

RESEARCH ARTICLE

Genotype CC of rs1800947 in the C-Reactive Protein Gene May Increase Susceptibility to Colorectal Cancer: a Meta-Analysis

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Abstract

Background: Single nucleotide polymorphisms of C-reactive protein (CRP) have been shown to be related to circulating CRP level, risk and prognosis in cancer patients. However, accumulating evidence of rs1800947 involvement in risk of cancer is inconsistent. Thus, a meta-analysis was performed to obtain a more precise relationship. **Materials and Methods:** The pooled odds ratio (OR) and its 95% confidence interval were assessed in 10 eligible articles with 12 studies containing 5,601 cancer cases and 8,669 cancer-free controls. **Results:** No significant association was observed overall and in subgroups in comparison of genotype GC vs GG ($P_H=0.847$, OR=0.939, 95% CI=0.810-1.087), GC/CC vs GG ($P_H=0.941$, OR=1.021, 95% CI=0.901-1.157) and allele C vs G ($P_H=0.933$, OR=1.026, 95% CI=0.909-1.159). However, statistically significance was evident in comparison of genotype CC vs GG in cancer risk ($P_H=0.586$, OR=2.854, 95% CI= 1.413-5.763), especially in colorectal cancer ($P_H=0.481$, OR=4.527, 95% CI= 1.664- 12.315). **Conclusions:** Genotype CC of rs1800947 in the CRP gene is strongly associated with increased cancer risk, particularly in colorectal cancer.

Keywords: C-reactive protein gene - rs1800947 - colorectal cancer - risk factor

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Introduction

Cancer has developed to be one of the most common and severe diseases that leads to high mortality worldwide in recent decades. According to 2012 American cancer report, in 2012, approximately 1.6 million persons were diagnosed as new cancer patients and 0.58 million patients were dead from cancer (Siegel et al., 2013). However, carcinogenesis is a complex process of multiple steps. Lots of factors are involved in carcinogenesis, and inflammation is an important factor that has been implicated in tumor initiation, promotion, progression, invasion and metastasis (Disis, 2010; Song et al., 2014; Li et al., 2014), and inflammation response could promote tumor progression by damaging DNA, stimulating angiogenesis, enhancing of cell proliferation and inhibiting apoptosis (Degenhardt et al., 2006; Bunt et al., 2007).

C-reactive protein (CRP), an acute phase reaction protein, is a nonspecific serologic indicator of inflammation that is dramatically elevated and predominantly produced by hepatocytes in process of responding to inflammation. Its transcription and expression can be positively regulated by IL-6 or IL-1 in response to advanced cancer or chronic inflammatory conditions (Gabay and Kushner, 1999). Over expression of IL-6 increases concentration of CRP. High circulating CRP correlates with T cell impairment and increased levels of serum angiogenic factors and shows

resistance to chemotherapy in tumor patients (Maccio et al., 1998; Ueno et al., 2000; Shimada et al., 2003). Serum high level of CRP is inversely associated with low tumor-infiltrating CD4+T-lymphocytes within the tumor microenvironment (Canna et al., 2005). Monomeric CRP, which is formed in inflamed tissue, can enhance neutrophil anti-apoptotic activity (Khreiss et al., 2002). So, it has been commonly recognized as a risk factor or prognostic biomarkers of malignant cancer, such as colorectal cancer (Lin et al., 2013; Guo et al., 2013), lung cancer (Koma et al., 2013) and prostate cancer (Kohler et al., 2013).

The CRP gene located in 1q23.2 contains two exons and one intron. Functional genetic variation of this gene may influence the production or action of CRP, which subsequently modulate inflammatory response to influence cancer risk. Single nucleotide polymorphism (SNP) of this gene has been widely investigated the association with serum CRP levels (Kong and Lee, 2012), tumoral expression of CRP (Motoyama et al., 2013) and risk of cancer (Yang et al., 2011; Huang et al., 2013; Xu et al., 2013). Several identified SNP of CRP gene were observed to be related to cancer risk and prognosis of patients with malignancy (Yang et al., 2011; Huang et al., 2013) meanwhile other findings supported the opposite results (Xu et al., 2013). However, whether genetic variation of CRP gene is a susceptible factor for malignant cancer

remains controversial.

Thus, we fully searched possible literatures and performed a meta-analysis with pooled data of eligible studies to comprehensively assess the relationship between CRP rs1800947 and risk of cancer.

Materials and Methods

Search literature

A systematic literature search for CRP polymorphism and cancer risk was conducted in the Pubmed and Wanfang databases dating up to Dec 10th of 2013. The search terms were used as follow: CRP polymorphism and tumor, cancer or carcinoma; rs1800947 and tumor, cancer or carcinoma. In order to gain substantial literatures, a manual search was also carried out by using reference lists of original articles and reviews.

Identification of eligible article

Reverent study was selected by its title and abstract, then eligible study was further identified by full-text if they met the following criteria: 1) case-control design; 2) rs1800947 and cancer risk; 3) controls' genotype distribution should be in Hardy-Weinberg equilibrium (HWE); 4) cases were confirmed by histopathology and controls were healthy or cancer-free individuals; 5) study provided sufficient data of genotype frequency, odds ratio(OR) and 95% confidence interval (95%CI). Exclusion criteria were as follows: 1) non case-control study; 2) review, meta-analysis, comment, letter, communication, correspondence; 3) case-control study with duplicated data or low level of quality score.

Data extraction

We used a standardized data collection form to extract the following information: the first author name or aberration of study name, publication year, country, ethnicity, genotyping assay, genotype or allele data, included criteria and number of cases and controls, HWE,

odds ratio (OR) and 95% confidence interval (95%CI).

Statistic analysis

The OR and 95%CI were used as the common measure of the strength across eligible studies. Heterogeneity analysis was conducted using Q statistic test and $P_H < 0.1$ were considered as the significance. I^2 statistics was also calculated to quantitatively assess the heterogeneity analysis (Huedo-Medina et al., 2006). The random model (DerSimonian-laird method) was selected to estimate the summary risk if there was a significant heterogeneity; otherwise the fixed model (Mantel-Haenszel method) was selected (Hedges and Vevea, 1998). Sensitivity analysis was performed to test the robustness of the association by omitting an eligible study in each turn or changing the regression model. Possible publication bias was estimated using Begg's funnel plot and Egger's test ($PE < 0.1$). All the calculations were conducted using STATA software (Version 11.0, Stata Corporation, College Station, TX). All statistical tests were two-sided and $p < 0.05$ was considered statistically significant, except where otherwise specified.

Results

Characteristics of eligible study

A total of 221 literatures were searched from the databases and references. 221 unrelated articles, 10 reviews and meta-analysis, 6 communications or letter, 7 single group design articles, 2 articles of controls were not healthy individuals and no data of two articles were excluded from the study in accordance with criteria of inclusion and exclusion. As a result, only 10 original studies (Wen et al., 2008; Motoyama et al., 2009; Pierce et al., 2009; Poole et al., 2009; Tsilidis et al., 2009; Chaturvedi et al., 2010; Ognjanovic et al., 2010; Slattery et al., 2011; Yang et al., 2011; Xu et al., 2013) were identified as eligible studies in our study. The detail flow chart of retrieval and identification and baseline characteristics of eligible studies were showed in Figure 1 and Table 1. As

Table 1. Baseline Characteristics of eligible study concerning rs1800947 and Cancer Risk

Author (year)	Cancer type	Country	Ethnicity	Resource of controls	Cases	Controls	Detection	HWE
Pierce (2009a)	prostate cancer	USA	Caucasian	population	175 prostate cancer patients	1934 aged 65 and older healthy participants	Taqman	Y
Pierce (2009b)	prostate cancer	USA	African	population	40 prostate cancer patients	300 aged 65 and older healthy participants	Taqman	Y
Chaturvedi (2010)	lung cancer	USA	mixed	Population	378 lung cancer patients	447 race-age-sex-tobacco behavior matched healthy controls	Golden Gate assay	Y
Tsilidis (2009)	colorectal cancer	USA	Caucasian	population	208 colorectal cancer patients	381 age-sex matched cancer-free controls	Taqman	Y
Poole (2009)	colorectal adenoma	USA	Caucasian	Population	491 colorectal adenoma patients	583 colorectal polyp-free controls	5' nuclease genotyping assays	Y
Motoyama (2009)	esophageal cancer	Japanese	Asian	hospital	110 esophageal cancer patients	139 ailments but cancer-free controls	PCR-RFLP	Y
Ognjanovic (2009)	colorectal adenoma	USA	Mixed	Population	271 colorectal adenoma patients	539 randomly selected and matched-age and sex individuals	Taqman	Y
Slattery (2011a)	colon cancer	USA	Mixed	Population	1574 colon cancer patients	1970 sex-race matched cancer-free controls	Golden Gate assay	Y
Slattery (2011b)	rectal cancer	USA	Mixed	Population	791 rectal cancer patients	999 sex-race matched cancer-free controls	Golden Gate assay	Y
Weng (2008)	Endometrial Cancer	Chinese	Asian	Population	1046 endometrial Cancer patients	1035 randomly selected age-matched healthy individuals	Taqman	Y
Xu (2012)	lung cancer	Chinese	Asian	Hospital	96 lung cancer patients	124 sex-age-tobacco use matched healthy individuals	Golden Gate assay	Y
Yang (2011)	colorectal cancer	Chinese	Asian	Population	421 colorectal cancer patients	218 healthy individuals	Taqman	Y

shown in Table 1, four, two and two studies were related to colorectal cancer, prostate cancer and lung cancer, respectively. Among them, two studies were conducted in Caucasian population, one in African population, four in mixed population, and four in Asian population. In addition, there were ten and two studies, for which the controls were from population and hospital, respectively.

Meta-analysis

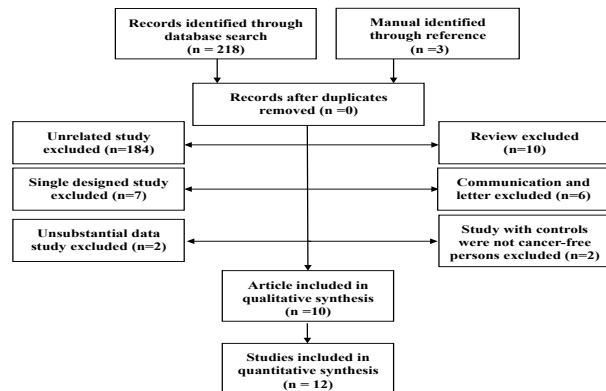


Figure 1. Flow Chart of Eligible Study of Retrieval and Identification

We identified 12 studies of CRP rs1800947 and cancer risk, involving 8669 controls and 5601 incident cases. Overall, no significant association was observed in comparison of genotype GC vs GG ($P_H=0.847$, OR=0.939, 95%CI=0.810-1.087), GC/CC vs.GG ($P_H=0.941$, OR=1.021, 95%CI=0.901-1.157), allele C vs G ($P_H=0.933$, OR=1.026, 95%CI=0.909-1.159). However, statistical significance was examined in comparison of genotype CC vs GG ($P_H=0.586$, OR=2.854, 95%CI=1.413-5.763). When stratification based on cancer type, there was no statistical association in contrast of genotype GC vs GG, GC/CC vs GG, allele C vs G in each subgroup. However, significant relationship was found in comparison of CC vs. GG in colorectal cancer ($P_H=0.481$, OR=4.527, 95%CI=1.664-12.315). The detail results of the heterogeneity test and meta-analysis were listed in Table 2 and Figure 2.

Sensitivity analysis

Sensitivity analysis was used to detect the stability of overall effect by changing regression model and omitting each eligible study subsequently in our study. The results in Table 2 and Figure 3 indicate that the overall effect was

Table 2. Results of Meta-analysis of rs1800947 and Cancer Risk

Comparison	Subgroup	<i>p</i> value*			OR and 95%CI	
		P_H	P_Z	P_E	Random model	Fixed model
GC vs.GG	overall	0.847	0.397	0.979	0.939 (0.811-1.087)	0.939 (0.810-1.087)
	Colorectal cancer	0.344	0.304	-	0.911 (0.764-1.087)	0.916 (0.774-1.083)
	Lung cancer	0.886	0.920	-	1.021 (0.683-1.526)	1.021 (0.683-1.526)
	Prostate cancer	0.679	0.965	-	1.013 (0.643-1.596)	1.010 (0.641-1.592)
CC vs.GG	overall	0.586	0.003	0.867	2.351 (1.112-4.972)	2.854 (1.413-5.763)
	Colorectal cancer	0.481	0.003	-	3.774 (1.350-10.554)	4.527 (1.664-12.315)
	Lung cancer	0.571	0.735	-	1.240 (0.346-4.438)	1.241 (0.355-4.341)
	Prostate cancer	-	0.573	-	1.842 (0.220-15.400)	1.842 (0.220-15.400)
GC/CC vs.GG	overall	0.941	0.746	0.740	1.022 (0.901-1.158)	1.021 (0.901-1.157)
	Colorectal cancer	0.567	0.821	-	1.017 (0.884-1.170)	1.016 (0.884-1.169)
	Lung cancer	0.791	0.850	-	1.038 (0.706-1.527)	1.038 (0.706-1.527)
	Prostate cancer	0.698	0.899	-	1.032 (0.660-1.613)	1.029 (0.659-1.609)
C vs. G	overall	0.933	0.676	0.632	1.026 (0.909-1.159)	1.026 (0.909-1.159)
	Colorectal cancer	0.355	0.727	-	1.028 (0.875-1.207)	1.028 (0.879-1.202)
	Lung cancer	0.704	0.784	-	1.052 (0.734-1.508)	1.052 (0.734-1.507)
	Prostate cancer	0.719	0.830	-	1.050 (0.687-1.605)	1.047 (0.685-1.601)

* P_H , *p*-value of heterogeneity; P_Z , *p*-value of Z test; P_E , *p*-value of Egg's test

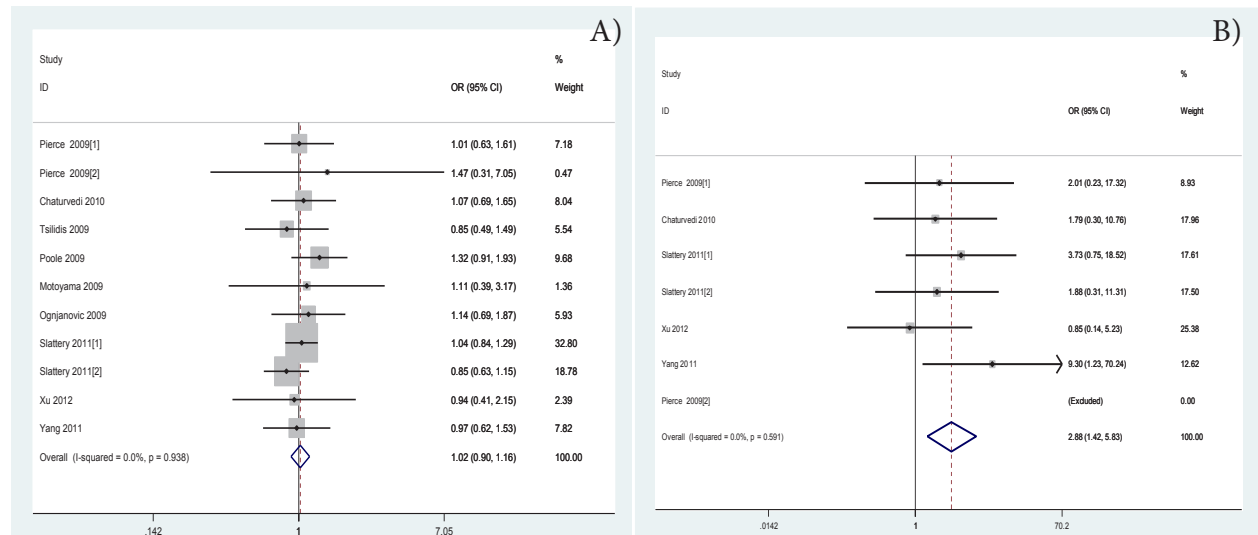


Figure 2. The Meta-Analysis Result of rs1800947 and Risk of Cancer. A: GC/CC vs GG; B: CC vs GG

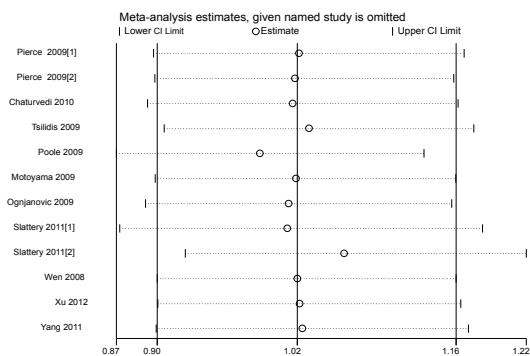


Figure 3. The Sensitivity Analysis of Incomparision of GC/CC vs GG

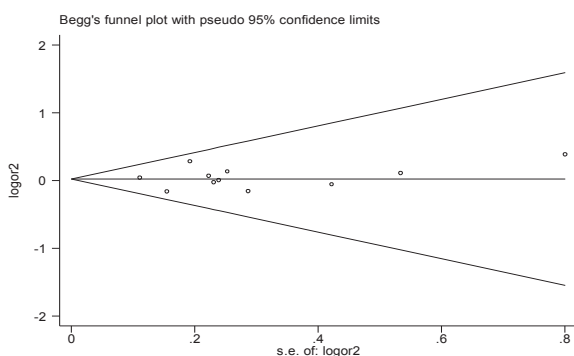


Figure 4. The Begg's Funnel Plot in Comparison of GC/CC vs GG

stable in condition of either changing regression model or omitting eligible study subsequently each time.

Publication bias

Begg's test and Egger's test were selected to estimate possible publication bias in our study. The results of Begg's test and Egger's test were summarized in Table 2 and Figure 4. As shown, no obvious asymmetry of funnel plot and significance of Egger's test were found in each group or subgroup.

Discussion

The present meta-analysis of retrospective and prospective studies supports a significant inverse association between genotype CC of rs1800947 and risk of cancer, especially colorectal cancer. These findings show that genotype CC of rs1800947 could increase susceptibility to cancer risk and might be a genetic susceptible factor for cancer, especially colorectal cancer.

Few studies have investigated the relationship between rs1800947 of CRP and cancer risk. A recent study reported by Xu et al. (2013) showed that rs1800947 was related to circulating CRP levels and higher CRP concentration tended to be in positive association with lung cancer risk, however, genotype of rs1800947 had no association with lung cancer risk. Study conducted by yang et al (2011) indicated that genotype CC of rs1800947 was strongly related to colorectal cancer risk. Slattery et al (2011) reported that allele C and genotype CC were interacted with BMI. When BMI<25, allele C and genotype CC of rs1800947 were significantly associated with colon and rectal cancer risk.

In this study, genotype CC of rs1800947 was found to associate with cancer risk, especially colorectal cancer. When allele G changed into C in rs1800947, circulating CRP of genotype GG carrier individual is higher than genotype CC carrier in healthy individuals (Suk et al., 2005; Lange et al., 2006; Kivimäki et al., 2007; Chaturvedi et al., 2010) and thoracic esophageal cancer patients after exophagotomy (Motoyama et al., 2009). It suggested that cancer patients with genotype CC carrier shared a lower serum level of CRP than GG carrier. Decreased circulating CRP level has a less efficient response to external noxious agents and impaired defense mechanism. In this way, decreased CRP might contribute to inflammation prolongation and increase of tissue and cell damage (Siemes et al., 2006). However, rs1800947 may not be involved in carcinogenesis. It is just genetic markers in linkage disequilibrium with other polymorphisms that are responsible for the increased cancer risk.

So far to our knowledge, this study is the first meta-analysis to explore the possible association between rs1800947 and cancer risk with the largest sample size and provide more reliable estimation when compared with single study. However some limitations should be addressed as follows: 1) due to literature search only in few databases in Chinese and English, some relevant articles in other languages may not be included, which might lead to possible selection bias; 2) although the largest sample size so far, it might be not large enough to obtain more precise result in present study, especially in subgroups; 3) Our results are pooled with crude genotype data, not adjusted with possible influent factors, such as gender, age, family history, BMI, smoking status and use of NSAIDs; 4) number of cases in eligible study were less than 1000, which may attenuate the statistical power.

In conclusion, genotype GC, GC/CC and allele C of rs1800947 of CRP gene are not associated with cancer risk in total or subgroup. Whereas genotype CC is strongly associated with cancer risk, particularly with colorectal cancer, indicating that genotype CC might be a susceptible genetic factor for risk of cancer. However, to better understand the role of CRP genetic factor in inflammation and carcinogenesis, more well designed study with large sample size and gene-environment interaction analysis are warranted to further validate the findings.

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