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Cognitive Functioning in Breast Cancer Survivors: A Controlled Comparison

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Abstract

Purpose—To determine whether neuropsychological functioning differs in breast cancer survivors six months after completion of adjuvant treatment as compared to women without cancer.

Methods—Participants were 187 women diagnosed with ductal carcinoma in situ (DCIS), Stage I, or Stage II breast cancer and 187 age- and geographic- matched women without cancer. Of survivors, 97 had been treated post-surgery with chemotherapy only or chemotherapy plus radiotherapy and 90 had been treated post-surgery with radiotherapy only.

Results—Small but statistically significant differences in cognitive functioning and cognitive impairment were observed in survivors treated with chemotherapy and their matched controls and also in survivors treated with radiotherapy only and their matched controls. No group differences were observed in cognitive complaints.

Conclusion—Data from the current study suggest that cognitive deficits are subtle and likely due to the general effects of cancer diagnosis and treatment rather than systemic treatment.

Keywords

cognition; neuropsychological tests; adjuvant chemotherapy; adjuvant radiotherapy; breast neoplasms

Anecdotal reports of “chemo brain,” or a loss of mental acuity associated with chemotherapy, are well-publicized among breast cancer survivors[1, 2] and are a source of significant concern.[3] Although self-reported cognitive complaints are not highly correlated with objective neuropsychological test results,[4–6] research indicates that survivors’ concerns are merited. Cognitive deficits appear to be pronounced during treatment. Cross-sectional data indicate rates of moderate or severe impairment ranging from 16–48% in patients during chemotherapy as compared to 4–11% in healthy controls.[7, 8] Moreover, longitudinal studies indicate that cognitive functioning tends to decline during treatment.[6, 9]

The extent to which cognitive deficits persist following treatment is less clear. Among breast cancer survivors 3 to 18 months post-chemotherapy, Weineke and colleagues[10] determined that 75% scored at least two standard deviations below population norms on one or more

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Participants signed informed consent.

tests. Using a longitudinal design, Fan and colleagues11 assessed breast cancer survivors during chemotherapy, one year later, and two years later as compared to non-cancer controls. Significantly more survivors displayed moderate to severe cognitive impairment at both follow-up assessment points than controls. Silverman and colleagues12 examined breast cancer survivors five to ten years after treatment using positron emission tomography (PET) and found altered frontocortical activation in those treated with chemotherapy as compared to those not treated with chemotherapy.

In contrast, results from other studies suggest that the cognitive sequelae of chemotherapy may be transient. Schagen and colleagues13 found that survivors' cognitive functioning improved from two years to four years post-chemotherapy, with survivors performing similarly to controls at four years. Jenkins and colleagues14 examined cognitive functioning in breast cancer patients receiving chemotherapy, patients receiving radiation, and non-cancer controls prior to treatment, 6 months post-treatment, and 18 months post-treatment. They found no differences between groups over time. Finally, we previously reported no differences in cognitive functioning at six months post-treatment between survivors treated with chemotherapy and radiotherapy as compared to survivors treated with radiotherapy only.15

Building on our previous report,15 we now present comparisons between breast cancer survivors assessed six months following treatment completion and age- and geographically-matched female non-cancer controls. The present report includes a larger set of patients than included in our previous report and also includes non-patient comparison data not reported previously. We hypothesized that survivors treated with chemotherapy would display lower mean-level cognitive functioning, higher rates of cognitive impairment, and greater cognitive complaints than their matched controls. To examine whether hypothesized differences were due to systemic treatment versus the general effects of cancer, we also examined cognitive functioning, cognitive impairment, and cognitive complaints in breast cancer survivors treated with radiotherapy only as compared to their matched controls.

Materials and Methods

Participant Eligibility and Recruitment

Breast Cancer Survivors—As part of a larger, IRB-approved study examining quality of life during and after breast cancer treatment, women diagnosed with ductal carcinoma in situ (DCIS) or Stage I or II breast cancer were recruited at the H. Lee Moffitt Cancer Center (HLMCC) at the University of South Florida and the Markey Cancer Center (MCC) at the University of Kentucky. Additional eligibility criteria were that participants: 1) be at least 18 years of age; 2) have no documented or observable psychiatric or neurological disorders that would interfere with study participation (e.g., dementia or psychosis); 3) be able to speak and read standard English; 4) have no history of cancer other than basal cell skin carcinoma; 6) have been treated surgically with lumpectomy or mastectomy; 7) be scheduled to receive a minimum of four cycles of chemotherapy and then radiotherapy (CT + RT group), a minimum of four cycles of chemotherapy only (CT group), or radiotherapy only following surgery (RT group); 8) have no prior history of treatment with either chemotherapy or radiotherapy; 9) have no other chronic or life-threatening diseases in which fatigue is a prominent symptom (e.g., multiple sclerosis); and 10) provide written informed consent.

Eligibility was determined by chart review and consultation with the attending physician. Eligible women were recruited and informed consent obtained during an outpatient clinic visit prior to the start of chemotherapy (CT + RT group, CT group) or radiotherapy (RT group). Approximately six months after completing radiotherapy (CT + RT group, RT

group) or chemotherapy (CT group), survivors were scheduled for an outpatient appointment at which data relevant to the current report were collected.

Non-Cancer Controls—Eligibility criteria for non-cancer controls were that they must: 1) be women within five years of the age of the patient to whom they were being matched; 2) reside in the same zip code as the patient to whom they were being matched; 3) have no discernable psychiatric or neurological disorders that would interfere with study participation; 4) be able to read and speak standard English; 5) report no history of cancer other than basal cell skin carcinoma; 6) report no chronic or life threatening diseases in which fatigue is a prominent symptom; and 7) provide written informed consent.

Potential control participants were identified using a database maintained by Marketing Systems Group, Inc. (Fort Washington, PA) that draws from all listed telephone households in the United States and is estimated to include demographic and contact information for approximately two-thirds of the U.S. population. For each survivor, a list was generated of 25 randomly selected females who resided in the same zip code as the survivor and were within five years of the survivor's age. An individual was selected at random from each list and a letter of introduction was sent out describing the study. If this individual did not opt out by calling a toll-free telephone number (HLMCC) or did return a postcard expressing interest (MCC), telephone contact was initiated to further determine eligibility. If the individual met all eligibility criteria and agreed to participate, an appointment was set up to obtain written informed consent and conduct the assessment. If the first individual on the list could not be reached, was ineligible, declined, or did not keep the appointment, another individual on the list was randomly selected and approached. This process continued until a matched comparison subject was recruited and completed the assessment that is the focus of this report.

Measures

Demographic and Clinical Data—Demographic data were obtained from all participants via a self-report measure. Survivor disease and treatment information was collected via medical chart review.

Cognitive Performance—Cognitive performance was assessed using a battery of neuropsychological tests that were selected based on a review of published literature at the time of study design.[5, 10, 16, 17] Preference was given to tests with demonstrated reliability, validity, and availability of published norms. The battery was designed to assess overall intellectual ability as well as three major domains of cognitive functioning: episodic memory, attention, and complex cognition.

Overall intellectual ability: The National Adult Reading Test (NART)[18] was administered to estimate overall intellectual ability. NART scores were converted to estimated WAIS-R full-scale intelligence quotient scores (FSIQ).[18]

Episodic memory: Verbal (California Verbal Learning Test; CVLT)[19] and non-verbal (Visual Reproduction subtest of the Weschler Memory Scales- III; WMS-III)[20] measures of episodic memory were administered. Scores used in analyses were CVLT immediate recall, long delay free recall, and recognition and WMS-III Visual Reproduction immediate, delayed recall, and delayed recognition.

Attention: The Digit Span subtest of the Weschler Adult Intelligence Scale – III (WAIS-III),[21] Spatial Span subtest of the WAIS-III,[21] Trails A subtest of the Trail Making Test,[22] and Ruff 2 & 7 Test[23] were administered to assess attention. Scores used in analyses were

number of items completed correctly on Digit Span and Spatial Span, total time to completion on Trails A, and total speed and total accuracy on Ruff 2 & 7.

Complex cognition: The Digit Symbol subtest of the WAIS-III,21 Trails B subtest of the Trail Making Test,22 and the Controlled Oral Word Association (COWA)24 were administered to assess complex cognition. Scores used in analyses were number of items completed on the Digit Symbol subtest, total time to completion on Trails B, and total number of words generated on the COWA.

Self-Report Measures

Cognitive Complaints: The Mental Abilities Questionnaire (MAQ)25 is a 48-item, self-report measure that assesses perceptions of cognitive functioning. Respondents rate on a five-point Likert scale (1 = almost never, 5 = almost always) how often they are able to perform a variety of everyday cognitive tasks compared to other people their age. The MAQ yields a total score and subscale scores for attention, language, verbal memory, visual-spatial memory, and visual-spatial perception. Cronbach's alpha in the current sample was . 93 for the total score and ranged from .72 to .79 for the subscales.

Fatigue: The Fatigue Symptom Inventory (FSI)26 is a 14-item measure that assesses the frequency and severity of fatigue and its perceived disruptiveness. Analyses were conducted using average of ratings of the degree to which fatigue interfered (0 = no interference, 10= extreme interference) with daily activities, relations with others, enjoyment of life, and mood. Previous research has demonstrated the reliability and validity of the FSI in women diagnosed with breast cancer.26, 27

Depressive Symptoms: The 20-item Center for Epidemiological Studies of Depression Scale (CES-D)28 identifies current symptoms of depression. It assess six components of depressed mood: guilt or worthlessness, feelings of helplessness and hopelessness, psychomotor retardation, loss of appetite, and sleep disturbance. Previous research has demonstrated the reliability and validity of the CESD in individuals with cancer.29, 30

Statistical Analyses—Raw test scores on neuropsychological tests were converted to standardized scores based on published normative data to facilitate comparisons between tests. CVLT, Trail Making Test, and Ruff 2 & 7 Test raw scores were converted to age- and education-corrected z scores.19, 22 COWA raw scores were converted to age- and education-corrected z scores.24 WMS-III and WAIS-III subtest raw scores were converted to age-corrected z scores.20, 21

Due to the small number of survivors treated with chemotherapy only (n=14), the chemotherapy only and chemotherapy plus radiotherapy groups were combined in all analyses. Differences in age, race, education, annual household income, and overall intellectual ability (i.e., NART scores) were examined between survivors and matched controls using dependent samples t-tests and McNemar tests. Variables that differed significantly between groups ($p < .05$) were entered as covariates in later analyses.

To examine mean-level differences in cognitive functioning and cognitive complaints between survivors and controls, linear mixed models were used. To examine differences in rates of cognitive impairment, participants were categorized as impaired or unimpaired on individual tests and overall. In accordance with previous research,31 impairment on individual tests was defined as −1.5 SD below the normative mean; overall impairment was defined as two or more impaired tests. Generalized estimating equations were used to

determine significant differences in rates of impairment between survivors and controls. The study was designed to yield power of at least .80 to detect an effect size of .30 at $\alpha = .05$.

Results

Sample Characteristics

Clinical characteristics of survivors are presented in Table 1 and sociodemographic comparisons between survivors and controls are presented in Table 2. Compared to controls, survivors treated with chemotherapy were significantly younger. Survivors treated with radiotherapy only were younger and more likely to have higher estimated overall intellectual ability. These two variables were included as covariates in all later analyses.

Mean-Level Cognitive Performance

As shown in Table 3, compared to controls survivors treated with chemotherapy performed significantly worse on tests assessing episodic memory (WMS-III Visual Reproduction delayed recall) and complex cognition (Digit-Symbol, COWA). Effect sizes were small (*d*s = .19–.24) by Cohen's criteria.32 Survivors treated with radiotherapy only performed significantly worse on tests measuring attention (Trails A) and complex cognition (Trails B). These effect sizes were also small (*d*s = .29–.31).32

Post-hoc analyses were conducted to explore potential contributing factors to cognitive differences between survivors and controls. Two additional sets of mixed models analyses were conducted as described above, but with the inclusion of depressive symptoms and fatigue as additional covariates. These analyses yielded the same pattern of statistically cognitive differences between survivors and controls as shown in Table 3. Regression analyses were then conducted to compare mean-level cognitive differences between: 1) survivors treated with chemotherapy and tamoxifen and survivors treated with chemotherapy but no tamoxifen; and 2) survivors treated with radiotherapy and tamoxifen and survivors treated with radiotherapy but no tamoxifen. No significant differences were observed (*p*s > .05).

Rates of Impairment

Rates of impairment are shown in Table 4. Survivors treated with chemotherapy were more likely than controls to categorized as impaired in episodic memory (CVLT recognition). Survivors treated with radiotherapy only were more likely than controls to be categorized as impaired in attention (Trails A).

Cognitive Complaints

No significant differences were found between survivors and controls in total cognitive complaints or subscales of attention, language, verbal memory, visual-spatial memory, and visual-spatial perception (*p*s ≥ .18).

Discussion

The current study assessed reports of "chemo brain," or loss of mental acuity following chemotherapy, in breast cancer survivors six months after completion of adjuvant treatment. We hypothesized that survivors treated with chemotherapy would display worse cognitive functioning relative to age- and geographic-matched women without cancer. Findings indicate that survivors treated with chemotherapy displayed poorer episodic memory and attention than controls, although effect sizes were small. Survivors treated with chemotherapy also displayed significant greater impairment in the domain of episodic memory. To examine whether differences in cognitive functioning were due specifically to

chemotherapy as opposed to the general effects of cancer, the current study also compared a group of survivors treated with radiotherapy only to age-and geographic-matched controls. Survivors treated with radiotherapy only displayed poorer attention and complex cognition, although effect sizes were small. Survivors treated with radiotherapy only also displayed higher rates of impairment in the domain of attention. There were no differences between survivors and controls in reports of cognitive complaints.

Taken together, these findings suggest that cognitive deficits seen in breast cancer survivors are relatively subtle and are due to the general effects of cancer rather than systemic treatment per se. Follow-up analyses were conducted to examine whether fatigue or depressive symptoms accounted for observed cognitive differences between survivors and controls. The same pattern of cognitive differences emerged when fatigue and depressive symptoms were statistically controlled, suggesting that differences were not attributable to these factors. This finding is consistent with previous literature suggesting that neither fatigue nor depression is significantly associated with objective cognitive functioning. 10, 11, 13, 16 Further research is needed to determine mechanisms that play a role in post-treatment cognitive functioning, such as cancer-related distress or worry about recurrence.

Post hoc analyses were also conducted to explore whether hormonal therapy contributed to cognitive differences between survivors and controls. Survivors treated with tamoxifen did not show significant differences in cognitive functioning as compared to survivors treated without tamoxifen. Previous research is mixed regarding the effects of hormonal therapy on post-treatment cognitive functioning. Some studies have reported that hormonal therapy33, 34 increases risk of cognitive deficits, while other studies have shown no effects of hormonal therapy.5, 11, 14 Nevertheless, our findings regarding tamoxifen should be interpreted with caution. Because of small numbers of survivors in some cells, the tamoxifen analyses were likely underpowered. Additionally, survivors were not randomly assigned to treatment in the current study, and thus may be systematically different in ways that were not statistically controlled. Since hormonal treatment is typically started after the completion of adjuvant treatment, some survivors may not have been on hormonal treatment for long enough for an effect to be seen. Future research should further examine the role of hormonal therapy in cognitive deficits following breast cancer treatment.

A number of strengths characterize the current study. Women were recruited prior to the start of adjuvant treatment as part of a longitudinal study examining quality of life. This may have reduced the potential recruitment bias of studies designed specifically to assess post-treatment cognitive functioning.35 With 187 pairs of survivors and matched controls, it is one of the largest studies to date examining cognitive functioning in cancer survivors. Non-cancer controls were matched in age and geographic residence to survivors and were recruited using a large database. This is a significant advantage over survivor-nominated controls, whose performance may be biased by their relationship to the survivor. Moreover, the inclusion of survivors treated with radiotherapy only and matched controls permits examination of the specific effects of chemotherapy as compared to the general effects of cancer on cognitive functioning. The current study was not without limitations, however. Survivors were not evaluated prior to the start of adjuvant treatment, so it is unclear whether the current findings reflect an improvement, deterioration, or no change from baseline. Well-powered longitudinal studies are needed to clarify cognitive change over time in breast cancer survivors as compared to women without cancer.

In summary, data from the current study suggest that on average, women treated for breast cancer display subtle cognitive deficits relative to women without cancer. Areas of specific deficits were noted regardless of treatment type, suggesting that mechanisms other than chemotherapy may affect cognitive functioning. Future research is needed to identify these

mechanisms. In addition, rates of impairment in the current study indicate that there appear to be a subset of survivors for whom cognitive deficits are pronounced. Additional efforts to evaluate and remediate these deficits are needed.

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Table 1

Disease and treatment characteristics of survivors (n=187)

Characteristic	n
Stage	
DCIS	17
Stage I	93
Stage II	77
Adjuvant treatment	
Radiotherapy only	90
Chemotherapy only	14
Chemotherapy plus radiotherapy	83
Chemotherapy regimen	
Doxorubicin and cyclophosphamide	52
Doxorubicin, cyclophosphamide, and taxotere	13
Doxorubicin, cyclophosphamide, and paclitaxel	14
Cytoxan, methotrexate, and 5-flourouracil	11
Doxorubicin and taxotere	2
Cyclophosphamide, epirubicin, and 5-flourouracil	2
Cyclophosphamide, epirubicin, 5-flourouracil, and paclitaxel	2
Missing data	1
Hormonal therapy	
No hormonal therapy	57
Tamoxifen only	113
Tamoxifen and anastrozole	2
Tamoxifen and megestrol	1
Toremifene only	2
Anastrozole only	8
Missing data	4

Table 2

Sociodemographic comparisons between survivors treated with chemotherapy (n=97) and radiotherapy only (n=90) and matched controls

	Chemo Patients	Controls	Statistic	Radiation Patients	Controls	Statistic
Age						
Mean (SD)	50 (9)	53 (8)	11.31**	58 (9)	59 (9)	4.78**
Race/ethnicity						
Caucasian	84 (88%)	90 (93%)	1.47	86 (96%)	85 (4%)	.14
Annual Household Income						
≥$40k	68 (73%)	74 (78%)	.33	59 (73%)	65 (74%)	.15
Education						
Some college or less	47 (48%)	44 (45%)	.18	54 (60%)	48 (53%)	.90
NART						
Mean (SD)	112 (7)	110 (8)	1.27	112 (7)	109 (7)	2.13*

* $p < .05$,

** $p < .01$

Table 3

Means, Standard Errors, and Group Differences in Cognitive Functioning Between Survivors and Their Matched Controls, Controlling for Age and Overall Intellectual Functioning

	Chemo	Controls	*F* (1, 188)	Radiation	Controls	*F* (1, 174)
Episodic memory						
CVLT immediate recall	−.05 (.11)	.06 (.11)	.09	.02 (.10)	−.03 (.10)	.08
CVLT long delay free recall	−.31 (.15)	−.32 (.13)	.05	−.24 (.13)	−.38 (.13)	.12
CVLT recognition	−.26 (.14)	−.11 (.12)	.31	−.08 (.11)	−.17 (.11)	.05
WMS-III Visual Reproduction immediate recall	.15 (.11)	.01 (.09)	.30	−.11 (.11)	−.06 (.11)	1.98
WMS-III Visual Reproduction delayed recall	−.04 (.10)	.15 (.11)	3.85*	−.13 (.10)	.01 (.10)	2.46
WMS-III Visual Reproduction recognition	−.01 (.11)	.07 (.09)	.76	.09 (.11)	−.15 (.11)	.92
Attention						
WAIS-III Digit Span	.01 (.10)	.02 (.10)	.40	.08 (.11)	−.11 (.11)	.25
WAIS-III Spatial Span	.07 (.09)	.04 (.10)	.01	−.00 (.11)	−.12 (.11)	.01
Trails A	.04 (.11)	.04 (.09)	.01	−.19 (.11)	.10 (.11)	4.51*
2 & 7 Test speed	.06 (.11)	.12 (.10)	.35	−.15 (.10)	−.04 (.10)	1.57
2 & 7 Test accuracy	−.02 (.10)	.15 (.10)	2.64	−.08 (.11)	−.06 (.11)	.62
Complex cognition						
WAIS-III Digit Symbol	−.08 (.10)	.16 (.10)	4.43*	−.11 (.11)	.03 (.11)	2.65
Trails B	−.05 (.11)	.09 (.10)	2.12	−.17 (.12)	.13 (.12)	6.78**
COWA total	−.14 (.09)	.08 (.11)	3.98*	−.00 (.10)	.07 (.10)	1.23

Note: Means are unadjusted.

* $p < .05$,

** $p < .01$

Table 4

Differences in rates of cognitive impairment between breast cancer survivors versus matched controls, controlling for age and overall intellectual ability

	Chemo	Controls	*z*	Radiation	Controls	*z*
Episodic memory						
CVLT immediate recall	12 (12%)	7 (7%)	1.07	6 (7%)	5 (6%)	.19
CVLT long delay free recall	21 (22%)	15 (15%)	.65	16 (18%)	15 (17%)	.41
CVLT recognition	16 (16%)	5 (5%)	1.99*	10 (11%)	7 (8%)	.98
WMS-III Visual Reproduction immediate recall	8 (8%)	4 (4%)	1.36	10 (11%)	9 (10%)	.67
WMS-III Visual Reproduction delayed recall	8 (8%)	8 (8%)	.30	7 (8%)	7 (8%)	−.10
WMS-III Visual Reproduction recognition	10 (10%)	7 (7%)	.74	6 (7%)	6 (7%)	.44
Attention						
WAIS-III Digit Span	5 (5%)	3 (3%)	.47	4 (4%)	4 (4%)	.65
WAIS-III Spatial Span	5 (5%)	7 (7%)	−.41	8 (9%)	9 (10%)	−.03
Trails A	8 (8%)	7 (7%)	.53	13 (14%)	4 (4%)	2.16*
2 & 7 Test speed	7 (7%)	6 (6%)	.13	5 (6%)	6 (7%)	−.32
2 & 7 Test accuracy	11 (11%)	8 (8%)	.79	10 (11%)	8 (9%)	.76
Complex cognition						
WAIS-III Digit Symbol	9 (9%)	4 (4%)	1.49	8 (9%)	5 (6%)	.81
Trails B	8 (8%)	7 (7%)	.38	11 (12%)	5 (6%)	1.95
COWA total	8 (8%)	3 (3%)	1.76	4 (4%)	1 (1%)	1.14
Overall Impairment	33 (34%)	22 (23%)	1.71	27 (30%)	21 (23%)	1.67

* $p < .05$,

** $p < .01$