



Published in final edited form as:

Cancer. 2005 December 1; 104(11): 2499–2507. doi:10.1002/cncr.21482.

Cognitive Functioning after Adjuvant Chemotherapy and/or Radiotherapy for Early-Stage Breast Carcinoma

Kristine A. Donovan, Ph.D.¹, Brent J. Small, Ph.D.^{1,2}, Michael A. Andrykowski, Ph.D.³, Frederick A. Schmitt, Ph.D.⁴, Pamela Munster, M.D.⁵, and Paul B. Jacobsen, Ph.D.¹

¹ Psychosocial and Palliative Care Program, Moffitt Cancer Center and Research Institute, Tampa, Florida

² School of Aging Studies, University of South Florida, Tampa, Florida

³ Department of Behavioral Science, University of Kentucky College of Medicine, Lexington, Kentucky

⁴ Department of Neurology, University of Kentucky College of Medicine, Lexington, Kentucky

⁵ Breast Cancer Program, Moffitt Cancer Center and Research Institute, Tampa, Florida

Abstract

BACKGROUND—Evidence suggests that women diagnosed with early-stage breast carcinoma may experience cognitive problems as a consequence of adjuvant chemotherapy treatment. The present study was conducted to examine whether there are differences in cognitive performance and cognitive complaints between women treated with and without chemotherapy for TNM Stage 0 to II breast carcinoma.

METHODS—As part of a larger study on quality of life, women were recruited with newly diagnosed Stage 0 to II breast carcinoma scheduled to be treated with chemotherapy plus radiotherapy ($n = 60$) or radiotherapy only ($n = 83$). Six months after the completion of treatment, participants were administered a standard neuropsychologic battery to assess cognitive performance and a self-report measure to assess perceived cognitive problems.

RESULTS—There were no statistically significant differences between women who received chemotherapy and those who did not with regard to their average performance on tests of episodic memory, attention, complex cognition, motor performance, or language. Likewise, there were no significant differences between the treatment groups in the prevalence of impairment in each of these cognitive domains. Women who underwent chemotherapy also did not report significantly more problems with cognitive functioning than women treated without chemotherapy.

CONCLUSIONS—The findings failed to confirm previous reports suggesting adjuvant chemotherapy is associated with problems in cognitive functioning among women who receive treatment for Stage 0 to II breast carcinoma. Future research should use prospective longitudinal research designs incorporating appropriate comparison groups to further explore this issue.

Keywords

cognition; chemotherapy; stage; breast carcinoma

Each year in the U.S. approximately 200,000 women are diagnosed with breast carcinoma.¹ The majority are diagnosed in the early stages and 90% of women can expect to live 5 years or more.¹ This high rate of survivorship has promoted an ever-increasing interest in quality of

life. In particular, systematic efforts have been made to identify and then minimize longer-term side effects of treatments. Recently, there has been growing recognition that women diagnosed with early-stage breast carcinoma may experience cognitive problems as a consequence of adjuvant chemotherapy.^{2,3}

To our knowledge, eight studies to date⁴⁻¹¹ have formally investigated the relationship between cognitive functioning and the receipt of chemotherapy in women treated for early-stage breast carcinoma. In general, findings from these studies suggest women who receive adjuvant chemotherapy are likely to experience some degree of cognitive dysfunction. These women also tend to report more cognitive problems. However, methodological limitations of existing research make it difficult to conclude that these difficulties are primarily a consequence of chemotherapy administration.

In some studies, data from breast carcinoma patients have been compared with published norms⁴ or healthy females with no history of breast carcinoma.⁸ These comparisons fail to account for the possibility that the difficulties observed are due to the diagnosis of breast carcinoma and are not specific to chemotherapy administration. In those studies that have compared cognitive functioning in breast carcinoma patients treated with or without chemotherapy, the results are mixed. Three studies found breast carcinoma patients treated with chemotherapy performed poorer than breast carcinoma patients not treated with chemotherapy,^{5,6,9} whereas two studies did not.^{7,10} Limiting conclusions further, three of these studies⁵⁻⁷ included the same group of women; that is, the group of breast carcinoma patients not treated with chemotherapy were identical across the three studies published by the same research group. Most existing research includes small sample sizes,^{4-9,11} which limits the statistical power to determine true differences. With only one exception,¹¹ women with breast carcinoma have been recruited to participate in these studies only after completing treatment. Whether women who agree to participate in a study of cognitive function are more likely to demonstrate cognitive deficits and to report more cognitive complaints is not known. Finally, the timing of cognitive assessments has been far from consistent across studies, ranging from 2 weeks postchemotherapy⁴ to 10 years after diagnosis.⁹ Even within studies, participants have been assessed across a wide range of time elapsed since treatment completion.⁴⁻⁸

To address these limitations, we recruited a sample of women newly diagnosed with early-stage breast carcinoma before they began adjuvant treatment. Women were evaluated approximately 6 months after completing treatment. As in most previous studies,^{4-7,9,11} we used a standard battery of neuropsychologic measures to assess several domains of cognitive functioning. Our primary aim was to determine whether there were differences in cognitive functioning between women treated with and without chemotherapy. Based on previous research, we hypothesized that women who received chemotherapy would demonstrate poorer cognitive functioning than women who did not.

MATERIALS AND METHODS

Participants

Participants were women with TNM Stage 0 to II breast carcinoma scheduled to be treated with chemotherapy followed by radiotherapy (CT+RT group) or radiotherapy only (RT group) at the Moffitt Cancer Center at the University of South Florida or at the Comprehensive Breast Care Center of the Lucille Parker Markey Cancer Center at the University of Kentucky. Eligibility criteria were that participants: 1) be at least 18 years of age; 2) have no documented or observable psychiatric or neurologic 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; 5) be diagnosed with Stage 0, I, or II breast 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 after surgery (CT +RT group), or be scheduled to receive only radiotherapy 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., acquired immunodeficiency syndrome [AIDS], multiple sclerosis, or chronic fatigue syndrome); and 10) provide written informed consent.

Procedure

Participants were recruited as part of a larger study evaluating quality of life during and after treatment for early-stage breast carcinoma.^{12,13} Eligibility was determined by chart review and consultation with the attending physician. Eligible patients were recruited and informed consent was obtained during an outpatient clinic visit following their surgical procedure but before the initiation of chemotherapy (CT+RT group) or radiotherapy (RT group). Those women who provided informed consent completed a questionnaire assessing demographic characteristics on the day of their first clinic visit for chemotherapy (CT+RT group) or radiotherapy (RT group). All of the participants received the treatment they were scheduled to receive. Approximately 6 months after completing radiotherapy, each participant was administered a comprehensive battery of tests designed to measure cognitive abilities and they completed a self-report measure of cognitive problems.

Measures

Demographic data—Demographic data were obtained through use of a standard self-report questionnaire. Variables assessed included age, menopausal status, race/ethnicity, marital status, annual household income, and educational level.

Clinical data—Medical charts were reviewed at the completion of study participation to obtain information about disease and treatment characteristics. Variables assessed included disease stage, type of breast surgery, days from the end of radiotherapy to the neuropsychologic assessment, and current use of hormonal therapy. In addition, types of chemotherapy agents (CT+RT group) and cumulative radiation doses were recorded for both groups.

Cognitive performance—Cognitive performance was assessed using a battery of neuropsychologic tests. Tests were selected based on a review of published literature at the time of study design, including our work on cognitive functioning in patients undergoing cancer and AIDS treatment.^{14–16} The battery was designed to assess five major domains of cognitive functioning: episodic memory, attention, complex cognition, motor skill, and language. The tests were also selected based on their reliability and validity and the availability of published norms.

The National Adult Reading Test (NART)¹⁷ contains 50 irregular words that cannot be easily decoded phonetically. Previous studies have shown that performance on the NART is highly correlated with general intelligence (factor ‘g’) as measured by the Wechsler intelligence scales.¹⁸ Accordingly, NART was included to estimate overall intellectual ability and was not combined with scores from the other cognitive measures.

Episodic memory—The California Verbal Learning Test (CVLT)¹⁹ assesses immediate memory span, learning ability, encoding strategies, along with interference effects, both retroactive and proactive. The test consists of 5 learning trials of a 15-word list. After a 20-minute delay during which the participant was engaged in nonverbal tests, the participant was asked to recall the list.

The Visual Reproduction of the Wechsler Memory Scales-III (WMS-III)²⁰ assesses nonverbal memory for designs. Cards with 5 novel designs were each presented one at a time for 10 seconds. Participants were then required to draw from memory the design they were just shown. A delayed recall and recognition paradigm was administered after a 30-minute delay.

Attention—The Digit Span subtest of the Wechsler Adult Intelligence Scale-III²¹ (WAIS-III) assesses immediate verbal memory and auditory attention. The examiner reads increasingly longer series of numbers and the participant is required to repeat the digit sequences. Next, the examiner reads sequences of numbers and the participant is required to repeat them in reverse order.

The Spatial Span subtest of the WAIS-III²¹ is a visual analog to the WAIS-III Digit Span test and assesses immediate visual memory and visual attention.

The Trail Making Test²² assesses sequencing, an executive function. For Trails A the participant is required to connect targets in number order as quickly as possible. For Trails B the participant is required to alternate between number and letter targets in a speeded fashion. Trails B assesses complex cognition, while Trails A assesses attention.

Complex cognition—The Digit Symbol subtest of the WAIS-III²¹ requires participants to match numbers with a geometric symbol according to a specific key code in a speeded fashion. Adequate performance requires motor persistence, sustained attention, memory, and visuomotor coordination.

Motor—The Finger Oscillation Test²² provides a measure of motor speed. The test requires the participant to manually depress a key with their index finger as rapidly as possible. Each hand is used for 5 10-second tapping trials to obtain an average speed.

Language—Controlled Oral Word Association from the Multilingual Aphasia Examination (COWA)²³ assesses the speed and ease of word production and is a measure of executive function. Participants are required to produce words beginning with a target letter over a series of 3 1-minute trials.

Cognitive complaints—The Multiple Abilities Questionnaire (MAQ)²⁴ is a self-report measure of cognitive problems encountered in daily life. Each of the 48 items is rated on a 5-point scale for frequency of cognitive lapses or successes (1 = almost never, 5 = almost always) yielding a total score, as well as scores for 6 domains (attention, language, remote memory, verbal memory, visual-spatial memory, and visual-spatial perception). Internal consistency for the total score in this sample was relatively high (alpha = 0.91). Internal consistencies for the 6 domains ranged from 0.52 to 0.77.

Statistical Analysis

Before analysis, test scores were converted into T-scores (mean of 50 and a standard deviation [SD] of 10) that were age-corrected for the WAIS-III and WMS-III measures,^{18,20} and age- and education-corrected for the CVLT,¹⁷ Trail Making,²⁵ Finger Oscillation Test,¹⁹ and COWA.²¹ A total neuropsychologic score was created by averaging performance across all measures. The percentage of persons scoring in the impaired range for each of the tests was also computed. Consistent with our previous research on cognitive functioning in patients undergoing cancer and AIDS treatment,^{14–16} impairment was defined as performance 2 or more SDs below the relevant published norm.

Before examining performance differences between the CT+RT group and the RT group, the groups were compared on demographic and clinical characteristics using analysis of variance

(ANOVA) or chi-square tests as appropriate. Differences between the groups on cognitive test scores were compared using ANOVA. In addition to calculating statistical significance, a measure of effect size (d), which represents the group differences expressed in SD units,²⁶ was calculated for each comparison. For comparisons of the percentage within each group falling in the cognitively impaired range, chi-square analyses were computed for each outcome measure. Finally, group differences on the cognitive complaints measure were compared using ANOVA.

RESULTS

Demographic and Clinical Characteristics

In the present study, 310 women were approached and 289 participants were enrolled in the study, resulting in an initial participation rate of 93%. Eighty-one women voluntarily withdrew between completing treatment and the 6-month follow-up when neuropsychologic testing was conducted. In addition, when the final analyses were conducted 10 women had not yet reached the 6-month follow-up point. Thus, 198 women participated in the neuropsychologic assessment. Of these, 143 (72%) of those women who underwent testing contributed complete data.

To examine whether there were differences between women who participated in neuropsychologic testing ($n = 198$) and those who did not participate in neuropsychologic testing ($n = 91$), ANOVAs and chi-square tests were conducted. The results indicated that the two groups were not significantly different with regard to age ($F(1,270)$ degrees of freedom) = 0.61, $P = 0.44$), race/ethnicity ($\chi^2(4) = 4.24$, $P = 0.37$), or whether they received CT+RT or RT only ($\chi^2(1) = 3.57$, $P = 0.06$). However, women who participated in the neuropsychologic testing were more likely to have had postsecondary education as compared with women who did not participate in the neuropsychologic testing (78.9% vs. 63.4%, respectively; $\chi^2(1) = 8.03$, $P = 0.005$). There were also no statistically significant differences in demographic or clinical characteristics between the women who underwent testing and contributed complete data ($n = 143$) and those women who underwent testing but did not contribute complete data ($n = 55$).

Table 1 presents demographic characteristics for the total sample and two treatment groups. Compared with the CT+RT group, the RT group was significantly older ($F(1,142) = 12.99$, $P < 0.001$), had a higher proportion of women who were postmenopausal ($\chi^2(1) = 5.17$, $P = 0.02$), currently receiving hormone therapy ($\chi^2(1) = 11.21$, $P < 0.001$), who underwent lumpectomy only ($\chi^2(1) = 7.53$, $P = 0.006$), and were diagnosed with Stage 0 or I breast carcinoma ($\chi^2(1) = 88.17$, $P < 0.001$). There were no significant group differences with regard to years of education, race/ethnicity, premorbid intelligence quotient, cumulative doses of radiotherapy, or the number of days between the end of radiotherapy and the neuropsychologic assessment ($P > 0.05$). Because the groups were different in terms of age and hormone therapy, both of which can deleteriously affect cognitive performance, these measures were used as covariates in subsequent analyses. Chemotherapy agents received were as follows: doxorubicin and cyclophosphamide ($n = 34$, 56.7%); doxorubicin, cyclophosphamide, and taxotere ($n = 6$, 10.0%); doxorubicin, cyclophosphamide, and paclitaxel ($n = 10$, 16.7%); cyclophosphamide, methotrexate, and 5-fluorouracil ($n = 8$, 13.3%); and doxorubicin and taxotere ($n = 2$, 3.3%). The mean number of days between the completion of chemotherapy and neuropsychologic assessment was 274.8 (SD = 43.0). Finally, we examined whether there were group differences in fatigue, as measured using the Fatigue Symptom Inventory,²⁷ or depression as measured using the Center for Epidemiologic Studies Depression Scale.²⁸ In previous research, both fatigue and depression have demonstrated a potential to impact cognitive performance.^{6,10} As shown in Table 1, no statistically significant treatment group differences were observed for these variables.

Mean-Level Cognitive Performance

Table 2 presents cognitive performance for the total sample and each treatment group. In ANOVAs with age and hormone therapy status as covariates, the treatment groups were not statistically different on the total neuropsychologic score or on the measures of episodic memory performance, attention, complex cognition, motor performance (finger oscillation–dominant hand; finger oscillation–nondominant hand), and language. The effect sizes for these comparisons are listed in Table 2. In general, the group differences corresponded to, at most, small size effects (range of $d = 0.00$ to 0.29), using the conventions articulated by Cohen.²⁶

Prevalence of Cognitive Impairment

The prevalence of cognitive impairment was also compared between the two treatment groups (Table 3). In general, the prevalence of cognitive impairment was low. The highest rate observed was 8.3% for the CT+RT group on Trails B. Chi-square analysis indicated that the treatment groups exhibited comparable levels of impairment across all tasks. In the total sample, the number of impaired tests per person was relatively low (median of 0.35, $SD = 0.73$; range, 0–4) and did not differ as a function of treatment group ($F(1,141) = 0.05$, $P = 0.82$). Given the relatively high educational attainment and premorbid intelligence of our sample, we also examined the prevalence of cognitive impairment using a 1.5-SD cut-off. In this case, the verbal fluency measure (COWA) showed the greatest prevalence of impairment, with 9.1% of the total sample falling below the criterion. However, no significant ($P < 0.05$) treatment group differences were present for this measure or any of the other cognitive test scores. Therefore, to maintain comparability with past research^{14–16} we decided to maintain the 2 SD criterion for cognitive impairment.

Cognitive Complaints

The final set of analyses examined whether there were differences in mean ratings across the treatment groups for overall cognitive complaints and for specific domains of functioning (Table 4). ANOVAs, with age and current hormone status as covariates, indicated no statistically significant group differences for the total score or any domain score. The average rating for the sample as a whole of how often they experienced cognitive problems in each of the domains was 4, corresponding to ‘frequently.’

DISCUSSION

The primary aim of the current study was to determine whether there were differences in cognitive functioning between women treated with and without chemotherapy for Stage 0 to II breast carcinoma. We found no statistically significant differences between women who received chemotherapy and those who did not with regard to their performance on tests of episodic memory, attention, complex cognition, motor performance, or language. Similarly, there were no differences between the treatment groups in the prevalence of impairment in each of these cognitive domains. We also found women who underwent chemotherapy did not report more cognitive problems than women who did not undergo chemotherapy. Although the actual rates of cognitive impairment for our sample were low, the sample as a whole perceived cognitive problems as happening ‘frequently.’ This discrepancy between objective cognitive performance and subjective cognitive complaints is consistent with previous research.^{5–7,9,29}

These findings differ from previous research suggesting an association between receipt of chemotherapy for breast carcinoma and poorer cognitive functioning.^{5,6,9} Among previous studies, the study by Schagen et al.⁶ most closely resembles the present study. Schagen et al.⁶ compared the cognitive functioning of 39 breast carcinoma patients treated with adjuvant chemotherapy with a median of 1.9 years previously with that of 34 breast carcinoma patients

who had not received chemotherapy and had completed treatment with a median of 2.4 years previously. The demographic and clinical characteristics of the participants were similar to the characteristics of the participants in the present study. Comparisons of mean test scores revealed that the chemotherapy group scored lower than the no-chemotherapy group on 12 of 21 tests of cognitive functioning. Additional analyses focused on the prevalence of cognitive impairment, defined as a score 2 SDs below the mean of the control group on at least three tests. The researchers found that the rate of cognitive impairment was significantly higher in the chemotherapy group than in the no chemotherapy group (28% vs. 12%). When reports of cognitive problems were examined, the researchers found women treated with chemotherapy were significantly more likely to report problems with memory and concentration than women not treated with chemotherapy.

There are several plausible explanations for the different findings between Schagen et al.⁶ and the present study. Perhaps the lack of significant differences between the CT+RT and RT groups in the current study reflects a lack of statistical power. Although to our knowledge the sample size of the current study was larger than most previous studies, fewer than 150 participants contributed to the analyses presented herein. Nevertheless, assuming a medium-sized effect²⁶ ($d = 0.5$) and a significance level of 0.05 two-tailed, the statistical power for our comparisons was adequate (0.83). However, the power to detect a small-sized effect ($d = 0.2$) was not found to be as good (0.21). The sample size needed to achieve a power level of 0.80 with this effect size is 788. This is many times greater than the sample sizes used in previous research.

Another plausible explanation may be that different measures to assess cognitive functioning and cognitive complaints were used. An argument against this possibility is that Schagen et al.⁶ and the current study yielded different results on some of the same measures. For example, Schagen et al.⁶ reported women who received standard dose chemotherapy performed significantly worse than the no chemotherapy group on Trails B; in the present study, there was no difference on this test. Another plausible explanation for the discrepant findings may be the timing of the cognitive assessments. In the present study, women had completed treatment approximately 6 months previously by the time they were assessed. In the study by Schagen et al.,⁶ women had completed treatment at least 6 months previously and were an average of 1.9 years posttreatment. In light of the difference in timing, the discrepant findings suggest the possibility that the impact of chemotherapy on cognitive functioning may be delayed (i.e., the impact of chemotherapy on cognitive functioning may only become apparent after an extended period of time has passed since the completion of treatment).

The use of a cross-sectional, between-subjects research design in which patients are assessed only after treatment completion is an important limitation of the present study, as well as previous studies. The possibility exists that differences between groups in cognitive functioning observed to date^{5,6,9} may reflect pre-existing or pretreatment differences. The lack of longitudinal data makes it impossible to draw conclusions about changes in cognitive functioning over time. A prospective longitudinal design in which women receiving different treatments for breast carcinoma are assessed before the start of treatment and at multiple timepoints thereafter would address this important limitation. The study by Wefel et al.,¹¹ although limited by its small sample size and the lack of comparison groups, is notable for being the first report of cognitive functioning in breast carcinoma patients to be based on such a design.

The use of a prospective longitudinal design would also assist in the identification of factors that may make some women more vulnerable to cognitive problems as a result of receiving chemotherapy. Researchers have suggested that chemotherapy may induce changes in gray or white matter, decrease metabolic activity, or alter cytokine levels in the brain.³⁰ Another factor

may be the presence of the apolipoprotein E $\epsilon 4$ (APOE $\epsilon 4$) allele. This gene has been associated with an increased risk of Alzheimer disease,³¹ neuropsychologic deficits among healthy older adults,³² and neuropsychologic deficits following an insult to the brain.³³ In a study of long-term survivors of breast carcinoma and lymphoma treated with chemotherapy, Ahles et al.³⁴ found preliminary evidence that carriers of the APOE $\epsilon 4$ allele may be more vulnerable to cognitive deficits associated with chemotherapy. Other factors may include the occurrence of chemotherapy-induced menopause. Based on research suggesting estrogen contributes to the maintenance of normal cognitive function in women,^{35,36} it would be worthwhile to investigate whether declines in estrogen levels reflected in chemotherapy-induced menopause are associated with declines in cognitive functioning in women receiving chemotherapy for Stage 0 to II breast carcinoma.

The results of the current study found no differences in cognitive functioning or cognitive problems between women treated with and without chemotherapy for Stage 0 to II breast carcinoma. These results differ from some previous studies that demonstrated an association between chemotherapy and poorer cognitive functioning. Given the limitations of existing studies, it is not yet possible to draw definitive conclusions regarding the impact of chemotherapy on cognitive functioning. Considered as a whole, the published research supports the need for adequately controlled, prospective longitudinal studies of women receiving chemotherapy for breast carcinoma. Such studies should also be designed to identify possible mechanisms that may underlie changes in cognitive functioning in these women.

Acknowledgements

Supported by Grant R01 CA82822 from the National Cancer Institute.

References

1. American Cancer Society. Cancer facts and figures 2004. Atlanta: American Cancer Society; 2004.
2. Phillips KA, Bernhard J. Adjuvant breast cancer treatment and cognitive function: current knowledge and research directions. *J Natl Cancer Inst* 2003;95:190–197. [PubMed: 12569140]
3. Morse R, Rodgers J, Verrill M, Kendell K. Neuropsychological functioning following systemic treatment in women treated for breast cancer: a review. *Eur J Cancer* 2003;39:2288–2297. [PubMed: 14556919]
4. Wieneke MH, Dienst ER. Neuropsychological assessment of cognitive functioning following chemotherapy for breast cancer. *Psychooncology* 1995;4:61–66.
5. Van Dam FS, Schagen SB, Muller MJ, et al. Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: high-dose versus standard dose chemotherapy. *J Natl Cancer Inst* 1998;90:210–218. [PubMed: 9462678]
6. Schagen SB, van Dam FS, Muller MJ, Boogerd W, Lindeboom J, Bruning PF. Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. *Cancer* 1999;85:640–650. [PubMed: 10091737]
7. Schagen SB, Muller MJ, Boogerd W, et al. Late effects of adjuvant chemotherapy on cognitive function: a follow-up study in breast cancer patients. *Ann Oncol* 2002;13:1387–1397. [PubMed: 12196364]
8. Brezden CB, Phillips K, Abdolell M, Bunston T, Tannock IF. Cognitive function in breast cancer patients receiving adjuvant chemotherapy. *J Clin Oncol* 2000;18:2695–2701. [PubMed: 10894868]
9. Ahles TA, Saykin AJ, Furstenberg CT, et al. Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. *J Clin Oncol* 2002;20:485–493. [PubMed: 11786578]
10. Servaes P, Verhagen CA, Bleijenberg G. Relations between fatigue, neuropsychological functioning, and physical activity after treatment for breast carcinoma: daily self-report and objective behavior. *Cancer* 2002;95:2017–2026. [PubMed: 12404297]

11. Wefel JS, Lenzi R, Theriault RL, Davis RN, Meyers CA. The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma. *Cancer* 2004;100:2292–2299. [PubMed: 15160331]
12. Andrykowski MA, Schmidt JM, Salsman JE, Beachman AO, Jacobsen PB. Use of a case definition approach to identify prevalence of cancer-related fatigue in women undergoing adjuvant therapy for early stage breast cancer. *J Clin Oncol* 2005;23:6613–6622. [PubMed: 16170168]
13. Donovan KA, Jacobsen PB, Andrykowski MA, et al. Course of fatigue in women receiving chemotherapy and/or radiotherapy for early stage breast cancer. *J Pain Symptom Manage* 2004;28:373–380. [PubMed: 15471655]
14. Andrykowski MA, Schmitt FA, Gregg ME, Brady MJ, Lamb DG, Henslee-Downey PJ. Neuropsychologic impairment in adult bone marrow transplant candidates. *Cancer* 1992;70:2288–2297. [PubMed: 1394058]
15. Schmitt FA, Bigley JW, McKinnis R, et al. Neuropsychological outcome of azidothymidine (AZT) in the treatment of AIDS and AIDS-related complex: a double-blind, placebo-controlled trial. *N Engl J Med* 1988;319:1573–1578. [PubMed: 3059187]
16. Schmitt, FA.; Wetherby, M.; Stern, Y. Neuropsychological aspects of HIV infection. In: Levy, R.; Berger, J., editors. *AIDS and the nervous system*. New York: Raven Press; 1996.
17. Nelson, HE. *The National Adult Reading Test (NART): test manual*. Windsor, Berks, UK: NFER-Nelson; 1982.
18. Crawford JR, Parker DM, Steward LE, et al. Prediction of WAIS IQ with the National Adult Reading Test: cross-validation and extension. *Br J Clin Psychol* 1989;28:267–273.
19. Delis, DC.; Kramer, JH.; Kaplan, E., et al. *California Verbal Learning Test: adult version*. San Antonio, TX: Psychological Corporation; 1987.
20. Wechsler, D. *Wechsler Memory Scale-III manual*. San Antonio, TX: Psychological Corporation; 1997.
21. Wechsler, D. *WAIS-III administration and scoring manual*. San Antonio, TX: Psychological Corporation; 1997.
22. Reitan, RM.; Wolfson, D. *The Halstead-Reitan Neuropsychological Test Battery: theory and clinical interpretation*. Tucson, AZ: Neuropsychology Press; 1993.
23. Benton, AL.; Hamsher, K. *Multilingual aphasia examination*. Iowa City, IA: AJA Associates; 1989.
24. Seidenberg M, Haltiner A, Taylor MA, et al. Development and validation of a multiple ability self-report questionnaire. *J Clin Exp Neuropsychol* 1994;16:93–104. [PubMed: 8150893]
25. Heaton, RK.; Grant, I.; Matthews, CG. *Comprehensive norms for an expanded Halstead-Reitan Battery: demographic correction, research findings, and clinical applications*. Odessa, FL: Psychological Assessment Resources; 1991.
26. Cohen, J. *Statistical power analysis for the behavioral sciences*. Vol. 2. Hillsdale, NJ: Lawrence Erlbaum; 1988.
27. Hann DM, Jacobsen PB, Azzarello LM, et al. Measurement of fatigue in cancer patients: development and validation of the Fatigue Symptom Inventory. *Qual Life Res* 1994;7:301–310. [PubMed: 9610214]
28. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psych Meas* 1977;1:385–401.
29. Cull A, Hay C, Love SB, Mackie M, Smets E, Stewart M. What do cancer patients mean when they complain of concentration and memory problems? *Br J Cancer* 1996;74:1674–1679. [PubMed: 8932354]
30. Tannock IF, Ahles TA, Ganz PA, van Dam FS. Cognitive impairment associated with chemotherapy for cancer: report of a workshop. *J Clin Oncol* 2004;22:2233–2239. [PubMed: 15169812]
31. Bennett DA, Wilson RS, Schneider J, et al. Apolipoprotein E epsilon4 allele, AD pathology, and the clinical expression of Alzheimer's disease. *Neurology* 2003;60:246–252. [PubMed: 12552039]
32. Small BJ, Rosnick C, Fratiglioni L, Backman L. Apolipoprotein E and cognitive performance: a meta-analysis. *Psychol Aging* 2004;19:592–600. [PubMed: 15584785]
33. Friedman G, Froom P, Sazbon L, et al. Apolipoprotein E-ε4 genotype predicts a poor outcome in survivors of traumatic brain injury. *Neurology* 1999;52:244–248. [PubMed: 9932938]

34. Ahles TA, Saykin AJ, Noll WW, et al. The relationship of APOE genotype to neuropsychological performance in long-term cancer survivors treated with standard dose chemotherapy. *Psychooncology* 2003;12:612–619. [PubMed: 12923801]
35. Bender CM, Paraska KK, Sereika SM, Ryan CM, Berga SL. Cognitive function and reproductive hormones in adjuvant therapy for breast cancer: a critical review. *J Pain Symptom Manage* 2001;21:407–424. [PubMed: 11369162]
36. Rugo HS, Ahles T. The impact of adjuvant therapy for breast cancer on cognitive function: current evidence and directions for research. *Semin Oncol* 2003;30:749–762. [PubMed: 14663776]

TABLE 1
Demographic Characteristics

No.	Total 143	CT + RT 60	RT 83	P value
Age in yrs				
Mean	55.44	52.33	57.65	< 0.001
SD	9.02	8.08	9.05	
Race/ethnicity				
% white	92.9	86.4	97.6	0.06
Yrs of education				
Mean	14.75	14.97	14.59	0.36
SD	2.40	2.46	2.36	
Estimated Intelligence (NART)				
Mean	112.43	112.28	112.54	0.83
SD	6.90	7.49	6.48	
Fatigue (FSI) ^a				
Mean	3.09	2.79	3.30	0.21
SD	2.36	2.12	2.51	
Depression (CES-D)				
Mean	8.53	7.98	8.92	0.46
SD	7.29	7.12	7.42	
Menopausal status				
% premenopausal or perimenopausal	34.1	44.8	26.3	0.02
% postmenopausal	65.9	55.2	73.8	
Current hormone therapy				
% yes	67.1	51.7	78.3	< 0.001
Surgery type				
% lumpectomy only	94.3	87.9	98.8	0.006
% mastectomy	5.7	12.1	1.2	
Disease stage				
% Stage 0 or I	62.9	18.3	95.2	< 0.001
% Stage II	37.1	81.7	4.8	
Cumulative radiation doses (cGy)				
Mean	5919.41	5842.18	5973.87	0.28
SD	693.23	655.91	717.53	
Days between completion of radiation and neuropsychologic assessment				
Mean	212.88	213.33	212.56	0.94
SD	63.10	66.07	61.36	

CT+RT: treated with chemotherapy followed by radiotherapy; RT: treated with radiotherapy only; SD: standard deviation; NART: The National Adult Reading Test; FSI: Fatigue Symptom Inventory; CES-D: Center for Epidemiologic Studies Depression Scale; cGy: centigrays.

^a Average fatigue in the past week (0 = not at all fatigued to 10 = as fatigued as I could be).

TABLE 2

Mean Level Cognitive Performance

	CT + RT	RT	F (1,138)	P value	d
No.	60	83			
Total neuropsychologic score					
Mean	50.53	49.71	0.81	0.37	0.15
SD	5.44	5.17			
Episodic memory					
CVLT					
Mean	50.21	49.74	0.29	0.59	0.05
SD	10.82	9.44			
Visual reproduction immediate recall					
Mean	51.74	48.83	3.71	0.06	0.29
SD	10.71	9.39			
Visual reproduction delayed recall					
Mean	51.17	49.31	0.66	0.42	0.19
SD	9.99	9.97			
Visual reproduction recognition					
Mean	49.64	50.33	0.06	0.81	-0.07
SD	10.83	9.46			
Attention					
Digit span					
Mean	49.95	50.03	0.10	0.76	-0.01
SD	9.88	10.20			
Spatial span					
Mean	50.57	49.74	0.02	0.89	0.08
SD	9.46	10.39			
Trails A					
Mean	50.96	49.39	0.12	0.73	0.16
SD	10.49	9.69			
Complex cognition					
Digit symbol					
Mean	50.08	50.11	0.09	0.77	0.00

	CT + RT	RT	F (1,138)	P value	d
SD	10.54	9.61			
Trails B					
Mean	50.11	50.21	0.51	0.48	-0.01
SD	10.26	9.57			
Motor (finger oscillation)					
Dominant hand					
Mean	51.43	49.23	0.21	0.27	0.22
SD	11.39	8.62			
Nondominant hand					
Mean	51.67	49.03	2.77	0.10	0.27
SD	10.82	9.13			
Language					
COWA					
Mean	48.88	50.69	0.20	0.66	-0.18
SD	10.64	9.53			

CT+RT: treated with chemotherapy followed by radiotherapy; RT: treated with radiotherapy only; F (1,138): test statistic; degrees of freedom; d: effect size; CVLT: California Verbal Learning Test; SD: standard deviation; COWA: Controlled Oral Word Association from the Multilingual Aphasia Examination. All measures were expressed in T-score metric.

TABLE 3

Percentage Impaired Cognitive Performance

	Total	CT + RT	RT	Chi-square test	P value
No.	143	60	83		
Total neuropsychologic score	0.0	0.0	0.0	—	—
Episodic memory					
CVLT	3.5	3.3	3.6	0.01	0.93
Visual reproduction-Immediate recall	1.4	0.0	2.4	1.46	0.23
Visual reproduction-Delayed recall	0.0	0.0	0.0	—	—
Visual reproduction-Recognition	2.8	3.3	2.4	0.11	0.74
Attention					
Digit span	1.4	6.7	4.8	0.23	0.64
Spatial span	2.1	0.0	3.6	2.2	0.14
Trails A	4.9	5.0	4.8	0.01	0.96
Complex cognition					
Digit symbol	5.6	1.7	1.2	0.05	0.82
Trails B	6.9	8.3	6.0	0.29	0.59
Motor (finger oscillation)					
Dominant hand	2.1	3.3	1.2	0.77	0.38
Nondominant hand	2.8	1.7	3.6	0.49	0.49
Language					
COWA	1.4	0.0	2.4	1.5	0.23

CT+RT: treated with chemotherapy followed by radiotherapy; RT: treated with radiotherapy only; CVLT: California Verbal Learning Test; COWA: Controlled Oral Word Association from the Multilingual Aphasia Examination.

TABLE 4

Cognitive Complaints^a

	Total	CT + RT	RT	F(1,130)	P value
No.	134	57	77		
Total complaints					
Mean	4.00	4.03	3.98	0.09	0.76
SD	0.43	0.41	0.45		
Language					
Mean	4.14	4.09	4.17	1.05	0.31
SD	0.51	0.51	0.51		
Visual-spatial perception					
Mean	3.90	3.97	3.85	1.19	0.28
SD	0.58	0.63	0.54		
Verbal memory					
Mean	3.83	3.86	3.81	0.00	0.99
SD	0.59	0.53	0.64		
Visual-spatial memory					
Mean	4.29	4.33	4.26	0.11	0.74
SD	0.46	0.48	0.45		
Attention					
Mean	3.94	3.96	3.92	0.31	0.58
SD	0.57	0.50	0.62		
Remote memory					
Mean	3.92	3.97	3.88	0.29	0.59
SD	0.52	0.52	0.53		

CT+RT: treated with chemotherapy followed by radiotherapy; RT: treated with radiotherapy only; F(1, 130): test statistic: degrees of freedom; SD: standard deviation.

^aResponse scale for the Multiple Abilities Questionnaire: 1 = almost never, 2 = rarely, 3 = sometimes, 4 = frequently, 5 = almost always (higher scores indicate more complaints).