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Authors

Patel, Sunita K

Breen, Elizabeth C

Paz, I Benjamin

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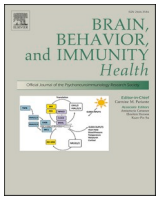

Inflammation-related proteins as biomarkers of treatment-related behavioral symptoms: A longitudinal study of breast cancer patients and age-matched controls

Sunita K. Patel [a,b,*], Elizabeth C. Breen [c], I. Benjamin Paz [d,e], Laura Kruper [d,e], Joanne Mortimer [d], F. Lennie Wong [f], Smita Bhatia [g], Michael R. Irwin [c], Carolyn E. Behrendt [h]

[a] Department of Population Sciences, City of Hope Comprehensive Cancer Center, USA
[b] Department of Supportive Care Medicine, City of Hope Comprehensive Cancer Center, USA
[c] Cousins Center for Psychoneuroimmunology, Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, Los Angeles, CA, USA
[d] Department of Medical Oncology, City of Hope Comprehensive Cancer Center, Duarte, CA, USA
[e] Department of Surgery, City of Hope Comprehensive Cancer Center, Duarte, CA, USA
[f] Department of Population Sciences, City of Hope Comprehensive Cancer Center, Duarte, CA, USA
[g] Institute for Cancer Outcomes and Survivorship, University of Alabama at Birmingham School of Medicine, Birmingham, AL, USA
[h] Department of Computational and Quantitative Medicine, Division of Biostatistics, City of Hope Comprehensive Cancer Center, Duarte, CA, USA

A B S T R A C T

Background: Behavioral symptoms in breast cancer (BC) survivors have been attributed to cancer treatment and resulting inflammation. However, studies linking behavioral symptoms to BC treatment have observed patients only after some treatment. Our prospective study with pre-treatment baseline investigates post-treatment changes in inflammation-related biomarkers and whether those changes correlate with changes in symptoms.

Methods: Participants were postmenopausal women, newly-diagnosed with stage 0–3 BC before any treatment (n = 173 "patients"), and age-matched women without cancer (n = 77 "controls"), who were assessed on plasma markers [soluble tumor necrosis factor receptor type 2 (sTNF-RII), interleukin (IL)-6, IL-1 receptor antagonist (IL-1RA), C-reactive protein (CRP)]) and symptoms (Physical Functioning, Pain, Attention/concentration, Perceived Cognitive Problems, Fatigue, Sleep Insufficiency, Depression). Participants were assessed again 1 month, 1 year, and 2 years after completing primary treatment or similar interval in controls. Generalized linear mixed models tested 4 treatments (surgery alone or with chemotherapy, radiation, or both) for association with change per marker. Joint models tested change per marker for association with change per symptom. Models considered demographic, socioeconomic, and clinical covariates. False Discovery Rate method controlled risk of error from multiple hypotheses.

Results: At one month post-completion of treatment, sTNF-RII and IL-6 were elevated by all BC treatments, as were IL-1RA and CRP after surgery alone (all, $p < 0.05$). By 1 year, markers' average values returned to baseline. Throughout 2-year follow-up, increase-from-baseline in sTNF-RII, IL-1RA, and IL-6 coincided with worsened Physical Functioning, and increase-from-baseline in sTNF-RII coincided with increased Pain (all, $p < 0.01$). These biomarker-symptom associations (excepting IL-6) were exclusive to patients. No other symptoms worsened, and baseline Fatigue and Depression improved in all participants.

Conclusions: BC treatment, even surgery, is associated with transient elevation in inflammatory markers. In patients post-treatment, increase-from-baseline in sTNF-RII accompanies increased Pain and decreased Physical Functioning, suggesting that sTNF-RII merits development as a clinical biomarker in BC patients.

1. Introduction

Advances in screening and treatment for breast cancer (BC) have improved survival rates dramatically, and there are now more than 3.8 million BC survivors in the United States (Miller et al., 2019). However, debilitating physical and behavioral symptoms may persist long after the cancer treatment, diminishing the quality of survivorship (Dodd et al., 2010). These symptoms have been attributed to the effects of chemotherapy on the central nervous system, but similar changes can also occur in BC survivors whose treatment did not include chemotherapy (Phillips et al., 2012; Santos and Pyter, 2018; Cleeland et al., 2003).

The attribution of behavioral symptoms to systemic inflammation induced by cancer treatment has a plausible physiological basis: Cancer treatments, such as chemotherapy and radiation, cause ancillary tissue injury, which activates an immunological response including release of pro-inflammatory cytokines into the blood (Coussens and Werb, 2002). Cytokines can cross the blood-brain barrier and induce behavioral

* Corresponding author. Building 173, Room 105, City of Hope, 1500 E. Duarte Rd, Duarte, CA. 91010, USA.
E-mail address: spatel@coh.org (S.K. Patel).

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changes, including decreased physical and social activity (Gutierrez et al., 1993; Banks, 2005; Wood et al., 2006; Dantzer et al., 1998, 2008). Similar to "sickness behaviors" in animals, behavioral symptoms commonly reported by patients undergoing cancer treatment include fatigue, reduced physical functioning, sleep disturbance, pain, cognitive dysfunction and depressed mood (Kim et al., 2008; Bender et al., 2008; Dodd et al., 2010; Fagundes et al., 2015; Santos and Pyter, 2018).

Reports of association support the idea that behavioral symptoms in BC patients are mediated by inflammatory cytokines (Cleeland et al., 2003; Lee et al., 2004). In BC survivors who have completed chemotherapy, higher interleukin (IL)-6 has been associated with reduced memory performance (Kesler et al., 2013), and elevations in other inflammatory markers, including soluble TNF receptor type 2 (sTNF-RII, also called TNFRSF1B), IL-1 receptor antagonist (IL-1RA), and C-reactive protein (CRP), have been associated with fatigue (Ganz et al., 2013; Bower et al., 2011; Collado-Hidalgo et al., 2006; Alexander et al., 2009), depression (Bouchard et al., 2016), and self-reported cognitive dysfunction (Carroll et al., 2023).

At BC diagnosis, inflammatory markers may be elevated already, due to the cancer or other non-treatment factors (Rutkowski et al., 2003; Lauta, 2003; Picotte et al., 2009; Patel et al., 2015). Therefore, rigorous examination of BC treatment-related changes in inflammatory markers and behavioral symptoms requires a longitudinal study design that includes both patients and non-cancer controls and initiates measurements prior to any local (i.e. surgical) or systemic treatment. Yet in longitudinal studies to date of inflammatory markers in BC patients (Cheung et al., 2015; Lyon et al., 2016; Bower et al., 2022; Carroll et al., 2023), the "pre-treatment" baseline was generally measured after patients had undergone surgical treatment; furthermore, except for Carroll et al. those studies did not include controls without BC, and one study (Bower et al., 2022) also monitored no behavioral symptoms.

To avoid these shortcomings, we undertook a longitudinal study of key inflammatory markers (IL-6, sTNF-RII, IL-1RA, CRP) and a diverse array of behavioral symptoms, all assessed from before any BC treatment through 2 years post-treatment, in postmenopausal women recently diagnosed with breast cancer and age-matched female controls without history of cancer. To control potential confounding of results, our analyses were adjusted for multiple hypothesis testing and considered demographic, socioeconomic, and clinical covariates. Among these are overweight and obesity, linked to chronic inflammation (Galic et al., 2010), and social support, reported to mitigate fatigue and psychological distress in BCsurvivors (Fagundes et al., 2012; Hurtado-de-Mendoza et al., 2022; Yang et al., 2022).

Our research aims were first, to determine the extent to which inflammatory marker levels change with specific types of cancer treatment. Second, we hypothesized that increases in these inflammatory markers would be associated with adverse changes in symptoms: increased fatigue, reduced physical functioning, objective and self-reported cognitive dysfunction, and greater pain, sleep disturbance, and depressed mood. If such associations were present, we were interested to learn whether the associations differed between patients and controls. Incidentally, we were also interested to examine 2 prevalent assumptions: that BC treatment promotes a classic constellation of behavioral symptoms (fatigue, pain, decreased physical functioning, sleep disturbance, cognitive dysfunction, depression) (Lee et al., 2004) and that these treatment-related symptoms improve with time (Ganz et al., 2011).

2. Methods

2.1. Subjects

This prospective cohort study was approved by the City of Hope Human Subjects Protection Committee. All participants provided informed consent before participation. Postmenopausal, English-speaking women were recruited in 2009–2012, as follows. After exclusions for neurological or severe psychiatric disorders (e.g., dementia, traumatic brain injury, stroke, bipolar disorder, schizophrenia), insufficient fluency in English, history of infection within the past 2 weeks and fever at evaluation time, or history of previous cancer, the original study (Patel et al., 2015) enrolled n = 174 "patients" (newly diagnosed with stage 0–3 breast cancer (BC) and scheduled for treatment at our center). Further, as "controls", n = 88 postmenopausal women with no history of cancer or other serious illness were recruited from women who came for routine screening mammograms. Recruitment of both patients and controls was by mailed invitation to participate, targeted to eligible women with upcoming appointments at the center. Each control was matched as closely as possible on age (generally within ±4 years) to 1–3 patients. Participants were queried at every study visit for a history of illness or infection in the past 2 weeks, and temperature was taken to screen for current fever; in cases of recent illness or current fever, visits were rescheduled.

To be eligible for the current analysis, participants must have contributed baseline data on inflammatory markers and on at least one behavioral symptom. Further, during follow-up, they must have contributed inflammatory marker data again at least once. Moreover, to contribute to Aim 2, participants must have contributed symptom data in tandem with inflammatory marker data at one or more follow-up visits.

For this study focused on inflammatory markers, body mass index (BMI, categorized at baseline as normal, overweight, or obese) was a key covariate, because inflammatory cytokines are secreted by adipose tissue and its associated macrophages (Visser et al., 1999; Galic et al., 2010). Participants with below-normal BMI (n = 3) were excluded from the current study, their being too few to analyze as a BMI category but too physiologically distinct to combine with the normal-weight category.

2.2. Study visits

Blood samples and data were designed to be collected at four visits: 1) baseline, before any systemic or local (surgical) cancer treatment; 2) approximately one month after completion of their primary cancer therapy: surgery, radiation, and/or chemotherapy (post-treatment visit); 3) 1 year after treatment completion (1-year visit); and 4) 2 years after treatment completion (2-year visit). Each control participant underwent sample and data collection at time intervals (±3 weeks) similar to the patient(s) with whom they were age-matched at the baseline visit. Participants could continue attending study visits and providing behavioral symptom data even if they stopped providing blood samples, and vice versa.

2.3. Covariates

Education, annual household income, self-identified race/ethnicity, and marital status were obtained from demographic survey at baseline. Additional characteristics at baseline (age, cancer stage, comorbidities, BMI, use of anti-inflammatory medication defined as statins and non-steroidal anti-inflammatory drugs) and hormonal inhibition therapy after completion of systemic treatment were extracted from the electronic medical record. The revised Charlson comorbidity index was calculated per Braithwaite et al. (2009). Covariates recorded at all visits included the timing of the visit (discussed in detail below, under Statistical Models) and self-reported Social Support, assessed using the Medical Outcomes Study Social Support Scale total score (Moser et al., 2012).

2.4. Inflammatory markers

Blood was collected into EDTA tubes from non-fasting participants before 11:00 a.m. Using enzyme-linked immunosorbent assays (ELISA) according to the manufacturer's protocols (R&D Systems, Minneapolis,

MN; ALPCO Immunoassays, Salem, NH), plasma concentrations were determined for sTNF-RII (Quantikine regular sensitivity, lower limit 234 pg/ml taking a 30-fold sample dilution into account), IL-1RA (Quantikine regular sensitivity, lower limit 31 pg/ml), IL-6 (Quantikine high sensitivity, lower limit 0.2 pg/ml), and CRP (Immundiagnostik high sensitivity with the standard curve extended to lower limit 0.2 mg/L). For CRP (assayed last), the samples from all 4 visits by all participants were assayed on the same plate using the same CRP kit lot; for the other markers under study, all participants' samples from baseline and 1-month post-treatment visits were assayed together, while those from 1-year and 2-year visits were assayed together on a different lot of assay plates. No sample tested below the limit of detection for any marker. Across all assay lots, inter-assay coefficient of variation (CV) was 7.4% for CRP, 5.7% for sTNF-RII, 12.1% for IL-6, and 18.9% for IL-1RA (where absolute values were lower in the combined 1- and 2-year samples). Mean intra-assay CVs were 4.0% (CRP), 2.3% (sTNF-RII), 3.5% (IL-6), and 3.6% (IL-1RA).

2.5. Behavioral symptoms

Perceived Cognitive Functioning. Self-reported cognitive functioning was assessed by the norm-referenced, Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A, Roth et al., 2005), which assesses the everyday behavioral manifestations of executive control functions in adults. Construct validity has been established (Roth et al., 2005). Respondents indicate frequency of dysfunction on a Likert scale of "never" to "often" a problem. The BRIEF-A contains 75 items and yields an overall Global Executive Composite (GEC) score. Internal consistency alpha coefficients for the GEC range from 0.93 to 0.96. Higher scores indicate greater difficulties experienced by the individual and are typically reported as age-adjusted T-scores using published normative data (Roth et al., 2005).

Attention/Concentration. Objective assessment of attention/concentration performance, also called working memory, was conducted with the Wechsler Digit Span scale (Wechsler, 2008), for which participants are asked to repeat strings of digits of increasing length and then to repeat them backwards. The first part measures the efficiency of attention, while the second part is more effortful activity that calls upon attention/concentration processes. The two aspects are combined into a single scaled score, adjusted for age using published normative data. Construct validity has been established (Wechsler, 2008). Higher values indicate better attention/concentration functioning. Alpha coefficients range from 0.74 to 0.93. Attention merits study in cancer patients, because it is a key cognitive process that may be disrupted following cancer treatments and because it is less vulnerable to practice effects than are learning memory tasks (Bernstein et al., 2017; Calamia et al., 2012).

Fatigue. Fatigue in the past week was assessed using the Fatigue Symptom Inventory (FSI), a 14-item self-report questionnaire created specifically for cancer populations using an 11-point scale (0 = not at all fatigued; 10 = as fatigued as I can be). The current study analyzed the FSI composite score, the average of 3 severity items, with an alpha coefficient of 0.86 for the current sample, similar to that reported in other samples (Donovan et al., 2008). Construct validity has been established (Hann et al., 2000). Higher scores reflect higher fatigue.

Pain. Pain over the past 24 hours was assessed using the Brief Pain Inventory (BPI), a self-report questionnaire originally developed for cancer patients (Cleeland, 1991). The BPI evaluates pain using an 11-point numerical rating scale (0 = no pain; 10 = pain as bad as you can imagine). Construct validity has been established (Atkinson et al., 2011; Medoza et al., 2006). The current study analyzed the pain severity composite score, an average of 4 pain item scores, with an alpha coefficient of 0.90 in the current sample. Higher scores reflect more pain. Alpha coefficients range from 0.76 to 0.91.

Physical Functioning. The Medical Outcomes Study (MOS) Short Form Survey 36 (SF-36) Physical Functioning subscale, with an alpha coefficient of 0.89 in the current sample, was used to assess limitations in performing daily physical activities (Ware and Sherbourne, 1992; McHorney et al., 1992) This 10-item self-assessment uses a Likert format to query the ability to engage in daily physical activities, from bathing to vigorous activities such as running, without limitations due to health (limited "a lot" to "not at all") Scores are typically reported as summed raw scores or transformed to a 0 to 100 scale. Construct validity has been established (Stewart et al., 1988; Brazier et al., 1992; Alonso et al., 2004). Higher summated ratings represent better functioning.

Depression. The Brief Symptom Inventory 18 (BSI-18) is a norm-referenced, self-reported measure of disordered mood (Derogatis, 2001). Depression, anxiety, and somatic symptoms are measured separately, using subscales to rate the extent to which the participant has been bothered by the symptom in the past week, from Not at all = 0 to Extremely = 4 for depression). Alpha coefficient for this scale is 0.84; raw scores are transformed to T-scores using published normative data. Construct validity has been established. Higher scores reflect higher depression (Derogatis, 2001).

Sleep Insufficiency. Participants were asked to respond to a survey question adapted from the Behavioral Risk Factor Surveillance System survey (Centers for Disease Control and Prevention, 2002). Validity has been reported (Jungquist et al., 2016). Current participants were asked, "In the past month, how often did you not get enough sleep?" Answers used a rating scale that ranged from 1 = "never" to 6 = "almost always".

2.6. Data management

Data on inflammatory markers, age, social support, and all behavioral symptoms except sleep insufficiency were ln-transformed to normalize their distributions, thereby better assuring the linear relationship assumed between the dependent and independent variables in all models. (Choi et al., 2022). After any ln-transformation had been performed, outcomes for the hypothesis-testing models were expressed as change from baseline by subtracting baseline from follow-up values. Continuous covariates (i.e., ln age, ln social support, ln inflammatory marker level at baseline) were centered on their median value in all participants by subtracting the median value. This centering was done to ensure that the model's referent category consists of subjects having the average observed values of such covariates instead of 0 values, which are usually unrealistic or uninterpretable. Missing data were handled as described below.

2.7. Statistical analysis

2.7.1. Preliminary analyses

To compare patients and controls on baseline characteristics, conditional logistic regression took into account the strata of matched patients and their controls.

2.7.2. Statistical Models

The models for Aims 1 and 2 (described below) considered all potential covariates listed above under the heading **Covariates** and retained all that improved the model's fit to the observed data per Akaike's Information Criterion (AIC) (Akaike, 1981). Timing of visit was considered both as a categorical variable (1-month, 1- and 2-year visit) and as a continuous covariate (days since baseline). Days since baseline could not be replaced by days since completing cancer treatment, because the analysis included controls, who by design had no date of completing cancer treatment. When timing of visit was retained as a covariate, potential time-by-treatment interaction was evaluated also.

Models recognized the nested clustering of observations, whereby visits clustered within individual participants who clustered within strata of matched patients and controls.

2.7.3. Analysis of aim 1: to evaluate whether each inflammatory marker's change from baseline varied according to type of treatment for breast cancer

Generalized linear mixed models (one per marker) tested hypothesized associations between BC treatment (Surgery Only; Surgery + Radiation Only; Surgery + Chemotherapy Only; Surgery + Chemotherapy + Radiation; relative to Control) and change from baseline in the inflammatory marker. In considering the above-listed covariates, the models of marker change were adjusted for marker level at baseline and assay lot. Based on prior reports suggesting possible differential impact by chemotherapeutic regimen (Wood et al., 2006; Ceylan and Metin, 2022), an exploratory analysis of Aim 1 evaluated whether the model was improved by distinguishing between Chemotherapy using a Taxotere-based regimen and Chemotherapy using other regimens.

2.7.4. Analysis of aim 2: to evaluate whether changes from baseline in behavioral symptoms are simultaneously associated with changes from baseline in inflammatory markers and if so, whether the associations differ for patients and controls

When repeatedly measured endpoints are associated (as were the symptoms under study), longitudinal multivariate linear mixed models can be useful for studying their joint evolution (Thiébaut et al., 2002). Therefore, for each inflammatory marker, a generalized joint model of symptom changes from baseline included 7 sub-models—one per behavioral symptom. The sub-models of symptom change considered effect modification by status as patient or control and were adjusted for symptom level at baseline, in addition to **Covariates** that improved the model's fit per AIC.

2.7.5. Multiple hypothesis testing

For each Aim, the p value threshold for accepting hypothesized associations as statistically significant was selected to maintain the False Discovery Rate below 5% (Benjamini and Hochberg, 1995). Non-hypothesized associations with covariates were not tested for statistical significance; they appear in the models solely to disclose the nature and extent of potential confounding that was controlled in the statistical analysis.

2.7.6. Missing data

Among **Covariates**, only Social Support included frequent missing values; furthermore, a participant's level of Social Support varied by baseline characteristics and did not vary significantly over time. Accordingly, level of Social Support was imputed when missing using a formula generated by a mixed linear model of Social Support at all visits. Retained as covariates in that model were all demographic, socioeconomic, and clinical factors that improved the model's fit per AIC. The resulting imputation formula was (ln)Social Support = 1.19 + (0.09 if married or divorced) – (0.17 × number of comorbidities, capped at 3) + (0.07 × 1 if annual household income $35,000 or less; × 2 if $35,000-$75,000 or not stated; × 3 if above $75,000) + (0.21 if self-reported as Black) + (0.33 × [(ln)baseline age – 4.09]). Imputation rendered data on Social Support complete for all participants at all visits.

At discontinuation of blood sampling, biomarker data and sometimes symptom data became terminally missing. Therefore, proportional hazards regression was used to evaluate factors potentially associated with time to blood sample discontinuation: baseline characteristics (demographic, socioeconomic, clinical, calendar year of entry), category of BCtreatment, level of same-visit social support, and concomitant hormonal inhibition therapy. Separately, the extent of intermittently missing data was quantified as the percentage of marker and behavioral assessments that were skipped prior to any discontinuation of blood sampling.

3. Results

3.1. Participants at baseline

Current eligibility criteria retained 173/174 patients and 77/88 age-matched controls from the original cohort. At baseline, prior to any treatment (Table 1), patients and controls had similar distributions of

Table 1
Baseline characteristics of participants (N = 250) by breast cancer status.

Categorical Characteristic	Patients, n = 173 N (%)	Controls, n = 77 N (%)	p*
Body Mass Index, kg/m^2			
20 to <25 (Normal)	50 (28.9)	29 (37.7)	0.41
25 to <30 (Overweight)	58 (33.5)	30 (39.0)	Referent
30+ (Obese)	63 (36.4)	18 (23.4)	0.21
Missing Data	2 (1.2)	0	
Comorbidities			
0	92 (53.2)	39 (50.7)	Referent
1	55 (31.8)	32 (41.6)	0.30
2	17 (9.8)	4 (4.2)	0.32
3+	9 (5.2)	2 (2.6)	0.30
Self-Identified Race, Ethnicity			
White, Non-Hispanic	97 (56.1)	63 (81.8)	Referent
White, Hispanic	38 (22.0)	4 (5.2)	0.0013
Asian	14 (8.1)	2 (2.6)	0.04
Black	12 (6.9)	2 (2.6)	0.05
Other (None of the Above)	12 (6.9)	6 (7.8)	0.57
Education			
Less than High School	11 (6.4)	1 (1.3)	0.21
High School Diploma	38 (22.0)	7 (9.1)	0.33
Some College	66 (38.2)	26 (33.8)	Referent
Bachelor's Degree	35 (20.2)	16 (20.8)	0.45
Graduate Degree	23 (13.3)	27 (35.1)	0.002
Marital Status			
Never Married	16 (9.3)	1 (1.3)	0.07
Married/Partnered	108 (62.4)	59 (76.6)	Referent
Divorced	11 (6.4)	2 (2.6)	0.19
Widowed	32 (18.5)	14 (18.2)	0.55
Missing Data	6 (3.5)	1 (1.3)	0.29
Annual Household Income			
Up to $45,000	56 (32.4)	10 (13.0)	0.001
>$45,000 to >$200,000	91 (52.6)	61 (79.2)	Referent
Declined to State	26 (15.0)	6 (7.8)	0.07
Using Anti-inflammatory Medication	86 (49.7)	52 (67.5)	0.02
Continuous Characteristic[a]	**Patients, n = 173 Median (Min-Max)**	**Controls, n = 77 Median (Min-Max)**	**p***
Age, Years	60 (45–84)	61 (45–86)	0.24
Social Support	4.50 (1.08–5.00)	4.42 (1.75–5.00)	0.52
Inflammatory Markers:			
sTNF-RII, pg/mL	2171 (1195–9784)	2215 (1126–4504)	0.44
IL-6, pg/mL	1.7 (0.4–33.7)	1.3 (0.4–6.1)	0.15
IL-1RA, pg/mL	310 (98–1606)	254 (107–1852)	0.009
C-Reactive Protein§, mg/L	2.6 (0.2–50.6)	2.2 (0.2–59.5)	0.16
Behavioral Symptoms:			
Physical Functioning	28 (11–30)	28 (14–30)	0.06
Pain	0.10 (0.10–7.25)	0.10 (0.10–7.00)	0.63
Attention/concentration	9.5 (3.5–16.0)	10.0 (4.0–17.5)	0.03
Perceived Cognitive Problems	51 (36–93)	49 (37–80)	0.09
Fatigue	3.67 (0.10–9.00)	3.33 (0.10–7.00)	0.92
Sleep Insufficiency	3.5 (1.6–6.0)	3.0 (1.0–6.0)	0.14
Depression	48 (40–79)	40 (40–66)	<0.001

*p values are from chi-square tests applied to the results of conditional logistic regression. For categorical variables, the most populous category per variable served as the Referent category.

[a] For continuous characteristics, raw values are presented, but where their distributions were skewed, p values were obtained using natural log-transformed values.

Table 2
Characteristics of participants with breast cancer (N = 173).

	N (%)
Cancer Stage	
0	27 (15.6)
I	75 (43.4)
II	55 (31.8)
III	16 (9.2)
Tumor Histology	
Hormone Positive, HER2-	110 (63.6)
Hormone Positive, HER2+	15 (8.7)
Hormone Positive, HER2 Unknown	18 (10.4)
Hormone Negative, HER2- (Triple Negative)	15 (8.7)
Hormone Negative, HER2+	9 (5.2)
Hormone Negative, HER2 Unknown	2 (1.2)
Not Tested	4 (2.3)
Treatment for Breast Cancer (in addition to Surgery[a])	
Chemotherapy Only	18 (10.4)
Radiation Only	64 (37.0)
Chemotherapy and Radiation	55 (31.8)
None of the Above (Surgery Only)	36 (20.8)
Hormonal Inhibition Therapy[b]	
Yes	124 (72.1)
No	48 (27.9)

Timing of First Post-Treatment Visit, by Treatment (in addition to Surgery)	Median Days (Interquartile Range)	
	Since End of Treatment	Since Baseline Visit
Chemotherapy Only	36 (21–65)	215 (175–261)
Radiation Only	28.5 (13–50)	135 (103–183)
Chemotherapy and Radiation	30 (13–53)	268 (240–300)
None of the Above (Surgery Only)	75 (38.5–100)	92.5 (59–122)

[a] All participants with breast cancer underwent surgery for their disease.
[b] When prescribed, hormonal inhibition therapy was in use at the 1-Year visit and continued through the 2-Year visit. Data on this therapy were missing for 1 patient.

BMI category and comorbidity, Social Support, and most inflammatory markers and behavioral symptoms, but patients scored significantly higher on Depression and IL-1RA (both, $p < 0.01$) and worse on Attention/concentration ($p < 0.05$) than controls. In addition, patients were more likely than controls to identify as lower income or other than Non-Hispanic White, and less likely to have a graduate degree or be taking anti-inflammatory medication (all comparisons, $p < 0.05$) (Table 1). Current smoking was uncommon in both groups (6/173 patients, 1/77 controls) and thus too infrequent to serve as a covariate.

The baseline demographic and socioeconomic characteristics of patients are stratified by treatment group in Supplemental Table 1. Their tumor characteristics and treatments are described in Table 2 and Supplemental Table 2. To summarize, among chemotherapy recipients (n = 73), most received regimens that included either Adriamycin + Cytoxan (n = 34) or Taxotere (docetaxel, n = 33); other regimens were Carboplatin + Paclitaxel (n = 3), Cytoxan + Methotrexate + Fluorouracil (n = 1), or not specified (n = 2). A minority of chemotherapy recipients (15/73) received neo-adjuvant treatment (chemotherapy prior to surgery), followed in most cases (13/15) by radiation. As is typical in breast cancer care, radiation consistently took place after surgery, rather than prior to surgery. By design, the first follow-up visit (at 1-month post-treatment) was timed similarly for patients [median 179 (114–257) days since baseline] and controls [median 177 (119–257) days since baseline). (Table 2).

3.2. Missing outcomes data

A single participant lacked behavioral symptom measurements at any follow-up visit. Thus this individual contributed data to Aim 1 (analyses of biomarker change from baseline) but not to Aim 2 (analyses of symptom change from baseline). Data on the outcomes of interest, i.e., inflammatory markers and behavioral symptoms, were generally complete as over 75% of participants provided blood samples at all 4 visits, and depending on the symptom, between 63.2% and 74.8% of participants provided behavioral data at all visits. Prior to any discontinuation of blood samples, few data were missing: just 5.9% of symptom and 1.9% of biomarker measurements were skipped. At the 1- or 2-year visit, 18.0% of participants discontinued blood samples, usually ceasing symptom measurements also. Discontinuation of blood samples did not differ between patients and controls or by demographic and socioeconomic characteristics, current Social Support, or use of hormonal inhibition therapy. For characteristics associated with missing data on symptoms, see Supplemental Table 3.

3.3. Aim 1: effects of breast cancer treatment on inflammatory markers

The analysis of Aim 1 yielded model-estimated fold-changes from baseline per inflammatory marker (i.e., 2.0-fold change denotes a doubling since baseline, 1.0-fold denotes no change, and 0.5-fold change denotes a halving since baseline). These fold-change estimates, shown in Table 3, were adjusted for the marker's level at baseline and all **Covariates** that improved the individual model (specifically, age, BMI, race/ethnicity, and assay lot). Because the models of Change in IL-6 and IL-1RA included BMI as a covariate, participants (n = 2) without data on BMI were excluded there; also, the model of Change in CRP excluded participants (n = 5) who lacked baseline data on CRP.

As shown in Table 3, the hypothesized associations between cancer treatment and change from baseline in inflammatory markers were evident among patients, but solely at the earliest post-treatment visit, and not among controls. For sTNF-RII and IL-6, all patient subgroups showed some degree of increase from baseline. In contrast, for IL-1RA and CRP, increases from baseline were detected only in patients treated with surgery alone (Table 3).

Uniquely for sTNF-RII, the 1-month post-treatment increase from baseline was especially marked among recipients of Chemotherapy; of note, this increase faded over time (Table 3) and was modest by the time subsequent radiation had been completed. Differentiating between treatment with Taxotere-based regimens and other chemotherapeutic regimens improved the fit of the sTNF-RII model (decreasing its AIC from −506 to −514). According to this exploratory model (Supplemental Table 4), the time-dependent associations between sTNF-RII and having undergone chemotherapy, with and without subsequent radiation, were of greater magnitude and statistical significance after Taxotere-based regimens than after other chemotherapy.

The covariates found informative in these models are shown in Table 3. To summarize these covariates' effects: The older the participant at baseline, the greater her changes in IL-6 and IL-1RA from baseline. The greater the participant's BMI, the greater her changes in IL-6 and IL-IRA from baseline. For all 4 markers, the higher the inflammatory marker's level at baseline, the smaller its increase during follow-up. In the case of IL-6, this relationship was even more pronounced in overweight participants than it was in the other BMI categories. Finally, changes from baseline in IL-6 and CRP varied by self-identified race, and changes from baseline in sTNF-RII and IL-1RA varied by assay lot (Table 3).

3.4. Aim 2: associations between change in inflammatory markers and change in behavioral symptoms

Similar to Aim 1, the analysis of Aim 2 yielded model-estimated fold-changes from baseline, this time in symptoms (Table 4). Unlike the inflammatory marker changes observed in Aim 1, symptom changes from baseline were constant throughout follow-up; hence the models of symptom change were not stratified by the timing of visits. To evaluate the hypothesized marker-symptom associations, each symptom change from baseline was assessed for association with inflammatory marker change at the same visit. Per Table 4, at all follow-up visits, increases from baseline in sTNF-RII, IL-1RA, and IL-6 coincided with worsened

Table 3
Model-estimated fold-change from baseline in inflammatory markers: Associations with breast cancer treatment.

	(ln)sTNF-RII	(ln)IL-6	(ln)IL-1RA	(ln)CRP
	Fold-Change Estimate (95% Confidence Interval)			
At 1-Month Post-Completion Visit, by Treatment				
Surgery Only	1.06 (1.02–1.10)*	1.20 (1.09–1.32)*	1.12 (1.03–1.21)*	1.12 (1.01–1.23)†
Surgery, Radiation Only	1.06 (1.02–1.10)*	1.28 (1.12–1.47)*	0.95 (0.86–1.05)	1.12 (0.92–1.36)
Surgery, Chemotherapy and Radiation	1.17 (1.13–1.22)*	1.43 (1.25–1.64)*	0.89 (0.80–0.98)†	1.11 (0.91–1.34)
Surgery, Chemotherapy Only, by Timing of Visit‡	*	1.26 (1.01–1.56)†	0.93 (0.81–1.07)	0.90 (0.63–1.27)
At 56 Days since Baseline	3.02 (1.03–8.90)	–	–	–
At 120 Days since Baseline	1.96 (0.66–5.76)	–	–	–
At 180 Days since Baseline	1.55 (0.53–4.57)	–	–	–
At 365 Days since Baseline	1.04 (0.35–3.06)	–	–	–
None (Controls)	1.00	1.00	1.00	1.00
At 1- and 2-Year Post-Completion Visits, by Treatment				
Surgery Only	1.00	1.00	1.00	1.00
Surgery, Radiation Only	1.00	1.00	1.00	1.00
Surgery, Chemotherapy and Radiation	1.00	1.00	1.00	1.00
Surgery, Chemotherapy Only	1.00	1.00	1.00	1.00
None (Controls)	Reference	Reference	Reference	Reference
Per Unit of (ln)Age at Baseline	1.21 (1.05–1.39)	1.49 (1.03–2.16)	–	–
Body Mass Index (BMI) at Baseline	–			–
Obese (BMI 30+)		1.25 (1.11–1.40)	1.16 (1.07–1.26)	
Overweight (BMI 25 to <30)		1.02 (0.92–1.13)	1.08 (1.02–1.15)	
Normal (BMI 20 to <25)		0.82 (0.74–0.90)	1.02 (0.94–1.10)	
Per Unit of (ln)Inflammatory Marker at Baseline	0.92 (0.87–0.98)		0.82 (0.77–0.87)	0.77 (0.73–0.82)
If Overweight (BMI 25 to <30)	–	0.55 (0.50–0.61)	–	–
If Not Overweight (BMI <25 or 30+)	–	0.73 (0.61–0.87)	–	–
Self-identified as Other than White[a]	–	0.81 (0.71–0.93)	–	–
Self-identified as Other than White[a] or Black	–	–	–	0.75 (0.60–0.93)
Assay Lot[b]	1.07 (1.03–1.12)	–	0.81 (0.76–0.86)	–

The t statistic was used to assess the hypothesized effects of Treatment, evaluating the fold change shown against the null hypothesis of no change.
*$p < 0.01$.
†$p < 0.05$. Maintaining the False Discovery Rate below 5% for this Table requires limiting statistical significance to those treatment-related associations with $p < 0.01$.
Note: The models of Change in IL-6 and IL-1RA included BMI as a covariate, hence excluded participants ($n = 2$) without data on BMI; also, the model of Change in CRP excluded participants ($n = 5$) who lacked baseline data on CRP.
- - - - - indicates that the covariate or interaction term was dropped from the model for lack of contribution to its fit to the observed data.
‡At the 1-Month Visit, significant interaction was present between Treatment with Chemotherapy Only and (ln)Days since Baseline, necessitating reporting this Treatment's effect over time, with extrapolation as shown.
[a] Self-identification as White includes Non-Hispanic White and Hispanic White.
[b] The kit lots used to assay the combined samples from the 1- and 2-Year visits were contrasted with the kit lots used to assay the combined samples from the baseline and 1-Month post-treatment visits.

Physical Functioning, and increase from baseline in sTNF-RII coincided with worsened Pain, relative to baseline. These marker-symptom associations were exclusive to patients, except for the IL-6 association, which was present in both patients and controls. Among all the potential covariates, only baseline level of symptoms and visit-level Social Support had useful effects: In both patients and controls, higher symptoms levels at baseline were associated with smaller symptom increases at follow-up visits. Also in patients and controls, the more Social Support the participant reported at the follow-up visit, the more favorably her symptoms differed from what they had been at baseline. In particular, the greater the current Social Support, the more marked the reductions in Pain, Fatigue, and Sleep Insufficiency from baseline (Table 4).

The final rows of results for each model in Table 4 present the general post-treatment fold-changes per symptom that remain after the effects of cancer status and covariates were accounted for. Some of these changes were adverse: throughout follow-up, patients (but not controls) reported worsened Physical Functioning, and patients (and to lesser extent, controls) reported greater Pain than they had reported at baseline. Other symptom changes were favorable: patients and controls alike reported reduced Fatigue and Depression relative to baseline. The objective and subjective measures of cognitive functioning (Attention/concentration and Perceived Cognitive Problems) were unchanged from baseline in patients but showed modest improvement in controls. Only Perceived Sleep Insufficiency remained virtually unchanged from baseline in all participants.

4. Discussion

The current study has used rigorous study design and statistical methodology to evaluate and correlate post-treatment changes in inflammatory markers and behavioral symptoms among BC patients. Taken together, current findings support the following original conclusions, discussed in sequential order.

According to this study, transient increases in sTNF-RII and IL-6 occur after all forms of BC treatment, even surgery. Previously, transient increases in these markers have been detected only after chemotherapy (Ganz et al., 2013; Cheung et al., 2015; Lyon et al., 2016; Bower et al., 2022).

Further, the current study demonstrates that transient increases in IL-1RA and CRP also occur but are limited to patients treated with surgery alone, a little studied subgroup (Bouchard et al., 2016). The surgery-only patients have the shortest duration of treatment, hence return earliest for the 1-month post-treatment visit, making them optimal for detecting the most short-lived effects of treatment on inflammatory markers. A recent longitudinal study of CRP in BC patients (Bower et al., 2022) did include a surgery-only subgroup but detected no elevation in CRP there, possibly because that study's baseline visit occurred after BC surgery, when our study indicates that CRP is already elevated. Instead, that study reported CRP to be elevated after chemotherapy, a finding not confirmed in the current study.

Regarding behavioral symptoms, our study confirms that BC patients develop worsened Physical Functioning and Pain after BC treatment and

Table 4
Model-estimated fold-change from baseline in symptoms: Association with change in inflammatory marker.

	(ln)Physical Function	(ln)Pain	(ln)Attention/ Concentration	(ln)Cognitive Problems	(ln)Fatigue	Sleep Insufficiency	(ln)Depression
	Fold-Change Estimate (95% Confidence Interval)						
JOINT MODEL 1 [Marker = sTNF-RII]							
Per Unit Change from Baseline in (ln)sTNF-RII							
If a Patient	0.79 (0.73–0.85)*	3.67 (1.64–8.20)*	0.99 (0.92–1.07)	0.98 (0.91–1.06)	1.26 (0.73–2.18)	0.70 (0.42–1.20)	1.04 (0.96–1.13)
If a Control	1.00 (0.84–1.19)	0.64 (0.10–4.10)	1.01 (0.83–1.23)	0.96 (0.82–1.12)	1.36 (0.39–4.78)	0.99 (0.32–3.09)	0.94 (0.81–1.10)
Per Unit of (ln)Symptom at Baseline							
If a Patient	0.69 (0.64–0.75)	0.49 (0.45–0.54)	0.85 (0.80–0.90)	0.66 (0.61–0.72)	0.51 (0.46–0.56)	0.49 (0.45–0.53)	0.56 (0.52–0.61)
If a Control	0.89 (0.71–1.10)	0.51 (0.42–0.60)	0.69 (0.61–0.78)	0.70 (0.61–0.81)	0.75 (0.63–0.89)	0.70 (0.60–0.82)	0.55 (0.47–0.64)
Per Unit of (ln)Social Support at Same Visit	1.08 (1.04–1.13)	0.44 (0.28–0.71)	1.06 (1.00–1.13)	0.91 (0.88–0.95)	0.54 (0.39–0.76)	0.56 (0.42–0.75)	0.86 (0.83–0.90)
General Change from Baseline, Any Visit							
If a Patient	0.92 (0.91–0.94)	3.60 (2.90–4.46)	1.01 (0.99–1.03)	1.01 (0.99–1.03)	0.72 (0.64–0.81)	1.04 (0.93–1.17)	0.96 (0.94–0.98)
If a Control	1.01 (0.99–1.03)	1.84 (1.29–2.62)	1.05 (1.03–1.07)	0.96 (0.94–0.98)	0.63 (0.51–0.78)	0.92 (0.76–1.12)	0.92 (0.91–0.94)
JOINT MODEL 2 [Marker = IL-1RA]							
Per Unit Change from Baseline in (ln)IL-1RA							
If a Patient	0.93 (0.90–0.97)*	1.14 (0.74–1.75)	1.00 (0.96–1.04)	0.96 (0.92–1.00)	0.84 (0.64–1.11)	0.76 (0.58–1.00)	0.97 (0.93–1.01)
If a Control	1.03 (0.95–1.11)	0.74 (0.34–1.59)	0.97 (0.90–1.05)	1.03 (0.97–1.09)	0.71 (0.43–1.18)	1.05 (0.66–1.68)	1.03 (0.97–1.09)
Per Unit of (ln)Symptom at Baseline							
If a Patient	0.70 (0.65–0.76)	0.50 (0.45–0.55)	0.83 (0.76–0.89)	0.66 (0.61–0.71)	0.51 (0.46–0.56)	0.49 (0.45–0.53)	0.57 (0.52–0.61)
If a Control	0.89 (0.71–1.10)	0.50 (0.42–0.60)	0.69 (0.60–0.79)	0.70 (0.61–0.81)	0.74 (0.62–0.88)	0.70 (0.60–0.82)	0.54 (0.46–0.64)
Per Unit of (ln)Social Support at Same Visit	1.08 (1.04–1.13)	0.43 (0.26–0.70)	1.08 (1.02–1.15)	0.91 (0.88–0.95)	0.54 (0.39–0.75)	0.56 (0.42–0.75)	0.86 (0.83–0.90)
General Change from Baseline, Any Visit							
If a Patient	0.90 (0.89–0.92)	3.74 (3.02–4.64)	1.01 (0.99–1.03)	1.01 (0.99–1.03)	0.73 (0.65–0.82)	1.02 (0.91–1.15)	0.96 (0.94–0.98)
If a Control	1.01 (0.99–1.03)	1.82 (1.26–2.64)	1.05 (1.03–1.07)	0.96 (0.94–0.98)	0.61 (0.49–0.76)	0.92 (0.76–1.12)	0.92 (0.91–0.94)
	(ln)Physical Function	(ln)Pain	(ln)Attention/ Concentration	(ln)Cognitive Problems	(ln)Fatigue	Sleep Insufficiency	(ln)Depression
JOINT MODEL 3 [Marker = IL-6]							
Per Unit Change from Baseline in (ln)IL-6							
In Patient or Control	0.96 (0.94–0.98)*	1.15 (0.91–1.46)	1.02 (1.00–1.04)	1.00 (0.98–1.02)	1.02 (0.87–1.19)	1.12 (0.95–1.31)	1.01 (0.99–1.03)
Per Unit of (ln)Symptom at Baseline							
If a Patient	0.70 (0.65–0.76)	0.50 (0.45–0.55)	0.85 (0.79–0.92)	0.66 (0.61–0.71)	0.51 (0.46–0.56)	0.49 (0.45–0.53)	0.56 (0.52–0.61)
If a Control	0.90 (0.72–1.11)	0.51 (0.42–0.60)	0.69 (0.60–0.79)	0.70 (0.61–0.81)	0.75 (0.63–0.89)	0.70 (0.60–0.82)	0.55 (0.47–0.64)
Per Unit of (ln)Social Support at Same Visit	1.09 (1.05–1.14)	0.41 (0.26–0.66)	1.06 (1.00–1.13)	0.91 (0.88–0.95)	0.54 (0.39–0.76)	0.57 (0.42–0.76)	0.86 (0.83–0.90)
General Change from Baseline, Any Visit							
If a Patient	0.91 (0.90–0.93)	3.63 (2.93–4.51)	1.01 (0.99–1.03)	1.01 (0.99–1.03)	0.73 (0.65–0.82)	1.02 (0.91–1.15)	0.96 (0.94–0.98)
If a Control	1.00 (0.98–1.02)	1.86 (1.28–2.70)	1.05 (1.03–1.07)	0.96 (0.94–0.98)	0.64 (0.52–0.80)	0.94 (0.79–1.12)	0.93 (0.91–0.95)
JOINT MODEL 4 [Marker = CRP]							
Per Unit Change from Baseline in (ln)CRP							
In Patient or Control	0.99 (0.97–1.01)	1.20 (1.02–1.40)	0.99 (0.97–1.01)	1.00 (0.98–1.02)	0.98 (0.89–1.08)	0.94 (0.85–1.04)	1.00 (0.98–1.02)
Per Unit of (ln)Symptom at Baseline							
If a Patient	0.70 (0.65–0.75)	0.50 (0.45–0.55)	0.85 (0.80–0.90)	0.66 (0.61–0.71)	0.52 (0.47–0.57)	0.50 (0.46–0.54)	0.56 (0.52–0.61)
If a Control	0.70 (0.55–0.91)	0.50 (0.42–0.60)	0.68 (0.60–0.78)	0.70 (0.61–0.81)	0.74 (0.61–0.90)	0.70 (0.60–0.82)	0.55 (0.47–0.64)
Per Unit of (ln)Social Support at Same Visit	1.08 (1.04–1.13)	0.44 (0.27–0.72)	1.05 (0.99–1.11)	0.91 (0.88–0.95)	0.54 (0.39–0.76)	0.57 (0.42–0.76)	0.86 (0.83–0.90)
General Change from Baseline, Any Visit							
If a Patient	0.90 (0.89–0.92)	3.86 (3.11–4.79)	1.01 (0.99–1.03)	1.01 (0.99–1.03)	0.73 (0.65–0.82)	1.03 (0.92–1.16)	0.96 (0.94–0.98)
If a Control	1.00 (0.96–1.04)	1.92 (1.32–2.78)	1.05 (1.03–1.07)	0.96 (0.94–0.98)	0.63 (0.50–0.78)	0.92 (0.76–1.12)	0.92 (0.91–0.94)

The t statistic was used to assess the hypothesized associations between marker change and symptom change, evaluating the fold change shown against the null hypothesis of no change.

* Hypothesized association with $p < 0.01$. When associations with $p < 0.01$ are accepted as significant, the Table's overall False Discovery Rate remains below 5%. Note: These models were not improved by adjusting for the timing of follow-up visits or for any other demographic or socioeconomic characteristics.

that these adverse effects remain stable without improving over time, at least not through the 2 years of current follow-up. This finding of symptom persistence confirms what earlier studies of BC survivors (Ganz et al., 2011; Mortimer and Behrendt, 2013) have suggested despite their lack of pre-treatment data.

In contrast to Physical Functioning and Pain, our study demonstrates that other behavioral symptoms do not worsen post-treatment as reported by studies that used cross-sectional design (Bower et al., 2011; Bouchard et al., 2016) or baseline assessment after local or systemic treatment (Ganz et al., 2013). Instead, our patients show sustained improvement in Fatigue and Depression post-treatment and no deterioration in cognitive measures or sleep. A similar absence of cognitive deterioration post-treatment has been reported by Phillips et al. (2012). As a recent meta-analysis (Bernstein et al., 2017) has concluded, previous reports of cognitive deficits after chemotherapy for BC "depend in large part on the comparison group, the cognitive domains examined, and whether prechemotherapy baseline neurocognition is measured."

Although patients in our study show no post-treatment change in either cognitive measure we studied, our controls do show modest improvement from baseline in both cognitive measures. This ability of controls but not BC patients to improve cognitively with re-testing has been observed previously for processing speed (Phillips et al., 2012) and verbal ability (Ahles et al., 2010). This improvement can be considered a practice effect (Calamia et al., 2012; Phillips et al., 2012) (i.e., ability to benefit from repeated exposure) that may be hampered by BC treatment (Phillips et al., 2012; Ahles et al., 2010).

On average in our study, initial treatment-related elevations in inflammatory markers return to baseline levels by 1 year. This pattern does not preclude individual patients from having elevated marker(s) in tandem with worsened symptom(s) at 1 or more follow-up visits. In fact, the current study demonstrates that, throughout at least 2 years post-treatment, increases from baseline in sTNF-RII, IL-6, and IL-1RA correlate with worsened Physical Functioning, and increase from baseline in sTNF-RII correlates with increased Pain. Because sTNF-RII increases with both these symptoms and does so exclusively in patients, we believe that this inflammatory protein merits development as a potential long-term clinical biomarker for the care of BC survivors.

In contrast to identifying biomarkers for Pain and Physical deterioration, the current study does not identify an inflammatory marker for post-treatment cognitive changes as some prior studies have done (Cheung et al., 2015; Lyon et al., 2016; Carroll et al., 2023). This discordance may be explained by the current study's methodological differences from prior studies: Our baseline assessment was made prior to any BC treatment, whereas prior study baseline assessments, although pre-chemotherapy, were generally done after BC surgery had been performed. Prior studies used a self-reported measure (Functional Assessment of Cancer Therapy-Cognitive Function, FACT-Cog) that was not used in the current study. In the study by Carroll et al. (2023), the association between inflammatory marker (CRP) and perceived cognitive impairment disappears when objective measures of Attention and Memory replace FACT-Cog in the same analysis. The current analyses limit the study's risk of error, in contrast to Lyon et al. (2016), who studied 8 neurocognitive domains and 17 cytokines across 5 visits without controlling the excessive risk of error from testing hundreds of potential associations.

An incidental finding from our study is that the more Social Support a participant reports at a follow-up visit, the less adverse are her symptom changes-from-baseline at that visit. This observation is consistent with previous reports (Fagundes et al., 2012; Hurtado-de-Mendoza et al., 2022; Yang et al., 2022) that BCsurvivors' Social Support helps to enhance quality of life and mitigate fatigue, anxiety and depression. As a modifiable target for intervention, Social Support represents a promising area for investigation into improving quality of life in breast cancer survivors (LeRoy et al., 2018).

We acknowledge the limitations of our study. Because inflammatory markers and behavioral symptoms were evaluated before and after, but not during, treatment, our findings cannot be generalized to the period of active treatment. Current findings are generalizable to most BC patients in the United States but not to those absent from our study sample, ie, patients who are younger than age 45, lean, and/or premenopausal. Patients and their age-matched controls differed on some characteristics at baseline. Nevertheless, by studying each participant's change from baseline and by including the endpoint's baseline value, participant's cancer status, and other relevant characteristics as covariates, the current analysis controlled for baseline differences between BC patients and controls.

Other study limitations include our use of a single question to measure sleep and the necessity to allocate our limited resources to collect data on anti-inflammatory medication usage but not data on antidepressant usage. Data collection for this study was informed by our conceptual model, namely that cancer treatments would impact selected inflammatory markers and that changes in these markers would associate with changes in behavioral symptoms. Further, the study's several behavioral outcomes included just 2 cognitive measures, limiting our ability to detect neurocognitive changes after BC treatment. Finally, as is typical in longitudinal cohort studies, some attrition occurred among current participants. However, as we report, attrition rates were relatively low and similar in patients and controls, and skipped assessments were uncommon.

In conclusion, this study finds that treatment for breast cancer, even surgery alone, is associated with transient elevation in inflammatory markers. Moreover, throughout at least 2 years post-treatment, patients experience persistently worse Pain and Physical Functioning than they had before BC treatment. Both adverse effects are accompanied by changes from baseline in sTNF-RII and IL-1RA that are specific to cancer patients regardless of their course of treatment or time since completion of therapy. Based on these findings, we believe that sTNF-RII merits development as a potential biomarker for pain and worsened physical health among BC patients after treatment and throughout their survivorship care. We envision that this biomarker would be used in conjunction with the patient's self-report. The objectivity of a serum biomarker can support clinical decision-making about intervention for these symptoms, especially because many cancer survivors may disclose behavioral symptoms only if prompted by questionnaires not routinely used outside the research setting.

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Disclaimers

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or American Cancer Society.

Author contributions

Conceptualization: SKP, SB, ECB, MIR, FLW; Investigation: SKP, ECB, IBP, LK, JM; Formal analysis: CB; Writing: SKP, CB; Editing of manuscript: All authors.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of City of Hope (IRB#07120).

Consent to participate

Informed consent was obtained from all participants in the study.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2023.100670.

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