Usual and Worst Symptom Severity and Interference With Function in Breast Cancer Survivors

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There are more than 2.5 million breast cancer survivors living in the United States.[1] The increased number of survivors has largely been due to the steadily increasing 5-year survival rate of women with breast cancer, with estimates now reaching 89%.[2] While survival has improved dramatically for breast cancer, adjusting to life after treatment is beset by a myriad of symptoms that affect how rapidly these survivors are able to return to pre-diagnosis/pretreatment status. In fact, studies have shown that it is more difficult to adjust to life after treatment when survivors regularly experience symptoms such as fatigue, sleep disturbance, distress, pain, and numbness/tingling.[3,4] Long-term effects are defined as any side effects or complications from therapy that continue beyond the end of treatment.[3] Long-term, unrelieved symptoms that are experienced by breast cancer survivors can interfere with activity and mood-related function.

To develop more effective interventions for symptomatic survivors, there is a need to understand the long-term effects of cancer treatment. This study reports the results of a cross-sectional survey on the usual and worst severity of 5 common symptoms experienced by breast cancer survivors,

ABSTRACT

Background: Breast cancer survivors receive routine medical follow-up but are screened less frequently to detect symptom severity and interference with function in daily life.

Objectives: Among breast cancer survivors, we describe the usual and worst severity of 5 common symptoms and the extent to which these symptoms interfere with general activity and enjoyment of life, we determine the associations among symptoms and the interference items, and we explore associations of interference with function and the most prevalent symptoms.

Methods: The cross-sectional, descriptive 1-page Breast Cancer Survivor Symptom Survey was mailed to breast cancer survivors identified in a clinical database (ONCOBASE). In total, 184/457 (40.3%) surveys were returned and 162 (35.4%) were used. Participants recorded usual and worst severity of 5 symptoms (fatigue, disturbed sleep, pain, distress, and numbness/tingling) and symptom interference with general activity and enjoyment of life during the past 7 days.

Results: Participants reported usual symptom severity as mild and highest for sleep disturbance, followed by fatigue, distress, numbness/tingling, and pain. Participants recorded worst sleep disturbance and fatigue as moderately severe. Higher pain and fatigue were associated with all other symptoms, whereas disturbed sleep and distress were related to all except numbness/tingling. All symptoms interfered with general activity and enjoyment of life. Pain and numbness/tingling were associated with lower function and disturbed sleep, and made a unique contribution to fatigue.

Limitations: Limitations of the study include relatively low response and use of a modification of an established scale.

Conclusion: Symptoms often coexisted and contributed to interference with daily function. Pain was most consistently associated with interference with function and severity of other symptoms.

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and the extent to which these symptoms interfered with general activity and enjoyment of life during the past week. We also describe the associations among these symptoms and the associations among patient characteristics, these symptoms, and interference with the 2 areas of functioning.

METHODS

Study Design

This is a cross-sectional study that surveyed a cohort of breast cancer survivors who completed treatments at the University of Nebraska Medical Center (UNMC).

Setting and Sample

A survey/questionnaire was mailed in February 2010 to the listed home address of 457 adult patients diagnosed with breast cancer and treated between January 1992 and December 2007 at UNMC. Participants who were invited for the study had previously provided informed consent to be part of a patient repository of clinical data of cancer patients (ONCOBASE). The consent also provided permission for these patients to be contacted for any future studies.

Procedures

The study was approved by the institutional review board (IRB). Participants were asked to complete a 1-page questionnaire that required less than 5 minutes. The instructions requested return of the questionnaire within 2 weeks of receipt using a postage-paid, addressed return envelope. Participants did not receive any monetary compensation but were provided an altruistic incentive of a donation to a breast cancer research organization. Return of the questionnaire was deemed as consent. Questionnaires were coded so that researchers could match the respondents' survey data with their demographic data previously collected in ONCOBASE.

Instruments

The Breast Cancer Survivor Symptom Survey was derived from the M. D. Anderson Symptom Inventory (MDASI).[5] The MDASI is a measure of the severity and impact of 13 cancer-related symptoms on an 11-point scale (0 to 10) to indicate the presence and severity of the symptom, with 0 meaning "not present" and 10 meaning "as bad as you can imagine." The MDASI also includes ratings of the extent to which symptoms interfere with 6 functional domains of daily life. The interference items are also measured on a 0 to 10 scale, with 0 meaning "did not interfere" and 10 meaning "interfered completely." On the well-established tool, there are items that measure worst pain, fatigue (tiredness), disturbed sleep, distress (upset), and numbness or tingling within the last 24 hours. Likewise, there are questions asking how symptoms interfered with general activity and enjoyment of life in the last 24 hours.

The Breast Cancer Survivor Symptom Survey used the same wording as did the MDASI and the same 11-point rating scale (0 to 10, with higher scores indicating more severe symptoms/greater interference). However, there were some differences: Only 5 of the symptoms were included, but all were rated on usual and worst severity. Among the 6 items dealing with symptom interference

with functioning, 1 activity-related and 1 mood-related item were selected. The time frame was extended from the last 24 hours to the past 7 days to capture the full range of the patient's current symptom experience. Severity ratings based on a recall period of 7 days correlated at ≥ 0.7 with those from a 24-hour recall for all symptoms except distress, which correlated at $r = 0.67$.[6] Participants were asked to rate the usual and worst severity of 5 symptoms (10 items) (1) fatigue (weariness, tiredness), (2) sleep disturbance, (3) pain, (4) distress, and (5) numbness/tingling in their hands and feet—and to rate how any experienced symptom(s) interfered with their general activity and enjoyment of life (2 items). To increase the response rate, the survey was kept brief (1 page) by focusing on the most prevalent symptoms in breast cancer survivors.

Demographic/Medical Data

At the top of the survey, participants were asked to provide their full name, birth date, and date of breast cancer diagnosis and to reply to questions related to treatments received (yes/no) and dates for surgery, radiation therapy, chemotherapy, and/or endocrine therapy (tamoxifen or aromatase inhibitor). ONCOBASE was used to determine respondents' age, race/ethnicity, and the rural-urban designation of their ZIP codes using the rural-urban commuting area codes.[7] Date of surgery recorded in ONCOBASE was used as an estimate of date of diagnosis for 6 respondents who did not report this information.

Data Analysis

Data were double-entered into a study database. We performed several preliminary analyses using SPSS for Windows, version 19.0 (SPSS, Inc., Chicago, IL), including examination of frequency distributions and descriptive statistics (means, standard deviations, skewness, kurtosis, and/or frequency distributions and percentages) to evaluate distributional characteristics and to identify outliers. Missing data were minimal (<1%). Descriptive statistics were calculated for each of the 10 symptoms and 2 interference-with-function items. Correlations between usual and worst symptom ratings ranged from 0.78 to 0.96. Correlation was 0.71 for the 2 items measuring interference with function for the past 7 days. The 2 ratings for each 5 symptoms (usual and worst) and the 2 ratings of interference with function (general activity and enjoyment of life) were averaged to create 6 new mean items. In 3 cases, a rating was missing for either usual or worst level of a single symptom; for these cases, the existing rating was used as an estimate of the mean rating. Chi-squared and *t* tests, respectively, were used to test differences between survey responders and nonresponders with respect to age, ethnicity, and rural-urban designation. In addition, responses were cross-tabulated to determine the percentage of participants who had usual and worst symptom severity at 4 levels most commonly used to categorize fatigue: none (0); mild (1-3), moderate (4-6), or severe (>7).[8] Scores >4 were defined as "caseness."[9]

Table 1

Demographic Characteristics of the Entire Sample[a]

VARIABLE	RESPONDERS (N = 162)[b]	NONRESPONDERS (N = 231)	COMPARISON BETWEEN GROUPS
Age (years)			
Mean ± SD	58.4 (SD, 10.7)	57.6 (SD, 12.5)	$t = 1.04$ ($P = .30$)
Range	23-83	30-88	
Ethnicity[c]			$\chi^2_1 = 7.5$ ($P = .006$)
Black	3	13	
Hispanic	0	2	
Asian	0	4	
Native American	0	1	
Other	0	1	
White	159	210	
Rural–urban status			$\chi^2_1 = 0.22$ ($P = .64$)
Mean	78.7 (SD = 39.2)	Tc >	
Range	14-197		
Rural	22.8%	20.3%	
Urban	77.2%	79.7%	
Time since diagnosis (months)			
Time since diagnosis (years)			
<5	63 (38.9%)		
≥5-<10	68 (42.0%)		
≥10	31 (19.1%)		
Treatment received			
Radiation therapy	101 (62.3%)		
Chemotherapy	109 (67.3%)		
Endocrine therapy	114 (70.4%)		

[a] Entire sample = 457 surveys mailed, 30 were returned as undeliverable, 8 informed us of the patient's death, and 4 did not have breast cancer, resulting in 415 eligible cases.

[b] There were 184 surveys returned; 6 were not completed, 15 reported recurrent disease, and 1 had a date of diagnosis that was not available; these 22 were not included in this report, for a final sample of 162 (39.0%).

[c] Of the survey of cases that were included, the return rate was lower for racial or ethnic minorities (3/24,12.5%) than for whites (159/369, 43%).

Regression analysis was used to identify significant associations among interference with function and symptom severity. All regression analyses used the mean scores of usual and worst levels of symptoms and interference with activity and enjoyment of life. Because the literature identifies fatigue, sleep disturbance, and distress as the most common and persistent symptoms, models were developed with each of these symptoms as the outcome. In addition, a model was designed to relate interference with function with the set of symptoms that have been reported as being most strongly correlated with function.[4] Age, time since diagnosis, and rural-urban designation were included as covariates in each regression analysis. Rural–urban designation was included to evaluate disparity between the 2 populations. Regression assumptions (linearity of predictor/outcome relations and normality and homoscedasticity of residuals) were evaluated graphically for all models. Standardized residuals and Cook's distance were examined to check for unusual or influential cases. All statistical tests were conducted at $\alpha = .05$.

RESULTS

Study Participants

Table 1 describes the responders' age, ethnicity, time since diagnosis, rural-urban designation, and treatments received.

Treatment and time since diagnosis of nonresponders were not accessed due to IRB regulations. Survey responders and nonresponders were similar in age and rural-urban designation. The return rate was lower for racial or ethnic minorities (4 of 23, 12.5%) than for whites (159 of 369, 43%) ($\chi^2 = 7.5$; $P = .006$). The frequency and percentage of the sample with comorbid conditions that are common in midlife women were hypertension (43; 26.5%), rheumatoid arthritis (2; 1.2%), osteoarthritis (20; 12.3%), and diabetes mellitus II (9; 5.6%).

Symptoms

Respondents reported mean scores for usual levels of symptom in the past 7 days that were highest for sleep disturbance, followed by fatigue, distress, numbness/tingling, and pain (Table 2). Only 7 women (4.3%) reported no symptoms, and this "0" response was not related to time since treatment or to age (dichotomized as <65 or ≥65). Respondents reported usual severity of all symptoms as being in the mild range. Respondents reported worst severity scores as being highest for sleep disturbance, followed in order by fatigue, distress, pain, and numbness/tingling. The worst severity scores for sleep disturbance and fatigue were in the moderate range, but other

Table 2

Mean Scores for Usual and Worse Levels of Symptoms in the Past 7 Days

VARIABLE	RANGE[a]	MEAN	SD	SKEWNESS	KURTOSIS
FATIGUE					
Usual	0-8	2.70	2.09	0.66	−0.34
Worst	0-10	4.02	2.72	0.29	−1.02
SLEEP DISTURBANCE					
Usual	0-8	3.06	2.27	0.58	−0.72
Worst	0-10	4.15	2.77	0.29	−0.99
PAIN					
Usual	0-7	1.38	1.76	1.30	0.70
Worst	0-10	2.08	2.47	1.18	0.48
DISTRESS					
Usual	0-7	1.60	1.84	1.27	0.89
Worst	0-10	2.35	2.52	1.08	0.24
NUMBNESS/TINGLING					
Usual	0-9	1.49	2.31	1.61	1.49
Worst	0-10	1.83	2.71	1.48	1.04
INTERFERENCE					
General activity	0-7	1.34	1.82	1.34	0.93
Enjoyment of life	0-10	1.32	1.92	1.99	4.49
Mean scores					
Fatigue[b]	0-8.5	3.35	2.27	0.40	−0.75
Sleep disturbance[b]	0-8.5	3.60	2.41	0.43	−0.84
Pain[b]	0-7	1.73	2.02	1.05	−0.10
Distress[b]	0-8	1.98	2.09	1.08	0.28
Numbness/tingling[b]	0-9	1.66	2.48	1.51	1.10
Interference with function[c]	0-7.5	1.35	1.75	1.34	1.08

Sample size ranged from 160 to 162.

[a] Symptoms were measured on a scale from 0 (none) to 10 (as bad as you can imagine); the scale for interference was 0 (did not interfere) to 10 (completely interferes).

[b] Mean of ratings of usual and worst levels of symptoms. For cases missing 1 rating (n = 3), the observed rating was used as the estimate of the mean for that symptom.

[c] Mean ratings of symptom interference with general activity and enjoyment of life.

symptoms were mild. On average, respondents reported mild symptom interference with general activity and with enjoyment of life. The same patterns were observed for the 5 items of mean ratings of usual and worst symptoms.

All respondents' symptom and interference scores were then divided into 4 categories commonly used to reflect severity (0, none; 1-3, mild; 4-6, moderate; and 7-10, severe) (Table 3).[8] The percentage of cases with moderate or severe symptom levels was highest for worst sleep disturbance (48.8%), followed by worst fatigue (47.6%), usual sleep disturbance (35.1%), and usual fatigue (27.8%). Fewer than 25% of cases reported moderate or severe levels of usual and worst distress, pain, and numbness/tingling or symptom interference with general activity and enjoyment of life.

Data were compared to determine whether specific treatments were associated with participants' usual and worst symptom severity. Almost all participants (n = 152; 94%) received multimodal therapy. There were no differences in symptom severity based on whether or not participants had received radiation therapy, chemotherapy, or endocrine treatments for breast cancer.

Associations Among Symptoms and Interference with Function

Presented in Table 4 are 0-order correlations among all variables used in the regression models. Age, time from diagnosis, and rural-urban designation did not correlate with participants' symptom severity. Fatigue and pain correlated with all other symptoms. Sleep disturbance and distress correlated with all symptoms except numbness/tingling. Pain and fatigue were the only correlates of numbness/tingling.

Multiple linear regression analyses are presented in Table 5. More severe pain ($P < .001$), fatigue ($P = .003$), and distress ($P = .008$) were associated with greater symptom interference with general activity and enjoyment of life (adjusted $R^2 = 0.471$; $P < .001$). Higher fatigue (adjusted $R^2 = 0.362$; $P < .001$) was significantly associated with more severe sleep disturbance ($P < .001$), worse pain ($P = .005$), and numbness/tingling ($P = .034$). Sleep disturbance (adjusted $R^2 = 0.446$; $P < .001$) was significantly associated with more severe fatigue ($P < .001$) and distress ($P < .001$). Distress was significantly associated (adjusted $R^2 = 0.408$; $P < .001$) with more severe pain ($P < .001$) and sleep disturbance ($P < .001$).

Table 3

Categories of Symptom Severity and Interference With Function

	NONE	MILD	MODERATE	SEVERE
	0	1-3.99	4–6.99	≥7
FATIGUE				
Usual	26 (16.0%)	90 (55.6%)	33 (20.4%)	12 (7.4%)
Worst	18 (11.1%)	66 (40.7%)	38 (23.5%)	39 (24.1%)
SLEEP DISTURBANCE				
Usual	17 (10.5%)	88 (54.3%)	37 (22.8%)	20 (12.3%)
Worst	15 (9.3%)	68 (42.0%)	40 (24.7%)	39 (24.1%)
PAIN				
Usual	72 (44.4%)	66 (40.7%)	23 (14.2%)	1 (0.6%)
Worst	64 (39.5%)	62 (38.3%)	24 (14.8%)	12 (7.4%)
DISTRESS				
Usual	58 (35.8%)	80 (49.4%)	20 (12.3%)	4 (2.5%)
Worst	51 (31.5%)	71 (43.8%)	21 (13.0%)	19 (11.7%)
NUMBNESS/TINGLING				
Usual	89 (54.9%)	42 (25.9%)	21 (13.0%)	10 (6.2%)
Worst	86 (52.8%)	42 (25.8%)	14 (8.6%)	20 (12.3%)
	NO INTERFERENCE			CONSTANT INTERFERENCE
Interference in general activity	83 (51.2%)	54 (33.3%)	21 (13.0%)	3 (1.9%)
Interference with enjoyment of life	79 (48.8%)	62 (38.3%)	14 (8.6%)	5 (3.1%)

Sample size ranged from 160 to 162.

In summary, concurrent symptoms of pain, fatigue, and sleep disturbance were present at a mild to moderate severity level and were independently associated with multiple symptoms and interference with general activity and enjoyment of life during the past 7 days.

DISCUSSION AND CONCLUSION

This cross-sectional study of breast cancer survivors representing varying amounts of time from diagnosis sheds new light on long-term symptoms and interference with general activity and enjoyment of life functioning. Although symptoms generally abated over time, many survivors reported moderate to severe symptoms years after completing primary treatment. As anticipated, usual and worst severity of fatigue and sleep disturbance were highest among the symptoms. Sleep disturbance was the most common moderate to severe usual symptom, followed in order by fatigue, numbness/tingling, pain, and distress. Survivors reported moderate to severe worst fatigue and sleep disturbance, yet they rated low interference with general activity and enjoyment of life during the prior week.

Table 4

Zero-Order Correlations Among Ratings of Symptoms,[a] Interference With Function,[b] and Control Variables

	1	2	3	4	5	6	7	8	9
1. Fatigue									
2. Sleep disturbance	0.499*								
3. Pain	0.453*	0.458*							
4. Distress	0.397*	0.588*	0.514*						
5. Numbness/tingling	0.263*	0.142	0.212*	0.117					
6. Interference with function	0.517*	0.424*	0.616*	0.501*	0.288*				
7. Urban-rural[c]	−0.103	−0.008	0.065	−0.010	−0.037	−0.064			
8. Months since diagnosis	−0.061	0.035	0.018	0.079	−0.120	−0.048	0.041		
9. Age	0.109	−0.042	0.157	−0.033	0.042	0.125	0.006	0.071	

N = 162.

[a] Interference with function was measured using the mean of 2 ratings: symptom interference with general activity, and with enjoyment of life. Higher scores indicate greater interference of symptoms on function.

[b] Mean ratings of usual and worst level of symptoms. Higher scores indicate more severe symptoms.

[c] Coded rural (0), urban (1).

*P < .05, two-sided test.

Table 5

Standardized Regression Coefficients for Fatigue, Sleep, Distress, and Interference With Function[a,b]

	INTERFERENCE WITH FUNCTION		FATIGUE		SLEEP DISTURBANCE		DISTRESS	
	β	P	β	P	β	P	β	P
Age	.047	.427	.090	.175	−.083	.179	−.076	.225
Rural–urban[c]	−.159	.312	−.107	.100	.018	.773	−.023	.705
Months since diagnosis	−.045	.441	−.068	.302	.024	.701	.068	.269
Pain	**.382**	<.001	**.224**	.006	.132	.084	**.312**	<.001
Distress	**.206**	.008	.074	.387	**.400**	<.001	—	—
Fatigue	**.213**	.003	—	—	**.294**	<.001	.066	.387
Sleep disturbance	.008	.922	**.338**	<.001	—	—	**.409**	<.001
Numbness/tingling	.117	.054	**.143**	.034	−.003	.959	−.013	.832
R^2 (adjusted R^2)*	.497 (.471)		.362 (.333)		.446 (.421)		.433 (.408)	

[a] Interference with function was measured using the mean of 2 ratings: symptom interference with general activity and with enjoyment of life. Higher scores indicate greater interference of symptoms with function.

[b] Mean ratings of usual and worst level of symptoms. Higher scores indicate more severe symptoms.

[c] Coded: rural (0), urban (1).

*$P < .001$ for all R^2 values. Boldface type indicates coefficients with $P < .05$.

This study confirmed fatigue as the common denominator of symptoms, correlating with all other symptoms and interfering with function. Pain was most consistently associated with other symptoms and with interference with function. These findings are consistent with previously reported concurrent symptoms of fatigue, sleep disturbance, pain, and distress during breast cancer treatment.[10,11] This survey, to our knowledge, is the first to report this symptom profile in a cohort of breast cancer survivors.

Consistent with previous findings, fatigue and sleep disturbance were the most prevalent symptoms in breast cancer survivors.[12,13] Both symptoms are frequently reported by healthy women as they age and become postmenopausal, and may be present before the diagnosis of cancer and cancer treatment. Fatigue has been reported as the most prevalent symptom in several studies,[14,15] but this is the first to report sleep disturbance as the most common. Prevalence rates of "cases" of usual fatigue (rating ≥4) were 27.8% in this survey, compared with 24% 1 year after starting treatment in the control group of a randomized clinical trial in the same geographical region.[16] These prevalence rates are lower than the 35% reported at 1-5 years and the 34% rate at 5-10 years after breast cancer treatment in another geographic area.[17]

Approximately 7% of this survey's respondents reported severe fatigue, whereas 24% of breast cancer patients in the Netherlands who were premenopausal and <50 years old at diagnosis reported severe fatigue to be a persistent problem 2.5 years after treatment.[18] Although usual pain and distress were moderate or severe in <15% of respondents, they were associated, when present, with higher severity of other symptoms.

There were several interesting findings regarding the associations among symptoms, their interference with functioning, and the covariates. Our expectation was that younger age, shorter time since diagnosis, and rural status would be associated with more severe symptoms and greater interfer-

ence with function, but none of these associations was found in this sample. All 5 symptoms were found to be associated with interference with function. Fatigue has been identified as a predictor of lower functioning in more than 1 domain of quality of life.[13,15,19,20] Physiological and psychological adjustment over time may explain the low interference of mild to moderate symptoms with activity- and mood-related function.

While this study included a heterogeneous group of community-dwelling breast cancer survivors in urban and rural areas in the central United States and spanned more than 15 years after treatment, it is limited by a relatively low response rate and, therefore, a potential for sampling bias. However, comparisons between the responders and nonresponders on key demographics showed no differences, except for race/ethnicity. Most of our responders were white. Further comparisons were not possible due to IRB regulations. Most of the covariates examined did not correlate with symptom severity, but respondents' ratings may better represent the experience of breast cancer survivors than does information collected only from the approximately 7% who participate in clinical trials; many of these are from major metropolitan areas. Nevertheless, in this sample, the subjects' current age and age at diagnosis were younger than those in most reports of survivors' symptoms. This difference may have affected the development and experience of the symptoms at a different phase of the aging process from what is usually reported and, thus, may have impacted the results. We also modified the MDASI, possibly affecting the reliability of the survey results. The items measuring interference with general activity and enjoyment of life may not capture multiple functional domains, but served as indicators of interference with activity- and mood-related function.

Future research needs to continue to address the importance of the experience of several symptoms that co-occur to lower symptom severity and its impact on function in breast

cancer survivors. We recommend designing interventions for 2 or more concurrent symptoms by combining strategies that are effective at treating individual symptoms (eg, cognitive-behavior therapy, physical activity, stress-reduction techniques).[21,22] When clinicians routinely screen for pain in breast cancer survivors and when moderate to severe intensity is reported, the clinicians are urged to also assess for fatigue, sleep disturbance, distress, and numbness/tingling. These symptoms commonly co-occur and may persist after treatment. Early identification and intervention may potentially reduce severity. Practice guidelines that recommend interventions for single symptoms are available (www.ons.org/Research/PEP/Topics), but improving one symptom may either improve or worsen another. Routine screening for all 5 of these common symptoms is indicated throughout the breast cancer survivorship journey. There is an urgent need to develop evidence-based guidelines for treating multiple concurrent symptoms and preventing functional decline.

In conclusion, usual symptoms were of mild to moderate severity. Symptoms often coexist and interfere with activity and mood functioning. Pain was most consistently associated with severity of other symptoms and lower functioning. Assessments and interventions need to address multiple symptoms concurrently to reduce symptom severity and functional limitations from symptoms in the increasing number of breast cancer survivors.

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