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Cognitive effects of chemotherapy in post-menopausal breast cancer patients 1 year after treatment

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Abstract

***Objective*: Studies in breast cancer patients indicate that chemotherapy may cause subtle cognitive disturbances in some women, but the course is unclear. The current study evaluated the cognitive effects of adjuvant chemotherapy in post-menopausal breast cancer patients 1 year following completion of treatment.**

***Patients and methods*: Breast cancer patients scheduled to receive adjuvant chemotherapy ($n = 53$) completed comprehensive neuropsychological testing before commencing chemotherapy (T1), 1 month after completing chemotherapy (T2), and again 1 year later (T3). A control group of women receiving adjuvant hormonal therapy ($n = 40$) was tested at comparable intervals. A standardized regression-based approach was used to identify cognitive decline, and incidence of decline was compared across treatment groups.**

***Results*: Whereas at T2, chemotherapy patients were more likely to show cognitive decline than hormonal patients, by T3, the frequency of reliable cognitive decline was the same in both groups (11 and 10%, respectively). However, those chemotherapy patients receiving hormonal therapy at T3 were inferior to the chemotherapy patients not receiving hormonal treatment on composite measures of processing speed and verbal memory.**

***Conclusion*: These data suggest that there is a subtle negative impact of chemotherapy on cognitive function in breast cancer patients shortly following completion of treatment, but that this resolves within 1 year. However, given that our control group comprises breast cancer patients receiving hormonal therapy, and indications that hormonal therapy may also adversely affect cognition, such conclusions must be considered tentative.**

Keywords: breast cancer; oncology; adjuvant chemotherapy; cognitive function; adjuvant hormonal therapy

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Introduction

Due to great advancements in the detection and treatment of breast cancer, there is a growing survivorship and an increasing emphasis on the long-term adverse effects of cancer treatments. Many breast cancer patients complain of poor concentration and memory, and muddled, inefficient, and effortful thought processes [1]—a condition known in patient circles as *chemo fog* or *chemo brain*. As cognition has indisputable and important implications for quality of life, there has been a burgeoning of research on this topic over the last several years.

The preponderance of studies investigating this phenomenon in the breast cancer population has found poorer neuropsychological performance in chemotherapy-treated patients than in control subjects [2–17]. However, most of these studies were retrospective in nature and many of them compared the chemotherapy-treated patients with healthy individuals without cancer. It is now well established that cancer patients are at increased risk for cognitive compromise, whether or not they have received chemotherapy [18–25]. Retrospective studies do not allow us to conclude that observed cognitive disturbances were not present prior to treatment. Moreover, reliance on a healthy control group does not control for a myriad of potentially confounding host- and disease-related factors that could account for incident cognitive decline in cancer patients.

These methodological shortcomings led to a call for studies that included pretreatment testing of cognition, as well as a disease-specific comparison group *not* receiving chemotherapy. The study that we report on here is one of only a handful of controlled prospective studies of cognitive function in breast cancer patients, and one of even fewer studies to include a treatment group with more

than 50 subjects [26]. In a previous publication reporting on results of testing conducted some 5–6 months after baseline (an average of 1 month following completion of chemotherapy in the chemotherapy group), we reported that the chemotherapy patients were significantly more likely than hormonal patients to show cognitive compromise (31 vs 12%), even after statistically controlling for age, education, intelligence, fatigue, psychological distress, and regression to the mean [27]. In keeping with findings from other recent neuropsychological and functional imaging studies [28–30], working memory seemed to be particularly vulnerable to chemotherapy effects in our sample, in so far as the only group mean comparison to reach significance involved a composite measure of change in working memory function. Like other prospective studies in early breast cancer patients [3,12,16,21], and in keeping with the results of meta-analyses [31–34], we found the effects of chemotherapy to be very subtle. No *mean* score, and very few *individual* scores, fell in the impaired range in either group, at either time point and, in some cases, mean scores in the chemotherapy group actually improved from T1 to T2. The adverse effect of chemotherapy was primarily evident as an attenuation of the expected practice effect on retest in the affected subgroup.

While the findings emerging from recent prospective studies generally confirm those of the earlier cross-sectional studies in indicating an association between chemotherapy exposure and cognitive disturbance (Jenkins *et al.* [35] being an important exception), the data are less consistent with regard to the course of these changes. Cross-sectional studies suggest that cognitive deficits may persist in some patients for many years following completion of treatment [2,5]. However, longitudinal and follow-up studies indicate that cognitive changes emerge during or shortly after chemotherapy, and tend to resolve over time [8,15,16,36]. Presumably, it is persistent adverse treatment effects that are of greatest concern to patients. The current study sought to further clarify this issue of chronicity by comparing cognitive function in chemotherapy-treated breast cancer patients with that of patients receiving adjuvant hormonal therapy without chemotherapy approximately 1 year following completion of chemotherapy. We expected that we might still find an elevated risk of cognitive compromise in our chemotherapy group at the 1-year follow-up, but that this would be less than that observed shortly following therapy.

Method

Study methods are described in detail in our previous paper [27]. The study was approved by the ethics board of The Ottawa Hospital and written informed consent was obtained from all participants.

Participants

The study included two groups of early stage breast cancer patients recruited from the Ottawa Hospital Regional Cancer Centre between February 2002 and March 2005. One group received standard dose adjuvant chemotherapy with or without hormonal treatment (chemotherapy group); the other received adjuvant hormonal therapy only (hormonal group). All subjects had at least eighth-grade education and were post-menopausal, between the ages of 50 and 65, and fluent in English. Exclusion criteria included a previous history of cancer or chemotherapy, advanced disease (metastasis beyond axillary lymph nodes), neo-adjuvant therapy, and unstable psychiatric, neurological, or substance use disorders that might affect cognition. Table 1 lists demographic and clinical characteristics of the groups. The two patient groups in these analyses did not differ from each other with respect to age, education, or IQ. The groups did differ in terms of disease stage: most of the patients in the chemotherapy group had stage II disease whereas most of the patients in the hormonal group had stage I disease ($\chi^2 = 32.3$, $p = 0.00$). This is unavoidable in a cohort study such as this one, as disease stage is a determinant of treatment.

Assessment

Assessment of cognition and mood was conducted at three time points. Patients in the chemotherapy group were assessed after recovery from surgery and prior to initiation of any chemotherapy (T1), an average of 1 month following completion of chemotherapy or 5–6 months following baseline assessment (T2), and approximately 1 year after the second assessment (T3). Hormonal patients were assessed at equivalent time points. We used a battery of 18 neuropsychological tests yielding 23 measures that tapped all major recognized domains of cognitive function (see Table 2). The Quick Test [48] was used to estimate premorbid intellectual function, and the Profile of Mood States (POMS) [49] to assess depression (Depression–Dejection subscale), fatigue (Fatigue–Inertia subscale), and anxiety (Tension–Anxiety subscale).

Data analysis

The Statistical Package for the Social Sciences (version 15.0) was used for all data analyses. Alpha was set at 0.05 (two-tailed). Only data from those subjects who completed all 3 assessments were analyzed ($n = 53$ in the chemotherapy group; $n = 40$ in the hormonal group). Thus, these

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Table 1. Demographic and clinical characteristics of chemotherapy and hormonal groups (means and standard deviations unless otherwise indicated)

	Chemotherapy ($n = 53$)		Hormonal ($n = 40$)	
Age (in years at baseline)	57.9 (3.7)		57.6 (4.0)	
Education[a] (in years at baseline)	14.6 (3.2)		14.6 (3.5)	
Quick Test[b] (at baseline)	44.4 (3.2)		44.1 (3.3)	
On depression meds (at baseline)	9.4% ($n = 5$)		17.5% ($n = 7$)	
T1–T2 interval (in days)	146.5 (35.4)		156.7 (28.3)	
T1–T3 interval* (in days)	537.9 (40.1)		556.1 (45.3)	
Interval between last chemotherapy cycle and T2 (in days)	29.6 (25.9)			
Interval between last chemotherapy cycle and T3 (in days)	421.9 (35.6)			
Stage of disease				
I	$n = 15$		$n = 35$	
II	$n = 36$		$n = 5$	
III	$n = 2$		$n = 0$	
Type of chemotherapy				
FEC × 6 cycles	$n = 26$			
CEF × 6 cycles	$n = 5$			
FAC × 6 cycles	$n = 3$			
AC × 4 cycles	$n = 13$			
AC × 4 cycles/Taxol (2–6 cycles)	$n = 3$			
EC × 4 cycles/Taxol (2–4 cycles)	$n = 2$			
Adriamycin & cisplatin × 4 cycles	$n = 1$			
No. of subjects receiving hormonal therapy prior to retesting (by type)	T2	T3	T2	T3
Tamoxifen	6 (11%)	18 (34%)	25 (63%)	24 (60%)
Arimidex	2 (4%)	14 (26%)	11 (27%)	11 (28%)
Letrozole	1 (2%)	2 (4%)	0	0
Switched (Tamoxifen to Arimidex primarily)	0	4 (8%)	4 (10%)	5 (12%)
None	44 (83%)	15 (28%)	0	0

*Significant at $p = 0.05$.
[a]Number of years in educational program leading to a diploma or degree.
[b]Quick Test raw score of 44 corresponds to IQ of 104.
FEC = 5-fluorouracil, epirubicin, cyclophosphamide
CEF = cyclophosphamide, epirubicin, 5-fluorouracil
FAC = 5-fluorouracil, adriamycin, cyclophosphamide
AC = adriamycin, cyclophosphamide
EC = epirubicin, cyclophosphamide

groups constitute subsets of those described in our previous paper.

A standardized regression-based (SRB) approach was used to assess cognitive change at the individual level [50,51], whereby the neuropsychological scores of the hormonal group were used to develop regression equations predicting retest scores from baseline scores. Age, education, IQ, and disease stage at baseline, as well as *change* on POMS depression, tension–anxiety, and fatigue scores were included as covariates in these analyses if they predicted change in the neuropsychological measure in a series of preliminary stepwise regression analyses. An SRB score was obtained for each subject, on each neuropsychological variable, by subtracting her actual retest score from the predicted retest score and dividing by the standard error of estimate of the prediction model in the hormonal group. The resultant SRB scores reflect the extent to which the observed change on each neuropsychological measure deviated from the change that would be expected on the basis of change in the control group (i.e. the change that occurs over the same interval in the absence of chemotherapy).

It is important to note that, even if an individual's raw score on a given test actually improved from T1 to T3, the SRB score would be negative if the retest score did not improve to the extent predicted. We considered an individual subject to have shown reliable overall cognitive decline if she had two or more SRB scores of −2.0 or less, and to have shown reliable cognitive improvement if she had two or more SRB scores of +2.0 or greater. These definitions of cognitive decline and improvement are admittedly somewhat arbitrary. However, the stringency of these criteria, while profoundly affecting the observed rate of decline *within* a given group [52], is not as critical when the rate of decline is being statistically compared with that in an appropriate control group. Chi-square was used to determine group differences in frequency of reliable cognitive decline and improvement.

Domain-specific cognitive summary scores were computed by adding the SRB scores for all

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Table 2. Test battery identified by cognitive domain

Tests (by cognitive domain)	Description	Variable(s) analyzed
Executive function		
Paced Auditory Serial Addition Task (PASAT) [37]	Subject is presented with a series of 61 single-digit numbers at a fixed pace on a tape recorder, and instructed to add each pair of consecutive numbers. Rate of presentation of the numbers increases over 4 consecutive trials. This is a very demanding task, especially for older adults, and many of our subjects discontinued their performance following the first trial. Therefore only trial 1 (2.4 s interval) scores were analyzed	Number correct on 2.4-s trial
Trail Making Test B (Trails B) [38]	A pencil-and-paper test of visuomotor tracking, requiring subjects to alternately connect, in sequence, numbers, and letters randomly distributed on a page	Completion time in seconds
Wisconsin Card Sorting Test (WCST) [39]	Requires the subject to sort cards in relation to four key cards, alternating sorting strategies deduced from examiner feedback. This test generates numerous scores. In an effort to keep our number of variables manageable, we opted to analyze the number of successful sorts divided by the number of trials, as this captures the most information in a single score	Number of sorts divided by number of trials
Language function		
Boston Naming Test [40]	Subject is required to name pictures of well-known objects. This test is known to be sensitive to anomia	Number correct with or without category cue
Controlled Oral Word Association Test (FAS) [41]	Scores on this test reflect the total number of words beginning with the letters F, A, and S generated orally in respective 1-min intervals	Total number correct for all letters
Motor		
Grooved Pegboard [42]	A test of manual speed and dexterity requiring the subject to insert 25 pegs into keyhole slots, using first the dominant, then the non-dominant, hand	Completion time in seconds, both hands
Processing speed		
Digit-Symbol Coding, WAIS-III [43]	A timed pencil-and-paper test that requires the subject to copy symbols to correspond with numbers, according to a key	Number correct in 120 s
Symbol Search, WAIS-III [43]	A timed test requiring the subject to scan a group of symbols in search of target symbols	Number correct in 120 s less errors
Trail Making Test A (Trails A) [38]	A pencil-and-paper test of visuomotor tracking, requiring subjects to connect, in sequence, numbers randomly distributed on a page	Completion time in seconds
Verbal learning and memory		
California Verbal Learning Test II (CVLT) [44]	Assesses ability to learn a list of 16 words over 5 trials, and to recall the list after a 20-min delay. Variables analyzed included recall of the list on trial 1 (CVLT Trial 1; a measure of short-term memory), free recall after delay (CVLT Delayed Recall; captures both learning and retention), and the score on a delayed multiple-choice test (CVLT Delayed Recognition; allows differentiation between retention and retrieval)	Trial 1 (number correct) Delayed recall (number correct) Delayed recognition (true positives+true negatives)
Logical Memory II, WMS-III [45]	Subjects try to recall 2 stories presented orally. Delayed recall was analyzed in order to capture both initial encoding and retention (immediate and delayed recall were highly correlated)	Delayed recall, total score
Visual learning and memory		
Rey Visual Learning Test (RVLT) [46]	A visual analogue of the CVLT that assesses an individual's ability to learn a series of 15 non-sense designs over 2 trials, and to recall the designs after a 20-min delay. Variables analyzed were chosen to correspond to those of the CVLT	Trial 1 (number correct) Delayed recall (number correct) Delayed recognition (true positives)

Table 2. (*Continued*)

Tests (by cognitive domain)	Description	Variable(s) analyzed
Family Pictures II, WMS-III [45]	A visual analogue of Logical Memory II where subjects try to recall 4 thematic pictures. Delayed recall was analyzed in order to capture both initial encoding and retention	Delayed recall, total score
Visuospatial function		
Block Design, WAIS-III [43]	Subjects attempt to reconstruct geometric designs using 3-dimensional blocks and are scored according to speed and accuracy	Total raw score
Working memory		
Arithmetic,WAIS-III [43]	Subjects are required to mentally solve a series of orally presented arithmetic problems	Total raw score
Consonant Trigrams (CCCs) [47]	Subjects attempt to retain orally presented letter trigrams for 0, 3, 9, or 18 s while simultaneously carrying out a serial subtraction task	Total letters correctly recalled for all intervals
Digit Span,WAIS-III [43]	Subjects recite strings of random digits of increasing length, first forward, then backward	Total raw score forward and backward
Letter-Number Sequencing,WAIS-III [43]	Subjects are required to re-order random alphanumeric sequences presented orally	Total raw score
Spatial Span,WMS-III [45]	Subjects are asked to tap out a spatial sequence illustrated by the examiner, first forward and then backward	Total raw score forward and backward

WAIS-III: Wechsler Adult Intelligence Scale-III.
WMS-III: Wechsler Memory Scale-III.

variables within a given cognitive domain (see Table 2 for tests and variables in each domain), and an overall summary score was obtained by adding SRB scores on *all* neuropsychological variables (in calculating the summary scores, missing data on individual neuropsychological measures were replaced by the group mean). These composite scores were compared for chemotherapy and hormonal groups using *t*-tests. *t*-Tests were also conducted to compare these summary scores in subgroups of chemotherapy subjects who did and did not receive additional hormonal treatment.

Results

Rate of attrition from T1 to T3 was 22% in the chemotherapy group and 31% in the hormonal group ($\chi^2 = 1.3$, $p = 0.25$). In the chemotherapy group, 3 subjects had disease progression, 10 could not be contacted or no longer wished to participate, and 2 discontinued due to unrelated health problems. In the hormonal group, 2 subjects had disease progression, 14 could not be contacted or no longer wished to participate, and 2 discontinued hormonal therapy during the course of the study. T1 scores on demographic, neuropsychological, and POMS variables for women who dropped out of the study were compared with those for participants who completed all three testing sessions. There were no baseline differences in age or in symptoms of anxiety, depression, or fatigue. However, those women who dropped out of the study were less educated and performed more poorly at baseline on several of the neuropsychological measures (see Table 3). There was a trend toward significance on the Quick Test, suggesting that the women who dropped out had lower verbal IQ than those who completed the study.

Scores on the neuropsychological measures and the POMS variables for the chemotherapy and hormonal groups at all 3 testing sessions are presented in Table 4. Chemotherapy and hormonal

Table 3. Means and standard deviations on baseline demographic and neuropsychological measures differentiating subjects completing all study phases (In) and subjects who dropped out (Out)

	In Mean (SD)	Out Mean (SD)	*p*
Education	14.7 (3.3)	12.8 (2.3)	0.00
Quick Test	44.2 (3.2)	42.8 (3.8)	0.05
WCST	0.06 (.03)	0.04 (.02)	0.01
Symbol Search	30.8 (5.7)	27.0 (5.0)	0.00
RVLT-Delayed Recognition	12.9 (1.3)	12.4 (1.2)	0.05
Block Design	36.6 (10.7)	29.0 (8.0)	0.00
Spatial Span	15.5 (2.5)	13.6 (2.6)	0.00

SD = Standard deviation.
WCST = Wisconsin Card Sorting Test
RVLT = Rey Visual Learning Test

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Table 4. Means and standard deviations for chemotherapy and hormonal groups on cognitive measures and POMS subscales

	Time 1				Time 2				Time 3			
	Chemo Mean (SD)	*n*	Hormonal Mean (SD)	*n*	Chemo Mean (SD)	*n*	Hormonal Mean (SD)	*n*	Chemo Mean (SD)	*n*	Hormonal Mean (SD)	*n*
Executive function												
PASAT	41.1 (9.2)	45	38.9 (10.1)	34	44.8 (10.3)	40	41.2 (9.6)	34	44.1 (10.7)	40	43.5 (9.3)	33
Trails B	70.8 (22.7)	53	68.3 (23.4)	40	65.8 (23.0)	53	68.4 (22.2)	40	62.5 (23.0)	53	67.9 (23.2)	40
WCST	0.058 (0.023)	51	0.051 (0.028)	39	0.060 (0.025)	51	0.052 (0.030)	40	0.062 (0.027)	50	0.049 (0.028)	39
Language												
Boston Naming Test	55.4 (4.2)	50	54.2 (5.7)	40	56.2 (3.9)	50	55.2 (5.2)	40	56.1 (4.6)	50	55.3 (6.2)	40
FAS	41.8 (13.0)	52	37.8 (10.8)	40	40.2 (12.9)	52	38.7 (11.1)	40	43.3 (14.0)	52	40.9 (10.5)	40
Motor												
Grooved Pegboard	154.0 (40.8)	52	154.2 (25.4)	38	152.8 (33.9)	52	151.7 (26.0)	39	153.9 (25.1)	51	155.4 (25.5)	39
Processing speed												
Digit-Symbol Coding	67.5 (12.3)	53	69.4 (12.5)	40	67.9 (13.0)	53	68.9 (13.2)	40	68.3 (12.7)	53	70.5 (14.7)	39
Symbol Search	30.6 (6.3)	53	31.1 (4.9)	40	31.1 (6.9)	53	31.1 (5.3)	40	31.2 (6.6)	53	31.5 (5.0)	39
Trails A	27.6 (8.3)	53	27.0 (9.1)	40	26.9 (7.9)	53	25.5 (6.4)	40	25.4 (6.1)	53	25.0 (6.8)	40
Verbal learning and memory												
CVLT Trial 1	7.1 (2.2)	53	6.1 (1.3)	40	7.2 (2.1)	53	7.3 (2.1)	40	8.0 (2.3)	53	7.3 (2.5)	40
CVLT Delayed Recall	12.5 (3.0)	53	12.1 (2.7)	39	13.1 (2.6)	53	12.9 (2.6)	40	13.5 (2.4)	53	13.2 (2.9)	40
CVLT Delayed Recognition	29.5 (2.9)	52	29.3 (2.8)	39	29.7 (3.2)	53	29.2 (2.9)	40	29.8 (3.1)	53	29.3 (3.2)	40
Logical Memory II	26.9 (7.2)	52	23.6 (7.8)	40	30.1 (6.0)	53	27.0 (7.6)	40	31.4 (6.5)	52	27.8 (7.2)	40
Visual learning and memory												
RVLT Trial 1	4.7 (1.6)	53	4.0 (1.7)	40	5.0 (1.7)	53	5.0 (2.0)	40	5.1 (1.4)	53	5.0 (1.7)	40
RVLT Delayed Recall	8.1 (2.3)	53	7.6 (2.7)	40	8.6 (2.5)	53	8.4 (2.7)	40	8.9 (2.4)	53	8.5 (2.7)	39
RVLT Delayed Recognition	13.1 (1.2)	53	12.7 (1.4)	40	13.1 (1.4)	53	13.3 (1.2)	40	13.5 (1.2)	53	13.1 (1.4)	39
Family Pictures II	45.8 (8.6)	52	41.2 (9.6)	39	46.3 (8.9)	53	47.3 (7.3)	39	47.7 (9.1)	53	46.2 (11.1)	40
Visuospatial function												
Block Design	37.3 (11.1)	53	35.7 (10.2)	40	37.9 (11.5)	53	36.2 (10.6)	40	38.3 (11.3)	53	36.3 (10.6)	39
Working memory												
Arithmetic	14.2 (3.4)	52	14.2 (3.0)	40	14.5 (3.3)	52	13.9 (3.4)	40	14.5 (3.1)	53	14.0 (3.4)	40
CCCs	43.6 (7.4)	50	43.3 (7.6)	39	43.3 (8.5)	50	46.0 (7.6)	38	45.1 (8.5)	49	47.4 (7.4)	39
Digit Span	17.1 (4.1)	53	17.3 (4.4)	39	17.1 (4.1)	53	18.6 (3.8)	40	17.2 (3.9)	53	18.1 (4.1)	40
Letter-Number Sequencing	10.8 (2.8)	53	10.6 (2.2)	40	10.3 (2.6)	53	11.2 (2.2)	40	10.9 (2.6)	53	10.9 (2.4)	40
Spatial Span	15.4 (2.5)	53	15.6 (2.3)	40	15.6 (2.6)	53	15.9 (2.3)	40	15.8 (2.6)	53	15.5 (2.6)	39
POMS												
Depression–Dejection	8.5 (9.7)	53	5.3 (7.0)	40	5.7 (8.6)	53	4.9 (5.4)	40	6.3 (10.1)	53	5.1 (7.1)	40
Fatigue–Inertia	7.5 (7.2)	53	7.9 (5.1)	40	10.2 (6.9)	53	8.3 (6.2)	40	6.8 (6.4)	53	7.5 (5.8)	40
Tension–Anxiety	11.1 (6.9)	53	8.6 (6.8)	40	7.4 (5.9)	53	7.7 (5.9)	40	7.1 (7.4)	53	7.5 (6.2)	40

SD = Standard deviation.
PASAT = Paced Auditory Serial Addition Test; WCST = Wisconsin Card Sorting Test; FAS = Controlled Oral Word Association Test; CVLT = California Verbal Learning Test; RVLT = Rey Visual Learning Test; CCCs = Consonant Trigrams
POMS = Profile of Mood States.

Table 5. Means and standard deviations of overall neuropsychological summary score and domain-specific summary scores for T1–T2 and T1–T3 for chemotherapy and hormonal groups

	T1–T2				T1–T3			
	Chemotherapy Mean (SD)	Hormonal Mean (SD)	*t*	*p*	Chemotherapy Mean (SD)	Hormonal Mean (SD)	*t*	*p*
Overall summary	−0.090 (0.355)	−0.001 (0.316)	−1.26	0.21	0.048 (0.375)	−0.001 (0.296)	0.68	0.50
Executive summary	0.205 (0.660)	−0.003 (0.792)	1.38	0.17	0.497 (0.837)	−0.011 (0.806)	2.94	0.00
Language summary	−0.147 (0.745)	−0.006 (0.739)	−0.91	0.37	−0.139 (0.943)	0.004 (0.731)	−0.79	0.43
Motor summary	−0.053 (1.118)	0.002 (0.947)	0.25	0.80	0.078 (1.156)	−0.004 (0.961)	0.36	0.72
Processing speed summary	0.099 (0.840)	0.000 (0.497)	0.71	0.48	0.010 (0.764)	0.002 (0.626)	0.06	0.96
Verbal memory summary	0.054 (0.616)	0.001 (0.648)	0.41	0.68	0.144 (0.553)	0.001 (0.609)	1.18	0.24
Visual memory summary	−0.290 (0.686)	0.000 (0.618)	−2.11	0.04	−0.043 (0.550)	0.000 (0.607)	−0.35	0.73
Visuospatial summary	0.038 (1.142)	0.000 (0.987)	0.17	0.87	0.111 (0.921)	0.000 (0.961)	0.57	0.57
Working memory summary	−0.286 (0.568)	0.000 (0.508)	−2.52	0.01	−0.057 (0.465)	−0.001 (0.504)	−0.56	0.58

SD = Standard deviation.

Table 6. Means and standard deviations of overall neuropsychological summary score and domain-specific summary scores for T1–T3 for chemotherapy subjects receiving hormonal therapy at T3 and for chemotherapy subjects not receiving hormonal therapy at T3

	On hormonal Tx Mean (SD)	Not on hormonal Tx Mean (SD)	*t*	*p*
Overall summary	−0.013 (0.378)	0.202 (0.333)	1.93	0.06
Executive summary	0.382 (0.852)	0.786 (0.745)	1.61	0.11
Language summary	−0.175 (1.068)	−0.048 (0.525)	0.44	0.67
Motor summary	0.189 (1.251)	−0.205 (0.841)	1.12	0.27
Processing speed summary	−0.168 (0.720)	0.462 (0.702)	2.89	0.01
Verbal memory summary	0.022 (0.544)	0.454 (0.457)	2.71	0.01
Visual memory summary	−0.091 (0.577)	0.080 (0.468)	1.02	0.31
Visuospatial summary	0.089 (0.946)	0.167 (0.881)	0.28	0.79
Working memory summary	−0.039 (0.477)	−0.102 (0.447)	−0.44	0.66

SD = Standard deviation.
Tx = Treatment.

groups differed at baseline on 4 of the 23 neuropsychological measures: Logical Memory II ($t = 2.08$, $p = 0.04$), Family Pictures II ($t = 2.41$, $p = 0.02$), CVLT Trial 1 ($t = 2.78$, $p = 0.01$), and RVLT Trial 1 ($t = 2.08$, $p = 0.04$), with the chemotherapy group scoring higher than the hormonal group in all cases. There were no significant differences between the treatment groups on any of the POMS measures at baseline.

Analysis of the T1–T2 data for the current groups yielded results that were very similar to those obtained in the larger samples described in our earlier paper: Again, we found a significantly higher rate of cognitive decline in the chemotherapy subjects than in the hormonal group (34 vs 13%; $\chi^2 = 5.64$, $p = 0.02$; OR = 2.72, $CI_{95\%} =$ 1.1–6.7), with no difference in rate of cognitive improvement (8% in either group; $\chi^2 = 0.00$, $p = 0.99$). With respect to the cognitive summary scores (Table 5), the working memory summary score was again significantly lower in the chemotherapy group ($t = -2.52$, $p = 0.01$). In these smaller subgroups, the visual memory summary score was also significantly lower in the chemotherapy group ($t = -2.11$, $p = 0.04$).

At T3, there was no significant difference between the chemotherapy subjects and hormonal subjects with respect to frequency of reliable cognitive decline (11 vs 10%, respectively; $\chi^2 = 0.04$, $p = 0.84$) or improvement (11 vs 5%, respectively; $\chi^2 = 1.16$, $p = 0.28$). The only group difference on the T1–T3 summary scores was in the area of executive function ($t = 2.94$, $p = 0.004$), and this was actually higher in the chemotherapy group (Table 5).

As depicted in Table 6, the speed summary score ($t = 2.89$, $p = 0.01$) and the verbal memory summary score ($t = 2.71$, $p = 0.01$) were significantly lower in those chemotherapy patients who were receiving hormonal agents at T3 ($n = 38$) than in those chemotherapy patients who were not on hormonal treatment ($n = 15$). There was a trend toward lower overall summary scores in the subjects who received both chemotherapy and hormonal therapy ($t = 1.93$, $p = 0.06$).

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Discussion

It has now been repeatedly demonstrated, by ourselves [27] and others [4,6,13], that a significant proportion of women with early stage breast cancer experience subtle cognitive disturbances during or immediately following standard dose adjuvant chemotherapy. However, arguably the greater concern for patients is the chronicity of these cognitive changes. The extant data are less clear on this issue, with more recent longitudinal and follow-up studies [8,15,16,36] generally suggesting that the disturbances resolve over time, and earlier cross-sectional studies indicating that significant cognitive deficits persist for 1 year or longer in a sizeable subgroup of breast cancer patients [2,5,9,10,14]. The current data are in keeping with the few other controlled prospective trials in breast cancer patients in indicating that the cognitive perturbations noted in the short term are no longer evident at 1 year following completion of therapy.

Discrepancies among studies with regard to chronicity of cognitive disturbance probably reflect failure of the cross-sectional studies to account for pretreatment group differences in cognitive function, as well as differences in the choice of control group. Reliance on healthy controls does not account for cancer-related factors other than chemotherapy that might contribute to cognitive changes. Even using a patient control group closely matched to the chemotherapy group on critical demographic variables such as age and education, we still found significant group differences at baseline on 4 of the 23 neuropsychological measures. These findings underscore the importance of using a controlled prospective design in trying to isolate the cognitive effects of treatments in cancer patients and to assess accurately their duration and magnitude.

As is typical of longitudinal studies, our rate of attrition from T1 to T3 was quite high. Selective attrition of subjects can significantly bias study results and so we compared those who completed the study with those who dropped out. We found that the dropouts scored lower on several neuropsychological tests at baseline (it is hardly surprising that the women who fared more poorly on initial testing may have been less inclined to repeat it), were less educated, and tended to have lower IQ scores. In our earlier analysis of the T2 follow-up data with larger subject groups [27], we found that lower education was a risk factor for cognitive decline. To the extent that this is so, the selective attrition of less-educated women from the current sample may have resulted in an underestimation of the prevalence, severity, or both of chemotherapy-related cognitive decline.

There is a wealth of data indicating that estrogen acts in the brain and influences cognitive function (see reviews by Bender *et al.* [53]; Sherwin [54,55]; Shilling *et al.* [56]), as well as emerging data to suggest that anti-estrogen treatments for breast cancer may themselves have adverse effects on cognition [3,5,53,57–60]. For example, Bender *et al.* [3] and Castellon *et al.* [5] found that breast cancer patients who received chemotherapy plus tamoxifen exhibited more widespread deficits than did women who received chemotherapy alone. In the current study, we found that chemotherapy subjects who also received hormonal therapy tended to perform more poorly on neuropsychological testing at T3 than those who were not receiving hormonal agents, especially on measures of processing speed and verbal memory. Interestingly, it is precisely these same cognitive functions that were found to be weaker in hormonally treated patients than in non-cancer control subjects in the ATAC trial (a double-blind comparison of Anastrazole and Tamoxifen *Alone* or in *Combination* in the treatment of early breast cancer) [58,60].

Given that hormone therapy itself may exert negative effects on cognition, we cannot be certain that the cognitive effects of chemotherapy have diminished by T3 on the basis of comparison with a control group receiving hormonal treatment: The failure to find group differences in frequency of cognitive decline at this later time point may reflect increasing cognitive disturbance in the hormonal group associated with longer duration of treatment. Although inspection of the data does not reveal any substantial decline in test scores in the hormonal group, this does not rule out the possibility of a subtle attenuation of the normal practice effect. In the absence of a non-treatment control group, we are not in a position to investigate this possibility. The ideal control group for studies of this nature would comprise cancer patients receiving no systemic adjuvant treatment. However, given current clinical practice, this is a rarity, even in patients with very early stage disease. It would seem that the best alternative is to include both a patient and a healthy control group, as recommended by Vardy *et al.* [26].

In making informed decisions about cancer treatments, particularly adjuvant treatments that may confer modest survival advantage, patients require accurate information about side effects [61,62]. It would seem that many of the early, cross-sectional studies of the cognitive effects of chemotherapy tended to over-estimate the risk, severity, and chronicity of cognitive impairment. On the basis of recent findings from this and other controlled prospective studies, it seems reasonable to advise breast cancer patients that approximately one-third of women receiving standard dose adjuvant chemotherapy experience very subtle disturbances in cognition, especially working memory, during and shortly following treatment but that, by 1 year after completion of treatment,

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cognitive function is not likely to differ from that of women receiving adjuvant hormonal therapy only.

It remains for future studies to address whether or not hormonal agents themselves cause cognitive side effects, the course of those cognitive changes, and whether or not they resolve with termination of treatment. A study of the cognitive effects of prophylactic hormonal treatment in women at risk for breast cancer would be very informative in this regard, as it would side-step many of the confounding host and disease factors in cancer patients. It will also be of great interest to compare the cognitive effects of selective estrogen receptor modulators, such as tamoxifen that may actually act as an estrogen receptor agonist in the brain, to the aromatase inhibitors such as anastrazole that block post-menopausal estrogen synthesis resulting in a profound lowering of estrogen levels throughout the body [63]. We eagerly await the results of the ATAC trial for further insights concerning the effects of different anti-estrogen agents on cognition. Study of the effects of hormone therapies, and the interactions of cytotoxic and hormone therapies, on mood and cognition is an important next step in understanding the impact of treatment on quality of life in breast cancer survivors.

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