

# With What Does Fatigue in Women with Breast Cancer Correlate: Biological Measures, Tumor Characteristics, or Function?



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**INTRODUCTION:** Cancer-related fatigue (CRF) is defined as an unusual tiredness that is persistent, interferes with normal, daily routines, and is not relieved by sleep or rest<sup>1</sup>. CRF affects 80% to 90% of patients who receive radiation or chemotherapy<sup>2</sup>. In severe instances, CRF can affect an individual's ability to complete treatment<sup>2</sup>. Patients report CRF as being among the most distressing symptoms of cancer<sup>2</sup>; more troublesome than pain, depression and nausea<sup>3</sup>. CRF has a significant effect on a patient's ability to complete activities of daily living (ADL's)<sup>4</sup>. Over 30% of breast cancer (BrCa) survivors experience long-term fatigue for up to five years after completing treatments<sup>5</sup>. CRF is a multifaceted phenomenon for which underlying mechanisms are poorly understood<sup>6</sup>.

**PURPOSE:** The purpose of this study was to determine the relationships among fatigue and select biological measures, tumor characteristics and functional level over time in women receiving treatment for BrCa.

**METHODS:** A collaborative, prospective, observational, natural history study between the Breast Care Center (BCC) at the National Naval Medical Center (NNMC) and the National Institutes of Health/Rehabilitation Medicine (NIH/RMD). Institutional Review Board (IRB) approval was obtained from both institutions.

**Participants**

> Women attending the BCC were invited to participate at the time of biopsy proven BrCa.

**Evaluations** were performed

> prior to surgery and at 1, 3, 6, 9, 12, 18, and 24 months after surgery.  
> We report 1 month (T<sub>0</sub>) and 12 months (T<sub>1</sub>), +/- 3 months.

**Measurements:**

> **Objective** patient characteristics including:

- \*ethnicity
- \*parity
- \*menopausal status
- \*body mass index (BMI)
- \*marital status

> **Patient self-reports** and symptoms obtained from:

- \* Harvard Activity Alumni Health Study Physical Activity (HAAHSPA), used to determine level, intensity and frequency of activity;
- \* Short Form 36 (SF36), as a measure of health status and to assess physical and mental well being and the vitality subscale score used as a measure of fatigue.

\* Visual Analog Scale (VAS) of fatigue (0-10)

> **Biological measures**, including:

- \* hemoglobin,
- \* white blood cell counts (WBC)
- \* blood glucose
- \* tumor size
- \* node status
- \* distant metastases
- \* receptor status (estrogen receptor (ER), and epidermal growth factor receptor (HER2/neu)).

**Data Analyses:** Data analyses consisted of determination of means and standard deviations of patient descriptors. Statistical significance was determined using chi square analysis in comparing those patients with severe fatigue to those without, with respect to the self-reports of activity and symptoms, physical findings and biological variables. Spearman Rank performed for BMI.

**References:**

<sup>1</sup>Mack V, Atkinson A, Barsevick A, et al. (2000). NCCN practice guidelines for Cancer related fatigue.  
<sup>2</sup>Holman, M., Ryan, J. L., Figueroa-Moseley. (2007) Cancer related fatigue: the scale of the problem. The Oncologist, 12 (Suppl. 1), 4-10. Retrieved June 29, 2007, from Web Site: <http://theoncologist.alphamedpress.org>  
<sup>3</sup>Curt, G. A., Breitbart, W., Cella, D., et al. (2000). Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. *Oncologist*, 5 (5), 353-360. Retrieved July 19, 2007, from Web Site: <http://theoncologist.alphamedpress.org>  
<sup>4</sup>Bower, J. E., Ganz, P. A., Desmond, K. A., et al. (2006). Fatigue in long-term breast carcinoma survivors. Retrieved June 19, 2007, from American Cancer Society Web Site: <http://www.interscience.wiley.com>  
<sup>5</sup>Forlenza, M. J., Hall, P., Lichenstein, P. (2005). Epidemiology of cancer-related fatigue in the Swedish Twin Registry. *Cancer*, 104 (9), 2022-2031. Retrieved July 3, 2007 from Web Site: <http://www.interscience.wiley.com>  
<sup>6</sup>Gustein, H. B. (2001) The biologic basis of fatigue. *Cancer*, 92 (6), 1678-1683.

**RESULTS:**

**TABLE 1. FATIGUE DISTRIBUTION**

| T <sub>0</sub> Total N=54 | n  | (%)     |
|---------------------------|----|---------|
| 0-3 None                  | 33 | (61.11) |
| 4-6 Moderate              | 14 | (25.93) |
| ≥ 7 Severe                | 7  | (12.96) |

**TABLE 2. DESCRIPTIVE AND TUMOR CHARACTERISTICS**

| T <sub>0</sub> FATIGUE (n=54) | none n (%) n=33 | moderate n (%) n=14 | severe n (%) n=7 | p value    |
|-------------------------------|-----------------|---------------------|------------------|------------|
| MARRIED                       | 51 (33(64.71))  | 11 (21.57)          | 7 (13.73)        | .1         |
| Y                             | 1 (1(100))      | 2 (1(100))          |                  |            |
| N                             | 2 (2(66.67))    |                     |                  | .43        |
| 54                            |                 |                     |                  |            |
| CHILDREN                      | 49 (30(90.91))  | 12 (85.71)          | 7 (100)          | .43        |
| Y                             | 3 (9.09)        | 2 (14.29)           |                  |            |
| N                             |                 |                     |                  | .55        |
| 54                            |                 |                     |                  |            |
| ETHNICITY                     |                 |                     |                  | .55        |
| White                         | 44 (28(63.64))  | 10 (22.73)          | 6 (13.64)        |            |
| African-America               | 8 (3(3.75))     | 4 (50.00)           | 1 (1.25)         |            |
| Asian                         | 1 (1(100))      |                     |                  |            |
| MENOPAUSE                     | 31 (16(51.61))  | 10 (3(23))          | 5 (16.13)        | .34        |
| Y                             | 20 (15(75.00))  | 3 (5.00)            | 2 (10.00)        |            |
| N                             | 3 (2(66.67))    |                     |                  | .43        |
| 54                            |                 |                     |                  |            |
| MEDS                          | 33 (16(48.48))  | 11 (33.33)          | 6 (18.18)        | .43        |
| Y                             | 6 (3(50.00))    | 2 (33.33)           | 1 (16.67)        |            |
| N                             | 15 (14(93.33))  | 1 (6.67)            |                  | .30 p=.08* |
| 54                            |                 |                     |                  |            |
| BMI                           | 14 (7(50.00))   | 5 (35.71)           | 2 (14.29)        | .30 p=.08* |
| ≥ 30                          | 9 (4(44.44))    | 3 (33.33)           | 2 (22.22)        |            |
| 26 - 30                       | 30 (21(70.00))  | 6 (20.00)           | 3 (10.00)        |            |
| ≤ 25                          | 1 (1(100))      |                     |                  |            |
| TUMOR SIZE                    | 28 (15(53.57))  | 8 (3(5.7))          | 5 (17.85)        | .39        |
| ≤ 2 cm                        | 16 (11(68.75))  | 3 (18.75)           | 2 (12.5)         |            |
| 2-5 cm                        | 3 (3(100))      |                     |                  |            |
| ≥ 5 cm                        | 7 (4(57.14))    | 3 (42.86)           |                  |            |
| METAST                        | 2 (2(100))      |                     |                  | .50        |
| Y                             | 52 (31(59.61))  | 14 (26.92)          | 7 (13.46)        |            |
| N                             |                 |                     |                  | .38        |
| 54                            |                 |                     |                  |            |
| NODES                         | 18 (15(83.33))  | 1 (5.56)            | 2 (11.11)        | .38        |
| Y                             | 35 (17(48.57))  | 13 (37.14)          | 5 (14.28)        |            |
| N                             |                 |                     |                  | .62        |
| 54                            |                 |                     |                  |            |
| ER+                           | 43 (24(55.81))  | 13 (30.23)          | 6 (13.95)        | .62        |
| Y                             | 9 (7(77.78))    | 1 (11.11)           | 1 (11.11)        |            |
| N                             | 2 (2(100))      |                     |                  | .66        |
| 54                            |                 |                     |                  |            |
| HER2/neu                      | 1 (1(100))      |                     |                  | .66        |
| Y                             | 41 (27(65.85))  | 9 (21.95)           | 5 (12.19)        |            |
| N                             | 12 (5(41.67))   | 5 (41.67)           | 2 (16.67)        |            |
| 54                            |                 |                     |                  |            |

P values were calculated comparing "None" versus "Severe" fatigue only. \*\*Spearman Rank order

**Designators:**

- Y = Yes
- N = No
- \* = No Data

**TABLE 3. FATIGUE DISTRIBUTION**

| T <sub>0</sub> N=52 | n  | (%)     | T <sub>1</sub> N=72 | n  | (%)     |
|---------------------|----|---------|---------------------|----|---------|
| 0-3 None            | 32 | (61.54) | 0-3 None            | 33 | (52.42) |
| 4-6 Moderate        | 14 | (26.92) | 4-6 Moderate        | 35 | (39.52) |
| ≥ 7 Severe          | 6  | (11.54) | ≥ 7 Severe          | 4  | (8.06)  |

**TABLE 4. BIOLOGICAL MEASURES**

| T <sub>0</sub> FATIGUE (n=52) | none n (%) n=32 | moderate n (%) n=14 | severe n (%) n=6 | p value | T <sub>1</sub> FATIGUE (n=72) | none n (%) n=33 | moderate n (%) n=35 | severe n (%) n=4 | p value |
|-------------------------------|-----------------|---------------------|------------------|---------|-------------------------------|-----------------|---------------------|------------------|---------|
| HGB                           |                 |                     |                  | .46     |                               |                 |                     |                  | .37     |
| < 12                          | 8 (5(62.50))    | 3 (3(7.50))         |                  |         | 13 (5(38.46))                 | 8 (6(15.4))     | 4 (8.00)            |                  |         |
| N                             | 43 (27(62.79))  | 11 (25.58)          | 5 (11.63)        |         | 50 (24(48.00))                | 22 (44.00)      | 5 (5.56)            |                  |         |
| WBC                           |                 |                     |                  | .68     |                               |                 |                     | .28              |         |
| <4.0                          | 1 (1(100))      |                     |                  |         | 14 (7(50.00))                 | 7 (50.00)       | 2 (4.34)            |                  |         |
| N                             | 49 (30 (61.22)) | 14 (28.57)          | 5 (10.20)        |         | 46 (22(47.82))                | 22 (47.83)      | 2 (4.34)            |                  |         |
| Glucose                       |                 |                     |                  | .25     |                               |                 |                     | .90              |         |
| >110                          | 12 (7(58.33))   | 2 (16.67)           | 3 (25.00)        |         | 13 (6(46.15))                 | 6 (48.15)       | 1 (7.69)            |                  |         |
| N                             | 35 (20(57.14))  | 12 (34.29)          | 3 (8.57)         |         | 44 (21(47.72))                | 20 (45.45)      | 3 (6.82)            |                  |         |

**TABLE 5. FATIGUE DISTRIBUTION**

| T <sub>0</sub> N=45 | n  | (%)     | T <sub>1</sub> N=61 | n  | (%)     |
|---------------------|----|---------|---------------------|----|---------|
| 0-3 None            | 25 | (55.55) | 0-3 None            | 25 | (40.98) |
| 4-6 Moderate        | 13 | (28.89) | 4-6 Moderate        | 32 | (52.46) |
| ≥ 7 Severe          | 7  | (15.56) | ≥ 7 Severe          | 4  | (6.56)  |

**TABLE 6. ASSOCIATION BETWEEN FATIGUE & ACTIVITY**

| ACTIVITY      | T <sub>0</sub> FATIGUE (n=45) | none n (%) n=25 | moderate n (%) n=13 | severe n (%) n=7 | p value | T <sub>1</sub> FATIGUE (n=61) | none n (%) n=25 | moderate n (%) n=32 | severe n (%) n=4 | p value |
|---------------|-------------------------------|-----------------|---------------------|------------------|---------|-------------------------------|-----------------|---------------------|------------------|---------|
| SF36          |                               |                 |                     |                  | .15     |                               |                 |                     |                  | .36     |
| Physical ≤ 45 | Y                             | 32 (14(43.75))  | 12 (37.50)          | 6 (18.75)        |         | 34 (12(35.29))                | 19 (55.88)      | 3 (8.23)            |                  |         |
| N             | 13 (11(84.61))                | 1 (7.69)        | 1 (7.69)            | 27 (21(34.84))   |         | 13 (48.14)                    | 1 (3.70)        |                     |                  |         |
| Mental ≤ 45   | Y                             | 32 (16(50.00))  | 11 (34.38)          | 5 (15.62)        | .02     | 37 (14(29.79))                | 19 (51.35)      | 4 (10.81)           | .09              |         |
| N             | 13 (9(69.23))                 | 2 (15.38)       | 2 (15.38)           | 24 (11(45.83))   |         | 13 (54.17)                    |                 |                     |                  |         |
| Vitality ≤ 45 | Y                             | 32 (14(43.75))  | 12 (37.50)          | 6 (18.75)        | .15     | 41 (14(34.15))                | 23 (56.10)      | 4 (9.76)            | .09              |         |
| N             | 13 (11(84.61))                | 1 (7.69)        | 1 (7.69)            | 20 (11(55.00))   |         | 9 (45.00)                     |                 |                     |                  |         |

**ASSOCIATION BETWEEN FATIGUE AND ACTIVITY LEVEL, HAAHSPA**

➤ Intensity of Activity and Fatigue at T<sub>0</sub>, p = 0.3; T<sub>1</sub>, p = 0.005.

➤ Frequency of activity at T<sub>0</sub>, p = 0.013; T<sub>1</sub>, p = 0.732.

**DISCUSSION**

- ✦ There were statistically significant associations at the p 0.05 level between mental composite score SF36 T<sub>0</sub>, report of intensity and duration of activity of HAAHSPA.
  - This suggests that self reports of fatigue correlate with self-reports of activity and health status measures.
- ✦ There were some relationships at the p <0.10, suggesting a trend in association between fatigue and BMI and mental and vitality scores at T<sub>1</sub>.
- ✦ Noteworthy is an absence of a significant correlations between hemoglobin and fatigue.
- ✦ These analyses were severely limited due to loss of repeated measure data points and inadequate sample size.