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Correlates of circulating C-reactive protein and serum amyloid A concentrations in breast cancer survivors

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Abstract

Introduction—Inflammatory status may be an important prognostic factor for breast cancer. Correlates of markers of inflammation in breast cancer survivors have not been thoroughly evaluated.

Methods—Using data from, the Health, Eating, Activity, and Lifestyle (HEAL) Study (a population-based, multiethnic prospective cohort study of female breast cancer patients) we evaluated the associations between circulating markers of inflammation (C-reactive protein [CRP] and serum amyloid A [SAA], measured ~31 months after diagnosis) and several demographic, lifestyle, and clinical characteristics in 741 disease-free breast cancer survivors. Analysis of variance and regression methods were used for statistical analyses of log-transformed values of CRP and SAA.

Results—After adjusting for age, BMI, ethnicity, and study site, higher concentrations of CRP were associated with increasing concentration of SAA (p-trend<0.0001), increasing age (p-trend<0.0001), increasing BMI (p-trend<0.0001), increasing waist circumference (p-trend<0.0001), positive history of heart failure (p=0.0007), decreasing physical activity (p-trend=0.005), Hispanic ethnicity (p=0.05 vs. non-Hispanic white), and current smoking (p=0.03 vs. never smoking). Vitamin E supplementation (p=0.0005), tamoxifen use (p=0.008), and radiation treatment (compared to no chemotherapy or radiation; p=0.04) were associated with reduced CRP. Associations of CRP with clinical characteristics were not significant in the adjusted models. In a multivariate analysis, CRP showed significant associations with waist circumference, BMI, age, history of heart failure, tamoxifen use, and vitamin E supplementation (R^2=0.35). Similar, yet fewer, associations were observed for SAA (R^2=0.19).

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Conclusions—This study highlights important correlates of inflammatory status in breast cancer patients. Our results are consistent with those from similar studies of healthy women.

Keywords

body mass index (BMI); breast cancer; C-reactive protein (CRP); inflammation; serum amyloid A (SAA)

Introduction

Inflammation has been implicated in the etiology of several diseases, including cardiovascular disease [1] and cancer [2]. Cancers associated with infection (e.g. cervical cancer) and chronic inflammatory conditions (e.g. esophageal cancer) suggest that inflammation may be a key microenvironmental factor contributing to the development and progression of other tumor types [2]. Supporting this hypothesis is the association between regular use of non-steroidal anti-inflammatory drugs (NSAIDs) and decreased risk of colon [3–5] and breast cancer [6], indicating that inhibition of inflammatory processes may reduce cancer risk [7].

C-reactive protein (CRP) and serum amyloid A (SAA) are nonspecific, acute-phase proteins. Both are secreted primarily by the liver in response to cytokines such as interleukin-1, interleukin-6 (IL-6), and tumor necrosis factor-α (TNFα) [8], resulting in correlated concentrations of these proteins in blood. CRP is involved in several immune-related processes, such as opsonization (for phagocytosis) and classical complement binding, while SAA is believed to be involved in cholesterol transport, extra-cellular matrix degradation, and the recruitment of inflammatory cells to cites of inflammation [8–10]. These biomarkers may be utilized as surrogate markers for low-grade chronic inflammation and are potential predictors of cancer risk and/or survival. Chronic inflammation, as measured by CRP, has been associated with poor survival for several cancers, including metastatic prostate [11], gastro-esophageal [12], colorectal (following curative resection) [13, 14], inoperable non-small cell lung [15], and pancreatic cancer [16].

CRP may also be an important prognostic factor for breast cancer. Breast cancer patients have elevated concentrations of CRP prior to surgery, and these concentrations are higher in women with more advanced stage of disease [17, 18]. Recently, elevated CRP blood concentrations were associated with decreased survival in a British study of 353 incident breast cancer patients, although elevated CRP was also associated with decreased overall survival in women without cancer [19]. CRP is also a risk factor for cardiovascular disease, for which breast cancer patients have an increased risk following radiation treatment [20].

In individuals without breast cancer, elevated levels of CRP have been associated with body mass index (BMI), waist to hip ratio [21, 22] and sedentary lifestyles [21, 23–26] in cross-sectional surveys. Body fatness is the most important known determinant of CRP, probably due to the fact that adipose tissue expresses and releases IL-6 [27], inducing hepatic CRP production. Weight loss and consistent exercise/exercise training interventions [28–30] are associated with a reduction in CRP levels. Elevated CRP is also associated with increasing age, African American ancestry, and female gender [31]. Medications such as COX-2 inhibitors, lipid lowering agents, and ACE inhibitors reduce CRP concentrations, and oral estrogen replacement therapy use increases CRP concentrations [32].

Few studies have explored factors that correlate with inflammatory markers in breast cancer survivors [33, 34], and none have examined the correlates of CRP and SAA specifically. The aim of the present study was to thoroughly evaluate the associations between markers of

inflammation (CRP and SAA) and various demographic and prognostic factors in a cohort of breast cancer survivors. We present our findings according to the Reporting Recommendations for Tumor Marker Prognostic Studies [35].

Methods

Study Setting, Participants, and Recruitment

The Health, Eating, Activity, and Lifestyle (HEAL) Study is a population-based, multicenter, multiethnic prospective cohort study that has enrolled 1,183 breast cancer patients who are being followed to determine whether weight, physical activity, diet, sex hormones, mammographic density, and other factors affect breast cancer prognosis. Women were recruited into the HEAL study through Surveillance, Epidemiology, End Results (SEER) registries in New Mexico, Los Angeles County (CA), and western Washington. Names and contact information were retrieved from the SEER registries. Details of the aims, study design, and recruitment procedures have been published previously [36–38].

Briefly, in New Mexico, we recruited 615 women, aged 18 years or older, diagnosed with in situ to Stage IIIA breast cancer between July 1996 and March 1999, and living in Bernalillo, Sante Fe, Sandoval, Valencia, or Taos Counties. In Western Washington, we recruited 202 women, between the ages of 40 and 64 years, diagnosed with in situ to Stage IIIA breast cancer between September 1997 and September 1998, and living in King, Pierce, or Snohomish Counties. In Los Angeles County, we recruited 366 Black women with stage 0 to IIIA primary breast cancer, who had participated in the Los Angeles portion of the Women's Contraceptive and Reproductive Experiences (CARE) Study, a case-control study of invasive breast cancer, or who had participated in a parallel case-control study of in situ breast cancer. HEAL study eligible participants from these two studies were a subset of the women who were diagnosed with breast cancer between May, 1995 and May, 1998. Both studies restricted eligibility to women aged 35 to 64 years at diagnosis who were English speaking and born in the U.S.

Participants completed in-person interviews at baseline (within their first year after diagnosis, on average 7.5 months post diagnosis) and 24-months after the baseline visit (within their third year of diagnosis; on average 31 months post diagnosis). Written informed consent was obtained from each subject. The study was performed with the approval of the Institutional Review Boards of participating centers, in accord with an assurance filed with and approved by the U.S. Department of Health and Human Services.

CRP and SAA measurements

A 30-ml fasting blood sample was collected from patients at the follow-up interview. The blood sample was processed within 3 hours of collection, and serum was stored at −70° to −80° C until analysis. CRP and SAA were measured by latex-enhanced nephelometry using high sensitivity assays on the Behring Nephelometer II analyzer (Dade Behring Diagnostics, Deerfield, IL) at the University of Washington Medical Center (Seattle, WA). The lower detection limit for CRP and SAA assays were 0.2 mg/L and 0.7 mg/L, respectively. Inter-assay coefficients of variation were 5–9% for CRP and 4–8% for SAA. Control materials from Bio-Rad Laboratories (Hercules, CA) were run with each assay for quality-control purposes. The performance of this assay has been shown to be good [39].

Anthropometrics

Trained staff measured weight and height in a standard manner at the three year post-diagnosis follow-up assessment. With the women wearing light indoor clothing and no shoes, weight was measured to the nearest 0.1 kg using a balance-beam laboratory scale at

New Mexico and Washington, and a portable Thinner Digital Electronic Scale at Los Angeles. Waist circumference was measured in centimeters at the smallest circumference (Washington) or just above the superior margin of the iliac crest (New Mexico). Height was measured, without shoes, to the nearest 0.1 cm using a stadiometer at New Mexico and Washington, and a tape measure at Los Angeles. All measurements were performed twice in succession, and averaged for a final value for analyses. BMI was computed as kg/m^2.

Stage of Disease and Cancer Treatment

We obtained data on disease stage from the local SEER registries prior to recruitment of women into the HEAL Study. Participants were classified as having in situ, Stage I or Stage II–IIIA breast cancer based on AJCC stage of disease classification contained within SEER. Estrogen receptor (ER) and progesterone receptor (PR) status of tumors was categorized as (1) positive, (2) negative, or (3) unknown/borderline. Treatment and additional clinical data was obtained from a medical records review. Adjuvant treatment was categorized into four mutually exclusive groups: surgery only, surgery and radiation, surgery and chemotherapy, or surgery, radiation and chemotherapy.

Other Variables

Standardized questionnaire information was collected at the baseline and follow-up visit on medical history and selected demographic data. Postmenopausal status, assessed at the follow-up interview, was defined as age 55 years or older or not menstruating in the last 12 months, an oophorectomy, or a hysterectomy. Information on physical activity was collecting during the follow-up interview [37]. Total average MET hours per week of moderate and/or vigorous sport and recreational activities in the year prior to follow-up was used to control for differences in physical activity. Individuals were defined as users of tamoxifen, NSAIDs, beta blockers, ACE inhibitors, lipid-lowering medications, or vitamin E supplements if they reported current use at the 24-month interview. Use of oral hormone replacement therapy was defined as any use of estrogen or progesterone since breast cancer diagnosis. Histories of conditions related to cardiovascular disease, and potentially inflammation, were self-reported at the 24–month follow-up interview.

Exclusions

Among the 1183 eligible women enrolled at baseline, 944 women completed the follow-up survey. Reasons for non-participation were death (44), refusal (104), spouse would not permit contact (1), unable to contact (17), unable to locate (55), moved from study area (16), and too ill (2). Serum samples were available for 814 participants, and CRP and SAA were measured successfully for 807 participants. Of these 807 participants, 46 were not disease-free at 24 month follow-up (24 new breast primaries; 20 recurrences; 2 unconfirmed new primaries or recurrences) and 20 lacked a BMI measure, resulting in a sample size of 741.

Secondary analyses were conducted excluding participants extreme CRP values (n=38), as determined using 95^{th} percentile cutoffs of the age- and race-specific NHANES distributions (white and Hispanic females: 95^{th} percentile = age/50 + 0.6; Black females: 95^{th} percentile = age/50 + 1.0) [31], resulting in a subset of 703 participants. These exclusions were made due to the possibility of an acute inflammatory state at the time of blood draw that did not reflect true long-term inflammatory status.

Statistical Analysis

Twenty-two eligible women (3%) reported a race/ethnicity that could not be classified into our three race/ethnicity categories and were assigned to a fourth race/ethnicity category for analysis purposes. Similar assignments were made for participants missing ER status (28%)

and PR status (35%), and thus, the sample size was not reduced. A race/ethnicity/study site variable was created to adjust for confounding because race/ethnicity and study site were highly correlated. This variable had 4 categories: Non-Hispanic whites at USC, non-Hispanic whites at FHCRC, Hispanic, and African American.

CRP and SAA values were log transformed to improve normality. Correlates of CRP and SAA concentrations were examined using analysis of variance (ANOVA). Beta coefficients were calculated for each of the sample characteristics, both unadjusted and adjusted for categorical age (quartiles: ≤50, 51– 56, 57– 64, ≥65), categorical BMI (quartiles: <25, 25–29.9, 26.5–31.0, ≥31.1), and race/ethnicity/study site. Associations for tamoxifen use, oral hormone replacement therapy, and treatment were adjusted for ER status, menopausal status, and tumor stage, respectively. Variables analyzed by quartiles were also included in linear regression analyses as ordinal variables to test for trends. Variables showing statistically significant associations with ln(CRP) or ln(SAA) were included in a multivariate linear regression analysis for both markers. This study was exploratory in nature, and we did not adjust for multiple tests.

Results

Characteristics of eligible HEAL participants are presented in Table 1. Statistically significant associations with ln(CRP), after adjustment for age, BMI, and race/ethnicity/study site (where appropriate), were observed for SAA (p-trend<0.0001), age (p-trend<0.0001), BMI (p-trend<0.0001), waist circumference (p-trend<0.0001), physical activity (p-trend=0.005), Hispanic ethnicity (compared to non-Hispanic whites), current smoking, UNM study site (compared to FHCRC), USC study site (compared to FHCRC), tamoxifen use, vitamin E supplementation, history of heart failure, and radiation treatment (compared to no chemotherapy or radiation) (Table 2). Statistically significant associations with ln(SAA), after adjustment for age quartiles, BMI quartiles, and race/ethnicity/studysite (where appropriate), were observed for CRP (p-trend<0.0001), age (p-trend<0.0001), BMI (p-trend<0.001), physical activity (p-trend=0.02), UNM study site (compared to FHCRC), vitamin E supplementation, history of myocardial infarction, and history of heart failure. In analyses unadjusted for age, BMI, and race/ethnicity/study site, many additional associations were observed that were attenuated or absent in adjusted models.

We performed similar univariate analyses after excluding the 38 individuals with extreme CRP values (see methods). After these exclusions and adjustments for age, BMI, and race/ethnicity/study site, additional significant associations were observed between ln(CRP) and African American race (compared to non-Hispanic whites; adjusted p=0.04), ln(SAA) and African American race (compared to non-Hispanic whites; adjusted p=0.05),and ln(SAA) and current smoking (reduced compared to never; adjusted p=0.01). Reductions to non-significance were observed for associations between CRP and current smoking (adjusted p=0.08), CRP and history of heart failure (adjusted p=0.33), SAA and heart failure (adjusted p=0.99) and CRP and radiation treatment (adjusted p=0.06).

The results of multivariate ANOVAs for ln(CRP) and ln(SAA), using only the variables with statistically significant univariate adjusted associations, are presented in Table 3. For ln(CRP), statistically significant associations were observed for BMI, age, waist circumference, history of heart failure, tamoxifen use, and vitamin E supplementation. Waist circumference had the highest univariate R^2 (0.27), and adding additional terms to the model in order of decreasing contribution to the overall R^2 resulted in the following order: BMI (R^2=0.29), age (R^2=0.31), history of heart failure (R^2=32), tamoxifen use (R^2=0.33), vitamin E supplementation (R^2=0.34), Inclusion of non-statistically significant variables

(smoking status, race/ethnicity/study site, physical activity, and treatment) resulted in a total R^2 of 0.35.

In the multivariate ANOVA for ln(SAA), statistically significant associations were observed for BMI, age, history of heart failure, history of myocardial infarction, vitamin E supplementation, African American race (at USC compared to non-Hispanic whites from UNM), and FHCRC study site compared to UNM (within the non-Hispanic white race/ethnicity category). BMI and age had the highest univariate R^2 (0.06 and 0.05, respectively) and an R^2 of 0.12 in a bivariate model. Adding additional terms to the model in order of decreasing contribution to the overall R^2 resulted in the following order: history of heart failure (R^2=0.14), race/ethnicity/study site (R^2=0.15) history of myocardial infarction (R^2=0.16), and vitamin E supplementation (R^2=0.18). Inclusion of non-statistically significant variables (physical activity only) resulted in a total R^2 of 0.18, much lower than the total R^2 for CRP.

Using continuous measures of age, BMI, and waist circumference, rather than categorical measures of continuous variables, did not change the overall R^2 values or the significance of specific variables in the multivariate regression analyses. Multivariate analyses restricted to black participants only and white participants only resulted in associations similar to those observed in the combined analyses (data not shown).

Discussion

This is the first large study to evaluate the correlates of CRP and SAA in a cohort of breast cancer survivors. In this cross-sectional analysis, several variables were associated with both CRP and SAA (measured ~31 months post diagnosis): age, BMI, study site, ethnicity, vitamin E supplementation and history of heart failure. CRP was associated with several additional factors: waist circumference, smoking status, tamoxifen use and treatment. SAA, but not CRP, was associated with history of myocardial infarction. All significant associations remained statistically significant or nearly significant in the context of a multivariate model, reducing the likelihood that these associations are due to confounding by other variables examined in this study. Excluding individuals with extreme CRP values did not change the interpretation of our results, with the exception of additional statistically significant associations between CRP and race/ethnicity/study site, SAA and race/ethnicity/study site, and SAA and smoking. These exclusions eliminated statistically significant associations between heart failure and both CRP and SAA. The variables examined explained more of the variation in CRP concentrations (R^2=0.35) than in SAA concentrations (R^2=0.18).

Many of the associations reported here are consistent with observations from previous studies of healthy individuals. Increasing age [40], African American race (compared to non-Hispanic white) [40], and smoking [41] are known to be associated with increasing CRP concentrations. In healthy individuals, elevated levels of CRP and SAA are associated with body fatness [21, 22] and sedentary lifestyles [21, 23–26]. Weight loss and exercise training have been shown to reduce CRP levels in healthy individuals [27–29], while the latter reduces CRP in breast cancer survivors [42]. Intervention studies have shown that alpha-tocopherol, a form of vitamin E with purported anti-inflammatory properties [43], reduces serum concentrations of CRP in healthy individuals [44], type 2 diabetics [44, 45], and smokers with acute coronary syndromes [46]. Intervention studies also suggest that low doses of tamoxifen decrease serum CRP concentrations in healthy women [47, 48] and in women with ER positive breast tumors [46], consistent with the observed association in this study.

Several biological mechanisms have been suggested to explain the relationships between CRP, SAA, and their correlates. Associations between CRP and body fatness or weight loss are believed to be linked to adipose tissue. Adipose tissue secretes IL-6 [27], an important trigger for CRP production, and its abundance is likely associated with CRP concentrations [49]. It has also been suggested that the accumulation of macrophages in adipose tissue contributes to a heightened inflammatory state, as macrophages are an additional source of pro-inflammatory molecules [50]. Obesity is a negative prognostic factor for breast cancer [51] and is hypothesized to influence prognosis through effects on circulating concentrations of estrogens, insulin and insulin-like growth factors. Recently, obesity was observed be of heightened prognostic significance for ER positive cancers [52], supporting the hypothesis that obesity effects prognosis through estrogens [53]. The relationship between obesity, inflammation, and breast cancer survival has not yet been explored.

Exercise may reduce CRP, independent of changes in body fatness, through modification of cytokine production at non-adipose sites such as skeletal muscles and mononuclear cells. Reductions in CRP may also occur indirectly, through improved endothelial function, increased insulin sensitivity, or reduced body weight [54]. Several studies suggest that physical activity is associated with a modest decrease in mortality for breast cancer patients [55, 56], although the evidence is not entirely consistent [57–59]. Physical activity may influence breast cancer survival through the inflammation-related mechanisms above, through decreases in estrogen exposure, or increases in energy expenditure [60].

The association between age and CRP is complex, and may be related to a wide variety of factors, including dysregulation of cytokine response due to a lifetime antigen exposure, decreases in production of sex hormones, and increases in cytokine-producing fat tissue [61]. Age is a prognostic factor for breast cancer; decreased survival has been observed for women (≥75 years), whose age limits diagnostic tests and examinations, as well as treatment choices [62]. Women diagnosed at a young age also have a poor prognosis [63], but these cancers appear to be etiologically distinct from cancers occurring in older women [64].

The well-established correlation between smoking and chronic inflammation [41] is likely due to smoking-induced tissue damage, alterations in leukocyte concentrations, and/or increases in concentrations of pro-inflammatory cytokines [41]. There is evidence that cigarette smoking is associated with an increased risk for total mortality [65–67], but not breast cancer mortality [67], although the evidence is not entirely consistent [68]. Smoking could influence breast cancer survival through many mechanisms, including changes in local immune function, systemic anti-tumor defenses, and coagulation status, in addition to the direct effects of smoke constituents that promote the growth of metastases [69].

Tamoxifen is a selective estrogen receptor modulator that competitively binds to the estrogen receptor, inhibiting the effects of estrogen. Adjuvant tamoxifen treatment decreases mortality in patients with ER positive tumors [70]. Tamoxifen also decreases serum concentrations of CRP in a dose-dependent fashion in women with ER positive tumors [71]. It has been hypothesized that tamoxifen-related decreases in CRP may be attributable to the anti-estrogenic effect of tamoxifen on adipocyte cytokine production [48]. If this is the case, tamoxifen may improve survival by reducing systemic, chronic inflammation, in addition to its effects on estrogen signaling in tumors.

CRP and SAA show associations with the use of beta blockers, ACE inhibitors, and lipid lowering medications when unadjusted for age, BMI, ethnicity, and study site. These are likely due to confounding as overweight and older individuals are more likely to be prescribed these medications and have elevated CRP and SAA concentrations. After adjustment, these associations are no longer observed. Similarly, CRP is associated with

both ER and PR status prior to adjustment, but not associated with ER and PR status after adjustment. The reductions in the magnitude of both of these associations are due primarily to adjustment for BMI. Interestingly, increased inflammation, as measured by the Glasgow prognostic score (based on CRP and albumin concentrations) has been shown previously to be associated with ER negative tumor status (borderline; p=0.06) in patients with metastatic breast cancer [33]; however, this association was not adjusted for BMI.

This is the first large study of well-assessed correlates of both CRP and SAA in breast cancer survivors. This study was limited by the timing of the measurements of CRP and SAA, which were taken approximately 31 months after diagnosis. We could not assess the correlates of CRP and SAA in women who died prior to this measurement or did not return for a follow-up interview. As a result, our sample is representative of long-term breast cancer survivors (≥2 years survival). Also, in this study, it is difficult to disentangle the effects of study site and ethnicity, because they are strongly associated, and the results must be interpreted with that in mind.

Because inflammation status may be an important prognostic factor for breast cancer, it is important to understand its relationships with other demographic, lifestyle, and clinical factors of prognostic importance. As in healthy women, measures of body fatness emerged as the most important predictors of these inflammatory markers in this cohort of breast cancer survivors.

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Table 1

Characteristics of HEAL participants stratified by race/ethnicity[1]

	All[1]	Non-Hispanic White	African American	Hispanic
N	741	451	191	78
Age (%)				
30–39	1.5	0.7	2.1	5.1
40–49	22.9	17.3	36.7	21.8
50–59	36.8	36.1	36.7	35.9
60–69	25.9	27.7	24.6	20.5
70–79	9.5	13.1	0.0	14.1
80–89	3.4	5.1	0.0	2.5
Mean ± SD	57.5 ± 10.4	59.6 ± 10.7	53.0 ± 7.7	57.1 ± 11.7
Education (%)				
High school only	26.6	19.1	36.7	43.6
College	54.8	56.3	54.5	47.4
Graduate School	18.5	24.4	8.9	9.0
Missing	0.1	0.2	0.0	0.0
Study Site[2] (%)				
FHCRC	22.0	31.0	0.5	3.9
UNM	52.4	69.0	0.0	96.2
USC	25.6	0.0	99.5	0.0
Smoking (%)				
Current	12.2	10.2	15.7	14.1
Former	39.5	43.2	34.6	30.8
Never	48.3	46.6	49.7	55.1
Physical activity (MET hrs/week)				
Mean ± SD	13.1 ± 18.7	14.2 ± 20.3	9.9 ± 15.4	16.2 ± 17.1
Median (IQR[3])	6.0 (0.8–18.0)	6.7 (1.3–18.3)	4.0 (0.07–12.6)	10.8 (2.2–25.5)
Body mass index (%)				
>25	40.5	47.7	23.6	39.7
25–29.9	30.0	30.4	28.3	38.5
≥30	29.6	22.0	48.2	21.8
Mean ± SD, kg/m^2	27.6 ± 6.5	26.3 ± 5.6	30.9 ± 7.6	27.0 ± 5.0
Waist circumference (n)	735	450	186	78
Mean ± SD, cm	90.4 ± 15.0	87.6 ± 13.8	97.8 ± 16.2	88.8 ± 12.4
Menopause status (%)				
Pre-menopause	18.1	18.0	17.3	21.8
Post-menopause	75.8	78.3	73.8	69.2

	All[1]	Non-Hispanic White	African American	Hispanic
Unknown	6.1	3.8	8.9	9.0
C-reactive protein (mg/L)				
Mean ± SD	4.5 ± 8.3	3.7 ± 5.5	6.4 ± 13.3	4.2 ± 5.2
Median (IQR[3])	2.2 (0.8–5.0)	1.9 (0.8–4.0)	2.9 (1.1–7.2)	2.8 (1.0–5.3)
Serum Amyloid A (mg/L)				
Mean ± SD	10.3 ± 29.4	10.5 ± 27.4	10.5 ± 39.3	8.8 ± 7.0
Median (IQR[3])	5.7 (3.5–10.1)	5.7 (3.5–9.7)	5.4 (3.0–10.7)	6.3 (4.4–10.5)
Above CRP threshold[4]	5.1	5.3	5.7	2.3
Medications used at follow-up (%)				
Tamoxifen	43.7	46.1	38.7	41.0
NSAIDs	37.9	44.4	19.4	41.0
Beta Blockers	7.6	6.9	9.4	5.1
ACE inhibitors	10.5	9.1	13.1	11.5
Lipid lowering	8.2	8.7	6.3	6.4
Oral estrogens	5.1	6.2	2.1	5.1
Vitamin E Supplement	60.1	63.9	52.4	60.3
Multivitamin	72.1	74.5	71.2	59.0
History of comorbidities (%)				
Angina	6.6	6.6	7.3	6.4
Diabetes	10.5	8.0	14.6	11.5
Myocardial Infarction	3.2	3.1	2.1	5.1
Heart Failure	2.3	2.2	3.1	0.0
Hypertension	35.22	29.9	48.7	30.8
SEER Summary Stage (%)				
In situ	23.2	25.1	19.4	21.8
Localized	54.5	57.2	45.0	62.8
Distant	22.3	17.7	35.6	15.4
Estrogen receptor status (%)				
Positive/elevated	56.3	60.5	48.7	47.4
Negative/normal	15.4	10.2	28.3	16.7
Unknown	28.3	29.3	23.0	35.9
Progesterone receptor status (%)				
Positive/elevated	44.5	44.5	49.5	31.9
Negative/normal	20.9	20.9	18.9	26.2
Unknown	34.6	34.5	31.7	41.9
Treatment (%)				
No chemotherapy or radiation	31.7	29.9	35.1	35.9
Radiation only	38.2	44.1	24.1	37.2

	All[1]	Non-Hispanic White	African American	Hispanic
Chemotherapy only	9.9	6.4	18.9	7.7
Radiation and chemotherapy	20.2	19.5	22.0	19.2

[1] 22 individuals do not fall into any of the three race/ethnicity categories

[2] FHCRC=Fred Hutchinson Cancer Research Center; UNM=University of New Mexico; USC=University of Southern California

[3] IQR=interquartile range

[4] Threshold is based upon age- and race-specific cutoffs (see methods)

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Table 2

Associations between characteristics of HEAL participants (n=741) and log-transformed blood concentrations of markers of inflammation, C-reactive protein (CRP) and serum amyloid A (SAA).

		ln(CRP)				ln(SAA)			
		Unadjusted		Adjusted [1]		Unadjusted		Adjusted [1]	
	n	β	p	β	p	β	p	β	p
CRP quartiles (mg/L)									
≤0.8	187	--	--	--	--	0.00	Ref	0.00	Ref
0.9–2.2	186	--	--	--	--	0.32	<0.0001	0.20	0.01
2.3–5.0	184	--	--	--	--	0.60	<0.0001	0.46	<0.0001
≥5.1	184	--	--	--	--	1.15	<0.0001	1.02	<0.0001
SAA quartiles (mg/L)									
≤3.5	193	0.00	Ref	0.00	Ref	--	--	--	--
3.6–5.7	182	0.51	<0.0001	0.29	0.006	--	--	--	--
5.8–10.0	185	0.87	<0.0001	0.62	<0.0001	--	--	--	--
≥10.2	181	1.86	<0.0001	1.41	<0.0001	--	--	--	--
Age quartiles (years)									
≤50	203	0.00	Ref	0.00	Ref	0.00	Ref	0.00	Ref
51–56	183	0.16	0.22	0.19	0.09	0.25	0.003	0.25	0.002
57–64	175	0.44	0.001	0.36	0.002	0.35	<0.0001	0.31	0.0001
≥65	180	0.37	0.006	0.64	<0.0001	0.53	<0.0001	0.55	<0.0001
BMI (kg/m^2) [2]									
<25	300	0.00	Ref	0.00	Ref	0.00	Ref	0.00	Ref
25–29.9	222	0.91	<0.0001	0.92	<0.0001	0.27	0.0002	0.31	<0.0001
≥30	219	1.49	<0.0001	1.53	<0.0001	0.47	<0.0001	0.58	<0.0001
Waist circumference quartiles (cm)									
≤79.0	187	0.00	Ref	0.00	Ref	0.00	Ref	0.00	Ref
79.1–88.5	180	0.76	<0.0001	0.48	0.0003	0.26	0.002	0.12	0.22
88.6–99.3	186	1.35	<0.0001	0.79	<0.0001	0.44	<0.0001	0.12	0.28

		ln(CRP)				ln(SAA)			
		Unadjusted		Adjusted [1]		Unadjusted		Adjusted [1]	
	n	β	p	β	p	β	p	β	p
≥99.4	182	1.81	<0.0001	0.96	<0.0001	0.61	<0.0001	0.16	0.27
Missing	6								
Physical activity quartiles (MET hours/week)									
≤0.8	187	0.0	Ref	0.0	Ref	0.00	Ref	0.00	Ref
0.9–6.0	184	−0.28	0.03	−0.08	0.50	−0.22	0.009	−0.13	0.13
6.1–18.0	186	−0.57	<0.0001	−0.29	0.02	−0.40	<0.0001	−0.27	0.001
≥18.1	184	−0.76	<0.0001	−0.29	0.02	−0.32	0.0002	−0.16	0.06
Race/Ethnicity									
Non-Hispanic White	451	--	Ref	--	Ref	--	Ref	--	Ref
African American	191	0.39	0.0004	0.16	0.12	−0.10	0.18	−0.12	0.11
Hispanic	78	0.30	0.06	0.27	0.05	0.12	0.23	0.13	0.19
Unknown	21								
Smoking									
Never	358	--	Ref	--	Ref	--	Ref	--	Ref
Former	293	−0.06	0.56	−0.08	0.36	−0.04	0.57	−0.08	0.23
Current	90	0.18	0.23	0.28	0.03	−0.17	0.09	−0.12	0.19
Education									
High school only	197	--	Ref.	--	Ref.	--	Ref	--	Ref
Some college	406	−0.31	0.006	−0.09	0.34	−0.11	0.13	−0.008	0.91
Graduate School	137	−0.54	0.0002	−0.19	0.14	−0.11	0.24	0.03	0.77
Missing	1								
Study Site									
FHCRC	163	--	Ref	--	Ref	--	Ref	--	Ref
UNM	388	0.14	0.24	0.27	0.02	0.21	0.007	0.20	0.01
USC	190	0.46	0.0008	0.31	0.01	0.05	0.60	0.003	0.96
Menopause status									
Pre-menopause	134	--	Ref	--	Ref	--	Ref	--	Ref

		ln(CRP)				ln(SAA)			
		Unadjusted		Adjusted [1]		Unadjusted		Adjusted [1]	
	n	β	p	β	p	β	p	β	p
Post-menopause	562	0.52	<0.0001	0.15	0.28	0.39	<0.0001	0.10	0.27
Unknown	45								
Tamoxifen use[2, 3]									
No	417	--	Ref	--	Ref	--	Ref	--	Ref
Yes	324	−0.27	0.004	−0.24	0.008	−0.03	0.68	−0.04	0.53
NSAIDs[3]									
No	460	--	Ref	--	Ref	--	Ref	--	Ref
Yes	281	−0.04	0.66	−0.008	0.93	0.09	0.15	0.05	0.41
Beta blockers[3]									
No	685	--	Ref	--	Ref	--	Ref	--	Ref
Yes	56	0.53	0.003	0.25	0.11	0.28	0.02	0.13	0.25
ACE inhibitors[3]									
No	663	--	Ref	--	Ref	--	Ref	--	Ref
Yes	78	0.52	0.0008	0.13	0.35	0.25	0.01	0.07	0.50
Lipid lowering medications[3]									
No	680	--	Ref	--	Ref	--	Ref	--	Ref
Yes	61	0.38	0.03	−0.03	0.84	0.41	0.0002	0.20	0.07
Oral hormone replacement therapy [4]									
No	703	--	Ref	--	Ref	--	Ref	--	Ref
Yes	38	0.09	0.68	0.27	0.15	0.15	0.28	0.20	0.14
Multivitamin use[3]									
No	207	--	Ref	--	Ref	--	Ref	--	Ref
Yes	534	−0.19	0.08	−0.05	0.61	−0.12	0.09	−0.07	0.27
Vitamin E supplement use[3]									
No	296	--	Ref	--	Ref	--	Ref	--	Ref
Yes	445	−0.36	0.0003	−0.29	0.0005	−0.19	0.003	−0.20	0.001

		ln(CRP)				ln(SAA)			
		Unadjusted		Adjusted [1]		Unadjusted		Adjusted [1]	
	n	β	p	β	p	β	p	β	p
History of Angina									
No	689	--	Ref		Ref	--	Ref	--	Ref
Yes	49	0.66	0.0006	0.30	0.07	0.41	0.0009	0.20	0.09
Missing	3								
History of Diabetes									
No	662	--	Ref		Ref	--	Ref	--	Ref
Yes	78	0.69	<0.0001	0.03	0.81	0.33	0.001	0.05	0.62
Missing	1								
History of Myocardial Infarction									
No	717	--	Ref		Ref	--	Ref	--	Ref
Yes	24	0.77	0.004	0.43	0.07	0.86	<0.0001	0.63	0.0002
History of Heart Failure									
No	724	--	Ref		Ref	--	Ref	--	Ref
Yes	17	1.49	<0.0001	0.94	0.0007	1.02	<0.0001	0.76	<0.0001
History of Hypertension									
No	479	--	Ref		Ref	--	Ref	--	Ref
Yes	261	0.56	<0.0001	0.12	0.19	0.27	<0.0001	0.08	0.23
Missing	1								
Tumor stage									
In situ	172	--	Ref	--	Ref	--	Ref	--	Ref
Localized	404	−0.10	0.41	−0.14	0.17	0.01	0.86	−0.04	0.60
Distant	165	0.06	0.65	−0.11	0.35	−0.006	0.94	−0.02	0.79
Estrogen receptor status									
Positive	417	--	Ref	--	Ref	--	Ref	--	Ref
Negative	114	0.32	0.02	0.15	0.23	−0.04	0.69	−0.01	0.92
Unknown	210								
Progesterone receptor status									

		ln(CRP)				ln(SAA)			
		Unadjusted		Adjusted [1]		Unadjusted		Adjusted [1]	
	n	β	p	β	p	β	p	β	p
Positive	330	--	Ref	--	Ref	--	Ref	--	Ref
Negative	155	0.33	0.01	0.16	0.14	0.01	0.92	−0.01	0.94
Unknown	256								
Treatment [5]									
No chemotherapy or radiation	235	--	Ref	--	Ref	--	Ref	--	Ref
Radiation only	283	−0.29	0.01	−0.21	0.04	−0.08	0.30	−0.07	0.34
Chemotherapy only	73	−0.06	0.76	−0.03	0.84	−0.27	0.03	−0.15	0.20
Radiation and chemotherapy	150	−0.29	0.06	−0.20	0.16	−0.29	0.004	−0.18	0.07

[1]Adjusted for age quartiles, BMI quartiles, and race/ethnicity/study site, where appropriate

[2]Additional adjustment for ER status for both adjusted and unadjusted βs

[3]Yes defined as current use

[4]Yes defined as any use since diagnosis. Additional adjustment for menopausal status for both adjusted and unadjusted βs.

[5]Additional adjustment for tumor stage for both adjusted and unadjusted βs

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Table 3

Multivariate associations[1] between selected characteristics of HEAL participants (p<0.05 in table 2) and log-transformed blood concentrations of CRP and SAA.

	ln(CRP) (n=735)		ln(SAA) (n=741)	
	β	p	β	p
BMI quartiles (kg/m^2)				
<25	--	Ref	--	Ref
25–29.9	0.46	0.0002	0.29	<0.0001
≥30	0.72	<0.0001	0.51	<0.0001
		P_{trend}<0.0001		P_{trend}<0.0001
Age quartiles				
≤50	--	Ref	--	Ref
51–56	0.21	0.06	0.27	0.0009
57–64	0.39	0.001	0.30	0.0003
≥65	0.45	0.0004	0.44	<0.0001
		P_{trend}=0.0001		P_{trend}<0.0001
Waist circumference quartiles (cm)				
≤79.0	--	Ref	**	**
79.1–88.5	0.52	<0.0001	**	**
88.6–99.3	0.82	<0.0001	**	**
≥99.4	1.02	<0.0001	**	**
		P_{trend}<0.0001		**
History of Heart Failure				
No	--	Ref	--	Ref
Yes	0.85	0.002	0.67	0.0007
History of Myocardial Infarction				
No	**	**	--	Ref
Yes	**	**	0.47	0.005
Vitamin E Supplementation				
No	--	Ref	--	Ref
Yes	−0.22	0.008	−0.16	0.007
Tamoxifen use				
No	--	Ref	**	**
Yes	−0.22	0.009	**	**
Smoking				
Never	--	Ref	**	**
Former	−0.05	0.60	**	**
Current	0.22	0.09	**	**
Physical Activity quartiles (MET hours/week)				

	ln(CRP) (n=735)		ln(SAA) (n=741)	
	β	p	β	p
≤0.8	--	Ref	--	Ref
0.9–6.0	−0.10	0.39	−0.10	0.25
6.1–18.0	−0.20	0.09	−0.21	0.01
≥18.1	−0.18	0.14	−0.11	0.20
		P_{trend}=0.10		P_{trend}=0.10
Treatment[6]				
No chemotherapy or radiation	--	Ref	--	Ref
Radiation only	−0.17	0.09	**	**
Chemotherapy only	0.08	0.60	**	**
Radiation and chemotherapy	−0.10	0.40	**	**
Race/Ethnicity/study site				
Non-Hispanic White –UNM	--	Ref	--	Ref
Non-Hispanic White – FHCRC	0.03	0.78	−0.15	0.07
Black (>99% from USC)	−0.03	0.79	−0.21	0.007
Hispanic (~94% from UNM)	0.22	0.11	0.08	0.40
Overall R^2	**0.35**		**0.18**	

** Not included in multivariate analysis due to p>0.05 in univariate analysis

1 Associations calculated using a multivariate ANOVA