Circulating C-Reactive Protein and Breast Cancer Risk—Systematic Literature Review and Meta-analysis of Prospective Cohort Studies
Doris S.M. Chan1, Elisa V. Bandera2, Darren C. Greenwood3, and Teresa Norat1

Abstract
We conducted a systematic literature review to explore the association between circulating C-reactive protein (CRP), a low-grade inflammation biomarker, and breast cancer risk. Relevant prospective studies in women were identified in PubMed and Web of Science until February 2015. Random-effects dose-response meta-analysis was conducted, overall and in postmenopausal women. Twelve out of 15 studies identified were included in the meta-analysis on any breast cancers (3,522 cases; 69,610 women) and nine on postmenopausal breast cancer (2,516 cases; 36,847 women). For each doubling of CRP concentration, a 7% [95% confidence interval (CI), 2%–12%] and 6% [95% CI, 1%–11%] increased risk was observed ($I^2 = 47\%$ and $32\%$; $P_{\text{heterogeneity}} = 0.04$ and 0.17, respectively. The association was linear over most of the range of CRP concentrations. Positive associations remained in the studies that examined the exclusion of early years of follow-up. Associations were attenuated in studies adjusted for lifestyle factors, which partly explained the significant heterogeneity between studies in the overall analysis. On average, the associations in studies adjusted or not adjusted for body mass index were similar. Low-grade inflammation may have a role in breast cancer development. Additional prospective studies are needed to better understand confounding and effect modification from lifestyle factors. Cancer Epidemiol Biomarkers Prev; 24(10); 1439–49. ©2015 AACR.

Introduction
Several studies have explored the intricate association between chronic inflammation and cancer, but whether chronic inflammation has a causal role in cancer pathogenesis, or is simply a marker of the disease is unclear. Indeed, some cancers arise at sites of chronic inflammation, whereas other cancers induce an inflammatory microenvironment (1). C-reactive protein (CRP) is a sensitive, nonspecific biomarker of inflammation that is produced in the liver. Circulating CRP level is acutely elevated in response to proinflammatory cytokines (TNFα and IL6) following an infection or tissue damage, and moderately elevated in the state of low-grade inflammation (1). High-sensitive assay methods with detection limits of <0.3 mg/L can readily measure lower concentrations of CRP in blood (2).

CRP levels have been shown to increase with obesity (3), smoking (4), postmenopausal hormone use (5), and to be lower with higher physical activity levels (6), better diet quality (7), and higher alcohol intake (8). Obesity-induced inflammation is associated with upregulation of proinflammatory cytokines, which promote neoplasia and tumor progression (9). Chronic inflammation is also linked directly to tumor initiation and promotion, through the production of reactive oxygen species and reactive nitrogen species that induce genomic instability and DNA damage (10).

Increased concentration of CRP is associated with increased risk of cardiovascular diseases and mortality (11), colorectal cancer (12), and lung cancer (13). Poorer prognosis in cancer patients, including those of breast cancer was also reported (1, 14), but evidence on the association of CRP with breast cancer risk is inconsistent. The association may also differ by degree of body adiposity. Stronger positive associations in overweight and obese women than in normal weight women were reported by a recent hospital-based case-control study (15), although reverse causation (inflammatory processes induced by occult cancer) could have influenced the results in this study.

In 2013, a meta-analysis of six prospective studies reported a nonsignificant positive association of CRP concentration and breast cancer risk, with moderate heterogeneity between studies (16). Since then, six more large-scale prospective studies (17–22)—three American (18–20), two French (17, 21), and one Chinese (22) studies—have been published, adding 2,038 cases and 27,968 study participants to the evidence. Hence, we conducted an updated systematic review and meta-analysis to investigate whether circulating CRP, a biomarker of chronic inflammation, is a risk factor for breast cancer development. We based the review on prospective studies because in these studies blood samples were collected before breast cancer diagnosis. We further examined the association in relation to possible biases from reverse causation, confounding, and effect modification by body adiposity.
Materials and Methods

A PRISMA checklist (23) of the items reported in this review is provided in Supplementary Methods and Materials S1.

Data sources and search

We searched systematically in PubMed and Web of Science (databases: MEDLINE, Web of Science Core Collection, CAB Abstracts, Current Contents Connect, and Journal Citation Reports) for articles on circulating CRP and breast cancer in humans that were published on any language from database inception to February 2015. The search strategy contained medical subject headings and/or variants of text words on CRP and breast cancer (Supplementary Methods and Materials S2). We also hand-searched the reference lists of relevant articles and reviews.

Study selection

Prospective studies (cohorts, follow-up of participants in randomized controlled trials, case–control nested within a cohort, and case–cohort) that reported a measure of association between prediagnosis circulating CRP concentrations in blood and subsequent risk of breast cancer development in women were selected. Abstract review and selection were conducted in duplicate (DSMC, TN).

Data extraction

Study and population characteristics, biomarker assessment methods and sample type, CRP concentrations, number of breast cancer cases and population at risk, and all relative risk (RR) estimates (hazard ratios and odds ratios) and the corresponding 95% confidence intervals (CI) or P values, matching factors, confounder adjustments, and effect modifiers used in the studies were extracted.

Statistical analysis

Fixed-effect and random-effects dose–response meta-analyses were conducted. As there was evidence of heterogeneity between studies, only results from random-effects model that allows for possible variations of associations across the studies were reported. We used the DerSimonian and Laird method (24) to calculate the weighted average of the natural logarithm (ln) of the RRs of each study, and back-transformed using the exponential function. CRP was natural log-transformed to normalize data for analysis. The increment unit of the meta-analysis was per doubling (100% increase) of CRP concentration. For studies that reported a dose–response slope per doubling of CRP concentration, we used the result directly. For studies that reported a dose–response slope per 1 ln unit increase, we rescaled the result to per doubling of CRP concentration by raising the RR and 95% CI to the power of 0.693 [ln(2)]. For studies that only reported categorical data, we estimated the study-specific slope using generalized weighted least-squares regression model (25) based on the method of Greenland and Longnecker (26). In this method, adjusted log RRs are regressed on the exposure doses across the categories in a study, taking into account the correlation between risk estimates that are calculated using a common reference group. The method requires that the numbers of breast cancer cases and population at risk for at least three categories of CRP concentrations and their means or medians values are provided. When the ranges of each category of CRP concentrations were instead reported, we assigned the corresponding RR to the midpoints of the category range. When the highest category was open-ended, we estimated the range using the width of the adjacent category. When the lowest category was open-ended, we used 0.1 mg/L as the lowest concentration. Studies without the required data for the procedures were excluded from the analysis.

Maximally adjusted RRs reported in the articles were used in the meta-analyses. To assess heterogeneity between studies, we calculated the Cochran Q test (P_Q) and I^2 statistic (% ref. 27). Sources of heterogeneity were explored in subgroups defined by number of cases, length of follow-up, publication year, study design, geographic location, CRP assessment method, and adjustments for confounders. To examine possible reverse causation, we restricted the studies into three groups based on exclusions of early years of follow-up as defined by the studies—studies with no exclusion of early years of follow-up; studies that reported a measure of association after the exclusion; and studies that reported no appreciably change of the estimates after the exclusion but did not show the results.

The Egger test and visual inspection of the funnel plot were performed to examine small study or publication bias (28). Each individual study was omitted in turn to examine the influence on the summary RR.

Furthermore, we examined the shape of the association using second order fractional polynomial models (29), including the studies with three or more categorical results and the required data for slope estimation as mentioned above. The fractional polynomial regression model with the lowest deviance was the best fitting model. Nonlinearity was tested using the likelihood ratio test (30).

P < 0.05 was considered statistically significant in all analysis, except for the Egger test, where P < 0.10 was used because of the low power of the test. All analyses were conducted using Stata version 12.0 (StataCorp; 2005; Stata Statistical Software: Release 12; StataCorp LP).

Results

Results of search

Fifteen studies (16 publications; refs. 17–22, 31–40) on CRP concentrations and breast cancer risk were identified in the literature search. Figure 1 shows the flowchart of search. Three studies (32, 36, 37) did not provide sufficient information to estimate a RR for each doubling of CRP concentration and could not be included in the meta-analysis (Supplementary Table S1). One study (32) reported a nonsignificant positive association when comparing CRP 6.5 with 0.4 mg/L. The result was attenuated with adjustment for BMI. Another study (36) reported a nonsignificant positive association per 3.2 mg/L increase of CRP concentration. BMI was accounted for in the study. The third study (37) reported a nonsignificant inverse association when comparing CRP ≥50.0 with <10 mg/L. The referent category in this study included low-grade inflammation, and may have resulted in an underestimation of the association between CRP and breast cancer (Supplementary Table S1). Hence, 12 studies (3,522 cases, 69,610 women; refs. 17–22, 31, 33–35, 38, 39) were included in the dose–response meta-analysis of all studies (any breast cancers) and nine studies (2,516 cases, 36,847 women; refs. 17–19, 22, 33–35, 38, 40) in the meta-analysis of postmenopausal breast cancer. Meta-analysis of premenopausal breast cancer was not conducted as only two studies (22, 40) reported results (Table 1). For the highest compared with the lowest CRP
concentrations, one study (40) reported a nonsignificant inverse association and the other study (22) reported a significant positive association with premenopausal breast cancer.

Study characteristics

Table 1 shows the characteristics and results of the prospective studies included in the present meta-analysis. There were one Asian study (22), five European studies (17, 21, 31, 33, 35), and six American studies (18–20, 34, 38, 39). In some studies, hormone therapy (HT) users (18), women with cardiovascular diseases (39) or liver cirrhosis (31) were excluded. Ollberding and colleagues (19) was a multiethnic cohort and Prizment and colleagues (20) was of white women only. Five studies (six publications) consisted of pre- and postmenopausal women (20–22, 31, 39, 40), of which only two studies further reported results by age groups (22) or menopausal status (40). Seven studies were of postmenopausal women only (17–19, 38), or in women aged ≥55 years (33–35).

The number of breast cancer cases ranged from 33 cases (34) to 892 cases (39). The study follow-up ranged from an average of 4.9 years (22) to 13 years (31). Concentrations of CRP varied between studies, with the highest categories ranging from <0.28 to ≥0.72 mg/L (38) to 0.1–1.1 to 2.7–28.6 mg/L (18).

Studies controlled for multiple risk factors (reproductive and lifestyle factors but no dietary factors) for breast cancer through matching or adjustment in the statistical models that were determined a priori or by whether its inclusion in the model changed the risk estimate significantly. Three studies (21, 22, 39) adjusted for BMI, alcohol consumption, physical activity, and smoking simultaneously. Two studies (20, 33) also adjusted for nonsteroidal anti-inflammatory drug (NSAID) use and three studies (20, 21, 33) adjusted for socioeconomic status.

Overall dose–response meta-analysis

Table 2 is a summary of the results from the dose–response meta-analyses. The studies included in each stratified analysis are listed in Supplementary Table S2.

Circulating CRP was statistically significantly positively associated with breast cancer risk (Table 2 and Fig. 2). The summary RR per doubling of CRP concentration was 1.07 (95% CI, 1.02–1.12). There was evidence of significant heterogeneity between studies ($I^2 = 47\%; P_h = 0.04$), which was partially explained by level of control for confounders. Studies that did not adjust for HT use, physical activity, or alcohol use reported on average stronger associations than studies adjusted for these factors. Positive associations although not always statistically significant were observed in most stratified analyses, with the exception of analyses restricted to studies that adjusted for physical activity and alcohol use. In the subgroup analyses by the exclusion of early...
<table>
<thead>
<tr>
<th>Author, study, country</th>
<th>Study design</th>
<th>Assessment period Follow-up length</th>
<th>Study size and cases Participant characteristics</th>
<th>CRP assessment</th>
<th>Biomarkers comparison</th>
<th>Results</th>
<th>Adjustments or matching factors</th>
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<tbody>
<tr>
<td>Wang et al. (22) CKFC, China</td>
<td>PC, 73.9% response 2006–2007 Average 4.9 y</td>
<td>19,437 women, 87 cases Mean age 49.2 y 10,130 women &lt; 50 y 9,307 women ≥ 50 y</td>
<td>High-sensitivity nephelometry assay Fasting sample</td>
<td>Plasma hs-CRP: &gt; 3.0 vs. &lt; 1 mg/L</td>
<td>Overall: 1.74 (1.01–2.97)</td>
<td>Adjustments or matching factors: Age, BMI, smoking, drinking, diabetes, physical activity, marital status</td>
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<td>Dossus et al. (17) E3N study, France</td>
<td>NCC 1995–1999 Maximum 10 y</td>
<td>549 cases, 1,040 controls Mean age 57.6 y</td>
<td>Immuno-turbidimetric assay Nonfasting sample CRP ≥ 2.5 vs. &lt; 1 mg/L</td>
<td>Serum hs-CRP: 2.5–10.0 vs. &lt; 1.5 mg/L Postmenopausal: 1.24 (0.92–1.66) BMI &lt; 25 kg/m²: 0.93 (0.61–1.4) BMI ≥ 25 kg/m²: 1.92 (1.20–3.08)</td>
<td>Postmenopausal: 1.89 (1.08–3.32)</td>
<td>Age, menopausal status, date and centre at blood collection, age at menopause</td>
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<tr>
<td>Gaudet et al. (18) CPS-II Nutrition Cohort, USA</td>
<td>NCC 1998–2001 Maximum 9 y 17 women lost to follow-up</td>
<td>302 cases, 302 controls Mean age 67.8 y Postmenopausal HT non-users</td>
<td>ELISA-based assays Nonfasting sample CRP ≥ 0.4 mg/L excluded</td>
<td>Plasma CRP: &gt; 2.7–28.6 vs. 0.1–1.1 mg/L Postmenopausal: 1.19 (0.79–1.79)</td>
<td>Per 1 natural log unit 1.13 (0.98–1.29)</td>
<td>Age, time from last meal to blood draw, alcohol in 24 hours before blood draw, prior diagnosis of diabetes, family history of breast cancer, race</td>
<td></td>
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<tr>
<td>Ollberding et al. (19) MEC, USA</td>
<td>NCC 2001–2006 Maximum 8 y</td>
<td>706 cases, 706 controls Mean age 67.8 y Postmenopausal Multi-ethnic</td>
<td>Latex-enhanced turbidimetric measurement 1–5 y &lt; diagnosis Fasting sample</td>
<td>Serum CRP: &gt; 4.0 vs. &lt; 0.9 mg/L Postmenopausal: 1.41 (1.01–1.96)</td>
<td>Postmenopausal: 1.19 (0.79–1.79)</td>
<td>Ethnicity, location, birth year, date and time of blood drawn, hours fasting before blood drawn, HRT use</td>
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<tr>
<td>Prizment et al. (20) ARIC, USA</td>
<td>PC, 81% response 1996–1998 35,888 person-years</td>
<td>4,009 women, 176 cases Mean age 62.8 y White 92.0% postmenopausal</td>
<td>Immuno-turbidimetric assay Plasma hs-CRP: &gt; 5.65 vs. 1.08 mg/L</td>
<td>Plasma hs-CRP: &gt; 5.65 vs. 1.08 mg/L</td>
<td>1.74 (1.00–3.05)</td>
<td>Age, BMI, waist, study center, education, aspirin use, smoking status, pack-years of smoking, HT use, menopausal status, age at menarche, number of live births</td>
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</tr>
</thead>
<tbody>
<tr>
<td>Touvier et al. (21) SUVIMAX, France</td>
<td>NCC from a RCT of antioxidant supplement 1994-1995</td>
<td>288 cases, 456 controls Mean age 49.2 y (cases), 51.5 y (controls)</td>
<td>ELISA Fasting sample</td>
<td>Plasma hs-CRP: ≥2.0 vs. ≤0.5 mg/L</td>
<td>1.25 (0.73–2.14) $P_{\text{trend}} = 0.70$</td>
<td>Age, BMI, height, intervention group, alcohol intake, physical activity, smoking status, educational level</td>
</tr>
<tr>
<td>Allin et al. (31) CCHS, Denmark</td>
<td>PC 1991-1994 (61.2% response) 2001-2003 (49.5% response)</td>
<td>5,369 women, 207 cases Age 44-63 y 68.4% postmenopausal Liver cirrhosis excluded</td>
<td>Turbidimetry or nephelometry</td>
<td>Plasma hs-CRP: ≥3.1 vs. ≤0.9 mg/L</td>
<td>0.70 (0.40–1.40) $P_{\text{trend}} = 0.40$</td>
<td>Age, BMI, smoking, alcohol consumption, OC use, menopausal status, HT use</td>
</tr>
<tr>
<td>Heikkila et al. (33) BWHHS, UK</td>
<td>PC 1999-2001 Maximum 7 y</td>
<td>3,274 women, 48 cases Age 60-79 y</td>
<td>Ultrasensitive nephelometric assay</td>
<td>hs-CRP: Per 1 natural log unit Postmenopausal: 1.00 (0.76-1.31)</td>
<td></td>
<td>Age, BMI, smoking, childhood and adult socioeconomic position, physical activity, HT use, NSAID use</td>
</tr>
<tr>
<td>Zeleniuch-Jacquotte et al. (38) NYUWHS, USA</td>
<td>NCC 6 mo–5.5 y before diagnosis (probably breast cancer already developed)</td>
<td>85 cases, 163 controls Postmenopausal</td>
<td>Behring NA latex test (nephelometry)</td>
<td>Serum CRP: ≥0.72 vs. &lt;0.28 mg/L</td>
<td>Postmenopausal: 2.43 (1.09-5.43)</td>
<td>Age, date of enrolment, and BMI</td>
</tr>
<tr>
<td>Zhang et al. (39) WHS, USA</td>
<td>PC from a RCT of aspirin and vitamin E 1992 Average 10.1 y 97.2%-99.4% follow-up</td>
<td>27,919 women, 892 cases Age 52.8-55.5 y 12,600 premenopausal women 15,318 postmenopausal women Cardiovascular diseases excluded</td>
<td>Latex-enhanced immunoturbidimetry</td>
<td>Plasma CRP: ≥5.1B vs. ≤0.64 mg/L</td>
<td>Overall: 0.90 (0.71-1.16) Excluded &lt;2 years follow-up: 0.96 (0.73-1.25)</td>
<td>Age, BMI, randomized treatment assignment, age at menarche, age at first pregnancy lasting 6 mo or longer, number of pregnancies lasting 6 mo or longer, menopausal status, age at menopause, HT use, family history of breast cancer in mother or a sister, history of benign breast disease, physical activity, multivitamin supplement use, smoking status, alcohol intake</td>
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<th>Adjustments or matching factors</th>
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<tr>
<td>Zhang et al. (40)</td>
<td>PC, 89% response</td>
<td>1989–1995</td>
<td>Average 10.2 y</td>
<td>Serum hs-CRP: 3.0-10.0 vs. &lt;1.0 mg/L</td>
<td>Premenopausal: 0.81 (0.46-1.42) BMI ≥25 kg/m²: Pinteraction = 0.24 (data not shown) Postmenopausal: 0.90 (0.66-1.25) BMI &lt;25 kg/m²: Nonsignificant positive association Pinteraction = 0.81 BMI ≥25 kg/m²: Significant inverse association Pinteraction = 0.04 (data not shown)</td>
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<tr>
<td>Siemes et al. (35)</td>
<td>PC, 89% response</td>
<td>1989–1995</td>
<td>Average 10.2 y</td>
<td>Serum hs-CRP: 3.0-10.0 vs. &lt;1.0 mg/L</td>
<td>Postmenopausal: 1.59 (1.05–2.41) Follow-up &gt;5 years: 1.48 (0.94–2.33)</td>
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<tr>
<td>Il'yasova et al. (34)</td>
<td>PC</td>
<td>1997–1998</td>
<td>Average 5.5 y</td>
<td>Serum hs-CRP: Per 1 natural log unit</td>
<td>Postmenopausal: 1.32 (0.91-1.93)</td>
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Abbreviations: ARIC, Atherosclerosis Risk in Communities study; BWHHS, British Women’s Heart and Health Study; CCHS, Copenhagen City Heart Study; CKFC, Chinese Kailuan Female Cohort; CPS, Cancer Prevention Study; E3N, Etude Épidémiologique auprès de femmes de l’Education Nationale; HABCS, Health Aging and Body Composition Study; MEC, Multiethnic Cohort Study; NCC, nested case-control study; NYUWHS, New York University Women’s Health Study; OC, oral contraceptive; PC, prospective cohort study; RCT, randomized controlled trial; SES, socioeconomic status; SUVIMAX, The Supplémentation en Vitamines et Minéraux Antioxydants study.

dDossus et al. (17): HT use, OC use, fasting sample status, smoking status, BMI, waist circumference, waist-to-hip ratio, education level, diabetes, physical activity, alcohol consumption, and other factors were tested but not included in the final model as none affected RRs by more than 10%.

eGaudet et al. (18): Former use of HT, OC use, alcohol consumption, and other factors, tested but not included in final model.

fGillberd et al. (19): OC use, alcohol consumption, physical activity, pack-years of cigarette smoking and other factors tested but not included in final model as none affected RRs by more than 10%.

gSiemes et al. (35): Only significant or well-known covariates were adjusted.

hIl’yasova et al. (34): BMI, visceral adiposity, smoking, physical activity, NSAID use, education, medical conditions, and other factors did not materially change the associations.
years of follow-up in the studies, the summary RR s were significantly different in studies without the exclusion, slightly weaker in studies that reported no change in the estimates after the exclusion, and nonsignificant in studies with the exclusion. Summary estimates were of similar magnitude for studies that adjusted and not adjust for BMI (Table 2).

### Table 2. Summary of dose-response meta-analyses of circulating CRP and breast cancer risk overall and in postmenopausal women

<table>
<thead>
<tr>
<th>Study design</th>
<th>Cases</th>
<th>RR (95% CI)</th>
<th>P (%)</th>
<th>P_{h}</th>
<th>Study design</th>
<th>Cases</th>
<th>RR (95% CI)</th>
<th>P (%)</th>
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<tbody>
<tr>
<td>BMI</td>
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<tr>
<td>Excluded</td>
<td>3</td>
<td>1.08 (1.02-1.12)</td>
<td>0.04</td>
<td>0.05</td>
<td>Not excluded</td>
<td>5</td>
<td>1.12 (1.02-1.24)</td>
<td>0.05</td>
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<tr>
<td>Location</td>
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<tr>
<td>Asia</td>
<td>1</td>
<td>1.08 (1.00-1.10)</td>
<td>0.02</td>
<td>0.03</td>
<td>Europe</td>
<td>5</td>
<td>1.09 (1.04-1.14)</td>
<td>0.04</td>
</tr>
<tr>
<td>10 years</td>
<td>8</td>
<td>1.07 (1.04-1.13)</td>
<td>0.03</td>
<td>0.04</td>
<td>North America</td>
<td>6</td>
<td>1.07 (1.00-1.14)</td>
<td>0.03</td>
</tr>
<tr>
<td>Excluded</td>
<td>3</td>
<td>1.06 (1.02-1.12)</td>
<td>0.04</td>
<td>0.05</td>
<td>Not excluded</td>
<td>5</td>
<td>1.06 (1.02-1.12)</td>
<td>0.04</td>
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<td>Location</td>
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<td>Asia</td>
<td>1</td>
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<td>0.02</td>
<td>0.03</td>
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<td>5</td>
<td>1.06 (1.01-1.14)</td>
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<tr>
<td>10 years</td>
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<td>1.07 (1.04-1.13)</td>
<td>0.03</td>
<td>0.04</td>
<td>North America</td>
<td>6</td>
<td>1.07 (1.00-1.14)</td>
<td>0.03</td>
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*NOTE: P_{h} denotes P value for heterogeneity between studies in each subgroup analysis.

*Studies reported no material change of risk estimate after early years of follow-up were excluded.

*Fasting status was missing in Allin et al. (31), Heikkila et al. (33), Prizment et al. (20), Zhang et al. (39), and Zeleniuch-Jacquotte et al. (38); blood sample was missing in Heikkila et al. (33).

*Excluded Gaudet et al. (18), which was of non-HT users only.
Dose–response meta-analysis for postmenopausal breast cancer

For postmenopausal breast cancer, the summary RR per doubling of CRP concentration was 1.06 (95% CI, 1.01–1.11) when all nine studies (17–19, 22, 33–35, 38, 40) were combined (Table 2 and Fig. 2). There was evidence of moderate heterogeneity between studies ($I^2 = 32\%$, $P_h = 0.17$), which was mostly explained by the Women’s Health Study (WHS; ref. 40), which had the biggest contribution (22% weight) in the analysis. When the study was excluded, the summary RR was 1.08 (95% CI, 1.04–1.13) and $I^2$ reduced to 0% ($P_h = 0.52$). The WHS was a follow-up of a randomized controlled trial evaluating the benefits and risks of low-dose aspirin and vitamin E in the primary prevention of cancer and cardiovascular disease in U.S. female health care professionals (39, 40).

The significant positive association persisted in studies that excluded early years of follow-up, or reported no change of estimates after the exclusion. Similar positive associations were observed in the meta-analyses of studies that were adjusted or not adjusted for BMI (Table 2). The summary RRs were 1.08 (95% CI, 1.04–1.13) and $I^2$ reduced to 0% ($P_h = 0.52$). The WHS was a follow-up of a randomized controlled trial evaluating the benefits and risks of low-dose aspirin and vitamin E in the primary prevention of cancer and cardiovascular disease in U.S. female health care professionals (39, 40).

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1.03–1.13) for four studies not adjusted for BMI (17–19, 34) and
1.06 (95% CI, 1.00–1.12) for seven studies adjusted for BMI (18,
19, 22, 33, 35, 38, 40). Moderate heterogeneity was only observed
between studies that were adjusted for BMI (not adjusted: \( I^2 = 0\%;
P_{h} = 0.64\); adjusted: \( I^2 = 40\%; P_{h} = 0.13\)). Only two studies (18,
19), both of postmenopausal women only, reported results for
both models; when the two studies were combined, the summary
RR was 1.07 (95% CI, 1.01–1.13) before adjustment for BMI and
1.06 (95% CI, 0.99–1.12) after adjustment (results not tabulated).
As in the meta-analysis for overall breast cancer, no associations
were observed in studies that adjusted for physical activity
and alcohol use (Table 2).

Three studies with data on postmenopausal women (17, 19, 40)
investigated whether the association between circulating CRP and
breast cancer risk varies according to BMI, and reported inconsistent results (Table 1). One study (17) reported a
significant positive association of CRP with breast cancer among
women with BMI \( \geq 25 \) kg/m\(^2\), whereas another study (40)
reported an inverse association for the same BMI group. The third
study (19) reported an association close to null among women
with BMI \( \geq 25 \) or between 25 and 29.9 kg/m\(^2\) (all \( P \leq 0.03
for interaction or heterogeneity).

**Other sensitivity analysis and test of publication bias**

The summary RRs remained similar when each study was
omitted in influence analyses including all studies or studies of
postmenopausal women. Egger tests showed some evidence of
publication or small study bias (overall: \( P = 0.08 \); postmeno-
pausal: \( P = 0.10 \)). Visual inspection of the funnel plots showed
that small studies with a null or weaker association than the
average may be missing (Supplementary Fig. S1).

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**Figure 3.**

Nonlinear dose–response meta-analysis of circulating CRP and breast cancer risk. A, scatter plot showing data from all studies. B, overall nonlinear dose–response curve. C, scatter plot showing data from studies of postmenopausal women. D, nonlinear dose–response curve in postmenopausal women. Bubbles in the scatter plots represent the RR of breast cancer for the corresponding CRP concentration comparison as reported in the studies. Size of bubbles is proportional to the number of cases and non-cases included in the analysis. Crosses show the reference CRP concentrations of the studies. The middle line of the curves represents the RR of breast cancer compared with reference CRP concentration and the upper and lower side lines represent 95% CI of the RR. Statistical analysis for nonlinearity was determined with the likelihood ratio test.
Nonlinear dose–response meta-analysis

In the analysis of all studies (any breast cancers), although the test for departure from linearity was statistically significant, the shape of the association was linear over most of the CRP range on the logarithmic scale \( P_{\text{nonlinearity}} = 0.01; \) 10 studies (17–22, 31, 35, 38, 39); Fig. 3). In postmenopausal women, the increase in risk was sharper and tailed off after 4 mg/L \( P_{\text{nonlinearity}} < 0.001; \) seven studies (17–19, 22, 35, 38, 40)\}, probably because of the low number of points contributing to the analysis after this value, resulting in wide CIs.

Discussion

By combining the current evidence from prospective studies of circulating CRP, a systemic low-grade inflammation biomarker, and breast cancer risk, 3,522 breast cancer cases, and 2,516 postmenopausal breast cancer cases could be included in meta-analyses. Overall, we found a modest statistically significant positive association. For each doubling (100% increase) of CRP concentration, there was a 7% increase in breast cancer risk and a 6% increase in postmenopausal breast cancer risk. The relationship was linear on the logarithmic scale. The observed association with circulating CRP was also present in studies that examined reverse causation by excluding cases diagnosed in early years of follow-up. Our meta-analysis is consistent with a recently published meta-analysis that showed an inverse negative association \( \text{RR} = 0.97, \) established meta-analysis that showed an inverse negative association \( \text{RR} = 0.97, \)

Discussion of Potential Conflicts of Interest

D.C. Greenwood is a consultant/advisory board member for World Cancer Research Fund. No potential conflicts of interest were disclosed by the other authors.

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Systematic Literature Review and Meta-analysis of Prospective
Cohort Studies


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