Cancer Related Fatigue: A Focus on Breast Cancer Patients Under Chemotherapy

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Abstract: *Introduction*: Fatigue is a common and frequently disabling symptom in cancer patients and cancer survivors. Fatigue may be caused by the disease itself, by treatment for the disease, by physical symptoms or conditions resulting from the disease or its treatment. The aim of this study was to assess fatigue and related factors in breast cancer patients.

Material & Methods: We conducted a cross-sectional study on 119 random samples of breast cancer patients. The Iranian version of QLQ-C30 and QLQ-BR23 questionnaires were used. Univariate methods and multiple regression analysis were performed to identify predictors of fatigue.

Results: Overall, 78% of the patients indicated that they were experiencing fatigue to some degree. The mean score on the fatigue subscale was 41.74±26.91.

Of all functional subscales, fatigue showed the strongest influence on social functioning. Linear regression analyses showed that total fatigue was best predicted by pain, appetite loss, body image and type of treatment.

Conclusion: Our results support the notion that fatigue in cancer patients is a major problem, which deserves yet more attention from health professionals, and that quality of life in cancer patients might be improved markedly by interventions that effectively reduce fatigue.

INTRODUCTION

Fatigue is a common and frequently disabling symptom in cancer patients and cancer survivors [1,2]. Cancer-related fatigue (CRF) is a complex multidimensional concept that includes psychological, social, and physiological aspects. It is defined as a "subjective feeling of tiredness that is influenced by circadian rhythms and can vary in unpleasantness, duration, and intensity"[3].

The occurrence of fatigue varies across tumor sites and treatment stage [4, 5]. Specific to breast cancer, fatigue is reported by a substantial majority of patients during their initial treatment (surgery, radiation, and/or chemotherapy) [6]. Studies examining the prevalence of fatigue among breast cancer patients have found that up to 99% experience some level of fatigue during the course of radiation therapy and/or chemotherapy, and more than 60% rate their level of fatigue as moderate to severe [7]. There is growing evidence to suggest that fatigue may persist for months or even years after completion of breast cancer treatment, particularly among patients who have received adjuvant chemotherapy [8]. However, the exact mechanisms underlying the onset and persistence of fatigue in women with breast cancer have not yet been determined [9].

Various risk factors for fatigue have been identified in the literature on post treatment breast cancer patients. Fatigue may be caused by the disease itself, by treatment for the disease, by physical symptoms or conditions resulting from the disease or its treatment (eg, menopausal symptoms), and/or by psychological responses to breast cancer [10]. A limited number of studies have examined correlates of fatigue among breast cancer patients and may provide insight into potential causative factors. Interestingly, medical and treatment-related factors are not consistently associated with fatigue in studies of breast cancer patients [11-13]. Therefore, the specific aims of this study were to [1] describe the frequency of fatigue symptom [2], and examine correlates of fatigue in relation to sociodemographic and clinical characteristics and symptoms.

MATERIALS & METHODS

We conducted a cross-sectional study on 119 random samples of breast cancer patients that admitted and treated in chemotherapy ward of Namazi hospital in Shiraz city, south of Iran during Jan to Feb 2007. This center is a referral center in south of province. Inclusion Criteria were: Any patients with a new diagnosis of breast cancer, according to pathology report, under chemotherapy were eligible to enter the study.

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The exclusion criteria were: cancer diagnosis less than 2 months; recurrence of breast cancer; cognitive impairment; other previous or concurrent malignancies.

The Iranian version of QLQ-C30 and QLQ-BR23 questionnaires were used to assess the quality of life (QOL) and Fatigue in these patients. These questionnaires are valid and reliable questionnaires for evaluation of quality of life in breast cancer patients in Iran [14,15]. The QLQ-C30 questionnaire are a self-report multidimensional general cancer-specific questionnaire, which was designed to assess QOL in cancer patients. The QLQ-C30 proved useful in many clinical trials, because it assesses the main factors influencing HRQOL of patients with cancer [16]. The QLQ-C30 is multidimensional, made up of 30 items (five functional domains: physical, role, emotional, cognitive, and social, one global QOL domain, three symptom domains: fatigue, nausea-vomiting, pain, and six single items). The fatigue subscale of the QLQ-C30 consists of three items that assess how much of the time the individual "need to rest", "felt week" and "felt tired" during the past week. The EORTC QLQ-BR23 was designed for patients with different disease stages and treatment modalities (surgery, chemotherapy, radiotherapy, or hormonal treatment). The module incorporates 23 questions grouped into five multi-item scales to assess the effect of therapy on systemic side effects, arm symptoms, breast symptoms, body image, and sexual functioning. Sexual enjoyment, being upset by hair loss, and perceived future perspective are assessed as three separate items [17].

The scores are transformed into 0-100 point scales. In the case of the five functional scales and the global QOL scale, the high score means: 'high level of functioning or global QOL'. On the other hand, in the case of symptom scales and single items, the higher score implies the higher level of symptoms or problems [18].

Sociodemographic data included age, education, occupation and marital status, and Clinical data including grade of tumor, metastasis, type of treatment, type of first treatment, co-morbidity, type of treatment, type of first treatment, duration of disease and status of menopause gathered by additional questionnaire. The study protocol has been approved in ethical committee of Shiraz University of medical science. Before the interview survey, the interviewer explained the purpose of these questions to all eligible individuals and requested their participation. We used univariate methods such as one way ANOVS, independent t-test and Pearson's correlation tests. A multiple regression analysis was performed to identify predictors of fatigue. For this procedure, the fatigue score of the EORTC QLQ-C30 was treated as the dependent variable. Sociodemographic, medical characteristics and symptom of disease were entered as explanatory factors in the model [19, 20]. All calculation performed using SPSS.V.13.

RESULTS

Total of 119 patients with breast cancer were interviewed. The demographic and clinical characteristics of the baseline sample are shown in (Table **1**). The mean age was 48.27 (SD=11.42) years, and most of the patients were married (73.9%). The level of education in our study sample was relatively low and concerning employment status, most

of women were housekeeper or retired and only 17.6% were employed before the cancer was diagnosed. Table **1** lists the subject characteristics in detail.

Table 1.   Distribution of Demographic Characteristics in Subjects Under Study

Variable		Number	%
Age	<35	14	11.8
	35-50	55	46.2
	>50	50	42
Education	illiterate & primary	68	57.1
	diploma & lower	41	34.5
	university	10	8.4
Occupation	employee	21	17.6
	house keeper & retired	98	82.4
Marital status	married	88	73.9
	other	31	26.1

Overall, 99 cases (78%) of the patients indicated that they were experiencing fatigue to some degree (from quite bit to very much). Ninety eight cases (74.2%) reported that needed to rest, 53% felt week and 78% felt tired. The mean score on the fatigue subscale was 41.74±26.91. In addition to evaluating the level of fatigue experienced by this group of women, we were interested in examining the association between fatigue and other components of quality of life. Results showed significant correlations between fatigue and each subscale. Of all functional subscales, fatigue showed the strongest influence on social functioning.

In univariate analysis, among demographic factors (such as age, education, marital status and occupation) only marital status was associated with fatigue, and single patients had higher fatigue score (P<0.001). All of the independent variables were modestly, but significantly, associated with fatigue. Fatigue scores were inversely correlated with body image and future perspective, and positively associated with pain, dyspnea, constipation, diarrhea, appetite loss, insomnia and financial difficulties, breast symptoms, arm symptoms and Systemic therapy side effects (Table **2**). Higher fatigue scores were significantly associated with poor grade of tumor (p=0.034).

Linear regression analyses showed that total fatigue was best predicted by pain, appetite loss, body image and type of treatment (Table **3**). The other variables including tumor metastasis, grade of tumor, type of first treatment, occupation and other symptoms were not significant predictors of fatigue.

DISCUSSION

The results indicate that body image and type of treatment are related to fatigue. The presence of dyspnea, insomnia, appetite loss, constipation, arm symptoms, and breast symptoms were all associated with increased risk of fatigue. In regression analysis, pain, appetite loss, body image and adjuvant chemotherapy were significant and

Table 2.   Mean and Standard Deviation of EORTC QLQ-C30 & BR-23 Subscale Scores in Breast Cancer Patients and their Correlation with Fatigue

p-Value	Correlation Coefficient	Standard Deviation Mean	Subscales
Functining			
<0.0001	-0.512	57.31±23.76	Physical
<0.0001	-0.502	65.27±34.89	Role
<0.0001	-0.441	56.26±30.84	Emotional
0.001	-0.304	72.27±27.47	cognitive
<0.0001	-0.595	69.61±32.95	Social
Symptoms			
<0.0001	0.369	16.39±28.37	Nausea & Vomiting
<0.0001	0.46	33.19±28.25	Pain
0.011	0.233	16.25±27.05	Dyspnea
0.002	0.281	43.74±0.65	Insomnia
<0.0001	0.446	22.69±36.29	Appetite loss
0.001	0.302	14.85±29.34	Constipation
0.027	0.203	3.92±16.34	Diarrhea
0.030	0199	50.98±41.81	Financial difficulties
0.029	-0.200	47.34±36.69	Future perspective
0.015	-0.350	37.51+6.15	Body image
<0.0001	0.426	38.14+19.56	Systemic therapy side effect
0.004	0.261	12.46+17.22	Breast symptoms
0.008	0.243	32.68+26.13	Arm symptoms
0.063	0.188	52.04+39.49	Upset by hair loss

independent predictors of fatigue scores. Clinical characteristics were not significant determinants of fatigue except grade of tumor.

Table 3.   Predictors of Fatigue by Using Linear Regression Model

Variable	β	SE (β)	P-Value
Pain	0.323	0.067	<0.0001
Appetite loss	0.217	0.054	<0.0001
Body image	-0.255	0.057	<0.0001
Type of treatment (chemotherapy)	15.45	6.38	0.017

Adjusted R Square: 0.58.

With regard to physical symptoms the analysis revealed that fatigue was significantly predicted by pain, but not by dyspnea, and insomnia. An association between fatigue and the severity of pain has been confirmed in several research studies [21,22]. The contribution of pain to fatigue in cancer patients might be explained in several ways. One explanation is that most patients with cancer experience pain and this could lead to many other complicated symptoms both physical and psychological that in turn make patients feel fatigue [23].

The role of dyspnea and arm symptoms also must be acknowledged for the management of fatigue in breast cancer patients. Servaes and colleagues found that reduced physical activity after cancer treatment was related to more severe fatigue, and it is possible that dyspnea might follow from the same activity reduction [24]. Like another studies [10, 25], our finding shows increasing physical functioning decreases fatigue scores, therefore, physical activity intervention should be valuable for the management of fatigue symptoms in breast cancer patients.

Arm symptoms could be a long-term effect of surgery or adjuvant therapy and have been previously reported as a significant factor related to fatigue [10]. However, the clustering of fatigue and arm symptoms has not been studied sufficiently, nor is it routinely assessed in follow-up clinics.

The present study showed that appetite loss, constipation and diarrhea were associated to fatigue. These symptoms in conjunction with having a gastrointestinal disease (such as gastric or duodenal ulcers) were significantly associated with fatigue. It is possible that these contribute to fatigue *via* malnutrition or anemia [26].

Financial difficulties were identified as another factor influencing fatigue. These findings are consistent with those of earlier studies [15, 27] and clinicians who care for breast cancer patients experiencing fatigue, therefore, be aware of patients' socioeconomic status.

We found significant association between fatigue and type of treatment. This is in agreement with many, previous studies [7, 15] that women who received chemotherapy (with or

without radiotherapy) reported more severe fatigue than those who did not.

There were several limitations in our study. First, we used a cross-sectional design, which makes it difficult to identify cause. The study did not include a control group and therefore it is difficult to conclude whether breast cancer patients were more fatigued as compared to patients with benign breast problems or healthy women [28]. Second, we did not assess psychosocial factors (such as anxiety, coping style, self-efficacy, and social support) or biological factors (such as alterations in immune or neuroendocrine function) that might have a strong impact on fatigue or depression [29, 30].

In conclusion, results support the notion that fatigue in cancer patients is a major problem, which deserves yet more attention from health professionals, and that QOL in cancer patients might be improved markedly by interventions that effectively reduce fatigue. Further research is needed to reproduce these results in patients of different tumor types and at different stages of disease and therapy, ranging from diagnosis to the palliative treatment stage.

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