

# RELATIONSHIP OF CANCER-RELATED FATIGUE WITH PSYCHONEUROPHYSIOLOGICAL SYMPTOMS IN BREAST CANCER SURVIVORS

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## ABSTRACT

**Introduction:** Cancer-related fatigue (CRF) is a highly prevalent and debilitating symptom reported by breast cancer survivors (BCS). It has been associated with the co-occurrence of anxiety, depression, poor sleep quality, cognitive impairment, which are collectively termed as psychoneurophysiological (PNP) symptoms. It is unclear how each of these PNP symptoms influence each other. This study aimed to examine the relationship of CRF with other PNP symptoms in BCS.

**Methods:** This is part of a larger descriptive, correlational, and cross-sectional study examining factors associated with cancer-related cognitive impairment in breast and colorectal cancer survivors. Validated instruments were used to measure PNP symptoms. Descriptive statistics, Pearson correlation, and multiple linear regression models were used to analyze this subset data.

**Results:** A unique finding was that patients who reported less bodily pain had worst CRF ( $r = -.45, p < .01$ ). Significant predictors of CRF included depression, sleep disorder, bodily pain, perceived cognitive ability, and dispositional (state) optimism. Depression alone accounted for 31% of the variance in CRF, and bodily pain accounted for about 7% of the variance in CRF.

**Conclusions:** The study affirms the strong relationship between depression and CRF; however, further investigation is necessary to explore the inverse relationship of bodily pain and CRF. Depression screening may be crucial for addressing the comorbidity of symptoms. Evidence-based strategies/interventions are needed to palliate CRF and other PNP symptoms in BCS.

## INTRODUCTION

- Breast cancer (BC) is a highly prevalent carcinoma, the most common malignancy, and the second leading cause of cancer mortality among women in the United States (US).<sup>1</sup>
- CRF is a highly prevalent, debilitating, and persistent symptom during and after cancer treatment, and are commonly reported to co-occur with other PNP symptoms, including depression, anxiety, pain, cognitive impairment, and sleep disturbance, causing long-lasting distress.<sup>2-5</sup>
- Current evidence is unclear how each of these PNP symptoms influence each other. Although CRF has been reported to be an important risk factor for other PNP symptoms in cancer patients receiving treatment.
- This study aimed to (1) determine relationship of CRF with other PNP symptoms, and (2) explore predictive factors (i.e., PNP symptoms and demographic factors) of CRF in BCS

## METHODS AND MATERIALS

- This was part of a larger descriptive, correlational, and cross-sectional study (ClinicalTrials.gov Identifier: NCT04611620). The parent study was approved by a large Midwest Comprehensive Cancer Center and a University Institutional Review Board (IRB).
- The Patient-Reported Outcomes Measurement Information System (PROMIS<sup>®</sup>) short forms were used to measure PNP symptoms of depression, anxiety, CRF, neuropathic pain, and sleep disturbance, with reliability of 0.72 to 0.99.<sup>6-7</sup>
- The 36-Item Short-Form Health Survey (SF-36) was used to measure bodily pain, with high reliability of 0.80 to 0.94.<sup>8</sup>
- The PROMIS<sup>®</sup> Applied Cognition, version 1.0 short-form 8-item subscales of Cognitive Abilities and Cognitive Concerns assessed perceived cognitive impairment.<sup>9</sup> Reliability for both perceived cognitive function measures for this subsample was 0.80 to 0.83.
- The 10-item Life Orientation Test-Revised (LOT-R) was used to assess dispositional/state optimism, with a reliability of 0.79 to 0.85.<sup>10</sup>
- Descriptive statistics, bivariate Pearson correlation, and linear multiple regression models were used to answer the research questions proposed in this study; only the significant predictors were included in the final multiple regression model.
- All the statistical analyses were performed in SPSS 28.0 (IBM Corporation, Armonk, NY).

## RESULTS

- The majority of subjects were White (348/373, 93%), married (255/373, 68%), with a mean age of 55.9 years ( $\pm 9.8$ ). More than half of subjects were with clinical stage I (33%) and stage II (43%) treated with both chemotherapy and radiation therapy (66%).
- CRF was related to depression, bodily pain, anxiety, perceived cognitive function and dispositional/state optimism.

Table 1. Description of cancer- psychoneurophysiological (PNP) symptoms .

Symptoms	Questionnaire	N	Mean (S.D)	T Score (Mean raw score rounded)
Lower scores=Better Fatigue	PROMIS 8a Adult SF	373	24.3 (8.6)	57.5*
Depression	PROMIS 8a Adult SF	373	16.6 (7.4)	55.9*
Anxiety	PROMIS 8a Adult SF	373	18.7 (6.9)	57.4*
Sleep Disturbance	PROMIS 8a Adult SF	373	23.9 (8.3)	56.2*
Neuro Pain	PROMIS 5a Adult SF	373	9.4 (5.1)	48.8
Cognitive Concerns Higher scores=Better	PROMIS 8a Adult SF	373	26.9 (7.6)	43.3
Cognitive Abilities State Optimism	PROMIS 8a Adult SF Life Orientation Test-Revised	373 373	21.0 (6.9) 14.9 (4.7)**	40.71*
Bodily Pain	SF-36 Subscale	373	57.7 (25.6)	

Table 2. Correlations between CRF and other PNP symptoms  
Means, standard deviations, and correlations with confidence intervals.

Variable	M	SD	Cancer-Related Fatigue	Anxiety	Bodily Pain	Depression	Cognitive Abilities
Cancer-Related Fatigue	24.29	8.59					
Anxiety	18.70	6.88	.47** [.39, .54]				
Bodily Pain	57.71	25.57	-.45** [-.53, -.37]	-.25** [-.34, -.15]			
Depression	16.63	7.42	.56** [.48, .62]	.70** [.64, .74]	-.30** [-.39, -.21]		
State Optimism	14.92	4.74	-.32** [-.40, -.22]	-.48** [-.55, -.40]	.26** [.16, .35]	-.59** [-.65, -.52]	
Cognitive Abilities	20.96	6.88	-.49** [-.56, -.40]				
Cognitive Concerns	26.89	7.58	.46** [.38, .54]				-.75** [-.79, -.70]

Table 3. Predictors of cancer-related fatigue (CRF) - Regression results using fatigue as the criterion.

	b	b 95% CI [LL, UL]	beta	beta 95% CI [LL, UL]	sr <sup>2</sup>	sr <sup>2</sup> 95% CI [LL, UL]	r	Fit
(Intercept)	19.14**	[13.62, 24.66]						
Depression	0.42**	[0.30, 0.54]	0.36	[0.26, 0.47]	.07	[.03, .11]	.56**	
Sleep Disturbance	0.21**	[0.12, 0.30]	0.20	[0.12, 0.29]	.03	[.01, .06]	.46**	
Bodily Pain	-0.09**	[-0.11, -0.06]	-0.26	[-0.34, -0.17]	.06	[.02, .09]	-.45**	
Cognitive Abilities	-0.24**	[-0.35, -0.13]	-0.19	[-0.28, -0.10]	.03	[.00, .05]	-.49**	
State Optimism	0.20*	[0.03, 0.37]	0.11	[0.02, 0.21]	.01	[-.01, .02]	-.32**	
								R <sup>2</sup> = .470**
								95% CI [.39, .52]

## Discussion and CONCLUSIONS

- Major findings included:
  - The severity of CRF was positively correlated with anxiety, depression, and perceived cognitive concerns, but inversely related to bodily pain and perceived cognitive abilities;
  - Significant predictors of CRF were depression, sleep disorder, bodily pain, perceived cognitive abilities, and dispositional (state) optimism;
  - Depression was the highest predictor of CRF in this population.
- A unique finding in this study is the inverse relationship between bodily pain and CRF.
- Our study finding combined with the evidence that central sensitization can predict fatigue independent of the presence of pain raises additional possibilities that perhaps roles of various physiologic mechanisms such as inflammation and genetic predisposition may contribute to our unique study finding.
- Limitations included the cross-sectional design, the subjective nature of symptom reporting, and the roles of psychosocial factors.
- We affirms the strong relationship between depression and CRF.
- Follow up assessments of late and long-term PNP symptoms and evidence-based strategies are needed to palliate CRF and other PNP symptoms.

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