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ORIGINAL REPORT

Fatigue, Menopausal Symptoms, and Cognitive Function in Women After Adjuvant Chemotherapy for Breast Cancer: 1- and 2-Year Follow-Up of a Prospective Controlled Study

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ABSTRACT

Purpose
We previously evaluated fatigue, menopausal symptoms, and cognitive dysfunction in patients receiving adjuvant therapy for breast cancer and matched healthy women. Here we report assessment of these women 1 and 2 years later.

Patients and Methods
Patients without relapse and controls were evaluated by the Functional Assessment of Cancer Treatment-General Quality of Life questionnaire, with subscales for fatigue and endocrine symptoms, and by the High Sensitivity Cognitive Screen.

Results
There were 104, 91, and 83 patients and 102, 81, and 81 controls assessed at baseline and at 1 and 2 years, respectively. Median Functional Assessment of Cancer Treatment-Fatigue scores (range, 0 to 52) for patients improved from 31 (on chemotherapy) to 43 and 45 at 1 and 2 years, respectively, but were stable in controls (46 to 48). Median Functional Assessment of Cancer Treatment-Endocrine Symptoms scores (range, 0 to 72) for patients improved from 57 (on chemotherapy) to 59 and 61 at 1 and 2 years, respectively, and were stable in controls (64 to 65). Differences between patients and controls remained significant for these scales. The incidence of moderate-severe cognitive dysfunction by the High Sensitivity Cognitive Screen decreased in patients from 16% (on chemotherapy) to 4.4% and 3.8% and in controls from 5% to 3.6% and 0% at 1 and 2 years, respectively. There were minimal differences between estrogen receptor–positive patients who started hormonal therapy (mainly tamoxifen) after chemotherapy and estrogen receptor–negative patients who did not. Differences in quality of life between patients and controls were significant only at baseline.

Conclusion
Fatigue, menopausal symptoms, and cognitive dysfunction are important adverse effects of chemotherapy that improve in most patients. Hormonal treatment has minimal impact on them.

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INTRODUCTION

Most patients with primary breast cancer are offered adjuvant chemotherapy after surgery, followed by hormonal therapy in patients whose tumors express the estrogen receptor (ER). The management of many adverse effects of chemotherapy, such as nausea and vomiting, has improved. Concern has shifted to more subtle and potentially chronic problems such as fatigue, menopausal symptoms, and cognitive dysfunction. Although there have been several studies of the frequency and severity of these

symptoms in patients after adjuvant chemotherapy for breast cancer,[1-10] there are limited longitudinal data documenting the evolution of these problems. This knowledge is important for providing appropriate informed consent to patients and for the design of interventions for the prevention and treatment of these symptoms.

To assess the impact of fatigue, menopausal symptoms, and cognitive impairment in women undergoing adjuvant chemotherapy for breast cancer, we undertook a study of 100 pairs of patients and patient-nominated age-matched healthy controls. In an analysis of initial findings,[11] we found that women undergoing chemotherapy experienced substantially more fatigue and menopausal symptoms than the control group and that these symptoms were associated with each other and with overall quality of life. Also, a higher incidence of moderate-severe cognitive impairment was observed in patients who were receiving chemotherapy as compared to controls. Here we present the results of 1- and 2-year follow-up assessments of subjects in this study.

PATIENTS AND METHODS

Study Population and Assessments

To recruit 100 eligible pairs of patients and matched controls, 104 patients undergoing adjuvant or neoadjuvant chemotherapy for resectable breast cancer met inclusion criteria and were assessed. The control group consisted of 102 healthy women: each control was an acquaintance or relative of a patient differing in age by no more than 5 years.[11] Reasons for exclusion included a psychiatric history or use of psychotropic medications other than benzodiazepines for nausea, sleep, or anxiety. Four patients and two controls whose partners either refused initial assessment or did not meet inclusion criteria are included in this analysis.

Initial assessment was undertaken toward the end of chemotherapy after at least three cycles of chemotherapy were completed. At that time, patients and controls were asked to provide demographic/medical information and complete a series of Functional Assessment of Cancer Therapy (FACT) self-assessment questionnaires for fatigue (FACT-F),[12] menopausal symptoms (FACT-ES),[13] and general quality of life (FACT-G).[14] Cognitive function was evaluated by the High Sensitivity Cognitive Screen (HSCS),[15,16] the Mini-Mental Status Exam,[17] Conner's Continuous Performance Test,[18,19] and the Trail-Making Test.[20] In addition, blood was collected for measurement of serum estradiol, follicle-stimulating hormone, and luteinizing hormone from patients and controls who consented to this additional procedure.

The HSCS assesses the neurocognitive domains of memory, language, attention/concentration, visual motor, spatial, and self-regulation with six subtests comprising between one and five test items. Each individual item on the test produces a numeric score. An interpretive algorithm is then applied to generate a result of normal, borderline, or mild, moderate, or severe impairment for each subtest. Another algorithm is then applied to the subtest results to generate an overall classification of neurocognitive function.

For ease of data analysis, the menopausal status of participants was classified as either premenopausal (menses in the last 12 months) or postmenopausal (>12 months ago). This differs from the more traditional classification of premenopausal (< 3 months ago), perimenopausal (3 to 12 months ago), and postmenopausal (> 12 months ago) used in the original publication of this study.[11]

The study was designed prospectively to reassess patients and controls at 1 and 2 years (± 2 months) after their initial assessment. Reasons for exclusion from the follow-up assessments were relapse from breast cancer, death, or participant refusal. Participants whose matched control had withdrawn from the study after the baseline assessment were eligible to continue their involvement. The follow-up assessments followed the same format as the initial assessment. Conner's Continuous Performance Test was omitted when results of the initial assessment became available, showing no difference between the performance of patients and controls for this test. Medical information provided by the patients, such as the use of adjuvant hormonal therapy, was verified by cross-referencing with medical records.

The protocol for this study was approved by the review boards of the participating institutions, and all subjects gave written informed consent.

Statistical Analysis

Four primary end points were evaluated at each of the three time points (during chemotherapy and the 1- and 2-year follow-ups): fatigue as evaluated by the FACT-F scale, menopausal symptoms as evaluated by the FACT-ES scale, overall classification of cognitive function as evaluated by the HSCS, and overall quality of life as evaluated by the FACT-G scale. Because of the multiple planned analyses, differences between patients and controls for the primary end points were regarded as significant for two-sided P values of less than .01.

The planned sample size of 100 patients and 100 controls was selected on the basis of incidence of cognitive dysfunction in the published literature available at the time and issues of feasibility. It was estimated that at least 70 patients and 70 controls would be available for assessment at 2 years. With a power of 90%, a significance level of .01, and the calculated standard deviations for the distribution of the primary end points, the sample allows detection or exclusion of differences in the FACT-F score of 5.5 and 6.5, in the FACT-ES score of 4.5 and 5.5, in the FACT-G score of 7.5 and 9.5, and in the proportion of moderate-severe dysfunction by the HSCS of 19% and 24% at the beginning and end of the study, respectively.

The four primary end points were found not to be normally distributed, and in the published analysis of the initial assessment, the paired Wilcoxon test was used to compare results of the four primary end points between matched pairs of patients and controls.[11] We also performed unpaired comparisons with all the data available, and the results were similar. Because subjects did not drop out as pairs in the follow-up analysis, we based the present analysis on unpaired comparisons for all the patients and controls who were assessed initially, at 1 and 2 years, by using the unpaired Wilcoxon test. A secondary analysis of matched pairs was undertaken also.

We also formally examined the trend of the four outcomes with time from baseline to years 1 and 2, and compared the difference in the trend between groups, by using a longitudinal data-analysis approach. For the continuous outcomes of fatigue (FACT-F score), menopausal symptoms (FACT-ES score), and quality life (FACT-G score), linear mixed models were fitted. For the categoric outcome of cognitive function (HSCS category), a generalized estimating equation model was applied in which moderate-severe impairment of cognitive function was fitted.

Correlation between repeated measurements from the same subject was appropriately handled by including either a random effect in the model or a robust variance covariance matrix.[21]

The interrelationship between the four primary end points at each assessment was calculated by using Spearman correlation coefficients. In addition, multivariate linear-regression analyses were performed to determine the influence of various relevant factors on fatigue and menopausal symptoms in the patient population. Factors included were those deemed to be clinically important. Menopausal symptoms, type and number of courses of chemotherapy, and use of adjuvant hormonal or radiation therapy were evaluated for effects on fatigue; menopausal status and its progression during chemotherapy, adjuvant hormonal therapy, and treatment of hot flashes were evaluated for effects on menopausal symptoms. Stepwise selection was not used.

Table 1. Treatment Received by Patients

	Baseline (N = 104)	1 Year (N = 91)	2 Years (N = 81)
Radiotherapy	7	62	53
Hormonal therapy	5	57	54
Tamoxifen	5	49	44
Aromatase inhibitor*	0	9	10
Treatment for hot flashes†	4	13	9

*Includes anastrozole, letrozole, or exemestane. Two patients changed their hormonal agent, one from goserelin to tamoxifen and the other from tamoxifen to an aromatase inhibitor.
†Includes treatment with venlafaxine, other serotonin-reuptake inhibitors, and clonidine.

RESULTS

Patients and Controls

Of the 104 eligible patients and 102 controls (100 matched pairs) who underwent baseline assessment, data are available from 91 patients and 81 controls (81 matched pairs) at 1 year and 83 patients and 81 controls (73 matched pairs) at 2 years of follow-up. Six patients were not eligible for the first-year assessment because of relapse of disease (three patients) or death (three patients), and an additional two patients experienced relapse by the time of the 2-year assessment; others had scheduling problems or withdrew consent. Reasons for controls withdrawing from the study included withdrawal of their matched patient or loss of interest. Four controls and one patient missed the 1-year assessment but completed the 2-year assessment.

The patient and control groups remained well matched for age and education status at the 1- and 2-year follow-up assessments. The median age of patients and controls at recruitment was 48 and 47 years, respectively, and 60% to 70% of them had postsecondary education.[11] There was no significant difference in results from the initial assessment for any of the four primary end points between participants who did and did not complete the follow-up assessments. Therefore, it is unlikely that changes in outcome measures resulted from bias in subjects withdrawing from the study.

Treatment Received by Patients

All patients completed adjuvant chemotherapy. The most common regimens were six cycles of cyclophosphamide, epirubicin, and fluorouracil (63%) or four cycles of doxorubicin and cyclophosphamide (19%). Additional treatment received by the patients is summarized in Table 1. Most patients underwent lumpectomy and received radiation therapy to the residual breast after their chemotherapy. Adjuvant hormonal therapy (most often tamoxifen 20 mg/day) was usually commenced after chemotherapy in ER-positive patients: it was administered to 63% (57 of 91) and 67% (54 of 81) of patients who underwent assessment at 1 and 2 years, respectively. One patient who initially received goserelin switched to tamoxifen, and another switched from tamoxifen to an aromatase inhibitor. A minority of patients received pharmacotherapy (usually venlafaxine) for symptomatic hot flashes or other menopausal symptoms.

Fatigue

Levels of fatigue in patients and controls and the influence of hormonal treatment on fatigue in patients are listed in Tables 2 and 3. At the initial assessment, patients receiving chemotherapy experienced substantially more fatigue than controls ($P < .0001$). Patients experienced improvement in fatigue over the 2-year period, although differences with controls were still significant at the 1- and 2-year assessments. Mixed-model analysis also indicates significant time-dependent improvement in fatigue in patients but not in controls (Table 2). Hormonal therapy had only small effects on fatigue, with a trend for patients receiving hormonal therapy to be more tired at the 2-year assessment (Table 3).

We performed multivariate analyses at each time point to evaluate associations with fatigue (Table 4). At the initial assessment, fatigue was found to be influenced by the severity of menopausal symptoms (FACT-ES score) and by the

Table 2. Fatigue in Patients and Controls at Serial Assessments

	Patients, FACT-F		Controls, FACT-F		
	No.	Median	No.	Median	P*
Initial	104	31	102	46	< .0001
1 year	91	43	83	47	< .0001
2 years	81	45	81	48	.01

NOTE. Median FACT-F scores (range, 0 to 52) are indicated. Higher scores indicate less fatigue. In the mixed model, the interaction between time and group and the trend for change in FACT-F with time are highly significant ($P < .0001$ for both), consistent with improvement in fatigue in patients but not in controls.
Abbreviation: FACT-F, Functional Assessment of Cancer Therapy, fatigue subscale.
*P values are derived from the unpaired Wilcoxon test.

Table 3. Fatigue in Patients Receiving Hormonal Therapy or Not

	Hormonal Treatment, FACT-F		No Hormonal Treatment, FACT-F		
	No.	Median	No.	Median	P*
1 year	57	42	34	43	.59
2 years	54	42	27	48	.02

NOTE. Median FACT-F scores (range, 0 to 52) are indicated. Higher scores indicate less fatigue.
Abbreviation: FACT-F, Functional Assessment of Cancer Therapy, fatigue subscale.
*P values are derived from the unpaired Wilcoxon test.

serum hemoglobin level.[11] Hemoglobin levels were not available at follow-up, and variables analyzed for their impact on fatigue were menopausal symptoms, type of chemotherapy, number of courses of chemotherapy, adjuvant radiotherapy, and adjuvant hormonal therapy. A significant association between menopausal symptoms and fatigue was observed at both 1 and 2 years ($P < .0001$). No other significant associations were found.

Menopausal Symptoms

Menopausal symptoms in patients and controls, as assessed by the FACT-ES questionnaire, and the influence of hormonal treatment on menopausal symptoms in patients are summarized in Tables 5 and 6. Consistent with a chemotherapy-induced menopause, patients who had received chemotherapy experienced substantially more menopausal symptoms than controls. These symptoms improved, but there were significant differences in FACT-ES scores observed at each of the three time points ($P < .0001$ for each comparison). Mixed-model analysis also indicates significant time-dependent improvement in menopausal symptoms in patients but not in controls (Table 5). The trend over time was toward minor improvement in symptoms despite an increasing proportion of both groups becoming postmenopausal (Table 5). Surprisingly, hormonal therapy had no detectable effect on menopausal symptoms in patients (Table 6).

Table 4. Multivariate Analyses for Factors Influencing Fatigue and Menopausal Symptoms in the Patient Group

Analysis	1-Year Assessment, P*	2-Year Assessment, P*
Fatigue		
Menopausal symptoms	< .0001	< .0001
Type of CT	.43	.20
Number of courses of CT	.96	.32
Adjuvant RT	.54	.65
Adjuvant hormonal therapy	.90	.45
Menopausal symptoms		
Menopausal status	.11	.69
Progression of menopausal status from initial assessment	.18	.33
Adjuvant hormonal therapy	.62	.20
Treatment of hot flashes	.001	.016

Abbreviations: CT, chemotherapy; RT, radiotherapy.
*P values were extracted from the four fitted multivariate models and indicate the level of significance for the independent impact of each variable on fatigue or menopausal symptoms.

Table 5. Menopausal Symptoms in Patients and Controls at Serial Assessments

	Patients, FACT-ES		Controls, FACT-ES		
	No.	Median	No.	Median	P*
Initial	104	57	102	64	< .0001
1 year	91	59	83	64	< .0001
2 years	81	61	80	65	< .0001

NOTE. Median FACT-ES scores (range, 0 to 72) are indicated. Higher scores represent fewer symptoms. In the mixed model, the interaction between time and group is marginally significant ($P = .03$) and the trend for change in FACT-ES with time is highly significant ($P < .0001$), consistent with improvement in menopausal symptoms in patients but not in controls.
Abbreviation: FACT-ES, Functional Assessment of Cancer Therapy, menopausal symptoms subscale.
*P values are derived from the unpaired Wilcoxon test.

The percentage of patients and controls who were postmenopausal increased from 30% to 84% and from 32% to 46%, respectively, over the 2-year period. Data relating to the effects of chemotherapy on menopausal symptoms are summarized in Table 7 and are separated for patients who were premenopausal or postmenopausal at initiation of chemotherapy. Because only a minority of patients and controls agreed to have blood taken for hormone-level tests at follow-up, these results have not been reported. The severity of menopausal symptoms, as indicated by the FACT-ES scores, differed minimally between women who were premenopausal and those who were postmenopausal at initiation of chemotherapy (Table 7) but were worse than for controls.

We also performed a multivariate analysis in which initial menopausal status, progression from the premenopausal to postmenopausal state, adjuvant hormonal therapy, and treatment of hot flashes were examined for their

Table 6. Menopausal Symptoms in Patients Receiving Hormonal Therapy or Not

	Hormonal Treatment, FACT-ES		No Hormonal Treatment, FACT-ES		
	No.	Median	No.	Median	P*
1 year	57	58	34	59	.9
2 years	54	61	27	61	.80

NOTE. Median FACT-ES scores (range, 0 to 72) are indicated. Higher scores represent fewer symptoms.
Abbreviation: FACT-ES, Functional Assessment of Cancer Therapy, menopausal symptoms subscale.
*P values are derived from the unpaired Wilcoxon test.

Table 7. Menopausal Status and Menopausal Symptoms in Patients and Controls

Status at Baseline Assessment	Premenopausal			Postmenopausal (≥ 12 months)		
	Baseline*	1 Year	2 Years	Baseline*	1 Year	2 Years
Patients		n = 73			n = 31	
Median time since last period, months	2.8	15	24	44	58	71
Median FACT-ES score	56.6	57.1	61.0	58.0	61.0	61.0
Controls		n = 69			n = 33	
Median time since last period, months	0.5	0.6	0.8	76	117	137
Median FACT-ES score	64.0	65.0	66.0	62.5	62.0	62.5

Abbreviation: FACT-ES, Functional Assessment of Cancer Therapy, menopausal symptoms subscale.
*Patients were receiving chemotherapy at the time of baseline assessment.

effect on the FACT-ES score (Table 4). The only significant association was for a better FACT-ES score at 1 year in patients who received treatment for hot flashes ($P = .001$).

Cognitive Function

At the initial assessment near the end of chemotherapy, more patients than controls had moderate-severe cognitive dysfunction as assessed by the HSCS, although the level of significance ($P = .02$) is borderline when corrected for the four primary end points (Table 8). Over the 2 years of follow-up, the proportion of patients with moderate-severe cognitive impairment improved from 16% to 4%. All the patients with moderate-severe impairment at initial assessment who underwent subsequent assessment improved to a level of mild impairment or better. Of patients and controls who scored as having mild impairment or better at their initial assessment, three patients (3.8%) and no controls were noted to have moderate-severe impairment at the 2-year follow-up assessment. An improvement in HSCS scores for the control group was also observed, with the proportion demonstrating moderate-severe cognitive impairment dropping from 5% to 0% over the 2-year period. The generalized estimating equation model that evaluated association of moderate-severe dysfunction with group and time was consistent with improvement in both patients and controls, without major differences between them (Table 8). There was no significant difference in HSCS scores between patients who had hormonal treatment and those with ER-negative tumors who did not.

Results for the Trails A and Trails B tests for patients and controls at the 1- and 2-year follow-up are summarized in Table 9. Patients seemed to have poorer performance than controls on the Trails B test at 1 and 2 years of follow-up, but the results should be viewed cautiously, because this was not a primary end point.

Quality of Life

Quality of life, as assessed by the FACT-G, was found to be worse for patients than for controls at the initial assessment (Table 10). This difference subsequently resolved with similar levels of quality of life reported by patients and controls at 1 and 2 years of follow-up. Mixed-model analysis also indicates significant time-dependent improvement in quality of life in patients but not in controls (Table 10). There was no significant effect of hormonal therapy on quality of life.

The Spearman correlation test indicated a strong association between fatigue, menopausal symptoms, and overall quality of life at all three time points assessed ($P < .0001$ for each association). No association was observed between these factors and cognitive function at any assessment.

Table 8. Percentage of Subjects With Cognitive Dysfunction as Assessed by the High Sensitivity Cognitive Screen

	Patients (%)				Controls (%)				
	No.	Normal/Borderline	Mild	Moderate-Severe	No.	Normal/Borderline	Mild	Moderate-Severe	P*
Initial	104	49.4	34.6	16	102	58.7	36.3	5	.02
1 year	91	64.8	30.8	4.4	83	77.1	19.3	3.6	.03
2 years	81	74.9	21.3	3.8	81	88.9	11.1	0	.07

NOTE. In the generalized estimating equation model fitting moderate-severe cognitive dysfunction, the interaction between time and group is not significant ($P = .88$), but the trend in time is significant ($P = .0023$), suggesting that cognitive function improved significantly, with similar trends for patients and controls.
*The P value is for the difference in distribution across the categories of cognitive dysfunction according to the High Sensitivity Cognitive Screen.

Table 9. *T* Scores for the Trails A and B Tests in Patients and Controls

	Patients		Controls		
	No.	Median	No.	Median	*P*
Trails A					
Initial	104	42.0	102	45.0	.02
1 year	91	44.0	83	45.0	.25
2 years	81	47.0	80	49.0	.61
Trails B					
Initial	104	47.5	102	48.5	.26
1 year	91	49.0	83	54.0	.0005
2 years	81	50.0	80	53.0	.048

NOTE. Higher scores represent better function.

DISCUSSION

The present study demonstrates that fatigue and menopausal symptoms are substantial problems for patients during and shortly after chemotherapy. Although these symptoms improved over time, patients remained more symptomatic than controls over 2 years of follow-up. There was no significant difference in overall quality of life between patients and controls by 1 year of follow-up, perhaps reflecting adaptation to their symptoms and a change in their frame of reference as to what is regarded as normal quality of life.[22] However, patients continued to report more severe fatigue and menopausal symptoms than controls, so any adaptation to these symptoms was incomplete. An ongoing association between fatigue, menopausal symptoms, and overall quality of life was documented throughout the study period. The proportion of patients in whom moderate-severe cognitive dysfunction was observed at the initial assessment improved subsequently, although the patients still had somewhat poorer overall cognitive performance than controls during follow-up. Overall, the results show a reassuring long-term trend for patients undergoing adjuvant chemotherapy for breast cancer, although fatigue and symptoms related to menopause improve slowly.

Table 10. Quality of Life in Patients and Controls

	Patients, FACT-G		Controls, FACT-G		
	No.	Median	No.	Median	*P**
Initial	104	77	102	94	< .0001
1 year	91	89	83	91	.53
2 years	81	91	81	91	.87

NOTE. Median FACT-G scores (range, 0 to 104) are indicated. Higher scores represent better quality of life. In the mixed model, the interaction between time and group and the trend for change in FACT-G with time are highly significant ($P < .0001$ for both), consistent with improvement in patients but not in controls. As indicated, the major improvement in quality of life was gained during the first year.

Abbreviation: FACT-G, Functional Assessment of Cancer Therapy, quality-of-life subscale.

**P* values are derived from the unpaired Wilcoxon test.

Of the three symptom complexes assessed in this study, the most controversial remains cognitive dysfunction. Several cross-sectional studies have investigated cognitive dysfunction in women undergoing adjuvant chemotherapy for breast cancer.[2,3,5,6] Criticisms of these studies have included small sample size, lack of baseline assessment, lack of longitudinal design, and failure to control for confounding variables such as hormonal factors.[23] Despite these limitations, the results have been consistent in demonstrating cognitive dysfunction in a substantial minority of patients. A recently published meta-analysis of 30 studies investigating the neuropsychological effects of systemic (chemotherapy or biologic) therapies in patients with a variety of malignancies found consistent adverse effects on executive function, verbal memory, and motor function.[24] However, limitations of the data precluded definitive conclusions about causality, clinical significance, or duration of the problem. To date, only one other prospectively designed longitudinal study of cognitive dysfunction in women undergoing adjuvant chemotherapy for breast cancer has been published.[25] In this small study, 18 patients underwent a battery of neuropsychological tests before commencing chemotherapy and at short-term ($\geq$ 3 weeks) and long-term (1 year) intervals postchemotherapy. Approximately one third of patients were reported to have cognitive impairment at baseline and two thirds at the conclusion of chemotherapy; approximately half of these patients demonstrated improvement at the final follow-up, and half remained stable. However, these are probably overestimates of cognitive deficits, because multiple tests of cognitive function were used without correction for multiplicity.

Our study makes an important additional contribution to the literature by supplying data from a large cohort of patients over a 2-year period. The rationale to use a control group of healthy women rather than baseline assessment has been discussed previously.[11] Recruitment and assessment of patients in the traumatic period between surgery and chemotherapy is difficult. Several factors may contribute to abnormal prechemotherapy assessments such as recent general anesthetic and the shock of diagnosis; these may be reversible over the time frame of chemotherapy in the absence of additional insults. In addition, the adverse effect of chemotherapy might be masked by unrecognized practice effect. Although including a control group of patients with breast cancer who do not receive systemic therapy would assist in resolving these issues, current practice now precludes this. The peer-nominated control procedure used in the current study was selected as the best available method of choosing controls well matched to patients for socioeconomic status, education, and cultural background as well as age and baseline pretreatment menopausal status. However, there are also potential biases inherent in allowing patients to choose their own controls. For example, they

may select those friends or relatives who are more academically inclined and therefore more likely to be comfortable with undergoing neurocognitive testing. Baseline analysis suggests that the peer-nominated procedure was successful in achieving a well-matched group of healthy controls.[11] This feature of the study design, plus the use of a relatively brief instrument for assessment, has facilitated recruitment and a high compliance with follow-up of a large cohort of patients.

Limitations of our follow-up assessments of cognitive function include the relatively low power to direct differences between the groups (especially with the lower-than-expected incidence of moderate-severe cognitive dysfunction at baseline) and the presence of practice effect such that the HSCS may be underestimating the level of cognitive dysfunction in patients, as compared to the initial evaluation. We sought to keep practice effect to a minimum by restricting reevaluation to yearly intervals. Practice effect will apply to both patients and controls, and the change in distribution of cognitive classification for control subjects listed in Table 8 provides evidence of practice effect. Despite practice effect, the patients still performed slightly worse than controls, but this difference was not significantly significant by year 2. The Trails A and B tests were included to complement the HSCS, and patients seemed to perform significantly more poorly than controls on the Trails B test at year 1 (Table 9); however, because these tests were not primary end points of our study, the data should be regarded as exploratory. There is also a smaller trend for practice effect from the data for the Trails A and B tests (Table 9).

Mechanisms that lead to cognitive dysfunction in some patients during chemotherapy remain unclear. Several factors might contribute, including the chemotherapy drugs themselves, concomitantly prescribed medications such as antiemetics, and hormonal changes caused by chemotherapy-induced menopause and adjuvant hormonal therapy. The observation that cognitive impairment improved despite the majority of patients becoming menopausal after chemotherapy suggests that this is not a major causative factor. Likewise, the majority of patients who commenced adjuvant hormonal therapy did so after their baseline assessment, the time point at which maximal cognitive impairment was observed. Although this finding is reassuring for patients receiving adjuvant tamoxifen, practice effect might have masked a small effect of tamoxifen on cognitive function, because subtle adverse effects of tamoxifen on cognitive ability were reported in a small study by Castellon et al.[26] In our study, only a small number of patients received an aromatase inhibitor. It is possible that this class of drugs, which lacks any proestrogen effect and causes profound lowering of serum estradiol levels, may have a significant impact on cognitive function. Cognitive data generated from the Arimidex, Tamoxifen, Alone or in Combination study will provide insight into this potential toxicity.

Patients have substantial menopausal symptoms after chemotherapy for breast cancer. Most patients were postmenopausal at 2 years of follow-up, as could be predicted from their median age at the time of chemotherapy.[27] Symptoms in controls remained stable, whereas patients showed a trend toward improvement in menopausal symptoms over the 2-year period after chemotherapy. This occurred despite the initiation of adjuvant hormonal therapy in approximately 60% of patients and an increase in the proportion of postmenopausal subjects in both populations. Although this is reassuring for patients, the severity of menopausal symptoms remained substantially worse for patients compared with controls for the duration of the study. The minority of patients who received medical therapy for hot flashes seemed to benefit from this intervention.[28] Because of the use of an age-matched control population in this study, it fails to answer the question of whether the menopausal symptoms experienced during chemotherapy-induced menopause are more frequent or severe than those experienced by women during a natural menopause. To address this question, an additional control group of older women going through natural menopause is being recruited. The results of this comparison will be reported separately.

The most striking finding from the baseline assessment of this study was the profound difference in the level of fatigue experienced by patients and controls. Previous studies have suggested that fatigue can remain a significant problem for several years postchemotherapy.[4,7] The improvement observed in patients over the 2 years of follow-up supports the findings of others[10] and is reassuring, although patients remained more fatigued than controls 2 years after chemotherapy. The interaction between fatigue and menopausal symptoms raises the possibility that nocturnal vasomotor symptoms interfere with the quality or duration of sleep. Although this inference is not conclusive, it supports the aggressive management of hot flashes in breast cancer survivors.

Cognitive dysfunction, menopausal symptoms, and fatigue are important adverse effects of chemotherapy that improve slowly over the following 2 years in most patients.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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