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Cognitive function in breast cancer patients prior to adjuvant treatment

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Abstract

Purpose—To compare the neuropsychological functioning of breast cancer patients with invasive cancer and noninvasive cancer prior to adjuvant treatment.

Patients and Methods—Breast cancer patients (N = 132) with invasive (Stages 1–3, N = 110, age = 54.1 ± 8.1) or noninvasive (Stage 0, N = 22, age = 55.8 ± 8.0) disease completed a battery of neuropsychological and psychological instruments following surgery but prior to initiation of chemotherapy, radiation or hormonal therapy. Matched healthy controls (N = 45, age = 52.9 ± 10.0) completed the same battery of instruments. For the patients, data on menstrual status, type of surgery, time of general anesthesia, CBC and platelets, nutritional status (B12 and folate), and thyroid function were collected.

Results—Comparison of mean neuropsychological test scores revealed that all groups scored within the normal range; however, patients with Stage 1–3 cancer scored significantly lower than healthy controls on the Reaction Time domain (p = 0.005). Using a definition of lower than expected cognitive performance that corrected for misclassification error, Stage 1–3 patients were significantly (p = 0.002) more likely to be classified as having lower than expected overall cognitive performance (22%) as compared to Stage 0 patients (0%) and healthy controls (4%). No differences were observed between patients classified as having lower than expected cognitive performance compared to those classified as normal performance on measures of depression, anxiety, fatigue, menstrual status, surgery/anesthesia or any of the blood work parameters.

Conclusion—Patients with Stage 1–3 breast cancer were more likely to be classified as having lower than expected cognitive performance prior to adjuvant treatment as compared to Stage 0 patients and healthy controls, although correction for misclassification error produced a lower rate than previously reported.

Keywords

Breast cancer; Cognitive function; Psychological function; Neuropsychological testing

Introduction

Cognitive side effects of adjuvant chemotherapy for breast cancer have received increasing research attention over the last several years. Early cross-sectional studies supported the hypothesis that chemotherapy can be associated with short- and long-term cognitive changes [1-8]. Recent longitudinal studies have provided additional support for the validity of cognitive changes associated with chemotherapy [9-11], although a recent study found that very few women treated with adjuvant therapy demonstrated change in cognitive functioning [12].

Another complication in understanding the impact of chemotherapy on cognitive functioning is recent data suggesting that as many as 35% of breast cancer patients demonstrate evidence of cognitive “impairment” prior to chemotherapy [9, 13]. These data raise interesting methodological and conceptual questions. First, in most reported and ongoing studies, pretreatment assessments occur after surgery, but prior to the initiation of chemotherapy [8]. Therefore, several factors could influence performance on neuropsychological tests at this time, including psychosocial factors [depression, anxiety, and fatigue, 14-15], lingering effects of general anesthesia [16-17], or other biological effects of the disease and/or surgery [e.g., reduced hemoglobin (hgb) levels or nutritional status, 18, 19].

Second, although many breast cancer patients express concerns about post-treatment cognitive problems, there have been few reports of women self-reporting cognitive problems

prior to surgery [14]. In part, women may not notice cognitive problems because of the level of distress associated with cancer diagnosis. If they do notice cognitive problems, they may attribute them to psychological factors. Alternatively, breast cancer patients may not perceive that their cognitive abilities have changed in the period prior to and at the time of diagnosis. Given that even post-treatment cognitive changes are often described as subtle changes within the normal range [8], one wonders whether the term “impairment” is appropriate to describe neuropsychological performance in this context. Nevertheless, if cognitive performance is not at the level of populations traditionally considered impaired (e.g., patients with Alzheimer’s disease or stroke), even subtle differences in cognitive performance at diagnosis may be important for understanding post-treatment cognitive changes. In this paper, we have adopted the phrase “lower than expected cognitive performance” to describe our results.

Finally, the above considerations lead to the methodological issues of the definition used to classify people as having normal versus lower than expected cognitive performance and the appropriate control groups used for comparison. With regard to the definition, there is no universally accepted classification system for lower than expected cognitive performance, and changes in the definition can dramatically influence classification rates [20]. Further, misclassification of patients is influenced by the number of tests administered and the intercorrelations among the tests (i.e., misclassification increases with increasing numbers of tests and higher intercorrelations among the tests).

There is also debate in the field regarding the most appropriate comparison groups: norms for individual tests, matched healthy controls given the same battery of tests, administered under identical conditions as the patient group, or another patient group who experience similar levels of distress. For patients with invasive breast cancer, patients with noninvasive breast cancer (Stage 0) may be an appropriate comparison group, although this has not been studied. Ultimately, having the ability to compare patients to normative samples and locally tested comparison groups is ideal.

As part of a longitudinal study of the impact of chemotherapy on cognitive functioning, we conducted neuropsychological assessments on a cohort of breast cancer patients with invasive (Stages 1–3) or noninvasive (Stage 0) disease following surgery, but prior to the initiation of chemotherapy, radiotherapy or hormonal therapy, and on a matched cohort of healthy controls. Therefore, the purpose of this study was to compare the neuropsychological performance of breast cancer prior to beginning adjuvant therapy to the performance of healthy controls. In addition, we sought to evaluate the potential misclassification rate associated with definitions of lower than expected cognitive performance based upon the intercorrelations among the neuropsychological tests for the current sample, and identify medical and psychological factors that were related to pretreatment neuropsychological performance.

Patients and methods

Patients

Female breast cancer patients (N = 132) who agreed to participate in a longitudinal study of the cognitive impact of cancer treatments were evaluated with a standardized battery of neuropsychological and psychological tests following surgery, but prior to beginning chemotherapy, radiation therapy or hormonal therapy.

Inclusion criteria

(1) Diagnosis of noninvasive (Stage 0) or invasive (Stages 1, 2 or 3A) breast cancer; (2) First treatment with systemic chemotherapy or surgery and/or local, non-CNS radiotherapy;

(3) Between 18 and 70 years of age at time of diagnosis; (4) Fluent in English and able to read English; (5) Provided informed consent.

Exclusion criteria

(1) CNS disease; (2) Previous history of cancer (except basal cell carcinoma) or treatment with chemotherapy, CNS radiation or intrathecal therapy; (3) Neurobehavioral risk factors including history of neurological disorder (e.g., Parkinson's disease, seizure disorder, and dementia), alcohol/substance abuse or moderate to severe head trauma (loss of consciousness > 60 min or history of structural brain changes on imaging); (4) Axis I psychiatric disorder (DSM-IV) (e.g., schizophrenia, bipolar disorder, depression, and substance use disorder).

Healthy controls (N = 45) were recruited through newspaper ads. These participants were screened with the same exclusion criteria as the patients, frequency matched on age and education, and completed the same battery of tests. All methods and procedures were approved by the Institutional Review Board of Dartmouth Medical School and all participants provided written informed consent.

Neuropsychological test battery

1. *Verbal ability:* Wide Range Achievement Test-3 (Reading) [WRAT-3, 21], Vocabulary (Wechsler Abbreviated Scale of Intelligence, WASI, 22), Verbal Fluency Test [D-KEFS, 23];
2. *Verbal memory:* California Verbal Learning Test-II [24], Logical Memory I and II [Wechsler Memory Scale, Third Edition, WMS-III, 25];
3. *Visual memory:* Faces I and II [WMS-III, 25];
4. *Working memory:* Paced Auditory Serial Addition Test [PASAT, 26];
5. *Processing speed:* Trail Making Test (D-KEFS, 23), Color-Word Interference Test (D-KEFS, 23), Grooved Pegboard [27]; Digit Symbol [25];
6. *Sorting:* Sorting Test [D-KEFS, 23];
7. *Distractibility:* Continuous Performance Test [CPT, 28];
8. *Reaction time:* Continuous Performance Test [CPT, 28].
9. *Block design* [WASI, 22]

Measures of demographics, psychological function, and quality of life

Center for epidemiological study: depression [CES-D, 29, 30]—A 20-item measure of depressive symptoms. Patients are asked to rate how frequently they have experienced each symptom on a four-point scale ranging from "Rarely or none of the time" to "Most or all of the time."

Spielberger state anxiety inventory [STAI, 31]—The State measure contains 20-items which measure current level of anxiety.

Fatigue symptom inventory [FSI, 32]—A 14-item measure designed to assess the intensity, frequency and disruptiveness of fatigue experienced by cancer patients. Patients rate each item on an 11-point scale ranging from 0 (not a problem) to 10 (an extreme problem).

Multiple ability self-report questionnaire [MASQ; 33]—A 48-item self-report measure of cognitive function across five neurocognitive domains: language, visual-perceptual, verbal memory, visual memory, and attention. Patients rate how frequently they have a particular cognitive problem at the present time ("Now, compared to others my age") on a 5-point scale from "Almost Never" to "Almost Always."

Blood work—At the time of testing, a blood draw was taken and the following values obtained: white blood count (wbc), red blood count (rbc), hgb, platelets, B12, folate, and thyroid stimulating hormone (TSH).

Surgery/anesthesia data—In order to evaluate the potential impact of surgery and anesthesia on neuropsychological performance, the following data was gathered from chart review: type of surgery, whether general anesthesia was used, and time under general anesthesia.

Statistical analysis—All raw test scores were *z*-transformed based on the mean and standard deviation of the scores of the healthy control group. Group differences were examined using Analysis of Variance. Differences in rates of lower than expected cognitive performance were examined with Chi-Square tests. A $p < 0.01$ was considered statistically significant. This represents an adjustment for multiple comparisons based on an overall significance level of 0.05.

Creation of domains—To reduce the dimensionality of the cognitive test data and to decrease the chance for type I error, we adopted the approach of creating domains based on the expert opinion of the two neuropsychologists involved with the study (AJS, BCM) who were guided by the results of a factor analysis which identified the tests that shared the most variance. Specifically, principal components analysis with extraction of principal components followed by orthogonal rotation (SAS/STAT.v8, Proc Factor Varimax Rotation) was applied to 35 key neuropsychological test scores in order to identify natural groups of tests that could be used to form meaningful domain scales. The analysis suggested that 8–10 factors best characterized the domains assessed by the test battery, and tests with the highest loadings within factors were selected for inclusion into the domains. Block Design [22], was also administered, but did not load in any domain. Similarly, the vigilance scores from the CPT (number correct and number false positives) did not consistently load on any single domain. However, for completeness, these results are presented as "additional measures" in the tables.

Monte Carlo simulation—A simulation was designed to estimate the misclassification (Type I error) rate for the definition of "lower than expected cognitive performance" applied in previous research using the eight domain scores. The secondary purpose was to empirically derive a new definition of lower than expected cognitive performance that would yield a misclassification error rate among healthy controls of 5%. One hundred sample datasets containing eight-multivariate normally distributed variables (representing the eight domains) for 200 "healthy controls" were generated. The correlation matrix used for the simulation was the same as the observed correlation from our sample data to create a realistic correlation structure of the domains [Cholesky Decomposition, 34]. A commonly used definition of lower than expected cognitive performance (two domains below 1.5 standard deviations from the mean or one domain below 2.0 standard deviations from the mean) was applied to each data set and the proportion of patients classified as exhibiting lower than expected cognitive performance was computed. The average rate of lower than expected cognitive performance rate over the 100 datasets was 19.8%, considerably higher than the conventional 5% misclassification error rate. A second definition was also applied

to each of the 100 datasets, where any subject with three or more domains below 1.5 standard deviations from the mean or two or more domains below 2.0 standard deviations from the mean was classified as having lower than expected cognitive performance. This method produced an average false-positive rate of 3.6%; therefore, this definition was used in the analysis.

Results

A total of 440 breast cancer patients who were being evaluated and treated at the Norris Cotton Cancer Center or affiliated clinics were identified. Following screening, 131 were found to be ineligible based on the exclusion criteria. Of the remaining 309 patients, 152 (49%) declined to participate, primarily because of feeling overwhelmed by the diagnosis and treatment and/or feeling that there were too many appointments between surgery and beginning the next round of treatment to participate. Another 22 (14%) patients agreed to participate, but testing was not able to be scheduled prior to beginning treatment for logistic reasons and 3 (1%) patients signed consents, but then withdrew prior to completing the baseline assessment. Examination of the demographic data (Table 1) demonstrated the three groups were well matched on age, education, race, and menstrual status.

Comparison of domain and individual test scores

Table 2 displays the means and standard deviations for the domain scores (*z*-scores) and the raw scores for the individual tests, both corrected for age and education. The only significant difference to emerge after controlling for multiple comparisons was that patients with invasive cancer performed more poorly on the Reaction Time domain as compared to healthy controls ($p = 0.005$). Examination of the individual test scores in relation to the published norms revealed that patients and controls score within the normal range on all tests.

Comparison based on the lower than expected cognitive performance index

Applying the definition of lower than expected cognitive performance derived from the Monte Carlo simulation revealed that the lower than expected cognitive performance rate for healthy controls (4%) and Stage 0 patients (0%) were comparable, whereas 22% of patients with invasive cancer had lower than expected cognitive performance ($p = 0.002$). The most common domains to contribute to the classification of lower than expected cognitive performance were Verbal Ability, the memory domains (Verbal, Visual, and Working Memory), and Sorting.

Comparison of self-report measures of cognitive function, depression, anxiety, and fatigue

Comparisons of the MASQ scores revealed no group differences on the MASQ total score ($p = 0.94$) or any of the MASQ subscales (see Table 3). However, examination of the remaining self-report measures revealed that the non-invasive and invasive breast cancer patients scored significantly higher on the CES-D, State Anxiety Inventory, and the Fatigue Symptom Inventory as compared to the healthy controls; however, they did not differ from each other (Table 3). Using a CES-D cut-off score of 19 or greater, which indicates possible major depression in medical populations [35], the percentage of Stage 0 (17%) and Stages 1–3 (14%) patients scoring in the depressive range did not differ. Comparison of the Stages 1–3 breast cancer patients who scored in the lower than expected cognitive performance range to those who did not revealed no differences on any of the self-report measures (Table 4).

Correlations among self-report measures and neuropsychological scores

No significant correlations were found between any of the neuropsychological domains and the self-report measures of depression, anxiety or fatigue. Comparing patients who scored in the possibly depressed range (19 or above on the CES-D) with those in the non-depressed range revealed no significant between group differences on any of the neuropsychological domain scores.

Comparison of demographic, surgical and blood work variables by cognitive performance

t-Test and chi-square comparisons revealed that patients categorized as exhibiting lower than expected cognitive performance did not differ in age, education, menstrual status (pre-, peri-, and post-menopausal), surgery type, duration of exposure to general anesthesia, use of hormones, and blood work variables compared to those with normal performance (Table 4). There were trends for patients with lower than expected cognitive performance to have lower levels of folate ($p = 0.066$) and TSH ($p = 0.082$). However, since group means were within the normal range, these trends would require replication with larger samples before any interpretation is justified.

Discussion

Researchers examining cognitive side effects of chemotherapy have emphasized the importance of using longitudinal designs that include pretreatment neuropsychological assessments. However, in order to interpret longitudinal change, it is critical to understand whether cognitive performance is lower than expected prior to the initiation of treatment for a subgroup of breast cancer patients. Data from the current study suggest that when examining mean pretreatment performance across multiple domains of cognitive functioning, Stage 0 patients do not differ from healthy controls, and Stage 1–3 patients differ significantly from healthy controls only in the Reaction Time Domain. Importantly, despite the statistical significance, performance on the tests that make up the Reaction Time Domain are within normal limits for the Stage 1–3 patients based on published norms. Therefore, based on this analysis, one would conclude that there are minor or no pretreatment differences in neuropsychological performance between patients with invasive or noninvasive breast cancer and healthy controls. Consistent with this interpretation, there were no group differences on the self-report measure of cognitive problems, the MASQ.

Examination of the percentage of patients who fell below the cutoff of lower than expected cognitive performance is important. However, when comparing the performance of patients to normative data, there is the problem of the unknown misclassification error rate. Inclusion of the healthy control group allowed us to empirically examine the misclassification error rate. This analysis was based on the number of domains examined and the intercorrelations among the domains, and we were able to modify the definition of lower than expected cognitive performance so that the error rate of classification as impaired would be ~5% for the healthy control group. Utilizing this definition, we found that patients with Stage 0 disease did not differ from healthy controls, but that patients with Stage 1–3 breast cancer were significantly more likely to be categorized as having lower than expected cognitive performance as compared to healthy controls.

Interestingly, patients categorized as having lower than expected cognitive performance did not self-report more cognitive problems, suggesting that they have not perceived a change in cognitive abilities since the diagnosis of cancer and/or that they have developed strategies for compensating for their deficits. Lack of a relationship between subjective reports of cognitive functioning and performance on neuropsychological testing is not uncommon [2, 3, 7]; however, the most common pattern is that patients self-report higher levels of

cognitive problems relative to healthy controls that are not identified on formal testing [20]. In this study the opposite pattern was seen.

The significantly greater rate of lower than expected cognitive performance for the Stage 1–3 breast cancer patients is consistent with previous reports [20]. However, the correction for misclassification error resulted in a lower rate (22%) than has been previously reported in a similar population [35%, 20]. On one level, it could be argued that the absolute percentage is less relevant than the relative difference between patients and controls. However, in order to examine factors that differentiate between patients who exhibit lower than expected cognitive performance and those who do not prior to adjuvant treatment, it is important to have an accurate classification strategy. We provide a method for controlling for misclassification error that resulted in a more stringent definition of lower than expected cognitive performance, hence the lower rate. However, it is important to note that we are not advocating that this is the "correct" definition, since the error rate will vary depending on the specific tests administered, their sensitivity and specificity for a given classification, the number of tests, and the intercorrelations among the tests. Furthermore, a cut-off based on high specificity (95%) may attenuate sensitivity to subtle deficits.

Importantly, patients classified as having lower than expected cognitive performance did not differ from those classified as normal on measures of depression, anxiety or fatigue. Additionally, the groups did not differ on any other measured variable, including age or education, menstrual status, length of general anesthesia or blood work.

The lack of a difference in the lower than expected cognitive performance rate between Stage 0 patients and healthy controls was a somewhat unexpected, but potentially important finding. The obvious hypothesis would be that patients with Stage 0 disease were less distressed than patients with Stage 1–3 cancer; however, the data demonstrated that both patient groups reported significantly higher levels of depression, anxiety and fatigue as compared to the healthy control group and that the cancer groups did not differ from each other on any of these variables.

The pattern of results raises the question of why a larger subgroup of patients with invasive breast cancer might perform in the lower than expected range prior to treatment as compared to healthy controls and patients with noninvasive cancer. Paraneoplastic syndromes, which include cognitive symptoms, have been reported in patients diagnosed with breast cancer [36, 37]. Although these syndromes are relatively rare, they may partially explain the pattern of results seen in this study. Alternatively, cancer and development of cognitive problems may share common risk factors. A study of twins discordant for cancer found evidence that cancer is a risk factor for the development of cognitive problems after the age of 65 [38]; however, there are methodological limitations to this study [39]. Although the factors that confer risk to both the development of cancer and cognitive problems have not been identified, several potential candidates have been suggested [40]. Stimulation of proinflammatory cytokines have been linked to the development of cancer [41, 42] and neurocognitive disorders [43-45]. Similarly, DNA damage and deficiencies in DNA repair mechanisms have been related to increased risk for the development of cancer [46, 47] and neurodegenerative disorders [48, 49].

Limitations of the study include the relatively small sample size for the Stage 0 group; therefore, the difference in the rate of lower than expected cognitive performance seen between the invasive and noninvasive cancer groups requires replication with a larger sample. Additionally, we recognize that the sample size for the study was low for conducting a formal factor analysis. However, the intent was not to determine the ideal factor/domain structure for the combination of tests administered, but to guide the

neuropsychologists when deciding in which domain to include a specific test based on shared variance.

In conclusion, patients with invasive breast cancer were more likely to be categorized as exhibiting lower than expected cognitive performance based on neuropsychological testing, even after controlling for misclassification error, as compared to patients with noninvasive cancer and healthy controls. Interestingly, patients categorized as having lower than expected cognitive performance did not self-report more cognitive problems and factors such as depression, anxiety, fatigue, type of surgery, length of anesthesia, and biological markers were not associated with lower than expected cognitive performance. Future research is warranted to test whether other variables noted above, such as elevated levels of proinflammatory cytokines and/or DNA damage are related to cognitive performance in women with invasive breast cancer prior to adjuvant treatment.

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Table 1

Demographic variables

	Healthy controls (*N* = 45)	**Patient stage 0 (*N* = 22)**	**Patient stages 1–3 (*N* = 110)**	**Overall *p*-value**	**Control versus stage 0**	**Control versus stages 1–3 (*p*)**	**Stage 0 versus stages 1–3 (*p*)**
Mean age (SD)	52.9 (10)	55.4 (8)	54.2 (8.2)	0.49	0.30	0.39	0.53
Education—years (SD)	15.2 (2.1)	15.0 (2.2)	15.2 (2.5)	0.91	0.75	0.89	0.68
Percent caucasian	44 (100%)	22 (100%)	107 (98%)	0.54	–	1	1
Menstrual status—regular periods	14 (32%)	4 (18%)	28 (27%)	0.50	0.38	0.55	0.59
Breast cancer stage							
0		22 (100%)	0 (0%)				
1		0 (0%)	62 (56%)				
2		0 (0%)	37 (34%)				
3		0 (0%)	11 (10%)				

Table 2

Neuropsychological Test Scores (Mean, SD) for cancer patients and healthy controls and comparison *p*-values

	Healthy controls (*N* = 45)	Patient stage 0 (*N* = 22)	Patient stages 1–3 (*N* = 110)	Control versus stage 0	Control versus stages 1–3 (*p*)	Stage 0 versus stage 1–3 (*p*)
Verbal	−0.02 (0.6)	−0.12 (0.7)	−0.25 (0.9)	0.54	0.11	0.52
WRAT-3 reading	51.5 (2.8)	50.6 (2.5)	50.7 (3.4)	0.25	0.19	0.94
WASI vocabulary	68.3 (5.6)	65.7 (5.6)	65.7 (7.7)	0.073	0.04	0.98
Semantic fluency total score	44.4 (5.8)	46.0 (7.7)	43.3 (7.7)	0.35	0.38	0.13
Phonemic fluency total score	42.8 (10.8)	43.6 (10.0)	42.4 (11.0)	0.78	0.84	0.64
Verbal memory	−0.04 (0.7)	−0.25 (0.8)	−0.22 (0.9)	0.29	0.25	0.89
CVLT-II total score trials 1–5	55.4 (7.4)	54.1 (6.8)	54.0 (9.1)	0.48	0.36	0.97
CVLT-II long delay raw score	12.5 (2.5)	11.5 (2.2)	12.0 (2.6)	0.10	0.23	0.41
Logical memory I	47.0 (7.1)	46.6 (9.0)	46.0 (8.9)	0.81	0.50	0.80
Logical memory II	29.5 (5.3)	28.2 (8.2)	28.2 (7.4)	0.46	0.29	0.97
Visual memory	−0.05 (0.9)	−0.07 (1.0)	−0.04 (0.8)	0.92	0.94	0.86
Faces I	38.2 (4.5)	38.9 (4.7)	38.1 (4.5)	0.59	0.90	0.49
Faces II	38.3 (3.9)	37.5 (4.4)	38.5 (3.9)	0.47	0.78	0.31
Working memory	−0.02 (0.9)	−0.28 (1.0)	−0.44 (1.4)	0.31	0.09	0.65
Rao PASAT 2″ trial	36.0 (9.9)	34.5 (9.1)	34.3 (10.1)	0.57	0.34	0.92
Rao PASAT 3″ trial	49.8 (7.0)	47.5 (8.0)	46.6 (11.2)	0.26	0.09	0.72
Processing speed	−0.06 (0.6)	−0.13 (0.5)	−0.24 (0.6)	0.63	0.11	0.45
Digit symbol-coding	80.7 (13.7)	76.0 (11.1)	76.0 (14.2)	0.16	0.061	0.99
Grooved pegs time R hand	77.3 (16.8)	81.7 (16.2)	80.3 (22.0)	0.31	0.42	0.78
Grooved pegs time L hand	72.1 (13.8)	70.1 (15.8)	73.4 (15.7)	0.60	0.63	0.37
D-KEFS trails trial 1	20.8 (5.7)	19.8 (3.3)	21.7 (4.8)	0.43	0.33	0.08
D-KEFS trails trial 2	30.7 (8.1)	32.1 (8.0)	32.1 (11.0)	0.49	0.42	1.00
D-KEFS trails trial 3	30.0 (8.4)	29.1 (9.8)	31.4 (11.0)	0.69	0.44	0.36
D-KEFS trails trial 4	66.3 (23.9)	71.2 (26.2)	69.0 (21.2)	0.44	0.49	0.66
D-KEFS trails trial 5	24.3 (9.7)	23.3 (8.2)	26.4 (17.0)	0.65	0.45	0.40
D-KEFS color-word trial 1	27.4 (5.0)	27.7 (4.0)	28.3 (4.8)	0.79	0.27	0.57
D-KEFS color-word trial 2	20.5 (3.5)	20.6 (3.3)	21.2 (3.0)	0.98	0.25	0.39
D-KEFS color-word trial 3	51.6 (9.9)	55.1 (13.5)	55.2 (11.4)	0.24	0.068	0.96

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	Healthy controls (*N* = 45)	Patient stage 0 (*N* = 22)	Patient stages 1–3 (*N* = 110)	Control versus stage 0	Control versus stages 1–3 (*p*)	Stage 0 versus stage 1–3 (*p*)
Sorting	−0.07 (0.7)	−0.06 (0.7)	−0.15 (1)	0.97	0.59	0.67
D-KEFS sorting # confirmed correct sorts	9.7 (1.9)	10.1 (2.1)	9.7 (2.7)	0.44	0.89	0.45
D-KEFS sorting free sorting description	37.1 (8.1)	38.4 (9.1)	36.8 (10.5)	0.54	0.86	0.49
D-KEFS sorting recognition description	37.0 (9.0)	33.8 (8.4)	34.7 (11.3)	0.16	0.22	0.71
Distractibility	−0.02 (0.9)	−0.14 (1.1)	−0.05 (0.7)	0.66	0.82	0.68
CPT distractibility # correct	26.3 (4.7)	25.8 (5.1)	25.4 (5.8)	0.72	0.40	0.81
CPT distractibility # false positives	2.1 (4.0)	2.8 (6.1)	1.7 (2.6)	0.63	0.49	0.24
Reaction time	−0.02 (0.9)	−0.13 (1.3)	−0.56 (1.1)	0.70	0.005	0.12
CPT vigilance reaction time	41.5 (8.3)	43.6 (9.5)	46.2 (9.4)	0.38	0.005	0.25
CPT distractibility reaction time	42.5 (7.5)	42.6 (14.2)	46.4 (9.6)	0.95	0.018	0.16
Global	−0.05 (0.3)	−0.16 (0.4)	−0.25 (0.5)	0.23	0.015	0.42
Additional measures						
Block design	46.9 (13.0)	45.7 (11.4)	43.7 (13.3)	0.71	0.17	0.52
CPT vigilance # correct	29.6 (0.8)	29.6 (0.8)	29.6 (0.7)	0.91	0.79	0.96
CPT vigilance # false positives	0.43 (0.8)	0.51 (0.7)	0.43 (0.8)	0.69	1.00	0.64

Scores are adjusted for age and education

Domain scores are *z*-scores and test scores are raw scores

Table 3

Psychosocial and self-report of cognitive functioning measures for patients and healthy controls

	Control (*N* = 45)	Patient stage 0 (*N* = 22)	Patient stages 1–3 (*N* = 110)	Overall *p*-value	Control versus stage 0	Control versus stages 1–3 (*p*)	Stage 0 versus stages 1–3 (*p*)
Depression (CESD)	5.1 (3.6)	9.4 (7.7)	9.5 (7.7)	0.002	0.002	<0.001	0.99
Anxiety (STAI)	26.9 (6.5)	32.9 (12)	32.5 (11.7)	0.009	0.01	0.003	0.90
Fatigue	1.7 (1.2)	2.5 (1.5)	2.4 (1.7)	0.041	0.02	0.019	0.71
MASQ Total	85.9 (17.9)	86.9 (23.4)	85.2 (22.3)	0.94	0.85	0.86	0.76

Table 4

Demographic, psychosocial, surgical, and blood work variables by cognitive performance status (Stages 1–3 pts only)

	Lower than expected cognitive performance (*N* = 24)[a]	Normal performance (*N* = 86)	*p*-value
Age	55.8 (9.4)	53.8 (7.9)	0.28
Education	15.8 (3.2)	15.1 (2.3)	0.26
CESD Depression	10.5 (8.5)	9.1 (7.5)	0.44
STAI Anxiety	35.2 (12.5)	31.7 (11.4)	0.20
FAT Fatigue	2.3 (1.7)	2.4 (1.7)	0.87
MASQ Total	87.9 (26.5)	84.5 (21)	0.50
Menstrual status			
Regular periods	4 (17%)	24 (29%)	0.40
Irregular periods	2 (9%)	5 (6%)	
Stopped/pregnancy	0 (0%)	0 (0%)	
Begun to stop	3 (13%)	4 (5%)	
Stopped permanently	14 (61%)	49 (60%)	
Regular alcohol use	8 (33%)	46 (56%)	0.084
Smoking			
Yes	0 (0%)	9 (13%)	0.16
Previous smoker	13 (76%)	36 (52%)	
Never smoked	4 (24%)	24 (35%)	
Surgery[a]			
Lumpectomy	8 (33%)	32 (37%)	0.13
Lumpectomy + re-excision	9 (38%)	16 (19%)	
Mastectomy	2 (8%)	24 (28%)	
Mastectomy + reconstruction	5 (21%)	12 (14%)	
None/other	0 (0%)	2 (2%)	
Hours of exposure to general anesthesia	3.9 (2.7)	3.4 (2.7)	0.55
Taking hormones	1 (4%)	4 (5%)	0.66
Bloodwork			
White blood count	7.8 (3)	7.3 (2.2)	0.40
Red Blood Count	4.4 (0.4)	4.3 (0.4)	0.44
Hemoglobin	13.2 (1.3)	13.3 (1.4)	0.80
Platelets	289.8 (67.4)	307.8 (73.2)	0.28
B12	667.8 (316.5)	705 (334.5)	0.63
Folate	17.3 (5.5)	20.1 (6.5)	0.066
Thyroid Stimulating Hormone	1.5 (0.9)	1.9 (1)	0.082

[a] Prior to assessment