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Review Article

Relationship between *cyclooxygenase-2* rs20417 G>C polymorphism and the risk of colorectal carcinoma: a meta-analysis involving 26,390 subjects

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Abstract: To assess the possible role of the *Cyclooxygenase-2* (*COX-2*) rs20417 G>C polymorphism in the etiology of colorectal carcinoma (CRC), we conducted an updated meta-analysis, which included nineteen eligible studies with 8,097 CRC cases and 18,293 controls published up to May 25, 2016. The crude odds ratios (ORs) with their 95% confidence intervals (95% CIs) were harnessed to determine the correlation between *COX-2* rs20417 G>C polymorphism and CRC risk. Overall, *COX-2* rs20417 G>C polymorphism was not associated with CRC susceptibility for all genetic models. In a subgroup analysis by ethnicity, the results showed that individuals with *COX-2* rs20417 C allele had a significantly higher CRC susceptibility among Asians in two genetic models (C vs. G: OR = 1.46; CI = 1.14 - 1.88; *P* = 0.003 and CC+GC vs. GG: OR = 1.43; CI = 1.16 - 1.78; *P* = 0.001). When restricting the analysis to the source of controls and region of CRC, no significant association was found in any subgroup. Begg's funnel plot and Egger's regression test were applied to assess publication bias. No significant publication bias was found for the association between *COX-2* rs20417 G>C polymorphism and CRC susceptibility. Influence of each included study on the findings was determined by omitting each study in turn and re-calculating the ORs. And the results were not materially altered. In summary, our findings suggest that *COX-2* rs20417 G>C polymorphism may be a risk factor for the development of CRC among Asians.

Keywords: Polymorphism, COX-2, colorectal carcinoma, susceptibility, meta-analysis

Introduction

The incidence of colorectal carcinoma (CRC) is the third common malignancy in males and the second in females with approximately 1,360,600 CRC patients and 693,900 CRC-related mortality occurring worldwide in 2012 [1]. The aetiology of CRC is very complex and has not been well identified. Increasingly 'westernized lifestyle' including being physically inactive, a decreased intake of fiber, overweight, heavy drinking and smoking, has been considered as vital susceptibility factors for the development of CRC [2]. Meanwhile, altered genetic, environmental factors and inflammatory bowel diseases may also be involved in the cause of CRC. Recently, studies have focused on the possible role of the inflammatory factors (e.g. COX-1, COX-2, TNF-α, IL-1β, IL-6 and IL-8) in the susceptibility of CRC, which has attracted attention in the etiology of CRC. Investigation of these inflammation-related genes variants correlated with CRC risk may enrich our discernment in understanding the pathology of CRC.

It is reported that there are two isozymes of COX: COX-1 and COX-2. COX-1 is continuously expressed and maintains normal physiological function. While COX-2 is an inducible form, which is induced in the production of prosta-

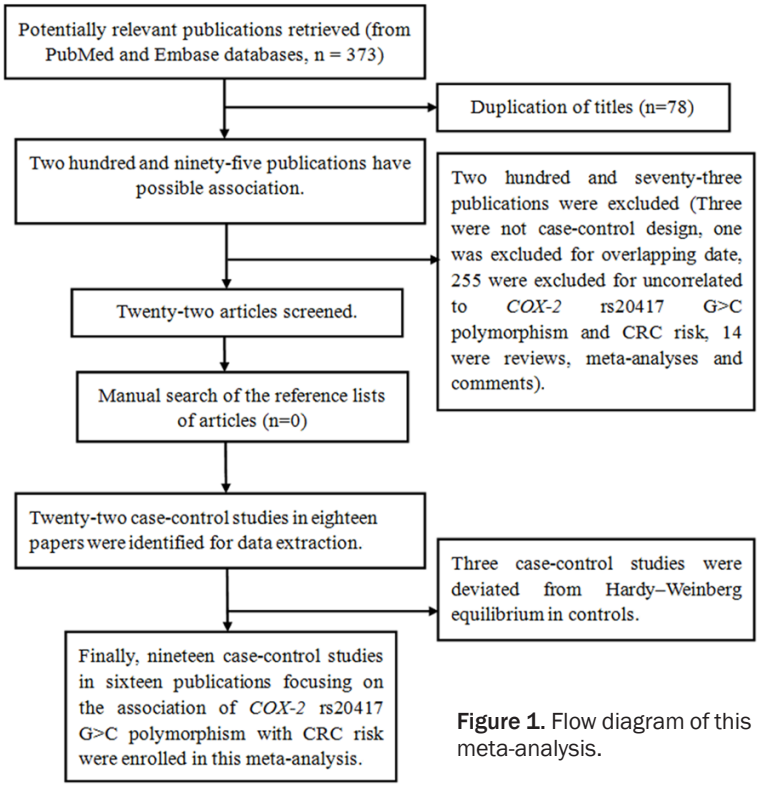

Figure 1. Flow diagram of this meta-analysis.

glandins throughout the inflammatory response and mitogenicstimuli [3]. The overexpression of COX-2 may attenuate apoptosis, facilitate proliferation, accelerate the invasion of malignancy, and lead to angiogenesis [4, 5]. Regular use of aspirin could decrease the production of COX-2 and then appear to reduce the susceptibility of CRC in COX-2 overexpression cases [6]. Thus, COX-2 may play an important role in the development of CRC.

COX-2 is polymorphic, and more than 1,400 polymorphisms have been well established (http://www.ncbi.nlm.nih.gov/snp/?term=COX-2), such as rs20417 (-765G>C), rs689466 (-1195G>A), rs5275 (-8473T>C), rs2745557 (-202C>T), and rs689466 (-1290A>G) *et al.* Among them, the *COX-2* rs20417 G>C polymorphism was the most extensively studied for their implication in CRC. *COX-2* rs20417 G>C, a common SNP in the upstream region of the *COX-2* gene, alters a transcription factor-binding site and is considered to be correlated with the susceptibility of colorectal adenoma and CRC. Recently, a number of studies considering *COX-2* rs20417 G>C variants with CRC susceptibility were conducted; however, the findings of these studies were conflicting rather than conclusive. With respect to *COX-2* rs20417 G>C polymorphism, two meta-analysis conducted by Peng *et al.* [7] and Wang *et al.* [8] found that *COX-2* rs20417 G>C polymorphism conferred an increased risk to CRC in dominant genetic model among Asians; however, more epidemiological studies with larger sample sizes were carried out. Therefore, an updated meta-analysis on all eligible studies was needed to measure CRC risk associated with *COX-2* rs20417 G>C polymorphism.

Materials and methods

Search strategy

Two authors independently searched PubMed and EMBASE databases (updated to May 25, 2016) using the searching words related to *COX-2* rs20417 G>C polymorphism and CRC: (cyclooxygenase-2 or COX-2) and (polymorphism or variant or SNP) and (cancer or carcinoma or tumor or malignance or Neoplasm) and (colorectal or colon or rectal). There was no limit for language. References from eligible articles or reviews were also manually-searched to identify relevant articles. If the publications were duplicated, the most recent study was given precedence.

Inclusion and exclusion criteria

The major inclusion criteria were used in the present meta-analysis as follows: (1) case-control or cohort study design; (2) CRC was confirmed by histopathology; (3) study evaluating the association between *COX-2* rs20417 G>C polymorphism and CRC risk; (4) considering human beings and (5) presenting sufficient data to calculate Hardy-Winberg equilibrium (HWE), the odds ratios (ORs) and 95% confidence intervals (95% CIs). Accordingly, duplicated study, letter, reviews, meta-analysis and comments were excluded.

Data extraction

For each study, the following original data were checked and collected by two investigators (Y.

Table 1. Characteristics of the candidate studies in the meta-analysis

Study	Year	Country	Ethnicity	Source of control	No. of cases/ controls	Type of colorectal cancer	Genotyping method
Basavaraju *et al.* [24]	2015	United kingdom	Mixed	Population-based	388/496	Mixed region	TaqMan
Pimenta *et al.* [25]	2014	Brazil	Mixed	Hospital-based	185/146	Mixed region	PCR-RFLP
Andersen *et al.* [23]	2013	Denmark	Caucasians	Population-based	970/1789	Mixed region	Taqman
Makar *et al.* [13]	2013	USA	Mixed	Population-based	1470/1837	Colon cancer	Taqman
Makar *et al.* [13]	2013	USA	Mixed	Population-based	959/1535	Colon cancer	Taqman
Makar *et al.* [13]	2013	USA	Mixed	Population-based	583/775	Rectal cancer	Taqman
Daraei *et al.* [22]	2012	Iran	Caucasians	Population-based	110/120	Mixed region	PCR-RFLP
Wang *et al.* [26]	2012	Multiple center	Mixed	Family-based	305/359	Mixed region	PCR-RFLP
Pereira *et al.* [21]	2010	Portugal	Caucasians	Hospital-based	117/256	Mixed region	PCR-RFLP
Hoff *et al.* [20]	2009	Netherlands	Caucasians	Hospital-based	326/369	Mixed region	PCR-RFLP
Iglesias *et al.* [19]	2009	Spain	Caucasians	Hospital-based	284/123	Mixed region	PCR-RFLP
Thompson *et al.* [27]	2009	USA	Mixed	Population-based	421/479	Colon cancer	Taqman
Siemes *et al.* [18]	2008	Netherlands	Caucasians	Population-based	164/5535	Mixed region	Taqman
Xing *et al.* [14]	2008	China	Asians	Hospital-based	137/199	Mixed region	PCR-RFLP
Tan *et al.* [3]	2007	China	Asians	Population-based	403/1300	Colon cancer	PCR-RFLP
Tan *et al.* [3]	2007	China	Asians	Population-based	597/1300	Rectal cancer	PCR-RFLP
Cox *et al.* [17]	2004	Spain	Caucasians	Hospital-based	220/257	Mixed region	Taqman
Koh *et al.* [15]	2004	Singapore	Asians	Population-based	310/1177	Mixed region	Taqman
Hamajima *et al.* [16]	2001	Japan	Asians	Hospital-based	148/241	Mixed region	PCR-CTPP

PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism.

Chen and J. Lin): first author's name, year of publication, country where the study was performed, ethnicity, source of control, region of CRC, genotyping methods, number of cases/controls, and genotype frequency in cases/controls. If the data collection generated different results, another investigator (W. Tang) was consulted to resolve the dispute. The data would be checked again and every item reached consensus through a detailed discussion between the three reviews.

Statistical analysis

Meta-analysis was conducted using the STATA software (version 12.0; Stata Corporation, College Station, Texas USA). The risk of CRC associated with the *COX-2* rs20417 G>C polymorphism was assessed for each included study by the crude ORs and their 95% CIs. Four different ORs and 95% CIs were calculated in the following genetic models: the dominant model (CC+GC vs. GG), the recessive model (CC vs. GG+GC), allele comparison (C vs. G) and homozygote comparison (CC vs. GG). I^2 test and Chi-square based Q test was performed to assess the heterogeneity. $I^2 > 50\%$ or $P < 0.10$ indicated statistically significance, the DerSimonian-Laird method (random-effects model) was used to calculate the pooled ORs and their 95% CI [9, 10]. The Mantel-Haenszel method (fixed-effects model) was applied when there was no statistically significance for heterogeneity [11]. Before the assessment of *COX-2* rs20417 G>C polymorphism with CRC, we measured whether genotype distribution of controls was in HWE using an online software (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). Stratification analyses were conducted on ethnicity, region of CRC and the source of control. To evaluate the stability of the results, one-way sensitivity analysis was performed. Finally, potential publication bias was measured using Begg's funnel plot and Egger's regression test [12]. For publication bias, a $P < 0.10$ (two-sides) was regarded as statistically significant.

Results

Characteristics

A total of 373 relevant publications were retrieved through the initial searching. Two publications reported several independent groups [3, 13]. In this study, we treated them separately. Finally, 19 independent studies were enrolled to determine the relationship between *COX-2* rs20417 G>C polymorphism and CRC risk, and

Table 2. Distribution of *COX-2* rs20417 G>C polymorphism genotypes and alleles

Study	Case			Control			Case		Control		HWE
	GG	GC	CC	GG	GC	CC	C	G	C	G	
Basavaraju *et al.* [24]	270	105	12	363	122	9	129	645	140	848	Yes
Pimenta *et al.* [25]	49	111	25	56	77	13	161	209	103	189	Yes
Andersen *et al.* [23]	701	213	22	1256	435	43	257	1615	521	2947	Yes
Makar *et al.* [13]	979	404	37	1232	495	44	478	2362	583	2959	Yes
Makar *et al.* [13]	648	258	23	1059	393	40	304	1554	473	2511	Yes
Makar *et al.* [13]	433	134	16	553	211	11	166	1000	233	1317	Yes
Daraei *et al.* [22]	38	67	5	53	58	9	77	143	76	164	Yes
Wang *et al.* [26]	207	87	11	238	111	10	109	501	131	587	Yes
Pereira *et al.* [21]	77	38	2	166	83	7	42	192	97	415	Yes
Hoff *et al.* [20]	241	75	10	249	112	8	95	557	128	610	Yes
Iglesias *et al.* [19]	172	99	13	76	43	4	125	443	51	195	Yes
Thompson *et al.* [27]	291	119	11	343	121	15	141	701	151	807	Yes
Siemes *et al.* [18]	123	36	5	4083	1324	128	46	282	1580	9490	Yes
Xing *et al.* [14]	119	17	1	169	29	1	19	255	31	367	Yes
Tan *et al.* [3]	369	34	0	1237	63	0	34	772	63	2537	Yes
Tan *et al.* [3]	550	47	0	1237	63	0	47	1147	63	2537	Yes
Cox *et al.* [17]	150	59	11	170	77	10	81	359	97	417	Yes
Koh *et al.* [15]	273	37*	N/A	1067	110*	N/A	N/A	N/A	N/A	N/A	Yes
Hamajima *et al.* [16]	140	8	0	230	11	0	8	288	11	471	Yes

HWE: Hardy-Weinberg equilibrium; N/A: not available; *indicate CC+GC genotype.

a total number of 8,097 CRC cases and 18,293 controls were included. **Figure 1** showed the detailed screening process. There were five studies conducted in Asians [3, 14-16], and seven studies conducted in Caucasians [17-23], and seven studies conducted in mixed population [13, 24-27]. Of them, four investigated colon cancer [3, 13, 27] and two investigated rectal cancer [3, 13] and 13 investigated mixed region colorectal cancer [14-26]. Characteristics of the included studies [3, 13-27] and the genotype distribution of *COX-2* rs20417 G>C polymorphism are shown in **Tables 1** and **2**, respectively.

Quantitative synthesis

The relationship between *COX-2* rs20417 G>C polymorphism and CRC susceptibility is summarized in **Table 3**. Overall, *COX-2* rs20417 G>C polymorphism was not associated with CRC susceptibility for all genetic models (**Table 3**). In a subgroup analysis by ethnicity, the results showed that individuals with *COX-2* rs20417 C allele had a significantly higher CRC susceptibility among Asians in two genetic models (C vs. G: OR = 1.46; CI = 1.14 - 1.88; *P* = 0.003 and CC+GC vs. GG: OR = 1.43; CI = 1.16 - 1.78; *P* = 0.001; **Table 3** and **Figure 2**). When restricting the analysis to the source of controls and region of CRC, no significant association was found in any subgroup (**Table 3**).

Tests for publication bias, sensitivity analyses, and heterogeneity

Begg's funnel plot and Egger's regression test were applied to assess publication bias [12]. No significant publication bias was found for the association between *COX-2* rs20417 G>C polymorphism and CRC risk (C vs. G: Begg's test *P* = 0.256, Egger's test *P* = 0.160; CC vs. GG: Begg's test *P* = 1.000, Egger's test *P* = 0.430; CC+GC vs. GG: Begg's test *P* = 0.142, Egger's test *P* = 0.135; CC vs. GC+GG: Begg's test *P* = 1.000, Egger's test *P* = 0.531; **Figure 3**).

Influence of each included study on the findings was determined by omitting each study in turn and re-calculating the ORs. And the results of the pooled ORs were not materially altered (**Figure 4**, data not shown).

Table 3 indicated that significant heterogeneity existed in the dominant model. Results of sub-

Table 3. Meta-analysis of the *COX-2* rs20417 G>C polymorphism and colorectal carcinoma risk

	No. of study	C vs. G			CC vs. GG			CC+GC vs. GG			CC vs. GC+GG		
		OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)
Total	19	1.05 (0.97-1.14)	0.227	0.097	1.16 (0.95-1.41)	0.142	0.864	1.07 (0.96-1.18)	0.218	0.018	1.14 (0.94-1.38)	0.197	0.885
Ethnicity													
Caucasians	7	0.94 (0.84-1.04)	0.224	0.805	1.05 (0.75-1.45)	0.787	0.940	0.91 (0.81-1.03)	0.129	0.461	1.05 (0.76-1.46)	0.754	0.836
Asians	5	1.46 (1.14-1.88)	0.003	0.245	1.42 (0.09-22.93)	0.805	-	1.43 (1.16-1.78)	0.001	0.321	1.46 (0.09-23.48)	0.791	-
Mixed population	7	1.05 (0.98-1.14)	0.188	0.420	1.22 (0.92-1.56)	0.107	0.404	1.05 (0.96-1.14)	0.304	0.203	1.18 (0.93-1.51)	0.176	0.541
Region													
Colon cancer	4	1.06 (0.97-1.16)	0.202	0.115	0.98 (0.72-1.34)	0.913	0.889	1.08 (0.98-1.20)	0.128	0.114	0.97 (0.71-1.32)	0.828	0.856
Rectal cancer	2	1.22 (0.70-2.11)	0.488	0.012	1.86 (0.85-4.04)	0.119	-	1.18 (0.62-2.26)	0.616	0.005	1.96 (0.90-4.26)	0.089	-
Mixed region	13	1.00 (0.92-1.09)	0.986	0.399	1.24 (0.95-1.61)	0.121	0.854	0.99 (0.90-1.09)	0.842	0.146	1.20 (0.92-1.56)	0.178	0.913
Source of control													
Population-based	11	1.08 (0.97-1.19)	0.163	0.042	1.08 (0.86-1.35)	0.526	0.712	1.11 (0.98-1.25)	0.100	0.014	1.06 (0.85-1.33)	0.600	0.572
Hospital-based	7	1.01 (0.88-1.17)	0.884	0.307	1.45 (0.95-2.22)	0.087	0.793	0.97 (0.82-1.15)	0.702	0.159	1.37 (0.90-2.06)	0.139	0.947
Family-based	1	0.97 (0.74-1.29)	0.859	-	1.26 (0.53-3.04)	0.599	-	0.93 (0.67-1.29)	0.667	-	1.31 (0.55-3.12)	0.548	-

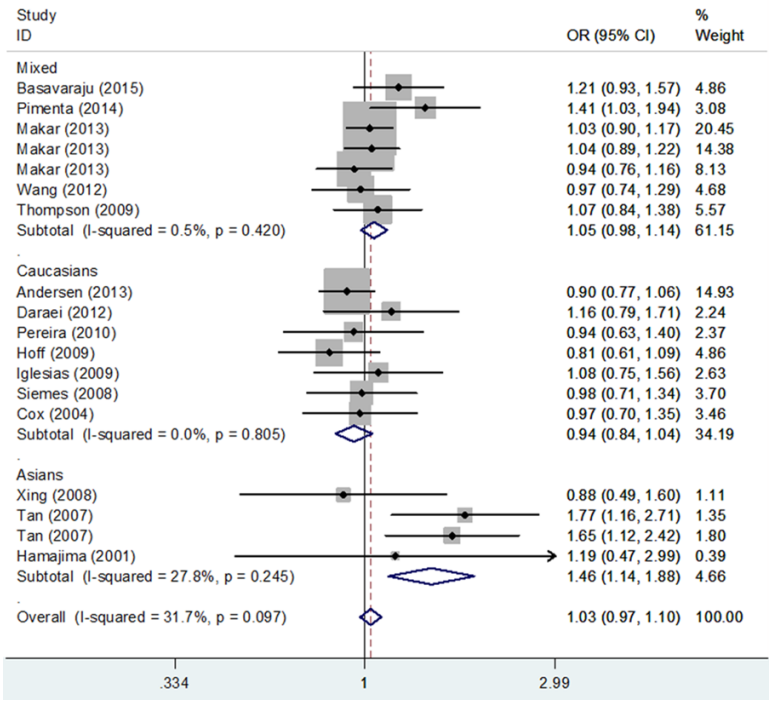

Figure 2. Meta-analysis for the association between *COX-2* rs20417 G>C polymorphism and colorectal carcinoma risk in the different ethnicity (fixed-effects model,C vs. G genetic comparison).

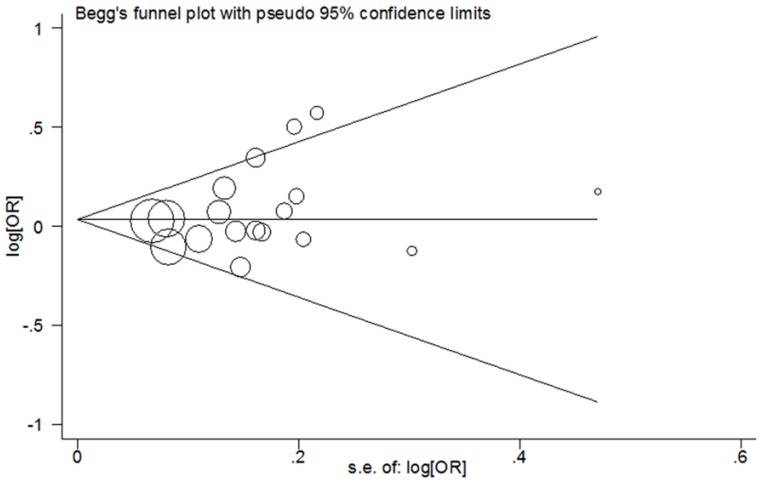

Figure 3. Begg's funnel plot of meta–analysis of the association between the *COX-2* rs20417 G>C polymorphism and the risk of colorectal carcinoma (C vs. G genetic model).

group analyses detected that population-based study and rectal cancer subgroups may lead to the major source of heterogeneity.

Discussion

Recently, a number of epidemiologic studies have focused on the role of polymorphism in disease susceptibility to human [28-32]. Some functional genovariations, which impact on the expression of these gene, could alter the susceptibility to multiple cancers [33-36]. Of late, many studies explored the correlation between *COX-2* polymorphism and multiple malignancies including CRC. COX-2 is located on the chromosome 1q25.2-eq25.3. It has 10 exons and encodes a 68 kDa protein. Prior study indicated that *COX-2* rs20417 C-allele may decrease the transcription of the *COX-2* gene [37]. This pooled-analysis, including 8,097 CRC cases and 18,293 controls from 19 independent studies, was carried out systematically to explore the relationship between *COX-2* rs20417 G>C polymorphism and CRC risk. To the best of our knowledge, our study is the most comprehensive study to date to determine the association of *COX-2* rs20417 G>C polymorphism with CRC risk. Our results showed that *COX-2* rs20417 G>C polymorphism was not associated with overall CRC susceptibility. In a subgroup analysis by ethnicity, the results showed that individuals with *COX-2* rs20417 C allele increased CRC susceptibility among Asians in two genetic models (C vs. G: OR = 1.46; CI = 1.14 - 1.88; *P* = 0.003 and CC+GC vs. GG: OR = 1.43; CI = 1.16 - 1.78; *P* = 0.001).

A great many of epidemiologic studies have investigated the association of *COX-2* polymorphisms with CRC risk [3, 13-27]. The most prevalent *COX-2* genovariation, rs20417 G>C polymorphism, has been extensively studied. The *COX-2* rs20417 G>C polymorphism is located on promoter which is a stimulatory protein 1 binding site, and *COX-2* rs20417 C-allele decreased the promoter activity compared with

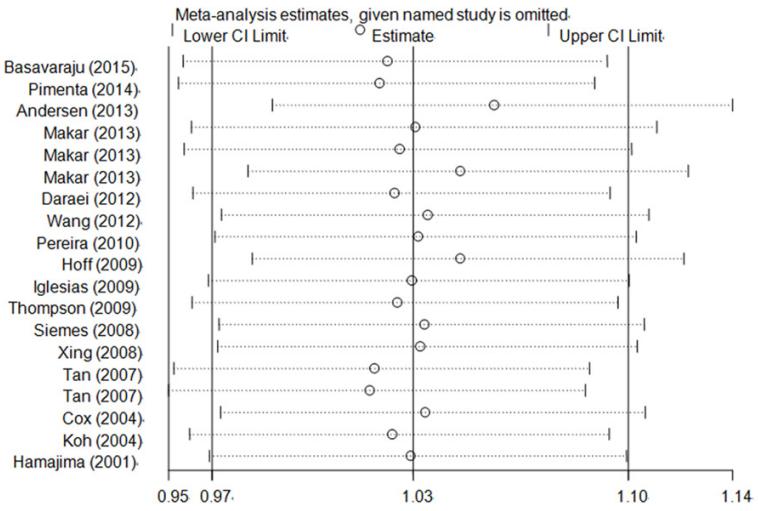

Figure 4. Sensitivity analysis of the influence of CC+GC vs. GG genetic model (random-effects estimates).

COX-2 rs20417 G allele [38]. Pimenta *et al.* and Tan *et al.* reported that *COX-2* rs20417 G>C polymorphism conferred the increased risk to CRC [3, 25]. Nevertheless, in the present meta-analysis, we found that *COX-2* rs20417 G>C variants as well as alleles were not associated with overall CRC susceptibility (**Table 3**). However, When restricting the analysis to ethnicity, individuals with *COX-2* rs20417 C allele increasing CRC susceptibility among Asians were found in two genetic models (C vs. G: OR = 1.46; CI = 1.14 - 1.88; *P* = 0.003 and CC+GC vs. GG: OR = 1.43; CI = 1.16 - 1.78; *P* = 0.001; **Table 3**). Our results were similar to the previous study [7, 8]. Results of the present meta-analysis highlighted the influence of *COX-2* rs20417 G>C polymorphism and difference in different ethnicities to the susceptibility of CRC. However, only five studies focusing on *COX-2* rs20417 G>C polymorphism and CRC susceptibility among Asians were enrolled. Therefore, these findings should be interpreted with caution. In addition, the genovariations and environmental factors could alter the risk of CRC on different levels. For insufficient data provided in the original studies, we could not perform further analysis on environmental factors (e.g., alcohol consumption, the status of smoking and other life styles). Considering the complex aetiology of CRC and a limited influence on CRC susceptibility from *COX-2* rs20417 G>C polymorphism, these important environmental and life style factors should not be neglected.

The limitations of the present meta-analysis should be acknowledged. Firstly, in our study, only published studies were taken into account. Studies with 'negative' results may be unpublished, whereas 'positive' results are easy to be published. This could lead to a certain bias. Secondly, for lack of sufficient data of the eligible studies, some co-variates (e.g. body mass index, family history, smoking and drinking, and so on) were not considered in our study. Results of our study were only based on unadjusted assessments. Finally, large heterogeneity existed in some genetic models, which meant these results should be interpreted with very caution.

In conclusion, results of the present pooled-analysis highlight that *COX-2* rs20417 G>C polymorphism was correlated with the increased risk of CRC among Asians. In the future, *COX-2* polymorphisms might be a therapy target and a prognostic factor for CRC patients. Therefore, for practical reasons, further prospective studies with an adequate methodological quality and larger sample sizes are expected to obtain a comprehensive decision on the important role of *COX-2* polymorphisms in CRC.

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Disclosure of conflict of interest

None.

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