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

Introduction

Chronic inflammation plays an important role in various aspects of cancer involving cancer initiation, promotion, progression, metastasis and clinical features (Balkwill et al., 2001; Mantovani et al., 2008; Babu et al., 2012) which has gradually attracted the attention of relevant researchers worldwide due to the rising incidence of cancer in public. Cancer-related inflammation has been recognized as the seventh hallmark of cancer (Colotta et al., 2009).

C-reactive protein (CRP), a nonspecific marker of systemic inflammation, has been widely used to detect and monitor systemic inflammatory response in clinical practice and empirical research (Pearson et al., 2003). Most studies suggested that CRP levels were higher in cancer cases than healthy subjects, and CRP levels for prediction of treatment efficacy and patients mortality with various types of cancer have been extensively reported. Whereas whether elevated CRP levels share an identical value in predicting future cancer incidence remains uncertain.

Numbers of prospective epidemiological studies have explored the elevated CRP levels in relation to an increased risk for cancer. Among them, most case–control studies have shown a higher cancer risk in people with elevated CRP levels (Gunter et al., 2006; Helzlsouer et al., 2006; Otani et al., 2006; Aleksandrova et al., 2010; Chaturvedi et al., 2010; Lee et al., 2011; Pine et al., 2011), while, the findings from prospective cohort studies have been inconsistent (Il’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).

A previous meta-analysis exploring the association between CRP levels and cancer risk has been published in 2009 (Heikkila et al., 2009). From then on, more results from large-scale prospective cohort studies have been published, but the results were inconsistent. In addition, previous meta-analysis included case–control studies which may be prone to selection and information bias, and reduced precision of effect estimates (Austin et al., 2012). To provide more precise and reliable effect estimates, a meta-analysis of prospective cohort study is conducted to renew previous conclusion and reassess the association between the elevated levels of CRP and cancer risk.

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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, participants 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) and Longnecker (Greenland et al., 1992; Orsini et al., 2009) which reported HRs for men and women separately, the combined HR was computed by fixed-effects model prior to pooling. The pooled HR was estimated using random-effects model. Sensitivity analyses were conducted by omitting one study at a time to explore the robustness of the result. A specific meta-analysis was conducted to assess association of CRP levels with cancer risk in different sites. The dose-response relationship between CRP levels and cancer risk was calculated by using the “pool-first” method where the number of participants and cancer cases and the HRs (95% CIs) for at least 3 categories were requested (Greenland et al., 1992; Orsini et al., 2006).

Subgroup and meta-regression analyses were performed to explore possible sources of heterogeneity that might explain the association between CRP levels and cancer risk. Subgroup analyses were according to study location (Europe and USA), marker (common CRP and high-sensitivity CRP (hs-CRP)), age (<60 and ≥60 years), gender composition (female, male and both), the length of follow-up (<10 and ≥10 years) and several adjustment variables including BMI, non-steroidal anti-inflammatory drugs (NSAIDs) use, hormone use, cardiovascular disease and smoking.

The Q and I² statistics were used to examine statistical heterogeneity amongst studies. For $P_{heterogeneity} <0.10$ or $I^2 >60\%$ were considered to indicate significant heterogeneity (Higgins et al., 2011). Publication bias was evaluated visually with funnel plot and statistically with the Begg’s and Egger’s tests (Higgins et al., 2011). 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 (Il’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 (Heikkila 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.

![Figure 1. Selection Process for Studies Included in the Meta-analysis](image-url)
Figure 2. Meta-analysis of 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 ID</th>
<th>Cohort name</th>
<th>Country</th>
<th>Year of recruitment</th>
<th>Follow-up (y)</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</td>
<td>USA</td>
<td>1996</td>
<td>Age ≥45 y</td>
<td>Gender: women</td>
<td>Latex-enhanced</td>
<td></td>
</tr>
<tr>
<td>Il’Yasova 2005</td>
<td>The Health Aging and Body Composition study</td>
<td>USA</td>
<td>1996</td>
<td>Age ≥70-79 y</td>
<td>Gender: both (women, 53%)</td>
<td>ELISA</td>
<td></td>
</tr>
<tr>
<td>Siemes 2006</td>
<td>The Rotterdam Study</td>
<td>Netherlands</td>
<td>1989</td>
<td>Age ≥55 y, non-CVD</td>
<td>Gender: both (women, 40%)</td>
<td>Immunoassay†</td>
<td></td>
</tr>
<tr>
<td>Zhang 2007</td>
<td>The Women’s Health Study</td>
<td>USA</td>
<td>1993</td>
<td>Age ≥45-59 y</td>
<td>Gender: men Age: 57.4 y</td>
<td>Ultrasensitive Nephelometry</td>
<td></td>
</tr>
<tr>
<td>Pierce 2009</td>
<td>Cardiovascular Health Study</td>
<td>USA</td>
<td>1989</td>
<td>Age 50–61 y</td>
<td>Gender: women Age: 69.2 y</td>
<td>Ultrasensitive Nephelometry</td>
<td></td>
</tr>
<tr>
<td>Heikkila 2009</td>
<td>The Caerphilly Cohort study</td>
<td>UK</td>
<td>1979</td>
<td>Age ≥20 y, liver cirrhosis</td>
<td>Gender: men Age: 56.0 (0.1 y)</td>
<td>No mentioned</td>
<td></td>
</tr>
<tr>
<td>Allin 2009</td>
<td>The Copenhagen City Heart Study</td>
<td>Denmark</td>
<td>1991</td>
<td>Age 60–79 y</td>
<td>Gender: women Age: 69.2 y</td>
<td>Turbidity or Nephelometry</td>
<td></td>
</tr>
<tr>
<td>Dos 2010</td>
<td>The second Northwick Park Heart Study (NPHS-II)</td>
<td>UK</td>
<td>2005</td>
<td>Age 50-61 y, pulse pressure ≤15 mmHg</td>
<td>Gender: both (men, 57%)</td>
<td>Immunobeads†</td>
<td></td>
</tr>
<tr>
<td>Van Hemelrijk 2011</td>
<td>The Rotterdam Study</td>
<td>Netherlands</td>
<td>1989</td>
<td>Age ≥45-59 y</td>
<td>Gender: both (women, 57%)</td>
<td>Immunobeads†</td>
<td></td>
</tr>
</tbody>
</table>

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

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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; Bouma et al., 2004).
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 conclusion, the findings of this meta-analysis supported a site-specific association between elevated CRP levels and cancer risk. Although evidences for causal relation were insufficient, these results seemed to support a role of chronic inflammation in carcinogenesis. 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.
References


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