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Inflammatory Biomarkers, Comorbidity, and Neurocognition in Women With Newly Diagnosed Breast Cancer

Sunita K. Patel, Andrew L. Wong, F. Lennie Wong, Elizabeth Crabb Breen, Arti Hurria, Mackenzie Smith, Christine Kinjo, I. Benjamin Paz, Laura Kruper, George Somlo, Joanne E. Mortimer, Melanie R. Palomares, Michael R. Irwin, Smita Bhatia

Affiliations of authors: Department of Population Sciences (SKP, ALW, FLW, MS, CK, MRP), Department of Supportive Care Medicine (SKP), Department of Medical Oncology (AH, IBP, LK, GS, JM, MRP), Department of Surgery (IBP, LK), City of Hope Medical Center and Beckman Research Institute, Duarte, California; Institute of Cancer Outcomes and Survivorship, University of Alabama at Birmingham, Birmingham, AL (SB); Cousins Center for Psychoneuroimmunology, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, Los Angeles, CA (ECB, MRI).

Correspondence to: Sunita K. Patel, PhD, Building 173, Room 105, City of Hope, 1500 E. Duarte Rd, Duarte, CA 91010 (e-mail: spatel@coh.org).

Abstract

Background: Neurocognitive dysfunction is reported in women with breast cancer even prior to receipt of adjuvant therapy; however, there is little understanding of underlying mechanisms. We tested the hypothesis that pretreatment neurocognitive dysfunction in newly diagnosed patients is related to immunological activation, as indexed by pro-inflammatory cytokines.

Methods: One hundred seventy-four postmenopausal patients with newly diagnosed breast cancer underwent a comprehensive neuropsychological evaluation (assessment of cognitive function, mood, and fatigue) and measurement of key cytokine levels prior to surgery. Age-matched control participants without cancer were evaluated concurrently. Multivariable regression analyses examined the contribution of circulating Interleukin-6 (IL-6), interleukin-1 receptor antagonist (IL-1ra), and soluble TNF receptor type two (sTNF-RII) in predicting neurocognitive performance in patients after controlling for key factors thought to impact functioning. All tests of statistical significance were two-sided.

Results: Memory performance was statistically significantly reduced, in patients compared with controls ($P = .02$). Of the three cytokines measured, only IL-1ra was statistically significantly elevated in cancer patients when compared with control participants (mean ± SD, 375 ± 239 pg/mL vs 291 ± 169 pg/mL, $P = .007$). After controlling for age, education, race, mood, fatigue, body mass index, and comorbidity, cytokines independently explained 6.0% of the total variance in memory performance ($P = .01$) in cancer patients but not control participants, with higher sTNF-RII associated with worse functioning. Exploratory analyses found that comorbidity statistically significantly explained variance in processing speed and executive functioning ($P = .03$ and $P = .03$, respectively).

Conclusion: An association of TNF with memory, previously reported in patients after exposure to chemotherapy, was found prior to initiation of any treatment, including surgery. This association requires further investigation as sTNF-RII was not higher in cancer patients relative to control participants.

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Breast cancer survivors often report neurocognitive dysfunction and fatigue, during and after cancer treatment (1). These symptoms have been termed "chemo brain" and are thought to reflect the impact of systemic chemotherapy on the central nervous system (CNS) (1). However, more recent studies that included a prechemotherapy baseline evaluation report neurocognitive symptoms even prior to adjuvant treatments, with impairment rates ranging from 16% to 33% (2,3).

Remarkably, there is little understanding of the pathogenesis of reduced cognitive function prior to initiation of treatment in patients with newly diagnosed breast cancer. There is evidence to support the hypothesis that behavioral symptoms may be caused by perturbations in cytokines likely driven by an immunologic response to proliferating cancer cells (4). Animal data have demonstrated that circulating pro-inflammatory cytokine levels such as TNF, IL-6, and IL-1 trigger changes in behavior (eg, depressed activity and decreased learning, etc.) (5). Similar behavioral changes have been experimentally induced in humans and support a relation between circulating cytokines and cognitive performance (6); however, comparable associations among clinical populations are limited.

Elevated levels of cytokines and their receptors have been documented and correlated with clinical features (eg, cancer stage) prior to treatment in patients with multiple myeloma (7), bone sarcoma (8), and breast cancer (9). The systemic effects of these elevated pro-inflammatory cytokines are thought to be associated with the behavioral symptoms experienced by some cancer patients and have been investigated after treatment (10,11). Elevated concentrations of soluble interleukin-6 receptor (sIL-6R) and IL-1ra in plasma have been associated with post-treatment fatigue in long-term survivors of breast cancer (11). Preliminary support for an association between TNF and IL-6 and neurocognitive dysfunction was recently reported among breast cancer survivors (12). However, it is not known whether these cytokines play a role in neurocognitive dysfunction identified prior to any therapy. Further understanding of this issue is necessary to help identify the extent of attribution of clinical symptoms to therapy vs those that may exist prior to initiation of cancer treatment. Furthermore, previous studies in breast cancer patients have defined "pretreatment" as prior to adjuvant therapy but after surgical resection of the tumor; this can be problematic, because cytokine levels can be altered following surgery (13).

We aimed to address these gaps by examining the association between neurocognitive functioning and a biologically plausible set of cytokines, selected a priori, in newly diagnosed breast cancer patients, prior to any treatment, including surgery. We further wanted to take into account the fact that patients with breast cancer frequently have other age-associated health conditions that could influence cognitive function. For example, patients with diabetes mellitus show deficits in white matter microstructure that correlate with reduced neurocognitive function (14), and chronically elevated blood pressure is associated with vascular dementia and decline of cognitive function (15). We hypothesized that after controlling for common, previously reported predictors of neurocognitive functioning as well as comorbidity, higher levels of pro-inflammatory cytokines would be associated with worse functioning in breast cancer patients prior to any local or systemic therapies.

While our objective was to elucidate possible explanations of pretreatment neurocognitive dysfunction previously identified in breast cancer patients specifically, women without cancer (ie, controls) were included primarily to compare cytokine levels, as we hypothesized that levels would be higher in breast cancer patients because of cancer-related factors, and would therefore explain pretreatment cognitive dysfunction previously reported in patients.

In our prestudy sample size calculations, after assuming a Type I error of .05, a 0.5 correlation between the key circulating pro-inflammatory cytokine and the key neurocognitive score, it was determined that a sample of 137 women with breast cancer and 50 control participants would provide 86.0% power to detect an effect size of 0.35 between groups in either the mean cytokine levels or mean scores for our primary neurocognitive outcome. The projected correlation of 0.5 was based on two sources: Meyers et al. (2005) (16) reported a spearman r of 0.62 between circulating cytokine and cognitive scores at pretreatment in their sample of AML and MDS patients, and Reichenberg et al. (2001) (6) found a correlation of r = 0.5 between levels of circulating TNF and IL-6 and verbal memory performance following the administration of low-dose endotoxin in healthy volunteers.

Methods

Study Population

Women with newly diagnosed breast cancer at City of Hope were eligible if they were postmenopausal (to control for variability in cytokine levels associated with pre- vs postmenopausal status) (17), had no history of other cancer in the past five years, had no history of major neurologic or psychiatric disorder, were English speaking, had no metastatic disease (to eliminate impact of CNS involvement on neurocognitive functioning), and had no history of infection in the past two weeks (18).

Potentially eligible participants were initially identified by new patient appointments with breast surgeons and, if the new patients were more than a week away from beginning cancer treatment, mailed an invitation letter, followed by a recruitment phone call. A total of 357 eligible patients were identified over a period of three years (2009 to 2012). Of these, 62 patients were not contacted because of short interval to treatment initiation. Of the 295 women contacted, 216 consented (73.2% participation rate). Nonparticipants were more likely to present with stage II or III disease (47.1% vs 40.2%), and were older (mean age: 64 years vs 60 years) when compared with participants. The most common reason for study refusal was feeling overwhelmed. Thirty-five women were deemed inevaluable based on new information following consent (stage IV disease [n = 9], dementia [n = 3], insufficient English fluency [n = 8], cancer care transferred to another facility [n = 15]), reducing the evaluable sample to 181. Patients with a prior cancer diagnosis (n = 7) were excluded from the current analyses to eliminate the potential confound of treatment-related chronic inflammation, decreasing the number to 174.

Data collection procedures were completed prior to any local or systemic cancer treatment and included a nonfasting blood draw into EDTA tubes before 11:00 am, neurocognitive assessment by a trained examiner, and completion of self-report questionnaires.

For approximately every two patients, age-matched, postmenopausal women without history of cancer or other serious illness (ie, noncancer comparison control participants) seen for their routine mammograms at City of Hope were recruited with invitation letters, and eligible women were assessed using the same protocol as the breast cancer patients. A total of 88 women were confirmed as eligible and enrolled (90.7% participation rate), with 9.3% declining enrollment because of limited time. The study was approved by the City of Hope Human Subjects Protection Committee. All participants provided informed consent before study participation.

Measures

Demographic and Health Information

Participants completed a questionnaire providing sociodemographic and health information.

Comorbidity Measure

The revised hypertension-augmented Charlson comorbidity index (hCCI) was used to measure the presence of comorbid chronic health conditions such as diabetes, hypertension, cardiovascular and pulmonary disease, etc. (19). Information on the presence of comorbid health conditions at pretreatment was abstracted from medical records and supplemented by self-report to calculate hCCI scores (Supplementary Table 1, available online).

Clinical Information

Other clinical variables extracted from medical records included histological type and stage of cancer, hormone receptor status, and height and weight to calculate pretreatment body mass index (BMI).

Neurocognitive Measures

The assessment battery consisted of standardized tests to measure cognitive functions. Performance on the tests was consolidated into cognitive domains based on factor analyses and conceptual considerations (Supplementary Table 2, available online). For this study, we focused on executive functioning, memory, and processing speed as these three domains are identified as the predominant neurocognitive processes impacted in patients with non-CNS cancer (20,21). Trails 4, color-word inhibition, and inhibition switching from the Delis Kaplan Executive Function battery (DKEF) (22) measured executive functioning, Hopkins Verbal Learning Test (HVLT) (23) total and delayed recall measured verbal memory, and the Processing Speed Index (PSI) from the Wechsler Adult Intelligence Scale-Fourth Edition (24) measured processing speed.

Fatigue

Fatigue was assessed using the composite score from the Fatigue Symptom Inventory, which is comprised of three fatigue severity items on a scale of 1 to 10 (25).

Mood

The Brief Symptom Inventory (BSI-18) (26) is a standardized, self-report measure to assess mood. The anxiety subscale was used as anxiety is the predominant mood disturbance in newly diagnosed patients and also found to influence neurocognition prior to adjuvant treatment (27).

Cytokines

Three cytokines, interleukin-6 (IL-6), interleukin-1 (IL-1), and tumor necrosis factor (TNF), were assessed based on literature that links them to "sickness" behaviors following activation of an immune response and in processes which signal the brain that infection or injury has occurred. These cytokines are elevated in clinical conditions associated with an inflammatory response and also have been previously correlated with neurocognitive impairment in patients with acute myeloid leukemia (16). Plasma concentrations of IL-6 were determined by high sensitivity ELISA. IL-1 and TNF cytokine activity were assessed by plasma levels of the biomarkers IL-1 receptor antagonist (IL-1ra) and soluble TNF receptor type 2 (sTNF-RII), which can be measured more reliably in plasma than the pro-inflammatory cytokines that induce their production (28–30). Assays were conducted in duplicate according to the manufacturer's protocols (R&D Systems, Minneapolis, MN). Assays included internal control samples to monitor plate-to-plate variability and, when necessary, repeat determinations on diluted samples to confirm preliminary off-scale high value. Information on factors that potentially might influence cytokine levels was obtained from participants in the health and demographic questionnaire and examined in preliminary analyses with correlation tests (Supplementary Methods, available online).

Statistical Analyses

Scores on neurocognitive tests were converted to standardized scores using published normative data. Cytokines had a skewed distribution and were log-transformed for normality. For our primary hypothesis, multivariable linear regression analyses examined the contribution of cytokines in predicting performance on each of the three cognitive domains (executive functioning, processing speed, memory) in cancer patients after controlling for the effects of demographic (education, age, race) and other factors (mood, fatigue, BMI, comorbidity) thought to influence neurocognitive functioning in midlife (31–33). The aforementioned covariates, except for comorbidity, were entered together as the first block. Comorbidity was entered separately in the second block to explore its unique contribution as, despite recent attention, it is not yet an established predictor of neurocognition in the newly diagnosed breast cancer population (34).

All three cytokines were entered together in the final block to examine their effects after controlling for all covariates. Regression models with the above set of predictors were constructed for each of the three neurocognitive domains in the breast cancer group. A P value of less than .02 was considered statistically significant after Bonferroni's correction (.05/3=.017). All other analyses were viewed as exploratory where a P value of less than or equal to .05 was deemed meritorious of future investigation. The effect of each cytokine was subsequently evaluated in post-hoc analyses if they simultaneously indicated statistically significant associations with neurocognition in the primary analyses.

Exploratory analyses involved similar multivariable regressions combining the breast cancer and control sample with a group indicator (controls vs patients) added to examine if neurocognitive performance differed between cancer patients and control participants after controlling for all predictors in the model (age, race, education, mood, fatigue, BMI, comborbidity, cytokines). For any cognitive domains where the control vs patient predictor emerged as statistically significant, we tested the interaction between cytokine, cognition, and group to examine whether the relationship between cytokine and neurocognition was different between patients and controls (ie, did group status moderate the relationship?).

As secondary analyses, cytokines levels were compared between breast cancer patients and control participants using analysis of covariance, controlled for covariates. All tests of statistical significance were two-sided.

Results

Demographic and clinical characteristics and descriptive neurocognitive data are presented in Table 1. While the two groups were similar in comorbidity and BMI, control participants averaged one more year of education, had a higher percentage of non-Hispanic whites and intact cognitive scores than the breast cancer group and had lower mood disturbance.

Table 1. Demographic, clinical characteristics, and neurocognitive scores*

Variable	Control participants (n = 88) No. (%)		Breast cancer (n = 174) No. (%)		C vs BC P†
Age of participant at baseline, mean (SD), y	61.82 (8.13)		60.48 (7.16)		.17
Race/ethnicity					.003‡
Anglo American	70 (80.5)		98 (58.0)		
Hispanic/Latina	7 (8.0)		35 (20.7)		
African American	2 (2.3)		12 (7.1)		
Asian	8 (9.2)		24 (14.2)		
Years of education, mean (SD)	14.89 (1.48)		13.96 (1.92)		<.001
Body mass index, mean (SD)	27.71 (5.91)		28.95 (6.56)		.14
Charleston Comorbidity Index, mean (SD)	0.63 (0.84)		0.69 (0.97)		.63
Number of comorbidity issues calculated based on Charleston Index					.71‡
No comorbidity	45 (5.17)		87 (52.7)		
1 comorbid condition	33 (37.9)		56 (33.9)		
>1 comorbid condition	9 (10.3)		22 (13.2)		
Cancer stage					
0	-		27 (15.5)		-
I	-		77 (44.3)		-
II	-		54 (31.0)		-
III	-		16 (9.2)		-
Estrogen hormone receptor status					
Positive	-		135 (77.6)		-
Negative	-		36 (19.5)		-
Data not available	-		5 (2.9)		-
Progesterone hormone receptor status					
Positive	-		118 (67.8)		-
Negative	-		50 (28.7)		-
Data not available	-		6 (3.4)		
Cancer type					
Ductal carcinoma in situ	-		28 (16.1)		-
Infiltrating ductal carcinoma without CIS	-		127 (73.0)		-
Infiltrating lobular carcinoma without CIS	-		14 (8.0)		-
Mixed infiltrating ductal and lobular carcinoma	-		2 (1.1)		-
Other	-		2 (1.1)		-
Self-reported fatigue, mean (SD)§	3.28 (1.79)		3.53 (2.18)		.29
Self-reported mood, mean (SD)‖	46.38 (8.28)		54.77 (11.26)		<.001
Neurocognitive domains, mean (SD)		<1SD		<1SD	
Executive functioning¶	11.23 (1.73)	1.1%	10.44 (2.5)	8.4%	.02‡
Processing speed#	109.79 (12.89)	1.1%	104.35 (13.69)	7.8%	.02‡
Verbal memory‖	51.88 (6.85)	3.4%	46.00 (11.09)	28.0%	<.001‡

* <1SD = percentage of participants with scores below one standard deviation the normative mean based on published norms from the standardization sample; higher scores on cognitive tasks represent better functioning, while higher scores on fatigue and mood represent worse functioning; - indicates cells which are not plausible (ie, cancer variables for control participants, nontestable group differences). BC = breast cancer patients; C = controls; CIS = carcinoma in situ.

† Indicates two-sided t test probability.

‡ Indicates two-sided chi-square test probability.

§ Scores ranges from 0 to 10 (0 = not at all fatigued; 10 = as fatigued as I could be).

‖ Scores reported in T-scores.

¶ Scores reported in scaled scores.

Scores reported in standard scores.

Multivariable Analysis

Breast Cancer Group

Predictors that were statistically significantly and independently associated with neurocognitive functioning in the breast cancer patients are presented in Table 2. The a priori covariates in block 1 (age, education, race, mood, fatigue, BMI) collectively explained 22.0% to 28.2% variance in all three cognitive domains ($P < .001$). After controlling for block 1 covariates, comorbidity statistically significantly explained an additional 2.4% towards the variance in executive functioning and 2.8% towards processing speed, where the presence of a comorbid condition predicted lowered cognitive performance ($P = .03$ and $P = .03$, respectively).

After controlling for block one covariates and comorbidity, the cytokines block was statistically significantly associated with only one neurocognitive domain: verbal memory ($P = .01$). Specifically, the three cytokines simultaneously explained 6.0% of the variance in memory performance. In post-hoc analyses, sTNF-RII was the only cytokine that was statistically significant as an independent predictor for memory ($P = .01$), with higher

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Table 2. Summary of multivariable regressions analyses predicting pretreatment neurocognitive functioning in breast cancer patients*

Predictor	Executive functioning (n = 151)					Processing speed (n = 136)					Verbal memory (n = 151)				
	β	R^2	ΔR^2	P†	CI	β	R^2	ΔR^2	P†	CI	β	R^2	ΔR^2	P†	CI
Block 1:	-	.282	.282	<.001	(0.17 to 0.40)	-	.235	.235	<.001	(0.12 to 0.35)	-	.220	.220	<.001	(0.11 to 0.33)
Age, y	.10	-	-	.39	(-0.08 to 0.28)	-0.04	-	-	.67	(-0.24 to 0.16)	0.26	-	-	.006	(0.08 to 0.50)
Years of education	0.24	-	-	<.001	(0.08 to 0.40)	0.37	-	-	<.001	(0.19 to 0.54)	0.20	-	-	.01	(0.04 to 0.36)
Race	-0.30	-	-	<.001	(-0.44 to -0.16)	-0.20	-	-	.01	(-0.36 to -0.04)	-0.31	-	-	<.001	(-0.47 to -0.15)
Mood	0.14	-	-	.09	(-0.02 to 0.30)	0.11	-	-	.19	(-0.07 to 0.29)	-0.02	-	-	.85	(-0.19 to 0.16)
Fatigue	-0.12	-	-	.16	(-0.28 to 0.04)	-0.11	-	-	.19	(-0.29 to 0.07)	-0.05	-	-	.60	(-0.23 to 0.13)
BMI	-0.06	-	-	.53	(-0.26 to 0.14)	0.05	-	-	.73	(-0.19 to 0.29)	0.09	-	-	.36	(-0.11 to 0.29)
Block 2:	-	.306	.024	.03	(0.01 to 0.07)		.263	.028	.04	(0.01 to 0.07)	-	.234	.013	.12	(-0.02 to 0.04)
Comorbidity	-0.17	-	-	.04	(-0.33 to -0.01)	-0.18	-	-	.04	(-0.36 to -0.00)	-0.13	-	-	.11	(-0.29 to 0.03)
Block 3:	-	.317	.011	.29	(-0.02 to 0.04)	-	.268	.005	.83	(-0.01 to 0.02)	-	.294	.060	.01	(0.00 to 0.12)
Log IL-6	-0.08	-	-	.33	(-0.26 to 0.10)	0.00	-	-	.91	(-0.22 to 0.22)	-0.02	-	-	.85	(-0.22 to 0.18)
Log sTNFR-II	-0.07	-	-	.29	(-0.27 to 0.13)	0.02	-	-	.87	(-0.18 to 0.22)	-0.31	-	-	.002	(-0.51 to -0.11)
Log IL-1ra	0.13	-	-	.07	(-0.07 to 0.33)	0.08	-	-	.76	(-0.14 to 0.30)	0.23	-	-	.02	(0.03 to 0.43)

*Sample size varies because of missing data as assessments were occasionally shortened to accommodate patients' clinic appointment schedule. Results for block 2 are adjusted for block 1, and results for block 3 are adjusted for all other blocks in the model; - indicates cells which are not plausible. β = standardized regression coefficients; CI = confidence interval; R^2 = R square; ΔR^2= R square change.
† P = relevant probability value associated with the appropriate test (F statistics for ΔR^2 and t statistics for beta weights, all tests two-sided).

levels predicting lower memory (Supplementary Table 3, available online).

Combined Groups

After controlling for all covariates including comorbidity and cytokines, the control vs patient group variable was a statistically significant predictor of memory (*P* = .02), but not executive functioning (*P* = .22), and was suggestive for processing speed (*P* = .08) with lower scores in cancer patients relative to control participants (Supplementary Table 4, available online). Results of the interaction analyses to explore if the relationship between sTNF-RII and memory was different in control participants vs cancer patients were statistically significant (*B* = -19.22, 95% confidence interval [CI] = -38.10 to -0.34, *P* = .05). Specifically, the relationship between sTNF-RII and memory was statistically significant in the cancer patient group (*B* = -13.87, 95% CI = -26.77 to -0.96, *P* = .04); however, this relationship was not evident in the control group (*B* = 5.35, 95% CI = -8.42 to 19.13, *P* = .44,).

Results of the secondary analyses to examine cytokine differences between cancer patients and control participants showed that plasma concentrations of IL-Ira, but not sTNF-RII or IL-6, were higher in patients (mean ± SD, 375 ± 239 pg/mL vs 291 ± 169 pg/mL, *P* = .007) after controlling for study covariates (education, race, age, BMI, comborbidity, mood, and fatigue) (Table 3).

Discussion

In this study we evaluated the hypothesis that neurocognitive compromise in women with newly-diagnosed breast cancer previously observed prior to adjuvant therapy (2) is related to an activated immunological response, indexed by elevated pro-inflammatory cytokines. The only study that examined a cytokine model of neurocognitive dysfunction prior to any treatment was in patients with myelodysplasia/acute myeloid leukemia (16) and was limited by small sample, absence of a control group, and did not control for common factors associated with neurocognitive compromise. To examine relationships between cytokines and cognition, we controlled for factors commonly associated with neurocognitive functioning in midlife (age, education, race, mood, fatigue, BMI) (31–33). Further, a primary concern in this study was to evaluate and control for effects of comorbid health conditions on pretreatment functioning, given the research supporting such a link in other clinical populations (14,15).

Results of the primary multivariable analyses and subsequent post-hoc analyses found that higher TNF, as measured by sTNF-RII, predicted reduced memory performance in patients. This association was recently demonstrated in breast cancer patients three months after completion of chemotherapy, where higher TNF was associated with increased self-report of memory complaints (35).

Neuroscience literature indicates that TNF is essential for the normal function of memory and learning, and that elevated TNF is associated with hippocampal damage in animals (36,37). TNF is known to contribute to neuronal and oligodendroglia cell death (38,39). Higher circulating TNF has been associated with smaller hippocampal volumes in older adults (40) and decreased left hippocampal volumes and lower memory in breast cancer survivors an average of five years from treatment (12). Peripheral cytokines are thought to cross the blood-brain barrier via a saturable transport system, by crossing at circumventricular

Table 3. Differences in baseline cytokine levels between control and breast cancer participants after controlling for education level, race (anglo American vs non-anglo American), BMI, age, mood, fatigue, and comorbidity*

	Control		Breast cancer				
Cytokines†	Mean	SD	Mean	SD	df	F	P‡
sTNFR-II pg/mL	2268	595	2361	904	236	0.522	.47
[minimum, maximum]	[1126–4504]		[1213–9784]				
Range	3378		8571				
IL-6 pg/mL	1.84	1.21	2.43	3.22	236	0.069	.79
[minimum, maximum]	[0.40–6.10]		[0.40–33.70]				
Range	5.70		33.30				
IL-1ra pg/mL	291	169	375	239	236	7.54	.007
[minimum, maximum]	[107–974]		[98–1606]				
Range	867		1508				

* Minimum and maximum values for each cytokine are indicated in brackets. df = degrees of freedom; F = F statistic.
† Cytokine scores presented in raw form pg/mL; analyses were conducted using the log-transformed values.
‡ P value associated with two-sided analysis of covariance result.

organs and by binding to receptors in the blood vessels that permeate the brain, and may subsequently alter neural activity (41). Within this context, the TNF association with memory in patients appears plausible; however, it is not clear why this relationship was not observed in the control group, as this cytokine was not statistically significantly higher in patients compared with control participants.

It is possible the sTNF-RII and memory relationship was evident in cancer patients but not in control participants, because of increased sample size and variability in the patient group. Specifically, the range for cognitive dysfunction was narrow in control participants, with the majority performing well, but was broader in the patient group, where a statistically significantly greater portion (see Table 1) of women obtained memory scores at least one standard deviation below the age expected mean. It is possible that the sensitivity of higher sTNF-RII with lower memory is discernible only when the range of scores is wide enough and includes individuals in the lower range. Of note, after controlling for covariates, memory was the only cognitive domain which remained different between cancer patients and control participants.

Results showed statistically significantly higher IL-Ira in patients even after controlling for covariates, but it was not an independent predictor of cognition. In exploratory analyses, higher IL-Ira predicted increased fatigue in cancer patients, but not in control participants, suggesting possible relationships with other behavioral symptoms.

This study demonstrates for the first time that there exists an association between cytokines and cognition in patients with breast cancer, prior to any treatment. Previous studies demonstrating an association between inflammatory markers and cognition have attributed the association to cancer treatment, but our results suggest these links could be attributed to factors other than cancer treatment, possibly to factors that contribute towards the cancer diagnosis.

Study results also highlight the relevance of other health factors, such as comorbidity, in explaining compromised functioning in breast cancer patients prior to treatment. After controlling for covariates, comorbidity predicted reduced executive functioning and processing speed. While these and other exploratory results require further investigation, we speculate that comorbidity effects on these specific domains may be driven by hypertension, as over a third of our patients were hypertensive. Deficits in executive functioning and processing speed have been identified as the central neuropsychological correlates of cerebral small vessel disease and ischemic pathology in individuals with hypertension (42–44).

This study needs to be considered in the context of its limitations. Inclusion of only postmenopausal breast cancer patients limited generalizability. Evaluation of a limited set of biomarkers could have precluded a more comprehensive assessment of the association between cytokines and neurocognition. Also, while we assessed some factors prior to blood draw that might influence inflammatory markers (Supplementary Methods, available online), our analyses did not control for additional factors that might have influenced cytokine levels (eg, diet/nutrition, medication use, physical activity, etc.). Further, the associations between cytokines and neurocognitive scores in our sample were smaller than we projected when performing prestudy power calculations; therefore, it is possible that the study was unable to detect smaller effects that possibly existed between cytokines and cognitive functioning in either group. Further research with larger samples is needed to clarify results as increased understanding will help distinguish which clinical symptoms are because of the adverse effects of cancer therapy. These limitations notwithstanding, this study is the first to examine the association between systemic levels of proinflammatory cytokines and cognitive deficits prior to treatment in breast cancer patients.

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