# Fatigue in Long-Term Breast Carcinoma Survivors

## *A Longitudinal Investigation*

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**BACKGROUND.** A longitudinal study was designed to evaluate the prevalence, persistence, and predictors of posttreatment fatigue in breast carcinoma survivors.

**METHODS.** A sample of 763 breast carcinoma survivors completed questionnaires at 1–5 and 5–10 years after diagnosis, including the RAND 36-item Health Survey, Center for Epidemiological Studies – Depression scale (CES-D), Breast Cancer Prevention Trial Symptom Checklist, and demographic and treatment-related measures.

**RESULTS.** Approximately 34% of study participants reported significant fatigue at 5–10 years after diagnosis, which is consistent with prevalence estimates obtained at 1–5 years after diagnosis. Approximately 21% reported fatigue at both assessment points, indicating a more persistent symptom profile. Longitudinal predictors of fatigue included depression, cardiovascular problems, and type of treatment received. Women treated with either radiation or chemotherapy alone showed a small improvement in fatigue compared with those treated with both radiation and chemotherapy.

**CONCLUSIONS.** Fatigue continues to be a problem for breast carcinoma survivors many years after cancer diagnosis, with 21% reporting persistent problems with fatigue. Several factors that may contribute to long-term fatigue are amenable to intervention, including depression and comorbid medical conditions. ***Cancer* 2006;106:751–8.** © *2006 American Cancer Society.*

**KEYWORDS: breast carcinoma, cancer survivor, fatigue, quality of life.**

Fatigue is increasingly recognized as the most common and distressing side effect of cancer and its treatment.[1] Fatigue is prominent among cancer patients undergoing treatment and may persist for months or years after successful treatment completion. Indeed, research conducted with breast carcinoma survivors has shown that approximately 30% report significant fatigue within the first 5 years after diagnosis.[2–4] However, to our knowledge, only a few studies to date have examined fatigue in long-term cancer survivors (i.e., individuals who are more than 5 years postcancer diagnosis). As survival times for women with early-stage breast carcinoma lengthen, understanding the long-term effects of cancer treatments on this central aspect of women's functioning has taken on increasing importance.

Early research on quality of life in breast carcinoma survivors up to 10 years after diagnosis found that fatigue was the most commonly reported symptom, providing initial evidence for the prevalence and

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persistence of this problem.[5,6] In a more recent study, breast carcinoma survivors assessed at 5–15 years after diagnosis reported increased fatigue relative to a matched control group with no cancer history.[7] Similar results have been observed among long-term survivors of Hodgkin lymphoma and testicular carcinoma, who report greater fatigue than population controls.[8–10] Cella et al.[11] recently examined the prevalence of cancer-related fatigue in a U.S. sample of mixed cancer survivors. Among patients who completed treatment more than 5 years before, 33% reported at least 2 weeks of fatigue in the previous month. It is interesting to note that none of these studies found an association between time since cancer diagnosis/treatment and fatigue severity, suggesting that fatigue may not improve even in the late posttreatment period. However, conclusions regarding the course of posttreatment fatigue are limited by the cross-sectional nature of these reports.

Fatigue is a multidimensional condition that involves subjective feelings of tiredness, weakness, and/or lack of energy. The etiology of cancer-related fatigue has not yet been determined, although tumor and treatment-related factors, psychosocial factors, physical symptoms, and medical conditions have been proposed as potential contributors.[12] Studies conducted with patients undergoing treatment and in the first 5 years after treatment completion have identified depressed mood as one of the strongest correlates of fatigue, although fatigue cannot be explained entirely by depression.[13] Other correlates of fatigue include pain, sleep disturbance, presence of medical comorbid conditions, and age.[2,14] In contrast, disease- and treatment-related factors are not found to be consistently correlated with fatigue,[14–16] nor do biological factors such as anemia fully account for fatigue symptomatology.[17] The few studies of long-term survivors conducted to date have yielded similar results; in particular, the one study to assess psychologic symptoms found that depressed mood and anxiety were strongly correlated with fatigue severity,[9] whereas none of the studies found an association between type of treatment and fatigue[5,8–10] or between hemoglobin and fatigue.[10] Other factors that are known to be relevant for cancer survivors, such as fear of cancer recurrence, to our knowledge have not been examined in relation to fatigue.

The current study was designed to evaluate the prevalence and persistence of fatigue in a large sample of disease-free breast carcinoma survivors assessed longitudinally at 1–5 and 5–10 years after diagnosis. In an earlier investigation of this sample, we reported on the prevalence and correlates of fatigue at the 1–5-year assessment point.[2] Results showed that approximately one-third of breast carcinoma survivors reported significant fatigue, and that the primary correlates of fatigue were depressed mood and pain. In contrast, treatment-related factors were found to be only weakly correlated with fatigue. The current study had two primary goals: 1) to provide information regarding the prevalence and persistence of fatigue in long-term breast carcinoma survivors; and 2) to identify predictors of fatigue at 5–10 years after diagnosis in an effort to determine potential mechanisms for this symptom.

## MATERIALS AND METHODS

### Procedures

Participants were initially recruited to participate in a study examining health-related quality of life in the first 5 years after breast carcinoma diagnosis. Recruitment for this initial study was conducted between September 1994 and June 1997 in Los Angeles and Washington, DC. The sample included 1957 women who had been diagnosed with early-stage breast carcinoma between 1–5 years earlier, were free of disease, and had completed all cancer therapies other than tamoxifen. Details regarding study recruitment procedures have been provided in earlier publications.[18,19]

In 1998, we recontacted women from the initial study who were at least 5 years postdiagnosis to participate in a follow-up assessment. We sent each woman an invitation letter that included a response form and postage-paid return envelope. Respondents who indicated an interest in participating were mailed the study questionnaires with a postage-paid return envelope. All questionnaires were reviewed for completeness and participants were contacted to obtain missing data. Study procedures were approved by the institutional review boards at the University of California, Los Angeles, and at Georgetown University School of Medicine. All subjects provided informed consent.

### Measures

Study participants completed standardized questionnaires assessing health-related quality of life, physical symptoms, affect, social support, and psychologic responses to the cancer experience. A complete description of these outcomes is provided by Ganz et al.[20] The current study focuses on the following measures.

#### *RAND SF-36*

The SF-36 contains eight individual subscales that represent the three general areas of health-related quality of life: physical, emotional, and social well-being.[21,22] The two scales of interest in this study were the vitality subscale and the bodily pain subscale, which were completed at each assessment.

The vitality subscale of the SF-36 consists of 4 items assessing how much of the time the individual "felt full of pep," "had a lot of energy," "felt worn out," and "felt tired" during the past 4 weeks. As with the other subscales on this instrument, standardized scores on the vitality subscale range from 0–100, with higher scores indicating better functioning (i.e., higher levels of energy). The vitality subscale is bipolar in nature; scores above the midpoint of 50 represent well-being whereas scores below 50 represent limitations or disability related to fatigue. Thus, a score of 100 is only earned by individuals who report feeling full of pep and energy all of the time, and a score of 0 is earned only by those who report feeling tired and worn out all of the time. This scale has been used as the principal validation measure for more detailed fatigue inventories developed specifically for cancer patients (e.g., Fatigue Symptom Inventory and Multidimensional Fatigue Symptom Inventory) and there is a high correlation between scores on these measures.[23,24] Indeed, breast carcinoma survivors who score at or below 50 on the vitality scale demonstrate alterations in biologic and psychologic/behavioral processes relative to survivors who score above 50, supporting the validity of this cut-point.[2,25–28]

The bodily pain subscale of the SF-36 includes 2 items that assess the severity of bodily pain and the extent to which pain interfered with daily activities over the past 4 weeks. Higher scores on this measure indicate lower levels of pain and pain-related disruption. Scores range from 0–100.

### *Center for Epidemiologic Studies – Depression Scale (CES-D)*

This 20-item self-report questionnaire was designed to assess depressive symptomatology in the general population.[29] Respondents indicate how often they have experienced a variety of symptoms during the past week on a four-point scale ranging from "rarely or none of the time" to "most or all of the time." Higher scores on this measure indicate higher levels of depressive symptomatology, with scores equal to or greater than 16 indicating an increased risk of clinical depression. Scores range from 0–60. This measure was completed at each assessment point.

### *Breast Cancer Prevention Trial (BCPT) Symptom Checklist*

This 43-item list of commonly reported physical and psychologic symptoms was developed specifically for the BCPT[30]. Respondents indicate how much they have been bothered by each symptom in the past 4 weeks on a 4-point scale ranging from "not at all" to "extremely." For this study, we used only those items that assessed vasomotor symptoms (hot flashes, night sweats) based on research showing an association between menopausal symptoms and fatigue in breast carcinoma survivors.[15] Because of skewed distributions, responses to these items were grouped and coded categorically (present/not present). The BCPT symptom checklist was completed at each assessment point.

### *Fear of Recurrence Scale*

A modified version of the Fear of Recurrence Scale was administered at the follow-up assessment.[31] This six-item scale assesses worries about cancer recurrence and regarding one's future health status. Respondents indicate how much they agree with each statement on a five-point scale ranging from "strongly disagree" to "strongly agree." Scores range from 0–5, with higher scores indicating greater fear and uncertainty concerning the possibility of cancer returning.

### *Demographic and medical data*

Information regarding demographics, medical conditions, and breast carcinoma treatment was obtained by self-report at the initial assessment and updated at follow-up.

## Statistical Methods

Our analytic approach proceeded in several steps. First, we identified a group of women who scored in the fatigued range on the SF-36 vitality subscale (i.e., scored at or below the scale midpoint of 50) at the follow-up assessment. Second, we compared these women with women who scored above 50 at the follow-up assessment on selected demographic, treatment-related, and psychosocial variables and conducted logistic regression analyses to identify predictors of fatigue status at Time 2. Third, we conducted logistic regression analyses to identify longitudinal predictors of fatigue status using baseline values of predictor variables. We also conducted ordinary least-squares multiple regression analyses to identify concurrent and longitudinal predictors of fatigue using continuous scores on the SF-36 vitality scale as the dependent variable.

Standard statistical tests were performed for continuous and categoric variables, including Pearson product-moment correlation to calculate associations among continuous variables, $\chi^2$ tests to calculate associations among categorical variables, Student $t$ tests to compare means of continuous variables for two groups and one-way analysis of variance to compare means of continuous variables for three or more groups. Logistic regression was used to evaluate the effect of selected predictor variables on the likelihood of being fatigued, and multiple regression was used to

evaluate the effect of selected predictor variables on level of fatigue.

## RESULTS

### Recruitment Results and Characteristics of Participants and Nonparticipants

A total of 1336 subjects met the study eligibility criteria (i.e., were at least 5 years postdiagnosis) and were sent recruitment letters. Response forms were received from 1063 participants: 914 (86%) indicated that they were interested in participating, 79 (7%) were not interested, 58 (5%) could not be located, and 12 (1%) were deceased. Questionnaires were sent to the 914 interested respondents: 817 (89%) returned the questionnaires, 22 (2%) explicitly refused, and 75 (8%) failed to return the booklet despite reminder calls. Overall, completed questionnaires were received from 61% of the 1336 survivors initially contacted.

We compared women who participated in the follow-up study ($n$ = 817) with women who either did not respond to the invitation letter or did not return the study questionnaires ($n$ = 519). Student $t$ tests indicated that study participants reported significantly higher levels of vitality (mean, 61.1) compared with nonparticipants (mean, 58.5; $P$ = 0.03), although the absolute difference was not larger (2.6-point difference). Participants were also better educated, more likely to be white, were less depressed, and scored higher on several measures of quality of life than nonparticipants. There were no differences in type of cancer treatment received. Further details of recruitment results and characteristics of responders and nonresponders are provided elsewhere.[20]

Of the 817 respondents, 54 reported a breast carcinoma recurrence and were not included in the current study given our focus on fatigue in disease-free survivors.[20,32] Therefore, the final sample was comprised of 763 disease-free survivors. The average time between the initial (Time 1) and follow-up (Time 2) assessments was 2.8 years (range, 1–4 yrs).

### Prevalence of Fatigue

As reported by Ganz et al.,[20] there was no change in mean vitality scores noted from Time 1 (mean, 61.4; standard deviation [SD] of 20.4) to Time 2 (mean, 60.9; SD of 20.9). A similar percentage of women scored in the 'fatigued' range of the vitality scale at each assessment point. In our initial examination of fatigue at 1–5 years after diagnosis, 35% of the women were classified as fatigued; at the 5–10-year follow-up, 34% were classified as fatigued.

In addition to determining the point prevalence of fatigue at each assessment, a primary goal of this study was to evaluate the persistence of fatigue over time. Among women classified as fatigued at Time 1, 63% ($n$ = 160) continued to score in the fatigued range of the vitality scale at Time 2. Among women classified as nonfatigued at Time 1, 81% ($n$ = 409) continued to score in the nonfatigued range at Time 2. When calculated as a percentage of the total sample, 21% of study participants scored in the fatigued range at each assessment point, 54% scored in the nonfatigued range at each assessment point, 12% scored in the fatigued range at baseline and in the nonfatigued range at follow-up, and 13% scored in the nonfatigued range at baseline and in the fatigued range at follow-up.

### Concurrent Predictors of Fatigue

To probe factors that may underlie fatigue in long-term survivors, we first compared women who scored in the fatigued range of the SF-36 vitality scale at Time 2 (mean vitality score, 36.8; SD of 12.1) with those who scored in the nonfatigued range at Time 2 (mean vitality score, 73.2; SD of 11.6) on selected variables (Table 1). Several demographic variables were assessed, including age, income, and marital status, each of which was associated with fatigue in our initial report.[2] Only income was associated with fatigue group at follow-up, with fatigued women reporting lower income than nonfatigued women ($P$ = 0.05). We also examined the association between fatigue and several medical conditions that may influence fatigue levels, including diabetes, high blood pressure, heart problems, and arthritis. All of these conditions were more prevalent among fatigued women than nonfatigued women. Psychologic and physical symptoms were found to be strongly associated with fatigue, a finding that was consistent with our initial report. Fatigued women reported significantly higher levels of depressive symptoms, more bodily pain (as indicated by lower scores on the SF-36 pain scale), and more hot flashes and night sweats than nonfatigued women. Fear of cancer recurrence was also significantly higher in the fatigued group. In terms of treatment-related factors, the results demonstrated that type of cancer treatment was significantly associated with fatigue group at follow-up. This difference appeared to be driven by two treatment groups: radiation alone, and radiation and chemotherapy. Fatigued women were *less* likely to have been treated with radiation alone than nonfatigued women, and were *more* likely to have been treated with a combination of radiation and chemotherapy. The use of tamoxifen and time since diagnosis were not found to be significantly associated with fatigue group.

A logistic regression analysis was conducted including predictor variables that were significantly as-

**TABLE 1**
**Characteristics of Fatigued and Nonfatigued Survivors at Follow-Up**

| Characteristic | Fatigued ($n$ = 257) | Nonfatigued ($n$ = 504) | $P$ [a] |
|---|---|---|---|
| Mean age in yrs (SD) | 58.8 (11.5) | 59.0 (10.3) | 0.86 |
| Income | | | |
| < $45,000 | 30.7% | 24.1% | 0.05 |
| $45,000–100,000 | 46.6% | 45.8% | |
| > $100,000 | 22.7% | 30.1% | |
| Married/committed relationship | | | |
| Yes | 69.3% | 73% | 0.29 |
| No | 30.7% | 27% | |
| High blood pressure | 28.4% | 19.4% | 0.005 |
| Diabetes | 6.2% | 2.8% | 0.02 |
| Heart disease | 9.7% | 3.4% | 0.003 |
| Arthritis | 40.9% | 32.1% | 0.02 |
| CES-D depression, mean (SD) | 14.6 (9.1) | 5.65 (5.3) | < 0.0001 |
| SF-36 bodily pain, mean (SD) | 65.6 (24.5) | 82.2 (19.4) | < 0.0001 |
| Hot flashes/night sweats | | | |
| Bothered | 60.3% | 50% | 0.007 |
| Not bothered | 39.7% | 50% | |
| Fear of recurrence, mean (SD) | 3.19 (0.67) | 2.85 (0.78) | < 0.0001 |
| Type of cancer treatment | | | |
| Surgery alone | 23.7% | 24.5% | 0.03 |
| Radiation | 28.8% | 36.4% | |
| Chemotherapy | 19.1% | 19.5% | |
| Radiation and chemotherapy | 28.4% | 19.7% | |
| Use of tamoxifen | | | |
| Current | 23.1% | 16.1% | 0.08 |
| In past | 37.8% | 40.1% | |
| Never took | 39.0% | 43.8% | |
| Mean yrs since diagnosis, (SD) | 6.3 (1.0) | 6.3 (1.1) | 0.92 |

SD: standard deviation; CES-D: Center for Epidemiological Studies – Depression scale.
[a]$P$ values were derived from Student $t$ tests for continuous variables and $\chi^2$ for categoric variables. Percentages are based on available data and may not add up to 100 due to rounding.

**TABLE 2**
**Multivariate Logistic Regression with Concurrent Predictors of Fatigue Status at Follow-Up**

| Follow-up predictor variable | OR | 95% CI |
|---|---|---|
| Income[a] | | |
| Under $45,000 | 1.20 | (0.70–2.06) |
| $45,000–100,000 | 1.25 | (0.78–1.99) |
| High blood pressure | 1.80[b] | (1.14–2.86) |
| Diabetes | 1.16 | (0.44–3.08) |
| Heart disease | 1.89 | (0.83–4.28) |
| Arthritis | 0.75 | (0.49–1.16) |
| CES-D depression | 1.17[c] | (1.13–1.21) |
| SF-36 bodily pain[d] | 0.98[c] | (0.97–0.98) |
| Hot flashes/night sweats | 1.33 | (0.90–1.96) |
| Fear of cancer recurrence | 1.04 | (0.79–1.37) |
| Type of cancer treatment[e] | | |
| Surgery only | 0.62 | (0.36–1.09) |
| Radiation | 0.53[b] | (0.31–0.89) |
| Chemotherapy | 0.84 | (0.47–1.48) |

OR: odds ratio; 95% CI: 95% confidence interval; CES-D: Center for Epidemiological Studies – Depression scale.
[a]Comparison group is income > $100,000.
[b]$P < 0.05$.
[c]$P < 0.0001$.
[d]Higher scores indicate less pain.
[e]Comparison group is radiation and chemotherapy.

sociated with fatigue in the bivariate analyses (i.e., income, medical conditions, depressive symptoms, bodily pain, hot flashes/night sweats, fear of recurrence, and type of cancer treatment). All of the predictors, with the exception of treatment type, were measured at follow-up. The model including all explanatory variables was significant ($P < 0.0001$). As shown in Table 2, depressive symptoms, pain, and high blood pressure were all found to be significant predictors of being fatigued at 5–10 years after diagnosis. Treatment category was found to be a marginally significant predictor ($P = 0.08$ for overall treatment group). Follow-up pairwise comparisons demonstrated that women treated with both radiation and chemotherapy were more likely to be fatigued than women treated with radiation alone ($P = 0.016$), which is consistent with bivariate results. Income was not significant in the regression model. These results are largely consistent with logistic regression analyses conducted at Time 1 in the full sample of study participants ($n$ = 1927). As reported by Bower et al.,[2] depression, pain, and high blood pressure were significant cross-sectional predictors of fatigue at Time 1, as were arthritis and age; however, treatment category was not found to be a significant predictor at this assessment point.

Multiple regression analyses also were conducted to evaluate the association between predictor variables and level of fatigue at the follow-up assessment. Results were largely consistent with logistic regression; depressive symptoms and pain were found to be significant predictors of fatigue, as was treatment with radiation and chemotherapy (compared with radiation alone). In the multiple regression model, heart disease was found to be a significant predictor of fatigue ($P = 0.049$), and high blood pressure was marginally significant ($P = 0.097$). Overall, the predictor variables explained 45% of the variance in fatigue scores at followup ($R^2 = 0.45$; $P < 0.0001$).

### Longitudinal Predictors of Fatigue

In addition to examining concurrent predictors of fatigue, a primary goal of the current study was to identify longitudinal predictors of fatigue. Logistic regression analyses were conducted including variables that were significant predictors of fatigue in logistic regression models conducted at either Time 1 (identified in

**TABLE 3**
**Multivariate Logistic Regression with Longitudinal Predictors of Fatigue Status at Follow-Up**

| Baseline predictor variable | OR | 95% CI |
|---|---|---|
| SF-36 vitality[a] | 0.94[b] | (0.93–0.96) |
| Age[c] | | |
| < 50 yrs | 0.87 | (0.50–1.52) |
| 50–60 yrs | 0.62 | (0.35–1.10) |
| Income[d] | | |
| Under $45,000 | 1.27 | (0.74–2.20) |
| $45,000–100,000 | 1.11 | (0.67–1.84) |
| High blood pressure | 1.75[e] | (1.08–2.81) |
| Diabetes | 1.10 | (0.40–3.05) |
| Heart disease | 1.82 | (0.75–4.39) |
| Arthritis | 0.92 | (0.58–1.45) |
| CES-D depression | 1.04[f] | (1.01–1.06) |
| SF-36 bodily pain[g] | 0.99 | (0.98–1.00) |
| Hot flashes/night sweats | 1.05 | (0.70–1.58) |
| Type of cancer treatment[h] | | |
| Surgery only | 0.66 | (0.38–1.15) |
| Radiation | 0.47[f] | (0.27–0.80) |
| Chemotherapy | 0.56[e] | (0.32–0.98) |

OR: odds ratio; 95% CI: 95% confidence interval; SF-36: ; CES-D: Center for Epidemiological Studies – Depression scale.
[a]Higher scores indicate more vitality/less fatigue.
[b]$P < 0.0001$.
[c]Comparison group is age over 60 years.
[d]Comparison group is income over $100,000.
[e]$P < 0.05$.
[f]$P < 0.01$.
[g]Higher scores indicate less pain.
[h]Comparison group is radiation and chemotherapy.

Bower et al.[2]) or Time 2. These included age, income, medical conditions, depressive symptoms, pain, menopausal symptoms, and type of treatment received, all measured at baseline. Baseline fatigue score was also included as a predictor.

The results are shown in Table 3. As expected, baseline fatigue score was a strong predictor of fatigue group at follow-up; women who reported higher levels of fatigue at 1–5 years after diagnosis were significantly more likely to be fatigued at 5–10 years after diagnosis. In addition, women who reported higher levels of depressive symptoms and who had high blood pressure at baseline were significantly more likely to be fatigued at follow-up. Bodily pain was a marginal predictor of fatigue group. The overall test for treatment category was significant ($P = 0.04$). Pairwise comparisons of the treatment groups indicated that women treated with radiation and chemotherapy were more likely to be fatigued than women treated with radiation alone ($P = 0.005$) or chemotherapy alone ($P = 0.04$).

Multiple regression analyses with continuous scores on the SF-36 vitality scale as the outcome variable showed a similar pattern of results. Baseline fatigue, depression, and bodily pain were all found to be significant predictors of fatigue severity at follow-up, as was type of cancer treatment received. Consistent with the concurrent multiple regression model, heart disease was found to be a significant predictor of fatigue and high blood pressure was not. Overall, baseline predictor variables accounted for 46% of the variance in follow-up fatigue scores ($R^2 = 0.46$; $P < 0.0001$).

## DISCUSSION

To our knowledge, the current study is the first large-scale, longitudinal study of fatigue symptoms in long-term breast carcinoma survivors. At 5–10 years after diagnosis, 34% of the women surveyed reported elevated fatigue as indicated by scores on the SF-36 vitality scale. The prevalence of fatigue at this assessment point was nearly identical to that observed at 1–5 years after diagnosis (35%), highlighting the lack of change in this symptom over time.[20] These prevalence estimates are similar to those seen in studies conducted with breast carcinoma survivors in the first years after diagnosis[3,4] and with longer-term survivors. For example, Cella et al.[11] found that 33% of cancer survivors who had completed treatment more than 5 years previously had experienced a 2-week period of fatigue in the month before assessment. The present findings are also consistent with studies demonstrating no association between time since diagnosis and fatigue.[8–10]

The current study results also provide information regarding the prevalence of *persistent* fatigue in breast carcinoma survivors. Approximately 21% of the women surveyed reported fatigue at both assessment points, suggesting a more enduring problem. Interestingly, a similar percentage (20%) of the long-term survivors assessed by Cella et al.[11] reported that they had not only experienced a 2-week period of fatigue, but that the fatigue had caused significant disruption in their daily activities. It is possible that, whereas one-third of survivors report fatigue at any given time, a smaller group of patients may experience more persistent and/or debilitating fatigue symptoms that lead to impairment in functioning. There was also evidence for fluctuations in fatigue status; approximately 25% of study participants moved from 1 fatigue group to the other over the course of the follow-up period. To date, there is little information available regarding the temporal pattern of fatigue in cancer survivors; it is unclear whether this symptom waxes and wanes, with some periods of increased energy, or is relatively constant from day to day. Descriptive accounts highlight the pervasiveness of cancer-related fatigue,[33] but empiric research is lacking. Longitudinal studies involving repeated assessment of fatigue in survivor populations are required to address this important issue.

A second goal of the current study was to identify

predictors of long-term fatigue. Analyses conducted in the full sample highlighted two factors associated with fatigue in breast carcinoma survivors: cardiovascular problems and presence of depressive symptoms. Cross-sectional studies support an association between comorbid medical conditions and fatigue in cancer survivors, including cardiovascular disorders.[9] The results of the current study extend these findings by demonstrating that breast carcinoma survivors with high blood pressure or heart disease face an increased risk of fatigue in the 5–10 years after diagnosis. The majority of women who reported high blood pressure also reported use of antihypertensive medications, which are associated with fatigue in noncancer populations.[34] These findings suggest that attention to comorbid medical conditions and related medications are an important part of caring for the fatigued patient.

Fatigue is known to co-occur with depression in cancer patients and survivors,[13] although the lack of longitudinal research has complicated the interpretation of these results. In particular, it is unclear whether depression predicts changes in fatigue over time, which might suggest that depression underlies or perpetuates fatigue symptoms. A recent longitudinal study conducted with breast carcinoma patients undergoing radiation therapy found that depressed mood before treatment was associated with increased fatigue 2.5 years later, although pretreatment fatigue levels were not controlled in this report.[35] The current study results indicate that women who experience depressive symptoms in the first years after diagnosis are at increased risk for long-term fatigue, even after controlling for initial fatigue scores. Overall, the results of the current study confirm the close links between fatigue and depression and highlight the importance of carefully assessing depression in cancer survivors who report problems with fatigue.

The third predictor of long-term fatigue in this sample was the type of cancer treatment received. Previous studies have not found a strong association between cancer treatments and fatigue in long-term survivors of Hodgkin disease or testicular carcinoma.[8–10] The few studies to evaluate treatment effects in breast carcinoma survivors have yielded similar results,[10,14] including our initial examination of this patient cohort at 1–5 years after diagnosis.[2] The current results suggest that the effects of cancer treatments may be most apparent in longer-term breast carcinoma survivors. In particular, women treated with either radiation or chemotherapy showed a small improvement in fatigue at 5–10 years after diagnosis compared with those treated with both radiation and chemotherapy. It is possible that some of the fatigue experienced at the initial assessment point was related to these cancer treatments and resolved over a longer follow-up period. The lack of recovery among women treated with radiation and chemotherapy is consistent with results from the parent study, which found detrimental effects of adjuvant therapy among long-term survivors,[20] and suggests that more aggressive treatments may have long-term, subtle effects on quality of life.

The current study has several limitations that merit attention. First, the study focused on women in 2 large urban areas and yielded a response rate of 61% at the follow-up assessment, which may have biased results. Furthermore, participants in the follow-up study scored several points higher on the SF-36 vitality scale than nonparticipants at the baseline assessment, suggesting that the most fatigued women may have been underrepresented in our sample. It is noteworthy that our estimates of fatigue prevalence are quite similar to those obtained by Cella et al.,[11] who recruited cancer survivors from a representative sample of 575,000 households across the U.S. In addition, the predictors of fatigue identified in this report (e.g., depressed mood) are consistent with those found in previous research with cancer survivors,[9] supporting the validity of the current results. Second, because participants were initially assessed after cancer diagnosis and treatment, we cannot determine whether their fatigue was specifically related to cancer. It is possible that fatigue is a stable characteristic of certain individuals that has little to do with the cancer experience. Previous studies have shown elevated fatigue levels in breast carcinoma survivors relative to healthy controls,[36,37] suggesting that fatigue is driven at least in part by aspects of the cancer experience. The current results also support cancer-specific factors (i.e., type of cancer treatment) as contributors to long-term fatigue. Prospective studies that assess women before treatment onset and include a healthy comparison group are needed to determine whether fatigue is linked to cancer diagnosis and treatment, and to identify unique and common predictors of fatigue in cancer survivors and healthy women. A third limitation of this study is the brief measure of fatigue, which provides information regarding fatigue frequency but does not assess intensity, interference, or dimensions of fatigue. Although this scale is highly correlated with more comprehensive fatigue inventories,[23,24] use of these measures in future studies should provide a more in-depth portrait of cancer-related fatigue.

Overall, the findings of the current study highlight the resilience of breast carcinoma survivors and suggest that persistent fatigue is experienced by a minority of women in the aftermath of cancer diagnosis and treatment. Further, they offer some hope that improvements in fatigue may be possible even up to 10 years after diagnosis and identify potential targets for intervention, including depression and other comorbid medical conditions.

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