Cognitive functioning and quality of life following chemotherapy in pre- and peri-menopausal women with breast cancer

Jennifer R. Klemp[1], **Jamie S. Myers**[2,4], **Carol J. Fabian**[1], **Bruce F. Kimler**[3], **Qamar J. Khan**[1], **Susan M. Sereika**[4], and **Annette L. Stanton**[5]

[1]University of Kansas Cancer Center, 2330 Shawnee Mission, Parkway, Westwood, KS 66205, USA

[2]University of Kansas School of Nursing, 3901 Rainbow Blvd, MS 4043, Kansas City, KS 66160, USA

[3]University of Kansas Medical Center, 3901 Rainbow Blvd, MS 4033, Kansas City, KS 66160, USA

[4]School of Nursing, University of Pittsburgh, 360 Victoria Building, 3500 Victoria Street, Pittsburgh, PA 15261, USA

[5]Department of Psychology, University of California, 1285 Franz Hall, Los Angeles, CA 90095-1563, USA

Abstract

Purpose—The purpose of the study was to prospectively examine changes in subjective and objective cognitive functions and quality of life (QOL) for pre- and peri-menopausal women receiving chemotherapy for breast cancer and to explore potential predictors of cognitive changes.

Methods—Participants were assessed as follows: prior to chemotherapy (T1), after cycle 3 (T2), within 2–3 weeks of completing adjuvant chemotherapy (T3) ($N = 20$), and 8+ years later (T4; $n = 18$). Objective cognitive function was measured with the High Sensitivity Cognitive Screen (T1, T3, T4). Subjective measures for cognitive function, depressive symptoms, fatigue, and mental and physical QOL were assessed at all time points. Estradiol levels were measured at T1, T2, and T3. The Functional Assessment of Cancer Therapy-Cognition and the MD Anderson Cancer Symptom Inventory item for neuropathy were administered at T4.

Results—No significant changes in objective cognitive function were found. However, participants reported decreased cognitive function over the course of treatment accompanied by depressive symptoms and fatigue. Depression and fatigue returned to near-baseline levels at T4, but over half of the participants continued to report mild to moderate depression. Estradiol levels were not associated with cognitive function. Neuropathy and higher body mass index (BMI) were associated with persistent cognitive complaints at T4 (adjusted $R^2 = 0.712$, $p = 0.001$). Higher

QOL was correlated with better subjective cognitive function ($r = 0.705$, $p = 0.002$) and lower body mass index ($r = -0.502$, $p = 0.017$) at T4.

Conclusions—Further investigation of BMI, neuropathy, and depressive symptoms as predictors of persistent cognitive dysfunction following chemotherapy for breast cancer is warranted.

Keywords

Breast cancer; Cognitive function; Pre-menopausal; Chemotherapy; Quality of life

Intro and study purpose

Decreased cognitive function following cancer diagnosis and subsequent treatment frequently are reported by survivors of breast cancer and are associated with significantly diminished quality of life [1–3]. Complaints of decreased cognitive function typically include difficulty with memory, attention and concentration, verbal fluency, processing speed, and executive function [4–7] but are not consistently congruent with performance on objective measures of cognitive function [8]. Research is ongoing to identify specific predictors and to determine causal mechanisms for these cognitive changes. One confounding aspect in investigating cognitive changes in breast cancer survivors is the impact of aging and changes in menopausal status that result from chemotherapy-induced cessation of menses and lowered levels of estradiol [9–11]. To date, few studies have explored the influence of breast cancer diagnoses and chemotherapy among pre- and peri-menopausal women [12]. The purpose of this exploratory, prospective study was to examine changes in subjective and objective cognitive functions and quality of life for pre- and peri-menopausal women receiving chemotherapy for breast cancer and to explore predictors of cognitive changes. The original predictors of interest included age, estradiol levels, depressive symptoms, and fatigue. Exploration of additional predictors, including neuropathy, body mass index, and exercise frequency, were based on the results from our related work [13].

Methods

Recruitment

Women were recruited between 2005 and 2006 from the University of Kansas Medical Center following diagnosis of breast cancer (and prior to receiving chemotherapy). Eligibility criteria included the following: age between 25 and 55 years; pre- (i.e., regular menses) or peri-menopausal (i.e., at least one period within the previous 6 months) status; no evidence of concurrent disease; no history of mental illness, hematological disorders, or other malignancies; and planned neoadjuvant or adjuvant chemotherapy. Twenty-eight eligible women were identified by the clinical oncology team. Of these, 20 were consented by the primary investigator (PI; JK) for participation after biopsy and/or definitive surgery, but prior to the initiation of chemotherapy.

Procedures

Institutional Review Board (IRB) approval was obtained prior to consent and data collection. Initial study time points included baseline/pre-chemotherapy (T1), mid-treatment (T2, following third cycle of chemotherapy), and post-treatment (T3, within 2–3 weeks after completion of chemotherapy). Subsequent IRB approval was obtained to collect data at long-term follow-up (T-4, eight or more years following completion of chemotherapy). Serum was collected (T1, T2, T3) and analyzed for levels of estradiol. Serum analyses were conducted at the Ligand Assay and Analysis Laboratory at the Center for Research in Reproduction at the University of Virginia Health Sciences. Participants concurrently completed both objective and subjective measures of cognitive function over the course of the study (see the section "Measures"). An objective measure of cognitive function was administered by the PI (JK) at T1, T2, and T3 and at T4 by the PI and one co-investigator (JM). All objective and subjective data were collected on campus at the University of Kansas Medical Center with the exception of one participant at T4 who had moved outside a 2-h driving radius. The PI collected data from this participant in a mutually agreeable location within the participant's city of residence.

Measures

Medical, laboratory, and demographic data—Stage of disease and planned treatment regimen were obtained from chart review. Estradiol levels were measured from serum drawn at T1, T2, and T3. Age, race, education, marital and employment status (T1), and exercise frequency (T4) were obtained from patient report. Body mass index (BMI) at T1 and T4 was calculated from participants' clinically assessed height and weight.

Objective cognitive functioning—The High Sensitivity Cognitive Screen (HSCS) was administered at T1, T3, and T4. The HSCS was designed to assess language, attention and concentration, self-regulation and planning, visual/motor and spatial abilities, and memory [14, 15]. This instrument was selected due to the succinct administration time (25 min), high interrater reliability (0.98), accuracy compared to comprehensive neuropsychological testing (93%), and the detection of cognitive dysfunction for cancer survivors in previous studies [14, 16].

Subjective cognitive functioning—Participants completed two self-report scales at all four study time points. The 26-item version of the Cognitive Difficulties Scale (CDS) (items ranked from 0/not at all to 4/extremely) is highly correlated with objectively assessed memory and attention performance ($r = -0.51$) with good test-retest reliability ($r = 0.77$) [17, 18]. The Cognitive Problems Scale from the Breast Cancer Prevention Trial (BCPT) Symptom Checklist (three items ranked from 0/not at all to 4/extremely) has been validated with over 2000 women who are breast cancer survivors or at high risk for breast cancer (Cronbach's alpha = 0.85) [19]. Additionally, participants were asked to respond to four questions related to self-report on changes in cognitive functioning during the post-treatment (T3) and long-term follow-up (T4) interviews (see Table 1). Over the course of the study, the Functional Assessment for Cancer Therapy-Cognition (FACT-COG) was published [20]. The FACT-COG was designed specifically to measure subjective cognitive function for cancer survivors and includes subscales for perceived cognitive impairment (PCI), perceived

cognitive abilities (PCA), comments from others, and quality of life (QOL). The study was amended to include responses to the FACT-COG (version 3) with PCI subscale scores as a dependent variable of perceived cognitive function at T4. Higher subscale scores indicate better perceived cognitive function. Internal consistency for PCI (Cronbach's alpha = 0.95) and intra-class correlation coefficients (ICC) for test-retest reliability (0.82) has been demonstrated (L. Wagner, personal communication, February 2014). Total scores are not applicable for version 3.

Quality of life—The Mental (MCS) and Physical (PCS) Component summary scores on the Medical Outcomes Study Short Form 36 (MOS-SF36) were used to capture participants' self-report of quality of life at all four study time points [21–23]. The MOS-SF36 is a measure of functional health and well-being with excellent psychometrics (Cronbach's alpha = 0.70–0.90) and frequently is used as a health-related QOL measure for the oncology population. The RAND scoring method was used to calculate the MCS and PCS [24]. High scores indicate a more favorable health state. Each item is scored on a 0 to 100 range. Scores represent the percentage of total possible score achieved. Items in the same scale then are averaged together to create scale scores. Additionally, health-related QOL scores from the FACT-COG QOL subscale were collected at T4 (Cronbach's alpha = 0.89, ICC for test/retest reliability = 0.86).

Depressive symptoms—Two well-validated measures of depressive symptoms were employed. The Beck Depression Inventory I (BDI) includes 21 items on a four-point scale (0 = none, 3 = severe) and has high internal consistency (Cronbach's alpha = 0.86 and 0.81 for psychiatric and non-psychiatric populations, respectively) [25, 26]. We used the original standard cut points for depression (0–9 = none, 10–18 = mild to moderate, 19–29 = moderate to severe, 30–63 = severe). The Center for Epidemiologic Studies Depression Scale (CES-D) is comprised of 20 items with total scores ranging from 0 to 60. Scores 16 suggest clinically significant depression. Adequate psychometrics have been demonstrated in the oncology population (Cronbach's alpha = 0.90; test retest reliability = 0.51) [27].

Fatigue—Fatigue was measured with the Brief Fatigue Inventory (BFI), an instrument designed for rapid assessment in patients with cancer [28]. Participants ranked severity of fatigue from 0 (no fatigue) to 10 (fatigue as bad as you can imagine) and the interference of fatigue (0 = does not interfere, 10 = completely interferes) on mood and activities. A Global BFI score is obtained by calculating the mean score of the nine items on the instrument. Internal reliability has been demonstrated (Cronbach's alpha = 0.95–0.96) [28].

Neuropathy—Neuropathy was rated between 0 (not present) and 10 (as bad as you can imagine) within the previous 24 h at T4 per the MD Anderson Symptom Inventory (MDASI) [29]. MDASI single-item validity for symptom severity (including neuropathy) has been demonstrated ($r > 0.7$) [29, 30].

Statistical analyses

IBM SPSS Statistics 22 was used for all data analyses. The nominal level of significance used was alpha < 0.05. The sample size of 20 was estimated to achieve 75% power to detect

a 10% decline between pre- and post-treatment scores on the HCSC. Descriptive statistics analyses included means, standard deviations, and percentages. The data were screened for outliers, patterns of missingness, and assumptions of normality, independence, and collinearity. All co-investigators took part in the interpretation of the data analyses.

Longitudinal analysis—Repeated measures analysis of variance with time as a within-subjects factor with three levels (T1, T3, T4) was conducted to examine longitudinal changes in *objective* cognitive function. A four-level factor (T1, T2, T3, T4) was used to examine changes over time in *subjective* cognitive function as well as measures of health-related quality of life. In instances where the assumptions of sphericity were not met, the Geisser-Greenhouse adjustment for the degrees of freedom for the *F* test is reported. Significant changes over time were explored further by conducting paired *t* tests with Bonferroni correction (*p* value set at 0.05/6 = 0.0083).

Cross-sectional analysis—Pearson's correlation coefficients were computed between each independent variable and the measures of perceived cognitive function to inform the linear regression modeling.

Predictors analysis—Linear regression analyses were planned to explore relationships of predictor variables with the BCPT Cognitive Problems Scale (at T3) (change in estradiol levels: T1 to T3, depressive symptoms, and fatigue). Linear regression analyses were conducted to explore relationships of predictor variables with the BCPT Cognitive Problems Scale and PCI (at T4) (depressive symptoms, fatigue, BMI, neuropathy). Current age (at T4) was explored as a potential confounding variable due to the relationship between aging and cognitive concerns. Due to the small sample size, indicator coding was used to collapse exercise frequency into the categorical variable, regular exercise (0 = no regular exercise, 1 = regular exercise). However, we were unable to explore this variable in the regression model due to the strong correlation with BMI.

Results

Sample

Participants included 17 pre- and 3 peri-menopausal women (see Table 2). The standard of care for chemotherapy regimens in 2005–2006 included doxorubicin or epirubicin plus cyclophosphamide and trastuzumab or carboplatin plus docetaxel. Participants primarily were diagnosed with early-stage disease and were estrogen- and progesterone-receptor positive. Most of the women underwent lumpectomy. The 14 participants who were hormone-receptor positive went on to receive endocrine therapy after the completion of chemotherapy. No participants were receiving endocrine therapy at baseline (T1), T2, or T3. One participant was receiving endocrine therapy (exemestane) at T4. The median age at T1 was 43 years (range 28–51). The majority were Caucasian (85%), married (75%), well educated (80%), and employed full or part-time (85%). The mean time since diagnosis was 8.35 years.

All 20 participants in the study completed assessments at T1, T2, and T3 and 16 participants were assessed at T4. Reasons for not participating at T4 (*n* = 4) included the following: (1)

initial agreement and then changed mind due to lack of time, (2) family health issues for participant who was the primary caregiver, (3) initial agreement but did not respond to requests to reschedule after initial schedule conflict for participant, and (4) progressive disease with brain metastases. The missing data from these participants were determined to be missing completely at random as no significant differences were found between these four participants and the remainder of the sample on any study variable.

According to the World Health Organization classification, percentage of overweight participants increased from 25% at T1 to 44% at T4 [31]. One third of the participants remained obese. The mean change in weight was an increase of 7.75 lb (range from − 53 to + 35 lb) and the mean change in BMI was 1.18. Fifty percent reported exercising regularly; of these, 50% exercised three or more times per week.

Longitudinal results

Cognitive functioning—No significant changes in the High Sensitivity Cognitive Screening (HSCS) total scores and five of six subscales were demonstrated (see Table 3). However, participants did improve significantly in Self-Regulation and Planning scores over time ($p = 0.046$).

Significant decline over time was shown for the BCPT Cognitive Problems Scale ($p = .007$). Further exploration demonstrated significant change between T2 and T3 ($t = −3.15$, $p = 0.007$) as well as T1 and T3 ($t = − 2.91$, $p = 0.004$). No significant change was noted for participants' scores on the CDS.

No significant complaints about decreased cognitive function were reported at the baseline (T1) interview. However, the majority of the participants ($n = 19$, 95%) reported decreased cognitive function at T3. Complaints included issues with word finding, memory, and speed of processing. Subsequently, most participants ($n = 12$, 75%) indicated they continued to experience issues with cognitive function at T4.

Quality of life—The SF-36 PCS scores significantly improved over time ($p = .037$). No significant change in the MCS was demonstrated.

Depressive symptoms—Depressive symptoms increased over the course of treatment, as measured by the BDI ($p = 0.015$) particularly from T2 to T3 ($t = − 3.08$, $p = 0.008$) and T1 to T3 ($t = − 4.34$, $p = 0.001$). In contrast, no significant change in depressive symptoms was detected with the CESD. Of note, a substantial percentage of the participants scored above the cut points for clinical depression on both measures (10 BDI; 16 CESD) at all time points (see Table 4) [26, 27].

Fatigue—Participants' complaints of fatigue as measured by the BFI increased over the course of treatment ($p = 0.003$). Significant increase in fatigue was noted from T1 to T3 ($t = − 3.13$, $p = 0.006$). However, fatigue decreased from T3 to T4 ($t = 3.96$, $p = 0.001$).

Estradiol levels—Significant decrease in estradiol levels occurred over time ($p = 0.001$), from T1 to T2 ($t = 4.88$, $p < 0.01$), T1 to T3 ($t = 5.88$, $p < 0.01$), and T2 to T3 ($t = 3.74$, $p < 0.01$).

Cross-sectional results

Neuropathy—Twenty-five percent reported neuropathy at T4. The mean neuropathy score was 1.0 (SD = 2.1) on a scale of 0–10 and ranged from 0 to 7 (see Table 5).

Cognitive functioning—The mean PCI score on the FACT-COG at T4 was 51 (range 31–66) and below a cut point of 59 that recently was established for clinically significant PCI [32].

Quality of life—Better perceived cognitive function (higher PCI scores) was associated with higher QOL scores on the FACT-COG ($r = 0.705$, $p = 0.002$). Significant negative correlation was demonstrated between BMI and QOL ($r = -0.502$, $p = 0.047$).

Predictors of subjective cognitive function

At T3, significant correlations were noted between the BCPT Cognitive Problems Scale and BDI scores (depressive symptoms) ($r = 0.471$, $p = 0.036$) and BFI scores (fatigue) ($r = 0.548$, $p = 0.012$). However, depressive symptoms and fatigue also were correlated significantly with each other ($r = 0.569$, $p = 0.009$). No correlation was seen between the longitudinal variables and estradiol levels.

At T4, age and BCPT Cognitive Problems Scale scores were not correlated. Significant correlations were demonstrated between worse scores on the BCPT Cognitive Problems Scale and depressive symptoms ($r = 0.639$, $p = 0.008$), fatigue ($r = 0.542$, $p = 0.030$), and neuropathy ($r = 0.621$, $p = 0.010$). Linear regression explained 57% of the variance for worse scores on the BCPT Cognitive Problems Scale (adjusted $R^2 = 0.571$, df = 2, 14, $F = 10.965$, $p = 0.002$). Fatigue did not contribute significantly to the model (see Table 6).

At T4, no association between PCI and age was demonstrated. Linear regression with BMI, neuropathy, depression, and fatigue explained 66% of the variance for worse PCI (adjusted $R^2 = 0.664$, df = 4, $F = 8.395$, $p = 0.002$) although neither depression nor fatigue was a significant contributor. The most succinct regression model included BMI and neuropathy and explained 71% of the variance for worse PCI (adjusted $R^2 = 0.712$, df = 3, $F = 12.060$, $p = 0.001$). Of note, worse scores on the BCPT Cognitive Problems Scale and PCI scores at T4 were not correlated ($r = -0.310$, $p = 0.242$) (see Table 6).

Discussion

The study purpose was to prospectively examine changes in subjective and objective cognitive functions and quality of life for pre- and peri-menopausal women receiving chemotherapy for breast cancer and to explore predictors of cognitive changes. We examined age, estradiol levels, depressive symptoms, fatigue, neuropathy, and body mass index for association with cognitive function.

Our results differed from some previous studies in which participants demonstrated cognitive complaints prior to the initiation of chemotherapy [33–35]. The lack of correlation between objective and subjective measures is consistent with other studies [8, 36–38]. A number of researchers have postulated that this inconsistency may be due to a lack of sensitivity of objective measures as well as the potential for objective and subjective instruments to measure different constructs [39, 40].

Neither age nor estradiol levels were associated with cognitive complaints. Previous research results have indicated that younger women perceive more changes in cognitive function. These results are suggested to be related to the lifestyle challenges of younger women, such as balancing family and work responsibilities, as well as to the abrupt decline in estradiol due to breast cancer treatment [41, 42]. Our small sample size and homogeneity related to age and menopausal status may explain the lack of association between age and estradiol levels with cognitive complaints.

Our sample did demonstrate a significant increase in depressive and fatigue symptoms between baseline and T3 with a return to near baseline at T4. These variables have been identified as potential covariates of perceived cognitive function in other studies [36, 40, 43]. Depression and fatigue were associated with participants' scores on the BCPT Cognitive Problems Scale at T3 and T4. However, neither depression nor fatigue was correlated with participants' PCI scores at T4 despite the fact that many of the participants scored above the cut point for mild to moderate depression on the BDI (44%) and CES-D (69%) at T4.

Interestingly, the study results indicated a lack of correlation between subjective cognitive complaints as measured by the BCPT versus the PCI scale of the FACT-COG. By T4, scores on the BCPT Cognitive Problems Scale had returned to near-baseline values. However, mean PCI scores were below the cut point for clinical meaningful cognitive complaints at T4. Of note, the BCPT Cognitive Problems Scale is composed of three items addressing memory and concentration. The PCI scale items are designed to assess additional domains of perceived cognitive function including verbal fluency and functional interference [20].

The significant relationship between BMI and neuropathy with PCI is congruent with the results of our previous research [13, 44]. We noted that 27% of women within 6 to 12 months of completing chemotherapy for breast cancer participating in our qualitative study of chemotherapy-induced cognitive impairment ($N = 18$) complained of residual neuropathy [44]. In a subsequent cross-sectional study, we found a significant inverse correlation between perceived cognitive function and neuropathy for women with breast cancer ($n = 317$; $r = -0.23$; $p < 0.0001$) [13]. Regression analyses in the cross-sectional study indicated that the relationship between BMI and PCI for women with breast cancer was moderated by exercise frequency ($F_{3, 198} = 2.4$, $p = 0.07$). This moderating effect was significant for women with breast cancer who had received chemotherapy ($F_{3, 133} = 3.1$, $p = 0.03$). Interestingly, results of a recent registry study conducted to investigate the association of chemotherapy-induced peripheral neuropathy (CIPN), physical activity, and health-related QOL (HRQOL) for survivors of colorectal cancer demonstrated a significant association between neuropathy severity and worse self-report of cognitive function for participants with low physical activity ($p < 0.001$) [45]. Together, these findings are intriguing and suggest

that further research investigating BMI and neuropathy as predictors of cognitive function may be warranted. In the current study, depression and neuropathy predicted subjective cognitive function for the BCPT Cognitive Problems Scale scores while BMI and neuropathy predicted subjective cognitive function for the FACT-COG PCI subscale. These differences, in addition to the lack of correlation noted between the two measures, may indicate that these two instruments actually measure different constructs of perceived cognitive function for breast cancer survivors. Additionally, since the PCI scores were consistent with participants' indication of persistent complaints of decreased cognitive function while the BCPT Cognitive Problems Scale scores at T4 were not significantly different from baseline, we speculated that the PCI score may be more sensitive to breast cancer treatment-related cognitive complaints.

Study limitations

Our study design had a number of limitations. The very small exploratory sample size significantly limited our power for examination of multiple variables. At the time the study was designed, the HSCS was known to be a succinct measure of cognitive function. However, this instrument has since been shown to be affected by significant practice effects [33] which may have masked subtle changes in cognitive performance for the participants. The FACT-COG and the neuropathy item for the MDASI only were administered once at T4. Thus, we were unable to assess the longitudinal trajectory of scores on these instruments. Future prospective work should employ the use of the core set of objective measures recommended by the International Cancer and Cognition Task Force (ICCTF) [7], as these measures were selected by the task force based upon pertinent cognitive domains (learning and memory, processing speed, and executive function), availability of alternate forms to reduce practice effects, and adequate psychometric properties.

Conclusions

Pre- and peri-menopausal women receiving treatment for breast cancer reported significant worsening of cognitive function over the course of treatment that was accompanied by depression and fatigue. Fatigue returned to near-baseline levels by T4. Many participants continued to report levels of depression consistent with clinical depression greater than 8 years following completion of chemotherapy, although depression was not consistently associated with persistent complaints of changes in cognitive function. Significant positive correlation was demonstrated between better subjective cognitive function and quality of life. Excess body weight (higher BMI) was negatively correlated with quality of life. Our study results provide additional support for further investigation of important breast survivorship issues, including excess body weight, neuropathy, and depression, as predictors of persistent cognitive complaints and their relationship to diminished quality of life following chemotherapy for breast cancer. Our results also add to the evidence for the sensitivity of the PCI subscale of the FACT-COG to long-term cognitive complaints for women with breast cancer after completion of chemotherapy.

Acknowledgments

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Table 1

Self-report of cognitive function questions

1	Did you experience any changes in cognition (memory or thinking) before you started chemotherapy?	
	a.	No
	b.	Yes
2	Do you currently have any changes in cognition (memory or thinking)?	
	a.	No
	b.	Yes
3	If you do currently have issues with cognition, how have these issues affected your day-to-day life?	
4	Are you having to make any special accommodations to cope with changes in cognition? If so, please describe:	

Table 2

Sample Characteristics

Characteristic	Time point	M (SD)	Min	Max	Normal n (%)	Overweight n (%)	Obese n (%)
Age	T1 (N=20)	43.15 (5.82)	28	51			
	T4 (n = 16)	53 (4.62)	45	60			
Body mass index		M (SD)	Min	Max			
	T1 (n = 20)	27.63 (7.4)	19	47	9 (45)	5 (25)	6 (30)
	T4 (n = 16)	28.25 (16)	19	40	4 (25)	7 (44)	5 (31)

Characteristic	Subcategory	n (%)
Race	Caucasian	17 (85)
	African American	1 (5)
	Hispanic	2 (10)
Education	High School	4 (20)
	College	14 (70)
	Post-graduate	2 (10)
Employment	Not working	3 (15)
	Part-time	2 (10)
	Full-time	15 (75)
Marital Status	Married/coupled	15 (75)
	Single/divorced/widowed	5 (25)
Tumor stage	Not reported	1 (5)
	I	11 (55)
	II	6 (30)
	III	1 (5)
	IV	1 (5)
Lymph node status	Negative	15 (75)
ER/PR status	ER+/PR+	14 (75)
Chemotherapy type	Standard	7 (35)
	Dose-dense	13 (65)
Chemotherapy regimen	Anthracycline and cyclophosphamide	14 (70)

Characteristic	Time point		
	Docetaxel/carboplatin		4 (20)
	Docetaxel/trastuzumab		2 (10)
Hormonal therapy regimen	Arimidex		2 (14.3)
	Exemestane		1 (7.0)
	Letrozole		3 (21.4)
	Tamoxifen		2 (14.3)
	Multiple agents		6 (43.0)
Surgery type	Lumpectomy		14 (70)
	Mastectomy		6 (30)

Table 3

Longitudinal measures ($N = 20$)

Instrument	Domain	T1 M(SD)	T2 M(SD)	T3 M(SD)	T4 M(SD)	F	df	p	Partial eta²
HSCS	Memory	15.44 (10.41)		13.06 (7.48)	14.19 (11.10)	0.91	2,30	.41	0.054
	Language	2.63 (2.80)		1.63 (2.63)	2.44 (3.71)	0.89	2,30	.42	0.056
	Attention	0.50 (0.63)		.56 (.73)	.94 (1.40)	0.8	1.47,21.99	.46	0.051
	Self-regulation and planning	2.94 (2.18)		1.94 (1.65)	1.25 (1.61) 4.42	4.42	1.16, 17.31	.046	0.227
	Visual/motor	0.20 (.41)		.20 (.41)	0 (0)	2.47	2,28	.1	0.5
	Spatial	0.53 (0.64)		.53 (.74)	.40 (1.30)	0.102	1.27, 17.83	.81	0.007
	Total score	21.56 (11.25)		17.44 (9.06)	10.69 (13.10)	1.72	2,30	.196	0.103
CDS		24.2 (15.13)	23.2 (15.84)	28.2 (15.11)	25.8 (14.92)	0.86	1.9,28.78	.428	0.54
BCPT	Cognitive problems	0.68 (.66)	.85 (.72)	1.3 (.80)	.83 (.70)	4.54	3,45	.007	0.23
BDI	Total score	7.81 (5.06)	9.94 (7.0)	12.5 (7.69)	9.31 (6.59)	4.84	1.98,20.68	.015	0.244
BFI	Global score	2.40 (1.95)	3.33 (2.49)	3.78 (2.60)	1.90 (1.81)	6.86	.98,31.67	.003	0.3
CES-D		13.5 (10.98)	13.69 (12.18)	16.13 (9.63)	18.25 (6.68)	1.96	3,45	.134	0.116
MOS-SF36	PCS	50.64 (8.38)	47.39 (11.14)	46.18 (9.95)	56.05 (12.43)	4.01	.91, 19.05	.037	0.286
	MCS	48.48 (10.59)	50.10 (10.26)	47.01 (10.28)	52.16 (9.92)	1.41	3,39	.256	0.098
Estradiol level		65.35 (27.61)	41.12 (16.08)	28.68 (10.93)		27.96	1.41,26.83	.001	.595

HSCS High Sensitivity Cognitive Screen, *CDS* Cognitive Difficulties Scale, *BCPT* Breast Cancer Prevention Trial, *BDI* Beck Depression Inventory, *BFI* Brief Fatigue Index, *CES-D* Center for Epidemiologic Studies Depression Scale, *MOSSF-36* Medical Outcome Study Short Form 36, *PCS* Physical Component Score, *MCS* Mental Component Score

Table 4

Depression cut points

Depression scale	Tl	T2	T3	T4
	% (*n*)	% (*n*)	% (*n*)	% (*n*)
BDI elevated (10)	20 (4/20)	35 (7/20)	55 (11/20)	44 (7/16)
CES-D elevated (16)	30 (6/20)	20 (4/20)	50 (10/20)	69 (11/16)

Table 5

Cross-sectional measures at T4 ($n = 16$)

Instrument	Domain	Mean	SD	Range	Maximum possible score
FACT-COG	PCI	51.31	11	31 to 66	72
	QOL	12.81	2.97	7 to 16	16
MDASI	Neuropathy	1.0	2.1	0 to 7	10

FACT-COG Functional Assessment of Cancer Therapy-Cognition, *MDASI* MD Anderson Symptom Inventory, *PCI* perceived cognitive impairment, *PCA* perceived cognitive abilities, *QOL* quality of life

Table 6

Linear regression results for subjective cognitive function T4

Breast Cancer Prevention Trial (BCPT) Cognitive Problems Scale ($N = 16$) $R^2 = .679$, adjusted $R^2 = .559$

	Unstd coefficients			95% CI for b	
	b	SE	p value	Lower bound	Upper bound
(Constant)	.021	.223	.927	−.464	.506
BDI (depressive symptoms)	.049	.018	.021	.009	.089
BFI (fatigue)	.099	.071	.190	−.056	.254
Neuropathy	.134	.060	.046	.003	.265

Perceived Cognitive Function (PCI) Scale of the FACT-COG full-regression model ($N = 16$) $R^2 = .753$, adjusted $R^2 = .664$

	Unstd coefficients			95% CI for b	
	b	SE	SIG	Lower bound	Upper bound
(Constant)	99.543	11.307	.001	74.656	124.429
BM	−1.589	.334	.001	−2.324	−.855
Neuropathy	−2.356	.939	.029	−4.422	−.291
BDI (depressive symptoms)	−.011	.303	.971	−.678	.655
BFI (fatigue)	.363	1.126	.754	−2.841	2.116

Parsimonious PCI regression model ($N = 16$) $R^2 = .751$, adjusted $R^2 = .712$

	Unstd coefficients			95% CI for b	
	b	SE	SIG	Lower bound	Upper bound
(Constant)	97.884	8.188	.001	80.195	115.573
BM	−1.559	.281	.001	−2.167	−.951
Neuropathy	−2.482	.782	.007	−4.172	−.792

BDI Beck Depression Inventory, *BFI* Brief Fatigue Index, *BMI* body mass index