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COGNITIVE IMPAIRMENT ASSOCIATED WITH ADJUVANT THERAPY IN BREAST CANCER

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SUMMARY

The purpose of this study was to determine whether cognitive function changes over time in women with breast cancer who received adjuvant therapy as compared to women with breast cancer who received no adjuvant therapy. Three groups of women ($n = 46$) were studied; groups 1 and 2 consisted of women with stage I or II breast cancer. Group 1 received chemotherapy and group 2 received chemotherapy plus tamoxifen. Group 3 consisted of women with ductal carcinoma *in situ* who received no chemotherapy or tamoxifen. Cognitive function was evaluated at three timepoints. Time 1 occurred after surgery and before chemotherapy initiation in groups 1 and 2. Time 1 for group 3 occurred post-surgery. Time 2 occurred within 1 week after the conclusion of chemotherapy for groups 1 and 2 and at a comparable time for group 3. Time 3 occurred 1 year after Time 2. Women who received chemotherapy plus tamoxifen exhibited deterioration on measures of visual memory and verbal working memory and reported more memory complaints. Women who received chemotherapy alone also exhibited deteriorations in verbal working memory. Conversely, cognitive function scores improved in women who received no therapy, indicating practice effects. In conclusion, adjuvant chemotherapy in women with breast cancer can be associated with deteriorations in memory and this may persist over time. The addition of tamoxifen may lead to more widespread memory deficits. Copyright © 2005 John Wiley & Sons, Ltd.

KEY WORDS: cognitive changes after adjuvant therapy; cancer; cognitive function; breast cancer; adjuvant therapy; oncology

INTRODUCTION

A growing body of literature suggests that adjuvant therapy for breast cancer may be associated with cognitive impairments (Olin, 2001; Ahles *et al*., 2002) which may persist for years and can impair decision-making abilities and disrupt the ability of women to fulfill family, career, and community responsibilities. Cognitive impairments ranging from deficits in attention and concentration (Cimprich, 1992) to deficits in nearly all cognitive domains have been reported (Wieneke and Dienst, 1995; van Dam *et al*., 1998; Schagen *et al*., 1999). The magnitude of these deficits may be moderated by depression, anxiety, fatigue and concomitant medications (Oxman *et al*., 1986; Bender, 1994).

Results from virtually all of these studies need to be interpreted cautiously, however because of a variety of inherent methodological problems, the most serious of which includes the use of cross-sectional instead of longitudinal designs and the lack of pre-treatment evaluations of cognitive function. This latter issue is especially problematic because it makes it impossible to determine whether deficits were present before treatment or to detect changes from baseline (Olin, 2001;

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Ahles *et al*., 2002; Wefel *et al*., 2004). Many studies either compared scores on cognitive function measures with normative scores (Wieneke and Dienst, 1995) or compared scores of women with breast cancer who did and did not receive adjuvant therapy (Schagen *et al*., 1999; Paganini-Hill and Clark, 2000). The timing of cognitive function assessment after the completion of therapy was also not uniform (Berglund *et al*., 1991; Wieneke and Dienst, 1995; Schagen *et al*., 1999; Paganini-Hill and Clark, 2000; Phillips and Bernhard, 2003). Most studies lacked non-treated comparison groups (Berglund *et al*., 1991; Wieneke and Dienst, 1995) and failed to measure potential moderators of cognitive function.

Several studies failed to include a comprehensive assessment of the multiple domains of cognitive function (Berglund *et al*., 1991; Brezden *et al*., 2000; Paganini-Hill and Clark, 2000) and occasionally relied on the use of a screening measure (Brezden *et al*., 2000) or self-report questionnaire (Berglund *et al*., 1991; Nystedt *et al*., 2003).

We conducted a prospective, three-group comparative study to determine whether there were differences, over time, in cognitive function in pre- and peri-menopausal women with breast cancer who received two different types of adjuvant therapy as compared to pre- and peri-menopausal women with breast cancer who received no adjuvant therapy.

We hypothesized that after controlling for pre-chemotherapy levels of cognitive function and as well for concurrent levels of depression, anxiety, and fatigue, pre- or peri-menopausal women with breast cancer who receive chemotherapy (alone or plus tamoxifen) will have poorer cognitive function, immediately and long term (1 year) following chemotherapy, as compared to pre- or peri-menopausal women with breast cancer who receive no adjuvant therapy. We also predict that women receiving chemotherapy plus tamoxifen will have poorer cognitive function, immediately and long term following chemotherapy, than pre- or peri-menopausal women with breast cancer receiving chemotherapy alone.

PATIENTS AND METHODS

Three groups of pre- and peri-menopausal women (menstruating) comprised the study subjects. Groups 1 and 2 consisted of women with stage I or II breast cancer. Women in group 1 had hormone receptor negative breast cancer and received chemotherapy alone. Women in group 2 had hormone receptor positive breast cancer and received chemotherapy plus tamoxifen. Women in group 3 (control) had ductal carcinoma *in situ* (DCIS) and received no chemotherapy or tamoxifen.

Eligible women had a minimum 8 years of education, were at least 21 years of age and able to speak and read English. Women who had clinical evidence of distant metastasis or a prior cancer diagnosis were deemed ineligible.

Measurement of cognitive function occurred at three timepoints. The first assessment, Time 1 (T_1) occurred after surgery and prior to the initiation of adjuvant therapy in groups 1 and 2 and post-surgery for group 3. Time 2 (T_2) occurred within 1 week after the conclusion of chemotherapy for groups 1 and 2 and at a comparable time for group 3. Time 3 (T_3) occurred 1 year after T_2.

The study was approved by the University of Pittsburgh Institutional Review Board. Written informed consent was obtained from every subject.

Instruments

Cognitive function was measured with a battery of neuropsychological tests administered to assess attention, learning and memory, psychomotor speed, mental flexibility, visuoconstructional ability, executive function and general intelligence. A table summarizing these measures appears elsewhere (Paraska and Bender, 2003). The measures were selected based on their psychometric properties, their sensitivity to change in domains of cognitive function with cancer treatment and the availability of alternate, equivalent versions in order to minimize practice effects at follow-up testing. Measures for which alternate, equivalent forms were available included the Digit Vigilance Test (Lafayette Clinical Instrument Company, 1989), Trail Making test-B (Reitan, 1985), Rey Auditory Verbal Learning Test and Rey Complex Figure Test (RCF) (Osterrieth, 1944). Inclusion of the control group permitted us to examine the degree of practice effects present in a comparable group not receiving treatment. Subjects' perceived cognitive function was assessed with the Patient's Assessment of Own Functioning (Chelune *et al*., 1986), a self-report measure on which higher scores indicate perceived poorer cognitive function.

Potential moderators of cognitive function including depression, anxiety, fatigue and concomitant medications were also assessed (Paraska and Bender, 2003). Average battery administration time was 90 min. A nurse trained by a neuropsychologist administered the battery and results were interpreted by a doctorally prepared nurse and neuropsychologist.

Statistical analysis

A detailed descriptive analysis of all data was performed. The distributions of important baseline sample characteristics were compared among the groups to identify imbalances to check for possible confounding. The level of significance was established at 0.05 (two-tailed).

Mixed effects modeling was used to evaluate the effects of adjuvant therapy on cognitive function over time. Depression scores based on the Beck Depression Inventory-II (BDI-II) were controlled as time-dependent covariates across all cognitive function measures (Beck *et al.*, 1996). Anxiety and fatigue as measured by the Profile of Mood States (POMS) were also considered as potential time-dependent covariates (McNair *et al.*, 1992). Planned comparisons based on the hypothesized differences in cognitive function were investigated, after testing for overall effects.

RESULTS

Fifty women were approached for participation in this study. Of these, four (8%) declined to participate because they lacked the time to commit to the assessments. Forty-six women consented to participate: 19 (41.3%) received chemotherapy alone, 15 (32.6%) received chemotherapy plus tamoxifen and 12 (26.1%) received no chemotherapy or tamoxifen. Ten women (22%) who enrolled in the study dropped out at T_2; four in group 1, three in group 2 and three in group 3. An additional 14 (30%) dropped out at T_3; six in group 1, four in group 2 and four in group 3. Of the women who dropped out, most (80%) withdrew because they were 'too busy'. The remaining 20% were no longer eligible due to the advent of disease progression. The attrition rate was not different across the groups and there were no significant differences between women who dropped out and women who remained in the study on any study variables.

Table 1 displays the sample characteristics. Age is the only characteristic that is significantly different between groups with subjects in group 1 being younger than subjects in the other groups but it is doubtful that this age difference is clinically meaningful. The groups are also significantly different on the characteristics that defined the groups (stage, tumor type and type of surgery).

Nearly all women in groups 1 and 2 received a cyclophosphamide-containing chemotherapy regimen. Twenty percent in group 1 received cyclophosphamide, methotrexate and 5-fluorouracil (CMF) and 80% received cyclophosphamide and doxorubicin (CA). Of the women in group 1 who received CA, 50% also received a taxane. Seventy-five percent in group 2 received CA with (56%) or without (44%) a taxane. Three women in group 2 (25%) received adriamycin plus docetaxel.

Cognitive function measures

Table 2 presents the results for the time 1–time 3 objective and subjective measures and normative values for each measure. With the exception of performances on specific objective memory measures, there were no significant group by time interactions on measures of any other cognitive domains. There are no significant differences between groups on any memory measure at baseline. With the exception of scores on the Four Word Short Term Memory Test (4WSTM), subjects' scores are better than normative values. However, as described below, the performance of subjects in groups 1 and 2 on memory measures deteriorates over time.

There was a significant group by time interaction on the 4WSTM Test 30-s trial, a measure of verbal working memory and marginally significant group by time interactions on the 4WSTM 5- and 15-s trials. There were no significant changes in performance on the 4WSTM 5-s trial by women who received chemotherapy alone or women who received chemotherapy plus tamoxifen. However, the performance of women who received no therapy significantly improved from T_2 to T_3 ($p = 0.008$), presumably due to practice effects. When comparing groups at individual timepoints, there were no significant differences between scores at T_2. However, at T_3 the performance of women who received chemotherapy plus tamoxifen was

Table 1. Sample characteristics

Characteristic	Overall	Chemotherapy	Chemotherapy plus tamoxifen	No chemotherapy		
	M (SE)	M (SE)	M (SE)	M (SE)	F	df$p$
Age	42.57 (5.43)	40.11 (6.52)	44.13 (3.50)	44.50 (4.17)	3.75	2 0.03
Years of education	14.33 (2.71)	14.11 (2.28)	14.67 (3.56)	14.25 (2.26)	0.18	2 0.06
Characteristic	N (%)	n (%)	n (%)	n (%)	χ^2	df$p$
Marital status	46 (100)	19 (100)	15 (100)	12 (100)	0.372	0.86
Married	29 (63.0)	11 (58)	10 (67)	8 (67)		
Not married	17 (37.0)	8 (42)	5 (33)	4 (33)		
Number of children	46 (100)	19 (100)	15 (100)	12 (100)	3.384	0.53
None	9 (20)	3 (16)	2 (13)	5 (42)		
1–2	29 (63)	13 (68)	9 (60)	6 (50)		
$\geqslant 3$	8 (17)	3 (16)	4 (27)	1 (8)		
Cancer stage	46 (100)	19 (100)	15 (100)	12 (100)	32.304	0.00
DCIS	12 (26)	0	0	12 (100)		
Stage I	12 (26)	6 (32)	6 (40)	0		
Stage IIA or IIB	22 (48)	13 (68)	9 (60)	0		
Type of surgery	46 (100)	19 (100)	15 (100)	12 (100)	28.556	0.00
Radical mastectomy	3 (6)	2 (11)	1 (7)	0		
Modified mastectomy	7 (15)	2 (11)	3 (20)	2 (17)		
Lumpectomy	15 (33)	4 (21)	2 (13)	9 (75)		
Lumpectomy and node dissection	21 (46)	11 (58)	9 (60)	1 (8)		

marginally significantly poorer than that of women who received no therapy ($p = 0.050$) and the performance of women who received chemotherapy alone was marginally significantly poorer than that of women who received no therapy ($p = 0.062$). When the T_3 scores of women who received therapy (alone or with tamoxifen) were combined, they were also marginally significantly poorer than those of women who received no theraphy ($p = 0.050$).

Performance on the 4WSTM 15-s trial marginally significant declined from T_2 to T_3 in women who received chemotheraphy alone. No significant differences were found between groups at T_2, but at T_3, the performance of women who received chemotheraphy plus tamoxifen was significantly poorer than that of women who received no therapy ($p = 0.009$). In general, women who received chemotherapy, alone or with tamoxifen, had marginally significant worse performances when compared to women who received no therapy at T_3 ($p = 0.026$).

For the 4WSTM 30-s trial there was a marginally significant deterioration in performance from T_2 to T_3 in women who received chemotherapy alone ($p = 0.072$). The performance of women who received no therapy significantly improved from T_2 to T_3 ($p = 0.007$). At T_2, the performance of women who received chemotherapy plus tamoxifen was marginally significantly worse than that of women who received chemotherapy alone ($p = 0.19$) and of women who received no therapy ($p = 0.047$). Similarly, at T_3, the performance of women who received no therapy was significantly better than the performance of women who received chemotherapy plus tamoxifen ($p = 0.007$) and the performance of women who received chemotherapy alone ($p = 0.004$). The performance of women who received chemotherapy (alone or with tamoxifen) was significantly poorer than that of women who received no therapy at T_3 ($p = 0.004$).

There was marginally significant group by time interaction on the immediate recall RCF test trial, a measure of visual memory, and a significant group by time interaction on the delayed RCF recall trial 6. There was a marginally significant decline from T_2 to T_3 in performance on the

Table 2. Least squares means (M) and standard errors (SE) for objective and subjective cognitive function measures at baseline, 6 months (Time 2; T_2) and 18 months (Time 3; T_3) with normative values (objective measures) and mean values in 105 healthy controls (subjective measure)

		Chemotherapy only			Chemotherapy + tamoxifen			No chemotherapy		
		T_1 ($n = 19$) M (SE)	T_2 ($n = 15$) M (SE)	T_3 ($n = 9$) M (SE)	T_1 ($n = 19$) M (SE)	T_2 ($n = 12$) M (SE)	T_3 ($n = 8$) M (SE)	T_1 ($n = 19$) M (SE)	T_2 ($n = 9$) M (SE)	T_3 ($n = 5$) M (SE)
Learning and memory measure	Normative values M (SE)									
RAVL (total score)	50.60 (7.1)	56.47 (2.14)	56.89 (1.75)	58.63 (2.56)	51.00 (2.45)	54.90 (5.06)	62.99 (1.60)	53.17 (2.79)	55.84 (2.32)	53.64 (3.77)
RAVL (trial 6)	10.40 (2.7)	11.42 (0.44)	11.85 (0.52)	11.41 (0.67)	10.47 (0.81)	11.96 (0.42)	13.77 (0.43)	9.42 (0.53)	13.14 (0.79)	11.99 (1.08)
RAVL (delayed recall)	10.60 (2.5)	10.79 (0.59)	11.96 (0.46)	12.26 (0.56)	10.00 (0.77)	12.38 (0.53)	12.98 (0.65)	10.50 (0.71)	12.28 (0.60)	11.29 (0.75)
4WSTM (5 s)	14.60 (3.3)	6.38 (1.12)	7.34 (1.00)	6.60 (0.57)	5.42 (0.40)	7.51 (1.00)	6.82 (0.50)	4.86 (0.83)	5.04 (1.35)	10.38 (1.32)
4WSTM (15 s)	11.00 (3.5)	6.15 (1.24)	6.40 (1.33)	2.92 (0.73)	5.58 (0.63)	4.75 (1.35)	5.64 (0.67)	3.57 (0.65)	5.38 (1.87)	8.64 (1.48)
4WSTM (30 s)[a]	9.20 (4.2)	3.38 (1.06)	4.41 (0.63)	1.89 (1.06)	3.17 (0.57)	2.11 (0.65)	0.86 (1.01)	1.57 (0.30)	2.10 (0.94)	9.14 (2.23)
RCF (immed. recall)	21.00 (7.8)	22.84 (1.62)	27.45 (1.13)	28.21 (1.36)	25.18 (1.74)	27.41 (1.35)	23.79 (1.59)	23.67 (2.11)	24.48 (1.46)	27.14 (1.81)
RCF (delayed recall)[a]	20.80 (8.0)	23.58 (1.45)	25.52 (1.34)	27.43 (1.59)	24.00 (2.22)	28.08 (1.91)	22.44 (2.74)	21.71 (2.13)	25.29 (1.67)	28.30 (0.94)
Perceived cognitive domains	Healthy control values (M)									
Memory	12.95	7.79 (1.32)	0.83 (0.12)	0.81 (0.14)	6.64 (1.18)	0.93 (0.14)	1.19 (0.16)	11.36 (1.57)	1.01 (0.18)	0.65 (0.20)
Language and Communication	11.64	5.49 (1.43)	0.72 (0.14)	0.75 (0.17)	5.31 (1.02)	0.67 (0.17)	0.78 (0.20)	10.45 (1.98)	0.90 (0.21)	0.80 (0.25)
Use of Hands	1.62	1.41 (0.23)	0.22 (0.06)	0.19 (0.05)	1.86 (0.49)	0.18 (0.08)	0.24 (0.05)	0.64 (0.43)	0.23 (0.09)	0.08 (0.06)
Sensory/Perceptual	1.12	0.68 (0.20)	0.49 (0.20)	0.40 (0.28)	0.43 (0.20)	0.88 (0.24)	0.45 (0.31)	1.00 (0.66)	0.80 (0.28)	0.63 (0.37)
Cognitive/Intellectual	6.59	3.00 (1.02)	0.57 (0.14)	0.57 (0.12)	5.00 (1.03)	0.48 (0.16)	0.69 (0.13)	6.21 (1.82)	0.70 (0.19)	0.39 (0.15)
Total score	35.33	18.49 (3.71)	0.70 (0.11)	0.71 (0.13)	19.24 (2.43)	0.73 (0.13)	0.93 (0.15)	29.67 (5.71)	0.86 (0.16)	0.57 (0.18)

RAVL = Rey Auditory Verbal Learning Test; 4WSTM = Four Word Short Memory Test; RCF = Rey Complex Figure Test.
[a] Significant group by time interaction.

immediate RCF recall in women who received chemotherapy plus tamoxifen ($p = 0.018$). There were no significant changes from T_2 to T_3 in the performance of women in the other two groups. The scores of women who received chemotherapy plus tamoxifen were marginally significantly lower at T_3 than those of women who received chemotherapy alone ($p = 0.043$). At T_2, the performance of women who received chemotherapy alone or with tamoxifen was marginally significantly worse than that of women who received no therapy ($p = 0.090$).

On the delayed RCF recall, the scores of women who received chemotherapy plus tamoxifen marginally significantly declined from T_2 to T_3 ($p = 0.017$), while the scores of women who received no therapy marginally significant improved ($p = 0.104$). There was no change from T_2 to T_3 in women who received chemotherapy alone and there were no significant differences among the groups at T_2. There were marginally significant differences at T_3 between women who received chemotherapy alone and women who received no therapy ($p = 0.058$) and between women who received chemotherapy (alone and plus tamoxifen) and women who received no therapy ($p = 0.089$). There were no significant group by time interactions on the remaining learning and memory measures.

There are no significant differences between groups on the total PAOF or PAOF subscale scores at baseline. There was a marginally significant group by time interaction in total PAOF scores. There were no significant changes in total scores from T_2 to T_3 in women who received chemotherapy alone or chemotherapy plus tamoxifen. However, there was a marginally significant improvement in total scores in women who received no therapy ($p = 0.084$). No significant differences between groups were found T_2 or T_3.

Examination of PAOF subscales revealed a marginally significant group by time interaction on only the memory subscale. There was a marginally significant deterioration in the perceptions of memory from T_2 to T_3 in women who received chemotherapy plus tamoxifen ($p = 0.044$) and marginally significant improvements in perceptions of memory in women who received no therapy ($p = 0.024$). There were no changes in the perceptions of memory in women who received chemotherapy only. Women who received chemotherapy plus tamoxifen perceived that their memory was marginally significantly poorer than women who received chemotherapy alone at T_3 ($p = 0.082$). Interestingly, women who received chemotherapy alone perceived that their memory was marginally significantly better than women who received no therapy at T_3 ($p = 0.052$).

Potential covariates

Most women in each group were not depressed. The average scores on the BDI-II (Beck *et al.*, 1996) were 10.0 at T_1, 8.2 at T_2 and 7.5 at T_3 each indicating minimal depression. There were no significant differences in baseline BDI-II scores between groups. The scores on only one objective cognitive measure was related to BDI-II scores; the 4WSTM (15-s trial) ($p = 0.008$). Conversely, nearly all PAOF subscale scores were significantly related to BDI-II scores ($p = 0.001$–0.0001). Thus, women scoring higher on the BDI-II, indicating greater depressive symptomatology, perceived more cognitive problems.

We found no interaction between anxiety as measured by the POMS Tension–Anxiety subscale and any of the cognitive function measures at any timepoint. We also found no interaction between fatigue, as measured by the POMS Fatigue–Inertia subscale and any of the objective cognitive measures at any timepoint. However, Fatigue–Inertia scores were marginally related to the PAOF Memory ($p = 0.02$) and Use of Hands ($p = 0.02$) subscales.

Most women were not taking any concomitant medications during this study. Vitamins were the most frequently reported concomitant agent taken. Other agents included antihypertensives ($n = 5$), antibiotics ($n = 4$) and antidepressants, herbal agents, and skeletal muscle relaxors, each taken by three women. Use of each concomitant medication was distributed similarly across study groups.

DISCUSSION

The results of this exploratory study suggest that women with breast cancer who receive chemotherapy have deteriorations on measures of memory. There was evidence of memory impairment in both groups of women who received adjuvant therapy. Women who received chemotherapy plus tamoxifen exhibited the broadest deteriorations in memory with declines in visual memory and verbal

working memory. Most of these deteriorations were detected at T_3, 1 year following the conclusion of chemotherapy, when women in this group were still receiving tamoxifen, while women in the chemotherapy alone group had not received any therapy for 1 year. These results are different from those of Paganini-Hill and Clark (2000) who found no significant differences between tamoxifen users and non-users in their study. That study was limited by a lack of a pre-treatment cognitive function evaluation, inconsistent assessment timepoints and use of a limited set of cognitive measures that were mailed to subjects precluding assurance that the measures were completed without assistance.

Women who received chemotherapy alone exhibited declines in verbal working memory but these impairments did not extend to visual memory. The performance of women who received no therapy improved on the measures of verbal working memory and visual memory on which there was significant deterioration in the two treatment groups, presumably due to practice effects. These findings suggest that future studies should incorporate a control group of women who receive no therapy to further examine the degree of practice effects present in this group. We assume that practice effects are also present in the performance of the treatment groups. However, treatment-related deteriorations in performance outweighed the practice effects.

Our results suggest that deteriorations in cognitive function with adjuvant therapy in women with breast cancer are domain specific. These findings are different from those of previous studies in which impairment in most cognitive domains was found (Wieneke and Dienst, 1995; Schagen *et al.*, 1999). A primary reason for these differences may be that our study is one of the only studies to include a pre-treatment cognitive function evaluation. Thus, we were able to statistically control for baseline cognitive function levels in all study groups and detect changes over time. We also evaluated cognitive function at uniform times after chemotherapy. Whereas, the timing of cognitive function assessment in previous, cross-sectional studies ranged from one-half to 10 years post-chemotherapy (Cimprich, 1992; Wieneke and Dienst, 1995; van Dam *et al.*, 1998; Schagen *et al.*, 1999; Brezden *et al.*, 2000; Phillips and Bernhard, 2003).

The results of our objective and subjective cognitive function measures were not correlated. This is a common finding that calls into question the ecological validity of some objective cognitive function measures (Schagen *et al.*, 1999) and reinforces the possibility that one's perceived cognitive function is affected by numerous factors such as depression. The significant relationship between BDI-II scores and PAOF scores supports this possibility.

Perceptions of cognitive impairments were evident immediately following the conclusion of chemotherapy. Few objectively measured cognitive impairments were observed at T_2. Thus, the subjective reports of cognitive impairment preceded declines detected by the objective measures. This finding has been reported in previous studies of cognitive function in breast cancer patients. (Wieneke and Dienst, 1995) Because 6 months elapsed between T_1 and T_2 and 1 year elapsed between T_2 and T_3, it is not clear when cognitive declines emerged. Future studies should include assessments at shorter intervals in order to more precisely define the pattern of cognitive decline.

Several limitations of this study should be noted. We did not randomly assign patients to groups because the treatments used are considered standard therapy for breast cancer. However, we did include a control group of women with DCIS who received no therapy. These women have less disease than those in the treatment groups. However, the number of women with early stage breast cancer who do not receive adjuvant therapy is limited to those who refuse therapy or are not eligible due to comorbidity. Women who refuse therapy may possess characteristics that make them different from those who accept therapy and the comorbidities may confound the results.

Another limitation is that women in the treatment groups received different types of chemotherapy. While most women received cyclophosphamide-containing regimen, the agent was combined with different drugs. The small sample precludes evaluation of the differential effects of these drugs on cognitive function. Future studies are needed to examine these differential effects.

The study sample is small and the attrition rate, particularly at T_3, is a limitation. Subject attrition is a common problem in longitudinal studies that can introduce attrition bias and affect the generalizability of results. It can be argued that subjects who decline follow-up measures differ from those who remain in the study on important characteristics. We were able to confirm that our attrition rate was not different across the groups and that

there were no significant differences between women who dropped out and women who remained in the study on any study variables.

It is not possible to compare the attrition rate in this study to that of other cognitive function studies in women with breast cancer because longitudinal studies have not been reported in this population. However, the attrition rate in longitudinal cognitive function studies in other samples ranges from 22 to 34% at the first follow-up assessment (Levin *et al*., 2000; Newman *et al*., 2001; Van Beijsterveldt *et al*., 2002). This is similar to the attrition rate at our first follow-up assessment.

We believe that the benefits of the longitudinal design, in terms of the information that is yielded with respect to treatment-related change in cognitive function, outweigh the problem of attrition. Future, larger studies will need to over-sample to balance the effects of attrition and ensure adequate power to detect changes in cognitive function (Levin *et al*., 2000).

Most women who receive chemotherapy for breast cancer do not exhibit profound cognitive impairments. Our results suggest that the problems they experience are subtle and that they may be limited to memory deficits. The cognitive impairments may be manifested when women try to recall recently learned information, particularly in situations when distractions occur. Deficits in these cognitive domains can make it difficult to work effectively in cognitively challenging situations. With the high cure rate for early-stage breast cancer, women are facing challenges associated with changes they experience following therapy. More studies are needed to comprehensively describe the cognitive impairments associated with adjuvant therapy for breast cancer, particularly long term following the conclusion of treatment.

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REFERENCES

Ahles TA, Saykin AJ, Furstenberg CT *et al*. 2002. Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. *J Clin Oncol* **20**(2): 485–493.

Beck AT, Steer RA, Brown GK *et al*. 1996. *Beck Depression Inventory-II*. The Psychological Corporation: San Antonio.

Bender CM. 1994. Cognitive dysfunction associated with biological response modifier therapy. *Oncol Nurs Forum* **21**(3): 515–523; quiz 524–525.

Berglund G, Bolund C, Fornander T *et al*. 1991. Late effects of adjuvant chemotherapy and postoperative radiotherapy on quality of life among breast cancer patients. *Eur J Cancer* **27**(9): 1075–1081.

Brezden CB, Phillips KA, Abdolell M *et al*. 2000. Cognitive function in breast cancer patients receiving adjuvant chemotherapy. *J Clin Oncol* **18**(14): 2695–2701.

Chelune GJ, Heaton RK, Lehman RAW *et al*. 1986. Neuropsychological and personality correlates of patients' complaints of disability. In *Advances in Clinical Neuropsychology*, vol. 3, Goldstein G, Tarter RE (eds). Plenum Press: New York; 95–126.

Cimprich B. 1992. Attentional fatigue following breast cancer surgery (comment). *Res Nurs Health* **15**(3): 199–207.

Lafayette Clinical Instrument Company. 1989. *Lafayette Clinical Repeatable Neuropsychological Test Battery*. Lafayette Clinical Instrument Company: Sagamore.

Levin BE, Katzen HL, Klein B, Llabre ML. 2000. Cognitive decline affects subject attrition in longitudinal research. *J Clin Exp Neuropsychol* **22**(5): 580–586.

McNair D, Lorr M, Droppleman LF. 1992. *EdITS Manual for the Profile of Mood States*. EdITS/Educational and Industrial Testing Service: San Diego.

Newman MF, Kirchner JL, Phillips-Bute B *et al*. 2001. Longtitudinal assessment of neurocognitive function after coronary-artery bypass surgery. *N Engl J Med* **344**(6): 395–402.

Nystedt M, Berglund G, Bolund C, Fornander T, Rutqvist LA. 2003. Side effects of adjuvant endocrine treatment in premenopausal breast cancer patients: A prospective randomized study. *J Clin Oncol* **21**(9): 1836–1844.

Olin JJ 2001. Cognitive function after systemic therapy for breast cancer. *Oncology* (*Huntington*) **15**(5): 613–618; discussion 618.

Osterrieth PA. 1944. Test of copying a complex figure; contribution to the study of perception and memory. *Arch Psychol* **30**: 206–356.

Oxman TE, Schnurr PP, Silberfarb PM *et al*. 1986. Assessment of cognitive function in cancer patients. *Hospice J* **2**(3): 99–128.

Paganini-Hill A, Clark LJ. 2000. Preliminary assessment of congnitive function in breast cancer patients treated with tamoxifen. *Breast Cancer Res Treatment* **64**(2): 165–176.

Paraska KK, Bender CM. 2003. Cognitive dysfunction following adjuvant chemotherapy for breast cancer: Two case studies. *Oncol Nurs Forum* **30**(3): 473–478.

Phillips K, Bernhard J. 2003. Adjuvant breast cancer treatment and cognitive function: Current knowledge and research directions. *J Natl Cancer Inst* **95**(3): 190–196.

Reitan RM. 1985. *The Halstead–Reitan Neuropsychological Test Battery*. Neuropsychology Press: Tuscon.

Schagen SB, van Dam FS, Muller MJ *et al*. 1999. Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. *Cancer* **85**(3): 640–650.

Van Beijsterveldt CEM, van Boxtel MPJ, Bosma H, Huox PJ, Buntinx F, Jolles J. 2002. Predictors of attrition in a longitudinal cognitive aging study: The Maastricht aging study (MAAS). *J Clin Epidemiol* **55**: 216–223.

van Dam FS, Schagen SB, Muller MJ *et al*. 1998. Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: High-dose versus standard-dose chemotherapy (comment). *J Natl Cancer Inst* **90**(3): 210–218.

Wefel JS, Lenzi R, Theriault R, Buzdar AU, Cruickshank S, Meyers M. 2004. 'Chemobrain' in breast carcinoma? *Cancer* **101**: 466–475.

Wieneke MH, Dienst ER. 1995. Neuropsychological assessment of cognitive functioning following chemotherapy for breast cancer. *Psycho-Oncology* **4**(2): 61–66.

