



Breast Cancer

Prevalence, Characteristics, and Correlates of Fatigue in Indian Breast Cancer Survivors: A Cross-Sectional Study

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Abstract



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Background Fatigue is one of the commonest sequelae of breast cancer treatment that adversely impacts quality of life (QOL) of breast cancer survivors (BCSs). However, very limited data are available about cancer-related fatigue in Indian patients. Hence, this study was planned with the objectives to study (1) prevalence of fatigue in short-, intermediate-, and long-term follow-up; (2) severity and characteristics of fatigue; (3) impact of fatigue on QOL; and (4) correlation of fatigue with other survivorship issues.

Materials and Methods The study was conducted on ($n = 230$) BCSs who had completed their primary treatment (surgery, radiotherapy, and chemotherapy) and were coming for follow-up. The prevalence of fatigue was noted from a screening tool, which comprised of 14 commonly reported survivorship issues. Assessment of fatigue was done by using survivorship fatigue assessment tool-1 score and QOL was assessed by functional assessment of cancer therapy-breast (FACT-B) questionnaires. To understand how fatigue evolved over time, survivors were divided into three groups according to the time elapsed since initial treatment: Group 1: <2 years ($n = 105$); Group 2: 2–5 years ($n = 70$); Group 3: >5 years ($n = 55$).

Statistical Analysis Data was analyzed by using simple descriptive statistics, one way analysis of variance followed by Tukey's test for comparison of quantitative data among the three groups, and Pearson correlation coefficients for association of fatigue with other survivorship issues.

Results Clinically significant fatigue (≥ 4) was noted in 38% of BCSs. However, high overall prevalence of fatigue (60%) was seen, which persisted in long-term survivors (51%) as well. Severity of fatigue was mostly mild (37.7%) to moderate (47.1%). Fatigue scores were significantly higher in short-term survivors (5.01 ± 2.06) than intermediate- (4.03 ± 1.42) and long-term BCSs (3.57 ± 1.37). The mean score on FACT-B was 90.07 ± 10.17 in survivors with fatigue and 104.73 ± 7.13 in those without fatigue ($p = 0.000$). Significant correlation of fatigue was seen with other survivorship issues.

Keywords

- ▶ breast cancer survivors
- ▶ fatigue
- ▶ quality of life
- ▶ survivorship care

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like limb swelling, chronic pain, premature menopause, and its related symptoms and emotional distress.

Conclusion Fatigue is highly prevalent in BCSs. Survivorship care programs should include appropriate measures to evaluate and address fatigue.

Introduction

Fatigue is recognized as one of the most common and distressing side effects of cancer and its treatment. The National Comprehensive Cancer Network (NCCN) defined cancer-related fatigue (CRF) as “a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness, related to cancer or cancer treatment, that is not proportional to recent activity and interferes with usual functioning.”¹ Prevalence estimates of fatigue during treatment of breast cancer (BC) range from 25 to 99% depending on the patient population, type of treatment received, and method of assessment.^{2,3} Generally after completion of treatment, there is an improvement in fitness levels, although approximately one-quarter to one-third of long-term cancer survivors are reported to experience persistent fatigue for up to 10 years after cancer diagnosis.⁴ CRF affects multiple domains and has physical, mental, and emotional manifestations including generalized weakness, diminished concentration or attention, decreased motivation or interest to engage in usual activities, and emotional lability.⁵ Fatigue may also be a predictor of shorter survival.⁶

The common barriers to assessment and management of fatigue are lack of information about mechanisms underlying this symptom, risk factors, and effective treatment protocols. The knowledge about status of fatigue in Indian breast cancer survivors (BCSs) is nonexistent. The major focus in follow-up clinics of cancer survivors is usually on cancer recurrence or on clinically manifest issues such as lymphedema, shoulder restriction, or pain. Fatigue as a problem is hardly reported or treated. Hence, this study was planned with the objective to study prevalence, characteristics, and correlates of fatigue in our population of BCSs.

Materials and Methods

This study was conducted from February 2014 to April 2018 on ($n=230$) BC patients, who had completed their primary treatment of BC (surgery, radiotherapy, and chemotherapy), and were coming to surgery outpatients department for follow-up at an academic center in Delhi, as part of a large data collection on BC survivorship. Patients with metastatic, recurrent, or inoperable disease or with other serious comorbidities such as hypothyroidism, heart failure, chronic obstructive pulmonary diseases, end-stage renal diseases, psychiatric diseases, autoimmune disorders such as rheumatoid arthritis at the time of BC diagnosis were excluded from the study. The study was approved by the institutional research board and ethics committee. A written informed consent was obtained from all the participants before inclusion in the study.

The demographic, clinical, and follow-up data were recorded in a predesigned proforma.

Evaluation of survivors was done by conducting personal interviews. BCSs were asked to respond to a checklist of 14 commonly reported survivorship issues such as (1) fatigue, (2) postmastectomy chronic pain, (3) arm swelling, (4) restriction of shoulder movement, (5) body and joint pains, (6) cessation of menstruation, (7) hot flashes, (8) vaginal dryness, (9) loss of sexual desire, (10) sleeplessness, (11) memory loss, (12) depression/anxiety, (13) weight gain, and (14) body image. This list was prepared after an extensive review of the relevant literature.

Assessment of fatigue was done by using survivorship fatigue assessment tool-1 (SFAT-1).⁷ This simple screening tool for fatigue was drawn from NCCN guidelines version 1.2013. Survivors were asked to rate their severity of fatigue on a scale of 0 to 10 over the past 7 days, where 0 is no fatigue and 10 is worst fatigue imaginable. The grading of severity was done as: none to mild (0–3), moderate (4–6), and severe (7–10). A rating of ≥ 4 was taken as clinically significant fatigue.

Assessment of quality of life (QOL) was done by using functional assessment of cancer therapy-breast (FACT-B version 4).⁸ FACT-B questionnaire has a generic part, functional assessment of cancer therapy-general (FACT-G), and a breast cancer-specific subscale. It has 36 items scale consisting of four general subscales, such as physical well-being (PWB), social well-being, functional well-being (FWB), and emotional well-being (EWB). The fifth subscale contains nine items and is specific for BC. All FACT-B scales are scored so that a high score is good. The instrument has multiple scoring options: subscale scores, total score (FACT-B and FACT-G), and trial outcome index (TOI) that are the sum total of PWB, FWB, and BCS. The test was administered and scored in accordance with the instructions in the manual for the version 4 of the functional assessment of chronic illness therapy measurement. The score range for FACT-B is 0 to 144, for FACT-G 0 to 108, and TOI 0 to 92. The instrument is easy to complete and has been shown to have good validity and reliability properties.^{9,10}

Statistical Analysis

Data was analyzed using SPSS 22.0 statistical software. For different QOL tools, scoring was done as per specified guidelines. Simple descriptive analysis was done for demographic and clinical characteristics and frequency and severity of fatigue. To understand how profile of fatigue changed over time, survivors were divided into three groups according to the time elapsed since initial treatment: Group 1: <2 years ($n=105$); Group 2: 2–5 years ($n=70$); Group 3: >5 years

(n = 55). Student's *t*-test for quantitative data and chi-squared test for qualitative data were used to evaluate statistically significant difference between the groups as appropriate. *p*-Value of <0.05 was considered statistically significant. For comparison of quantitative data in the three groups, one way analysis of variance followed by Tukey's test was applied.

To evaluate the correlation of fatigue with various survivorship issues, Pearson correlation coefficients were calculated.

Results

Demographic and Clinical Details of BCSs

The mean age of the survivors was 49.74 ± 9.58 years. Most of the survivors were Hindus (84.8%), married (83.5%), housewives (89%), and postmenopausal (84.8%). Almost half of these menopausal women had chemotherapy-induced menopause. Stage II was the most common stage of presentation (46%). Majority underwent modified radical mastectomy (70%). Over 96% patients received chemotherapy, 83% radiotherapy, and 58% hormone treatment. Further details of the study population are presented in [Table 1](#).

Prevalence of Fatigue

Fatigue was reported by 60% of the survivors overall and clinically significant fatigue (SFAT-1 score ≥4) was noted in 38% of survivors. Though with longer duration of follow-up the rate of fatigue declined, it was still experienced by nearly 50% of the survivors, even after 5 years of follow-up. Frequency of fatigue was highest (72.4%) in Group 1 survivors, whereas rates of fatigue in Group 2 and Group 3 patients were comparable at 48.6 and 50.9%, respectively.

Severity of Fatigue in Different Groups of Survivors

Severity of fatigue was considered none to mild for a score of 0 to 3, moderate for a score of 4 to 6, and severe for a score of 7 to 10. The severity of fatigue in three groups of BCSs was mostly mild (52; 37.7%) and moderate (65; 47.1%) in intensity. Only 21 (15%) survivors rated their fatigue to be severe (score of 7 or above).

The mean fatigue scores among survivors were mostly in moderate range. Group 1 survivors had significantly higher mean fatigue score (5.01 ± 2.06) than survivors in Group 2 (4.03 ± 1.42) and Group 3 (3.57 ± 1.37; [Fig. 1](#)). The rate and severity scores of fatigue in the three groups of survivors are shown in [Table 2](#).

Table 1 Demographic and clinical profile of the study population

Demographic and clinical Variables		BCSs Overall (n = 230)	BCSs with fatigue (n = 138)	BCSs without fatigue (n = 92)	p-Value
Age (years)	Mean ± SD	49.74 ± 9.58	53.20 ± 8.93	46.96 ± 7.68	0.04*
Religion	Hindu	195 (84.8%)	120 (86.7%)	75 (81.5%)	0.33
	Muslim	20 (8.7%)	11 (7.9%)	9 (9.7%)	
	Sikh	8 (3.5%)	3 (2.1%)	5 (5.4%)	
	Christian	7 (3%)	4 (2.9%)	3 (3.2%)	
Marital status	Single	6 (2.6%)	4 (2.9%)	2 (2.1%)	0.28
	Married	192 (83.5%)	120(86.9%)	72 (78.2%)	
	Widowed/divorced	32 (13.9%)	14 (10%)	18 (18.6%)	
Occupation	Housewife	204 (89%)	126 (91.3%)	78 (84.8%)	0.54
	Employed	26 (10.9%)	12 (8.6%)	14 (15.21%)	
Menopausal status	Premenopausal	35 (15.2%)	10 (7.24%)	25 (27.2%)	0.045*
	Postmenopausal	195(84.8%)	128 (92.8%)	67 (72.8%)	
Tumor stage	I	17 (7.39%)	7 (5.07%)	10 (10.8%)	0.28
	II	114 (49.6%)	62 (45%)	52 (56.6%)	
	III	99 (43.0%)	69 (50%)	30 (32.6%)	
Surgery performed	MRM	161 (70%)	98 (71%)	63 (68.4%)	0.34
	BCT	55 (23.9%)	31 (22.5%)	24 (26%)	
	MRM with reconstruction	14 (6.08%)	9 (6.52%)	6 (6.52%)	
Chemotherapy	Received	221 (96%)	135 (97.8%)	86 (93.4%)	0.84
Radiotherapy	Received	191 (83%)	119 (86.2%)	72 (78.3%)	0.55
Hormonal therapy	Received	134 (58.2%)	78 (56.5%)	56 (60.8%)	0.46

Abbreviations: BCSs, breast cancer survivors; BCT, breast-conserving therapy; MRM, modified radical mastectomy; SD, standard deviation.

*Significant (*p* < 0.05).

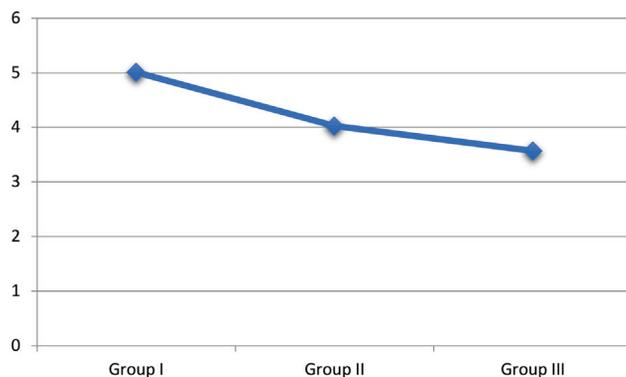


Fig. 1 Mean fatigue scores in three groups of survivors.

Correlation of Fatigue with Age and Demographic Parameters of the Breast Cancer Survivors

On assessing the relationship of fatigue with the age of the survivor, the younger survivors reported significantly lower levels of fatigue compared with older ones, irrespective of their duration of follow-up (mean scores: 3.50 ± 1.44 in women <40 ; 4.48 ± 1.92 in women 41–55 year; 4.98 ± 1.87 in women >55 years of age). **Table 3** shows correlation of fatigue scores with the age of the survivors. Demographic parameters like religion, occupation, or marital status were not found to have any significant association with fatigue.

Table 2 Fatigue in different groups of survivors

Fatigue	Group I n = 105	Group II n = 70	Group III n = 55	Total n = 230	p-Value
Frequency	76 (72.4%)	34 (48.6%)	28 (50.9%)	138 (60%)	I vs. II = .001 ^a I vs. III = 0.006 ^a II vs. III = 0.461
Mean score	5.01 ± 2.06	4.03 ± 1.42	3.57 ± 1.37	4.48 ± 1.88	I vs. II = 0.024 ^a I vs. III = 0.001 ^a II vs. III = 0.580
Severity of fatigue					
Mild	21 (20%)	15 (21.4%)	16 (29%)	52 (37.6%)	0.362
Moderate	35 (33.3%)	19 (27%)	11 (20%)	65 (47.15%)	0.043
Severe	20 (19%)	0 (0%)	1 (1.8%)	21 (15.2%)	0.016

Abbreviation: ANOVA, analysis of variance.

^aSignificant (chi-squared test; one-way ANOVA followed by Tukey's test).

– Chi-square test for mean fatigue score.

– One way ANOVA followed by Tubey's test for frequency and severity of fatigue.

Table 3 Correlation of fatigue scores with the age of the survivors

Age groups	n (%)	Mean \pm SD	Significance (between groups)
I ≤ 40 (n = 54)	26 (48%)	3.50 ± 1.44	I vs. II = 0.183 I vs. III = 0.000 ^a II vs. III = 0.414
II 41–55 (n = 113)	61 (54%)	4.48 ± 1.92	
III >55 (n = 63)	51 (81%)	4.98 ± 1.87	
Total (n = 230)	138 (60%)	4.48 ± 1.88	

Abbreviations: ANOVA, analysis of variance; SD, standard deviation.

^aSignificant (one-way ANOVA followed by Tukey's test).

Impact of Fatigue on QOL Scores

Presence of fatigue was associated with significantly lower QOL scores. The mean score on FACT-B was 90.07 ± 10.17 in survivors with fatigue, and 104.73 ± 7.13 in those without fatigue ($p = 0.000$). Among the various QOL domains, physical, functional, as well as EWB were significantly poorer in survivors with fatigue, while social well-being and breast-specific subscale scores were comparable between the two groups (**Table 4**). The worst scoring items were (1) I have lack of energy; and (2) because of my physical condition, I have trouble meeting the needs of my family on PWB scale; and (3) I worry about the effect of stress on my illness on additional concerns scale.

Minimally Important Differences

A minimally important difference (MID) is defined as the “smallest difference in the mean score in the domain of interest that patient perceives as important, either beneficial or harmful, and that would lead the clinician to consider a change in the patient's management.” The range of MID as identified for FACT-B instrument is as follows: BC subscale 2 to 3, TOI breast 5 to 6, and total FACT-B 7–8.⁸ In our study population, the difference of means on all the three scores was significant according to established MID between the two groups. Details of QOL scores in survivors with and without fatigue are provided in **Table 4**.

Table 4 FACT-B subscale and summary scores in survivors with and without fatigue

FACT-B Scores	BCSs with fatigue (mean ± SD)	BCSs without fatigue (mean ± SD)	p-Value
Physical well-being	17.16 ± 4.28	19.89 ± 3.66	0.000
Social well-being	20.03 ± 3.03	20.21 ± 2.64	0.345
Emotional well-being	17.61 ± 2.75	19.02 ± 2.72	0.001
Functional well-being	17.08 ± 2.73	18.67 ± 2.84	0.008
Breast cancer subscale	21.25 ± 3.39	24.04 ± 3.66	0.045
Total FACT-B	90.07 ± 10.17	104.73 ± 7.13	0.000
Total FACT-G	69.01 ± 9.18	81.10 ± 6.47	0.000
TOI	53.69 ± 8.17	64.67 ± 5.35	0.000

Abbreviations: FACT-B, functional assessment of cancer therapy-breast; FACT-G, functional assessment of cancer therapy-breast; BCSs, breast cancer survivors; SD, standard deviation; TOI, trial outcome index. Higher scores indicate better quality of life. Significant (Independent sample t-test).

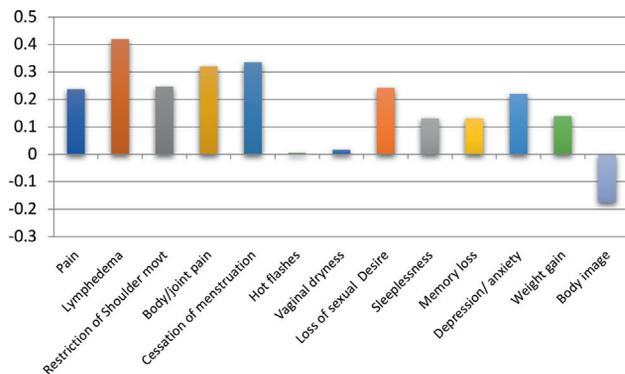


Fig. 2 Association of fatigue with other survivor's issues.

Association of Fatigue with Other Survivor's Issues

The presence of fatigue was significantly correlated with the occurrence of other survivors' issues such as postmastectomy chronic pain, lymphedema and restricted shoulder movement, emotional distress, chemotherapy-induced menopause, and its related symptoms (~Fig. 2). Strength of association was strongest with limb swelling ($r = 0.42$), and chemotherapy-induced cessation of menstruation ($r = 0.336$).

Discussion

Prevalence of clinically significant fatigue was seen in 38% of our patient population, whereas an overall prevalence of 60% was noted. Reported rates of fatigue in Indian women in the general population are in the range of 12.1% (95% confidence interval [CI]: 10.8–13.4%).¹¹ Hence, BCSs experience much more fatigue than their healthy counterparts. In other studies as well, 30 to 50% of BC patients have been reported to experience fatigue during survivorship.^{12,13} Fatigue is typically most severe during the course of treatment, although a significant minority of patients continues to experience fatigue for months or years after successful treatment.¹⁴ We too found that over 76% survivors in early follow-up

(<2 years) experienced fatigue, while nearly 50% of the survivors experienced some fatigue even after 5 years of follow-up. A high overall prevalence of fatigue in our survivors could be attributed to more advanced disease at presentation, more radical treatments, high rates of premature menopause, nonexistent survivorship services, and patient population largely from relatively lower socioeconomic strata of the society seeking treatment at a public hospital.

We found a lower prevalence of fatigue in younger women. However, in two systematic reviews performed on 24 and 22 studies, almost half the studies found no association between the age of BCSs and fatigue, whereas the other half reported that younger women had higher rates of fatigue.^{14,15} Lower rates of fatigue in younger women can probably be explained to the fact that emotional distress, which is the most likely contributor of fatigue in young women, is taken care of by strong social support by the spouse and family. In another study, BCSs with a partner were reported to have a lower risk of severe fatigue than BCS without a partner.¹⁶

Literature about association of demographic and clinical factors with fatigue is quite inconsistent. In our study, other than age, menopausal status was the only other factor that was found to have a significant association with fatigue. As regards clinical factors, the number of patients with early cancer or single modality treatment were too small for any valid analysis. In a meta-analysis by Abrahams et al, demographic and clinical factors that were found to have an association with fatigue were advanced stage of disease and multimodality treatments. BCSs with stage II or III cancer had a higher risk than BCSs with stage 0 or I cancer (relative risk [RR]: 1.18, 95% CI: 1.08–1.28). The risk was higher in BCS treated with chemotherapy than BCS without chemotherapy (RR: 1.12, 95% CI: 1.06–1.19). Radiotherapy, hormone therapy, and targeted therapy were no significant risk factors. Survivors treated with the combination of surgery, chemotherapy, and radiotherapy were at higher risk than other treatment combinations (RR: 1.18, 95% CI: 1.05–1.33). Notably, hormone therapy only was a significant risk factor if

received in addition to surgery, radiotherapy, and chemotherapy and increased the risk by 38%.¹⁷ While many recent studies have established a significant link between aromatase inhibitor-related symptoms of arthralgia and insomnia with fatigue in BC survivors,^{18,19} the evidence linking tamoxifen with fatigue is scarce.²⁰

Presence of fatigue was found to be significantly correlated with the occurrence of other survivors' issues such as arm swelling, postmastectomy chronic pain, premature menopause, and its related symptoms and emotional distress. Similar correlations have also been reported by other researchers as well. Bower et al reported that BCSs with more severe fatigue had significantly higher levels of depression, pain, and sleep disturbance. In addition, fatigued women were more bothered by menopausal symptoms and were somewhat more likely to have received chemotherapy (with or without radiation therapy) than nonfatigued women.¹³ Ruiz-Casado et al noted that women reporting fatigue often communicated symptoms such as pain, depression, insomnia, and cognitive dysfunction and that coping strategies such as catastrophizing could play an important role in the persistence of fatigue.²¹ Bjerkeset et al reported that BCSs may experience pain, fatigue, or psychological distress as a result of treatment and these symptoms may co-occur and form a cluster. In their study out of 834 survivors, 13% had the symptom cluster.²²

Meeske et al in their study on 1,183 disease-free BCSs found that significant correlates of fatigue included pain, cognitive problems, physical inactivity, weight gain/personal appearance, and use of antidepressant.²³ Reinertsen et al examined chronic fatigue cross-sectionally and longitudinally in relapse-free women up to 10 years after multimodal treatment for BC and found that psychological distress, treatment-area-related discomfort, and high body mass index were associated with chronic and persistent fatigue.²⁴

Presence of fatigue was associated with significantly lower QOL scores on FACT-B questionnaires. The mean score on FACT-B was 90.07 ± 10.17 in patients with fatigue and 104.73 ± 7.13 in those without fatigue. Physical, functional, and emotional domains were most affected. Adverse effect of fatigue on QOL of life has been reported in other studies as well and the most affected areas are those related to the daily functioning (physical and role functioning).^{3,5} In another study, fatigue was associated with poorer health-related QOL, most notably in areas of role and social functioning.²³

Since fatigue negatively affects a survivor's QOL, due attention should be paid to its assessment and addressal. Perhaps because the etiology of cancer-related fatigue is multifactorial and still poorly understood, there is currently no "gold standard" treatment of this symptom. Several modalities such as yoga, aerobics, cognitive behavior therapy, and pharmacological interventions are reported in the literature as possible interventions to alleviate fatigue.²²⁻²⁷ Innovative approaches such as the Better Life After Cancer: Energy, Strength, and Support program, a 12-week social capital-based exercise adherence program for BCSs, noted improvements in CRF, QOL, physical activity, and psychosocial characteristics.²⁸

Conclusion

Indian survivors have high rates of fatigue, and suffer from related sequelae of BC treatment like physical symptoms, emotional distress, and premature menopause. As a consequence, they suffer from poor QOL, and experience restriction predominantly in physical, functional, and EWB. Identification of patients requiring intervention for alleviation of fatigue should be a priority area in survivorship care clinics.

Strengths and Limitations of the Study

Strength: To the best of our knowledge, this is the first study on a large sample of disease-free survivors, which has collected and analyzed data about fatigue in BC patients in different stages of survivorship.

Limitations of the present study are related to the study design (cross-sectional). Further the study was conducted at a public hospital and hence the findings cannot be generalized across various healthcare settings. Despite limitations, this study provides useful insights about an important survivor' issue and may contribute to the management of fatigue in BCSs.

Source(s) of Support

Nil.

Note

Study approved by the Institutional Review Board and Ethics Committee.

Conflict of Interest

None declared.

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