RESEARCH ARTICLE

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

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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

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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) 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 I^2 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.

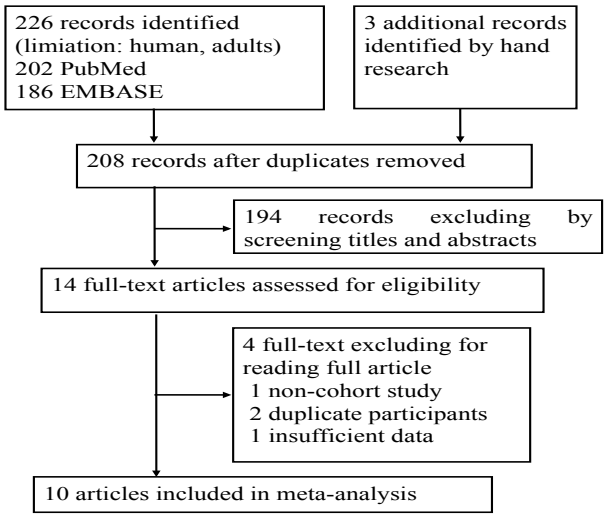

Figure 1. Selection Process for Studies Included in the Meta-analysis

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

Study	Cohort name Year of recruitment	Country Follow-up (y)	Enrollment criteria	Characteristics of participants	CRP measurement methods
Zhang 2005	The Women's Health Study; 1993	USA Median 10.2 Max 10.8	Age ≥45 y	Gender: women Age: 53 y BMI: 25.9	Latex-enhanced immunoturbidimetry
Il'Yasova 2005	The Health Aging and Body Composition study; 1997	USA Mean: 5.92/2.85 (non-cases/cases)	Age 70-79 y	Gender: both (women, 53%) Age: 73 (70-79) y BMI: 27 (24.1-30.7)	ELISA
Siemes 2006	The Rotterdam Study;1989	Netherlands Mean 10.2	Age >55 y, excluding CRP >10 mg/L	Gender; both (women, 40%) Age: 69.6 (9.2) y BMI: 26.2 (3.7)	Rate near-infrared particle immunoassay†
Zhang 2007	The Women's Health Study; 1993	USA Mean 10	Age ≥45 y, no CVD	Gender: women Age: 54.5 y BMI: 25.99	Latex-enhanced immunoturbidimetry
Pierce 2009	Cardiovascular Health Study; 1989	USA Mean 8.7	No prostate cancer	Gender: men Age: 73.3 (5.7) y BMI: 26.4 (3.8)	ELISA
Heikkila 2009	The Caerphilly Cohort study; 1979	UK 18-22	Age 45–59 y	Gender: men Age: 57.4 y BMI: 26.6	Ultrasensitive Nephelometry
Heikkila 2009	The British Women's Heart and Health Study; 1999	UK 5-7	Age 60–79 y	Gender: women Age: 69.2 y BMI: 27.5	Ultrasensitive Nephelometry
Allin 2009	The Copenhagen City Heart Study; 1991	Danish Median 13 Max 16	Age ≥20 y, excluding liver cirrhosis	Gender: both (women, 54%) Age: 57 (30-37) y	Turbidimetry or Nephelometry
Dos 2010	The second Northwick Park Heart Study (NPHS-II); 1989	UK 5	Age 50–61 y, excluding <3 y of follow-up	Gender: men Age: 56.0 (6.0) y BMI: 26.4 (3.5)	No mentioned
Van Hemelrijck 2011	Apolipoprotein (AMORIS) study; 1985	Sweden Mean: 9.74/5.9 (non-cases/cases)	Age ≥20 y	Gender: both (women, 58%) Age: 44.87(16.68) y	Turbidimetry
Prizment 2011	Atherosclerosis Risk in Communities (ARIC); 1996	USA Mean 8.9	Age 45-69 y, excluding CRP >10 mg/L	Gender: both (women, 57%) Age: 62.6 y BMI: 28.9"	Immunoturbidimetry†

BMI, body mass index (kg/m^2); 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;

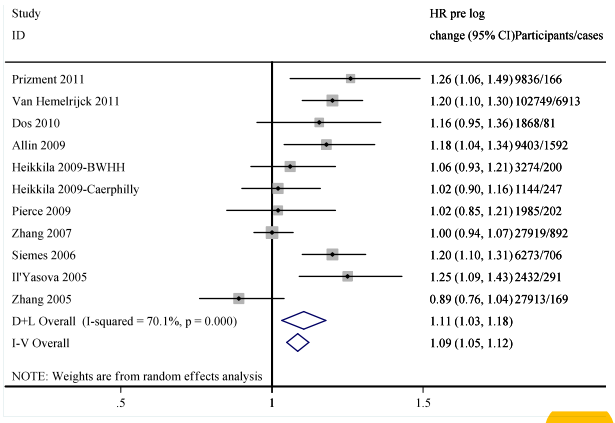

Figure 2. Meta-analysis of Association Between CRP and Cancer Risk in All-cancer

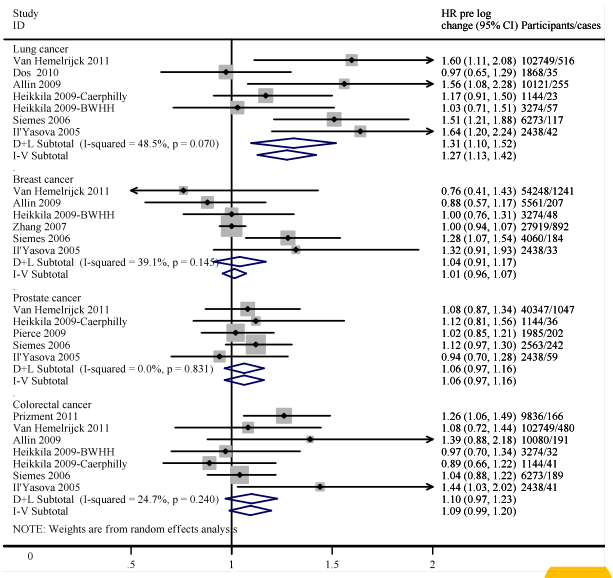

Figure 3. Meta-analysis of Associations Between CRP and Cancer Risk Stratified by Cancer Sites

The results of a pooled analysis in all 11 included cohort studies (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) 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, I^2=70.10%). When restricting the analysis to the multi-types of cancer (Il'Yasova et al., 2005; Siemes et al., 2006; Allin et al., 2009; Heikkila 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, I^2=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 (Van et al., 2011) and Zhang 2005 (Zhang et al., 2005), respectively. We also conducted additional sensitivity analysis by omitting two studies (Siemes 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

Table 2. The Results of Subgroup-analyses

Subgroup	No. of study	No. of participants/cases	Heterogeneity			Pooled HR (95% CI)	$P_{intergroup}$
			X^2	P	I^2 (%)	per natural log unit change	
Study location							
Europe	6	12,4711/9,739	7.40	0.193	32.4	1.142 (1.077-1.207)	0.001
USA	5	70,085/1,720	15.46	0.004	74.1	1.068 (0.943-1.192)	
Markers							
Hs-CRP	2	16,109/872	0.24	0.623	0.0	1.212 (1.117-1.306)	0.004
CRP	9	178,687/10,587	25.10	0.001	68.1	1.081 (1.004-1.158)	
Age of participants (years)							
<60	6	120,996/9,894	20.03	0.001	75.0	1.069 (0.971-1.167)	0.010
≥60	5	23,800/1,565	6.74	0.150	40.7	1.155 (1.065-1.245)	
Gender composition							
Female&Male	5	12,0857/9,502	0.64	0.959	0.3	1.207 (1.149-1.266)	0.000
Female	3	59,106/1,261	3.00	0.223	33.4	0.989 (0.912-1.065)	
Male	3	4,997/530	1.34	0.512	0.0	1.048 (0.955-1.142)	
The length of follow-up (years)							
<10	5	19,395/940	5.77	0.211	30.6	1.139 (1.042-1.235)	0.000
≥10	6	175,401/10,519	25.81	0.001	80.6	1.083 (0.982-1.183	
Main adjustment variables							
NSAID use							
Y	5	48,440/1,488	15.68	0.003	74.5	1.079 (0.955-1.203)	0.893
N	6	146,356/9,971	17.76	0.003	71.9	1.128 (1.028-1.228)	
BMI							
Y	8	83,342/3,549	14.55	0.420	51.9	1.055 (0.982-1.125)	0.000
N	3	111,454/7,910	0.28	0.869	0.0	1.208 (1.141-1.274)	
CVD							
Y	4	142,366/7,329	14.57	0.002	79.4	1.120 (0.948-1.292)	0.255
N	6	52,430/4,130	17.59	0.007	65.9	1.098 (1.018-1.179)	
Smoking							
Y	7	73,939/1,957	10.46	0.107	42.6	1.033 (0.963-1.102)	0.000
N	4	120,857/9,502	0.39	0.943	0.0	1.203 (1.142-1.264)	
Hormone use							
Y	4	123,288/8,100	18.10	0.000	83.3	1.067 (0.933-1.200)	0.025
N	7	71,508/3,359	10.39	0.109	42.3	1.132 (1.050-1.238)	

BMI, body mass index; CVD, cardiovascular disease; Hs-CRP, high-sensitivity C-reactive protein; N, not included; NSAID, nonsteroidal anti-inflammatory drugs; Y, included

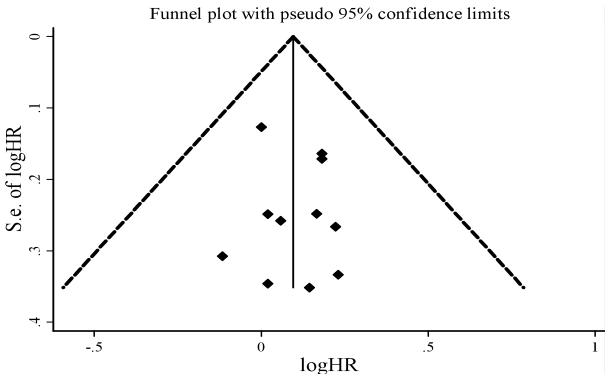

Figure 4. Funnel Plot of the Meta-analysis

(*P*=0.784) and BMI (*P*=0.835).

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;

Moore et al., 2010; Sgambato et al., 2010). 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 relative 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 a 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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