Published in final edited form as:

Support Care Cancer. 2017 January ; 25(1): 167–176. doi:10.1007/s00520-016-3400-2.

Relationships among psychoneurological symptoms and levels of C-reactive protein over 2 years in women with early-stage breast cancer

Angela Starkweather¹, Debra Lynch Kelly², Leroy Thacker³, Michelle L. Wright⁴, Colleen K. Jackson-Cook³, and Debra E. Lyon²

¹University of Connecticut School of Nursing, Storrs, CT, USA

²University of Florida College of Nursing, Gainesville, FL, USA

³Virginia Commonwealth University School of Nursing, Richmond, VA, USA

⁴Yale University, New Haven, CT, USA

Abstract

Purpose—The aim of the present study was to explore clusters of psychoneurological symptoms and inflammation (levels of C-reactive protein) over time in a cohort of women with early-stage breast cancer. Specifically, we examined the relationships among affective symptoms (depression, anxiety, fatigue, sleep disturbances, pain, and perceived stress), domains of cognitive performance, and levels of peripheral C-reactive over a period of 2 years.

Methods—This was a prospective, longitudinal study of 77 women diagnosed with early-stage breast cancer. Data collection, including symptom questionnaires, performance-based cognitive testing, and blood draws, took place at 5 time points: prior to initiating adjuvant chemotherapy, prior to the fourth chemotherapy treatment, and at 6, 12, and 24 months after the initiation of chemotherapy.

Results—Exploratory factor analysis with varimax orthogonal rotation was used to examine the covariance among symptoms at each visit. Using the factor scores and weighted sums, three clusters were identified: global cognition, affective symptoms, and cognitive efficiency. Peripheral levels of C-reactive protein were inversely correlated with the cognitive efficiency factor across time.

Conclusions—The findings suggest that objectively measured domains of cognitive function occur independently of other affective symptoms that are commonly reported by women with breast cancer in long-term survivorship. The cognitive efficiency symptom cluster may be amenable to interventions targeted to biological influences that reduce levels of C-reactive protein.

✉ Angela Starkweather, angela.starkweather@uconn.edu.

Electronic supplementary material The online version of this article ([doi:10.1007/s00520-016-3400-2](https://doi.org/10.1007/s00520-016-3400-2)) contains supplementary material, which is available to authorized users.

Compliance with ethical standards

Conflicts of interest For the remaining authors, none were declared.

Keywords

Breast cancer; Cognitive impairment; C-reactive protein psychoneurological symptoms; Symptom clusters

Introduction

Following skin cancer, breast cancer is the most frequently diagnosed cancer in women [1]. Advances in early detection and systemic therapies have led to an increased rate of long-term survival [2]. However, for some of these women, survivorship is coupled with the persistence of distressing symptoms including anxiety, depression, fatigue, pain, sleep disturbance, and cognitive impairment [3, 4]. Approximately 24–68 % of women report clinically meaningful levels of these symptoms, referred to as “psychoneurological (PN) symptoms,” across the treatment trajectory [5, 6]. In longer-term follow-up (i.e., 1 to 5 years after treatment), fatigue and cognitive complaints are common [7, 8]. One study found that 48 % of women reported cognitive complaints and 82 % reported fatigue at 5 years following adjuvant chemotherapy, high-dose chemotherapy, or radiation therapy [8]. Although cognitive complaints are common in women with breast cancer, a recent study reported that perceived cognitive impairment was not directly associated with objective measures of cognitive performance [9].

Yet among PN symptoms, fatigue and cognitive impairment are particularly concerning to breast cancer survivors because of the potential impact on maintaining employment and levels of productivity in daily activities [10]. Efforts to identify a common biological mechanism of PN symptoms have been based on the premise of “sickness behaviors” mediated by inflammatory activation through the release of proinflammatory cytokines [4]. Indeed, research has shown that chemotherapy results in elevated levels of circulating proinflammatory cytokines in the short term, but levels typically decline over the subsequent months [11]. While chemotherapy has often been cited as a causative factor of PN symptoms, several investigators have reported a high frequency of cognitive complaints [12, 13] and elevated levels of fatigue [14] prior to starting chemotherapy. Thus, it is important to evaluate other possible mechanisms that influence the symptom trajectory. In breast cancer survivors who exhibited high serum C-reactive protein (CRP) levels, Alfano et al. [15] reported a 1.8-fold greater chance of fatigue. More recently, Pomykala et al. [16] showed a positive association among subjective memory complaints, cerebral metabolism, CRP, and several cytokines at 3 and 12 months after chemotherapy. Collectively, these studies suggest that inflammation is a factor involved in the development and, possibly, the persistence of PN symptoms.

In order to further investigate the co-occurrence of PN symptoms during and after adjuvant chemotherapy and plausible biological mechanisms of the symptoms, our group completed a 2-year prospective, descriptive study among 75 women diagnosed with early-stage breast cancer [17]. In this study, we chose to use objective measures of cognitive performance using a previously described protocol [18] in order to evaluate the specific domains that may be related to affective symptoms (i.e., anxiety, depression, fatigue, pain, sleep disturbance).

For the analysis reported here, we chose to use serum CRP level as a marker of inflammation, which is commonly measured in the clinical setting and has been previously associated with impaired endothelial function, cerebral white matter hyper-intensities, and cognitive impairment in other patient populations [19–21].

Methods

Participants

Women ($n = 77$) between the ages of 23–71 years old with stages I to IIIA breast cancer were recruited from a National Cancer Institute designated Cancer Center affiliated with a major research university in the mid-Atlantic region and four collaborative sites around the region. The study protocol was approved by each of the Institutional Review Boards governing each site (IRB protocol #HM 13194). Women were eligible to participate in this study if they (1) were at least 21 years of age and (2) had a diagnosis of early-stage breast cancer with a scheduled visit to receive postsurgical chemotherapy. Women who received neoadjuvant therapy also had chemotherapy prior to surgical resection. Exclusion criteria included (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). Informed consent was provided to all eligible volunteers and written consent was obtained on the IRB-approved consent form.

Procedures

In order to evaluate the symptom trajectory during and after adjuvant chemotherapy, collection took place at 5 time points: T1—at least 1 month after surgical resection to serve as a baseline before starting adjuvant chemotherapy, T2—prior to the fourth post-surgical chemotherapy treatment for assessment during chemotherapy, and T3—at 6 months following the final administration of adjuvant chemotherapy, T4—at 12 months, and T5—at 24 months after the initiation of adjuvant chemotherapy. After obtaining informed consent, participants were asked to complete questionnaires (described in the following sections) and cognitive testing via a computerized system. Blood samples were collected by venipuncture or existing access device using standard protocols, transported to the laboratory in a secure biohazard-approved container, and processed within 2 h. All assays were processed and analyzed in the same laboratory. The investigators completing the analysis of the biological measures were unaware of participant information including symptom status at the time the biological measures were quantified. Participants were given a \$25 gift card after each data collection visit to compensate for their time and travel expenses.

Measures

Demographics—A comprehensive demographic and disease profile questionnaire and medical record review were completed at baseline, including age, ethnicity, menopausal status, educational attainment, and smoking/alcohol intake. Information was updated at subsequent visits.

Cognitive function—The CNS Vital Signs™ (CNSVS, <https://www.cnsvs.com>) [22] was used to measure multiple cognitive domains (verbal memory, visual memory, psychomotor

speed, reaction time, complex attention, cognitive flexibility, processing speed, and executive function). The battery takes approximately 30 min to complete per session. Test results are obtained in subject (raw) scores, age-matched standard scores (based on population norms), and percentile ranks. Population norms are age-matched to each assessment. CNSVS standard scores have a mean of 100 and a standard deviation of 15; higher scores indicated better performance. 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 ($r = 0.75$) [22]. While standard neuropsychological testing remains the “gold standard” for detecting cognitive impairment, performance-based computerized testing has been shown to be reliable and valid and does not carry the “burden” of traditional neuropsychological testing [9, 18]. A score below 70 on any dimension indicates impairment [22], which was used as the clinically meaningful threshold value.

Depressive symptoms and anxiety—The Hospital Anxiety and Depression Scale (HADS) [23] is 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 it 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. Participants rate the severity of each symptom (0–3) over a 7-day period. The HADS has well-established reliability and validity for both depression and anxiety in women with breast cancer [23]. A score of 6 or higher for depression or anxiety was used as the threshold based on previous recommendations in cancer patients [24].

Fatigue—The Brief Fatigue Inventory (BFI) [25] is a simple, 9-item scale that captures dimensions of fatigue severity (now, usual, worst) and the interference fatigue creates in daily life. The BFI is a clinically validated tool used to assess cancer-related fatigue and its impact on daily functioning [26]. The BFI uses simple numeric rating scales from 0 to 10 that are easily understood. On the BFI, severe fatigue can be defined as a score of 7 or higher. The BFI has demonstrated excellent reliability in clinical trials, with Cronbach’s alpha ranging from 0.82 to 0.97 [26]. A threshold value of 5 or above, indicating a clinically meaningful level of fatigue in women with breast cancer, was used for the analysis [26].

Sleep disturbance—Participants completed the 21-item General Sleep Disturbance Scale (GSDS) [27]. The GSDS consists of items that evaluate various aspects of sleep disturbance (quality and quantity of sleep, sleep onset latency, number of awakenings, excessive daytime sleepiness, and medication use) over the past week. Items are rated on a scale ranging from 0 (never) to 7 (every day). The 21 items are summed to produce a total score with a possible range from 0 (no sleep disturbance) to 147 (extreme sleep disturbance). In a study of the symptoms of fatigue, sleep disturbance, depression, and pain in 191 cancer patients, the Cronbach’s alpha for the GSDS was 0.82 [28]. A score of 43 or higher was used as the threshold value [28].

Pain—The Brief Pain Inventory (BPI) short form is a pain assessment tool that has well-established reliability and validity for adult patients in trajectory studies of cancer and its

symptoms [29]. The arithmetic mean of the four severity (pain now, average pain, least pain, worst pain) items was used as a measure of pain severity as recommended by the developers [29]. In widespread testing, Cronbach's alpha has ranged from 0.70 to 0.91 [29]. A threshold value of 3 or above was used for the analysis.

Stress—Levels of 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 [30]. The 10 items are general in nature and focus on the stressfulness of the situations in the past month. The PSS has well-documented reliability and validity [31]. The threshold value of 20 or above was used based on the sample distribution.

C-reactive protein—The innate inflammatory response includes the activation of the acute-phase protein, CRP. Because CRP has a long half-life and good stability over a long period of time and the CRP assay is a highly sensitive standard laboratory measure with well-established reference ranges [32], we used CRP measurement as an indicator of inflammatory activation. Plasma was stored at -80°C until assayed by standard enzyme-linked immunoassay (ELISA) kits and protocols (R&D Systems Inc., Minneapolis, MN). All specimens were processed and stored and assays were run in batches within the same laboratory. Interassay and intra-assay variability was $<10\%$ among all batches analyzed. CRP threshold for the analysis was set at $>1.0\text{ mg/L}$ as concentrations below 1.0 mg/L are considered as low risk for inflammatory-related conditions.

Statistical analysis—All data were analyzed using SAS (version 9.2 for Windows, SAS Institute, Cary, NC). Means and standard deviations were used to describe the study sample (Table 1). Due to non-normality of the CRP levels, values were log transformed and all analyses controlled for batch effects. Exploratory factor analysis (EFA) with principal components [rotated component matrix with varimax (oblique) rotation] was chosen because it functions on the assumption that symptoms in a cluster share a common underlying dimension (common or latent factor) that binds two or more symptoms together. Thus, symptoms associated with one latent factor covary more closely with each other compared with symptoms associated by a different latent factor. Eigenvalues, which reflect the amount of variance in the variables accounted for by a component, of 1 was the selection criteria for the number of factors retained. Variables included the eight dimensions of cognitive function (cognitive flexibility, executive functioning, complex attention, reaction time, processing speed, psychomotor speed, visual memory, verbal memory) and self-reported severity of stress, depression, anxiety, fatigue, pain, and sleep disturbances. Relationships were initially assessed between CRP (log transformed) and demographic variables (Table 2) using Spearman rho or point biserial correlations. To evaluate clinically meaningful scores, supplemental Table 6 shows the percent of participants with a symptom score above threshold values for affective symptoms and below threshold values on the cognitive domains. Using EFA, symptoms were grouped into a cluster based on covariance between symptoms (Table 3; data shown in supplemental Table 7). The maximum likelihood method with varimax orthogonal rotation was applied to approximate multivariate normal data to determine covariance between symptoms. The percent variation explained for each visit is presented along with the number of factors retained. Symptoms that had a rounded loading

of 0.40 or greater on a factor are shown unless indicated by (+), denoting that the symptom had a positive loading on the factor. To examine the relationship between the symptom clusters and peripheral levels of CRP over time, factor scores were tabulated using factor loading for all time points combined and weighted sums of variables that had a significant loading on a factor (Table 4). The association between levels of CRP and the cluster was assessed using the factor scores and weighted sums of variables, assuming a level of significance of $p < 0.05$ (Table 5).

Results

As previously described [17], a total of 154 women were approached about study participation. Of these, 77 met the study inclusion criteria and were consented for participation. Subsequently, two women were dropped from study participation (one who was diagnosed with osteomyelitis after the second data collection visit, one who was lost to follow-up after the first data collection visit). The remaining 75 women were included in this analysis. Demographic and treatment data are presented in Table 1. The study sample consisted of mostly Caucasian (71 %), non-Hispanic (96 %) women with an average age of 51.52 years. A majority had attained formal education beyond high school (79 %) and full-time employment (55 %). In addition, most were post-menopausal (57 %) and non-smokers (79 %).

Mean symptom scores over time were reported elsewhere [17]. Significant changes in the level of fatigue were shown over time ($F = 5.92$, $p = 0.0001$) and fatigue was the only affective symptom that remained higher at 2 years compared to baseline (baseline mean score 2.89 vs. visit 5 mean score 3.45). Anxiety, depression, and perceived stress also showed significant changes over the time, but mean scores were lower at 2 years compared to baseline.

Correlations between CRP and demographic variables are reported in Table 2. Significant correlations were identified between CRP and body mass index (BMI) at visits 1–5 ($p < 0.0001$ to $p = 0.0002$) and tobacco use at visit 3 ($p = 0.037$) and visit 4 ($p = 0.027$). CRP was correlated with non-white race at visit 1 ($p = 0.014$) and visit 5 ($p = 0.030$), lower education at visits 1–3 ($p = 0.0004$ to 0.0018) and visit 5 ($p = 0.040$), lower income at visits 1–5 ($p = 0.0043$ – 0.0184), and current alcohol use at visit 1 ($p = 0.023$) and visits 3–5 ($p = 0.021$ – 0.038).

Clusters varied across time

At visit 1, affective symptoms and cognitive performance domains clustered around four factors (Table 3). Factor 1 was composed of cognitive flexibility, executive functioning, complex attention, and reaction time. Factor 2 included symptoms of perceived stress, anxiety, depression, sleep disturbance, and fatigue. Factor 3 included pain, sleep disturbance, fatigue, and verbal memory. Factor 4 was composed of psychomotor speed, visual memory, and processing speed. At visit 2, although the same factor structure was retained, there were changes in the composition of factors 1, 3, and 4. Factor 1 was composed of the previous cluster along with psychomotor speed and pain. Factor 2 remained the same. Factor 3 included verbal memory, processing speed, psychomotor speed, and pain. Factor 4 was

composed of only psychomotor speed and visual memory. At visit 3, factor 1 was composed of the affective symptoms (perceived stress, depression, anxiety, sleep disturbance, pain, and fatigue). Factor 2 included cognitive domains of flexibility, executive functioning, complex attention, and reaction time. Factor 3 included processing speed, reaction time, psychomotor speed, pain, and fatigue. Factor 4 included psychomotor speed, verbal memory, and visual memory. At visits 4 and 5, the variables clustered on three factors and the composition of each factor was consistent as seen in Table 3.

Supplemental Table 6 shows the percent of participants who were above threshold values on affective symptoms and below threshold values on cognitive domains. There was a slight increase in the percent of women who fell above threshold on fatigue and pain from visit 1 (25 % for both) to visit 5 (26 and 30 %, respectively). For the cognitive performance domains, 10 % of the participants fell below threshold throughout the study duration. At visit 5, a higher percentage of participants fell below threshold compared to visit 1 on verbal memory, visual memory, and psychomotor speed (6 % for all at visit 5 vs. 3–5 % at visit 1). Thus, the clusters varied in their compositions over time as seen in Table 3 and supplemental Table 7.

C-reactive protein level was inversely correlated with the cognitive efficiency cluster

To examine the relationships among the clusters with levels of peripheral CRP (Table 4), total factor scores were calculated based on factor loading for all visits combined using values from the rotated factor pattern matrix. The three factors were labeled as global cognition (factor 1), affective symptoms (factor 2), and cognitive efficiency (factor 3). A correlational analysis between the symptom cluster total score and CRP at each time point was performed (Table 5). As shown, CRP was significantly negatively associated with global cognition at visit 2 ($p = 0.019$) and cognitive efficiency across all five visits (ranging from $p = 0.0016$ to 0.0385), meaning that higher levels of CRP were associated with lower scores on global cognition and cognitive efficiency. The correlation analysis using the weighted sums demonstrated a significant negative relationship between CRP and global cognition at visits 2, 3, and 5 ($p = 0.017$ – 0.05); affective symptoms at visit 3 ($p = 0.017$); and across all time points for cognitive efficiency ($p = 0.001$ to 0.010) as seen in Table 5. Thus, levels of CRP were inversely correlated with the cognitive efficiency cluster over time using either of the two clustering methods described.

Discussion

In this study, we sought to examine the relationships among psychoneurological symptoms and peripheral CRP levels over a 2-year period in women with early-stage breast cancer who received adjuvant chemotherapy. The results demonstrate that there was more variability in the composition of the clusters over the first 6 months after initiating adjuvant chemotherapy as compared to the later time points at 1 and 2 years post-chemotherapy. These findings suggest that associations among affective symptoms (fatigue and pain) and cognitive performance measures abate over time. Similarly, in a cohort of women with early-stage breast cancer, Collins et al. [19] reported that while fatigue increased over time up to 1 year

post-chemotherapy, the change in fatigue did not account for the changes in cognitive performance.

Several investigators have examined changes in cerebral metabolism after chemotherapy and found that altered perfusion in the precentral gyrus and decreased frontal grey matter were associated with a significant decline in neuropsychological performance [33–35]. However, it has also been reported that a treatment-related decline in overall cognitive performance typically rebounds over time to baseline levels among breast cancer survivors [36]. At 1 year post-chemotherapy, Collins et al. reported significant rebound in the overall neuropsychological summary score [9], although approximately 33 % of women in the sample who demonstrated immediate cognitive decline post-chemotherapy continued to have persistent cognitive decline 1 year later, particularly in verbal memory, visual memory, and processing speed. Similar findings have been reported in other cohorts, and importantly, the objective cognitive deficits were independent from self-reported symptoms [37, 38]. Thus, the results of the present study are aligned with findings of other investigators reporting persistent impairment in select cognitive domains, which is an observation that is consistent with the possibility that a common physiological mechanism may contribute to the cognitive efficiency cluster.

We therefore assessed whether CRP levels (>1.0 mg/L) were related to the cognitive efficiency cluster. Levels of CRP were significantly correlated with several demographic factors, including BMI at every time point, non-white race, low income, and low educational level. These findings suggest a potential health disparity in CRP expression based on income and education. In addition, it has been noted that African-Americans are at higher risk for elevated CRP levels compared with people of European descent. A common genetic variant, triggering receptors expressed by myeloid 2 (*TREM2*) has been associated with CRP in people of African ancestry [39]. Thus, future research in this area should consider the impact of both demographic and genetic factors on levels of CRP.

In the cluster analysis, we found that CRP was negatively associated with the cognitive efficiency cluster (factor 3: processing speed, psychomotor speed, visual memory, and verbal memory) across all visits. The only relationship noted between CRP and general symptoms was at visit 3 (6 months after initiation of chemotherapy when a subset of women were receiving radiotherapy). In a prior study, peripheral levels of CRP were found to predict fatigue at baseline (at the time of diagnosis) in women with breast cancer [40]. In the present sample, fatigue clustered with some measures of cognitive function at visits 1 and 3 but did not cluster with the cognitive performance domains at the 1- or 2-year follow-up. It is also important to note that inflammation reflects a complex cascade of interacting influences, so one needs to use caution when interpreting findings based on a single measure. For example, exposure to chemotherapeutic agents may activate other inflammatory mediators, such as tumor necrosis factor, the latter of which has been found to influence immediate memory complaints as well as diminished metabolism of the inferior frontal cortex in women receiving breast cancer treatment [41].

In the general population, a weak but significant association between levels of peripheral CRP and cognitive decline, defined by 2–5 years of cognitive change in general cognitive

function, has been reported [42]. Increased adiposity has been suggested as a source of increased CRP that may cause decreased cognitive function throughout the lifespan [43]. Although no causal associations can be generated from the present study, the findings suggest that symptoms of decreased cognitive efficiency in women with early-stage breast cancer may be amenable to interventions targeting biological processes that lead to a reduction in peripheral CRP levels. These interventions could include (but are not limited to) strategies such as muscle strengthening and weight loss to reduce adiposity, which may provide a protective role in preserving cognitive efficiency during breast cancer treatment.

Further research to prospectively examine the relationships among CRP, cognition, and cognitive efficiency are needed to confirm these results and explore methods to identify women at risk of cognitive impairment as well as to develop intervention strategies. EFA has been commonly used to identify symptom clusters because it functions on the assumption that symptoms in a cluster may share a common underlying mechanism and accounts for error due to unreliability in measurement. However, there is no consensus on the optimal method to use for analysis of symptom clusters as each approach has limitations. Other limitations of this analysis included variability in the timeframes on questionnaires; for instance, the Perceived Stress Scale assesses usual stress over the last month. However, prior studies have found that the daily vs. monthly assessment are highly correlated, with the exclusion of major life events [8, 9]. We did not measure subjective cognitive function, and due to the recruitment plan, we could not obtain baseline measures of symptoms and cognitive performance prior to surgery. In addition, we did not control for menopausal status, receipt of radiation, or hormonal status. Future studies evaluating cognitive performance in women with breast cancer should consider a study design that includes measures prior to surgery in order to elucidate the impact of baseline cognition and surgery/general anesthesia on the symptom trajectory during and after treatment.

Conclusions

In this study, we report that affective symptoms, particularly fatigue and pain, cluster with various measures of cognitive performance before, during, and up to 6 months following adjuvant chemotherapy in women with early-stage breast cancer. Affective symptoms independently cluster from cognitive performance at 1 and 2 years following adjuvant chemotherapy. We also found that CRP levels were associated with BMI across time points and was negatively associated with the cognitive efficiency cluster over time. Elevated CRP levels before or after 6 months from initiation of adjuvant chemotherapy may provide a way to identify women at risk of impaired long-term cognitive efficiency, which may be amenable to interventions targeting a reduction in levels of CRP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors would like to thank Jamie Sturgill, PhD, and Julie Stillman for their expertise in performing the assays reported in the study.

Source of funding This research was supported by the National Institute of Nursing Research (Lyon/Jackson-Cook; MPI; R01 NR012667). Dr. Jackson-Cook (NIH/NIA R01AG037986) and Dr. A. Starkweather (R01 NR013932) are currently receiving grants. The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Nursing Research (NINR), the National Institute on Aging (NIA), or the National Institutes of Health (NIH).

References

1. American Cancer Society. Cancer facts and figures 2015. Washington, D.C: American Cancer Society; 2015.
2. Jemal A, Ward E, Thun M. Declining death rates reflect progress against cancer. PLoS One. 2010; 5(3):e9584. [PubMed: 20231893]
3. Dodd M, Cho M, Cooper B, Miaskowski C. The effect of symptom clusters on functional status and quality of life in women with breast cancer. Eur J Oncol Nurs. 2010; 14(2):101–110. [PubMed: 19897417]
4. Kim HJ, Barsevick AM, Fang CY, Miaskowski C. Common biological pathways underlying the psychoneurological symptom cluster in cancer patients. Cancer Nurs. 2012; 35(6):E1–E20.
5. Kim H, Barsevick AM, Tulman L, McDermott PA. Treatment-related symptom clusters in breast cancer: a secondary analysis. J Pain Sympt Manag. 2008; 36(5):468–479.
6. Zhou Q, Jackson-Cook C, Lyon D, Perera R, Archer KJ. Identifying molecular features associated with psychoneurological symptoms in women with breast cancer using multivariate mixed models. Cancer Inform. 2015; 14(S2):139–145.
7. Collado-Hidalgo A, Bower JE, Ganz PA, Cole SW, Irwin MR. Inflammatory biomarkers for persistent fatigue in breast cancer survivors. Clin Cancer Res. 2006; 12(9):2759–2766. [PubMed: 16675568]
8. Mehnert A, Scherwath A, Schirmer L, Schleimer B, Peterson C, Schulz-Kindermann F, Zander AR, Koch U. The association between neuropsychological impairment, self-perceived cognitive deficits, fatigue and health-related quality of life in breast cancer survivors following standard adjuvant versus high-dose chemotherapy. Patient Educ Couns. 2007; 66(1):108–118. [PubMed: 17320337]
9. Collins B, MacKenzie J, Tasca GA, Scherling C, Smith A. Persistent cognitive changes in breast cancer patients 1 year following completion of chemotherapy. J Int Neuropsychol Soc. 2014; 20:370–379. [PubMed: 24229809]
10. Myers JS. Chemotherapy-related cognitive impairment: the breast cancer experience. Oncol Nurs Forum. 2012; 39(1):E31–E40. [PubMed: 22201666]
11. Ahles TA, Root JC, Ryan EL. Cancer and cancer-related treatment associated cognitive change: an update on the state of the science. J Clin Oncol. 2012; 30(30):3675–3686. [PubMed: 23008308]
12. Wefel JS, Saleeba AK, Buzdar AU, Meyers CA. Acute and late onset cognitive dysfunction associated with chemotherapy in women with breast cancer. Cancer. 2010; 116(14):3348–3356. [PubMed: 20564075]
13. Ahles TA, Saykin AJ, McDonald B, Furstenberg CT, Cole BF, Hanscom BS, Mulrooney TJ, Schwartz GN, Kaufman PA. Cognitive function in breast cancer patients prior to adjuvant treatment. Breast Cancer Res Treat. 2008; 111(1):143–152.
14. Goedendorp MM, Gielissen MF, Verhagen CA, Peters ME, Bleijenberg G. Severe fatigue and related factors in cancer patients before the initiation of treatment. Br J Cancer. 2008; 99(9):1408–1414. [PubMed: 18941462]
15. Alfano CM, Imayama I, Neuhaus ML, Kiecolt-Glaser JK, Wilder Smith A, Meeske K, McTiernan A, Bernstein L, Baumgartner KB, Ulrich CM, Ballard-Barbash R. Fatigue, inflammation and ω -3 and ω -6 fatty acid intake among breast cancer survivors. J Clin Oncol. 2012; 30(12):1280–1287. [PubMed: 22412148]
16. Pomykala KL, Ganz PA, Bower JE, Kwan L, Castellon SA, Mallam S, Cheng I, Ahn R, Breen AC, Irwin MR, Silverman DHS. The association between pro-inflammatory cytokines and region cerebral metabolism, and cognitive complaints following adjuvant chemotherapy for breast cancer. Brain Imaging and Behav. 2013; 7:511–523.
17. Lyon DE, Cohen R, Chen H, Kelly DL, Starkweather AR, Ahn H, Jackson-Cook CK. 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. *J Cancer Res Clin Oncol*. 2016 (epub ahead of print).

18. Scherling C, Collins B, Mackenzie J, Bielajew C, Smith A. Prechemotherapy differences in response inhibition in breast cancer patients compared to controls: a functional magnetic resonance imaging study. *J Clin Exp Neuropsychol*. 2012; 34(5):543–560. [PubMed: 22380580]
19. Noble JM, Manly JJ, Schupf N, Tang MX, Mayeux R, Luchsinger JA. Association of C-reactive protein with cognitive impairment. *Arch Neurol*. 2010; 67(1):87–92. [PubMed: 20065134]
20. Markus HS, Hunt B, Palmer K, Enzinger C, Schmidt H, Schmidt R. Markers of endothelial and hemostatic activation and progression of cerebral white matter hyperintensities: longitudinal results of the Austrian Stroke Prevention Study. *Stroke*. 2005; 36(7):1410–1414. [PubMed: 15905468]
21. Hoth KF, Tate DF, Poppas A, Forman DE, Gunstad J, Moser DJ, Paul RH, Jefferson AL, Haley AP, Cohen RA. Endothelial function and white matter hyperintensities in older adults with cardiovascular disease. *Stroke*. 2007; 38:308–312. [PubMed: 17204686]
22. Gualtieri C, Johnson L. Reliability and validity of a computerized neurocognitive test battery, CNS Vital Signs. *Arch Clinical Neuropsychol*. 2006; 21(7):623–643. [PubMed: 17014981]
23. Snaith RP. The Hospital Anxiety and Depression Scale. *Health Qual Life Outcomes*. 2003; 1:29. [PubMed: 12914662]
24. Singer S, Kuhn S, Gotze H, Hauss J, Hinz A, Liebmann A, Kraub O, Lehmann A, Schwarz R. Hospital anxiety and depression scale cutoff scores for cancer patients in acute care. *Br J Cancer*. 2009; 100(6):908–912. [PubMed: 19240713]
25. Mendoza TR, Wang XS, Cleeland CS, Morrissey M, Johnson BA, Wendt JK, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. *Cancer*. 1999; 85(5):1186–1196. [PubMed: 10091805]
26. Bower JE, Ganz PA, Aziz N, Fahey JL. Fatigue and proinflammatory cytokine activity in breast cancer survivors. *Psychosom Med*. 2002; 64(4):604–611. [PubMed: 12140350]
27. Lee KA, McEnany G, Weekes D. Gender differences in sleep patterns for early adolescents. *J Adolesc Health*. 1999; 24(1):16–20. [PubMed: 9890360]
28. Miaskowski C, Cooper BA, Paul SM, Dodd M, Lee K, Aouizerat BE, et al. Subgroups of patients with cancer with different symptom experiences and quality-of-life outcomes: a cluster analysis. *Oncol Nurs Forum*. 2006; 33(5):E79–E89. [PubMed: 16955115]
29. Caraceni A. Evaluation and assessment of cancer pain and cancer pain treatment. *Acta Anaesthesiol Scand*. 2001; 45(9):1067–1075. [PubMed: 11683654]
30. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Social Behav*. 1983; 24(4):385–396.
31. Cohen S, Williamson G. Perceived stress in a probability sample of the United States. *The Social Psychol Health*. 1988; 13:123–128.
32. Yeh ET, Willerson JT. Coming of age of C-reactive protein: using inflammation markers in cardiology. *Circulation*. 2003; 107(3):370–371. [PubMed: 12551854]
33. Nudelman KN, Wang Y, McDonald BC, Conroy SK, Smith DJ, West JD, O'Neill DP, Schneider BP, Saykin AJ. Altered cerebral blood flow one month after systemic chemotherapy for breast cancer: a prospective study using pulsed arterial spin labeling MRI perfusion. *PLoS One*. 2014; 9(5):e96713. [PubMed: 24816641]
34. McDonald BC, Conroy SK, Smith DJ, West JD, Saykin AJ. Frontal gray matter reduction after breast cancer chemotherapy and association with executive symptoms: a replication and extension study. *Brain Behav Immun*. 2013; 30:S111–S125.
35. Jansen CE, Dodd MJ, Miaskowski CA, Dowling GA, Kramer J. Preliminary results of a longitudinal study of changes in cognitive function in breast cancer patients undergoing chemotherapy with doxorubicin and cyclophosphamide. *Psychooncology*. 2008; 17(12):1189–1195.
36. Ono M, Ogilvie JM, Wilson JS, Green HJ, Chambers SK, Ownsworth T, Shum DHK. A meta-analysis of cognitive impairment and decline associated with adjuvant chemotherapy in women with breast cancer. *Front Oncol*. 2015; 5:59. [PubMed: 25806355]

37. Jansen CE, Cooper BA, Dodd MJ, Miaskowski CA. A prospective longitudinal study of chemotherapy-induced cognitive changes in breast cancer patients. *Support Care Cancer*. 2011; 19(10):1647–1656. [PubMed: 20820813]
38. Biglia N, Bounous VE, Malabaila A, Palmisano D, Torta DM, D'Alonzo M, Sismondi P, Torta R. Objective and self-reported cognitive dysfunction in breast cancer women treated with chemotherapy: a prospective study. *Eur J Cancer Care*. 2012; 21(2):485–492.
39. Reiner AP, Beleza S, Franceschini N, Auer PL, Robinson JG, Kooperberg C, Peters U, Tan H. Genome-wide association and population genetic analysis of C-reactive protein in African American and Hispanic American women. *Am J Hum Genet*. 2012; 91(3):502–512. [PubMed: 22939635]
40. Pertl MM, Hevey D, Boyle NT, Hughes MM, Collier S, O'Dwyer AM, Harkin A, Kennedy MJ, Conner TJ. C-reactive protein predicts fatigue independently of depression in breast cancer patients prior to chemotherapy. *Brain Behav Immun*. 2013; 34:108–119. [PubMed: 23928287]
41. Ganz PA, Bower JE, Kwan L, Castellon SA, Silverman DH, Geist C, Breen EC, Irwin MR, Cole SW. Does tumor necrosis factor-alpha (TNF- α) play a role in post-chemotherapy cerebral dysfunction? *Brain Behav Immun*. 2013; 30:S99–S108. [PubMed: 22884417]
42. Yang J, Fan C, Pan L, Xie M, He Q, Li D, Wang S. C-reactive protein plays a marginal role in cognitive decline: a systematic review and meta-analysis. *Int J Geriatr Psychiatry*. 2015; 30(2): 156–165. [PubMed: 25475551]
43. Marsland AL, Gianaros PJ, Kuan DC, Sheu LK, Krajina K, Manuck SB. Brain morphology links systemic inflammation to cognitive function in midlife adults. *Brain Behav Immun*. 2015; 48:195–204. [PubMed: 25882911]

Table 1

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)
Ethnicity	
Hispanic	4 % (3/75)
Non-Hispanic	96 % (72/75)
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 peri-menopause	43 % (32/75)
Post-menopause	57 % (43/75)
Luminal A	
Yes	51 % (38/75)

Variable	N = 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)
Adjuvant chemotherapy	
TAC	52 % (39/75)
TC	28 % (21/75)
TCH	14 % (11/75)
CMF	3 % (2/75)
AC	3 % (2/75)
Radiation	
Yes	79 % (59/75)
No	21 % (16/75)
Hormonal therapy T4	26 % (20/75)
Hormonal therapy T5	44 % (33/75)

TAC docetaxel (Taxotere) doxorubicin (Adriamycin), cyclophosphamide (Cytoxan); *TC* docetaxel (Taxotere), cyclophosphamide (Cytoxan); *TCH* docetaxel (Taxotere), carboplatin (Paraplatin), trastuzumab (Herceptin); *CMF* cyclophosphamide, methotrexate, fluorouracil; *AC* doxorubicin (Adriamycin), cyclophosphamide (Cytoxan)

Table 2

Correlations for ln(CRP) with demographics

	Visit 1 (<i>r</i> value <i>p</i> value)	Visit 2 (<i>r</i> value <i>p</i> value)	Visit 3 (<i>r</i> value <i>p</i> value)	Visit 4 (<i>r</i> value <i>p</i> value)	Visit 5 (<i>r</i> value <i>p</i> value)
Age ^a	0.0624	0.1252	0.0697	-0.0203	-0.0288
	0.5947	0.2843	0.5579	0.8657	0.8141
Race ^b	-0.2812	-0.1535	-0.2211	-0.2229	-0.2601
	0.0145	0.1887	0.0601	0.0599	0.0309
Ethnicity ^b	0.0846	0.0069	0.0518	0.2181	0.0996
	0.4707	0.9529	0.6632	0.0657	0.4157
Education ^a	-0.3975	-0.3555	-0.3588	-0.1874	-0.2470
	0.0004	0.0017	0.0018	0.1149	0.0408
Employment ^a	0.0693	0.0718	0.0652	0.1166	0.0069
	0.5548	0.5405	0.5838	0.3294	0.9552
Marital status ^a	-0.0654	-0.0536	-0.0747	-0.0811	-0.1913
	0.5772	0.6482	0.5299	0.4981	0.1153
Income ^a	-0.2829	-0.2715	-0.3067	-0.3323	-0.3093
	0.0139	0.0184	0.0083	0.0043	0.0097
Current ETOH use ^b	-0.2611	-0.1171	-0.2680	-0.2627	-0.2493
	0.0237	0.3171	0.0219	0.0258	0.0388
Current tobacco use ^b	0.1357	0.1610	0.2440	0.2607	0.1567
	0.2457	0.1678	0.0375	0.0270	0.1985
BMI ^a	0.4213	0.4409	0.4600	0.4327	0.4485
	0.0002	<0.0001	<0.0001	0.0001	0.0001
Menopausal status ^b	0.1003	0.1720	0.1860	0.0871	0.0506
	0.3920	0.1400	0.1152	0.4671	0.6798
Chemo type—TAC ^b	0.0770	-0.0529	0.0047	-0.0291	0.0344
	0.5174	0.6564	0.9693	0.8112	0.7824
Chemo type—TC ^b	-0.1572	-0.0114	-0.0820	-0.1458	-0.0434

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

	Visit 1 (<i>r</i> value <i>p</i> value)	Visit 2 (<i>r</i> value <i>p</i> value)	Visit 3 (<i>r</i> value <i>p</i> value)	Visit 4 (<i>r</i> value <i>p</i> value)	Visit 5 (<i>r</i> value <i>p</i> value)
Chemo type—TCH ^{<i>b</i>}	0.1842 0.0910 0.4440	0.9238 0.0854 0.4727	0.4968 0.0936 0.4374	0.2285 0.2132 0.0765	0.7272 0.0080 0.9487
Radiation ^{<i>b</i>}	0.0969 0.4084	−0.0078 0.9469	0.1357 0.2522	0.0421 0.7255	0.0523 0.6696
Neoadjuvant treatment ^{<i>b</i>}	0.0378 0.7477	0.1616 0.1659	0.1553 0.1895	0.1079 0.3672	0.1771 0.1455
Stage ^{<i>d</i>}	−0.0032 0.9784	0.0032 0.9783	0.0811 0.4955	0.1067 0.3725	0.1169 0.3387

Italics indicate significance at $\alpha = 0.05$

^{*a*} Spearman rho correlation

^{*b*} Point bi-serial correlation

Table 3**Clusters by visit**

Visit 1—75.01 % of variance explained by 4 factors	
Factor 1	Cognitive flexibility, executive functioning, complex attention, reaction time, processing speed
Factor 2	Perceived stress, anxiety, depression, sleep disturbance, fatigue
Factor 3	Sleep disturbance, pain, fatigue, verbal memory(+)
Factor 4	Psychomotor speed, visual memory, processing speed
Visit 2—71.36 % of variance explained by 4 factors	
Factor 1	Cognitive flexibility, executive functioning, complex attention, reaction time, processing speed, pain(+), psychomotor speed
Factor 2	Perceived stress, anxiety, depression, sleep disturbance, fatigue
Factor 3	Verbal memory, processing speed, psychomotor speed, pain(+)
Factor 4	Psychomotor speed, visual memory
Visit 3—76.23 % of variance explained by 4 factors	
Factor 1	Perceived stress, depression, anxiety, sleep disturbance, pain, fatigue
Factor 2	Cognitive flexibility, executive functioning, complex attention, reaction time
Factor 3	Processing speed, reaction time, psychomotor speed, pain(+), fatigue(+)
Factor 4	Psychomotor speed, verbal memory, visual memory
Visit 4—70.29 % of variance explained by 3 factors	
Factor 1	Cognitive flexibility, executive functioning, complex attention, reaction time, processing speed, psychomotor speed
Factor 2	Anxiety, perceived stress, depression, sleep disturbance, fatigue, pain
Factor 3	Psychomotor speed, visual memory, verbal memory
Visit 5—72.51 % of variance explained by 3 factors	
Factor 1	Cognitive flexibility, executive functioning, reaction time, complex attention, processing speed, psychomotor speed
Factor 2	Perceived stress, sleep disturbance, depression, anxiety, fatigue, pain
Factor 3	Verbal memory, visual memory, psychomotor speed

Table 4

Weighted sums of variables with significant loading on the factor

Factor 1—global cognition		Factor 2— affective symptoms		Factor 3—cognitive efficiency	
Symptom	Weight	Symptom	Weight	Symptom	Weight
Cognitive flexibility	0.30537	Perceived stress	0.26323	Verbal memory	0.42540
Executive Functioning	0.30472	Sleep disturbance	0.24263	Visual memory	0.43162
Complex attention	0.27399	Depression	0.24717	Psychomotor speed	0.31095
Reaction time	0.21073	Anxiety	0.24197	Processing speed	0.21149
		Fatigue	0.19707		
		Pain	0.10730		

Weighted sums of variables that had a significant loading (absolute value > 0.40) on a factor were calculated. The variables on each factor and their weighting are shown

Table 5

Correlations between CRP (ln) and symptom clusters

	Visit 1 <i>r</i> value (<i>p</i> value)	Visit 2 <i>r</i> value (<i>p</i> value)	Visit 3 <i>r</i> value (<i>p</i> value)	Visit 4 <i>r</i> value (<i>p</i> value)	Visit 5 <i>r</i> value (<i>p</i> value)
Symptom cluster total score					
Global cognition score	-0.1061 (0.3685)	-0.2721 (0.0199)	-0.1669 (0.1643)	-0.1706 (0.1580)	-0.1978 (0.1114)
Affective symptoms score	-0.0356 (0.7636)	0.01575 (0.8948)	0.1872 (0.1181)	0.1661 (0.1693)	0.0515 (0.6812)
Cognitive efficiency score	-0.2706 (0.0197)	-0.24277 (0.0385)	-0.3287 (0.0051)	-0.2746 (0.0214)	-0.3810 (0.0016)
Symptom cluster weighted sums					
Global cognition	-0.1036 (0.3796)	-0.2777 (0.0174)	-0.2335 (0.0500)	-0.2128 (0.0748)	-0.2590 (0.0330)
Affective symptoms	0.1289 (0.2706)	0.05461 (0.6417)	0.2781 (0.0172)	0.2080 (0.0840)	0.1410 (0.2550)
Cognitive efficiency	-0.3199 (0.0055)	-0.3367 (0.0036)	-0.3796 (0.0011)	-0.3018 (0.0105)	-0.3609 (0.0025)

Cluster total scores were derived from factor loading for all visits combined (top three rows). Weighted sums that had a significant loading (absolute value 0.40) on a factor were used for the cluster weighted sums. Italics indicate significance at $\alpha=0.05$.