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Neurocognitive Performance in Breast Cancer Survivors Exposed to Adjuvant Chemotherapy and Tamoxifen

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ABSTRACT

The primary aim of the current study was to examine whether neurocognitive functioning among breast cancer survivors (BCS) exposed to systemic adjuvant chemotherapy differs from that seen among BCS who did not receive chemotherapy. The performance of each of these BCS groups was compared to a demographically matched comparison group without history of breast cancer, a group not included in the majority of previous cognitive functioning studies. We also sought to explore whether usage of the anti-estrogen drug tamoxifen, a common component of breast cancer treatment, was related to neurocognitive functioning. Finally, we wished to examine the relationship between subjective report of cognitive functioning and objective performance on neurocognitive measures among BCS. Fifty-three survivors of breast cancer (all between 2–5 years after diagnosis and initial surgical removal of cancerous tissue) and 19 healthy non-BCS comparison subjects were administered a comprehensive neurocognitive battery, and measures of mood, energy level, and self-reported cognitive functioning. Those BCS who received adjuvant chemotherapy performed significantly worse in the domains of verbal learning, visuospatial functioning, and visual memory than BCS treated with surgery only. Those who received both chemotherapy and tamoxifen showed the greatest compromise. Although patients who received chemotherapy (with and without tamoxifen) performed worse than those treated with surgery only on several domains, neither group was significantly different from demographically matched comparison subjects without a history of breast cancer. Finally, we found no relationship between subjective cognitive complaints and objective performance, although cognitive complaints were associated with measures of psychological distress and fatigue. We highlight ways in which these data converge with other recent studies to suggest that systemic chemotherapy, especially in combination with tamoxifen, can have adverse yet subtle effects on cognitive functioning.

INTRODUCTION

With the more widespread use of chemotherapy for a variety of adult cancers, there have been increasing numbers of anecdotal reports among cancer patients of cognitive deficits during and after exposure to chemotherapy, commonly known as "chemobrain." While complaints are most

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typically of memory and attention/concentration deficits, self-report of difficulty in other cognitive domains have also been reported (Ahles & Saykin, 2001; Meyers, 2000). Large numbers of newly diagnosed breast cancer patients are receiving adjuvant treatment with chemotherapy with or without endocrine therapy (e.g. tamoxifen) every year (NIH Consensus Statement, 2001) and there are increasing numbers of long-term breast cancer survivors (BCS) as the mortality rate has fallen substantially for this disease (Jemal et al., 2003). Therefore, it is important to better understand the potential cognitive late effects of adjuvant systemic therapy, as one of many other late effects of cancer treatments (Castellon & Ganz, 2001; Ganz, 1998; Ganz et al., 2002). A rapidly accumulating literature with BCS suggests that adjuvant systemic therapies are indeed associated with performance decrements on several neurocognitive tasks (Ahles et al., 2002; Brezden, Phillips, Abdolell, Bunston & Tannock, 2000; Schagen et al., 1999; van Dam et al., 1998; Wieneke & Dienst, 1995). Deleterious effects of adjuvant therapy have been observed among women who received standard dose chemotherapy as well as those who received high dose chemotherapy and those currently undergoing treatment.

Neuropsychological outcomes vary across exact BCS population studied (e.g. by stage of tumor, dose of chemotherapy, exposure to hormonal treatment, length of time post-diagnosis and treatment), but these studies have not found a consistent association with a specific neurocognitive domain (Ahles et al., 2002; Brezden et al., 2000; Schagen et al., 1999; van Dam et al, 1998; Wieneke & Dienst, 1995). For example, verbal memory deficits have been associated with chemotherapy in some studies (Ahles et al., 2002; Weineke & Dienst, 1995) but not in others (van Dam et al., 1998). Similarly, non-verbal memory has been found affected in some studies (Schagen et al., 1999; van Dam et al., 1998; Weineke & Dienst, 1995), but not all (see Ahles et al., 2002). Other domains in which lower performance among BCS exposed to adjuvant therapy has been seen include information processing/psychomotor speed (Ahles et al., 2002; Schagen et al., 1999; van Dam et al., 1998) and visuospatial functioning (Brezden et al., 2000; van Dam et al., 1998).

While an accumulating literature suggests BCS exposed to adjuvant therapy perform worse than BCS who do not receive adjuvant therapy, we do not know how either of these groups performs relative to a demographically matched non-cancer comparison group. The few studies comprising the extant literature have typically used only a BCS control group (i.e those not exposed to adjuvant treatment) and/or compared the neuropsychological performance of their treatment groups to normative data. The only study of cognition among BCS that has used a group of healthy, non-cancer comparison subjects used a brief cognitive screening measure (Brezden et al., 2000). These investigators found that 20 of their 36 healthy, non-cancer controls scored in the mildly impaired range or worse on this screening measure, calling into question the control group or the screening measure.

There is also only a limited amount of information about the potential cognitive effects of the anti-estrogen drug tamoxifen (Nolvadex), which plays a central role in the adjuvant therapy of women with hormone receptor positive breast cancers. Tamoxifen, a selective estrogen receptor modulator, is widely used both to treat and to reduce the risk of developing breast cancer (Chelebowski, 2000; Fisher et al., 1998). While tamoxifen has been used for many years with advanced breast cancer, in the past decade it has been used as a standard component of adjuvant therapy following primary surgical treatment of early stage breast cancer. Tamoxifen prevents the uptake of estrogen in breast cancer cells that contain the estrogen receptor (in the breast and in metastatic sites), thus blocking growth and proliferation of malignant and precancerous cells in these target tissues. The extant literature suggests that estrogen may have beneficial effects on brain metabolism and cognitive function (Asthana et al., 2001; Maki & Resnick, 2000; Shaywitz et al., 1999; Sherwin, 1997, 1999 — although also see Grodstein et al., 2000; Wang et al., 2000) and animal studies have suggested that tamoxifen may act as an estrogen antagonist in the brain (Sumner et al., 1999).

The potential effects of tamoxifen on cognition are uncertain, due to a lack of careful study in randomized clinical trials. A few studies have suggested an association between tamoxifen and cognitive problems in women treated for breast

cancer (Arpels, 1996; Paganini-Hill & Clark, 2000). A recent study that provided only limited cognitive assessment (clock and pentagon drawing and also a narrative writing assignment to describe a pictured scene, each task "administered" as part of a mailed questionnaire) found that while subjects taking tamoxifen did not perform significantly worse on these cognitive tests, they were more likely to report seeing a physician or other professional for memory problems than were those women never exposed to tamoxifen (Paganini-Hill & Clark, 2000). In studies using a more extensive neurocognitive battery, administered in a traditional setting, and following a standard testing protocol, only one study found tamoxifen associated with cognitive impairment (van Dam et al., 1998). Of note, all of the adjuvant therapy patients in this study were treated with both chemotherapy and tamoxifen. In contrast, recent work from Ahles et al. (2002) did not find cognitive performance differences between tamoxifen users and non-users.

Due to the lack of prospective, longitudinal studies examining neurocognitive function pre- and post- adjuvant therapy among BCS, inferences of causality must be tempered. To date, the mechanism(s) driving cognitive compromise remain unclear. Direct effects on the CNS via cytotoxic agents in the chemotherapy regimens or indirect CNS effects via immune system dysregulation are potential mechanisms. The few cross-sectional studies comprising this literature suggest that potential confounds including menopause status, mood/emotional state, and/or physical functioning do not seem to be driving the association between systemic therapy and cognitive compromise.

While mood disturbance and physical functioning measures do not appear to mediate the relationship between adjuvant therapy and cognitive compromise, they may be related to self-report of cognitive difficulty. *Self-report* of cognitive compromise has not been found to be associated with actual performance on neuropsychological measures in the two studies that have measured both constructs among BCS (Ahles et al., 2002; van Dam et al., 1998). In fact, van Dam and colleagues (1998) found that cognitive complaints were associated with mood disturbance rather than actual neurocognitive performance, a relationship that has been observed in several other populations as well

(Cull et al., 1996; Hinkin et al., 1996; Rourke, Halman, & Bassel, 1999; Vermeulen, Aldenkamp, & Alpherts, 1993).

The goals of the current study were: 1) to evaluate the impact of adjuvant therapy on cognitive function in reference to a demographically matched, non-cancer comparison group; 2) to explore whether the anti-estrogen tamoxifen confers added risk for cognitive compromise in women who are also treated with chemotherapy; and 3) to evaluate the association between self-reported cognitive complaints and objective cognitive performance.

METHOD

Participants & Procedure

This research was conducted as a substudy from a larger cohort study of younger women with breast cancer, examining the interaction between reproductive health and breast cancer treatments. As part of the Cancer and Menopause Study (CAMS), we recruited women from two hospital tumor registries in the Los Angeles area (Pakilit et al., 2001). In the first phase of the study, 579 women completed a mailed survey booklet related to their health, reproductive history and quality of life. All of the women who were geographically accessible were then invited to the second phase of the study, which included an in-person visit for biological assessment, bone density, and anthropometric measurements. It was from this second phase of the research that we recruited the women for the current study.

Eligibility for the main CAMS study included having Stage 0, I or II breast cancer (determined by the hospital cancer registry), diagnosed at age 50 years or younger, between 2–10 years earlier, and having no evidence of disease recurrence. Stage 0 patients were explicitly included in CAMS as we wished to compare breast cancer patients unlikely to receive adjuvant systemic therapy (stage 0) with those more likely to receive such treatments, thus representing a breast cancer control group for those receiving adjuvant treatments in the main study. Women were also required to be able to provide informed consent and be able to speak and read English. For recruitment to the cognitive functioning study reported here, we targeted only the 115 participants in CAMS who were between 2–5 years after diagnosis and who had come in for the in-person biological assessments. For the cognitive functioning study we also excluded women with any of the following: 1) history of neurologic or psychiatric disorder, 2) current or past history of drug or alcohol use disorder, 3) the use of any medication that might impact neurocognitive performance.

A comparison group of healthy, age-matched women without a diagnosis of cancer was recruited specifically for this study. These women were primarily recruited through fliers, newsletter articles and advertisements posted throughout the medical center and in the Women's Health Center. A few volunteers were identified by research staff members from their acquaintances or from other research studies. Only one participant was an acquaintance of a BCS.

All cognitive testing was conducted by a technician trained and supervised by a licensed clinical neuropsychologist. The technician was masked to the treatment status of the BCS for all testing and scoring of the neurocognitive data. Participants received fifty dollars for participating in this study, which was approved by the institutional review board of the UCLA School of Medicine.

Measures

Neurocognitive Performance Tasks
A battery of neuropsychological tasks, comprising eight cognitive domains, was utilized for the current study. The eight cognitive domains included Verbal Fluency, Verbal Learning, Verbal Memory, Visual Memory, Visuospatial Function, Reaction Time, Psychomotor Speed, and Executive Attention. Grouping of tests into domains was based on both prior factor analytic studies of large neuropsychological data sets and groupings used by other investigators working with this population. As many of these tasks yield multiple outcome variables, we identified *a priori* those variables most salient for the

current study. Table 1 lists the measures comprising these eight cognitive domains, and the specific variables used for analysis. Administration of the neurocognitive battery took approximately 100–120 minutes.

Self-Reported Cognitive Function
The Cognitive Failures Questionnaire (CFQ: Broadbent, Cooper, Fitzgerald, Parkes, 1982) is a 25-item, 4 point Likert scale, self-report measure of everyday cognitive lapses such as forgetting appointments or where one has left things (e.g. keys, wallet), lapses in concentration or attention, or word-finding difficulty. Higher scores on the CFQ are indicative of greater number or severity of cognitive complaints. The CFQ has been used with diverse neurologic and medical populations and has been shown to have adequate psychometric properties (Mahoney, Dalby, & King, 1998; McKinney et al., 2002).

Depression, Anxiety, and Fatigue
Current level of self-reported depression was measured using the Beck Depression Inventory, 2nd Edition (BDI-2: Beck et al., 1996), a 21-item rating scale assessing the presence and prominence of depressive symptoms over the two weeks preceding test administration. Level of both state (current) and trait (general) anxiety were measured using the Spielberger State-Trait Anxiety Inventory (STAI: Spielberger, Gorusch & Lushene, 1971). The STAI is comprised of two 20-item forms that query the frequency and intensity of anxiety symptoms. Both the BDI-2 and the STAI have been used extensively with both general medical and neurologic populations to

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Table 1. Cognitive Domains, Associated Neurocognitive Tests, and Outcome Variables.

Verbal Fluency	**Controlled Oral Word Association Test (F-A-S)** (Lezak, 1995), Category (Animal) Fluency
Verbal Learning	**California Verbal Learning Test** (Delis, Kramer, Kaplan & Ober, 1987), total correct list A, total correct list B, short and long-delay free recall.
Verbal Memory	**Wechsler Memory Scale, Revised, Logical Memory** (Wechsler, 1987), total points, immediate and 30-minute delayed recall.
Visual Memory	**Wechsler Memory Scale, Revised, Visual Reproduction** (Wechsler, 1987), total points achieved, immediate and 30-minute delayed recall. **Rey Osterreith Complex Figure** (Meyers & Meyers, 1995; Osterrieth, 1944; Rey, 1942), total points achieved following 30-minute delay
Visuospatial Function	**Wechsler Adult Intelligence Scale, 3rd Edition, Block Design** (Wechsler, 1997), total points achieved. **Rey Complex Figure, Copy Trial** (Meyers & Meyers, 1995; Osterrieth, 1944; Rey, 1942)
Psychomotor Speed	**Wechsler Adult Intelligence Scale, 3rd Edition, Digit Symbol** (Wechsler, 1997), raw score. **Trailmaking Test,** (Reitan & Wolfson, 1985), completion time, parts A and B.
Reaction Time	**California Computerized Assessment Package** (Miller, Satz & Visscher, 1991), Simple Reaction Time, Choice Reaction Time, speed and accuracy.
Executive Attention	**Paced Auditory Serial Addition Test** (Gronwall, 1977), total correct over 4 trials, **Stroop Test -** (Comalli version; Mitrushina, Boone & D'Elia, 1999) **Interference Trial** number of seconds to complete

quantify mood symptoms, each having been shown to have acceptable psychometric properties. We measured fatigue using the four-item energy/fatigue scale from the Medical Outcomes Study (MOS) SF-36 (Ware & Sherbourne, 1992), which assesses how much of the time the individual has "felt full of pep", "had a lot of energy", "felt worn out", and "felt tired" during the 4 weeks preceding the evaluation. Higher scores on this scale, which ranges between 0 and 100 indicate more energy, less fatigue. This fatigue scale from the MOS SF-36 has been used previously with breast cancer survivors and is highly correlated with other, lengthier, fatigue measures (Bower et al. 2000; Bower, Ganz Aziz, & Fahey, 2002).

Data Analyses. The Statistical Package for Social Sciences, version 8.0 (SPSS,1997) was used for all statistical analyses. Neurocognitive outcomes were converted into standard scores (z-scores) using the mean and standard deviation of the non-cancer controls. When necessary, relevant transformations were made so that all positive z-scores represented better than average performance and all negative z-scores represented performance below the mean of the control group. Domain scores were calculated for each of the eight neurocognitive domains listed in Table 1. Three participants had one missing outcome variable; domain scores for these three subjects were calculated using only one of the two designated outcomes of interest. A Global Neurocognitive Performance score was calculated by taking the average of all domain z-scores.

To avoid elevating risk of Type I error, we utilized Multivariate analysis of variance (MANOVA) to compare BCS treatment group performances across the eight cognitive domains. When appropriate, follow-up univariate analysis of variance (ANOVA) was conducted to determine the specific domains contributing significantly to the overall multivariate effect. General Neurocognitive Performance scores were compared between groups using ANOVA with Tukey post-hoc comparisons used to follow-up significant ANOVA findings. Pearson's correlation coefficients were generated to evaluate the degree of relationship between mood, fatigue, self-reported cognitive, function, and neurocognitive performance domains.

The primary comparisons in the current study involved three groups: 1) BCS who received adjuvant therapy, 2) BCS who did not receive adjuvant therapy, and 3) non-cancer comparison subjects. However, exploratory analyses to ascertain the contribution of tamoxifen to cognitive functioning were also conducted. These analyses involved the comparison of four groups: 1) BCS who received adjuvant therapy with chemotherapy and tamoxifen, 2) BCS who received adjuvant therapy

chemotherapy only, 3) BCS who did not receive adjuvant therapy and 4) non-cancer comparison subjects.

RESULTS

Subjects

Seventy-two women participated in the current study, 53 breast cancer survivors (BCS) and 19 non-BCS, healthy comparison controls. All of the 53 BCS had undergone local therapy, which consisted of either a modified radical mastectomy, or breast conserving surgery with radiation therapy to the breast (with no radiation of central nervous system). For the BCS sample there was no difference in the rates of breast conserving surgery among the three groups. In addition to local therapy, 36 of the BCS had been exposed to adjuvant systemic therapy, which consisted of either chemotherapy alone (N = 18) or chemotherapy plus tamoxifen (N = 18). Systemic adjuvant chemotherapy regimens that were used included cyclophosphamide, methotrexate and 5 fluorouracil (CMF) in 41% of the women, a doxorubicin containing regimen along with cyclophosphamide alone or with CMF in 38%, with the remainder receiving a doxorubicin, cyclophosphamide combination with a taxane (ACT) in 9%. There was no significant difference between the two adjuvant therapy groups. There were 8 women who in addition to the standard adjuvant chemotherapy received high dose chemotherapy in addition; there was no significant difference in distribution by adjuvant therapy group (i.e. chemotherapy only or chemotherapy plus tamoxifen).

The women in the current study were well-educated (M = 16.5 years, SD = 2.4), bright (AmNart VIQ: M = 119.3, SD = 6.4), and relatively young (M = 47.8, SD = 5.8). As seen in Table 2, most participants were Caucasian and were currently employed either part- or full-time. The three groups (non-BCS, BCS-No Adjuvant Therapy, and BCS-Adjuvant Therapy) did not differ in terms of age, education, or estimated Verbal IQ using the North American version of the National Adult Reading Test (Blair & Spreen, 1989). As shown in Table 3, levels of self-reported

Table 2. Demographic Characteristics of Breast Cancer Survivors and Non-cancer Comparison Subjects.

	BCS-No Adj RX (N = 17)	BCS-Adj RX (N = 36)	Non-BCS (N = 19)	p
Variable Name				
Age, in years	48.3 (4.0)	46.8 (6.3)	49.2 (6.0)	.31
Education, years	16.6 (2.1)	16.2 (2.7)	17.0 (1.9)	.43
Estimated VIQ	120.1 (5.9)	118.1 (7.2)	121.4 (4.6)	.18
% Caucasian	65	71	67	.86
% Employed Full-time	59	60	56	.36

Note: BCS = Breast cancer survivor; BCS- No Adj RX = breast cancer survivors treated with local therapy only (i.e they did not receive adjuvant chemotherapy); BCS-Adj RX = breast cancer survivors treated with adjuvant chemotherapy (with or without tamoxifen) in addition to local therapy; Non-BCS = matched comparison group without history of breast cancer; VIQ = Verbal Intelligence Quotient; % = Percentage; No group differences on any demographic variable.

Table 3. Means and Standard Deviations on Mood, Energy Level, and Self-reported Cognitive Complaints Among Breast Cancer Survivors With and Without Adjuvant Therapy and Non-cancer Comparison Group.

Variable	BCS-No Adj RX (N = 17)	BCS-Adj RX (N = 36)	NON-BCS (N = 19)	p
Beck Depression Inventory	7.0 (4.5)	6.3 (5.1)	7.8 (7.9)	.63
State Anxiety Inventory	24.6 (3.6)	28.6 (8.8)	33.2 (8.0)	**.01**
Trait Anxiety Inventory	31.9 (7.3)	33.1 (8.1)	38.0 (9.3)	.07
MOS SF-36 Energy/Fatigue Scale	61.2 (19.1)	62.8 (18.9)	62.6 (14.0)	.95

Note: BCS = Breast Cancer Survivors; BCS-No Adj RX = breast cancer survivors treated with local therapy only (i.e they did not receive chemotherapy or tamoxifen); BCS-Adj RX = breast cancer survivors treated with adjuvant chemotherapy (with or without tamoxifen) in addition to local therapy; Non-BCS = matched comparison group without history of breast cancer.

depression, anxiety and fatigue were generally low and well within normal limits, compared with published normative data. A significant difference between treatment groups on the State Anxiety Inventory (SAI) was observed, with the non-BCS comparison group scoring higher (i.e. endorsing more symptoms/signs of anxiety) than those BCS who did not receive adjuvant therapy ($p < .05$), although all three groups scored within normal limits on the SAI. Otherwise there were no differences in self-reported mood or fatigue between groups.

Adjuvant Therapy and Neurocognitive Performance

We began by comparing breast cancer patients who had received adjuvant chemotherapy (BCS-Adj RX) to those who received surgery only (BCS – No Adj RX) and to non-cancer controls (non-BCS). Table 4 lists means and standard deviations of scores on neurocognitive measures used to calculate domain scores for these three groups. A MANOVA was run with Treatment Group as independent variable and the eight cognitive domain scores as dependent variables. A main effect of Group [$F (8, 63) = 2.09, p = .05$] was noted with univariate ANOVA showing that the domains of Visual Memory [$F (2, 69) = 3.59, p = .03$], Visuospatial function [$F (2, 69) = 4.41, p = .02$], and Verbal Fluency [$F (2, 69) = 3.91, p = .03$] differed significantly between the groups with a trend towards significance noted in the domain of Verbal Learning [$F (2, 69) = 2.94, p = .06$]. Compared to BCS treated with surgery

Table 4. Means and Standard Deviations on Neurocognitive Performance Measures for Breast Cancer Survivors with and Without Adjuvant Therapy and Non-cancer Comparison Group.

Domain/Measure	BCS No Adj RX (n=17)	BCS Ad RX (n=36)	Non-BCS (n=19)	F	p
Verbal Fluency					
COWAT (F-A-S)	46.8 (9.9)	41.9 (12.6)	47.0 (12.4)	1.57	.22
Animal Fluency	23.2 (3.3)	22.4 (5.1)	26.4 (4.6)	4.85	**.01**
Verbal Memory					
Logical Memory I (Raw)	32.6 (5.2)	29.4 (5.5)	31.2 (5.0)	2.29	.11
Logical Memory II (Raw)	28.9 (5.6)	26.1 (5.8)	28.2 (5.0)	1.38	.26
Verbal Learning					
CVLT List A Total	59.9 (7.6)	57.4 (7.3)	56.6 (7.2)	0.97	.38
CVLT List B	8.9 (1.9)	7.6 (1.9)	7.3 (1.7)	4.22	**.02**
CVLT Short-Delay Free	13.3. (1.6)	12.0 (2.3)	12.4 (2.4)	2.01	.14
CVLT Long-Delay Free	13.4 (1.7)	12.4 (2.4)	12.6 (2.5)	1.10	.34
Visual Memory					
WMS-R Visual Repro I	37.9 (1.6)	35.5 (3.8)	35.6 (2.3)	4.05	**.02**
WMS-R Visual Repro II	31.6 (7.4)	30.1 (7.3)	30.9 (4.7)	0.30	.74
Rey Complex Figure, Recall	22.1 (5.7)	17.6 (5.6)	21.3 (4.6)	5.36	**.007**
Visuospatial Function					
Block Design (total points)	48.2 (10.3)	38.6 (11.0)	41.3 (10.1)	4.65	**.01**
Rey Complex Figure, Copy	33.9 (2.1)	32.5 (2.7)	33.7 (1.6)	2.89	**.06**
Psychmotor Speed					
Digit Symbol (total points)	86.8 (16.9)	78.1 (12.6)	77.6 (13.2)	2.05	.14
Trails A	29.2 (7.6)	29.3 (8.8)	30.9 (8.6)	.27	.77
Trails B	61.1 (18.2)	62.2 (16.6)	59.9 (17.7)	.11	.90
Reaction Time					
CalCAP Median SRT	374.9 (203.8)	342.9 (72.2)	291.6 (81.3)	2.32	.11
CalCAP Median CRT	412.7 (42.0)	419.1 (67.8)	393.5 (91.9)	0.83	.44
CalCAP Accuracy [##]	16.3 (1.3)	15.5 (1.9)	15.6 (1.9)	1.15	.32
Executive Attention					
PASAT, total correct 1-4	133.2 (34.6)	120.3 (35.3)	135.7 (18.5)	1.80	0.17
Stroop Interference, time	107.8 (35.8)	109.0 (19.5)	108.5 (22.9)	0.01	0.99

Note: ## Cal CAP accuracy defined as the mean number of correct identifications on the three levels of the choice reaction time tasks. BCS = Breast Cancer Survivors; BCS-No Adj RX = breast cancer survivors treated with local therapy only (i.e they did not receive chemotherapy or tamoxifen); BCS-Adj RX = breast cancer survivors treated with adjuvant chemotherapy(with or without tamoxifen) in addition to local therapy; Non-BCS = matched comparison group without history of breast cancer.

only, BCS who received adjuvant therapy scored significantly lower in the Visual Memory (p = .01), Visuospatial (p = .005) and Verbal Learning (p = .03) domains (Figure 1). As seen by examining the univariate F statistics included in Table 4, the neurocognitive measures that best discriminated between BCS who received adjuvant therapy and those that did not included WAIS-III

Block Design (Cohen's d = .90, a large effect), ROCF Copy and Recall (d = .58 and .80, respectively), Visual Reproduction from the Wechsler Memory Scale (d = .81)), and CVLT, List B (d = .68). Compared to non-BCS subjects, BCS who received adjuvant therapy scored significantly lower in the Verbal Fluency domain (p = .007, d = .82). Of interest, BCS who did not receive adjuvant
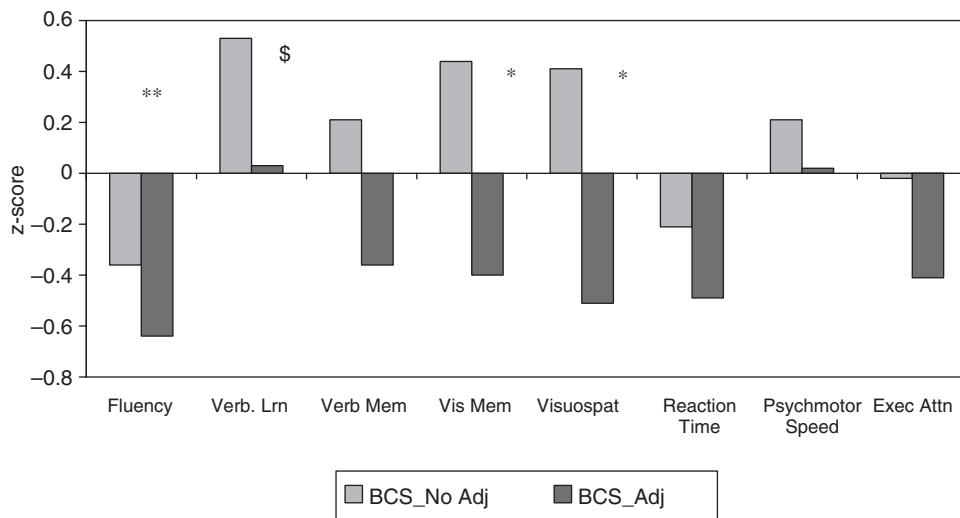
Fig. 1. Neurocognitive Performance Among Two BCS Groups Relative to Non-BCS Subjects.
    Note: BCS = Breast Cancer Survivor; BCS_No Adj = Breast Cancer Survivor never exposed to adjuvant therapy, N = 17; BCS-Adj= Breast Cancer Survivor who received adjuvant chemotherapy (with or without tamoxifen), N = 36. Z-score of 0 is equivalent to performance of non-BCS comparison subjects. Fluency = Verbal Fluency, Verb. Lrn = Verbal Learning, Verb Mem = Verbal Memory, Vis Mem = Visual Memory, Visuospat = Visuospatial, Exec Attn = Executive Attention.
    *BCS_No Adj > BCS-Adj, *p* < .05.
    **Non-BCS Subjects > BCS-Adj *p* < .01.
    $ BCS No Adj > BCS-Adj, Non-BCS Subjects *p* < .05.

therapy also scored *higher* than non-BCS comparison subjects in the Verbal Learning domain (p = .05).

To evaluate the impact of treatment group status on Global Neurocognitive Performance score (the mean of the 8 neurocognitive domain z-scores, defined in relation to the non-BCS control group), univariate ANOVA was used with the results depicted in Figure 2. A main effect of treatment group was noted [$F_{(2, 69)}$ = 4.89, p = .01] with follow-up pairwise comparisons showing that BCS who received adjuvant therapy scored significantly lower than did those BCS who did not receive adjuvant therapy (p = .01). Neither BCS group differed significantly in Global Neurocognitive Performance from the non-BCS controls.

Tamoxifen Use and Cognitive Performance
To explore whether exposure to tamoxifen as part of the adjuvant therapy regimen might impact neurocognitive performance, a MANOVA was

again run, with three BCS treatment groups [BCS-No Adjuvant therapy (n = 17), BCS-Chemo Only (n = 18) and BCS- Chemo + Taxoxifen (n =18)] compared with each other and with the non-BCS controls on the eight cognitive domain scores (Figure 3). The overall MANOVA again showed a significant main effect of Group [$F_{(8, 63)}$ = 2.38, p = .03), with follow-up univariate analyses showing that the domains of Verbal Learning [$F_{(3, 68)}$ = 3.03, p = .04], Visuospatial functioning [$F_{(3, 68)}$ = 3.51, p = .02], and Verbal Fluency [$F_{(3, 68)}$ = 3.81, p = .01] differed significantly between groups. Additionally, there was a trend towards significance noted in the domain of Visual Memory [$F_{(3, 68)}$ = 2.59, p = .06]. Follow-up pairwise comparisons among the groups demonstrated that the group of BCS who received both chemotherapy and tamoxifen scored significantly lower within the Verbal Learning (p = .005), Visual Memory (p = .009), and Visuospatial (p = .002) domains than did those BCS who received no adjuvant therapy. Those BCS who received
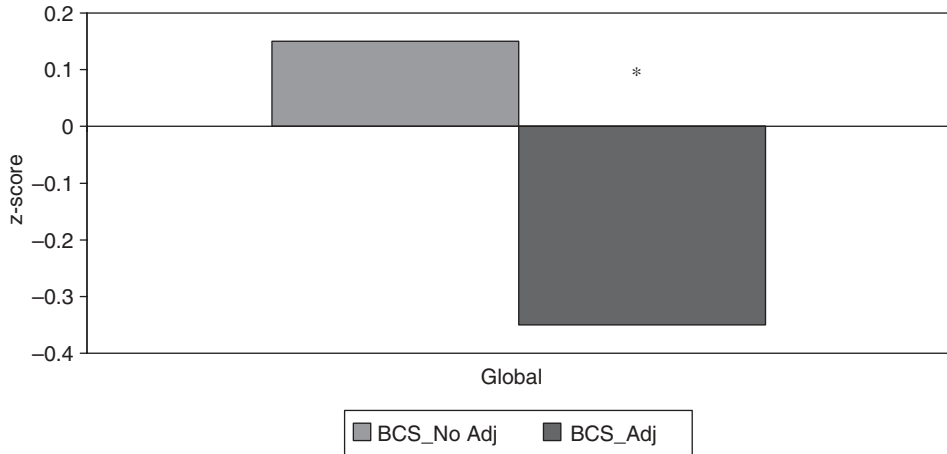
Fig. 2. General Neurocognitive Performance Score, relative to non-BCS comparison subjects, among BCS who did or did not receive adjuvant therapy.

BCS_No Adj = Breast Cancer Survivor never exposed to adjuvant therapy, N = 17; BCS-Adj= Breast Cancer Survivor who received adjuvant chemotherapy (with or without tamoxifen), N = 36. Z-score of 0 is equivalent to performance of non-BCS comparison subjects.
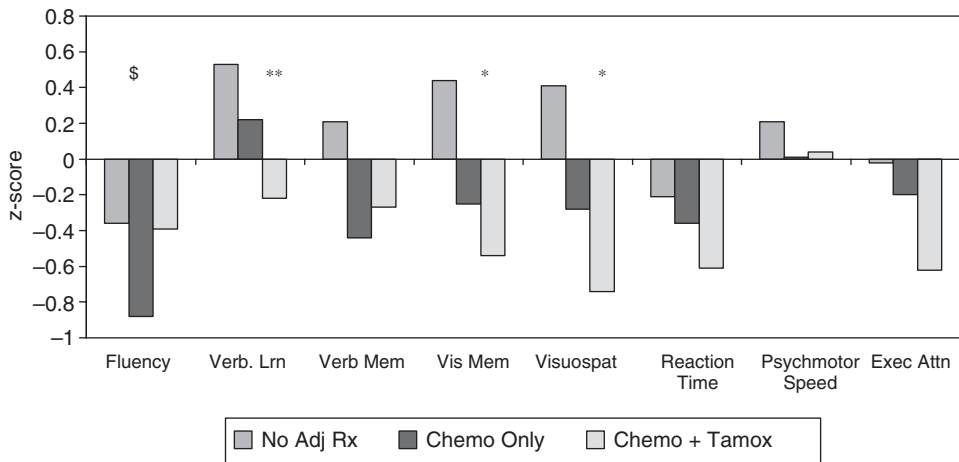
*BCS-No Adj > BCS Adj ($p = .01$).

Fig. 3. Neurocognitive Performance Among Three BCS Groups Relative to Non-BCS Controls.

Note: BCS = Breast Cancer Survivor. No Adj Rx = BCS not exposed to adjuvant treatment; Chemo Only = BCS exposed to chemotherapy only; Chemo + Tamox = BCS exposed to both adjuvant chemotherapy and tamoxifen. Z-score of 0 is equivalent to performance of non-BCS controls. Fluency = Verbal Fluency, Verb. Lrn = Verbal Learning, Verb Mem = Verbal Memory, Vis Mem = Visual Memory, Visuospat = Visuospatial, Exec Attn = Executive Attention.

*BCS-No Adj Rx > BCS-Chemo + Tam, $p < .05$.

**BCS-No Adj Rx > BCS-Chemo + Tamox, Non-BCS Subjects $p < .05$.
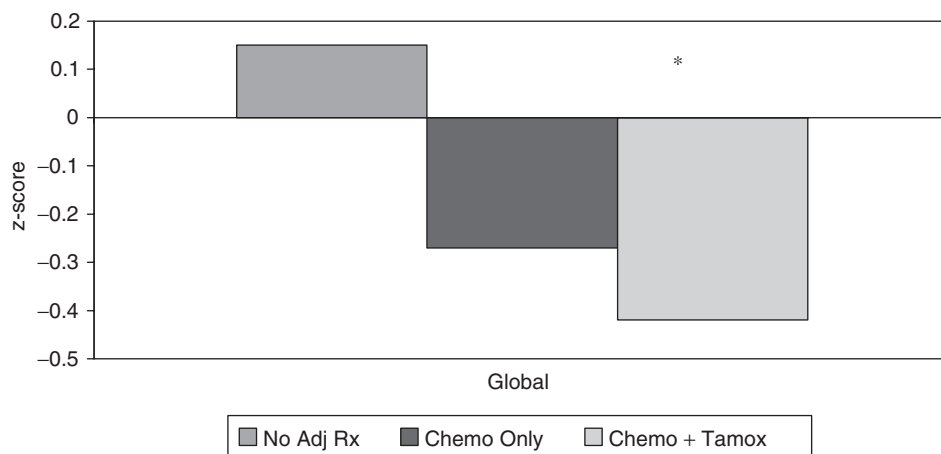
$ Non-BCS Subjects > BCS-Chemo, $p < .01$.

Fig. 4. General Neurocognitive Performance Score, relative to non-BCS comparison subjects, of three BCS groups (No Chemo, Chemo Only, Chemo + Tamoxifen).
No Adj Rx = BCS not exposed to adjuvant treatment; Chemo Only = BCS exposed to chemotherapy only; Chemo + Tamox = BCS exposed to both adjuvant chemotherapy and tamoxifen. Z-score of 0 is equivalent to performance of non-BCS controls.
*BCS-No Adj Rx > BCS-Chemo + Tamox ($p < .05$).

Chemotherapy performed significantly worse than non-BCS controls in the domain of Verbal Fluency (p = .001) and showed trends towards lower performance than those BCS who did not receive adjuvant therapy in the domains of Visual Memory (p = .06), Verbal Fluency (p = .06) and Visuospatial functioning (p = .07). Finally, as noted in the 3 group MANOVA, those BCS who did not receive adjuvant therapy performed better than non-BCS controls in the Verbal Learning domain (p = .04).

Those BCS who received both adjuvant chemotherapy and tamoxifen scored significantly lower (p = .02) on the Global Neurocognitve Performance measure than did BCS who did not receive adjuvant therapy (see Figure 4); otherwise, there were no other group differences.

Relationship between Objective and Subjective Cognitive Performance among BCS
Correlational analyses between the eight cognitive domain scores and total score on the CFQ are shown in Table 5. Correlation coefficients were generally small and non-significant, with the exception of an isolated positive correlation between CFQ score and Visuospatial performance ($r = .33$, $p < .05$), suggesting that BCS with more

prominent cognitive complaints actually show better performance on the tasks comprising the Visuospatial domain. In contrast, scores on the Beck Depression Inventory and Spielberger Trait Anxiety Inventory were positively correlated with CFQ total score ($rs = .44$ and $.42$, respectively, both $ps < .01$). Similarly, scores on the energy/fatigue subscale of the MOS SF-36 were negatively correlated with CFQ score, such that women who reported lower levels of energy also reported more cognitive complaints. Univariate correlations within the total sample (BCS and controls) yielded no significant correlations between self-reported mood or fatigue and objective neurocognitive performance among the total sample of BCS and non-BCS controls.

DISCUSSION

The current study shows that BCS exposed to chemotherapy as part of their adjuvant treatment regimen experience cognitive compromise relative to those BCS not exposed to such treatment. These group differences cannot be attributed to demographic factors, self-reported mood, or fatigue level at time of testing, and are consistent

Table 5. Correlation between self-reported cognitive Failures, Neurocognitive domain scores, mood, and Fatigue, among breast cancer survivors.

	CFQ	BDI	SAI	TAI	Fatigue
CFQ	--	.44**	.26	**.42***	**-.39***
Verbal Fluency	.15	.04	.12	.05	-.06
Verbal Memory	-.10	.03	-.07	.09	-.17
Verbal Learning	.03	.04	-.01	.05	-.06
Visual Memory	.10	-.13	**-.28***	-.20	-.09
Visuospatial	**.33***	.10	-.01	.06	-.24
Reaction Time	.08	.05	-.23	-.03	-.03
Psychomotor Speed	.03	-.10	-.04	-.11	.17
Executive Attention	.12	.16	-.01	.23	-.25

Note: For all correlational analyses (n = 72). BDI = Beck Depression Inventory, SAI = State Anxiety Inventory, TAI = Trait Anxiety Inventory, Fatigue = RAND SF-36 Fatigue/Energy Scale. *$p < .05$, **$p < .01$.

with those of other groups who have reported that chemotherapy adversely impacts cognition (Ahles et al., 2002; Brezden et al., 2000; Schagen et al., 1999; van Dam et al., 1998; Weineke & Dienst, 1995). In the current study, the domains most impacted by adjuvant systemic therapy were Visual Memory, Visuospatial Function and Verbal Learning, with moderate to large effect sizes noted for comparisons between BCS who were and those who were not exposed to adjuvant treatment. These findings are similar to those reported by two early Dutch studies of BCS (Schagen et al., 1999; van Dam et al., 1998) who found that, among their BCS sample, both verbal and non-verbal aspects of memory and visuospatial function were impacted. However, in spite of intentionally using very similar measures, we did not find prominent slowing of processing speed or reaction time among our BCS exposed to chemotherapy, as reported by Ahles and colleagues (2002) and van Dam et al. (1998).

An important finding of the current study that illustrates the potential importance of including non-cancer comparison subjects is that those BCS who received no adjuvant therapy (i.e. local therapy only) actually appeared to perform as well as, and in some cases, better than demographically matched healthy controls. While it can be argued that ours is a highly selected sample of BCS, our non-cancer comparison group was comprised of women in good health, free of psychiatric disturbance, and of similar educational and occupational attainment. We've recently speculated about the elevated life-time estrogen exposure among BCS in general and its potentially neuroprotective role that warrants further scrutiny (Ganz, Castellon, & Silverman, 2002). While such a suggestion clearly goes well beyond our current data, it is provocative given the statistically **better** Verbal Learning performance (comprised of CVLT variables) of those BCS who did not get adjuvant therapy relative to non-BCS controls. There is a well-documented relationship between estrogen levels and verbal learning and memory (e.g. see Sherwin, 1997, 1999) and others have reported an association between non-protein-bound estradiol concentrations — which are likely to be higher among those "at-risk" for breast cancer — and cognitive performance (Yaffe et al., 2000).

In an exploratory analysis, we found that those BCS who received chemotherapy and tamoxifen as systemic adjuvant therapy had a greater risk of cognitive compromise. They showed the lowest group means on five of the eight cognitive domains and, not surprisingly, scored lower on the Global Neurocognitive Performance measure than those BCS who received only local therapy. These findings are consistent with those of van Dam and colleagues (1998) who noted greater neurocognitive compromise among their BCS who had received adjuvant therapy (all had been exposed to both chemotherapy and tamoxifen) relative to those BCS who received no adjuvant therapy. However, these investigators did not include a group of BCS who received chemotherapy only in their study, making it difficult to determine

the degree to which each may have contributed independently or synergistically to cognitive compromise. We were unable to recruit sufficient numbers of a fourth group of BCS, those who received only adjuvant tamoxifen (and no chemotherapy); this group's performance would greatly inform the extent to which tamoxifen alone might contribute to cognitive compromise among BCS. Our preliminary findings suggest that the relationship between tamoxifen and cognitive performance warrants further study. For example, our findings differ dramatically from those offered in a recent paper by Ernst et al. (2002). These investigators speculated that tamoxifen might be neuroprotective in elderly BCS, based largely on proton magnetic resonance spectroscopy findings of lower levels of myo-inositol (a non-specific indicator of glial metabolism, a putative marker of cerebral toxicity) in subcortical brain regions. It is quite likely that the different levels of analysis of the two studies (behavioral vs. neurochemical/physiological) and the very different ages of the groups under study (Ernst's BCS were, on average more than 20 years older than our BCS) contributed to the differences in the findings from these two studies. Given the large number of breast cancer patients who have taken, are currently taking, or will someday take tamoxifen, it is crucial to better understand the potential late effects of this important component of adjuvant therapy regimens. However, it should be noted that all of these studies are cross-sectional and observational, and only data from randomized, prospective controlled trials can specifically address the question of how tamoxifen and other selective estrogen receptor modulators might affect neurocognitive functioning.

A particularly important finding, consistent with other studies of BCS (Ahles et al., 2002; van Dam et al., 1998) is that self-reported cognitive complaints were not related to objective performance on neurocognitive tasks. Poor cognitive performance was significantly correlated with self-reported mood disturbance (both depression and anxiety) as well as self-reported fatigue, similar to results reported among Dutch BCS by the van Dam group. This dissociation between perceived and actual performance has been documented in many other populations as well, including HIV/

AIDS, epilepsy, and mild head injury (Cull et al., 1996; Hinkin et al., 1996; Rourke, Halman, & Bassel, 1999; Vermeulen, Aldenkamp, & Alpherts, 1993). It may be that the types of real-world cognitive problems sampled on the CFQ (or other measures of self-reported cognitive efficiency) are not well captured by neurocognitive testing batteries. Alternatively, the cross-sectional nature of the studies examining subjective and objective cognitive performance may obscure the relationship between some degree of perceived and meaningful deterioration in cognitive efficiency. With no premorbid reference point with which to measure current point-in-time performance against, it is likely that a subset of women scoring well within normal limits have nonetheless experienced some degree of cognitive disruption. This may be particularly an issue for highly educated, professional women, who are often diagnosed with breast cancer. It will require prospective studies to better understand the reason(s) for the seeming lack of relationship between subjective complaints and objective cognitive performance, an issue that is intimately related to the real-world significance of the sometimes-subtle differences in cognitive performance between BCS.

Several limitations of the current study warrant discussion. First, the sample sizes of each of the groups in the current investigation are relatively small. This, in combination with the cross-sectional nature of the study, should encourage caution in discussing potential mechanisms of cognitive disruption. Pre- and post-treatment, longitudinal designs are clearly a needed next step in helping disentangle the impact and relative contribution of various adjuvant treatment modalities (e.g. chemotherapy alone, chemotherapy plus hormonal therapy, etc.). Also, while we've shown in this study that self-reported fatigue, depression, and anxiety are not driving the group differences in cognitive performance, we specifically excluded participants with evidence of current psychiatric disturbance. For this reason, it should not be concluded that prominent emotional or energy level disturbance (both of which are not atypical among a subset of BCS; Bower et al., 2000) cannot serve as the mechanism driving cognitive disruption in BCS exposed to adjuvant therapy. Finally, we wish to make clear that the term "compromise"

used throughout this article should be interpreted cautiously. For example, non-cancer control group performed significantly better than the BCS treatment group on only one of the eight cognitive domains (fluency). While moderate effect sizes (that did not reach statistical significance) were observed for some of the comparisons between non-cancer controls and BCS exposed to adjuvant therapy, cognitive compromise among these BCS was generally fairly mild in nature.

While verbal learning, visual memory, and visuospatial functioning were most impacted among the BCS exposed to adjuvant therapy in our study, the generally small sample sizes of the studies comprising the extant literature and the relative demographic heterogeneity of these samples prevent us from concluding much about a *neuropsychological profile* of BCS exposed to chemotherapy. Our study confirms and supports the growing body of literature that demonstrates that a subset of breast cancer survivors show meaningful deficits on psychometric testing, but that this subset generally does not overlap with those who complain of cognitive problems. Our results further raise the possibility that adjuvant tamoxifen may have subtle but lasting cognitive effects in these survivors. Ongoing studies in our laboratory are examining the stability of the neurocognitive changes in these women over time, as well as whether there are differences in brain metabolism and immune function across the study groups.

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REFERENCES

Ahles, T. A., & Saykin, A. J. (2001).Cognitive effects of standard-dose chemotherapy in patients with cancer. *Cancer Investigation, 19*, 821–820.

Ahles, T. A., Saykin, A. J., Furstenberg, C. T., Cole, B., Mott, L. A., Skalla, K., et al. (2002). Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. *Journal of Clinical Oncology, 20*, 485–493.

Arpels, J. C. (1996). The female brain hypoestrogenic continuum from premenopausal syndrome to menopause. *Journal of Reproductive Medicine, 41*, 633–639.

Asthana, S., Baker, L. D., Craft, S., Stanczyk, F. Z., Veith, R. C., Raskind, M. A., et al. (2001). High-dose estradiol improves cognition for women with AD: Results of a randomized study. *Neurology, 57*, 605–612.

Beck, A. T. et al. (1996). *Beck Depression Inventory, 2nd Edition.* San Antonio, TX: Psychological Assessment Resources.

Blair, J. R., & Spreen, O. (1989).Predicting premorbid IQ: A revision of the National Adult Reading Test. *The Clinical Neuropsychologist, 3*, 129–136.

Bower, J. E., Ganz, P. A., Aziz, N., & Fahey, J. L. (2002).Fatigue and proinflammatory cytokine activity in breast cancer survivors. *Psychosomatic Medicine, 64,* 604–611.

Bower, J. E., Ganz, P. A., Desmond, K. A., Rowland, J. H., Meyerowitz, B. E., & Belin, T. R. (2000). Fatigue in breast cancer survivors: Occurrence, correlates, and impact on quality of life. *Journal of Clinical Oncology, 18*, 743–753.

Brezden, C. B., Phillips, K. A., Abdolell, M., Bunston, T., & Tannock, I. F. (2000).Cognitive function in breast cancer patients receiving adjuvant chemotherapy. *Journal of Clinical Oncology, 18*, 2695–2701.

Broadbent, D. E., Cooper, P. F., Fitzgerald, P., & Parkes, K. R. (1982).The Cognitive Failures Questionnaire and its correlates. *British Journal of Clinical Psychology, 21*, 1–16.

Castellon, S. A. & Ganz, P. A. (2001).Cognitive function following adjuvant therapy for breast cancer. *Oncology, 15,* 622–624

Chelebowski, R. T. (2000).Reducing the risk of breast cancer. *New England Journal of Medicine, 343*, 191–198.

Cull, A., Hay, C., Love, S. B., Mackie, M., Smets, E., & Stewart, M. (1996).*What do patients mean when they complain of concentration and memory problems? British Journal of Cancer, 74*, 1674–1679.

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. (1987).*California Verbal Learning Test: Adult Version Manual.* San Antonio, TX, The Psychological Corporation.

Ernst T., Chang L., Cooray D., Salvador C., Jovicich J., Walot I., et al. (2002).The effects of tamoxifen and estrogen on brain metabolism in elderly women. *Journal of the National Cancer Institute, 94,* 592–597

Fisher B., Costantino J. P., Wickerham D. L., Redmond C. K., Kavanah M., Cronin W. M., et al. (1998)

Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study *Journal of the National Cancer Institute 90*, 1371–1388.

Ganz, P. A. (1998). Cognitive dysfunction following adjuvant treatment of breast cancer: A new dose-limiting toxic effect?. *Journal of the National Cancer Institute, 90*, 182–183.

Ganz, P. A., Castellon, S. A., & Silverman, D. (2002). Estrogen, tamoxifen, and the brain. *Journal of the National Cancer Institute, 94*, 547–549.

Ganz, P. A., Desmond, K. A., Leedham, B., Rowland, J. H., Meyerowitz, B. E., & Belin, T. R. (2002). Quality of life in long-term, disease-free survivors of breast cancer: A follow-up study. *Journal of the National Cancer Institute, 94*, 39–49.

Grodstein, F., Chen, J., Pollen, D. A., Albert, M. S., Wilson, R. S., Folstein, M. F., et al. (2000). Post-menopausal hormone therapy and cognitive function in healthy older women. *Journal of the American Geriatrics Society, 48*, 746–752.

Gronwell, D. M. A. (1977). Paced auditory serial-addition task: A measure of recovery from concussion. *Perceptual and Motor Skills, 44*, 367–373.

Hinkin, C. H., vanGorp, W. G., Satz, P., Marcotte, T., Durvasula, R. S., Wood, S., et al. (1996). Actual versus self-reported cognitive dysfunction in HIV-1 infeciton: Memory-metamemory dissociations. *Journal of Clinical and Experimental Neuropsychology, 18*, 431–443.

Jemal, A., Murray, T., Samuels, A., Ghafoor, A., Ward, E., & Thun, M. J. (2003). Cancer Statistics, 2003. *CA Cancer J Clin, 53*, 5–26.

Lezak, M. D. (1995). *Neuropsychological Assessment, 3rd Edition.* New York: Oxford University Press.

Mahoney, A. M., Dalby, J. T., & King, M. C. (1998). Cognitive failures and stress. *Psychological Reports, 82*, 1432–1434.

Maki P. M. & Resnick S.M. (2000). Longitudinal effects of estrogen replacement therapy on PET cerebral blood flow and cognition. *Neurobiol Aging 21*, 373–383.

McKinney, M., Blake, H., Treece, K. A., Lincoln, N. B., Playford, E. D., & Gladman, J. R. F. (2002). Evaluation of cognitive assessment in stroke rehabilitation. *Clinical Rehabilitation, 16*, 129–136.

Meyers, C. (2000). Neurocognitive dysfunction in cancer patients. *Oncology, 14*, 75–79.

Meyers, J. & Meyers, K. (1995). Rey-Complex Figure Test under four different administration procedures. *The Clinical Neuropsychologist, 9*, 63–67.

Miller, E. N., Satz, P., & Visscher, B. (1991). Computerized and conventional neuropsychological assessment of HIV-1 infected homosexual men. *Neurology, 41*, 1608–1616.

Mitrushina, M. N., Boone, K. B., & D'Elia, L. F. (1999). *Handbook of normative data for neuropsychological assessment.* New York: Oxford University Press.

National Institutes of Health Consensus Development Conference (2001) Statement: Adjuvant therapy for breast cancer, November 1–3, 2000. *Journal of the National Cancer Institute, 93*, 979–989.

Osterrieth, P. A. (1944). Le test de copie d' une figure complex: Contribution a l'etude de la perception et de la memoire [The Complex Figure Copy Test]. *Archives de Psychologie, 30*, 286–356.

Paganini-Hill, A., & Clark, L. J. (2000). Preliminary assessment of cognitive function in breast cancer patients treated with tamoxifen. *Breast Cancer Research and Treatment, 64*, 165–176.

Pakilit, A. T., Kahn, B. A., Petersen, L., Abraham, L. S., Greendale, G. A., & Ganz, P. A. (2001). Making effective use of tumor registries for cancer survivorship research. *Cancer, 92*, 1305–1314.

Reitan, R., & Wolfson, D. (1985). *The Halstead-Reitan Neuropsychological Test Battery.* Tuscon, AZ: Neuropsychology Press.

Rey, A. (1942). L'examen psychologique dans les cas d' encephalopathie traumatique [The psychological examination in cases of traumatic brain injury]. *Archives de Psychologie, 28*, 286–340.

Rourke, S. B., Halman, M. H., & Bassel, C. (1999). Neurocognitive complaints in HIV-infection and their relationship to depressive symptoms and neuropsychological functioning. *Journal of Clinical & Experimental Neuropsychology. 21*, 737–756.

Schagen, S. B., vanDam, F. S., Muller, M. J., Boogerd, W., Lindeboom, J., & Bruning, P. F. (1999). Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. *Cancer, 85*, 640–650.

Shaywitz S. E., Shaywitz B. A., Pugh K. R., Fulbright R. K., Skudlarski P., Mencl W. E., et al (1999). Effect of estrogen on brain activation patterns in postmenopausal women during working memory tasks. *JAMA, 281*, 1197–1202.

Sherwin, B. B. (1997). Estrogen effects on cognition in menopausal women. *Neurology, 7*, 21–26.

Sherwin, B. B. (1999). Can estrogen keep you smart? Evidence from clinical studies. *Journal of Psychiatry and Neuroscience, 24*, 315–321.

Spielberger, C. D., Gorsuch, R. L., & Lushene, R. G. (1971). *Manual for the State-Trait Anxiety Inventory.* Palo Alto, CA, Consulting Press.

SPSS, Inc. (1997). *Statistical Package for the Social Sciences, Version 8.0.* Chicago, SPSS Incorporated.

Sumner B. E., Grant, K. E., Rosie, R., Hegele-Hartung, C., Fritzemeir, K. H., & Fink, G. (1999). Effects of tamoxifen on serotonin transporter and 5-hydroxytryptamine (2A) receptor binding sites and mRNA

levels in the brain of ovariectomized rats with or without acute estradiol replacement. *Brain Research Molecular Brain Research, 73*,119–128

van Dam, F. S., Schagen, S. B., Muller, M. J, Boogerd, W., v.d Wall, E., Droogleever Fortuyn, M. E., et al. (1998). Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: High-dose versus standard-dose chemotherapy. *Journal of the National Cancer Institute, 90*, 210–218.

Vermeulen, J., Aldenkamp, A. P., & Alpherts, W. C. (1993).Memory complaints in epilepsy: correlations with cognitive performance and neuroticism. *Epilepsy Research, 15*, 157–170.

Wang, P. N., Liao, S. Q., Liu, R. S., Liu, C. Y., Chao, H. T., Lu, S. R., et al. (2000). Effects of estrogen on cognition, mood, and cerebral blood flow in AD: A controlled study. *Neurology, 54*, 2061–2066.

Ware, J. E. & Sherbourne, C. D. (1992).A 36-item Short Form Health Survey (SF-36): I. Conceptual framework and item selection. *Medical Care, 30*, 473–483.

Wechsler, D. (1987).*Wechsler Memory Scale – Revised (WMS-R).* San Antonio, TX: The Psychological Corporation.

Wechsler, D. (1997).*Wechsler Adult Intelligence Scale – 3rd Edition (WAIS-III).* San Antonio, TX: The Psychological Corporation.

Wieneke, M. H., & Dienst, E. R. (1995).Neuropsychological assessment of cognitive functioning following chemotherapy for breast cancer. *Psychooncology, 4*, 61–66.

Yaffe, K., Lui, L. Y., Grady, D., & Beck, A. T. (2000). Cognitive decline in women in relation to non-protein-bound oestradiol concentrations. *Lancet, 356*, 708.