



Jacob Ochtervelt, 1660. *The Doctor's Visit*. From the collection of Dr. Gordon and Adele Gilbert of St. Petersburg, Florida.

Is Fatigue a Long-term Side Effect of Breast Cancer Treatment?

Paul B. Jacobsen, PhD, and Kevin Stein, PhD

Breast cancer patients are more likely to experience fatigue following adjuvant chemotherapy or autologous bone marrow transplantation than following regional therapy.

Background: Fatigue is one of the most common and distressing symptoms experienced by breast cancer survivors. Despite its prevalence, relatively little is known about the characteristics, etiology, or treatment of fatigue in breast cancer survivors.

Methods: This report reviews studies that assessed fatigue in breast cancer patients previously treated with adjuvant radiotherapy, adjuvant chemotherapy, or autologous bone marrow transplantation.

Results: A review of the literature suggests that breast cancer patients who undergo adjuvant chemotherapy or autologous bone marrow transplantation experience clinically significant levels of fatigue for months or even years following the completion of active treatment. In contrast, there is little evidence that patients who receive only regional therapy (ie, surgery plus adjuvant radiotherapy) experience clinically significant fatigue as a long-term treatment side effect.

Conclusions: A growing body of evidence indicates that persistent fatigue can be a long-term side effect of certain forms of breast cancer treatment. The challenges for the future will be to determine the etiology of fatigue among breast cancer survivors and to develop interventions that are effective in preventing or reducing fatigue following breast cancer treatment.

Introduction

Breast cancer is the leading form of cancer in US women.¹ Of the 175,000 women expected to be diagnosed with this disease in 1999, it is estimated that 85% will survive five years or more.¹ A growing body of evidence indicates that these survivors experience a variety of problems that adversely affect their quality of life. Among the most common are problems associated with ovarian functioning, sexual functioning, body image, pain, and fatigue.^{2,3} Although fatigue is one of the most frequent and distressing symptoms experienced by breast cancer survivors, this topic has only recently begun to receive serious attention. Interest in the problem of fatigue is growing among clinicians and researchers alike⁴⁻⁷ and is consistent with a greater awareness of the importance of quality of life as an outcome in oncology.^{8,9} The aim of this report is to summarize research that has investigated fatigue among breast cancer survivors and to outline directions for future work in this area. Before reviewing the research, however, it is necessary to review several important methodologic issues in the study of fatigue.

Methodologic Issues in the Study of Fatigue

Previous research on fatigue in cancer patients has been characterized by a number of methodologic limitations. One issue pertains to the manner in which fatigue is measured. At present, there is no consensus regarding the optimal means of assessing fatigue in cancer patients. As a result, a variety of self-report techniques are used. Much of the time, fatigue is measured using a single item embedded in a symptom checklist such as the Symptom Distress Scale¹⁰ or the Rotterdam Symptom Checklist.¹¹ Visual analogue scales and the single-item Rhoten Fatigue Scale¹² are also used. Due to their format, these single-item measures have limited reliability and provide only the most perfunctory information about patients' experiences with fatigue. Fatigue is also frequently assessed using multi-item measures such as the Fatigue Scale of the Profile of Mood States (POMS).¹³ Although multi-item measures possess better psychometric properties than single-item measures, they are limited in that they provide information only about patients' general level of fatigue severity. In a more comprehensive approach to the assessment of fatigue, several investigators have developed multidimensional measures.^{14,15}

Two measures recently developed by our research group illustrate this approach. The Fatigue Symptom Inventory¹⁶ is a 14-item measure that consists of separate subscales assessing the intensity and duration of fatigue, as well as its perceived interference with quality of life. The Fatigue Symptom Inventory is designed to be used in conjunction with the 30-item Multidimensional Fatigue Symptom Inventory-Short Form,¹⁷ which provides information about the patient's experiences with the behavioral, cognitive, physical, and affective manifestations of fatigue.

A second methodologic limitation involves the frequent use of cross-sectional research designs to study changes in fatigue over time. In using a cross-sectional design, researchers attempt to draw conclusions about the persistence or resolution of fatigue by comparing individuals who vary in the time elapsed since they completed cancer treatment. This methodologic approach is limited by the fact that the observed changes over time also reflect individual differences in patients' experience of fatigue. A more methodologically sound approach is the use of a longitudinal design in which the same patients are assessed on multiple occasions following treatment completion. Although costly in terms of both time and resources, data from longitudinal studies could greatly clarify the natural history of fatigue in cancer survivors.

A third limitation of previous research involves the absence of comparison groups. Since fatigue is a common symptom in the general population, some frame of reference is necessary in order to evaluate reports of fatigue obtained from cancer patients.

Ideally, researchers should also obtain data about fatigue from samples of individuals without cancer whose sociodemographic characteristics (eg, age, gender, and education) are similar to those of the patients under study. In addition to providing useful reference values, data from comparison groups may also be helpful in evaluating the sensitivity of different fatigue measures and in identifying the symptoms of fatigue that distinguish different patient and nonpatient populations.

An additional limitation of previous research has been the tendency to recruit samples of breast cancer survivors that are heterogeneous with regard to the previous treatment. That is, the samples include women treated with varying combinations of surgery, chemotherapy, and/or radiotherapy. Typically, these samples do not include enough women who received comparable forms of therapy in order to conduct meaningful comparisons based on the type of treatment. A more useful strategy, illustrated in the studies reviewed below, is to recruit patients who received the same form(s) of therapy in sufficient numbers in order to be able to examine what may be important treatment-specific differences in fatigue.

With these considerations in mind, we now turn to a review of research that has examined fatigue in women with breast cancer previously treated with adjuvant radiotherapy, adjuvant chemotherapy, and autologous bone marrow transplantation.

Fatigue After Adjuvant Radiotherapy

Previous research has consistently shown that women with breast cancer generally experience heightened fatigue during the course of adjuvant radiotherapy treatment.¹⁸⁻²⁴ Table 1 lists studies that have examined the characteristics of fatigue in breast cancer patients after completion of adjuvant radiotherapy treatment.

Table 1. — Patient Characteristics in Studies of Fatigue Following Adjuvant Radiotherapy for Breast Cancer				
Study	Number of Patients	Mean Age (range)	Number of Treatments	Time Since Treatment Ended
Berglund et al ²⁵ (1991)	172	60 yrs (33-79)	Not reported (4-5 weeks duration)	Range = 2-10 years from start of treatment
Greenberg et al ²⁰ (1992)	15	46 yrs (38-56)	Range = 26-28	3 weeks, repeated at 11-14 weeks
Irvine et al ²¹ (1998)	76	60 yrs (33-81)	Mean = 23 (range = 16-30)	3 months, repeated at 6 months
Hann et al ²⁶ (1998)	45	64 yrs (36-86)	Mean = 29 (range = 25-33)	Mean = 22 months (range = 5-88)

Evidence of persistent fatigue following adjuvant radiotherapy comes primarily from a study conducted by Berglund and colleagues.²⁵ In this study, fatigue was assessed in women with breast cancer who were treated with adjuvant radiotherapy between two and 10 years previously and were recurrence-free at the time of follow-up. Data obtained using a symptom checklist indicated that fatigue was the most commonly reported symptom and was present in 76% of patients. Additional results indicated that fatigue severity was unrelated to either patient age or time since completion of radiotherapy treatment.

In contrast to these findings, results from three other studies suggest that fatigue does not persist following completion of adjuvant radiotherapy treatment. In one of the first studies to address this issue, Greenberg et al²⁰ assessed fatigue in women with breast cancer during the course of adjuvant radiotherapy treatment and then following treatment at 3 weeks and at 11 to 14 weeks. Fatigue was assessed using an average score derived from the administration of three separate fatigue scales: the POMS Fatigue Scale,¹³ the Pearson-Byars Fatigue Feeling Checklist,¹⁹ and a visual analog scale. Results indicated that fatigue decreased from baseline during the first two weeks of treatment but then increased steadily before reaching a plateau by the fourth week of treatment. Thereafter, levels of fatigue diminished significantly and were found to be at pretreatment levels by the third week following treatment completion. No further changes in fatigue severity were noted at the 11th week following treatment completion. Irvine and colleagues²¹ obtained similar results in a study in which fatigue was assessed in women with breast cancer during adjuvant radiotherapy and at three and six months following treatment completion by means of the Pearson Byars Feeling Checklist.¹⁹ Consistent with prior research, results indicated that levels of fatigue during radiotherapy treatment were significantly higher than the pretreatment level. However, by the three-month follow-up, the severity of fatigue had returned to the pretreatment level and remained at this level at the six-month follow-up. Hann et al²⁶ also obtained results indicating that fatigue does not persist following completion of adjuvant radiotherapy. In this study, the POMS Fatigue Scale,¹³ the Fatigue Symptom Inventory,¹⁶ and the Multidimensional Fatigue Symptom Inventory¹⁷ were used to assess fatigue in breast cancer patients who were treated with adjuvant radiotherapy an average of 22 months previously and were recurrence-free at the time of follow-up. Fatigue was also assessed in an age-matched comparison sample of women with no history of cancer. The two groups were not found to differ in terms of the duration or disruptiveness of fatigue or in their levels of global, somatic, cognitive, affective, or behavioral symptoms of fatigue. Differences in fatigue severity were also nonsignificant, with the exception of ratings of the most fatigue experienced in the past week. Compared to the age-matched comparison group, the former radiotherapy patients reported higher levels of fatigue on the day they felt most fatigued in the past week.

What conclusions, if any, can be drawn from these studies? Taken together, the findings fail to provide clear evidence that fatigue following adjuvant radiotherapy is a clinically significant phenomenon. Heightened fatigue does appear to be common during the course of radiotherapy; however, the studies reviewed indicate that recovery to a pretreatment level typically occurs within several weeks of completing treatment.^{20,21} Moreover, one study has shown that the level of fatigue experienced by women previously treated with adjuvant radiotherapy cannot be distinguished from the level experienced by women of similar age with no history of cancer.²⁶ Although one study reviewed did report a relatively high prevalence of fatigue among women previously treated with radiotherapy,²⁵ the significance of this finding remains unclear in the absence of comparison or normative data. To the extent that fatigue is common in the general population, relatively high prevalence rates may not be clinically significant. It should be noted that findings suggesting the absence of heightened fatigue following adjuvant radiotherapy refer to the experience of the "average" patient. In each of the studies reviewed, there was evidence of considerable variability in patient reports of fatigue. Accordingly, there may be a subgroup of former radiotherapy patients for whom fatigue is an important clinical problem. Identifying these patients and determining why they experience heightened fatigue should be a focus of future research.

Fatigue After Adjuvant Chemotherapy

Previous research has shown that fatigue is one of the most common symptoms experienced during the course of adjuvant chemotherapy for breast cancer. For example, Greene et al²⁷ reported that among women receiving adjuvant chemotherapy, 82% reported fatigue after the first treatment cycle and 77% reported fatigue after the second treatment cycle.

Table 2 lists those studies that have investigated the presence of fatigue after completion of adjuvant chemotherapy treatment. In one of the first studies to examine this issue, Knobf²⁸ surveyed women who had finished treatment an average of 28 months previously. Using the Symptom Distress Scale¹⁰ to assess seven common symptoms, the investigator found that fatigue and insomnia were perceived as causing the greatest distress.

Table 2. — Randomized Clinical Trials of Bisphosphonates in Breast Cancer-Related Skeletal Disease				
Study	Number of Patients	Mean age (years)	Common Regimens	Time Since Treatment Ended
Knobf ²⁸ (1986)	28	Not reported	Not reported	Mean = 28 months (range = 2-60)
Berglund et al ²⁵ (1991)	201	58 (range = 34-77)	CMF (100%)	Range = 2-10 years from start of treatment

Beisecker et al ²⁹ (1997)	18	49 (range = 32-66) CAF (24%)	CMF (57%)	Median = 7.5 months
Broeckel et al ³⁰ (1998)	61	52 (range = 29-75)	CA (39%) CMF (31%) CAF (18%)	Mean = 471 days (range=108-875)
C = cyclophosphamide M = methotrexate F = fluorouracil A = doxorubicin				

Two subsequent studies provide more specific information regarding the prevalence of fatigue among women treated with adjuvant chemotherapy. Berglund et al²⁵ assessed fatigue in a sample of women who received adjuvant chemotherapy between two and 10 years previously. All patients were treated with cyclophosphamide, methotrexate, and fluorouracil (CMF) for a minimum of 6 months and a maximum of 18 months and were recurrence-free at the time of assessment. Using a 16-item self-report symptom measure, the authors found that 68% of patients were currently experiencing fatigue. Additional findings indicated that the presence of fatigue was associated with more time elapsed since treatment completion. It should be noted, however, that the length of chemotherapy and the number of treatment cycles also tended to be greater in patients for whom more time had elapsed. In the other study to examine prevalence, Beisecker and colleagues²⁹ surveyed a sample of women with node-negative disease in which the median time since treatment completion was 7.5 months. Using a semistructured interview to assess common treatment side effects, the investigators found that 83% of patients reported the current presence of fatigue and 60% reported that fatigue interfered with their functioning.

A recent study by Broeckel et al³⁰ provides additional information about the characteristics and correlates of fatigue following adjuvant chemotherapy. Participants in this study were recurrence-free breast cancer patients who had completed adjuvant chemotherapy an average of 471 days previously and an age-matched comparison group of women with no history of cancer. Fatigue was assessed in both groups using the POMS Fatigue Scale,¹³ the Fatigue Symptom Inventory,¹⁶ and the Multidimensional Fatigue Symptom Inventory.¹⁷ Compared to women with no history of cancer, former adjuvant chemotherapy patients reported more severe fatigue, worse quality of life due to fatigue, and greater physical and mental symptoms of fatigue. Among the former chemotherapy patients, more severe fatigue was related to poorer sleep quality, more menopausal symptoms, and greater use of catastrophizing as a coping strategy. In contrast, fatigue severity was unrelated to age, time since treatment completion, additional treatment with radiotherapy, or current use of tamoxifen.

Several preliminary conclusions can be drawn from these studies. First, the data suggest that fatigue is an extremely common and distressing symptom following adjuvant chemotherapy.^{25,28,29} Second, fatigue following adjuvant chemotherapy appears to be a clinically significant phenomenon. Levels of fatigue among former adjuvant chemotherapy patients have been shown to be 50% greater than those reported by women with no history of cancer.³⁰ Third, there is evidence that the presence of menopausal symptoms may exacerbate the degree of fatigue experienced by former adjuvant chemotherapy patients.³⁰ One possible explanation for this relationship is that the occurrence of vasomotor symptoms of menopause (eg, night sweats) may produce disruptions in sleep that, in turn, result in heightened fatigue.³¹ Finally, there is preliminary evidence that the strategies patients use to cope with fatigue may also have an impact on the severity of their symptoms. In particular, the tendency to catastrophize (ie, to engage in overly negative thoughts about oneself and the future) appears to be associated with a worse experience of fatigue.

Fatigue After Autologous Bone Marrow Transplantation

Autologous bone marrow transplantation or, more precisely, high-dose chemotherapy with autologous stem-cell support, is one of the newest forms of breast cancer treatment. Once limited primarily to patients with metastatic disease, autologous bone marrow transplantation is increasingly being performed on women with earlier-stage disease characterized by lymph node involvement. Table 3 lists studies that have examined fatigue in women with breast cancer previously treated by means of autologous bone marrow transplantation.

Table 3. — Patient Characteristics in Studies of Fatigue Following Autologous Bone Marrow Transplantation for Breast Cancer				
Study	Number of Patients	Mean age (years)	Common High-Dose Regimens	Time Since Treatment Ended
Hann et al ³² (1998)	43	44 (range = 32-57)	Not reported	Mean = 20 months (range = 3-63)
van Dam et al ³³ (1998)	34	46 (SD = 62)	Cyclophosphamide, thiotepa, carboplatin	Mean = 1.6 years (SD = 0.8)
SD = standard deviation				

In one of the first studies to examine this issue, Hann and colleagues³² surveyed women who had completed autologous bone marrow transplantation for either metastatic or nonmetastatic breast cancer an average of 20 months previously and in an age-matched comparison group of women with no history of cancer. The patient sample was limited to women with no clinical evidence of disease at follow-up. Fatigue was assessed in both groups using the POMS Fatigue Scale,¹³ the Fatigue Symptom Inventory,¹⁶ and the Multidimensional Fatigue Symptom Inventory.¹⁷ Compared to women with no history of cancer, former transplant patients reported more severe fatigue, greater duration of fatigue, worse quality of life due to fatigue, and more behavioral, mental, and global symptoms of fatigue. Among former transplant patients, more severe fatigue was related to poorer sleep quality, higher levels of anxiety and depression, and more time elapsed since transplant. In contrast, fatigue severity was unrelated to patient age, disease stage at transplant, length of hospitalization for transplant, or current use of tamoxifen.

Additional evidence of fatigue following autologous bone marrow transplantation for breast cancer comes from a recently published study by van Dam et al.³³ Participants in this study were breast cancer patients with nonmetastatic disease who were randomly assigned to receive either standard-dose adjuvant chemotherapy or high-dose chemotherapy with stem-cell rescue (ie, autologous bone marrow transplantation). Patients with no evidence of disease recurrence were assessed an average of 1.6 years (transplant group) and 1.9 years (chemotherapy group) following treatment completion. Data also were obtained from a sample of breast cancer patients treated with surgery and radiotherapy alone an average of 2.4 years previously. As part of a larger investigation of quality of life, fatigue was assessed in all three groups using the fatigue symptom scale of the European Organization for Research on Treatment of Cancer (EORTC) QLQ-C30.³⁴ Results indicated that patients who underwent transplant reported they were more bothered by fatigue than were patients treated with surgery and radiotherapy alone. Differences between patients treated with standard-dose chemotherapy and those treated with surgery and radiotherapy were in the same direction; however, they did not reach statistical significance.

Taken together, the results of these studies provide preliminary evidence that fatigue following autologous transplantation for breast cancer is a clinically significant phenomenon. Women with breast cancer who were an average of more than one year posttransplant have been shown to be more fatigued than women with no history of cancer³² as well as women with breast cancer who were treated with surgery and radiotherapy only.³³ The magnitude of these differences is considerable. Former transplant patients reported 52% more fatigue than a comparison group of women with no history of cancer (as measured by the POMS Fatigue Scale)³² and 90% more fatigue than a

comparison group of breast cancer patients treated with surgery (as measured by the EORTC QLQ-C30).³³ Preliminary evidence also suggests that fatigue in former transplant patients is accompanied by sleep disturbance and heightened emotional distress.

Comparison of Fatigue Across Different Types of Treatment

The studies reviewed suggest that the degree of fatigue experienced following breast cancer treatment varies according to the specific type of treatment received. Specifically, there is evidence to indicate that fatigue is a significant clinical problem in patients treated with adjuvant chemotherapy and autologous bone marrow transplantation but not in patients treated with adjuvant radiotherapy. In order to directly address the issue of differences in fatigue related to type of treatment, it would be useful to compare patients who received different type treatments and who were assessed with the same measures of fatigue at comparable time points following treatment completion. Three research projects would appear to allow for comparisons of this type.

The first project is a study by Mast,³⁵ in which fatigue was assessed in 109 women who were recurrence-free and had completed breast cancer treatment an average of 35 months previously (range = 12 to 68 months). These patients were an average of 60 years of age (range = 20 to 90 years) and almost all (99.1%) had either stage I or II disease. Previous treatment consisted of surgery plus one of the following: neither radiotherapy nor chemotherapy, radiotherapy only, chemotherapy only, or chemotherapy plus radiotherapy. Fatigue was assessed in all patients using a revised version of the Symptom Distress Scale.³⁶ Results indicated that patients treated with chemotherapy with or without radiotherapy reported greater fatigue than patients treated without chemotherapy.

The second project consists of three studies conducted at our center in which fatigue was assessed in women previously treated with adjuvant radiotherapy,²⁶ with adjuvant chemotherapy,³⁰ or with autologous bone marrow transplantation.³² The demographic and medical characteristics of patients in these studies are described in the previous sections of this review. Since patients in each of these studies were administered the POMS Fatigue Scale, direct comparisons across type of treatment are possible. As shown in Fig 1, former transplant patients tended to have more fatigue than did former adjuvant chemotherapy patients who, in turn, tended to have more fatigue than did former radiotherapy patients.

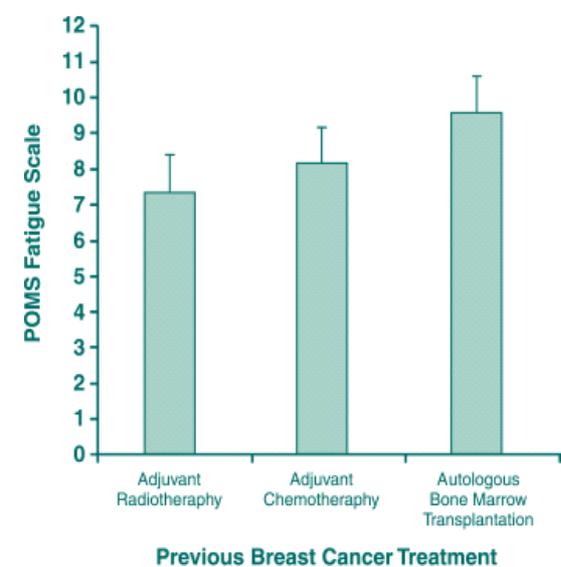


Fig 1. — Differences in fatigue according to type of treatment, as measured by the POMS fatigue scale. Adapted from Hann et al^{26,32} and Broeckel et al.³⁰

The third project is the study by van Dam and colleagues³³ in which fatigue was assessed in women treated with surgery and radiotherapy only, with standard-dose adjuvant chemotherapy, or with autologous bone marrow transplantation using the EORTC QLQ-C30 fatigue symptom subscale. Results from this project were similar to those from studies conducted at our center; former transplant patients tended to have more fatigue than did former adjuvant chemotherapy patients who, in turn, tended to have more fatigue than did former radiotherapy patients (Fig 2).

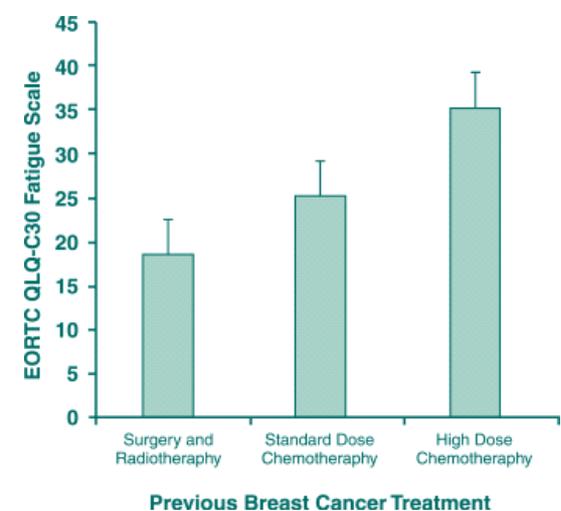


Fig 2. — Differences in fatigue according to type of treatment, as measured by the EORTC QLQ-C30 fatigue symptom subscale. Adapted from van Dam et al.³³

The pattern of results observed in these three projects is consistent with the view that fatigue following breast cancer treatment is more likely with systemic therapy (ie, adjuvant chemotherapy and autologous bone marrow transplantation) than with nonsystemic therapy (ie, radiotherapy only and surgery only). Since therapy (systemic vs nonsystemic) was not assigned randomly in these projects, the possibility remains that the observed pattern of results is attributable to disease characteristics that are

confounder with treatment selection. For example, the results could reflect the fact that women with lymph node involvement or larger tumors are more likely to be treated with systemic therapy than with surgery or radiotherapy only. Determining the relative contribution of disease and treatment factors is likely to be a major focus of future research on fatigue in breast cancer survivors.

Unanswered Questions

Although considerable progress has been made in identifying the characteristics and correlates of fatigue in breast cancer survivors, two major questions remain unanswered. First, why do women with breast cancer continue to experience fatigue months or even years following the administration of systemic therapy? Second, what interventions are effective in preventing or reducing this fatigue?

There is general agreement that fatigue in cancer patients who receive systemic therapy is multifactorial in origin.⁷ Fatigue in breast cancer patients may be the direct result of treatment-related physiologic changes (eg, occurrence of anemia and accumulation of toxic metabolites)³⁷ as well as the indirect result of other treatment-related side effects (eg, pain and fever).¹⁸ While these mechanisms can explain the occurrence of fatigue during treatment, they cannot easily account for the persistence of fatigue following treatment completion (ie, when most patients are no longer experiencing direct physiologic effects of treatment or acute side effects).

One possible explanation is that heightened fatigue following treatment completion is a consequence of longer-term changes in physiologic functioning that have yet to be identified and/or the occurrence of longer-term side effects, such as changes in ovarian functioning. Along these lines, it is possible that women with breast cancer experience persistent heightened fatigue due to the sudden and often irreversible onset of treatment-induced menopause and its accompanying vasomotor symptoms (eg, hot flashes). Among women who are postmenopausal prior to breast cancer diagnosis, discontinuation of estrogen replacement therapy³⁸⁻⁴⁰ may contribute to heightened fatigue if vasomotor symptoms of menopause are not well controlled by other means. If so, this would suggest that nonhormonal interventions that are effective in relieving vasomotor symptoms of menopause might also be effective in relieving fatigue in breast cancer survivors.

A second and not mutually exclusive explanation is that cognitive and behavioral responses to fatigue during the active phase of treatment contribute to the perpetuation of fatigue following treatment completion. Along these lines, there is evidence from other patient populations indicating that patients who respond to fatigue cognitively by catastrophizing and focusing on their symptoms and behaviorally by avoiding activity and accommodating their lifestyles to illness are more likely to develop chronic forms of fatigue.⁴¹ Two pieces of evidence suggest that this explanation is applicable to breast cancer patients. First, greater use of catastrophizing has been shown to be related to greater fatigue in breast cancer patients previously treated with adjuvant chemotherapy.³⁰ Second, restrictions in physical activity have been shown to be related to greater fatigue in breast cancer patients currently receiving adjuvant chemotherapy.⁴² Evidence in support of this explanation would suggest the use of a psychosocial intervention that is designed to change maladaptive cognitive and behavioral responses to treatment-related fatigue.

Conclusions

A growing body of evidence indicates that fatigue is indeed a long-term side effect of certain forms of breast cancer treatment. The challenge for the future will be to identify the causes of fatigue among breast cancer survivors and to develop interventions that are effective in preventing or reducing fatigue following completion of breast cancer treatment.

References

1. American Cancer Society. *Cancer Facts & Figures, 1999*. Atlanta, Ga: The American Cancer Society; 1999.
2. Dow KH, Ferrell BR, Leigh S, et al. An evaluation of the quality of life among long-term survivors of breast cancer. *Breast Cancer Res Treat*. 1996;39:261-273.
3. Ganz PA, Coscarelli A, Fred C, et al. Breast cancer survivors: psychosocial concerns and quality of life. *Breast Cancer Res Treat*. 1996;38:183-199.
4. Groopman JE. Fatigue in cancer and HIV/AIDS. *Oncology*. 1998;12:335-344.
5. Richardson A. Fatigue in cancer patients: a review of the literature. *Eur J Cancer Care*. 1995;4:20-32.
6. Smets EM, Garssen B, Schuster-Uitterhoeve AL, et al. Fatigue in cancer patients. *Br J Cancer*. 1993;68:220-224.
7. Winningham ML, Nail LM, Burke MB, et al. Fatigue and the cancer experience: the state of the knowledge. *Oncol Nurs Forum*. 1994;21:23-36.
8. Cella DF. Quality of life as an outcome of cancer treatment. In: Groenwald SL, Goodman M, Frogge MH, et al, eds. *Cancer Nursing: Principles and Practice*. 3rd ed. Boston, Mass: Jones and Bartlett Publishers; 1993.
9. Ganz PA. Quality of life and the patient with cancer: individual and policy implications. *Cancer*. 1994;74:1445-1452.
10. McCorkle R, Quint-Benoliel J. Symptom distress, current concerns and mood disturbance after diagnosis of life-threatening disease. *Soc Sci Med*. 1983;17:431-438.
11. de Haes JC, van Knippenberg FC, Neijt JP. Measuring psychological and physical distress in cancer patients: structure and application of the Rotterdam Symptom Checklist. *Br J Cancer*. 1990;62:1034-1038.
12. Rhoten D. Fatigue and the post surgical patient. In: Norris CM, ed. *Concept Clarification in Nursing*. Rockville, Md: Aspen Systems Corp; 1982.
13. McNair DM, Lorr M, Droppleman L. *Profile of Mood States*. 2nd ed. San Diego, Calif: Educational and Industrial Testing Service; 1992.
14. Piper BF, Dibble SL, Dodd MJ, et al. The revised Piper Fatigue Scale: psychometric evaluation in women with breast cancer. *Oncol Nurs Forum*. 1998;25:677-684.
15. Smets EM, Garssen B, Bonke B, et al. The Multidimensional Fatigue Inventory (MFI): psychometric qualities of an instrument to assess fatigue. *J Psychosom Res*. 1995;39:315-325.
16. Hann DM, Jacobsen PB, Azzarello LM, et al. Measurement of fatigue in cancer patients: development and validation of the Fatigue Symptom Inventory. *Qual Life Res*. 1998;7:301-310.
17. Stein KD, Martin SC, Hann DM, et al. A multidimensional measure of fatigue for use with cancer patients. *Cancer Pract*. 1998; 6:143-152.
18. Blesch KS, Paice JA, Wickham R, et al. Correlates of fatigue in people with breast or lung cancer. *Oncol Nurs Forum*. 1991;18:81-87.
19. Irvine D, Vincent L, Graydon JE, et al. The prevalence and correlates of fatigue in patients receiving treatment with chemotherapy and radiotherapy: a comparison with the fatigue experienced by healthy individuals. *Cancer Nurs*. 1994;17:367-378.
20. Greenberg DB, Sawicka J, Eisenthal S, et al. Fatigue syndrome due to localized radiation. *J Pain Symptom Manage*. 1992;7:38-45.
21. Irvine DM, Vincent L, Graydon JE, et al. Fatigue in women with breast cancer receiving radiation therapy. *Cancer Nurs*. 1998; 21:127-135.
22. Mock V, Dow KH, Meares CJ, et al. Effects of exercise on fatigue, physical functioning, and emotional distress during radiation therapy for breast cancer. *Oncol Nurs Forum*. 1997;24:991-1000.
23. Haylock PJ, Hart LK. Fatigue in patients receiving localized radiation. *Cancer Nurs*. 1979;2:461-467.
24. Kobashi-Schoot JA, Hanewald GJ, van Dam FS, et al. Assessment of malaise in cancer patients treated with radiotherapy. *Cancer Nurs*. 1985;8:306-313.

25. Berglund G, Bolund C, Fornander T, et al. Late effects of adjuvant chemotherapy and postoperative radiotherapy on quality of life among breast cancer patients. *Eur J Cancer*. 1991;27:1075-1081.
26. Hann DM, Jacobsen PB, Martin SC, et al. Fatigue and quality of life following radiotherapy for breast cancer: a comparative study. *J Clin Psychol Med Settings*. 1998;5:19-33.
27. Greene D, Nail LM, Fieler VK, et al. A comparison of patient-reported side effects among three chemotherapy regimens for breast cancer. *Cancer Pract*. 1994;2:57-62.
28. Knobf MT. Physical and psychologic distress associated with adjuvant chemotherapy in women with breast cancer. *J Clin Oncol*. 1986;4:678-684.
29. Beisecker A, Cook MR, Ashworth J, et al. Side effects of adjuvant chemotherapy: perceptions of node-negative breast cancer patients. *Psychooncology*. 1997;6:85-93.
30. Broeckel JA, Jacobsen PB, Horton J, et al. Characteristics and correlates of fatigue after adjuvant chemotherapy for breast cancer. *J Clin Oncol*. 1998;16:1689-1696.
31. Kronenberg F. Hot flashes: phenomenology, quality of life, and search for treatment options. *Exp Gerontol*. 1994;29:319-336.
32. Hann DM, Jacobsen PB, Martin SC, et al. Fatigue in women treated with bone marrow transplantation for breast cancer: a comparison with women with no history of cancer. *Support Care Cancer*. 1997;5:44-52.
33. van Dam FS, Schagen SB, Muller MJ, et al. Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: high-dose versus standard-dose chemotherapy. *J Natl Cancer Inst*. 1998;90:210-218.
34. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85:365-76.
35. Mast ME. Correlates of fatigue in survivors of breast cancer. *Cancer Nurs*. 1998;21:136-142.
36. Holmes S. Use of a modified symptom distress scale in assessment of the cancer patient. *Int J Nurs Stud*. 1989;26:69-79.
37. Glaspy J, Bukowski R, Steinberg D, et al. Impact of therapy with epoetin alfa on clinical outcomes in patients with nonmyeloid malignancies during cancer chemotherapy in community oncology practice. Procrit Study Group. *J Clin Oncol*. 1997;15:1218-1234.
38. Bines J, Oleske DM, Cobleigh MA. Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer. *J Clin Oncol*. 1996;14:1718-1729.
39. Couzi RJ, Helzlsouer KJ, Fetting JH. Prevalence of menopausal symptoms among women with a history of breast cancer and attitudes toward estrogen replacement therapy. *J Clin Oncol*. 1995;13:2737-2744.
40. Cobleigh MA, Berris RF, Bush R, et al. Estrogen replacement therapy in breast cancer survivors: a time for change. Breast Cancer Committees of the Eastern Cooperative Oncology Group. *JAMA*. 1994;272:540-545.
41. Wessely S, Hotopf M, Sharpe M. *Chronic Fatigue and Its Syndromes*. New York, NY: Oxford University Press; 1998.
42. Berger AM. Patterns of fatigue and activity and rest during adjuvant breast cancer chemotherapy. *Oncol Nurs Forum*. 1998;25:51-62.
-

From the Psychosocial Oncology Program at H. Lee Moffitt Cancer Center & Research Institute, Tampa, Fla.

Address reprint requests to Paul B. Jacobsen, PhD, Psychosocial Oncology Program, H. Lee Moffitt Cancer Center & Research Institute, MOD3-PSY, 12902 Magnolia Dr, Tampa, FL 33612.

This article has been supported by an Institutional Research Grant (IRG #202) from the American Cancer Society. No significant relationship exists between the authors and the companies whose products are referenced in this article.

 [Back to Cancer Control Journal Volume 6 Number 3](#)