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), 2.2–12.4%] and 6% [95% CI, 1.0–11.2%] increased risk was observed ($I^2 = 47.6$% and 32.0%; $P_{\text{heterogeneity}} = 0.04$ 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) methods and sample type, CRP concentrations, number of breast cancer cases, length of follow-up, publication year, study design, geographic location, CRP assessment method, and adjustments for confounders.

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).

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 concentration 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 (PQ) and I2 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).
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).

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 1. Characteristics and results of studies included in the dose-response meta-analysis of circulating CRP and breast cancer risk

<table>
<thead>
<tr>
<th>Author, study, country</th>
<th>Study design</th>
<th>Assessment period</th>
<th>Follow-up length</th>
<th>Study size and cases</th>
<th>CRP assessment</th>
<th>Biomarkers comparison</th>
<th>Results</th>
<th>Adjustments or matching factors</th>
</tr>
</thead>
<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: ≥3.0 vs. &lt;1 mg/L Overall: 1.74 (1.01–2.97) $P_{trend} = 0.05$ &lt;50 years: 2.76 (1.18–6.48) ≥50 years: 1.34 (0.68–2.64) $P_{interaction} = 0.03$</td>
<td>Adjustments or matching factors</td>
<td>Age, BMI, smoking, drinking, diabetes, physical activity, marital status</td>
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<tr>
<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 ≥3.0 vs. &lt;1 mg/L Overall: 1.89 (1.08–3.32) $P_{trend} = 0.03$ Postmenopausal: 1.24 (0.92–1.66) BMI &lt;25 kg/m²: 0.93 (0.61–1.41) $P_{interaction} = 0.03$ BMI ≥25 kg/m²: 1.92 (1.20–3.08)</td>
<td></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 ≥40 mg/L excluded</td>
<td>Plasma CRP: ≥2.7–28.6 vs. 0.1–11 mg/L Postmenopausal: 1.19 (0.79–1.79) $P_{trend} = 0.10$ Above factors + BMI</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>
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<tr>
<td>Ollberding et al. (19) MEC, USA</td>
<td>NCC 2001–2006 Maximum 8 y</td>
<td>706 case, 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: ≥4.0 vs. &lt;0.9 mg/L Postmenopausal: 1.41 (1.01–1.96) $P_{trend} = 0.014$ Above factors + BMI</td>
<td>Ethnicity, location, birth year, date and time of blood drawn, hours fasting before blood draw, HRT use</td>
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<tr>
<td>Prizment et al. (20) ARIC, USA</td>
<td>PC, 81% response 1996–1998 33,888 person-years</td>
<td>4,009 women, 176 cases Mean age 62.8 y White 92.0% postmenopausal</td>
<td>Immuno-turbidimetric assay</td>
<td>Plasma hs-CRP: ≥5.65 vs. ≤1.08 mg/L</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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(Continued on the following page)
## Table 1. Characteristics and results of studies included in the dose-response meta-analysis of circulating CRP and breast cancer risk (Cont'd)

<table>
<thead>
<tr>
<th>Author, study, country</th>
<th>Study design Assessment period</th>
<th>Study size and cases Participant characteristics</th>
<th>CRP assessment Biomarkers comparison</th>
<th>Results</th>
<th>Adjustments or matching factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Touvier et al. (21) SUVIMAX, France</td>
<td>NCC from a RCT of antioxidant supplement 1994-1995 Maximum 8 y</td>
<td>218 cases, 436 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 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>1991-1994 (61.2% response) 2001-2003 (49.5% response) Average 13 y 100% follow-up</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 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>1999–2001 Maximum 7 y</td>
<td>3,274 women, 48 cases Age 60–79 y</td>
<td>Ultrasonic nephelometric assay</td>
<td>hs-CRP: Per 1 natural log unit Postmenopausal: 1.00 (0.76–1.31)</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 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: ≥ 5.18 vs. ≤0.64 mg/L Overall: 0.90 (0.71–1.16) Excluded &lt;2 years follow-up: 0.96 (0.73–1.25) BMI ≥25 kg/m²: Statistically significant inverse association $P_{\text{interaction}} = 0.02$ (data not shown)</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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</table>

3.1–10 vs. <1 mg/L Overall: 1.02 (0.84–1.24) Per 1 natural log unit 1.00 (0.94–1.07) BMI ≥25 kg/m²: Statistically significant inverse association $P_{\text{interaction}} = 0.02$ (data not shown)
Table 1. Characteristics and results of studies included in the dose-response meta-analysis of circulating CRP and breast cancer risk (Cont’d)

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<th>Biomarkers comparison</th>
<th>Results</th>
<th>Adjustments or matching factors</th>
</tr>
</thead>
</table>
| Zhang et al. (40) | PC, 89% response | 3,790 women, 184 cases | Serum hs-CRP: 3.0-10.0 vs. <1.0 mg/L | Postmenopausal: 0.81 (0.46-1.42) | BMI ≥25 kg/m²: Nonsignificant positive association | Adjustments for BMI, age, menarche and menopause, hormone use, number of children

| Siemes et al. (35) | Rotterdam Study, The Netherlands | Age ≥55 y | Near-infrared particle immunoassay CRP > 10 mg/L excluded | Serum hs-CRP: 3.0-10.0 vs. <1.0 mg/L | Postmenopausal: 1.59 (1.05-2.41) | Adjustments for BMI, age, smoking, age at menarche and menopause, hormone use, number of children

| Il'yasova et al. (34) | HABCS, USA | Age 70-79 y | ELISA Fasting sample | Serum hs-CRP: Per 1 natural log unit | Postmenopausal: 1.32 (0.91-1.93) | Adjustments for age, race, study site

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’Éducation 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.

*Dossus 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%.

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

*Ollberding 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%.

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

*Il’yasova et al. (34): BMI, visceral adiposity, smoking, physical activity, NSAID use, education, medical conditions, and other factors did not materially change the associations.
Table 2. Summary of dose-response meta-analyses of circulating CRP and breast cancer risk overall and in postmenopausal women

<table>
<thead>
<tr>
<th>Length of FU</th>
<th>RR (95% CI)</th>
<th>F (%)</th>
<th>Publication year</th>
<th>Serum</th>
<th>Socioeconomic status</th>
<th>Physical activity</th>
<th>Alcohol use</th>
<th>Blood sample</th>
<th>CRP assay</th>
<th>Location</th>
<th>Smoking</th>
<th>HT use</th>
<th>NSAIDs use</th>
<th>Excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 years</td>
<td>1.07 (1.02–1.12)</td>
<td>0.42</td>
<td>2010</td>
<td>1.17</td>
<td>0.68</td>
<td>0.65</td>
<td>0.76</td>
<td>1.12</td>
<td>0.64</td>
<td>1.16</td>
<td>0.09</td>
<td>0.60</td>
<td>0.11</td>
<td>0.17</td>
</tr>
<tr>
<td>&gt; 10 years</td>
<td>1.04 (0.96–1.14)</td>
<td>0.02</td>
<td>2010</td>
<td>1.06</td>
<td>0.60</td>
<td>0.05</td>
<td>0.05</td>
<td>1.07</td>
<td>0.17</td>
<td>1.20</td>
<td>0.30</td>
<td>0.69</td>
<td>0.08</td>
<td>0.17</td>
</tr>
</tbody>
</table>

NOTE: P 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.

years of follow-up in the studies, the summary RRs were significant 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).
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% ($P_i = 0.52$). 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% ($P_i = 0.52$). 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).
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/m², 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 $< 25$ or between 25 and 29.9 kg/m² (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: $P = 0.08$; postmenopausal: $P = 0.10$). 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).
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 between NSAIDs use and breast cancer risk (summary RR, 0.97, 95% CI, 0.94–1.00; \( I^2 = 88\% \), \( P_{\text{heterogeneity}} < 0.001 \); 12 cohort studies; ref. 41). However, the few studies that examined genotypes that influence CRP levels in blood and breast cancer risk did not offer consistent results (20, 42–45). The elevated CRP could be a marker of host response to early malignancy or disease progression instead of a causal factor for breast cancer development. Our results therefore need to be confirmed in future studies.

A number of limitations should be considered when interpreting our findings. Seven out of 12 studies included in the overall analysis were of postmenopausal women only (17–19, 33–35, 38). Thus, premenopausal women were underrepresented in this review. Significant heterogeneity existed in the overall meta-analysis. Differences in the level of control for confounding in the studies may partly explain the heterogeneity, but the evidence provided by the meta-analysis is limited by the low number of studies in the subgroup analyses. Also, the studies included in the subgroups are different, which hinder direct comparisons between the results. On average, the associations in studies that were unadjusted for HT use, physical activity, or alcohol use appeared stronger compared with adjusted results. Similar significant associations were observed in the studies adjusted or not adjusted for BMI. However, direct comparison was only possible in two studies of postmenopausal women that reported multivariable results from both models adjusted and not adjusted for BMI (18, 19), and the results were slightly attenuated after adjustment for BMI. The association could also be mediated or modified by body adiposity, but the data were limited and equivocal (17, 19, 40).

Another limitation is that some studies could not be included in the meta-analyses because of insufficient data (32, 36, 37). If included, the summary association would have been weakened by one large study (1,241 cases; ref. 37), which reported a possibly underestimated (nonsignificant inverse) association of CRP that was detected by a conventional assay. Other excluded studies (32, 36) reported results similar to those included in the meta-analysis. Funnel plots showed that small studies with a null or weaker association than the average estimated in this meta-analysis may be missing. However, as our search included the major sources for searching related literature [MEDLINE using the platform of PubMed and the reference lists of related publications (46)], it is unlikely that we missed publications in our review.

Although CRP concentrations have good consistency over time (47, 48), the studies included in the review only performed one CRP assessment at study baseline and some misclassification cannot be excluded, possibly leading to attenuation of association.

Taken together, evidence suggested a role of chronic inflammation in breast cancer development. Breast cancer risk increases with increasing CRP concentration in a dose–response manner. Possible confounding and modifying effect of obesity and other lifestyle factors and the mechanisms underlying the association warrants further investigation.

Disclosure 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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