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Circulating C-reactive protein and breast cancer risk – systematic literature review and meta-analysis of prospective cohort studies

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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 post-menopausal 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 post-menopausal breast cancer (2,516 cases, 36,847 women). For each doubling of CRP concentration, a 7% (95% CI: 2%–12%) and 6% (95% CI: 1%–11%) increased risk was observed (I^2=47% and 32%; *P 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.

(198 words)

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, while other cancers induce an inflammatory microenvironment (1). C-reactive protein (CRP) is a sensitive, non-specific biomarker of inflammation that is produced in the liver. Circulating CRP level is acutely elevated in response to proinflammatory cytokines (tumour necrosis factor-alpha, interleukin-6) 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), post-menopausal 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 tumour progression (9). Chronic inflammation is also linked directly to tumour 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 non-significant 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 1.

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 2). We also hand-searched the reference lists of relevant articles and reviews.

Study selection

Prospective studies (cohorts, follow-up of participants in randomised controlled trials, case-control nested within a cohort, and case-cohort) that reported a measure of association between pre-diagnosis circulating CRP concentrations in blood and subsequent risk of breast cancer development in women were selected. Abstract review and selection was 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 DerSimonian and Laird's 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 normalise 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 re-scaled 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 generalised 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 lowermost concentration. Studies without the required data for the procedures were excluded from the analysis.

Maximally adjusted RRs reported in the papers were used in the meta-analyses. To assess heterogeneity between studies, we calculated the Cochran Q test (P_h) and I^2 statistic (%) (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.

Egger's 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. Non-linearity was tested using the likelihood ratio test (30).

$P<0.05$ was considered statistically significant in all analysis, except for Egger's 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. College Station, TX: StataCorp LP).

Results

Results of search

Fifteen studies (16 publications) (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 non-significant 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 non-significant positive association per 3.2 mg/L increase of CRP concentration. BMI was accounted for in the study. The third study (37) reported a non-significant 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 (17-22, 31, 33-35, 38, 39) (3,522 cases, 69,610 women) were included in the dose-response meta-analysis of all studies (any breast cancers) and nine studies (17-19, 22, 33-35, 38, 40) (2,516 cases, 36,847 women) in the meta-analysis of post-menopausal breast cancer. Meta-analysis of pre-menopausal 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 non-significant inverse association and the other study (22) reported a significant positive association with pre-menopausal 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 *et al.* (19) was a multi-ethnic cohort and Prizment *et al.* (20) was of white women only. Five studies (6 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 post-menopausal 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

non-steroidal 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, 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 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 non-significant in studies with the exclusion. Summary estimates were of similar magnitude for studies that adjusted and not adjust for BMI (Table 2).

Dose-response meta-analysis for post-menopausal breast cancer

For post-menopausal 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, 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) (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 randomised controlled trial evaluating the benefits and risks of low-dose aspirin and vitamin E in the primary prevention of cancer and cardiovascular disease in US female health 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: 1.03–1.13) 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 post-menopausal 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 ≥ 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 ≥ 30 kg/m^2, but non-significant positive associations in women with BMI <25 or between 25–29.9 kg/m^2 (all P ≤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 post-menopausal women. Egger's tests showed some evidence of publication or small study bias (Overall: P = 0.08; Post-menopausal: 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).

Non-linear 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 [$P_{non\text{-}linearity}$ = 0.01; 10 studies (17-22, 31, 35, 38, 39)] (Fig. 3). In post-menopausal women, the increase in risk was sharper and tailed off after 4 mg/L [$P_{non\text{-}linearity}$ < 0.001; 7 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 confidence intervals.

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 post-menopausal 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 post-menopausal 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_h <0.001; 12 cohort studies) (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 post-menopausal women only (17-19, 33-35, 38). Thus pre-menopausal women were underrepresented in the present 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 post-menopausal 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) (37) which reported a possibly underestimated (non-significant 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.

Words: 3,061 words

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

Author, Year Study, Country	Study design Assessment period Follow-up length	Study size and cases Participant characteristics	CRP assessment	Biomarkers comparison	Results	Adjustments or matching factors
Wang *et al.*, 2015 (22) CKFC, China	PC, 73.9% response 2006–2007 Average 4.9 y	19,437 women, 87 cases Mean age 49.2 y 10,130 women <50 y 9,307 women ≥50 y	High-sensitivity nephelometry assay Fasting sample	Plasma hs-CRP >3.0 vs. <1 mg/L	Overall: 1.74 (1.01–2.97) *P trend* = 0.05 <50 years: 2.76 (1.18–6.48) ≥50 years: 1.34 (0.68–2.64)	Age, BMI, smoking, drinking, diabetes, physical activity, marital status
				>3.0–≤10 vs. <1 mg/L	Overall: 1.89 (1.08–3.32) *P trend* = 0.03	
Dossus *et al.*, 2014 (17) E3N study, France	NCC 1995–1999 Maximum 10 y	549 cases, 1,040 controls Mean age 57.6 y Post-menopausal	Immuno-turbidometric assay Average 4.2 y < diagnosis Non-fasting sample CRP ≥ 10 mg/L excluded	Serum hs-CRP 2.5–<10.0 vs. <1.5 mg/L	Post-menopausal: 1.24 (0.92–1.66) BMI<25 kg/m^2: 0.93 (0.61-1.41) BMI ≥25 kg/m^2: 1.92 (1.20-3.08) *P interaction* = 0.03	Age, menopausal status, date and centre at blood collection, age at menopause. [a]
				Per 1 natural log-unit	1.13 (0.98–1.29)	
Gaudet *et al*. 2013 (18) CPS-II Nutrition Cohort, USA	NCC 1998–2001 Maximum 9 y 17 women lost to follow-up	302 cases, 302 controls Age ~65–75 y Post-menopausal HT non-users	ELISA-based assays Non-fasting sample CRP ≥40 mg/L excluded	Plasma CRP >2.7–28.6 vs. 0.1–1.1 mg/L	Post-menopausal: 1.19 (0.79–1.79) *P trend* = 0.10	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. [b]
					1.09 (0.70–1.70) *P trend* = 0.16	Above factors + BMI
Ollberding *et al.*, 2013 (19) MEC, USA	NCC 2001–2006 Maximum 8 y	706 case, 706 controls Mean age 67.8 y Post-menopausal Multi-ethnic	Latex-enhanced turbidimetric measurement 1–5 y < diagnosis Fasting sample	Serum CRP: >4.0 vs. ≤0.9 mg/L	Post-menopausal: 1.41 (1.01–1.96) *P trend* = 0.014	Ethnicity, location, birth year, date and time of blood drawn, hours fasting before blood drawn, HRT use. [c]
					1.33 (0.95–1.87)	Above factors + BMI
					BMI<25 kg/m^2: 1.26 (0.75-2.12) BMI 25-29.9 kg/m^2:	

					1.70 (0.94-3.06) BMI ≥30 kg/m^2: 1.02 (0.41-2.54) *P heterogeneity* = 0.008	
Prizment *et al*., 2013 (20) ARIC, USA	PC, 81% response 1996–1998 35,888 person-years	4009 women, 176 cases Mean age 62.8 y White 92.0 % post-menopausal	Immuno-turbidimetric assay	Plasma hs-CRP: ≥5.65 vs. ≤1.08 mg/L Per 1 natural log-unit	1.74 (1.00–3.03) 1.27 (1.07–1.51) Excluded <2 years follow-up: 1.40 (1.16–1.70)	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
Touvier *et al*., 2013 (21) SUVIMAX, France	NCC from a RCT of antioxidant supplement 1994–1995 Maximum 8 y	218 cases, 436 controls Mean age 49.2 y (cases), 51.5 y (controls)	ELISA Fasting sample	Plasma hs-CRP: ≥2.0 vs. ≤0.5 mg/L	1.25 (0.73–2.14) *P trend* = 0.70	Age, BMI, height, intervention group, alcohol intake, physical activity, smoking status, educational level
Allin *et al*., 2009 (31) CCHS, Denmark	PC 1991–1994 (61.2% response) 2001–2003 (49.5% response) Average 13 y 100% follow-up	5369 women, 207 cases Age ~44–63 y 68.4% post-menopausal Liver cirrhosis excluded	Turbidimetry or nephelometry	Plasma hs-CRP ≥3.1 vs. ≤0.9 mg/L	0.70 (0.40–1.40) *P trend* = 0.40	Age, BMI, smoking, alcohol consumption, OC use, menopausal status, HT use
Heikkila *et al*., 2009 (33) BWHHS, UK	PC 1999–2001 Maximum 7 y	3274 women, 48 cases Age 60–79 y	Ultrasensitive nephelometric assay	hs-CRP Per 1 natural log unit	Post-menopausal: 1.00 (0.76–1.31)	Age, BMI, smoking, childhood and adult socioeconomic position, physical activity, HT use, NSAID use
Zeleniuch-Jacquotte *et al*., 2008 (38) NYUWHS, USA	NCC 6 m–5.5 y before diagnosis (probably breast cancer already developed)	85 cases, 163 controls Post-menopausal	Behring NA latex test (nephelometry)	Serum CRP: ≥0.72 vs. <0.28 mg/L Per doubling of CRP	Post-menopausal: 2.43 (1.09–5.43) 1.25 (0.96–1.64)	Age, date of enrolment, and BMI
Zhang *et al*., 2007 (39) WHS, USA	PC from a RCT of aspirin and vitamin E 1992 Average 10.1 y 97.2%-99.4% follow-up	27919 women, 892 cases Age ~52.8–55.5 y 12, 600 pre-menopausal women 15, 318 post-menopausal women Cardiovascular diseases excluded	Latex-enhanced immunoturbidimetry	Plasma CRP: ≥5.18 vs. ≤0.64 mg/L 3.1-10 vs. <1 mg/L	Overall: 0.90 (0.71–1.16) Excluded <2 years follow-up: 0.96 (0.73–1.25) Overall: 1.02 (0.84–1.24)	Age, BMI, randomised treatment assignment, age at menarche, age at first pregnancy lasting 6 m 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

				Per 1 natural log unit	1.00 (0.94–1.07) BMI ≥25 kg/m^2: Statistically significant inverse association *P interaction* = 0.02 (data not shown)	benign breast disease, physical activity, multivitamin supplement use, smoking status, alcohol intake
Zhang *et al.*, 2008 (40)				≥5.18 vs. ≤0.64 mg/L	Pre-menopausal: 0.81 (0.46–1.42) BMI ≥25 kg/m^2: *P interaction* = 0.24 (data not shown) Post-menopausal: 0.90 (0.66–1.23) BMI <25 kg/m^2: Non-significant positive association *P trend*= 0.81 BMI ≥25 kg/m^2: Significant inverse association *P trend*= 0.04 *P interaction* = 0.06 (data not shown)	
Siemes *et al.*, 2006 (35) Rotterdam Study, The Netherlands	PC, 89% response 1989–1993 Average 10.2 y	3790 women, 184 cases Age ≥55 y	Near-infrared particle immunoassay CRP > 10 mg/L excluded Non-fasting sample	Serum hs-CRP: 3.0-10.0 vs. <1.0 mg/L	Post-menopausal: 1.59 (1.05–2.41) Follow-up >5 years: 1.48 (0.94-2.33)	Age, BMI, smoking, age at menarche and menopause, hormone use, number of children. [d]
				Per 1 natural log unit	Post-menopausal: 1.28 (1.07–1.54) Follow-up >5 years: 1.23 (1.02–1.50)	
Il'yasova *et al.*, 2005 (34) HABCS, USA	PC 1997–1998 Average 5.5 y	1305 women, 33 cases (mortality included) Age 70-79 y Black and White	ELISA Fasting sample	Serum hs-CRP Per 1 natural log unit	Post-menopausal: 1.32 (0.91-1.93)	Age, race, study site. [e]

[a] Dossus *et al.*, 2014: 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%.

[b] Gaudet *et al.*, 2013: Former use of HT, OC use, alcohol consumption, and other factors tested but not included in final model.

[c] Ollberding *et al.*, 2013: 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%.

[d] Siemes *et al.*, 2006: Only significant or well-known covariates were adjusted.

[e] Il'yasova *et al.*, 2005: BMI, visceral adiposity, smoking, physical activity, NSAID use, education, medical conditions, and other factors did not materially change the associations.

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 Epidémiologique auprès de femmes de l'Education Nationale, ELISA-enzyme-linked immunosorbent assay, 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-randomised controlled trial, SES-socioeconomic status, SUVIMAX-The Supplémentation en Vitamines et Minéraux Antioxydants study, WHS-Women's Health Study

Table 2 Summary of dose-response meta-analyses of circulating CRP and breast cancer risk overall and in post-menopausal women

	All studies				Post-menopausal women studies			
	Study	Cases	RR (95% CI)	I^2 (%), P_h	Study	Cases	RR (95% CI)	I^2 (%), P_h
			Per doubling of CRP				Per doubling of CRP	
Overall	12	3522	1.07 (1.02-1.12)	47, 0.04	9	2516	1.06 (1.01-1.11)	32, 0.17
Early years of follow-up								
Excluded	3	<1088	1.13 (0.98-1.30)	81, 0.006	1	158	1.15 (1.01-1.32)	-
No change[f]	7	<2098	1.05 (1.00-1.10)	0, 0.43	5	<1632	1.06 (1.02-1.12)	0, 0.64
Not excluded	5	1424	1.12 (1.02-1.24)	73, 0.005	4	883	1.09 (0.97-1.22)	65, 0.03
Length of FU								
< 10 years	8	1650	1.08 (1.04-1.13)	1, 0.42	6	1226	1.06 (1.01-1.12)	0, 0.59
≥ 10 years	4	1872	1.04 (0.96-1.14)	70, 0.02	3	1290	1.07 (0.97-1.19)	74, 0.02
Location								
Asia	1	87	1.13 (1.00-1.29)	-	1	57	1.07 (0.91-1.26)	-
Europe	5	1246	1.05 (0.97-1.14)	46, 0.12	3	781	1.10 (1.02-1.20)	17, 0.30
North America	6	2189	1.07 (1.00-1.14)	56, 0.04	5	1678	1.05 (0.98-1.11)	40, 0.15
Study design								
NCC	5	1855	1.07 (1.02-1.12)	0, 0.60	4	1637	1.07 (1.02-1.12)	0, 0.47
PC	7	1667	1.08 (0.99-1.17)	66, 0.008	5	879	1.07 (0.97-1.17)	52, 0.08
Number of cases								
<500	9	1375	1.09 (1.02-1.16)	42, 0.09	6	704	1.09 (1.01-1.17)	19, 0.29
≥500	3	2147	1.04 (0.98-1.11)	55, 0.11	3	1812	1.04 (0.98-1.12)	54, 0.12
Publication year								
<2010	6	1489	1.06 (0.97-1.16)	59, 0.03	5	907	1.09 (0.98-1.22)	60, 0.04
≥2010	6	2033	1.08 (1.04-1.13)	0, 0.47	4	1609	1.07 (1.02-1.12)	0, 0.76
CRP assay								
ELISA	3	548	1.04 (0.96-1.12)	0, 0.47	2	330	1.06 (0.92-1.23)	34, 0.22
Other assays	9	2974	1.08 (1.02-1.14)	59, 0.01	7	2186	1.07 (1.01-1.13)	40, 0.12
Blood sample[g]								
Plasma	6	1917	1.04 (0.98-1.11)	55, 0.05	3	911	1.00 (0.95-1.06)	0, 0.60
Serum	5	1557	1.11 (1.05-1.17)	0, 0.57	5	1557	1.11 (1.05-1.17)	0, 0.57
Fasting status[g]								
Fasting	4	1044	1.09 (1.03-1.15)	0, 0.65	3	796	1.09 (1.02-1.16)	0, 0.69
Non-fasting	3	1030	1.09 (1.00-1.18)	45, 0.16	3	1030	1.09 (1.00-1.18)	45, 0.16
Acute inflammation								
Not excluded	9	2492	1.06 (1.00-1.13)	50, 0.04	6	1486	1.05 (0.99-1.12)	28, 0.23
Excluded	4	1110	1.10 (1.03-1.17)	33, 0.22	3	1030	1.09 (1.00-1.18)	45, 0.16
Confounder adjustments								
BMI								
No	4	1585	1.08 (1.03-1.13)	0, 0.64	4	1585	1.08 (1.03-1.13)	0, 0.64
Yes	10	2940	1.06 (1.01-1.12)	53, 0.03	7	1934	1.06 (1.00-1.12)	40, 0.13
Smoking								
No	5	1670	1.07 (1.02-1.13)	0, 0.50	5	1670	1.07 (1.02-1.13)	0, 0.50
Yes	7	1852	1.06 (0.99-1.14)	63, 0.01	4	846	1.05 (0.96-1.16)	56, 0.08
NSAIDs use								
No	10	3298	1.06 (1.01-1.11)	46, 0.05	8	2468	1.07 (1.02-1.13)	39, 0.12
Yes	2	224	1.10 (0.94-1.30)	53, 0.15	1	48	1.00 (0.83-1.21)	-
Socioeconomic status								
No	9	3080	1.07 (1.01-1.12)	52, 0.03	8	2468	1.07 (1.02-1.13)	39, 0.12
Yes	3	442	1.08 (0.98-1.20)	35, 0.22	1	48	1.00 (0.83-1.21)	-
HT use[h]								
No	5	972	1.10 (1.04-1.17)	0, 0.65	4	724	1.11 (1.03-1.19)	0, 0.68
Yes	6	2253	1.06 (0.99-1.14)	67, 0.01	4	1495	1.06 (0.97-1.15)	62, 0.05
Physical activity								
No	8	2277	1.09 (1.03-1.16)	42, 0.10	6	1854	1.09 (1.04-1.14)	8, 0.37
Yes	4	1245	1.02 (0.97-1.08)	15, 0.32	3	662	1.00 (0.94-1.06)	0, 0.64
Alcohol use								
No	8	2078	1.10 (1.05-1.15)	11, 0.34	7	1902	1.08 (1.04-1.13)	2, 0.41
Yes	4	1444	1.02 (0.95-1.09)	41, 0.16	2	614	1.00 (0.94-1.06)	0, 0.34

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

[g] Fasting status was missing in Allin *et al*., 2009, Heikkila *et al*, 2009, Prizment *et al*., 2013 Zhang *et al*., 2007, and Zeleniuch-Jacquotte *et al*. 2008; Blood sample was missing in Heikkila *et al*., 2009.

[h] Excluded Gaudet *et al*., 2013, which was of non-HT users only.

Note: P_h denotes P value for heterogeneity between studies in each subgroup analysis.

Figure legends

Figure 1: Flowchart of systematic literature search of circulating C-reactive protein and breast cancer risk

Figure 2: Summary relative risk per doubling of circulating CRP concentration and breast cancer risk

A – Overall meta-analysis, B – Meta-analysis in postmenopausal women.

Forest plots show the relative risk of breast cancer per doubling of CRP concentration in each study. Error bars indicate 95% confidence intervals. Size of the squares indicates the weight of each study in the random-effects meta-analysis. Diamonds indicate the summary relative risks.

Figure 3: Non-linear dose-response meta-analysis of circulating CRP and breast cancer risk

A – Scatter plot showing data from all studies, B – Overall non-linear dose-response curve, C – Scatter plot showing data from studies of postmenopausal women, D – Non-linear dose-response curve in postmenopausal women.

Bubbles in the scatter plots represent the relative risk 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 relative risk of breast cancer compared with reference CRP concentration and the upper and lower side lines represent 95% confidence interval of the relative risk. Statistical analysis for nonlinearity was determined with the likelihood ratio test.

Figure 1.

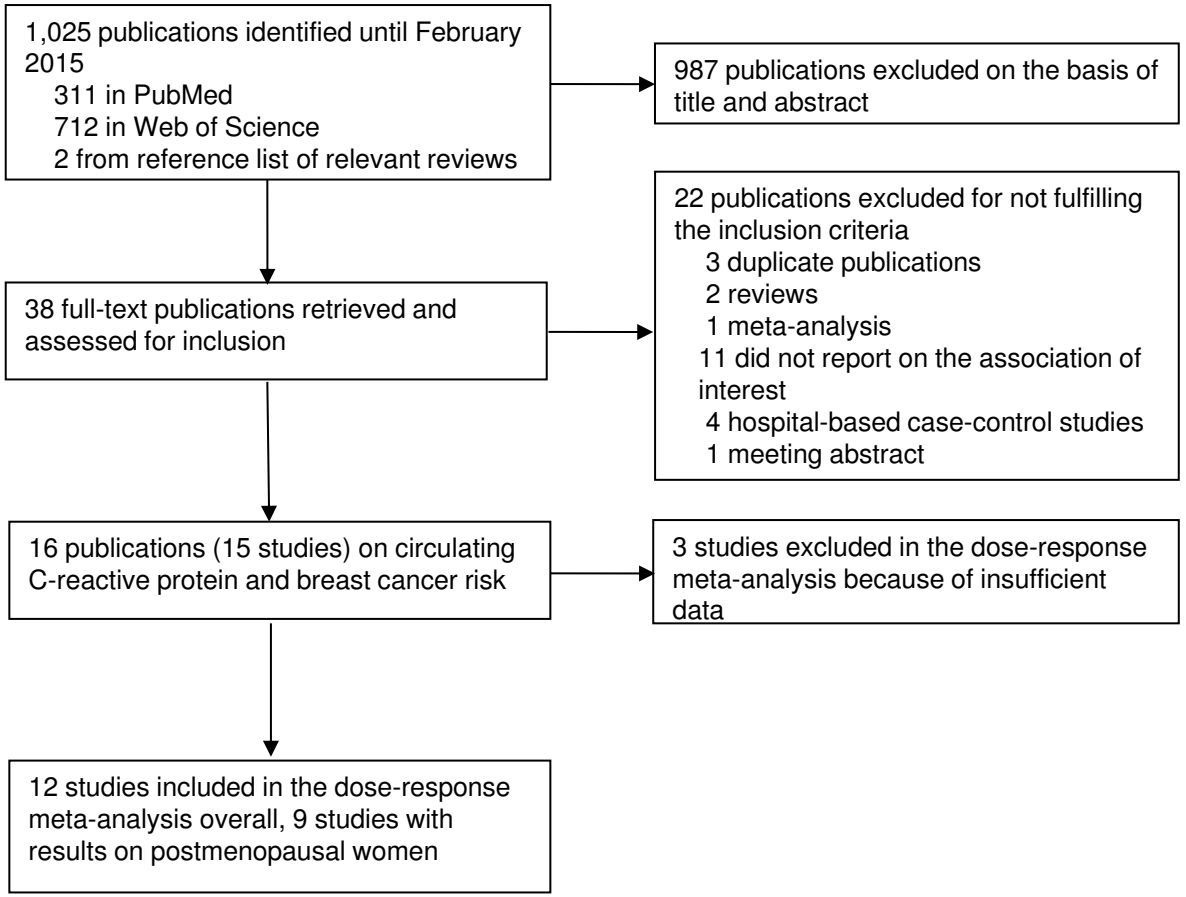

1,025 publications identified until February 2015
311 in PubMed
712 in Web of Science
2 from reference list of relevant reviews
987 publications excluded on the basis of title and abstract
38 full-text publications retrieved and assessed for inclusion
22 publications excluded for not fulfilling the inclusion criteria
3 duplicate publications
2 reviews
1 meta-analysis
11 did not report on the association of interest
4 hospital-based case-control studies
1 meeting abstract
16 publications (15 studies) on circulating C-reactive protein and breast cancer risk
3 studies excluded in the dose-response meta-analysis because of insufficient data
12 studies included in the dose-response meta-analysis overall, 9 studies with results on postmenopausal women

Figure 2.

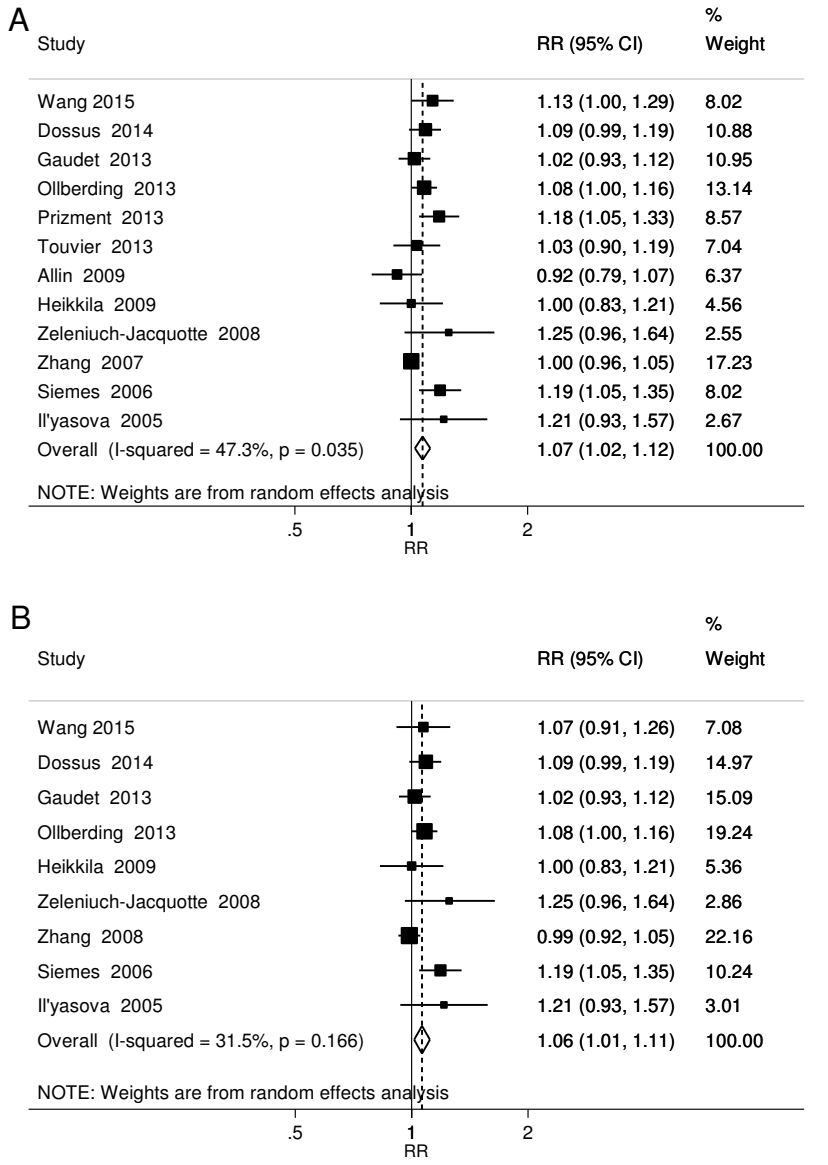
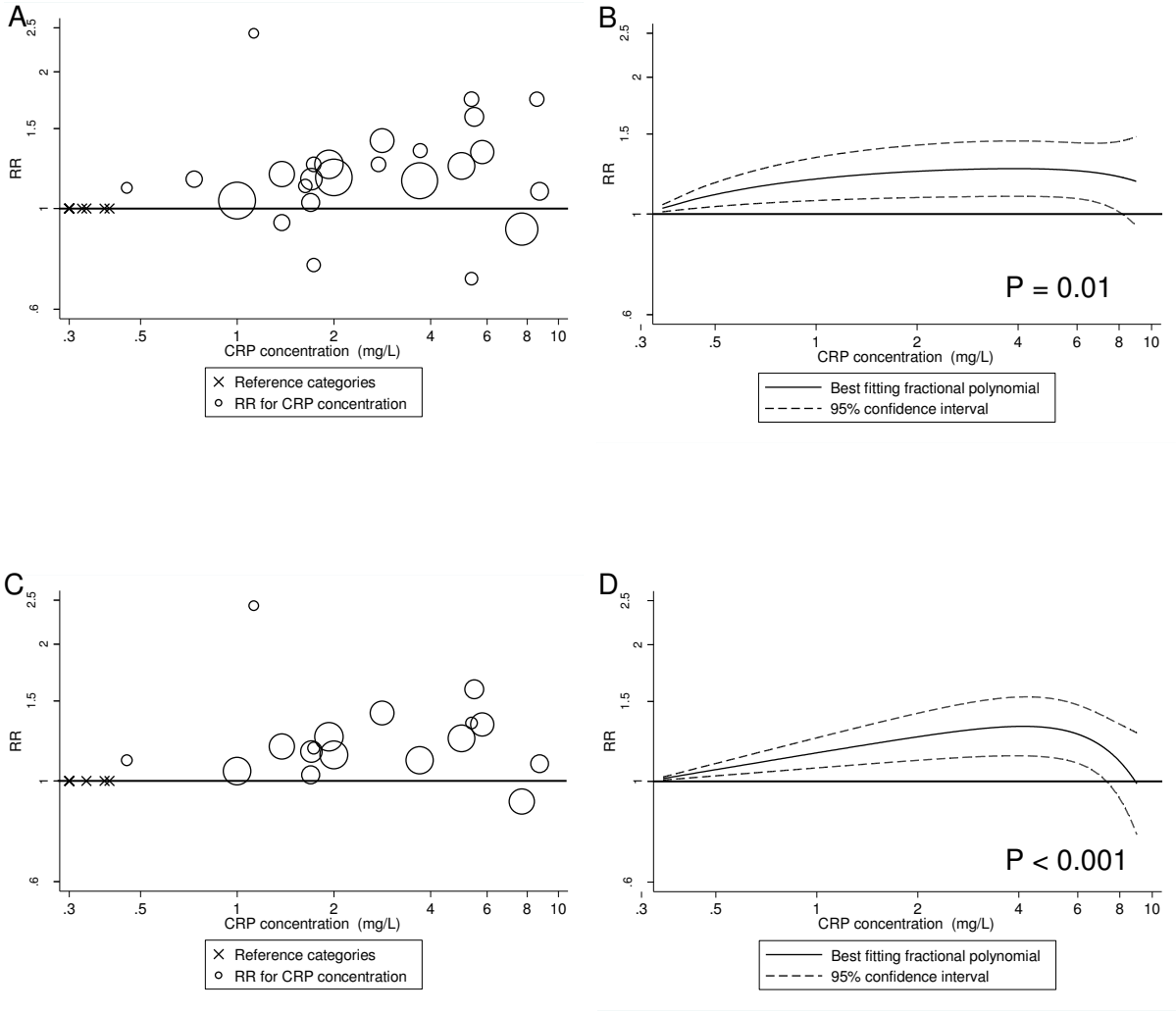

A
Study
RR (95% CI)
% Weight
Wang 2015 1.13 (1.00, 1.29) 8.02
Dossus 2014 1.09 (0.99, 1.19) 10.88
Gaudet 2013 1.02 (0.93, 1.12) 10.95
Ollberding 2013 1.08 (1.00, 1.16) 13.14
Prizment 2013 1.18 (1.05, 1.33) 8.57
Touvier 2013 1.03 (0.90, 1.19) 7.04
Allin 2009 0.92 (0.79, 1.07) 6.37
Heikkila 2009 1.00 (0.83, 1.21) 4.56
Zeleniuch-Jacquotte 2008 1.25 (0.96, 1.64) 2.55
Zhang 2007 1.00 (0.96, 1.05) 17.23
Siemes 2006 1.19 (1.05, 1.35) 8.02
Il'yasova 2005 1.21 (0.93, 1.57) 2.67
Overall (I-squared = 47.3%, p = 0.035) 1.07 (1.02, 1.12) 100.00
NOTE: Weights are from random effects analysis
.5
1
2
RR
B
Study
RR (95% CI)
% Weight
Wang 2015 1.07 (0.91, 1.26) 7.08
Dossus 2014 1.09 (0.99, 1.19) 14.97
Gaudet 2013 1.02 (0.93, 1.12) 15.09
Ollberding 2013 1.08 (1.00, 1.16) 19.24
Heikkila 2009 1.00 (0.83, 1.21) 5.36
Zeleniuch-Jacquotte 2008 1.25 (0.96, 1.64) 2.86
Zhang 2008 0.99 (0.92, 1.05) 22.16
Siemes 2006 1.19 (1.05, 1.35) 10.24
Il'yasova 2005 1.21 (0.93, 1.57) 3.01
Overall (I-squared = 31.5%, p = 0.166) 1.06 (1.01, 1.11) 100.00
NOTE: Weights are from random effects analysis
.5
1
2
RR

Figure 3.


A
B
C
D
RR
CRP concentration (mg/L)
Reference categories
RR for CRP concentration
Best fitting fractional polynomial
95% confidence interval
P = 0.01
P < 0.001