Association Between C-reactive Protein and Risk of Cancer: A Meta-analysis of Prospective Cohort Studies

Yong-Zhong Guo¹, Lei Pan², Chang-Jun Du¹, Dun-Qiang Ren³, Xiao-Mei Xie⁴*

Abstract

Background: Associations between elevated C-reactive protein (CRP) and cancer risk have been reported for many years, but the results from prospective cohort studies remains controversial. A meta-analysis of prospective cohort studies was therefore conducted to address this issue. Methods: Eligible studies were identified by searching the PubMed and EMBASE up to October 2012. Pooled hazard ratios (HR) was calculated by using random effects model. Results: Eleven prospective cohort studies involving a total of 194,796 participants and 11,459 cancer cases were included in this meta-analysis. The pooled HR per natural log unit change in CRP was 1.105 (95% confidence interval (CI): 1.033-1.178) for all-cancer, 1.308 (95% CI: 1.097-1.519) for lung cancer, 1.040 (95% CI: 0.910-1.170) for breast cancer, 1.063 (95% CI: 0.965-1.161) for prostate cancer, and 1.055 (95% CI: 0.925-1.184) for colorectal cancer. Dose-response analysis showed that the exponentiated linear trend for a change of one natural log unit in CRP was 1.012 (95% CI: 1.006-1.018) for all-cancer, No evidence of publication bias was observed. Conclusions: The results of this meta-analysis showed that the elevated levels of CRP are associated with an increased risk of all-cancer, lung cancer, and possibly breast, prostate and colorectal cancer. The result supports a role of chronic inflammation in carcinogenesis. Further research effort should be performed to identify whether CRP, as a marker of inflammation, has a direct role in carcinogenesis.

Keywords: C-reactive protein - cancer - cohort studies - meta-analysis
Materials and Methods

The eligible studies were identified by systematically searching the PubMed and EMBASE up to October 2012, limiting the search to human, adults (aged ≥18 years) and no language restrictions. The searches combined free-text and subjects terms, and the following search terms were used: “C-reactive protein” or “C reactive protein” or “CRP”, “cancer” or “neoplasm” or “carcinoma”, and “cohort”. The reference lists of relevant publications were also manually searched for additional studies.

The included studies must meet the following criteria: (1) Prospective cohort design; (2) Adult population; (3) The multivariate-adjusted relative risk (hazard ratios (HRs)) with 95% confidence intervals (CIs) for CRP as a continuous variable had to be included (or sufficient data to calculate them). If the participants in some studies were from the same population, the one with the largest number was inclusive. For the dose-response analysis, at least 3 categories of CRP levels and the number of participants and cancer cases had to be provided. Studies were excluded if there was insufficient information for extraction of data.

Two independent investigators carefully extracted information from all studies included by means of a standardized protocol if they met all of the inclusion criteria. Disagreements were resolved by three investigators. For each study, he following data were collected: first author’s name and year of publication, study location, cohort study name, participants enrolled criteria, year of recruitment, the length of follow-up, the number of participants and cancer cases, participant characteristics (gender composition, mean age, mean body mass index (BMI)), CRP measurement methods, multivariate-adjusted HRs with 95% CIs for CRP as a continuous variable or at least 3 categories of CRP levels.

The HR per natural log unit change in CRP with 95% CI was used to compute the pooled HR of elevated CRP levels and the risk of cancer. In study of Allin 2009 (Allin et al., 2009) which reported HRs for 3 categories of CRP levels, the computation of the HR per natural log change in CRP was according to the method described by Greenland and Longnecker (Greenland et al., 1992; Orsini et al., 2006). In study of Van Hemelrijck 2011 (Van et al., 2011) with the largest number was inclusive. For the trim and fill method was used to identify and correct for funnel plot asymmetry arising from publication bias (Duval et al., 2000). A two-tailed P<0.05 was considered to indicate statistical significance. All statistical analyses were conducted using software Stata 9.2 (StataCorp, College Station, TX, USA).

Results

Figure 1 shows the selection process for studies included in this meta-analysis. Three studies (Allin et al., 2009; Allin et al., 2010; Allin et al., 2012) participants from the same population, the one of Allin 2009 (Allin et al., 2009) with the largest number was inclusive. For reporting different cancer type, both studies of Zhang et al. (2007) and Zhang et al. (2005) were inclusive, although their participants were from the same population. At last, 10 articles (II’Yasova et al., 2005; Zhang et al., 2005; Siemes et al., 2006; Zhang et al., 2007; Allin et al., 2009; Heikkila et al., 2009; Pierce et al., 2009; Dos et al., 2010; Prizment et al., 2011; Van et al., 2011) including 11 cohort studies were eligible for inclusion criteria in this meta-analysis (one article including two separate cohorts (Heikilia et al., 2009)), involving a total of 194,796 participants and 11,459 cancer cases. Table 1 summarizes the baseline characteristics of 11 cohort studies included. In studies of Van et al. (2011) and Siemes et al. (2006) where HR was reported based on various length of follow-up, the HR with the longer follow-up was used to compute.
Association Between C-reactive Protein and Risk of Cancer: A Meta-analysis of Prospective Cohort Studies

Table 1. Characteristics of Studies Included in the Meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort name</th>
<th>Country</th>
<th>Year of recruitment</th>
<th>Enrollment criteria</th>
<th>Characteristics of participants</th>
<th>CRP measurement methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang 2005</td>
<td>The Women’s Health Study; 1993</td>
<td>USA</td>
<td>Medium 10.2</td>
<td>Age ≥45 y</td>
<td>Gender: women</td>
<td>Latex-enhanced</td>
</tr>
<tr>
<td>Il’Yasova 2005</td>
<td>The Health Aging and Body Composition study; 1997</td>
<td>USA</td>
<td>Mean: 5.92/2.85</td>
<td>Age 70-79 y</td>
<td>Gender: both (women, 53%)</td>
<td>ELISA</td>
</tr>
<tr>
<td>Siemers 2006</td>
<td>The Rotterdam Study; 1989</td>
<td>Netherlands</td>
<td>Mean 10.2</td>
<td>Age &gt;55 y, excluding CRP</td>
<td>Gender: both (women, 40%)</td>
<td>Rate near-infrared particle</td>
</tr>
<tr>
<td>Zhang 2007</td>
<td>The Women’s Health Study; 1993</td>
<td>USA</td>
<td>Mean 10</td>
<td>Age ≥45 y, no CVD</td>
<td>Gender: women Age: 45.4 (5.7) y</td>
<td>ELISA</td>
</tr>
<tr>
<td>Pierce 2009</td>
<td>Cardiovascular Health Study; 1989</td>
<td>USA</td>
<td>Mean 8.7</td>
<td>No prostate cancer</td>
<td>BM 26.4 (3.8)</td>
<td>ELISA</td>
</tr>
<tr>
<td>Heikkinen 2009</td>
<td>The Caerphilly Cohort study; 1979</td>
<td>UK</td>
<td>18-27</td>
<td>Age 45-59 y</td>
<td>Gender: men Age: 57.4 (5.5) y</td>
<td>Ultrasensitive nephelometry</td>
</tr>
<tr>
<td>Heikkinen 2009</td>
<td>The British Women’s Heart and Health Study; 1999</td>
<td>UK</td>
<td>Median 8.7</td>
<td>Age 60-79 y</td>
<td>Gender: women Age: 69.2 y</td>
<td>Ultrasensitive nephelometry</td>
</tr>
<tr>
<td>Allin 2009</td>
<td>The Copenhagen City Heart Study; 1991</td>
<td>Danish</td>
<td>Median 13 Max 16</td>
<td>Age ≥20 y, excluding liver cirrhosis</td>
<td>Gender: both (women, 54%)</td>
<td>Turbidity or nephelometry</td>
</tr>
<tr>
<td>Dos 2010</td>
<td>The second Northwick Park Heart Study (NPHS-II); 1989</td>
<td>UK</td>
<td>5</td>
<td>Age 50-61 y, excluding &lt;3 y of follow-up</td>
<td>Gender: men Age: 56.0 (6.0) y</td>
<td>No mention</td>
</tr>
<tr>
<td>Van Hemelrijck</td>
<td>Apolipoprotein study; 2011</td>
<td>Sweden</td>
<td>Mean: 5.92/2.85</td>
<td>Age ≥20 y</td>
<td>Gender: both (women, 58%)</td>
<td>Turbidity</td>
</tr>
<tr>
<td>Prizment 2011</td>
<td>Atherosclerosis Risk in Communities (ARIC); 1996</td>
<td>USA</td>
<td>Mean 8.9</td>
<td>Age ≥45 y, excluding CRP ≥10 mg/L</td>
<td>Gender: both (women, 57%)</td>
<td>Immuno-turbidimetry†</td>
</tr>
</tbody>
</table>

BMI, body mass index (kg/m²); CRC, colorectal cancer; CVD, cardiovascular disease; ELISA, enzyme-linked immunosorbent assay; NSAID, nonsteroidal anti-inflammatory drugs; SEP, socioeconomic position; SD, standard deviation. † High-sensitivity C-reactive protein;

Figure 2. Meta-analysis of Association Between CRP and Cancer Risk in All-cancer

The results of a pooled analysis in all 11 included cohort studies (Il’Yasova et al., 2005; Zhang et al., 2005; Siemers et al., 2006; Zhang et al., 2007; Allin et al., 2009; Heikkinen et al., 2009; Pierce et al., 2009; Dos et al., 2010; Prizment et al., 2011; Van et al., 2011) are shown in Figure 2. The overall pooled HR per natural log unit change in CRP for all-cancer was 1.105 (95% CI: 1.033-1.178), with substantial heterogeneity amongst studies (P_heterogeneity =0.000, I²=70.10%). When restricting the analysis to the multi-types of cancer (Il’Yasova et al., 2005; Siemers et al., 2006; Allin et al., 2009; Heikkinen et al., 2009; Dos et al., 2010; Van et al., 2011), the pooled HR per natural log unit change in CRP increased to 1.155 (95% CI: 1.106-1.205, P_heterogeneity =0.191, I²=31%).

Figure 3 provides the detailed results of association between CRP levels and cancer risk in different sites. Elevated CRP levels were significantly associated with an increased risk for lung cancer, and non-significantly with breast, prostate and colorectal cancer.

Sensitivity analyses (Figure 4) showed that pooled HRs per natural log unit change in CRP ranged from 1.093 (95% CI: 1.017-1.169) to 1.120 (95% CI: 1.045-1.195) after removing the studies of Van Hemelrijck 2011

Figure 3. Meta-analysis of Associations Between CRP and Cancer Risk Stratified by Cancer Sites

(Van et al., 2011) and Zhang 2005 (Zhang et al., 2005), respectively. We also conducted additional sensitivity analysis by omitting two studies (Siemers et al., 2006; Van et al., 2011) where the incident cancer cases diagnosed with early years of follow-up were excluded, and the pooled HR per natural log unit change in CRP was 1.076 (95% CI: 1.000-1.152).

Table 2 presents detailed results of subgroup analyses. The heterogeneity was abolished when grouped by gender composition and adjusted variables of BMI and smoking. A higher pooled HR per natural log unit change in CRP was found in participants from Europe and age ≥ 60 years, and marker of Hs-CRP. No potential sources of heterogeneity were found by meta-regression including the year of publication (P=0.651), the year of recruitment (P=0.765), the length of follow-up (P=0.960), the number of participants (P=0.793), the number of cancer cases (P=0.521), gender composition (P=0.737), mean age.
The dose-response analysis of the association between CRP levels and cancer risk in seven studies (Zhang et al., 2005; Siemes et al., 2006; Zhang et al., 2007; Allin et al., 2009; Pierce et al., 2009; Prizment et al., 2011; Van et al., 2011) showed that the exponentiated linear trend for a change of one natural log unit of CRP level was 1.012 (95% CI: 1.006-1.018, P=0.000).

No publication bias was found from either visualization of the funnel plot or statistics of Egger’s (P=0.534) and Begg’s (P=0.640) tests. The trim and fill method indicated that two other studies were needed to correct funnel plot asymmetry (Figure 4). After filling another two studies, no significant change was seen in the pooled estimate of ln (HR) (P=0.192).

### Discussion

This meta-analysis assessed the association between CRP levels and cancer risk in cancer-free individuals. Although there was substantial heterogeneity amongst studies, the result supported a significant positive association between the elevated levels of CRP and an increased risk of all-cancer. The overall estimate indicated an 11% increase in risk of all-cancer for a natural log unit increase in CRP levels. Sensitivity analysis further confirmed the robustness of this result. The significant exponentiated linear association was found between the elevated levels of CRP and risk of all-cancer.

Stratified by cancer sites, the results indicated a significant positive association with lung cancer, and a weak association with breast, colorectal and prostate cancer.

Numbers of researchers have investigated possible associations between chronic inflammation and cancer, whereas the precise mechanisms remain uncertain. Current knowledge suggests a reciprocal induction between chronic inflammation and cancer (Balkwill et al., 2001;...
Cancer growth could cause inflammatory response around the cancer, thereby increasing CRP levels. Alternatively, chronic inflammation could lead to the development of cancer. Unfortunately, a direct role of CRP in carcinogenesis has not been experimentally confirmed, and main evidences for the association between CRP and cancer were from human epidemiologic and genetic studies. Positive associations between CRP levels and risk of all-cancer and lung cancer have been consistently reported by several large epidemiological studies including a retrospective cohort study by Proctor et al. (2010) with 223,303 non-cancer patients and 22,715 cancer cases, a cross-sectional study by Lee et al. (2011) with 80,781 participants and two nested case-control studies (Trichopoulos et al., 2006; Chaturvedi et al., 2010). In accordance with the result of previous meta-analysis (Heikkila et al., 2009), less epidemiologic studies suggested a significant association between the elevated CRP levels and an increased risk of prostate and breast cancer (Platz et al., 2004; Trichopoulos et al., 2006), although a role for chronic inflammation in prostate (Haverkamp et al., 2008) and breast cancer (Ben-Baruch, 2003) has been identified. More controversy seemed to be from colorectal cancer (Otani et al., 2006; Gur et al., 2011; Lee et al., 2011) and previous meta-analysis gave an inconsistent result (Tsilidis et al., 2008; Heikkila et al., 2009). All above-mentioned information seemed to support the results of this meta-analysis that the association between CRP levels and cancer risk is site-specific, and significant with lung cancer, weak with breast, colorectal and prostate cancer.

When an association between the elevated CRP levels and increased cancer risk is established, it is essential to define what exactly CRP is: a participant in the pathogenesis of cancer, or simply a marker of cancer. Although observational epidemiologic study is difficult to prove causality, current findings from this meta-analysis seemed to support a role of CRP in carcinogenesis. First, the dose-response relationship between CRP levels and risk of all-cancer was found, although the strength of association was relatively weak. Second, after omitting two studies (Siemes et al., 2006; Van et al., 2011) where the incident cancer cases diagnosed with early years of follow-up was excluding, the pooled HR was reduced, which seemed to support a positive association between the elevated CRP levels and cancer risk. However, the genetic studies which could estimate a causal effect between a modifiable risk factor and an outcome of interest (Bochud et al., 2010) gave an inconsistent result for lung (Siemes et al., 2006; Allin et al., 2010; Chaturvedi et al., 2010; Heikkila et al., 2011) and colorectal cancer (Siemes et al., 2006; Allin et al., 2010), and null for prostate cancer (Siemes et al., 2006; Pierce et al., 2009; Allin et al., 2010; Heikkila et al., 2011). Based on current knowledge, a positive association between CRP and cancer might be existed, whereas the evidence for a causal relationship was insufficient. Whatever the causality between CRP and cancer, the finding from this meta-analysis has clinical importance, suggesting that the elevated CRP might possibly indicate a risk or incidence of cancer, if no other diseases associated with chronic inflammation existed.

Owing to the pathogenetic heterogeneity of cancer, the association between CRP levels and cancer risk might be influenced by multiple factors besides cancer sites, conforming with the results of subgroup analysis. A intergroup difference was significant when grouped by study location, marker, age, gender composition and the length of follow-up. Despite suffering the limitations of observational nature, several findings from subgroup-analysis deserved to be notable. Hs-CRP, as an inflammatory biomarker, is superior to common CRP in predicting risk of cancer. Consistent partially with notion of higher incidence rate of cancer in older people, a higher cancer risk was found in older patients, meaning more attention should be paid to older people with a high CRP levels. Corresponds with the results of Van et al. (2011) in which null-findings were found after excluding participants with follow-up time < 3, 5 or 7 years, a lower HR was found in follow-up time > 10 years, indicating there may be a “window period” for evolution of CRP in future incidence cancer. By reading our data, we found that differences in study location and gender composition might substantially be a difference in cancer site.

In addition, results from subgroup analyses showed that gender composition and adjustment variables of BMI and smoking might be possible sources of heterogeneity. Because gender, obesity and smoking may be influential factors for cancer risk (Bianchini et al., 2002; Lubin et al., 2007), it is plausible to think that differences in gender composition and adjusted variables of BMI and smoking might be possible sources of heterogeneity. Unexpectedly, no supportive results were found from meta-regression analyses. Considering the limitation of subgroup analyses to explain heterogeneity (Higgins et al., 2011), the above variables were hardly recognized as precise sources of heterogeneity amongst studies.

Interpreting the findings from this meta-analysis, however, several potential limitations should be noted. First, the precise source of heterogeneity was not found due to scarce data. Second, as an observational nature of meta-analysis, the potential role of systematic error, which may be as a potential explanation for the results of this meta-analysis, is inevitable. Third, cancer is a heterogeneous disease, consisting of different histological types that influence the treatment and prognosis. Limited by the finite data, the analysis for associations of CRP with cancer risk stratified by histological type and more sites were unable to determine. Finally, the increase magnitude of pooled HR was relative small despite of the large number of participants. All factors above-mentioned might lead to a false or spurious association, depress statistical power, or even reverse present results.

In conclusion, the findings of this meta-analysis supported a site-specific association between elevated CRP levels and increase cancer risk. Although evidences for causal relation were insufficient, these results seemed to support a role of chronic inflammation in carcinogenesis. But based on current knowledge, baseline CRP measurement is not recommended for prediction of cancer incidence and cancer screening. Further studies are needed to identify whether CRP, as a marker of inflammation, has a direct role in carcinogenesis.
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References


