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Research Article

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The Association of the C-Reactive Protein Inflammatory Biomarker with Breast Cancer Incidence and Mortality in the Women's Health Initiative

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Abstract

Purpose: To examine associations of prediagnosis high-sensitivity C-reactive protein (hsCRP) with breast cancer incidence and postdiagnosis survival and to assess whether associations are modified by body mass index (BMI).

Methods: A prospective analysis of the Women's Health Initiative was conducted among 17,841 cancer-free postmenopausal women with baseline hsCRP measurements. Cox proportional hazards models were used to examine associations between hsCRP concentrations and (i) breast cancer risk (n cases = 1,114) and (ii) all-cause mortality after breast cancer diagnosis. HRs are per 1 SD in log hsCRP.

Results: hsCRP was not associated with breast cancer risk overall [HR = 1.05; 95% confidence interval (CI), 0.98–1.12]; however, an interaction between BMI and hsCRP was observed ($P_{\text{interaction}} = 0.02$). A 1 SD increase in log hsCRP was associated with 17% increased breast cancer risk (HR = 1.17; 95% CI, 1.03–1.33) among lean women (BMI < 25), whereas no association was observed among overweight/obese (BMI ≥ 25) women. Prediagnosis hsCRP was not associated with overall mortality (HR, 1.04; 95% CI, 0.88–1.21) after breast cancer diagnosis; however, an increased mortality risk was apparent among leaner women with higher hsCRP levels (HR, 1.39, 95% CI, 1.03–1.88).

Conclusions: Prediagnosis hsCRP levels are not associated with postmenopausal breast cancer incidence or survival overall; however, increased risks are suggested among leaner women. The observed effect modification is in the opposite direction of a previous case–control study finding and warrants further investigation.

Impact: Associations of higher CRP levels with incident breast cancer and survival after breast cancer may depend on BMI. *Cancer Epidemiol Biomarkers Prev; 26(7); 1100–6. ©2017 AACR.*

Introduction

Chronic inflammation plays an important role in the initiation and progression of several cancers, including breast cancer (1). C-reactive protein (CRP) is a biomarker of low-grade systemic inflammation and is thought to be reflective of the total systemic burden of inflammation. CRP has been associated with the risk of cancer at several anatomic sites, including the colorectum and lung (2). A large meta-analysis of 15 published articles reported that a single log-unit increase in circulating CRP was associated with a 16% increase in breast cancer risk (3). Individual studies tended to be underpowered and only 7 used high-sensitivity CRP (hsCRP) measurements, which are considered to be less prone to measurement error. Furthermore, the studies combined results from pre- and postmenopausal women, for which associations may vary. A recent meta-analysis that restricted to only prospective studies (n = 12) found that each doubling of CRP was associated with a 7% increased risk of breast cancer, and when the meta-analysis was restricted to postmenopausal women, the results were slightly attenuated with a 6% increase in risk per doubling of CRP (4). Recent prospective data also suggest a possible interaction of CRP with body mass index (BMI, kg/m^2; ref. 5). Specifically, in a recent case–control analysis nested within a French cohort study of postmenopausal women, a 2-fold increased risk of breast cancer was found only among overweight and obese women (5). BMI is known to be a strong predictor of inflammation as measured by CRP (6), and this study raised the importance of examining BMI as an effect modifier of the association between CRP and breast cancer risk.

Herein, we utilized the Women's Health Initiative (WHI) cohort to examine the association between baseline hsCRP

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Note: Clinical Trial registration ID: ClinicalTrials.gov identified, NCT00000611.

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concentrations and breast cancer incidence. We further examined associations between baseline (i.e., prediagnosis) hsCRP and all-cause mortality risk after diagnosis of breast cancer among incident cases. We hypothesized *a priori* that associations would be modified by BMI. The WHI's large sample size, prospective design, length of follow-up, and subsequent number of incident breast cancer cases ($n = 1,114$) provide an excellent opportunity to examine these associations.

Materials and Methods

WHI

The WHI is a large, prospective study that was designed to examine the common causes of morbidity and mortality among postmenopausal women, including cancer, cardiovascular disease, and osteoporosis (7). The study consists of a multifactorial clinical trial (CT) and an observational study (OS). Detailed methods are given elsewhere (8, 9). Briefly, 161,808 postmenopausal women, ages 50 to 79 at baseline, were recruited from 40 U.S. centers between September 1, 1993, and December 31, 1998. The WHI CT ($n = 68,133$) included four overlapping components: two placebo controlled menopausal hormone therapy trials, a dietary modification trial, and a calcium/vitamin D supplementation trial (8). Participants in the OS were 93,676 women who were screened for participation in the CT but were ineligible or unwilling to participate in it, or who were directly recruited (9). After the original WHI study ended in 2005, the WHI Extension Study (2005–2010) was carried out to collect 5 more years of follow-up data, and the second WHI Extension Study (2010–2015) collected an additional 5 years. Women provided written informed consent prior to participation, and the study protocols and procedures were conducted in accordance with recognized ethical guidelines and were approved at the Institutional Review Boards of each participating center.

The WHI biospecimen subsample consisted of 22,124 participants. All white women were randomly selected from those enrolled in the menopausal hormone therapy trial, whereas non-white women were selected from all parts of the WHI to maximize ethnic diversity. The final biospecimen subcohort included 8,815 (38.9%) African American women and 3,642 (16.5%) Hispanic women. Selected biomarkers were measured in the biospecimen subsample to facilitate prediction of major cardiovascular disease and investigation of new risk factors. These biomarkers included glucose, insulin, lipids, creatinine, and hsCRP. For this analysis, we excluded women who reported a previous cancer diagnosis ($n = 1,251$), who had hsCRP levels >10 mg/L ($n = 2,665$; potentially indicating an acute infection), or who were missing baseline BMI ($n = 151$) or previous cancer diagnoses ($n = 216$), leaving an analytic sample of 17,841 that yielded 243,261 person years of follow-up, and a mean of 13.6 years follow-up (Fig. 1; flow diagram).

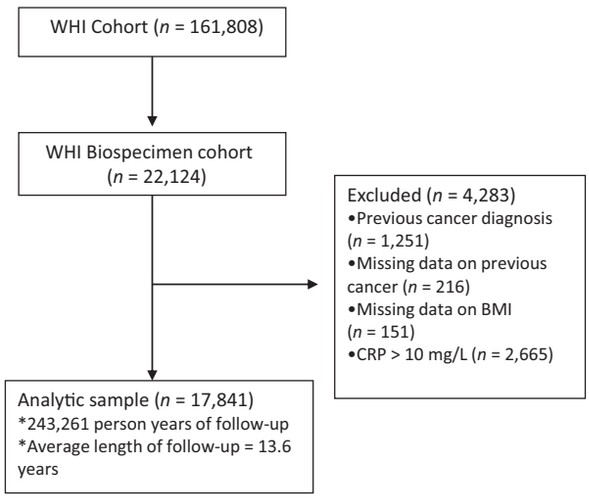

Figure 1.
Flowchart for analytic sample.

Data collection

All WHI participants attended baseline screening visits, during which they completed self-administered questionnaires that collected detailed self-reported information on demographics, medical and reproductive history, family history of cancer, physical activity, smoking history, alcohol use, diet, and other risk factors. During the baseline clinic visit, trained staff performed anthropometric measurements, including weight (measured to the nearest 0.1 kg via calibrated scales) and height (measured to the nearest 0.1 cm via wall mounted stadiometer). BMI was calculated as weight (kg) divided by the square of height (m^2).

CRP

All laboratory measurements were made at the Advanced Research and Diagnostic Laboratory at the University of Minnesota (Minneapolis, MN). Baseline hsCRP was measured using a latex particle–enhanced Immunoturbidimetric Assay Kit (Kimiya Biomedical Company) and read on the Roche/Hitachi 911 (Roche Diagnostics). The reference range is 0 to 0.5 mg/dL, and the interassay coefficient of variation was 4.5%.

Ascertainment of outcomes

Outcomes of interest included incident breast cancer (including *in situ*) and all-cause mortality after diagnosis of breast cancer. Follow-up was carried out annually in the OS and semiannually in the CT until 2005, after which it was performed annually for the OS and CT cohorts through 2014. Breast cancer cases were identified initially from mailed follow-up questionnaires or from nonroutine contact by the participant or proxy. Incident cases were verified by physician adjudicators after medical record review and coded on the basis of the NCI SEER guidelines (10).

Deaths were ascertained by the clinical centers via follow-up with the participant's family and surrogates and by review of the National Death Index for each participant every 2 years. Detailed methods have been published by Curb and colleagues (11). The last date of follow-up for this analysis was August 2014.

Statistical analysis

Baseline tables were generated using descriptive statistics (means and SD or %), stratified by hsCRP quartiles (<1.5, 1.5–<2.39, 2.39–<4.45, and 4.45–10 mg/L). Differences in hsCRP by participants' baseline characteristics were assessed using univariate linear regression models of log hsCRP on the variable of interest.

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The association between baseline hsCRP and incident breast cancer was assessed using a delayed-entry Cox proportional hazards regression model. The delayed entry model was used to account for varying baseline hazards by age at enrollment, using participants' age as the time metric and left-truncated for age at baseline. Association between prediagnosis hsCRP levels with all-cause mortality among incident breast cancer cases was similarly assessed using delayed-entry Cox proportional hazards regression models, with entry now based on age at incident diagnosis. CRP was analyzed as a continuous variable using the natural log of hsCRP with HRs provided per 1 SD (0.913 log mL/L) in log hsCRP for interpretability, as well as in categories (i.e., quartiles) of baseline concentrations. Analyses were carried out in the entire study population and stratified on BMI, with a further stratification by menopausal hormone therapy use, among women with BMI <25 kg/m^2, in the breast cancer risk model.

All models (including stratified models) controlled for a group of variables identified *a priori* from the literature: BMI, race/ethnicity, diabetes, hypertension, smoking status, and use of menopausal hormone therapy (by self-report OS or by CT randomization). Models assessing mortality among breast cancer survivors also controlled for cancer stage, except in sensitivity analysis where models were stratified by estrogen receptor (ER) status as the overparametrized model resulted in nonconvergence. Additional variables identified *a priori* from the literature included physical activity, age, anti-inflammatory use, alcohol use, cardiovascular disease, and pack-years of smoking were also assessed as confounders but were removed from the model because the effect size change was <10%.

We categorized BMI into four categories based on WHO criteria (12): <25, 25–29.9, 30–34.9, and ≥35 kg/m^2 corresponding to normal weight, overweight, obese I, and obese II, respectively. Because few women (n = 106, 0.5%) in the WHI were underweight (BMI < 18.5), these women were combined with the normal weight women for these analyses. BMI was examined as an effect modifier by examining the interaction between BMI and log hsCRP, with both treated as continuous variables. Subsequent models were stratified using the four BMI categories for ease of interpretation.

Table 1. Baseline demographics and physiologic characteristics in the WHI biospecimen cohort, stratified by CRP quartiles (n = 17,841)

Variable	CRP < 1.5 mg/L n = 4,433	1.5 ≤ CRP < 2.39 mg/L n = 4,470	2.39 ≤ CRP < 4.45 mg/L n = 4,470	4.45 ≤ CRP ≤ 10 mg/L n = 4,468
Demographics	%	%	%	%
Age at screening (years)				
50 ≤ age < 60	28	27.1	28.7	34.3
60 ≤ age < 70	42.8	44.3	45.6	46.8
70 ≤ age < 81	29.2	28.6	25.7	18.9
BMI group				
BMI < 25	48.8	26.7	16.1	10.3
25 ≤ BMI < 30	35.8	42.1	39.7	30.3
30 ≤ BMI <35	11.6	22.2	28.4	33
BMI ≥ 35	3.8	8.9	15.8	26.4
Some college education (0.8% missing)	64.9	60.8	56.8	57.7
Ethnicity				
Black or African American	30.5	30	34.5	43
Hispanic/Latino	13.1	15.9	17.5	17.9
White (not Hispanic)	56.4	54.1	48.1	39.1
Randomized to one or more clinical trials	79.3	79.6	78	74.2
Use of menopausal HT (randomized or self-report)	44.6	46.8	52.6	59.3
Randomized to menopausal HT				
Not randomized	32.6	33.8	38.6	46.4
Randomized to control	32.8	33.4	30.4	25.9
Estrogen only	11.3	12.2	13.3	12.5
Estrogen + Progesterone	23.3	20.6	17.7	15.3
Diabetes/high blood sugar ever (19.3% missing)	8.5	14.1	20.5	26.3
Hypertension (0.8% missing)	30.5	36.2	42.2	48.7
Cardiovascular disease (5.6% missing)	14.1	16.3	16.4	17.7
BC diagnosis	5.4	6.4	5.9	7.2
Smoking (1.4% missing)				
Never	54.2	54.1	52.6	50.7
Past	37.5	37.7	38.2	38.6
Current	8.4	8.2	9.2	10.7
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Age at screening (years)	64.6 (7.47)	64.7 (7.37)	64.2 (7.37)	62.9 (6.97)
BMI (kg/m^2)	25.9 (4.88)	28.3 (5.13)	30.0 (5.32)	31.9 (5.90)
Weight (kg)	67.5 (13.39)	73.4 (14.26)	77.7 (14.81)	83.0 (16.54)
Physical activity (METs; 4.42% missing)	13.5 (14.66)	11.6 (13.61)	10.0 (12.55)	8.8 (11.84)
Pack-years (3.53% missing)	7.9 (15.67)	9.0 (17.98)	8.9 (17.28)	10.3 (19.02)
Alcohol consumption (servings/wk; 4.42% missing)	2.2 (4.62)	2.2 (5.78)	1.6 (4.16)	1.5 (4.45)

NOTE: P values for test of trend omitted from the table as all trends were statistically significant (P < 0.005) due to large sample size. Test of trend using simple linear regression with log(hsCRP).

Abbreviations: BC, breast cancer; METs, metabolic equivalents.

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The proportional hazards assumption was verified for all models by examining the statistical significance of the product term for hsCRP and log time, and by using the Wald test for proportional hazards. All statistical tests were two-sided with a type I error rate set at 5%. Analyses were conducted in SAS version 9.4.

Results

Table 1 shows the distribution of selected baseline characteristics of WHI participants. There was no difference in the distribution of age by hsCRP quartiles. Of those in the highest quartile of hsCRP, a greater proportion were black/African American compared with those in the lower quartiles. Prevalence rates of baseline self-reported history of diabetes, hypertension, and cardiovascular disease were higher in the upper hsCRP quartiles. There also appeared to be a trend in BMI, weight, current smoking, and pack-years of smoking, with those in the highest hsCRP categories having the largest values for each. Physical activity and alcohol consumption had inverse associations across hsCRP quartiles, with those in the lowest quartile having the highest levels. All variables, even those with no apparent trend, were highly statistically significantly associated with hsCRP ($P < 0.005$ for linear trend) due to the large sample size.

Table 2 shows breast cancer characteristics stratified by hsCRP quartile among the incident cases. Women diagnosed with incident breast cancer were similar to the overall cohort with respect to a strong positive association between hsCRP and BMI levels ($P < 0.001$). Tumor stage and type (ER^+/ER^-, PR^+/PR^-) did not vary significantly across hsCRP quartiles in incident breast cancer cases (all $P > 0.1$). hsCRP specimens were collected, on average 7.8 years (SD = 4.7) prior to cancer diagnosis.

Figure 2 presents results of fitting delayed-entry Cox proportional hazards models for the association of log hsCRP with incident breast cancer. hsCRP was not significantly associated with incident breast cancer overall (HR = 1.05; 95% confidence interval (CI), 0.98–1.12); however, there was a statistically significant interaction between log hsCRP and continuous BMI ($P = 0.02$). When the analysis was stratified on BMI group, there was a significant association between hsCRP and breast cancer risk only among normal weight (BMI < 25 kg/m^2) women, with a 1 SD increase in log CRP corresponding to a 17% increased breast cancer risk (HR = 1.17; 95% CI, 1.03–1.33). No significant associations were apparent between hsCRP and breast cancer risk among overweight or obese women. This was not an artifact of differing sample sizes, as participants were distributed roughly similar between the BMI groups, with 25% ($n = 4,532$), 37% ($n = 6,599$), 24% ($n = 4,255$), and 14% ($n = 2,455$) in the normal weight, overweight, obese I, and obese II, respectively. In addition, when sensitivity analyses excluded participants with hsCRP collected less than 2 years prior to breast cancer diagnosis ($n = 131$), findings were the same, with only a slight increase in the strength of the relationship among normal weight women (HR = 1.23; 95% CI, 1.06–1.42). When hsCRP was modeled in quartiles, rather than in log hsCRP, those in the highest quartile of hsCRP had significantly greater breast cancer risk compared with the lowest quartile (HR = 1.22; 95% CI, 1.02–1.46). When stratified by BMI, there was a significant association between hsCRP and breast cancer risk only among normal weight (BMI < 25 kg/m^2) women, with those in the highest quartile of hsCRP having greater breast cancer risk has compared with the lowest quartile (HR = 1.73; 95% CI, 1.16–2.58). In a sensitivity analysis that examined the findings stratified by menopausal hormone therapy (HT) use, there was no difference in risk among HT users (HR = 1.05; 95% CI, 0.96–1.15) and nonusers (HR = 1.04; 95% CI, 0.95–1.15). Among normal weight women, breast cancer risk decreased slightly in HT nonusers (HR = 1.12; 95% CI, 0.92–1.35) and increased slightly in HT users (HR = 1.24; 95% CI, 1.04–1.48) but the association was only statistically significant among HT users.

In a further sensitivity analysis, we examined the association between hsCRP, dichotomized as high (>3 mg/L), a clinically relevant cut-off point, and low (≤3 mg/L). Relative to low levels, high hsCRP was not associated with breast cancer risk (Table 3); however, we again observed a statistically significant interaction of BMI with hsCRP category ($P_{interaction} = 0.02$). High hsCRP was associated with elevated breast cancer risk in normal weight women only (HR = 1.46; 95% CI, 1.07–1.98), corresponding to a 46% increase in risk of incident breast cancer for normal weight women with clinically elevated hsCRP (>3 mg/L). Although the increased risk was seen only in those with BMI < 25, this group had a much lower rate of clinically elevated hsCRP (19% vs. 68% in those with BMI >35). To further interpret these findings, we used a four-category variable based on clinically normal versus elevated

Table 2. All-cause mortality after diagnosis and breast cancer risk factors in the WHI biospecimen cohort among women diagnosed with incident breast cancer, by hsCRP level ($n = 1,114$)

Variable	CRP < 1.5 mg/L $n = 240$	1.5 ≤ CRP < 2.39 mg/L $n = 286$	2.39 ≤ CRP < 4.45 mg/L $n = 265$	CRP ≥ 4.45 mg/L $n = 323$	P^a
	%	%	%	%	
ER^+ (14.6% missing)	79.9	81.3	78.4	77	0.44
PR^+ (17.8% missing)	57.8	65.5	51.4	57.1	0.18
Stage (2.7% missing)					
In situ	22.6	14.9	21.2	17.2	0.35
Localized	58.3	63.7	54.4	58.9	
Regional	18.3	19.9	22	21.7	
Distant	0.9	1.4	2.3	2.3	
BMI group					
BMI < 25	41.7	21.3	14.3	11.1	<0.001
25 ≤ BMI < 30	35.8	40.2	34	28.5	
30 ≤ BMI <35	17.1	24.5	32.1	30.3	
BMI ≥ 35	5.4	14	19.6	30	
BMI (kg/m^2), mean (SD)	26.8 (5.34)	29.3 (5.85)	30.4 (5.04)	31.9 (5.76)	<0.001
Age at BC diagnosis mean (SD)	71.2 (7.56)	71.5 (7.94)	71.3 (8.12)	70.3 (7.41)	0.09

Abbreviations: BC, breast cancer; PR^+, progesterone receptor positive.
[a]Test of trend in simple linear regression with log(CRP).

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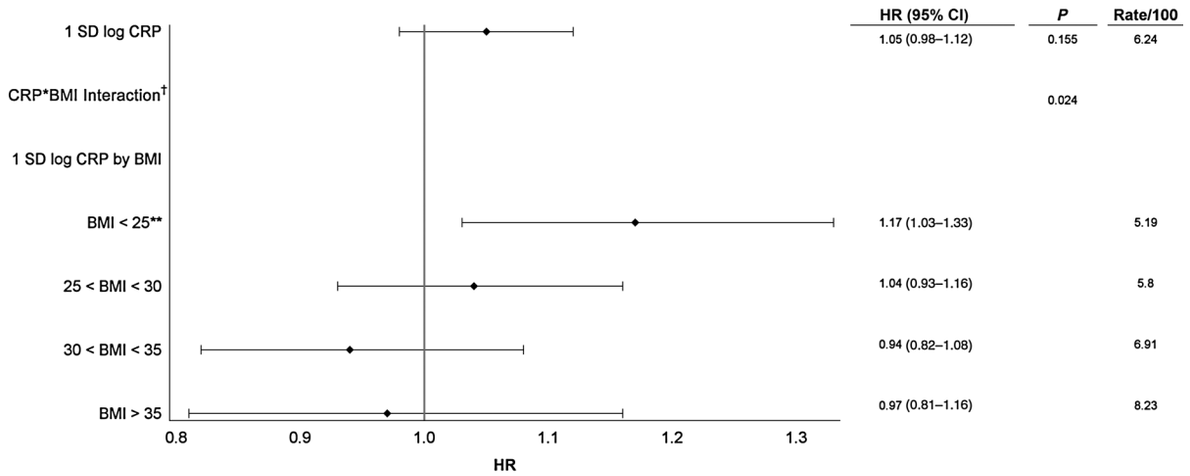

Abbreviations: High Sensitivity C-Reactive Protein (CRP), Body Mass Index (BMI), Standard deviation (SD), Hazard Ration (HR), Lower and Upper level of 95% confidence interval (LL and UL). † = interaction variable was created, ** = *P*-value < 0.05.

Figure 2.

Incident breast cancer HRs and 95% CIs in the WHI biospecimen cohort, per 1 SD natural log unit of hsCRP, overall, and by BMI level ($n = 17{,}841$).

hsCRP ($\leq$3 vs. >3 mg/L) and normal versus overweight (BMI < 25 vs. $\geq$ 25 kg/m^2). Compared with normal weight individuals with normal hsCRP, overweight women, regardless of hsCRP level, had significantly increased risk of incident breast cancer (HR = 1.4 and 1.3 for normal and elevated hsCRP, respectively; 95% CI, 1.1–1.6 for both), while normal weight women with elevated hsCRP had a similar significantly increased risk compared with normal weight women with normal hsCRP (HR, 1.5; 95% CI, 1.1–2.1).

Similar to our findings with breast cancer incidence, hsCRP was not associated with all-cause mortality after diagnosis of breast cancer (Fig. 3; HR = 1.04; 95% CI, 0.89–1.22). When stratified by BMI, normal weight women (BMI $\leq$ 25) had significantly increased risk of mortality (HR = 1.39; 95% CI, 1.03–1.89) corresponding to a 39% increase in risk for every 1 SD increase in log hsCRP. No significant increase in risk of all-cause mortality was observed among women in the higher BMI categories; however, the *P* value for interaction was statistically nonsignificant ($P_{\text{interaction}} = 0.459$).

In another sensitivity analysis, we again examined our models of all-cause mortality after diagnosis of breast cancer in the four BMI categories, this time stratified by those whose breast cancer was ER$^+$ ($n = 752$), ER$^-$ ($n = 199$), or had a missing ER status ($n = 163$). The relationship between CRP and all-cause mortality among normal weight women was completely attenuated in women with ER$^+$ or unknown ER status cancer ($P = 0.66$ and 0.95, respectively). The relationship only existed among those with ER$^-$ breast cancer (HR = 12.5; 95% CI, 1.79–87.65; $P = 0.01$).

Table 3. Incident breast cancer HRs and 95% CIs in the WHI biospecimen cohort, by hsCRP >3, overall, and by BMI level ($N = 17{,}841$)

BMI	HR (95% CI)	*P*
CRP > 3	1.00 (0.88–1.14)	0.964
CRP > 3 * BMI Interaction		*0.017*
Stratified by BMI		
BMI < 25**	1.46 (1.07–1.98)	
25 < BMI < 30	0.98 (0.79–1.21)	
30 < BMI < 35	0.86 (0.68–1.09)	
BMI > 35	0.92 (0.69–1.24)	

Abbreviations: BMI, body mass index; CPR, high sensitivity C-reactive protein.

Discussion

In this large cohort of postmenopausal women in the United States, baseline hsCRP concentrations were neither associated with breast cancer incidence nor all-cause mortality after diagnosis of incident breast cancer. However, we found that hsCRP was consistently associated with increased risk of both breast cancer and mortality after breast cancer among leaner women. In contrast, there were no clear associations among overweight or obese women.

In this study, hsCRP was not associated with breast cancer risk among women with BMI greater than 25. It may be that other risk factors, such as estradiol and insulin (13), that are elevated in overweight/obese women may overshadow or mask the increased risk associated with generalized inflammation (as measured by hsCRP). This hypothesis is supported by the results of another study also conducted in WHI, in which the associations of inflammatory biomarkers and breast cancer risk were seen only among menopausal HT nonusers (14). Thus, it is possible that hsCRP is only predictive in those without other, more powerful breast cancer risk factors.

To date, there have been mixed results regarding the association of hsCRP with incident breast cancer, with the majority of studies finding no significant association. A recent meta-analysis, mentioned earlier, of 15 studies, including 6 U.S. studies and 6 studies restricted to postmenopausal women, with 5,286 breast cancer cases, had a finding similar to the current study among the normal weight women in this study. Specifically, they reported a significant OR of 1.22 per natural log-unit change of hsCRP for incident breast cancer (95% CI, 1.10–1.35; ref. 3). The meta-analysis also found this association was stronger in Asian populations, for whom BMI is usually lower than in Caucasians (15), further supporting our findings. A recent study that examined the CRP–breast cancer association in the Nurses' Health Study (NHS) and the Women's Health Study (WHS) found no interaction between BMI and CRP in breast cancer risk (16). Both the NHS

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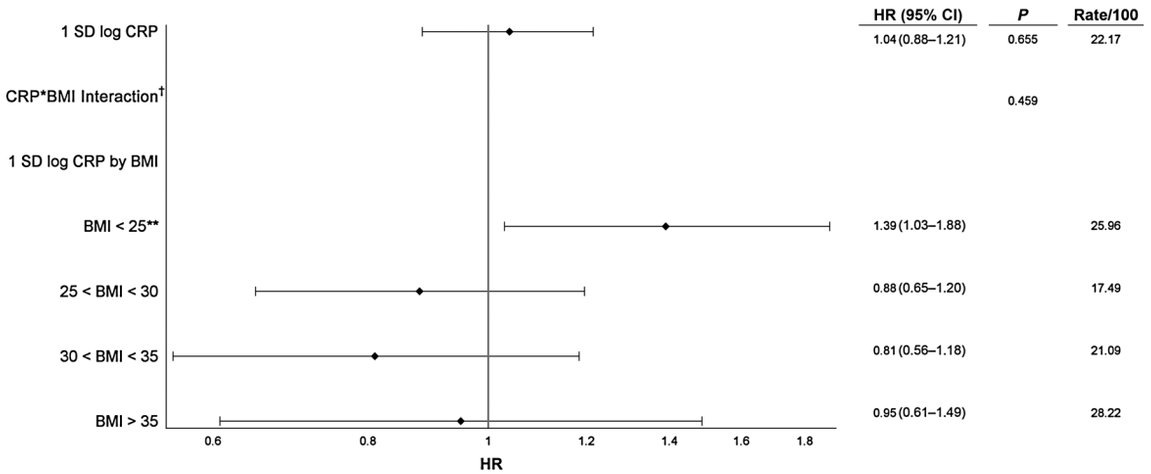

Abbreviations: High Sensitivity C-Reactive Protein (CRP), Body Mass Index (BMI), Standard deviation (SD), Hazard Ration (HR), Lower and Upper level of 95% confidence interval (LL and UL). † = interaction variable was created, ** = *P*-value < 0.05.

Figure 3.

All-cause mortality among incident breast cancer cases. HRs and 95% CIs in the WHI biospecimen cohort, per 1 SD natural log unit of hsCRP, overall, and by BMI level ($n = 1{,}114$).

and WHS included a mix of pre- and postmenopausal women, and their findings regarding CRP and breast cancer appeared to differ by menopausal status. Among postmenopausal women, there was a modest increased risk of breast cancer (RR = 1.35; 95% CI, 0.94–1.95), whereas no association was seen among premenopausal women. Another recent study that stratified by menopausal status also found that CRP risk only existed among postmenopausal women. To our knowledge, the NHS and WHS CRP study did not examine BMI interactions stratified by menopausal status, which may partially explain the difference in findings (17). Interestingly, two recent European studies directly examined possible effect modification by BMI and reached the opposite conclusion to ours, namely, that the association between hsCRP and incident breast cancer in postmenopausal women was only significant in overweight women (BMI > 25 and 24.8, respectively; refs. 5, 17). The first study was a retrospective nested case–control study, so it is possible that that this design influenced the results, or the differences could be due to the population (all of whom were French) having different dietary and lifestyle factors. The second study was a Norwegian prospective cohort study, and the diverging results could also be due to differences in dietary lifestyle factors.

A recent case–cohort analysis nested in the WHI observational study that examined the association of a wider variety of inflammatory biomarkers and incident breast cancer also found that hsCRP was not associated with breast cancer risk overall (14). This study also examined BMI as an effect modifier, but only as a binary variable (BMI < 30 or $\geq$30 kg/m^2), and found no evidence of effect modification. It is possible that the inclusion of overweight women (BMI, 25–30) with the normal weight women resulted in this null effect, as it was only in the normal weight women that an association was observed in our study.

The findings in our study regarding all-cause mortality in breast cancer survivors are different than those of a previous study by Villaseñor and colleagues (18), in which the authors found a significant association between postdiagnosis hsCRP and mortality in a cohort of around 3,000 breast cancer survivors. This discrepancy may be explained by the fact that they used postdiagnosis hsCRP levels, whereas we used prediagnosis levels, and they included women with hsCRP $\geq$ 10 mg/L, which is generally considered a marker of more acute inflammation (18). Our findings are also very different than a recent Norwegian study that found higher prediagnostic CRP levels to be associated with reduced mortality (HR = 0.78; 95% CI, 0.62–0.98 per 1 mg/L increase in hsCRP); this difference may be explained by the combination of pre- and postmenopausal women in the analysis, or due to the relatively small number of deaths ($n = 34$; ref. 17).

Our study has several limitations. Similar to most other studies, hsCRP was examined from a single blood draw, which may have contributed to measurement error. Multiple hsCRP measures would have reduced variability and enabled us to examine changes in hsCRP level; however, it is impractical and expensive to measure CRP levels longitudinally in epidemiologic studies. In addition, our analysis of all-cause mortality among incident cases relied on prediagnosis measurements of both BMI and hsCRP levels to examine the postdiagnosis mortality risk. Prediagnosis hsCRP may be a strength or limitation, as hsCRP levels postdiagnosis may change due to treatment or disease progression, and it is not clear which measure is a better predictor of overall mortality. In addition, we were only able to assess all-cause mortality, not breast cancer–specific mortality, because too few women in our analytic sample ($n = 90$) had breast cancer–specific mortality. Finally, this study relied on BMI as a measure of adiposity. BMI is not able to differentiate between lean mass and fat mass and thus does not have the accuracy of body composition assessment techniques such as dual-energy X-ray absorptiometry; nonetheless, BMI has been shown to be a sensitive measure in women and is a common clinical measure (19).

Aside from its prospective design, this study has several strengths, including its large sample size, large number of incident cases, inclusion of large numbers of minority women (≈50% of the sample), long follow-up for incident breast cancer (average of 13.6 years), physician adjudication of cases centrally, and analysis of CRP using high-sensitivity assays. In addition, BMI was based on measured, not self-reported, height, and weight.

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The current study adds to the literature with its examination, in a large prospective cohort, of how the association between hsCRP and postmenopausal incident breast cancer varies by BMI level. Although controlling for BMI is standard, few studies have adequate sample size to examine hsCRP in relation to breast cancer across BMI strata, or to evaluate effect modification by BMI. The study also adds to the literature in its use of high-sensitivity CRP in such a large cohort.

Overall, our data suggest a modest increase in the risk of postmenopausal breast cancer and poorer survival after diagnosis of breast cancer among lean women with higher levels of hsCRP. These findings imply that lean women should not be classified as having low risk of breast cancer based simply on their low BMI. These findings need replication, examination of a broader panel of inflammatory biomarkers, and further studies of both the pathways that lead to elevated hsCRP in women across the BMI spectrum and mechanisms by which hsCRP may increase or be correlated with increased cancer risk.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: S.H. Nelson, R.E. Patterson, D. Kritz-Silverstein, A.Z. LaCroix

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