.001	1.37	1.03	1.83	0.031
Current treatment	< 1 m v no treatment	1.91	1.48	2.46	<0.001	1.77	1.32	2.38	<0.001
	> 1 m and <1 yr v no treatment	1.24	0.99	1.55	0.066	1.28	0.95	1.72	0.104
	>1 yr v no treatment	0.97	0.56	1.03	0.080	0.75	0.53	1.07	0.112
Number of medicines currently taken	5–9 v 1–4	1.29	1.04	1.59	0.018	1.18	0.91	1.52	0.203
	> = 10 v 1–4	1.52	1.19	1.95	0.001	1.33	0.92	1.94	0.131
	Missing v 1–4	1.44	1.05	1.97	0.022	1.26	0.91	1.73	0.158
Exposure to SSRI/newer antidepressants	Yes v no	1.33	1.10	1.60	0.003	1.29	0.99	1.68	0.055
Exposure to other antidepressants	Yes v no	0.93	0.48	1.80	0.824	0.77	0.38	1.55	0.456
Exposure to anxiolytics	Yes v no	1.38	1.11	1.73	0.004	1.22	0.94	1.58	0.133
Exposure to sedative	Yes v no	1.04	0.76	1.43	0.790	0.83	0.57	1.20	0.319
Exposure to beta blockers	Yes v no	1.12	0.93	1.35	0.226	1.17	0.96	1.43	0.120
Undertreatment of pain	Yes v no	1.45	1.17	1.79	0.001	1.09	0.85	1.41	0.491
	Missing v no	1.13	0.67	1.91	0.648	1.13	0.61	2.11	0.699
Prior chemo/immuno/hormonal therapy	Yes v no	0.81	0.71	0.94	0.004	0.88	0.71	1.09	0.233

Variable		Univariate regression				Multivariable regression			
		OR	95% CI		P value	OR	95% CI		P value
Prior radiation	Yes v no	0.90	0.74	1.09	0.270	1.05	0.84	1.31	0.677
Type of institute	Community v academic	1.01	0.73	1.39	0.968	1.17	0.72	1.91	0.533
Receive counseling	Yes v no	1.14	0.86	1.51	0.373	1.08	0.73	1.58	0.701
Participate in support group	Yes v no	0.74	0.51	1.07	0.111	0.77	0.52	1.14	0.187
Quality of Life									
Fatigue at baseline	Continuous	0.85	0.83	0.88	<0.001	0.75	0.72	0.78	<0.001
History of depression	Yes v no	1.27	1.05	1.54	0.015	1.28	1.02	1.61	0.033
ECOG performance status	> = 1 v 0	1.28	1.06	1.54	0.009	1.38	1.13	1.69	0.002
Patient's perception of being bothered by comorbidity	Yes v no	1.12	0.94	1.33	0.224	1.26	1.03	1.54	0.028
Clinician's perception of being bothered by comorbidity	Yes v no	1.10	0.90	1.33	0.370	1.14	0.87	1.49	0.346
Patient-reported quality of life	Poor v good	1.01	0.80	1.28	0.930	1.13	0.86	1.47	0.383
Weight loss	> = 5% v < 5%	1.04	0.77	1.41	0.785	1.09	0.78	1.53	0.608
Cognitive difficulty	> = 5 v < 5	0.92	0.69	1.22	0.554	1.34	0.97	1.85	0.081
Drowsy at baseline	> = 5 v < 5	0.67	0.53	0.86	0.002	1.03	0.74	1.44	0.852
Sleep at baseline	> = 5 v < 5	0.84	0.68	1.04	0.104	1.15	0.86	1.54	0.346
Pain at baseline	> = 5 v < 5	0.72	0.54	0.95	0.019	1.04	0.69	1.56	0.845