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The relationship of cognitive performance to concurrent symptoms, cancer- and cancer-treatment-related variables in women with early-stage breast cancer: a 2-year longitudinal study

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Abstract

Purpose—Cognitive dysfunction in women with breast cancer continues to be an area of intense research interest. The prevalence, severity, timing, and cognitive domains that are most affected, as well as the contribution of cancer and its treatments to cognition, remain unresolved. Thus, longitudinal studies are needed that examine cognitive function during different stages of breast cancer treatment and survivorship. This longitudinal trial followed women with early-stage breast cancer, prior to chemotherapy through 2 years survivorship.

Methods—In women with early-stage breast cancer ($N = 75$), performance-based assessment of nine cognitive domains was performed at five time points beginning prior to chemotherapy and finishing 24 months after initial chemotherapy. Linear mixed effects models were used to examine the temporal changes in cognitive performance domains, while adjusting for cofactors, including those related to individuals, tumor attributes, chemotherapy (adjuvant or neoadjuvant), radiation, endocrine therapy, and concurrent symptoms.

Results—At baseline, scores on reaction time, complex attention, cognitive flexibility, executive function, and visual memory were lower than 90. At 2 years, all domains improved except for the memory domains (verbal, visual, and composite). Scores on six domains (psychomotor speed, reaction time, complex attention, cognitive flexibility, and visual memory) remained lower than 100 at 2 years. Neoadjuvant chemotherapy and fatigue had strong inverse relationship with cognitive functioning at multiple time points.

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Compliance with ethical standards

Conflict of interest None.

Ethical standards The experiments used in this study complied with the current laws of the country in which they were performed.

Conclusion—The low performance-based cognitive scores at baseline and over time warrant further study. Although most scores improved over time, memory did not improve. In all, the level of cognitive function is lower than expected for a majority college-educated sample. Thus, future studies are warranted to replicate these findings and to develop methods for identifying women with cognitive dysfunction pretreatment and into survivorship.

Keywords

Breast cancer; Cognition; Memory; Adjuvant; Chemotherapy

Introduction

While advances in therapeutic approaches have resulted in improved survival rates for women diagnosed with early-stage breast cancer, subsets of breast cancer survivors develop persistent cognitive dysfunction, which compromises their employment, social functioning, and quality of life (Calvio et al. 2010). Early reports indicated that cognitive dysfunction was highly prevalent in women receiving chemotherapy for breast cancer (van Dam et al. 1998). In fact, this phenomenon was known as “chemobrain” and was thought to be a widespread problem, affecting between 4 and 77 % of women treated for breast cancer in cross-sectional studies (Wefel et al. 2011). However, more recent reports, which used longitudinal study designs with objective performance-based measures, indicate that the incidence of cognitive dysfunction may be lower than researchers anticipated and may affect only a subset of women receiving breast cancer treatments (Ahles et al. 2012). Similarly, researchers initially thought chemotherapy “caused” cognitive dysfunction, but newer studies have revealed that 20–30 % of patients with breast cancer may have cognitive impairment *prior* to starting cancer treatment (Ahles 2012). Recent results from animal models indicate that further consideration of the role of the tumor in affective and cognitive symptoms is warranted, largely because interrelated biological mechanisms may contribute to pre-chemotherapy impairment (Schrepf et al. 2015).

Although cognition in breast cancer has been an area of intense scientific and clinical interest, the methodological heterogeneity of the studies, the lack of validated measures of cognition, and the retrospective and relatively short follow-up period have limited the ability to better understand the incidence, timing, and persistence of this adverse side effect. Moreover, most of the previous reports, which focused on the topic of cognitive function and breast cancer, have not considered the effects of potential confounding variables on cognitive performance, including host characteristics, breast cancer treatment characteristics, and levels of concurrent symptoms. Even if the prevalence of cognitive dysfunction in women with breast cancer is lower than anticipated, clinicians, researchers, and patients are still concerned about the long-term adverse effects of breast cancer treatment. For example, in a recent report on cognitive function for women with breast cancer, 60 % of female breast cancer survivors ($N = 2296$) who were at least 1 year post-treatment self-reported cognitive problems after treatment (Buchanan et al. 2015), highlighting the importance of research in this area. Other similar reports have consistently shown that cognitive dysfunction is one the “most feared” long-term sequela of cancer treatment (find this reference) (Myers 2012). Thus, further evidence is needed so that patients and healthcare providers can identify

individuals at greatest risk for side effects and tailor strategies to mitigate both the short-term and long-term consequences of cancer and its treatment (Hermelink 2015).

The EPIGEN study of women with early-stage breast cancer was conducted to address these concerns. Women diagnosed with breast cancer were assessed on a comprehensive cognitive test battery, as well as laboratory measures from serum and clinical indices prior to chemotherapy (Aboalela et al. 2015). These same measures were also obtained at multiple time points following the commencement of chemotherapy in this prospective 2-year longitudinal study. The overall study was designed to examine changes in cognitive performance: (1) over time (24-months), including four stages of treatment and post-treatment relative to baseline (pre-chemotherapy) performance; and (2) relative to potential associations with covariates over time, including individual patient demographic and health attributes, cancer factors, cancer treatment factors, and co-occurring symptoms of stress, fatigue and depression and anxiety, and biological markers. In this report, we present the results of longitudinal assessments of performance-based testing on nine cognitive domains (from prior to commencement of chemotherapy through 2 years after initiation of chemotherapy). Our primary hypothesis was that performance in cognitive testing across domains would change over time and would be associated with cancer- and cancer-treatment-related factors (particularly chemotherapeutic agents) and co-occurring symptoms.

Methods

Ascertainment

As described in a previous paper (Aboalela et al. 2015), women between the ages of 21 and 65 with Stage I to IIIA breast cancer were recruited from a designated National Cancer Center affiliated with a major research University in the mid-Atlantic region and 4 regional collaborative sites in Central Virginia. A total of 77 women with early-stage (I to IIIA) breast cancer, who ranged from 23 to 71 years of age, were ascertained. To identify potential study participants, each site had a study coordinator screen patients for eligibility. The eligibility criteria were as follows: (1) age of 21 years or older; (2) a diagnosis of early-stage breast cancer with a scheduled visit to receive chemotherapy; and (3) female gender (males were excluded because too few male participants were available for study). Exclusion criteria were as follows: (1) a previous history of cancer or chemotherapy; (2) a diagnosis of dementia; (3) active psychosis; or (4) immune-related diagnoses (e.g., multiple sclerosis; systemic lupus erythematosus). After providing informed consent (VCU IRB #HM 13194), participants were enrolled and the first study visit was scheduled prior to the initiation of chemotherapy. The five time points for evaluation in this longitudinal study were as follows: before the start of chemotherapy (T1), at the midpoint chemotherapy (T2), 6 months after the initial chemotherapy (T3), 1 year after the initial chemotherapy (T4), and approximately 2 years following the initiation of chemotherapy (T5). The initial assessment (T1) was conducted after surgery, but prior to commencing chemotherapy in women receiving adjuvant therapy. Women receiving neoadjuvant therapy had chemotherapy prior to surgical resection. Participants were asked to complete questionnaires and performance-based cognitive testing via a computerized system. Participants were given incentives (a \$25 gift card to a local store that has both food and personal items for sale) at each data collection

point. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee regarding the involvement of human participants and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Study participants completed the questionnaires and computerized testing in a private room within the oncology clinic setting.

Measures

Cognitive function—A performance-based computerized neurocognitive testing system, CNS Vital Signs™ (CNSVS, <https://www.cnsvs.com>) (Gualtieri and Johnson 2006) was used to measure multiple cognitive domains. This instrument has been used across multiple patient populations, including individuals with major depression disorder (Rele et al. 2015), traumatic brain injury (Barker-Collo et al. 2015), sickle cell disease (Crawford and Jonassaint 2015), and brain cancer (Meskal et al. 2015). The battery takes approximately 30 min to complete per session. CNSVS was originally standardized with a normative sample of 1069 subjects, ranging in age from 7 to 90. This reference group was drawn from the American population and has been used in multiple populations in research and clinical settings. Test results are obtained in subject (raw) scores, age-matched standard scores, and percentile ranks. CNSVS standard scores have a mean of 100 and a standard deviation of 15; higher scores indicate better performance memory and attention. The CNSVS scores individual tests and calculates a report of the clinical domains of neurocognitive functioning. The clinical domains include a neurocognitive index, which is an average of five neurocognitive domains, including (1) memory, (2) psychomotor speed, (3) reaction time, (4) complex attention, and (5) cognitive flexibility. Description of these domains and relevance are described in Table 1. The subscales of the CNSVS have good test–retest reliability: attention ($r = 0.65$), memory ($r = 0.66$), psychomotor speed ($r = 0.88$), cognitive flexibility ($r = 0.71$), and reaction time ($r = 0.75$) and have been used previously to evaluate cognition in women with breast cancer (Scherling et al. 2011).

Covariates—Demographic, cancer- and cancer-treatment-related variables were collected by medical record review and participant interview. Demographic variables included age, race, educational level, and body mass index. Body mass index (BMI) was calculated as weight divided by height squared. Cancer-related variables included breast cancer stage (TNM) and hormone receptor status. Treatment-related variables included type of surgery, treatment regimen (adjuvant or neoadjuvant), chemotherapeutic regimen, radiation status, and hormonal agent status.

Concurrent symptoms were measured with well-validated instruments. Symptoms of perceived stress were measured by the Perceived Stress Scale (PSS). The PSS measures the degree to which situations in one's life are appraised as stressful (Cohen et al. 1983). The 10 items are general in nature and focus on the level of stress of situations that occurred in the last month. The PSS has well-documented reliability and validity (Cohen and Williamson 1988). Severity of fatigue and the impact of fatigue on daily functioning in the past 24 h were self-reported using the Brief Fatigue Inventory (Mendoza et al. 1999). Depressive and anxiety symptoms were measured with the Hospital Anxiety and Depression Scale (HADS), a brief (14-item) self-report questionnaire developed to detect the presence and severity of

both anxiety and depressive symptoms at the time of reporting. Because the HADS was developed for use in medically ill patients, it does not rely upon somatic symptoms of depression and anxiety, such as pain and weight loss. The HADS has well-established reliability and validity for assessments of women with breast cancer (Snaith 2003).

Statistical analysis—Descriptive statistics were obtained in the form of means, medians, and ranges for the continuous variables, and frequencies and percentages for the categorical variables. Linear mixed effects models were used to examine the temporal changes in cognitive performance domains, while adjusting for cofactors, including individual-level attributes (education, race, BMI), cancer-related traits (breast cancer stage (TNM), hormonal receptor status), cancer-treatment-related factors (surgical type, chemotherapy status (adjuvant or neoadjuvant), radiation status, and hormonal agent status), and concurrent symptoms (fatigue, perceived stress, depression, and anxiety). A random intercept was included in the models to account for the within subject correlation. The temporal changes in cognition across the five visits were tested using F-tests, and the model-based means at each visit were estimated. Similarly, linear mixed effects models were used to model and test for potential differences in the temporal changes of the symptoms. Standard scores (i.e., scores normalized and standardized by age) were used in all analyses. Each cognitive domain was tested separately to determine the changes in specific domain(s) over time. Effects were considered statistically significant at a p value of 0.05. Because treatment-related variables and symptom covariates can change over time, each covariate was tested separately at each time point to determine the following: (a) the contribution of each covariate to each cognitive measure, (b) any significant associations between covariates and changes over time, and (c) whether or not these associations were consistent. Differences were considered statistically significant at a p value of 0.05. To efficiently study the association between the covariates, symptoms, and cognitive outcomes, the backward model selection method was used and stratified by visit. Specifically, at each visit, linear models were fitted with cognitive performance as the outcomes, and cofactors and symptoms as the predictors; then a backward selection method was applied and important predictors were chosen using the p values. All the analysis was conducted using SAS 9.4.

Results

One hundred and fifty-four women were approached about study participation. Of these, 77 met study inclusion criteria and were consented for participation. Of the 77, 3 women (all Caucasians; ages 48, 62, and 66) failed to complete the multiple visits required for this longitudinal investigation, which resulted in a 96 % retention rate. Two of the three women who did not complete the study elected to withdraw after T1 due to feeling “overwhelmed”. The third woman, who developed osteomyelitis after T2, no longer met eligibility criteria and was excluded from further follow-up. A total of 75 women who had at least two measurement points were included in the analysis.

Sample characteristics

The demographic and treatment data for the study participants are displayed in Table 2. The study sample consisted of a majority of Caucasian (71 %) non-Hispanic women with an

average age of 51.52 years ($SD = 10.34$). A majority of participants were married (63 %), had attained education beyond high school (79 %), were employed full-time (55 %), were post-menopausal (57 %) and non-smokers (79 %), and had received adjuvant chemotherapy (89 %). The mean body mass index was 29.85 ($SD = 7.47$).

Cancer stages were Stage I (27 %), Stage IIA (41 %), Stage IIB (21 %), and Stage IIIA (11 %). Three primary types of chemotherapy regimens were administered to the study participants. These were categorized as the following: (1) TAC, which included women who received sequential administration of doxorubicin (Adriamycin), cyclophosphamide (Cytosan), and docetaxel (Taxotere); (2) TC, which included women who received docetaxel (Taxotere) and cyclophosphamide (Cytosan); or (3) TCH, which included women who received docetaxel (Taxotere), carboplatin (Paraplatin), and trastuzumab (Herceptin). The majority ($n = 39$) of participants received a TAC chemotherapy regimen. A total of 21 participants received TC treatment, and 11 women received TCH treatment. Two study participants received a cyclophosphamide, methotrexate, and 5-fluorouracil regimen. At T4, 20 of the 74 received hormonal therapy and at T5, 33 of the 74 women were taking hormonal agents.

Cognitive domains

Group means and standard errors on the cognitive domains are presented in Table 3. There were significant improvements over time in psychomotor speed ($p = 0.02$), reaction time ($p < 0.0001$), complex attention ($p = 0.04$), complex flexibility ($p < 0.0001$), and executive functioning ($p < 0.0001$). The three memory domains (visual, verbal, and complex) were not significantly different over time ($p = 0.38$, $p = 0.55$, and $p = 0.93$, respectively). At T1 (baseline), the mean scores on two memory domains were above 90 (verbal memory $M = 99.57$) and composite memory ($M = 90.67$). The trajectory for all domains showed slight improvement at T2 except for visual memory and composite memory (Fig. 1). The slight improvement of cognitive domains continued with the exception of the visual memory at T3 and T4 and composite memory at T4. After 2 years, scores on six cognitive domains remained lower than 100: (1) psychomotor speed, (2) reaction time, (3) complex attention, (4) cognitive flexibility, (5) visual memory, and (6) composite memory. After 2 years, compared to baseline, all domains improved except for the memory domains (verbal, visual, and composite memory) at $p < 0.05$. The greatest improvements over time occurred in cognitive flexibility ($\beta = 10.29$, $p < 0.0001$) and executive functioning ($\beta = 10.45$, $p < 0.0001$). Moderate improvement was noted in reaction time ($\beta = 7.81$, $p < 0.0001$) and smaller improvements in psychomotor speed ($\beta = 2.84$, $p = 0.025$) and complex attention ($\beta = 2.54$, $p = 0.04$).

Concurrent symptoms

While levels of concurrent symptoms were generally in the mild-to-moderate range, symptom severity had a higher degree of variability than the cognitive measures over time (Table 3). Significant differences over time were noted for fatigue ($p = 0.0001$), anxiety ($p < 0.0001$), depression ($p = 0.0003$), and stress ($p < 0.0001$). Fatigue increased between T1 and T2, reached its highest level at T2, then decreased over T3 and T4, and yet remained higher at T5 than at T1. Anxiety levels were highest at T1: levels then moderated and became stable

at T2. Depression increased from T1 to T2, then decreased at T3, and continued to decline at T4 and T5. Perceived stress levels were highest at T1 and decreased over time (Fig. 2).

Covariates by cognitive domain

A multivariate analysis revealed that several variables (demographic, clinical, and concurrent symptom) had varying relationships to cognition domains over time. There were thirteen variables (three demographic, six clinical, and four concurrent symptoms) that were significantly associated with the eight cognitive domains assessed. The three demographic variables associated with cognition were BMI, education level, and race. The six clinical variables associated with cognition were neoadjuvant chemotherapy, hormone status (positive or negative for herceptin, estrogen, and progesterone), and surgery type (biopsy, lumpectomy, or segmental mastectomy). The four concurrent symptoms associated with cognition were fatigue, anxiety, depression, and stress (Tables 4, 5).

Psychomotor speed—Psychomotor speed was associated with four (two demographic, one clinical, and one concurrent symptom) covariates over time. BMI ($\beta = -0.86$, $p = 0.015$) and stress ($\beta = -0.79$, $p = 0.022$) were significant covariates at T1. Education level was significant at T2 ($\beta = 53.4$, $p < 0.0001$ for college and $\beta = 57.5$, $p < 0.0001$ for high school) and T3 ($\beta = 28.99$, $p = 0.005$ for college and $\beta = 27.05$, $p = 0.285$). At T3, BMI ($\beta = -0.79$, $p < 0.05$) and neo-adjuvant chemotherapy ($\beta = 25.63$, $p = 0.023$) were associated with lower scores. Significant covariates at T4 were education level ($\beta = 47.43$, $p < 0.0001$ for college and $\beta = 39.59$, $p = 0.0007$ for high school) and neoadjuvant chemotherapy ($\beta = 22.43$, $p = 0.0151$). Significant covariates for T5 were education level ($\beta = 43.99$, $p = 0.0002$ for college and $\beta = 35.93$, $p = 0.0098$ for high school). BMI was noted as a significant covariate at T1 and T2. Except for T1, education level (college and high school) was a significant covariate of psychomotor speed across all time points. Neoadjuvant chemotherapy was a significant covariate only after chemotherapy cessation at T4 and T5. Stress was noted as a significant covariate only at T1.

Reaction time—Reaction time was associated with three (one demographic and two concurrent symptom) variables over time. Variables education level ($\beta = 27.68$, $p < 0.001$ for college and $\beta = 29.13$, $p = 0.001$ for high school), depression ($\beta = 1.78$, $p = 0.030$), and stress ($\beta = 0.75$, $p = 0.025$) were significant covariates at T1. A significant covariate at T2 was education level ($\beta = 19.81$, $p = 0.0021$ for college and $\beta = 21.7$, $p = 0.0082$ for high school). A significant covariate for T3 was education level ($\beta = 18.66$, $p = 0.0016$ for college and $\beta = 17.75$, $p = 0.0154$ for high school). A significant covariate for T4 was education level ($\beta = 22.30$, $p = 0.0003$ for college and $\beta = 24.00$, $p = 0.0014$ for high school). Significant covariates for T5 were education level ($\beta = 22$, $p = 0.0015$ for college and $\beta = 23.94$, $p = 0.0054$ for high school) and depression ($\beta = -1.56$, $p = 0.0147$).

There were noted significant covariates of reaction time over time. Education level (college and high school) was noted as a significant covariate across all time points T1–T5. Stress was noted as a significant covariate only at T1. Depression was noted as a significant covariate at T1 and T5.

Complex attention—Complex attention was associated with five (one demographic, one clinical, and three concurrent symptom) variables over time. Variables race ($\beta = -9.68$, $p = 0.031$), fatigue ($\beta = -2.17$, $p = 0.019$), anxiety ($\beta = -2.32$, $p = 0.003$), and stress ($\beta = 0.85$, $p = 0.034$) were significant covariates at T1. A significant covariate at T2 was fatigue ($\beta = -3.34$, $p = 0.0002$). A significant covariate at T3 was race ($\beta = -16.59$, $p = 0.0004$). There were no significant covariates at T4. Significant covariates at T5 were tumor hormone receptor status of herceptin 2 positive and estrogen and progesterone negative ($\beta = 18.25$, $p = 0.0113$) and fatigue ($\beta = -1.57$, $p = 0.0339$).

There were noted significant covariates of complex attention over time. Race was noted at two time points (T1 and T3) as a significant covariate but not over consecutive time points. Hormone status was only noted as a significant covariate at T5. Fatigue was noted at three time points (T1, T2, and T5) as a significant covariate. Anxiety and stress were noted only at T1 as significant covariates. Complex attention is the only cognitive domain that does not have a covariate at any given time point.

Cognitive flexibility—Cognitive flexibility was associated with five (two demographic and three concurrent symptom) variables over time. Variables race ($\beta = 12.14$, $p = 0.011$), fatigue ($\beta = -2.63$, $p = 0.008$), anxiety ($\beta = -1.73$, $p = 0.035$), and stress ($\beta = 0.92$, $p = 0.03$) were significant covariate at T1. Significant covariates at T2 were education ($\beta = 22.5$, $p = 0.0035$ for college) and fatigue ($\beta = -2.70$, $p = 0.0016$). A significant covariate at T3 was race ($\beta = -16.84$, $p = 0.0136$). A significant covariate at T4 was race ($\beta = -10.73$, $p = 0.0136$). A significant covariate at T5 was education ($\beta = 27.06$, $p = 0.001$ for college and $\beta = 26.13$, $p = 0.008$ for high school).

There were noted significant covariates of cognitive flexibility over time. Race was a significant covariate over three time points (T1, T3, and T4). Education level was a covariate at T2. Fatigue was a significant covariate at T1 and T2, and anxiety and stress were covariates only at T1.

Executive function—Executive function was associated with three (one demographic and two concurrent symptom) variables. Variables race ($\beta = 11.74$, $p = 0.013$) and fatigue ($\beta = -1.74$, $p = 0.027$) were significant covariates at T1. A significant covariate at T2 was fatigue ($\beta = -2.80$, $p = 0.0014$). A significant covariate at T3 was race ($\beta = -16.99$, $p = 0.0006$). Significant covariates at T4 were race ($\beta = -11.18$, $p = 0.013$) and depression ($\beta = -1.36$, $p = 0.0336$). A significant covariate at T5 was fatigue ($\beta = -1.53$, $p = 0.042$). Race was a significant covariate at T1, T3, and T4. Fatigue was a significant covariate at T1, T2, T5, and depression was a significant covariate only at T4.

Verbal memory—Verbal memory was associated with four (two demographic and two concurrent symptom variables). Variables race ($\beta = -11.44$, $p = 0.005$) and fatigue ($\beta = -1.48$, $p = 0.025$) were significant covariates at T1. A significant covariate at T2 was race ($\beta = -9.32$, $p = 0.0224$). A significant covariate at T3 was race ($\beta = -17.83$, $p = 0.0224$). Significant covariates at T4 were BMI ($\beta = -0.69$, $p = 0.012$) and race ($\beta = -11.57$, $p = 0.0119$). Significant covariates at T5 were race ($\beta = -16.12$, $p = 0.0009$), fatigue ($\beta = -2.37$, $p = 0.0148$), and stress ($\beta = 0.80$, $p = 0.196$). BMI was a significant covariate only at T2.

Fatigue was a significant covariate at T1 and T5. Stress was a significant covariate only at T5.

Visual memory—Visual memory was associated with five demographic (two demographic, two clinical, and one concurrent symptom) variables. Variables surgery biopsy ($\beta = -19.69$, $p = 0.002$), surgery segmental mastectomy ($\beta = -11.41$, $p = 0.009$), and depression ($\beta = 1.14$, $p = 0.033$) were significant covariates at T1. A significant covariate at T2 was race ($\beta = -9.74$, $p = 0.0157$). A significant covariate at T3 was race ($\beta = -15.85$, $p = 0.0007$). Significant covariates at T4 were neoadjuvant chemotherapy ($\beta = 13.47$, $p = 0.038$) and hormone ($\beta = 9.09$, $p = 0.026$). Significant covariates at T5 were education level ($\beta = 21.72$, $p = 0.0054$ for college) and neoadjuvant chemotherapy ($\beta = 21.73$, $p = 0.008$), fatigue ($\beta = -2.27$, $p = 0.0145$), and stress ($\beta = 0.87$, $p = 0.0119$). Race was a significant covariate at T2 and T3. Education level was noted for college only at T5. Surgical variables were noted for the first time in this cognitive domain and were noted only at T1. Neoadjuvant chemotherapy was noted at T4 and T5. Hormone variable was noted only at T4. Depression was noted only at T1, and fatigue and stress were noted only at T5.

Composite memory—Composite memory was associated with nine (one demographic, five clinical, and three concurrent symptom) variables. Variables surgery biopsy ($\beta = -18.95$, $p = 0.002$), surgery lumpectomy ($\beta = -8.45$, $p = 0.023$), and surgery segmental mastectomy ($\beta = 13.69$, $p = 0.002$) were significant covariates at T1. A significant covariate at T2 was race ($\beta = -12.25$, $p = 0.0013$). Significant covariates at T3 were race ($\beta = -19.94$, $p < 0.0001$) and anxiety ($\beta = -1.28$, $p = 0.0112$). Significant covariates at T4 were race ($\beta = -11.98$, $p = 0.006$) and hormone ($\beta = 9.49$, $p = 0.028$). Significant covariates at T5 were race ($\beta = -11.93$, $p = 0.0146$), neoadjuvant chemotherapy ($\beta = 23.46$, $p = 0.0070$), hormone ($\beta = 8.80$, $p = 0.0361$), fatigue ($\beta = -3.24$, $p = 0.0011$), and stress ($\beta = 1.32$, $p = 0.0006$).

Race was a significant covariate at T2, T3, T4, and T5. All surgical variables were significant at T1; adjuvant endocrine therapy was significant at T4 and T5. Neoadjuvant chemotherapy was noted only at T5. Anxiety was significant at T3 while lower fatigue and higher stress scores were associated with composite memory at T5.

Discussion

This prospective longitudinal study is one of the first to examine cognitive function across multiple domains in women with early-stage breast cancer at multiple time points, starting prior to chemotherapy administration and into 2 years of survivorship. This study is unique because it considers the effects of cancer, cancer treatment, and concurrent symptoms on multiple cognitive domains to understand the inter-relationships among these variables. Strengths of the design included a low attrition rate, psychometrically sound instruments, and data collection by consistent study personnel over time. The computerized objective testing for this study has been used in other breast cancer cohorts and is reported to be valid and reliable (Breckenridge et al. 2012; Scherling et al. 2012). Although the study did not have a comparison group, the case-control design, which used a normed and validated neuropsychological performance-based testing platform with alternative forms of testing, yielded results that have several notable findings.

The scores over time remained lower than anticipated from a predominately college-educated cohort and are consistent with results from a prospective study completed by Jansen et al. (2011) in which cognitive impairment was found in 23 % of women ($N=16/71$) prior to the initiation of chemotherapy. Although most mean scores for cognition improved over time, visual memory and composite memory remained low at 2 years (Fig. 1). Memory-related cognitive deficits have been noted in multiple studies (van Dam et al. 1998; Schagen et al. 1999) of women with breast cancer, including recent neuroimaging studies that have noted decreased brain gray matter density shortly after breast cancer chemotherapy (McDonald et al. 2010) and increased bifrontal and decreased left parietal activation in women with breast cancer compared with controls (McDonald et al. 2012). The trend toward improvement across non-memory-related domains over time is consistent with a recent meta-analysis which found that when assessing studies of cognition in women with breast cancer with a longitudinal design, long-term memory was the only cognitive domain to produce a significant mean effect size ($d=0.41$); this finding indicates that chemotherapy patients typically exhibited *improvements* in long-term memory when studied prior to chemotherapy and over time (Ono et al. 2015). However, an alternate explanation is that cognitive performance at baseline may have been lower than usual as a result of emotional distress (Pérez et al. 2014), recovery from surgery (Kyranou et al. 2013), and anxiety over the initiation of chemotherapy (Lyon et al. 2015). Further, it is also possible that baseline deficits in cognitive performance observed prior to the initiation of chemotherapy reflect the interactive effects of pre-morbid factors including comorbid medical conditions (Mandelblatt et al. 2014), systemic inflammation (Cheung et al. 2015), residual anesthesia effects (Ramaiah and Lam 2009), and/or individual differences in cognitive and physiological reserve (Opdebeeck et al. 2015). Therefore, improvements in performance over time may be due to the altered representation of actual cognitive status at baseline or repeated assessment (practice) effects. Given these possibilities, statistical methods for considering practice effects would have led to *lower* scores over time (Theadom et al. 2015) and attenuated improvements in performance. However, practice effects for computerized neurocognitive testing are mitigated by multiple forms of testing and in this study, the relatively long intra-study measurement intervals (Zygouris and Tsolaki 2014).

Several non-modifiable variables were related to differences in performance levels (Mandelblatt et al. 2014). Lower levels of education were related to lower performance scores across domains, with the relationship between cognitive performance and educational level remaining a strong predictor on multiple domains. While a relationship between race and cognitive performance was also observed at early time points, given the relatively small proportion of non-Caucasian women in the sample (22 %), it is important to consider that other variables, such as income, social support or educational level, may have contributed to this observation. Of the breast cancer-treatment-related variables, the receipt of neoadjuvant chemotherapy had negative effects on multiple cognitive domains that persisted over time and into survivorship. Few investigators have compared adjuvant to neoadjuvant treatment regimens in a longitudinal manner; however, findings from this study are similar to those of another study that included 111 women who received neoadjuvant chemotherapy and had scores that were a standard deviation or more below the test norms on 5 of 12 tests prior to chemotherapy (Kesler and Blayney 2015). In that sample, toward the completion of

chemotherapy, approximately a quarter of patients showed a decline in cognitive function, whereas another quarter demonstrated improvement in cognitive function (Hermelink et al. 2007). Because neoadjuvant therapy is typically used to treat more locally advanced breast cancers and large tumors, it is not possible to determine whether lower cognitive performance is related to higher anxiety about advanced breast cancer stage or tumor size, or from interrelated biological mechanisms such as heightened inflammation. However, given that the subset in this sample receiving neoadjuvant chemotherapy was small ($N = 7$), no conclusions can be made about these relationships without further study.

Contrary to several studies reporting declines in cognitive function associated with adjuvant endocrine therapy (ET) (Pérez et al. 2014), results from this longitudinal study demonstrate a positive effect of endocrine therapy (ET) on visual and composite memory. These results, although they should be considered in the context of a relatively small sample size, indicate no adverse effect of ET on cognition. An early longitudinal study of 104 women with early-stage breast cancer patients and 102 controls assessed cognition at baseline and at 1 and 2 years. There were minimal differences between estrogen receptor–positive patients who started hormonal therapy (mainly tamoxifen) after chemotherapy and estrogen receptor–negative patients who did not (Fan et al. 2005). Another study of women with early-stage breast cancer scheduled for chemotherapy, women scheduled for endocrine therapy and/or radiotherapy, and healthy control subjects showed that although a few women experienced objective measurable change in their concentration and memory following standard adjuvant therapy, the majority were either unaffected or improved over time (Jenkins et al. 2006). However, most studies have not been designed to address the additional effects of endocrine therapy on cognition in the context of sequential, multimodal cancer treatments (Zwart et al. 2015). In a recently completed, well-designed longitudinal trial, Bender et al. (2015) found that in comparison with controls, women who received anastrozole alone or chemotherapy plus anastrozole had significantly poorer executive function from the period before therapy through the first 18 months of treatment along with a consistent pattern of changes in visual working memory and concentration with therapy. However, women in the chemotherapy-anastrozole and anastrozole-alone groups performed better 12 months after anastrozole initiation. This time interval is concordant with the T5 interval in our current study, which demonstrated a positive effect of ET. Hence, further study of the timing of measures, and extended longitudinal follow-up is needed to better understand this interesting finding. Although it did not include a measure of cognition, a recent study determined that breast cancer patients on extended adjuvant endocrine therapy have significantly and clinically relevant better global quality of life compared with other Stage I–II breast cancer patients and the general population, 6–8.5 years after diagnosis (Kool et al. 2015). These findings, although not confirmatory, may indicate that ET, when used as part of a multi-modal treatment regimen, may not, by itself, be associated with cognitive dysfunction. A recent meta-analysis concluded that further longitudinal study of endocrine therapy on cognition in women treated for breast cancer is needed to more conclusively establish this complex relationship (Bakoyiannis et al. 2015).

At baseline, levels of perceived stress, depression, and anxiety were associated with lower cognitive scores, similar to the findings of Calvio et al. (2010). While most of these relationships diminished over time, levels of fatigue remained a consistent, strong predictor

of lower scores in multiple cognitive domains, even at the 2 years time point. High levels of fatigue have been noted in multiple studies of breast cancer survivors (Meeske et al. 2007; Bower et al. 2000), but there has been relatively little research focusing on the relationship of fatigue with cognitive outcomes. In this sample, the inter-relationship of cognition and fatigue illuminates a possible shared target for intervention. Body mass index at baseline was also associated with lower scores on several cognitive domains over time. The importance of considering BMI in breast cancer cognition studies is highlighted by recent research showing that there was an increase in body weight, waist and hip circumferences, triglyceride, and total cholesterol serum levels over 24 months in women diagnosed with breast cancer who received adjuvant therapy (Arpino et al. 2015). Obesity is now recognized as a risk factor associated with reduced cognitive functioning. Indeed, research has shown that in the general population, elevated BMI is associated with weaker cognitive performance even among people without clinically significant obesity (Gunstad et al. 2013). Furthermore, reductions in BMI following bariatric surgery have been associated with improvements in cognitive functioning (Alosco et al. 2014). Accordingly, there is a need for future studies focused on the relationship between obesity, associated metabolic disturbances (e.g., diabetes, fatty liver disease), cognitive performance, and brain functions in the context of chemotherapy, and other clinical and treatment factors in women with breast cancer (Alosco et al. 2013).

A limitation of this study was the lack of concurrent “controls” with breast cancer who did not receive breast cancer treatments but who were given standards of care; however, the ascertainment of such a cohort is not feasible given that the majority of women with early-stage breast cancer receive multiple treatment modalities. Another question raised in this study is if the “baseline” value for assessment of cognitive measures is indicative of the subject’s “typical” performance. The results of this study showed that pre-chemotherapy performance was generally lower than expected, although the majority of changes over the 2 years period were in the direction of improvement. Thus, one is left with the vexing issue that an individual’s levels of cognitive performance at pre-chemotherapy assessment may be lower than their “pre-cancer” performance. As a result, changes identified over time are based on an “anchor” that may be fraught with various types of noise, thereby affecting the relative improvement or decline over time. Hence, the development of more precise models for estimating expected performance, given age and levels of education, are needed to better understand the differences in predicted versus actual performance in baseline cognitive performance; in this way, changes over time may be considered within the context of “pre-cancer” as well as “pre-chemotherapy.” The use of other models, including reliable change indices, may provide a higher degree of reliability in longitudinal studies (Andreotti et al. 2015). Additionally, given the complex relationship between concurrent symptoms and cognitive performance, further investigation of the “dose” of an individual symptom or the number of multiple concurrent symptoms necessary to affect cognitive performance is needed. Because tailored intervention strategies have been used successfully in cancer and other populations for symptom management and weight control, continued focus on potentially modifiable factors such as BMI and concurrent symptoms of fatigue that contribute to cognitive outcomes is needed to enhance the quality of life of women with breast cancer (Henneghan 2016).

Conclusion

This study demonstrated lower than expected outcomes on cognitive testing prior to chemotherapy in women with early-stage breast cancer. Although improved somewhat over time, cognitive measures remained at a level that is lower than expected for a predominately college-educated cohort. Scores on cognitive measures were negatively associated with cancer-related variables, including higher stage of breast cancer and receipt of neoadjuvant chemotherapy and demographic variables of educational level and race. In addition, our results suggest that cognitive performance is influenced by potentially modifiable variables, including levels of concurrent symptoms, particularly fatigue, and higher body mass index. In sum, future studies are needed that replicate these findings in diverse samples of women with breast cancer, focusing on disease, treatment, and potentially modifiable variables such as level of symptoms and BMI.

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Fig. 1.
Trajectory of cognitive domains over time

Fig. 2.
Trajectory of concurrent symptoms over time

Table 1

Description of neurocognitive domains

Domain	Description	Relevance	Subtests
Memory	Identification of storing information, critically interpreting information, and retrieving information	Difficulty remembering which medications to take as well as when and how Difficulty remembering to lock the door or turn off the stove Difficulty remembering important medical appointments	Verbal memory Visual memory
Psychomotor Speed	Perceptions about where hands and fingers are relative to surroundings and how quickly tasks may be performed Identifies issues with slowed processing of information	May impact ability to safely operate a motor vehicle	Finger tapping Symbol digit coding
Reaction time	Time elapse from receiving a stimulus and responding to the stimulus, speed of reaction to complex directions Identifies issues with reacting to stimuli	Safely operating a motor vehicle Holding a conversation Responding to simple instructions	Stroop (how quickly subject responds)
Complex attention	Process of focusing, releasing and seeking stimuli, also ignoring distractions Identifies issues with attending to multiple stimuli	Ability to self-regulate Learning Productivity	Stroop (correct responses) Continuous Performance (correct responses) Shifting Attention (correct responses)
Cognitive flexibility	Allows comparison and contrasting of information from different perspectives Identifies issues with shifting attention between two stimuli Adaptation to rapidly changing situations Manipulation of information	Decision making Impulse control Changing tasks	Stroop (correct responses) Shifting Attention (correct responses)

Table 2

Sample demographics

Variable	N = 75
Age (mean (SD) [range])	51.52 (10.34) [23.00, 71.00]
Race	
Caucasian	71 % (53/75)
African-American	29 % (22/75)
Other	0 % (0/75)
Ethnicity	
Hispanic	4 % (3/75)
Non-hispanic	96 % (72/35)
Educational level (%)	
Did not finish high school	9 % (7/75)
High school	12 % (9/75)
Any education beyond high school	79 % (59/75)
Employment (%)	
Unemployed	15 % (11/75)
Disabled	8 % (6/75)
Student	1 % (1/75)
Part-time	7 % (5/75)
Full-time	55 % (41/75)
Retired	15 % (11/75)
Marital status	
Married/partner	63 % (47/75)
Divorced/separated	24 % (18/75)
Single never married	13 % (10/75)
Household income (%)	
Less than \$30,000	25 % (19/75)
\$30,000–\$59,999	20 % (15/75)
\$60,000–\$89,999	25 % (19/75)
\$90,000 +	29 % (22/75)
Current ethanol use (%)	
Yes	55 % (41/75)
No	45 % (34/75)
Current tobacco use (%)	
Yes	21 % (16/75)
No	79 % (59/75)
BMI (mean (SD) [range])	29.85 (7.47) [19.11–54.34]
Menopausal status (%)	
Pre- and perimenopause	43 % (32/75)
Post-menopause	57 % (43/75)
Luminal A	

Variable	N = 75
Yes	51 % (38/75)
No	49 % (37/75)
Luminal B	
Yes	11 % (8/75)
No	89 % (67/75)
Triple negative	
Yes	29 % (22/75)
No	71 % (53/75)
HER2+, ER- and PR-	
Yes	9 % (7/75)
No	91 % (68/75)
Grade	
1	7 % (5/75)
2	37 % (28/75)
3	56 % (42/75)
Stage	
I	27 % (20/75)
IIA	41 % (31/75)
IIB	21 % (16/75)
IIIA	11 % (8/75)
Surgery	
Biopsy	8 % (6/74)
Lumpectomy	28 % (21/74)
Segmental	20 % (15/74)
Simple	43 % (32/74)
Neoadjuvant	
Yes	11 % (8/75)
No	89 % (67/75)
Radiation	
Yes	79 % (59/75)
No	21 % (16/75)
Hormonal therapy T4	(20/75)
Hormonal therapy T5	(33/75)

Table 3

Longitudinal Changes of Cognitive Domain over Time

Cognitive domains	Visit	T1 (baseline)	T2 (4 weeks)	T3 (6 months)	T4 (1 year)	T5 (2 years)	F value	p value
Psychomotor speed	Mean	93.32	96.60	97.72	100.93	97.44	2.84	0.0249
	SE	7.55	7.53	7.52	7.51	7.53		
Reaction time	Mean	86.67	91.21	92.96	93.94	94.45	7.81	<0.0001
	SE	5.14	5.12	5.12	5.11	5.12		
Complex attention	Mean	88.90	90.81	93.98	94.77	94.44	2.54	0.0401
	SE	5.48	5.46	5.45	5.43	5.46		
Cognitive flexibility	Mean	87.47	92.78	96.48	97.48	98.57	10.29	<0.0001
	SE	6.20	6.19	6.18	6.17	6.19		
Processing speed	Mean	117.00	119.88	127.05	130.07	126.98	6.63	<0.0001
	SE	10.70	10.68	10.66	10.65	10.68		
Executive functioning	Mean	89.40	94.13	97.97	99.36	100.24	10.45	<0.0001
	SE	6.15	6.13	6.12	6.11	6.13		
Verbal memory	Mean	99.57	100.09	103.43	101.94	102.65	1.04	0.3849
	SE	4.55	4.53	4.51	4.50	4.53		
Visual memory	Mean	85.77	84.11	83.05	82.08	83.38	0.76	0.5499
	SE	4.47	4.45	4.44	4.42	4.45		
Composite memory	Mean	90.67	89.95	91.13	89.57	90.87	0.21	0.9339
	SE	4.71	4.69	4.68	4.67	4.69		

SE standard error

Table 4

Concurrent symptoms over time

Visit		T1 (baseline)	T2 (4 weeks)	T3 (6 months)	T4 (1 year)	T5 (2 years)	F value	p value
Fatigue	Mean	2.89	4.30	3.96	3.34	3.45	5.92	0.0001
	SE	0.87	0.87	0.87	0.87	0.87		
Anxiety	Mean	9.32	7.79	7.95	7.81	7.68	7.87	<0.0001
	SE	1.27	1.27	1.28	1.28	1.28		
Depress	Mean	4.61	5.74	5.07	4.47	4.39	5.49	0.0003
	SE	1.05	1.05	1.05	1.05	1.06		
Stress	Mean	19.18	17.28	16.64	15.84	15.60	7.43	<0.0001
	SE	2.73	2.74	2.74	2.74	2.75		

SE standard error

Table 5

Multivariate analyses over time

Visit	T1 (baseline)			T2 (4 weeks)			T3 (6 months)			T4 (1 year)			T5 (2 years)		
	Factor	β	P	Factor	β	P	Factor	β	P	Factor	β	P	Factor	β	P
Psychomotor speed	BMI	-0.86	0.015	College	53.34	<0.0001	College	28.99	0.005	College	47.43	<0.0001	College	43.99	0.0002
	Stress	-0.79	0.022	High school	57.54	<0.0001	High school	27.05	0.0285	High school	39.59	0.0007	High school	35.93	0.0098
Reaction time							BMI	-0.79	0.0464	Neoadjuvant no	22.43	0.0151	Neoadjuvant no	39.24	0.0007
	College	27.68	<0.001	College	19.81	0.0021	Neoadjuvant no	25.63	0.0232						
	High school	29.13	0.001	High school	21.75	0.0082	College	18.66	0.0016	College	22.30	0.0003	College	22.70	0.0015
	Depression	-1.78	0.030				High school	17.75	0.0154	High school	24.00	0.0014	High school	23.94	0.0054
Complex attention	Stress	0.75	0.025							Depression			Depression	-1.56	0.0147
	Black race	-9.68	0.031	Fatigue	-3.34	0.0002	Black race	-16.59	0.0004				HER2+ ER/PR-	18.25	0.0113
	Fatigue	-2.17	0.019										Fatigue	-1.57	0.0339
	Anxiety	-2.32	0.003												
Cognitiv flexibility	Stress	0.85	0.034												
	Black race	-12.14	0.011	College	22.52	0.0035	Black race	-16.84	0.0007	Black race	-10.73	0.024	College	27.06	0.001
	Fatigue	-2.63	0.008	High school	17.39	0.0768							High school	26.13	0.008
	Anxiety	-1.73	0.035	Fatigue	-2.70	0.0016									
Executive function	Stress	0.92	0.030												
	Black race	-11.74	0.013	Fatigue	-2.80	0.0014	Black race	-16.99	0.0006	Black race	-11.18	0.0136	Fatigue	-1.53	0.042
	Fatigue	-1.72	0.027							Depression	-1.36	0.0336			
Verbal memory	Black race	-11.44	0.005	Black race	-9.32	0.0224	Black race	-17.83	<0.0001	BMI	-0.69	0.012	Black race	-16.12	0.0009
	Fatigue	-1.48	0.025							Black race	-11.57	0.0119	Fatigue	-2.37	0.0148
Visual memory													Stress	0.80	.0196
	Surgery biopsy	-19.69	0.002	Black race	-9.74	0.0157	Black race	-15.85	0.0007	Neoadjuvant no	13.47	0.038	College	21.72	0.0054
	Surgery Lumpectomy	-5.23	0.175							Hormone	9.09	0.026	High School	10.13	0.2671
	Surgery segmental	-11.41	0.009										Neoadjuvant no	21.73	0.008
Composite memory	Depression	1.14	0.033										Fatigue	-2.27	0.0145
													Stress	0.87	0.0119
	Surgery biopsy	-18.95	0.002	Black race	-12.25	0.0013	Black race	-19.94	<0.0001	Black race	-11.98	0.006	Black race	-11.93	0.0146

Visit	T1 (baseline)			T2 (4 weeks)			T3 (6 months)			T4 (1 year)			T5 (2 years)		
	Factor	β	P	Factor	β	P	Factor	β	P	Factor	β	P	Factor	β	P
	Surgery lumpectomy	-8.45	0.023				Anxiety	-1.28	0.0112	Hormone	9.49	0.028	Neoadjuvant no	23.46	0.0070
	Surgery segmental	-13.69	0.002										Fatigue	-3.24	0.0011
													Stress	1.32	0.0006
													Hormone	8.80	0.0361