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Elevated C-Reactive Protein and Subsequent Patient-Reported Cognitive Problems in Older Breast Cancer Survivors: The Thinking and Living With Cancer Study

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abstract

PURPOSE To examine longitudinal relationships between levels of C-reactive protein (CRP) and cognition in older breast cancer survivors and noncancer controls.

METHODS English-speaking women age ≥ 60 years, newly diagnosed with primary breast cancer (stage 0-III), and frequency-matched controls were enrolled from September 2010 to March 2020; women with dementia, neurologic disorders, and other cancers were excluded. Assessments occurred presystemic therapy/enrollment and at annual visits up to 60 months. Cognition was measured using the Functional Assessment of Cancer Therapy-Cognitive Function and neuropsychological testing. Mixed linear effect models tested for survivor-control differences in natural log (ln)-transformed CRP at each visit. Random effect–lagged fluctuation models tested directional effects of ln-CRP on subsequent cognition. All models controlled for age, race, study site, cognitive reserve, obesity, and comorbidities; secondary analyses evaluated if depression or anxiety affected results.

RESULTS There were 400 survivors and 329 controls with CRP specimens and follow-up data (average age of 67.7 years; range, 60-90 years). The majority of survivors had stage I (60.9%), estrogen receptor–positive (87.6%) tumors. Survivors had significantly higher adjusted mean ln-CRP than controls at baseline and 12-, 24-, and 60-month visits (all $P < .05$). Higher adjusted ln-CRP predicted lower participant-reported cognition on subsequent visits among survivors, but not controls (P interaction = .008); effects were unchanged by depression or anxiety. Overall, survivors had adjusted Functional Assessment of Cancer Therapy-Cognitive Function scores that were 9.5 and 14.2 points lower than controls at CRP levels of 3.0 and 10.0 mg/L. Survivors had poorer neuropsychological test performance (v controls), with significant interactions with CRP only for the Trails B test.

CONCLUSION Longitudinal relationships between CRP and cognition in older breast cancer survivors suggest that chronic inflammation may play a role in development of cognitive problems. CRP testing could be clinically useful in survivorship care.

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ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

The majority of 3.9 million US breast cancer survivors are age 60 years and older.[1-3] Many of these older survivors live with long-term symptoms after treatment.[4] Cognitive problems are among the most concerning of these symptoms, potentially leading to decrements in functioning and social and emotional well-being.[5-14]

Despite decades of recognition of cognitive problems after breast cancer and its therapy, underlying mechanisms remain elusive.[15-17] One candidate mechanism is inflammation driven by cellular damage occurring with cancer and its therapies.[7,15,18-21] Preclinical models of peripheral inflammatory activation document neuroinflammation and impaired cognition, raising the possibility that peripheral indicators of increased inflammation may precede the development of cognitive decline in cancer survivors.[15,22]

Higher levels of inflammatory markers have been associated with cognition in noncancer populations.[23-31] C-Reactive protein (CRP)[32-34] is a measure of chronic inflammation signaling risk for cardiovascular disease[32,35] and mortality,[32,36] and higher levels have been associated

CONTEXT

Key Objective

To determine if higher inflammation predicts later cognitive function in a large, prospective national cohort of older breast cancer survivors and matched noncancer controls followed for up to 60 months.

Knowledge Generated

Older breast cancer survivors had persistently higher C-reactive protein (CRP) levels than controls over time. Survivors with high CRP levels were significantly more likely to report clinically meaningful levels of cognitive problems at later points in time, but this relationship was not seen in controls.

Relevance

Longitudinal relationships between CRP and cognition in older breast cancer survivors suggest that chronic inflammation plays a mechanistic role in development of cognitive problems. CRP testing could be clinically useful in survivorship care to identify survivors needing intervention to prevent and/or long-term surveillance for cognitive decline.

with cognitive problems in patients with cancer.[26,37,38] However, previous studies have been cross-sectional or focused on largely younger patients with cancer pre- and post-chemotherapy, limiting inference about the potential casual role of CRP in longer-term cognitive problems in cancer survivors.[26,37,38]

We used longitudinal data from the Thinking and Living with Cancer (TLC) study to evaluate CRP as an inflammatory signal predicting subsequent changes to cancer-related cognitive problems. TLC is a large, multisite cohort study that enrolled survivors before systemic therapy and followed them and frequency-matched noncancer controls for up to 60 months. We describe long-term CRP levels and evaluate directional relationships by testing if higher CRP levels predict later cognitive problems and explore if effects of higher CRP on cognition are stronger in survivors than controls.[21,39] The results are intended to build the evidence base about biologic pathways involved in cancer-related cognitive problems and determine whether CRP could be useful to identify older breast cancer survivors at risk for cognitive problems.

METHODS

TLC enrolled participants from five cancer centers and affiliated community hospitals and practices.[8,40] We report a planned analysis among participants enrolled from September 1, 2010, to March 1, 2020. All institutional review boards approved the study protocol (ClinicalTrials.gov identifier: NCT03451383).

Population

English-speaking women age 60 years and older, newly diagnosed with primary breast cancer (stage 0-III), were eligible. Noncancer controls were frequency-matched at enrollment within each study site to survivors on the basis of age (within 5 years), education level, and race (White *v* non-White). Exclusion criteria for survivors and controls were non–English-speaking, history of stroke, head injury, major psychiatric or neurodegenerative disorder, treatment for another cancer within 5 years (except nonmelanoma skin cancers) or receipt of past systemic cancer treatment at any time, and a Mini-Mental State Examination score of < 24 or less than a third-grade reading level on the Word Reading subtest of the Wide Range Achievement Test (WRAT4).

In 2016, the protocol was amended (with reconsent) to extend follow-ups and add blood collection. Thus, reconsenting participants enrolled before 2016 could only provide samples at follow-up visits, whereas those entering in 2016 provided enrollment and follow-up samples.

There were 705 survivors and 569 controls enrolled by March 2020, and 529 survivors and 422 controls were active in the study in 2016 (Fig 1). Reasons for no longer being active in the study included completing the study before 2016 or declining consent for the 2016 protocol (115 survivors and 113 controls), death (three survivors and two controls), or study dropout (58 survivors and 32 controls). Among active women, 87.1% of survivors and 88.2% of controls consented to blood collection, and 400 survivors and 329 noncancer controls provided one or more specimens for CRP assays, constituting the analytic sample. Data from survivors who experienced cancer recurrence (n = 6) or developed exclusion conditions during follow-up (n = 2) were removed from that point forward. The analytic sample was similar to the remainder of the overall TLC sample except for higher percentages of White participants (83.1% *v* 77.2%, $P = .008$) and more women with > 2 comorbidities (49.1% *v* 42.3%, $P = .021$). Survivors in the analytic sample had breast-conserving surgery more often than those in the remainder of the overall survivor sample (71.5% *v* 61.7%, $P < .001$).

Data and Sample Collection

Neuropsychological tests and questionnaires were completed at each visit. The baseline visit occurred after

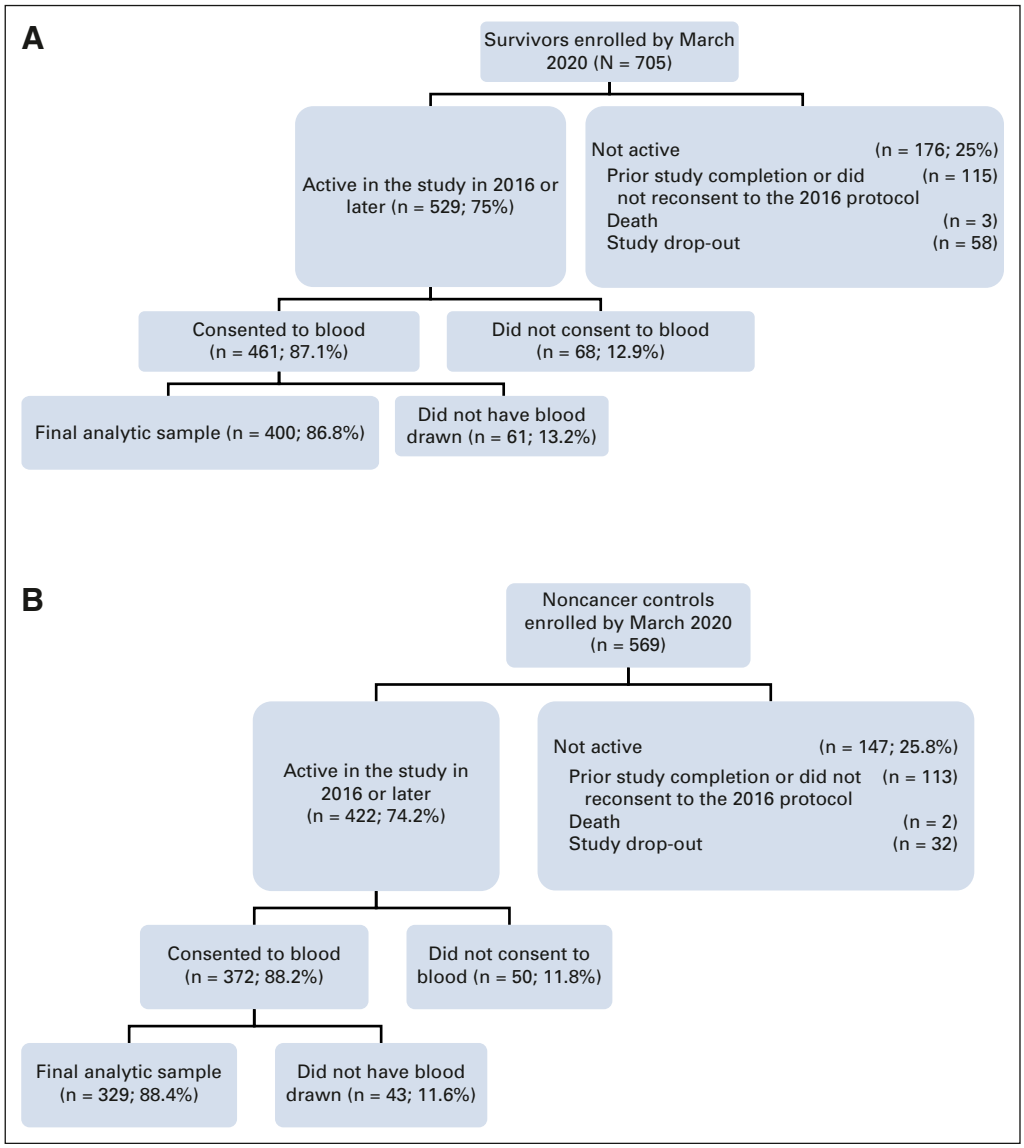

FIG 1. Flow diagram of older breast cancer survivors and noncancer controls included in analyses of the relationships between CRP and cognition. The final analytic sample had one or more CRP result. Reasons for not having blood drawn among those consenting to blood collection included being unable to obtain a specimen and participants choosing to skip the blood draw. Since blood specimens for CRP were not obtained until 2016 under a protocol revision, participants enrolled from 2010 to 2015 might have already completed the study, decided not to continue, or have died or dropped out before blood collection. (A) Survivors. (B) Noncancer controls. CRP, C-reactive protein.

cancer-related surgery but before initiation of systemic therapies and/or neoadjuvant therapy; controls were assessed contemporaneously. Questionnaires ascertained sociodemographic, clinical (eg, comorbidities, height, and weight), and psychosocial (eg, anxiety and depression) factors, and participant-reported cognition and medical record data were abstracted for survivors.

Venous blood specimens were chilled and processed within 8 hours. Platelet-poor EDTA plasma was obtained by centrifugation at 4°C (2,000*g* for 15 minutes or 3,000*g* for 10 minutes), frozen immediately at −80°C, and later shipped on dry ice to the UCLA Cousins Center for Psychoneuroimmunology for storage at –80°C until being assayed.

CRP was assayed on a single kit lot, using the Human CRP Quantikine ELISA (R&D Systems, Minneapolis, MN) according to the manufacturer's protocol with minor modifications, including using a 500-fold sample dilution and extension of the standard curve to obtain a lower limit of detection of 0.2 mg/L.[23] Samples falling below the lower limit of detection (15 samples, 1%) were assigned a value of 0.1 mg/L to retain these samples in our analyses, per standard practice.[23] Three samples were above the upper

TABLE 1. Characteristics of Older Breast Cancer Survivors and Noncancer Controls at Study Enrollment (baseline)

Characteristics of Sample	All (n = 729)	Survivors (n = 400) Mean (SD) or % (No.)	Controls (n = 329)	P[a]
Sociodemographic				
Age, years [range]	67.7 (5.7) [60-90]	67.8 (5.3)[60-85]	67.6 (6.2)[60-90]	.539
Race				.764
Non-White (Black, Hispanic, Asian, and Others)	16.9 (123)	17.3 (69)	16.4 (54)	
White, non-Hispanic	83.1 (606)	82.8 (331)	83.6 (275)	
Education, years	15.5 (2.2)	15.5 (2.1)	15.6 (2.2)	.317
Cognitive reserve, WRAT4 Word Reading score	110.8 (15.7)	109.8 (14.8)	111.9 (16.7)	.072
Clinical				
High comorbidity, > 2	49.1 (345)	56.2 (214)	40.7 (131)	< .001
No. of comorbidities	2.7 (2.0)	3.0 (2.0)	2.5 (2.0)	.001
Diabetes	10.0 (70)	12.4 (47)	7.1 (23)	.021
Cardiovascular diseases (with hypertension)	50.4 (354)	55.4 (211)	44.5 (143)	.004
Psychosocial				
Depression, CES-D score[b]	5.7 (6.7)	6.7 (7.2)	4.5 (5.8)	< .001
Anxiety, STAI State score[c]	27.9 (6.9)	28.8 (7.6)	26.9 (5.9)	< .001
Cognition				
FACT-Cog total[d]	128.6 (17.4)	127.7 (18.3)	129.6 (16.3)	.165
Attention, processing speed, and executive function (APE domain), *z*-score[e]	-0.01 (0.62)	-0.07 (0.61)	0.06 (0.62)	.007
Learning and memory (LM domain), *z*-score[e]	0.03 (0.77)	0.00 (0.77)	0.06 (0.78)	.357
Clinical				
High comorbidity, > 2	49.1 (345)	56.2 (214)	40.7 (131)	< .001
Obesity, BMI ≥ 30 kg/m^2	33.6 (243)	39.3 (157)	26.5 (86)	< .001
AJCC tumor stage				
0	—	17.4 (68)	—	
I	—	60.9 (238)	—	
II	—	18.2 (71)	—	
III	—	3.6 (14)	—	
ER-positive		88.6 (351)	—	
HER2-positive		12.0 (42)	—	
Surgery	—		—	
Lumpectomy		71.5 (284)		
Mastectomy		28.5 (113)		
Survivor treatment				
Any chemotherapy with or without hormonal therapy and without or with radiotherapy	—	23.3 (93)	—	
Hormonal therapy + radiotherapy	—	47.5 (190)	—	
Hormonal therapy, no radiotherapy, or surgery alone[f]	—	29.3 (117)	—	

Abbreviations: AJCC, American Joint Committee on Cancer; ANOVA, analysis of variance; APE, Attention, Processing speed, and Executive function; APE, Attention, Processing speed, and Executive; BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression Scale; DCIS, ductal carcinoma in situ; ER, estrogen receptor; FACT-Cog, Functional Assessment of Cancer Therapy-Cognitive Function; HER2, human epidermal growth factor receptor 2; LM, Learning and Memory; SD, standard deviation; STAI, State-Trait Anxiety Inventory; TLC, Thinking and Living with Cancer; WRAT4, Wide Range Achievement Test.

[a] *P* values from *t*-tests, ANOVA, or chi-square tests comparing survivors versus controls.

[b] On the basis of CES-D continuous scores (range, 0-60); scores of 16+ are considered clinical depression.

[c] On the basis of the STAI State continuous scores (range, 20-80); a score of 54 is considered clinical anxiety in older adults.

[d] FACT-Cog total scores range from 0 to 148; higher scores are better cognition.

[e] *Z*-scores for neuropsychological test performance are age and education standardized to the overall TLC control sample mean at baseline. Scores range from –1 to +1, where zero indicates having the same score as the control group average, scores from > 0 to 1 are better than the average, and scores from < 0 to –1 are worse than the average.

[f] Forty-two women did not receive any local or systemic therapy after surgery (64.3% DCIS); 89.2% of hormonal therapy was with aromatase inhibitors, and 37.6% of chemotherapy regimens included doxorubicin.

limit of detection (75 mg/L) and were assigned a value of 75 mg/L to remove outlier effects. All samples from the same participant at different study visits were run on the same ELISA plate, with a balance of samples from survivors and controls, from at least three recruitment sites, on each plate. All assays were performed in duplicate, with an interassay coefficient of variation of < 6% and a mean intra-assay coefficient of variation of < 4%.

Measures

CRP was the primary predictor of cognition outcomes. The Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) version 3[41] measured participant-reported cognition. The FACT-Cog Total score was the primary cognition outcome, as specified in the study protocol, and captured perceived ability and self-reported difficulties, which can precede decrements on neuropsychological tests.[42] The FACT-Cog Total score (higher scores indicate better cognition) has been used in previous work from our group and others,[8,43] has established thresholds for a clinically significant decline (decrease of 7-10 points), and can be compared across populations with a high degree of reliability in our sample (Cronbach's alpha .95).[44,45] Two FACT-Cog subscales, the Perceived Cognitive Impairments (PCI; Cronbach's alpha = .93) and Perceived Cognitive Abilities (PCA; Cronbach's alpha .84), were used in supplemental analyses.

Secondary cognitive outcomes were based on performance in 11 neuropsychological tests[46-48] of two domains (Attention, Processing speed, and Executive function [APE], and Learning and Memory [LM]).[8,49] Individual tests were also examined.[6,50,51] Scores were standardized (*z*-scores) to the control means at baseline by the age group and education level.

Variables were examined as potential confounders of CRP-cognition relationships, including age, study site, race (White *v* non-White), cognitive reserve (WRAT4 Word Reading score), number of comorbidities (≤ 2 *v* > 2), and obesity (body mass index ≥ 30 *v* < 30 kg/m^2). We also considered depression (CES-D scores[52]) and state anxiety (STAI scores[53]) at each study visit. Among survivors, we considered cancer stage, molecular subtype, and types of therapy.

Analyses

Natural log-transformed CRP (ln-CRP) values were used in all analyses since values were not normally distributed. Results are shown for both ln-CRP and back-transformed non-log CRP mg/L for ease of clinical interpretation: CRP levels are generally categorized as normal/low risk (< 1 mg/L), moderately elevated (1 to < 3 mg/L), and high (≥ 3 mg/L).[54] T-tests, analysis of variance, and chi-square tests were used to test bivariate differences in characteristics of survivors and controls and whether covariates were associated with both CRP and cognition (ie, potential confounders). We tested the stability of a woman's CRP values on repeated assessments using intraclass and median pairwise correlations.

Mixed linear effect models were used to test for differences in adjusted ln-CRP levels for survivors and controls at each study visit. Covariates included in all models were age, race, site, WRAT score, obesity, and comorbidities.

To evaluate the relationship between CRP and cognition, we used a random effect–lagged fluctuation model to test effects of ln-CRP levels at one study visit (baseline and 12, 24, 36, and 48 months) on subsequent cognition (ie, FACT-Cog, APE, and LM) score at the next visit (through 60 months) among survivors versus controls.[55,56] All models include the following covariates: enrollment age, race, site, WRAT score, obesity, and comorbidities. Because of the time-varying nature of the ln-CRP variable, we created between-person and within-person predictors. The between-person predictor tested whether participant's average ln-CRP differed from others and was associated with subsequent FACT-Cog scores. The within-person variable measured whether ln-CRP was associated with subsequent FACT-Cog scores at visits when a participant's ln-CRP value differed from their own average ln-CRP value.

TABLE 2. Plasma CRP Levels at Baseline Presystemic Therapy in Older Breast Cancer Survivors and Noncancer Controls in the Subset Enrolled in 2016 or Later When Specimen Collection Began[a]

		Survivors (n = 245)		
C-Reactive Protein Variable	All (n = 406)	Mean (SD) or % (No.)	Controls (n = 161)	*P*[a]
Mean natural log-transformed CRP, ln mg/L	0.8 (1.2)	1.0 (1.2)	0.4 (1.1)	< .001
Back-transformed mean CRP, mg/L	4.6 (8.7)	5.9 (10.5)	2.7 (3.9)	< .001
Clinical CRP categories, mg/L, %				< .001
< 1	29.3 (119)	21.6 (53)	41.0 (66)	
1 to < 3	34.7 (141)	35.9 (88)	32.9 (53)	
3+	36.0 (146)	42.4 (104)	26.1 (42)	

Abbreviations: CRP, C-reactive protein; SD, standard deviation.

[a]Since plasma CRP was not collected before 2016, only a subset of women had baseline, postsurgery but presystemic therapy data. Natural log-transformed CRP (ln-CRP) data were used in all analyses; back-transformed mean value and clinical categories on the basis of nontransformed CRP values are shown for ease of reference to clinical values.

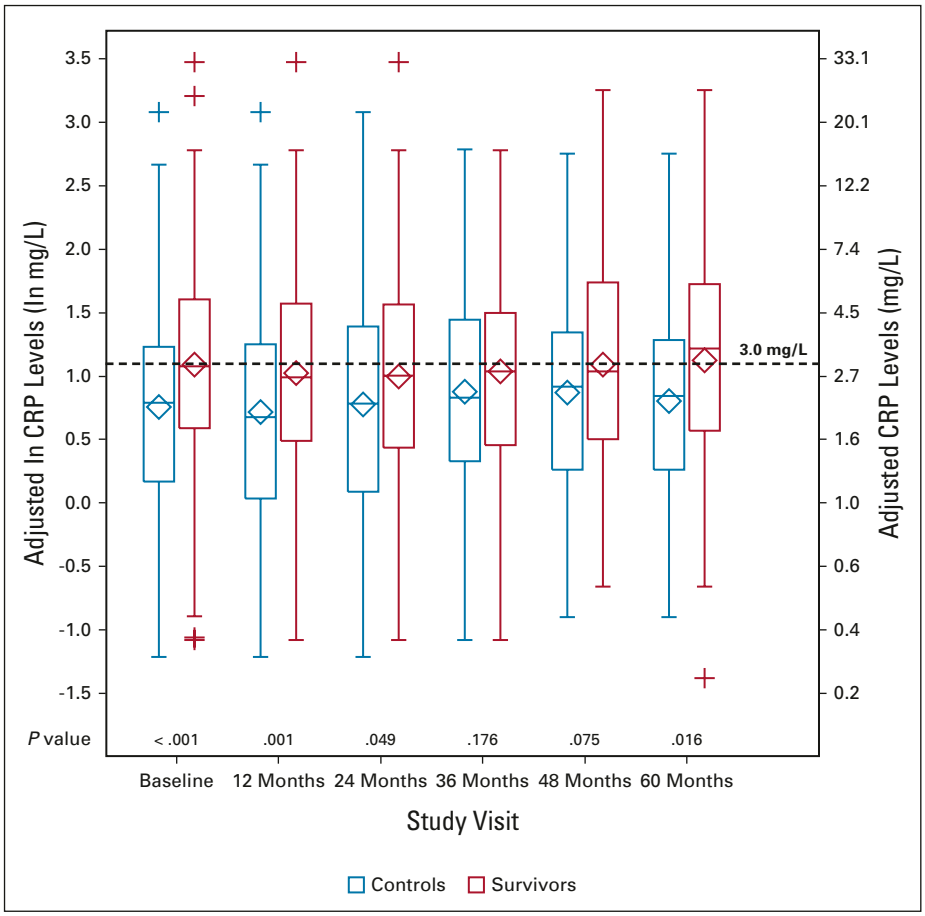

FIG 2. Adjusted CRP levels by study visit for older breast cancer survivors and noncancer controls. Results of mixed model analyses in survivors (red, n = 380 total) and noncancer controls (blue, n = 318 total) at each study visit (baseline and 12, 24, 36, 48, and 60 months) using natural log-transformed CRP data (ln-CRP, left axis), adjusted for age, race (White *v* Others), cognitive reserve (WRAT4 Word Reading score), study site, obesity (≥ 30 *v* < 30 kg/m^2), and comorbidities (> 2 *v* ≤ 2). The results for adjusted ln-CRP values were also back-transformed to mg/L (right axis), and a horizontal dotted line at 3 mg/L (considered high CRP) has been added for ease of interpretation. The boxes indicate the interquartile range (ie, 25th-75th percentiles) of adjusted ln-CRP values, the whiskers above and below the boxes indicate the 5th and 95th percentiles, and + signs indicate values below the fifth or above the 95th percentile. Diamonds represent the mean CRP values; heavy lines inside the box are the median. *P* values from the mixed models for survivor versus control differences in adjusted ln-CRP at each study visit are shown along the *x* axis. See the Data Supplement for detailed data at each study visit. CRP, C-reactive protein; WRAT4, Wide Range Achievement Test.

We included interactions of survivor versus control status and within-person and between-person ln-CRP values. Significant interactions were decomposed by stratifying by survivor-control status. Finally, exploratory analyses evaluated Fact-Cog PCA and PCI scores as outcomes.

Secondary random effect-lagged mixed fluctuation model analyses tested (1) if the interaction between the survivor-control group and ln-CRP effects on subsequent cognition changed if depression or anxiety at each visit was considered, (2) effects of ln-CRP on FACT-Cog subscales (PCI and PCA) and neuropsychological test performance domain Z-scores and individual test *Z*-scores, and (3) if CRP interacted with treatments in effects on cognition in survivor-only analyses. Since stage and molecular subtype were strongly colinear with therapy, we considered therapies only. All models were conducted using SAS Version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

The study participants ranged in age from 60 to 90 years (average 67.7, standard deviation 5.7) and were largely White and well-educated (Table 1). The survivors were comparable with frequency-matched noncancer controls at enrollment in demographics, but survivors were more likely to have > 2 comorbidities (56.2% *v* 40.7%, $P = .001$) and be obese (39.3% *v* 26.5%, $P < .001$); subsequent analyses controlled for these imbalances. Most survivors had stage I disease (60.9%), with estrogen receptor–

TABLE 3. Effects of ln-CRP at One Visit on Cognition in the Subsequent Visit Among Older Breast Cancer Survivors and Controls

	FACT-Cog Total (n = 705)		APE (n = 705)		LM (n = 705)	
Variable	**Estimate (SE)[a]**	***P***	**Estimate (SE)[a]**	***P***	**Estimate (SE)[a]**	***P***
Age	–0.18 (0.15)	.203	**–0.02 (0.004)**	**< .001**	**–0.02 (0.006)**	**< .001**
Cognitive reserve, WRAT4 Word Reading score	0.01 (0.05)	.866	**0.02 (0.002)**	**< .001**	**0.02 (0.002)**	**< .001**
Obesity, ≥ 30 *v* < 30 kg/m^2	**–3.78 (1.75)**	**.031**	–0.09 (0.05)	.087	0.02 (0.08)	.824
Comorbidities, > 2 *v* ≤ 2	–0.12 (1.55)	.936	0.002 (0.05)	.960	0.11 (0.07)	.114
Survivor *v* control	**–5.80 (2.08)**	**.005**	**–0.13 (0.06)**	**.033**	**–0.20 (0.10)**	**.037**
Between-person differences in mean ln-CRP	0.70 (1.03)	.494	–0.02 (0.03)	.558	–0.02 (0.04)	.575
Interaction of survivor/control group and between-person differences in ln-CRP[b]	**–3.43 (1.39)**	**.014**	0.004 (0.04)	.922	–0.02 (0.06)	.746
Within-person difference in mean ln-CRP	0.94 (1.31)	.859	–0.03 (0.03)	.405	–0.06 (0.05)	.254
Interaction of survivor/control group and within-person differences in ln-CRP	0.936 (1.31)	.475	0.03 (0.04)	.521	0.11 (0.07)	.096

NOTE. *P* values < .05 are given in bold.

Abbreviations: APE, Attention, Processing speed and Executive function domain; CRP, C-reactive protein; FACT-Cog, Functional Assessment of Cancer Therapy-Cognitive Function; LM, Learning and Memory domain; WRAT4, Wide Range Achievement Test.

[a]Results from random effect–lagged fluctuation models to test the effects of ln-CRP levels at one study visit (baseline and 12, 24, 36, and 48 months) on subsequent cognition scores at the next visit (through 60 months) by survivor versus control group, controlling for enrollment age, race, study site, cognitive reserve, obesity, and comorbidities. The between-person variable tested whether ln-CRP was associated with subsequent cognition at visits when a participant's average ln-CRP across all her study visits differed from the overall sample average ln-CRP. The within-person variable measured whether ln-CRP was associated with subsequent cognition scores at study visits when a participant's ln-CRP value differed from their own average ln-CRP value.

[b]Adding depression or anxiety to the model for participant-reported cognition did not change the between-person CRP-survivor/control interaction (see the Data Supplement).

positive (87.6%) and human epidermal growth factor receptor 2–negative (88.0%) tumors.

CRP Levels

CRP levels were obtained from 1,550 specimens (819 among 400 survivors; 731 among 326 controls); 62.5% and 70.5% of survivors and controls, respectively, provided two or more specimens (Data Supplement, online only). Among participants with a baseline sample, survivors had a significantly greater percentage of unadjusted, nontransformed baseline CRP values ≥ 3 mg/L than controls (42.4% *v* 26.1%, *P* < .001; Table 2). Baseline CRP levels were significantly associated with obesity in survivors and controls (*P* < .001), but not with other covariates, so obesity was included in subsequent models.

Women's ln-CRP values were stable over time (0.74 and 0.76 for intraclass correlation and median pairwise correlations). Survivors had higher adjusted mean ln-CRP levels than controls at all time points, and these were statistically significantly higher at baseline and 12-, 24- and 60-month study visits (all *P* < .05; Fig 2 and Data Supplement).

Relationships of CRP Levels at One Visit to Cognition at Later Visits

Self-reported cognition. In longitudinal analyses testing directionality of effects, there was a differential impact of adjusted ln-CRP levels on subsequent participant-reported cognition among survivors versus controls, after controlling for age, race, study site, cognitive reserve, obesity, and comorbidities. When survivors had higher ln-CRP values than others (ie, between-person differences), they reported statistically worse cognition on the next study visit (*P* = .040); this relationship was not seen in controls (*P* = .795; *P* for interaction = .014, Table 3 and Fig 3). Notably, as survivor back-transformed CRP levels increased from 1.0 to 3.0 to 10.0 mg/L, adjusted FACT-Cog scores were 5.2, 9.5, and 14.2 points lower, respectively, than controls (Fig 3). The interaction of CRP with survivor/control status was unchanged after considering depression or anxiety (Data Supplement). Similar results were observed examining relationships with FACT-Cog PCI and PCA subscales (Data Supplement).

Neuropsychological test performance. Adjusted ln-CRP levels did not predict subsequent scores in either survivors or controls on overall neuropsychological test performance for the APE or LM domains (Table 3). Survivors did have small decreases in neuropsychological test performance (*v* controls) with significant interactions with CRP for the Trails B test (a component of the APE domain) and trends for other tests (Data Supplement) although after considering multiple testing, these did not remain significant.

Survivors only. Among survivors, only 23.3% received chemotherapy, and different combinations of systemic and radiotherapy did not interact with ln-CRP levels in effects on participant-reported cognition or neuropsychological test performance (Data Supplement). The majority of women received aromatase inhibitors (Data Supplement), so we were unable to test differences by specific hormonal treatment.

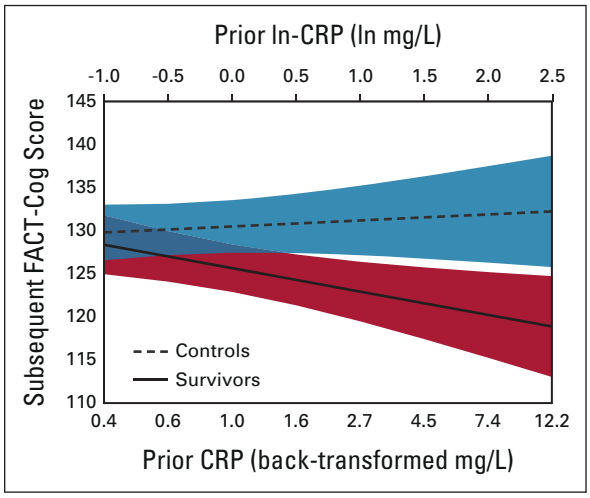

FIG 3. Relationship between CRP levels and participant-reported cognition score on the subsequent visit among survivors and controls (n = 641). The graph illustrates subsequent FACT-Cog Total scores on the basis of the CRP level at the prior visit from fluctuation model analyses using adjusted natural log-transformed CRP (ln-CRP) values (upper axis); corresponding back-transformed CRP values shown on the lower axis for ease of interpretation. The model adjusted ln-CRP for age, race (White *v* Others), cognitive reserve (WRAT4 Word Reading score), study site, obesity (≥ 30 *v* < 30 kg/m^2), and comorbidities (> 2 *v* ≤ 2). Possible FACT-Cog scores range from 0 to 148, with higher scores indicating better cognition; analyses include the full FACT-Cog score range, but the graph shows a truncated scale. The interaction of between-person differences in ln-CRP and the survivor/control group in effects on participant-reported cognition was significant at $P = .008$. CRP, C-reactive protein; FACT-Cog, Functional Assessment of Cancer Therapy-Cognitive Function; WRAT4, Wide Range Achievement Test.

DISCUSSION

To our knowledge, this is one of the first studies examining the long-term longitudinal relationship between chronic inflammation and cognition in older breast cancer survivors and comparing these effects with those seen in noncancer controls. We found that higher CRP levels predicted having lower participant-reported cognition on later visits among survivors, but not controls. There were also suggestive but nonsignificant trends in the relationship of CRP to subsequent performance on standardized neuropsychological tests. Interestingly, older survivors had significantly higher circulating CRP levels than controls even before systemic therapy, and survivors' CRP levels remained consistently higher at visits up to five years postsurgery.

Our results add to the body of evidence linking inflammation to cognition in cancer survivors[57-59] by determining longitudinal relationships between CRP and cognition over a period of up to 60 months. We found that having higher-than-average CRP on one study visit significantly predicted decrements in participant-reported cognition at the next visit in older survivors but not controls. This effect was unchanged by depression or tanxiety. The effects of higher CRP on participant-reported cognition were clinically meaningful, with survivors having adjusted FACT-Cog scores that were 9.5 points lower than controls at CRP levels of ≥ 3 mg/L.

Although suggestive, our results were less robust for the impact of CRP on subsequent neuropsychological test performance. Others have reported declines in neuropsychological test performance in short-term investigations mainly in patients receiving chemotherapy.[57,58] Our results for neuropsychological test performance may differ from previous work because the TLC sample has low chemotherapy rates. It is also possible that well-educated women like those enrolled in TLC noticed cognitive problems, but had sufficient cognitive reserve to maintain neuropsychological test performance. Alternatively, neuropsychological testing might have low ecological validity since it is performed in a highly structured environment[60] although subjective measures can capture challenges that individuals experience in their everyday lives and be more sensitive to change.[60] In addition, it is also plausible that the effects of chronic systemic inflammation on the brain manifest years after self-reported problems and only become evident on objective measures with declines in compensatory capacity as individuals age or accumulate greater comorbidity. Longitudinal neuroimaging studies will be useful to understand these longitudinal relationships.

Our observation that older breast cancer survivors had significantly higher CRP levels compared with controls before beginning any systemic therapy suggests that having cancer may be related to or cause higher inflammation. Baseline elevations in CRP in survivors versus noncancer controls also persisted over time at most visits, independent of covariates. This observation suggests that CRP remains higher well after surgical removal of the primary cancer and is independent of some of the most common risk factors for cancer and inflammation, including medical comorbidities and obesity.

Taken together, our prospective results suggest that inflammation may be involved in mechanistic pathways leading to cancer-related cognitive problems. This idea is biologically plausible since peripheral inflammation results in subsequent impairments in cognitive performance in preclinical models,[22] has a known relationship with cognitive disorders, can increase brain inflammation seen with neurodegeneration,[59,61] and can further promote inflammation in a feed forward loop.[61] In the case of cancer and its treatments, compromised integrity of the blood brain barrier because of chemotherapy exposure[38] may also elevate risk for subsequent inflammation-mediated cancer-related cognitive problems.[62] Although we did not observe an effect of chemotherapy in these analyses, only a small proportion of our survivors had this treatment modality.

Our data support the need for studies to test the hypothesis that behavioral and/or pharmacological interventions targeting inflammation may prevent or reduce cancer-related cognitive problems in older breast cancer survivors.[17,63]

Potential interventions targeting inflammation include increasing physical activity, improving sleep, reducing stress, and administering drugs that block inflammatory pathways.[64-72]

This study has many strengths, including the large cohort, long follow-up, and inclusion of matched controls. However, there are several limitations that should be considered in evaluating our findings. First, although women in our sample were representative of the communities served by our tertiary academic medical centers and their community affiliates, they were predominantly White and well-educated, limiting external generalizability. It will be critical to replicate our results in more diverse samples, especially groups with lifetime experiences associated with increased chronic inflammation.[39] Second, there were insufficient numbers receiving chemotherapy and limited variability in types of regimens to determine if the relationship between CRP and cognition varied by specific regimens. Others have found that radiotherapy and/or chemotherapy induce cellular damage that can, in turn, increase peripheral inflammation[73,74] and cognitive problems.[23,25-28,58,75-77] Although our sample of survivors were predominantly prescribed aromatase inhibitors, future research will need to investigate whether differences in hormonal treatments (eg, tamoxifen *v* aromatase inhibitors) differentially relate to hepatic production of CRP. This is an important future direction given existing data linking hormonal therapy to perceived impairments in cognition[78] and CRP levels.[79,80] Third, since blood collection was added to an established cohort, not all survivors had plasma CRP data before systemic therapy. Fourth, it will be important to replicate results with other inflammatory markers. Finally, there may be critical windows during and immediately after active treatment when inflammation is particularly higher and drives changes in cognition that we might have missed with having our first follow-up visit at 12 months.

Overall, this large longitudinal multisite study demonstrated that older breast cancer survivors had higher inflammation as measured by circulating levels of CRP starting before systemic therapy and continuing over time. This higher inflammation was predictive of clinically meaningful participant-reported cognitive problems at later time points in survivors but not controls. The results underscore the importance of asking about survivors' perceptions of their cognitive function and suggest that CRP data may be useful to oncology providers to identify older breast cancer survivors at risk for cognitive problems.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Elevated C-Reactive Protein and Subsequent Patient-Reported Cognitive Problems in Older Breast Cancer Survivors: The Thinking and Living With Cancer Study

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