

# Factors Related to Persistent Fatigue Following Completion of Breast Cancer Treatment

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**Purpose/Objectives:** To verify the predictive capacity of the stress-process theory to explain persistent fatigue following completion of breast cancer treatments; to verify the relationship between interleukin-1 $\beta$  and fatigue.

**Design:** Correlational.

**Setting:** Tertiary medical center in Quebec City, Canada.

**Sample:** A systematic sample of 103 women in remission from breast cancer was recruited. The mean age was 54 years. Participants with a depressive mood, insomnia, or stage IV cancer were excluded.

**Methods:** Participants were met during their follow-up appointment after the end of radiation therapy. Questionnaires on fatigue, stress variables, and other confounding variables were completed by telephone interview. Blood samples also were collected to measure the serum level of interleukin-1 $\beta$ .

**Main Research Variables:** Fatigue, several variables from the stress-process theory, pain, menopausal symptoms, and demographic and medical variables.

**Findings:** Fatigue was related theoretically and coherently to many stress-process variables. By controlling for pain, the final regression model included cancer stressors and passive and active coping as predictors, which accounted for 41% of the variance in fatigue. No relationship was found between fatigue and interleukin-1 $\beta$ .

**Conclusions:** The results supported the relevance of the stress-process theory for explaining cancer-related fatigue.

**Implications for Nursing:** Nursing interventions based on this theoretical framework could be developed. In addition, further clinical research that tests the efficacy of these psycho-educative interventions in preventing persistent fatigue and improving the quality of life of women with breast cancer is recommended.

## Key Points . . .

- ▶ Persistent fatigue may be observed even several years after completion of breast cancer treatments.
- ▶ Cancer-related stressors and passive coping strategies are associated with fatigue.
- ▶ Stress and coping psychoeducational interventions may be a way to prevent fatigue.

Garssen, Schuster-Uitterhoeve, et al., 1998; Vogelzang et al., 1997; Woo, Dibble, Piper, Keating, & Weiss, 1998).

Persistent fatigue may compromise patients' quality of life (Bower et al., 2000; Shimozuma et al., 1999; Smets, Visser, Willems-Groot, Garssen, Schuster-Uitterhoeve, et al., 1998; Vogelzang et al., 1997). Research still is needed to document fatigue-related factors and to eventually alleviate this symptom or prevent it from occurring. This study has been conducted to contribute to the knowledge base in this area.

Fatigue is a general feeling of decreased energy that can be associated with difficulty concentrating, decreased motivation, and decreased physical activity (Cimprich, 1992; Irvine, Vincent, Graydon, Bubela, & Thompson, 1994; Pearce & Richardson, 1996; Richardson & Ream, 1997; Stone, Richards, & Hardy, 1998). Cancer-related fatigue (CRF) can be defined as a multidimensional phenomenon that includes physical, emotional, cognitive, and behavioral components (Smets, Garssen, Bonke, & de Haes, 1995).

Although several studies have documented the factors associated with CRF during medical treatments (Broeckel, Jacobsen, Horton, Balducci, & Lyman, 1998; Cella, 1998; Fillion & Gagnon, 1998; Gaston-Johansson, Fall-Dickson, Bakos, & Kennedy, 1999; Greenberg, Gray, Mannix, Eisenhal, & Carey, 1993; Irvine et al., 1994; Irvine, Vincent, Graydon, & Bubela, 1998; Jacobsen & Stein, 1999; Pearce &

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Cancer now represents the second largest cause of mortality and an important cause of morbidity in North America. Breast cancer is the most widespread type of cancer in women in Canada. A total of 21,100 new cases of breast cancer occurred in Canada in 2003 (National Cancer Institute of Canada, 2003).

Fortunately, more patients are in remission from cancer, mainly because of early detection and important advances in treatment. Nevertheless, cancer treatments may have a number of side effects that have negative impacts on quality of life (Berglund, Bolund, Fornander, Rutqvist, & Sjöden, 1991; Ferrell, Dow, Leigh, Ly, & Gulasekaram, 1995). Among potential side effects, fatigue is reported by patients with cancer as the most frequent symptom, with a prevalence greater than 75% (Foltz, Gaines, & Gullatte, 1996; Greenberg, Sawicka, Eisenhal, & Ross, 1992). Long after the treatments have ended, more than 50% of patients with cancer still complain of persistent fatigue (Andrykowski, Curran, & Lightner, 1998; Jacobsen & Stein, 1999; Okuyama et al., 2000; Shimozuma, Ganz, Petersen, & Hirji, 1999; Smets, Visser, Willems-Groot,

Richardson, 1996; Richardson & Ream, 1997; Smets, Visser, Garssen, et al., 1998; Smets, Visser, Willems-Groot, Garssen, Oldenburger, et al., 1998), fewer studies have explored factors associated with CRF after the treatments have ended (Akechi, Kugaya, Okamura, Yamawaki, & Uchitomi, 1999; Ferrell, Grant, Funk, Otis-Green, & Garcia, 1998; Hoskins, 1997; Mast, 1998; Okuyama et al., 2000; Smets, Visser, Willems-Groot, Garssen, Schuster-Uitterhoeve, et al., 1998; Stein, Jacobsen, Hann, Greenberg, & Lyman, 2000; Vogelzang et al., 1997). Those factors can be divided into the following categories: (a) biologic, (b) physical, (c) psychological, (d) cognitive, (e) behavioral, and (f) environmental.

Most **biologic variables** described in the literature correspond to hematologic changes. During chemotherapy, more severe neutropenia and anemia were associated with an increased level of fatigue in patients with cancer (Cella, 1998; Irvine et al., 1994). In addition, immunologic changes potentially related to radiation treatment and cell destruction were described in a pilot study conducted on 15 patients with prostate cancer receiving radiation therapy (Greenberg et al., 1993). Greater fatigue was associated with a higher serum level of interleukin-1b, a cytokine released by macrophages and lymphocytes during the inflammatory process. To the authors' knowledge, no research has explored the relationship among these biologic variables after the end of treatment.

In terms of **physical factors**, some cancer treatment-related symptoms were studied in relation to cancer fatigue. For instance, more severe menopausal symptoms have been associated with greater fatigue (Bower et al., 2000; Stein et al., 2000). Similarly, more severe pain has been related to greater fatigue (Jacobsen & Stein, 1999; Stone, Richards, A'Hern, & Hardy, 2000). Because menopausal and pain symptoms could persist over time after the end of treatment (Ferrell et al., 1998), they have to be considered as potential confounding variables in the study of persistent CRF.

In terms of **psychological factors**, emotional distress (described as negative emotion such as anxiety, fear, anger, sadness, and depressive mood) has been documented as contributing to CRF during and after cancer treatments (Fillion & Gagnon, 1998; Hilfinger, Yeager, Dibble, & Dodd, 1997; Irvine et al., 1994; Jacobsen et al., 1999) and long periods of time after the treatments have ended (Bower et al., 2000; Woo et al., 1998). More specifically, emotional distress has been suggested to contribute to increased mental fatigue and decreased concentration (Cimprich, 1992).

In regard to **cognitive factors**, perception of loss has been described in association with greater fatigue in a qualitative study (Pearce & Richardson, 1996). In a quantitative study, a greater perceived impact, which includes greater perception of loss as well as greater perception of negative consequences and uncertainty, was related to greater emotional distress among women with breast cancer (Fillion, Lemyre, Mandeville, & Piché, 1996). After the end of treatment, uncertainty also helped explain CRF among patients with breast cancer (Mast, 1998). Moreover, lower sense of control was associated with severe fatigue in patients with breast cancer (Servaes, Verhagen, & Bleijenbergh, 2002). These studies suggest the importance of cognitive factors such as perception of loss, negative impact, lower sense of control, and uncertainty in explaining fatigue during and after treatment.

**Behavioral factors** related to CRF often are conceptualized in terms of coping strategies that may relieve it. In many

cases, greater passive coping strategies, such as increasing sleep and naps or sleep disturbance and decreasing the level of physical activity, were associated with greater fatigue (Hilfinger et al., 1997; Irvine et al., 1998; Servaes et al., 2002). Increasing these coping strategies appears inefficient in relieving CRF (Irvine et al., 1998; Richardson & Ream, 1997). The use of these passive coping strategies seems to persist after the end of treatment (Vogelzang et al., 1997) and may contribute to deconditioning (Wessely, 1996).

Finally, **environmental factors**, defined as stressors related to cancer and treatment, also have been described as variables helping to explain CRF (Fillion & Gagnon, 1998; Smets, Visser, Garssen, et al., 1998). Stressors experienced by patients with cancer are future concerns, functional disabilities, social problems, self-image concerns, and medical and treatment problems (Fillion, Kohn, Gagnon, Van Wijk, & Cunningham, 1999).

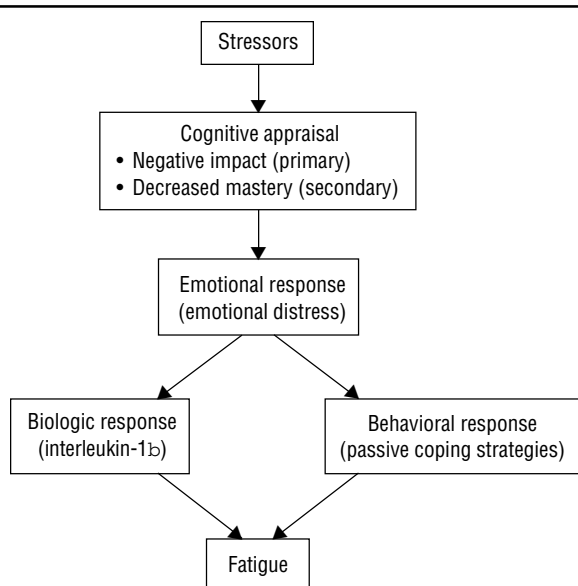
In summary, CRF has been related to factors in different categories. More precisely, these factors are described as biologic conditions, menopausal symptoms and pain, emotional distress, cognitive appraisal, coping strategies, and stressors. Most studies have been conducted during cancer treatments, and only a few were conducted after the end of treatment to document the persistent state of fatigue. In addition to their limited numbers, studies conducted after the end of treatment have methodologic limitations. Indeed, small sample sizes, heterogeneity of samples (different types and severity of cancers), and lack of control for confounding variables such as pain and menopausal symptoms limit the conclusions. Moreover, the absence of conceptual frameworks is observed. The goals of this study were to document persistent fatigue after the end of cancer treatments by including all of the factors identified in previous studies of cancer fatigue, improving the recruitment method, and including a conceptual framework.

## Conceptual Framework

The stress-process theory proposed by Herbert and Cohen (1996) relates all of the factors potentially associated with cancer fatigue. From this conceptual framework, adapted from Lazarus and Folkman (1984), stress is the result of the appraisal of a situation or stressor that a person is experiencing. Appraisal is a cognitive process by which a person simultaneously evaluates the negative impact of a stressor (primary appraisal) and the capacity to cope with it (secondary appraisal). Cognitive appraisal is the central concept of the stress-process theory. When the negative impact perceived exceeds the estimated coping capacity, stress is experienced. The stress response consists of emotional, behavioral, and biologic responses that appear approximately at the same moment in time. An emotional response corresponds to negative emotions or emotional distress resulting from the appraisal of the stressor. A behavioral response is a coping strategy used to adapt to the stressor. A biologic response involves all of the stress hormones released by the nervous, endocrine, and immune systems when facing a stressor. From this theory, fatigue can be conceptualized as a consequence of a prolonged stress response (see Figure 1).

## Purpose

The main objective of this study was to verify the predictive capacity of the stress-process theory to explain persistent fatigue



**Figure 1. Adaptation of the Stress-Process Theory to Cancer-Related Fatigue**

*Note.* Based on information from Herbert & Cohen, 1996.

after treatment for breast cancer. A secondary objective was to verify the relationship between the biologic response to stress (interleukin-1b) and fatigue.

The first hypothesis was that the stress-process theory may account for a significant percentage of the variance in persistent fatigue after treatment for breast cancer. The second hypothesis was that interleukin-1b, as an indicator of the biologic stress response, was related positively to fatigue.

## Methods

### Participants

This correlational study was conducted on a systematic sample (Fortin, 1996) of 103 women in remission from breast cancer after the end of treatment. This sample was recruited during follow-up visits at the Radiation Therapy Center of the Centre Hospitalier Universitaire de Québec, a cancer center located in Quebec City, Canada. All participants had received radiation therapy and met the following inclusion criteria: (a) had received an initial breast cancer diagnosis, (b) had completed their cancer treatments (3–24 months after the end of radiotherapy or chemotherapy), (c) were from 30–75 years of age (homogenous sample), and (d) understood and spoke French. All participants who manifested depressive mood as measured by the Hospital Anxiety and Depression Scale (HADS) (Savard, Laberge, Gauthier, & Bergeron, 1999; Zigmond & Snaith, 1983), had insomnia as defined by Diagnostic and Statistical Manual-IV (DSM-IV) (American Psychological Association, 1994), and had received a metastatic breast cancer diagnosis (stage IV) were excluded.

### Sample Size

Sample size was based on the first hypothesis, which was to test the prediction of the stress-process theory to explain CRF with a multiple regression analysis. The stress-process theory includes six independent variables (i.e., cancer-related stressors,

impact, mastery, emotional distress, active coping, and passive coping). To calculate sample size needed for a multiple regression analysis, a rule mentioned by Tabachnick and Fidell (2001) was used ( $N = 50 + 8$  [independent variables]). Consequently, a sample of  $50 + 8(6) = 98$  participants was needed.

### Measurements

Fatigue was the dependent variable in this study. All other concepts described in the stress-process theory were included and treated as predictive variables: stressors, cognitive appraisal, and psychological, behavioral, and biologic responses. The conceptual and empirical research structure is presented in Table 1.

Fatigue was measured using the **Multidimensional Fatigue Inventory (MFI)** (Fillion, Gélinas, Simard, Savard, & Gagnon, 2003; Smets et al., 1995). This instrument was developed specifically for a cancer population and was designed to measure four aspects: general and physical fatigue, reduced activity, reduced motivation, and mental fatigue. A total score can be calculated. Reliability and validity are well supported (Smets et al., 1995). Only general and physical fatigue was used in this study, which showed acceptable reliability with an alpha coefficient of 0.90 for internal consistency.

Cancer-related stressors were measured using the **Inventory of Recent Life Experiences for Cancer Patients** (Fillion et al., 1999). This instrument consists of 30 hassles developed specifically with patients with cancer. The total score was used for this study. The instrument also showed acceptable reliability with an alpha coefficient of 0.90 for internal consistency.

Cognitive appraisal was measured using the **Subjective Appraisal Rating Scale (SARS)** (Lemyre, 1986). SARS initially was developed and validated in French and consists of 10 items designed to assess the subjective appraisal of a cancer diagnosis and its treatment as a stressful event. From this instrument, two factor-based scores, perceived impact and mastery, theoretically corresponding to Lazarus' primary and secondary appraisal concepts (Lazarus & Folkman, 1984), were used in this study. Internal consistency was acceptable for both subscales, with alpha coefficients of 0.78 and 0.63, respectively. Alpha was lower for mastery but almost reached the guideline criteria (i.e., 0.70) suggested by Nunnally and Bernstein (1994). Because this subscale includes only a few items and other considerations must be made, such as its previous values around 0.70 in several other studies, this result is acceptable.

Emotional distress was measured using the shortened **Profile of Mood States** (Fillion & Gagnon, 1999; Shacham, 1983). The shortened version contains 37 items representing different feelings such as tension, depression, anger, fatigue, confusion, and vigor. Two subscales also can be derived: emotional distress (tension, depression, anger, and confusion) and vitality (fatigue and vigor). To avoid contamination of constructs, only emotional distress was used for this study. An alpha coefficient of 0.92 supports reliability for emotional distress.

Finally, coping was measured using the **Coping With Health Injuries and Problems Scale** (Endler, Courbasson, & Fillion, 1998; Endler, Parker, & Summerfeldt, 1993). This instrument includes 32 items consisting of four eight-item subscales assessing distraction, palliative, instrumental, and emotional preoccupation coping. These subscales can be computed in terms of passive (palliative and emotional) and active (distraction and instrumental) coping and were used for this study.

**Table 1. Conceptual and Empirical Research Structure**

Concepts of the Stress Theory	Research Variables	Empirical Measures	Scale Unit (Likert Scales)
Fatigue	Fatigue	Multidimensional Fatigue Inventory	1 (totally disagree) to 5 (totally agree)
Biologic response	Interleukin-1b	Blood sample; analysis in a research laboratory of the cancer research center (enzyme-linked immunosorbent assay method)	pg/ml
Cognitive appraisal	Cognitive appraisal 1. Impact 2. Mastery	Subjective Appraisal Rating Scale	1 (not at all) to 8 (enormously)
Emotional response	Emotional distress	Profile of Mood States	1 (not at all) to 5 (enormously)
Behavioral response	Coping strategies 1. Active 2. Passive	Coping With Health Injuries and Problems	1 (not at all) to 5 (enormously)
Stressors	Cancer-related stressors	Inventory of Recent Life Experiences for Cancer Patients	1 (not experienced) to 4 (experienced very often)

Internal consistency was acceptable for both subscales with alpha coefficients of 0.76 and 0.79, respectively.

Pain and menopausal symptoms were measured using two valid instruments: the **Brief Pain Inventory** (Daut, Cleeland, & Flanery, 1983) and the **Menopause-Specific Quality of Life Questionnaire** (Hilditch et al., 1996). Both showed good reliability and validity. Pain intensity, vasomotor, and physical menopausal symptoms were computed in this study. Alpha coefficients were 0.88, 0.90, and 0.84, respectively.

Also, questionnaires were developed to document demographic and medical variables. The demographic variables, namely age, marital status, education, income, and employment status, were documented. Cancer severity, number of treatments, chemotherapy, and hormonal therapy also were documented as medical variables.

Blood samples were collected to measure interleukin-1b. Blood samples were analyzed in a laboratory of the research center using a standardized procedure called enzyme-linked immunosorbent assay that is well described in the literature (Born, Lange, Hansen, Mölle, & Fehm, 1997).

## Procedure

This study was approved by the hospital's human research committee. Participants were recruited during their follow-up appointments. Before the patients were approached, their medical files were reviewed to verify the medical selection criteria. Only women who fulfilled these conditions were approached to participate in the study. A total of 141 women were invited and 103 agreed to participate in the study, a 72% participation rate. Reasons for refusal included lack of time, no interest in participating in the study, being already involved in a different research project, not knowledgeable about the topic, and disinclined to talk more about the cancer. During this first meeting, the project was explained to the participants and a consent form was signed. An initial interview was conducted at the same time to verify the selection criteria. Briefly, the participants completed a short questionnaire, including HADS and DSM-IV insomnia criteria. Participants were eligible if they obtained a score of 11 on the HADS depression scale (Savard et al., 1999; Zigmond & Snaith, 1983), to eliminate participants who could be suffering from depression, and if they answered "yes" to all four DSM-IV insomnia criteria. The researcher informed all participants of their eligibility to continue in the study. Partici-

pants who were not eligible because of psychological criteria were referred to the psycho-oncology service for support or to other professional resources.

Once a participant was deemed eligible, an appointment was made to complete a telephone interview. For a subsample of 44 participants, a second appointment was made to collect a blood sample to measure interleukin-1b. This blood sample was collected in a three-hour period during the day, in the afternoon from 3–6 pm, to control for circadian variations. Because of this restraint in time for biologic data collection, only participants living in the close area to the radiation center were approached for a blood sample. Data collection was based on a standardized procedure validated in a previous study (Fillion & Gagnon, 1998).

## Statistical Analysis

SAS<sup>®</sup> software (version 6.12) (SAS Institute, Inc., Cary, NC) was used to perform the statistical analysis. To achieve the main objective, a multiple regression analysis was done using the MFI general and physical subscale as the dependent variable and the stress-process measurements as predictive variables. Many analyses were performed to select confounding variables to add to the regression model to be tested. Correlations were calculated for continuous confounding variables in relation to fatigue. For noncontinuous confounding variables, such as dichotomous and ordinal variables, multivariate analysis, Hotelling T<sup>2</sup>, and Wilks lambda were used. Only significant confounding variables were included in the regression analysis. Finally, to achieve the secondary objective, correlations between the serum level of interleukin-1b and fatigue were calculated.

## Results

### Sample Description

Demographic and medical variables for the sample of 103 participants are described in Table 2. The mean age was 54 years. Most of the participants were married and were equally almost distributed among different income groups. A significant percentage (62%) of participants still were active at work, either full- or part-time. Cancer severity was classified according to stages I–IV defined by the International Union Against Cancer (1997). Stage IV is not represented in this sample because it was an exclusion criterion.

**Table 2. Demographic and Medical Variables**

Variable	n	%
<b>Sociodemographic</b>		
<b>Marital status</b>		
Single	10	10
Separated, divorced	11	11
Widowed	4	4
Married	73	71
Live with other people	5	5
<b>Income (Canadian dollars)<sup>a</sup></b>		
≤ \$14,999	7	7
\$15,000–\$29,999	23	23
\$30,000–\$44,999	30	30
≥ \$45,000	40	40
<b>Employment status<sup>b</sup></b>		
Full-time	44	40
Part-time	20	18
Absence for disease	8	7
Retired	31	30
No employment	8	7
<b>Medical</b>		
<b>Cancer stage</b>		
I	54	52
II	43	42
III	6	6
<b>Surgery</b>		
Tumorectomy (partial mastectomy)	98	95
Total mastectomy	5	5
<b>Hormonal therapy (e.g., tamoxifen, anastrozole)</b>	58	56
<b>Chemotherapy</b>	52	50
<b>Bone marrow transplant</b>	4	4
<b>Number of different treatments</b>		
2	25	24
3	50	49
4	24	23
5	4	4

N = 103

<sup>a</sup> Three participants did not answer questions about income.<sup>b</sup> Eight patients had more than one type of employment status.*Note.* Because of rounding, percentages may not equal 100.

Most of participants had stage I and II disease, or early-stage breast cancer. All participants had surgery and radiation therapy. Half of the participants received chemotherapy or had been undergoing hormonal therapy. Only four of them had bone marrow transplants because of more advanced breast cancer (stage III). On average, most of the participants received two to four different types of treatments.

## Descriptive Statistics

Descriptive statistics showed a moderate intensity of fatigue ( $\bar{X} = 3$ , range = 1–5, SD = 0.9). Cancer-related stressors still were experienced by the participants ( $\bar{X} = 1.7$ , range = 1.03–3.23, SD = 0.4). For cognitive appraisal, perception of impact ( $\bar{X} = 4.7$ , range = 1.83–7.83, SD = 1.4) and mastery ( $\bar{X} = 5.2$ , range = 2.5–8, SD = 1.3) were almost equal, meaning that participants still perceived an impact from cancer but believed they were in control of the disease. Participants experienced a low intensity of emotional distress ( $\bar{X} = 2$ , range = 1–4.23, SD = 0.6). For coping strategies, active ( $\bar{X} = 3.6$ , range =

2.25–4.88, SD = 0.6) and passive ( $\bar{X} = 3.1$ , range = 1.88–4.81, SD = 0.6) coping were used equally moderately.

Descriptive statistics for interleukin-1b showed a wide variability ranging from 9–3,952 ( $\bar{X} = 1,152$  pg/ml, SD = 901). For confounding variables, menopausal symptoms were moderate in intensity (vasomotor:  $\bar{X} = 2.7$ , range = 0–6, SD = 2; physical:  $\bar{X} = 2.2$ , range = 0.11–5.33, SD = 1.3 on a Likert scale from 0 [no problem] to 6 [severe problem]) and pain was low in intensity ( $\bar{X} = 1.9$ , range = 0–7, SD = 2, Likert scale from 0 [no pain] to 10 [worst pain ever experienced]).

## Preliminary Statistical Analysis

To select confounding variables to be added to the regression model, preliminary statistical analyses were performed. For continuous variables, including age, education, vasomotor menopausal symptoms, physical menopausal symptoms, pain, and number of treatments, correlations were calculated and are presented in Table 3. For noncontinuous variables, including marital status, income, employment status, cancer severity, hormonal therapy, and chemotherapy, multivariate analyses were used and are presented in Table 4.

Continuous variables, namely age, menopausal symptoms (both vasomotor and physical), pain, and number of treatments, were related to either fatigue or stress variables. Among the demographic variables, age was negatively related to cancer stressors and impact. No significant correlation was found for education. Menopausal symptoms and pain were moderately related to fatigue, cancer stressors, emotional distress, and passive coping. The number of treatments as a medical variable was weakly related to mastery and active coping. These variables were added to the regression model tested for confirmatory analysis.

For noncontinuous variables, only hormonal therapy was found to be statistically significant. However, a positive trend was noticed for employment status. Both of these confounding variables were added to the regression.

## Confirmatory Statistical Analysis

To verify the main objective, a statistical regression analysis was performed to test the predictive capacity of stress variables to explain fatigue after the end of treatment. First, a correlation matrix was calculated among fatigue and stress concepts. Then, statistical regression analysis using a stepwise method was performed with confounding variables added to the model. Finally, to verify the secondary objective, a correlation matrix was calculated between interleukin-1b and fatigue.

The correlation matrix is presented in Table 5. As expected, greater fatigue is related to more cancer stressors, a negative perceived impact, emotional distress, and passive coping. In the same way, more cancer stressors are related to a higher perceived negative impact, emotional distress, and passive coping. Other positive and consistent relationships are observed among impact, emotional distress, and passive coping. Higher perception of mastery is related to lower emotional distress and greater active coping.

The results of multiple regression analysis show that the best final model included three predictive variables, namely cancer stressors and passive and active coping, and one confounding variable, pain (see Table 6). This regression model accounted for 44% of fatigue variance. More precisely, the stress-process theory helped explain 41% of fatigue variance, whereas pain added an additional 3%. In relation to the

**Table 3. Correlations Among Continuous Confounding Variables With Fatigue and Stress-Process Theory Variables**

Variable	Age	Education	Vasomotor Menopausal Symptoms	Physical Menopausal Symptoms	Pain	Number of Treatments
Fatigue	-0.09	0.060	0.15	0.29**	0.300**	-0.18
Cancer-related stressors	-0.25**	0.080	0.22*	0.32†	0.190*	-0.16
Impact	-0.26*	-0.020	0.15	0.14	0.080	-0.25**
Mastery	-0.15	0.006	-0.04	-0.07	-0.006	0.28*
Emotional distress	-0.13	-0.030	0.11	0.20*	0.220*	-0.17
Active coping	-0.07	-0.070	0.04	0.09	0.080	0.23*
Passive coping	-0.16	-0.080	0.13	0.22*	0.120	-0.05
Pain	0.06	0.170	0.10	0.30**	1.000	-0.08
Vasomotor menopausal symptoms	-0.11	-0.150	1.00	0.56**	0.100	0.14
Physical menopausal symptoms	0.04	-0.050	0.56**	1.00	0.300**	0.09
Number of treatments	-0.11	-0.010	0.14	0.09	-0.080	1.00

N = 103

\*p &lt; 0.05; \*\*p &lt; 0.01; † p &lt; 0.001; \*\* p &lt; 0.0001

stress-process theory, persistent fatigue after the end of treatment was explained by cancer stressors and the way the person copes with them.

Multicollinearity and distribution of residuals also were verified. The absence of multicollinearity was supported by a variance inflation below 10 and a condition index below 30 for all variables included in the final regression model (Draper & Smith, 1998). Also, no strong correlations were found between these variables in the correlation matrix (see Table 3 and Table 5). Residuals were distributed normally as supported by the W test with a p value higher than 0.05 ( $W = 0.97$ ,  $p = 0.07$ ) (Draper & Smith).

No correlation was obtained between interleukin-1b and fatigue. Only one positive correlation almost reached the significant threshold between interleukin-1b and item 16 ( $r = 0.29$ ,  $p = 0.06$ ) of the MFI—"I tire easily." However, concluding that a positive relationship exists between this biologic indicator and fatigue based on a single relationship with one item in an exhaustive instrument is not relevant. So the biologic stress response, as measured by interleukin-1b, is not indicative of the presence of fatigue after the end of treatment in this study.

## Discussion

### Verification of Hypothesis

The main objective was supported by the results of the regression analysis. Indeed, the stress theory helped to explain

**Table 4. Multivariate Analysis for Noncontinuous Confounding Variables in Relation With Fatigue and Stress-Process Theory Variables**

Variable	Multivariate Analysis of Variance	Value	F	df	p
Marital status	Wilks lambda	0.6902	1.11	(32, 337)	0.3117
Income	Wilks lambda	0.8416	0.66	(24, 259)	0.8868
Employment status	Hotelling T <sup>2</sup>	0.1628	1.91	(8, 94)	0.0670
Cancer severity	Wilks lambda	0.9355	0.39	(16, 186)	0.9828
Hormonal therapy	Hotelling T <sup>2</sup>	0.2172	2.55	(8, 94)	0.0146
Chemotherapy	Hotelling T <sup>2</sup>	0.0936	1.10	(8, 94)	0.3702

N = 103

41% of the total variance in fatigue. Pain, as a confounding variable, helped to explain an additional 3% of the variance. These results support the relevance of the stress-process theory in explaining fatigue after the end of treatment. The secondary objective was not supported because no correlation was obtained between the serum level of interleukin-1b and fatigue.

### Fatigue, Stress, and Confounding Variables

Many confounding variables were related to either fatigue or stress variables. Age as a demographic variable showed that the younger the woman, the more she perceives cancer stressors in her life and the negative impact associated with them. These results are consistent with those of Woo et al. (1998).

As side effects of treatments and cancer, menopausal symptoms and pain were related to fatigue and stress variables. Chemotherapy or hormonal therapy (e.g., tamoxifen) may generate menopausal symptoms that can be temporary or permanent (Love, Cameron, Connell, & Leventhal, 1991). In relation to fatigue, pain can be secondary to lymphedema (accumulation of lymph in soft tissue) as reported in some studies (Longman, Braden, & Mishel, 1999; Shimosuma et al., 1999). Lymphedema is a frequent complication of breast cancer surgery, especially when axillary lymph nodes are removed (Hack, Cohen, Katz, Robson, & Goss, 1999). However, the relationship between lymphedema and pain is not well documented. Pain seems to persist over time after the end of breast cancer treatment and is related to persistent fatigue (Jacobsen et al., 1999; Stone et al., 2000).

In the current study, pain as well as menopausal symptoms were related to cancer stressors. Also, pain and menopausal symptoms are important factors in emotional distress in cancer remission (Couzi, Helzlsouer, & Fetting, 1995; Longman et al., 1999; Tasmuth, Von Smitten, & Kalso, 1996).

Among medical variables, only hormonal therapy was found to be statistically significant in relation to passive coping. More specifically, women undergoing hormonal therapy treatment seem to use more passive coping strategies than active coping strategies. This treatment can be perceived to be a chronic cancer stressor because it lasts for five years. Woo et al. (1998) found that the combination of cancer treatments was related to increased fatigue in women in remission from breast cancer. Hormonal therapy was included in this combination of treatments. All other medical variables were not significant.

**Table 5. Pearson Correlation Matrix: Fatigue and Stress-Process Theory Variables**

Variable	Fatigue	Cancer-Related Stressors	Impact	Mastery	Emotional Distress	Active Coping	Passive Coping
Fatigue	1.00	0.61 <sup>**</sup>	0.30 <sup>**</sup>	-0.18	0.42 <sup>**</sup>	-0.09	0.36 <sup>+</sup>
Cancer-related stressors		1.00	0.50 <sup>**</sup>	-0.18	0.61 <sup>**</sup>	-0.04	0.37 <sup>**</sup>
Impact			1.00	-0.06	0.38 <sup>**</sup>	0.01	0.42 <sup>**</sup>
Mastery				1.00	-0.21 <sup>*</sup>	0.46 <sup>**</sup>	0.12
Emotional distress					1.00	-0.10	0.40 <sup>**</sup>
Active coping						1.00	0.49 <sup>**</sup>
Passive coping							1.00

N = 103

\*p &lt; 0.05; \*\*p &lt; 0.01; + p &lt; 0.001; \*\* p &lt; 0.0001

This is consistent with many other previous studies that failed to find significant results among medical treatments and persistent fatigue (Andrykowski et al., 1998; Servaes et al., 2002; Smets, Visser, Willems-Groot, Garssen, Schuster-Uitterhoeve, et al., 1998). More research is needed in this area to document the contribution of hormonal therapy to higher levels of fatigue.

The small size of the samples (including this study) may explain the absence of relationships between cancer treatments and fatigue. In three studies with larger samples (i.e., more than 300), a positive relationship was obtained between chemotherapy treatment or the combination of treatments and persistent fatigue in cancer remission for up to six years (Bower et al., 2000; Mast, 1998; Woo et al., 1998). In addition, the time elapsed since the end of treatment varies from one study to another. In the current study, cancer treatments had been completed for at least three months, so the effects of these treatments may have dissipated, possibly explaining why the treatments did not contribute to the persistent fatigue. In summary, in the literature as well as in the current study, the small size of the sample and the time period after the end of treatment may explain the absence of a relationship between cancer treatments and fatigue.

### Fatigue and Stress

Participants showed a moderately intense persistent fatigue. This result is consistent with other studies (Mast, 1998; Smets, Visser, Willems-Groot, Garssen, Schuster-Uitterhoeve, et al., 1998; Stone et al., 2000) and helps to document the importance of persistent fatigue as a problem after the end of breast cancer treatment.

Among the stress variables described in the current study, cancer stressors still were present after the end of treatment and related to persistent fatigue. Perceived impact and perceived mastery were almost equal in the current study's

**Table 6. Fatigue Multiple Regression Analysis**

Variable	R <sup>2</sup>	Adjusted R <sup>2</sup>	F	β	t
Pain	0.4658	0.4438	21.15 <sup>**</sup>	0.20	2.68 <sup>*</sup>
Cancer-related stressors				0.47	5.54 <sup>**</sup>
Passive coping				0.26	2.79 <sup>*</sup>
Active coping				-0.22	-2.49 <sup>*</sup>

N = 103

\* p &lt; 0.01; \*\* p &lt; 0.001

sample. Compared to the results obtained in a previous study where the perception of a negative impact was described to be higher than perceived mastery around the cancer diagnosis phase (Fillion et al., 1996), these results suggest and are consistent with the longitudinal pattern described in Fillion et al. (1998) that the negative impact associated with cancer and its treatments seems to diminish and ease over time. Even if the perceived impact was moderate at the breast cancer remission stage, it still was related to persistent fatigue. In the same way, even if emotional distress was lower in intensity in this sample after the end of treatment compared to earlier in the treatment process, it still was related to persistent fatigue. This is consistent with several studies (Longman et al., 1996; Smets, Visser, Garssen, et al., 1998; Smets, Visser, Willems-Groot, Garssen, Schuster-Uitterhoeve, et al., 1998; Woo et al., 1998). Finally, active and passive coping also were moderate and almost equal. This means that active strategies were used as often as passive strategies. However, only passive coping was related to persistent fatigue. Here again this finding is consistent with previous studies that also described an association between passive coping strategies and CRF (Foltz et al., 1996; Irvine et al., 1998; Richardson & Ream, 1997).

### Predictive Capacity of the Stress-Process Theory to Explain Fatigue

Results of the statistical regression showed that the combined cancer-related stressors and passive and active coping helped to explain persistent fatigue after the end of breast cancer treatments. In other words, persistent fatigue was associated with the cancer stressors perceived by participants and with how they coped with them. The more a woman perceived cancer stressors, the more fatigued she was. Also, the more a woman used passive coping, the more fatigued she was; the more she used active coping, the less fatigue she reported. So, women who describe less exposure to cancer-related stressors and who are more likely to use active coping strategies than passive coping strategies seem to report less CRF.

These results are consistent with the study of Fillion and Gagnon (1998) in which cancer stressors, negative impact, and distraction coping also helped to explain 43% of the variance in fatigue during a course of radiation therapy for breast cancer. Smets, Visser, Garssen, et al. (1998) also found that cancer stressors explained persistent fatigue after the end of cancer treatment. In the current study, stress variables that were found to contribute to fatigue during cancer treatments, such as stressors and coping, seem to last for three months to two years after the end of treatment.

Another interesting finding is that pain also helped to explain persistent fatigue. As documented in previous studies, lymphedema pain appears to be related to CRF (Longman et al., 1999; Shimozuma et al., 1999). Combined with previous findings, the current study's results suggest that pain may persist over time after the end of treatment and affect the fatigue experienced. If pain contributes to persistent fatigue, it should be taken into consideration in intervention. For instance, pain control should be added to guidelines developed to manage CRF (Portenoy & Itri, 1999).

## Fatigue and Biologic Stress Response

No correlation was found between interleukin-1 $\beta$  and persistent fatigue. Cytokines, including interleukin-1 $\beta$ , are known to be involved in the inflammatory process to repair injured tissues. This result is not consistent with the findings of Greenberg et al. (1993). A possible explanation to support the absence of a relationship between fatigue and this biologic indicator is the absence of an inflammatory process. In the current study, the time period covered began three months after the end of breast cancer treatments. All treatment effects can be assumed to have dissipated, suggesting that no active inflammatory process exists. Furthermore, because participants were in remission from breast cancer, no more damage was done to cells. Because cancer might be controlled, the absence of an inflammatory process can be proposed. This could become more consistent with the findings of Greenberg et al. (1993) in which participants with prostate cancer were undergoing radiation therapy. Under these conditions, the inflammatory process was assumed to be active, involving cell destruction. But no conclusion can be drawn from that study because the size of the sample was too small.

## Study Limitations

First, an important limitation of this study is its cross-sectional design. Indeed, a single time measurement does not allow the dynamic changes in the stress variables to be investigated over time according to different cancer and treatment phases. Second, limitations related to the study sample exist. The size of the sample was limited. In addition, the sample was recruited from the radiation center and did not include women treated only with surgery and chemotherapy for breast cancer. Because these women were not included, the results cannot be generalized to all women with breast cancer. The choice of the time period since the end of treatment may represent another limitation, as previously discussed. Third, the choice of regression as confirmatory statistical analysis for this study limits the results in that it does not allow the exploration of mediation relationships between variables. Fourth, in the study, intensity was the only pain characteristic documented despite the fact that some women presented lymphedema as the cause of their pain, a characteristic that was not further documented. Fifth and finally, the choice of interleukin-1 $\beta$  as a biologic indicator may not be appropriate in this context of the end of cancer treatment. In

addition, the high degree of variability responses of this indicator, despite special care in controlling for physiologic (e.g., circadian rhythms) and technical (same technician and standardized procedure) factors, may have decreased the reliability of this indicator.

## Future Recommendations

First, the study design should be longitudinal to allow for the investigation of stress concepts through the cancer and treatment process. Second, a larger sample and a better representation of all avenues of care, including nonradiation therapy, also would add to the power of the statistical analysis and improve external validity. Third, structural equation modeling could be explored to specify mediation relationships among stress variables. Fourth, lymphedema represents a specific side effect of breast cancer surgery and may contribute to pain as a persistent symptom that increases CRF. Documenting lymphedema in the description of pain and in relation to fatigue could be interesting. Finally, although interleukin-1 $\beta$  may appear to be a relevant biologic marker at stages of cancer treatment that involve destruction of cells, a more general biologic indicator of stress, such as cortisol, may be more appropriate after treatment completion.

## Implications for Nursing

The nurse is a healthcare professional involved in the cancer control process, including prevention, treatment, and rehabilitation. Nurses possess the competence to assess health and develop education plans. As supported in this study, the stress-process theory represents a relevant theoretical framework to develop educational programs for patients with breast cancer. Persistent fatigue is an important problem after the end of cancer treatments. Many women also have identified a need for education on persistent symptoms of breast cancer treatments (Ferrell et al., 1998). With the aim of reducing cancer-related stressors and improving active coping, nursing interventions based on this theoretical framework could be developed. For instance, the authors currently are conducting a randomized clinical trial to test the efficacy of a psycho-educative intervention to decrease persistent fatigue. This intervention is co-led by nurses and includes information about persistent cancer-related symptoms (e.g., fatigue, stress, menopausal symptoms, sleep disturbance) and different tools such as relaxation, physical activity (walking individual programs), and cognitive-behavioral techniques for stress management. Further clinical research that tests the efficacy of these psycho-educative interventions in preventing persistent fatigue and improving the quality of life of women with breast cancer is recommended.

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