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Cyclooxygenase-2 Polymorphisms and Susceptibility to Colorectal Cancer: A Meta-Analysis

Jun Wang, Xufeng Guo, Jixiang Zhang, Jia Song, Mengyao Ji, Shijie Yu, Jing Wang, Zhuo Cao, and Weiguo Dong

Department of Gastroenterology, Renmin Hospital of Wuhan University, Wuhan, Hubei Province, China.

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Corresponding author: Dr. Weiguo Dong, Department of Gastroenterology, Renmin Hospital of Wuhan University, 238 Jiefang Road, Wuhan 430060, Hubei Province, China.
Tel: 86-27-88041911, Fax: 86-27-88042292
E-mail: dwg@whu.edu.cn

· The authors have no financial conflicts of interest.

Purpose: Four polymorphisms, -765G>C, -1195G>A, 8473T>C, and Val511Ala, in the cyclooxygenase-2 (*COX-2*) gene were identified to be associated with colorectal cancer (CRC) risk. However, the results are inconsistent. The objective of this meta-analysis was to evaluate the association between these four polymorphisms and the risk of CRC. **Materials and Methods:** All eligible case-control studies published up to December 2012 on the association between the four polymorphisms of *COX-2* and CRC risk were identified by searching PubMed and Web of Science. The CRC risk associated with the four polymorphisms of the *COX-2* gene was estimated for each study by odds ratio (OR) together with its 95% confidence interval (CI), respectively. **Results:** A total of 15 case-control studies were included. Overall, no evidence has indicated that the -1195A allele, -765C allele, 8473C allele, and 511Ala allele are associated with susceptibility to CRC (-1195G>A: OR=1.11, 95% CI: 0.82-1.51, p=0.78; -765G>C: OR=1.08, 95% CI: 0.96-1.21, p=0.07; 8473T>C: OR=1.03, 95% CI: 0.89-1.18, p=0.91; Val511Ala: OR=0.71, 95% CI: 0.46-1.09, p=0.94). However, stratified analysis with ethnicity indicated that individuals with -765GC or GC/CC genotypes had an increased risk of CRC among Asian populations (GC vs. GG: OR=1.05, 95% CI: 0.87-1.28, p=0.03; GC+CC vs. GG: OR=1.08, 95% CI: 0.96-1.21, p=0.07). **Conclusion:** This meta-analysis indicated that -765G>C polymorphism was significantly associated with susceptibility to CRC in Asian populations.

Key Words: Colorectal cancer, cyclooxygenase-2, polymorphism, meta-analysis

INTRODUCTION

Colorectal cancer (CRC) is a common digestive malignancy, the incidence of which is just lower than gastric and esophageal cancer. With continuous improvement in living standards, general health has improved greatly; however, the incidence of CRC has markedly ascended. Molecular epidemiology has confirmed that tumorigenesis is close related to interactions between one's genetic background and the environment. Most CRC occurrences arise due to interactions between environmental and genetic factors.[1]

Cyclooxygenase-2 (*COX-2*) is an inducible isoform of COX enzymes that converts arachidonic acid to prostaglandins, which are potent mediators of inflammation. *COX-2* is related to several biological processes, including carcinogenesis, cell proliferation, angiogenesis, and mediating immune suppression. A growing body of evidence has shown that increased expression of *COX-2* is closely related to malignant progression.[2-5] Moreover, it is reported that selective *COX-2* inhibitors could prevent carcinogenesis.[6] The human *COX-2* gene, mapped to chromosome 1q25.2-q25.3, is 8.3 kb in length and contains 10 exons and 9 introns. There are different polymorphism sites in the *COX-2* gene,[7,8] and four of these polymorphisms, rs20417 (-765G>C), rs689466 (-1195G>A), rs5275 (8473T>C) and rs5273 (Val511Ala), are the most extensively studied polymorphisms in CRC.

Recently, 15 studies have investigated the association between these four polymorphisms and the susceptibility of CRC in diverse populations.[9-23] However, the results remain controversial. To better address the association between *COX-2* polymorphisms and CRC risk, we performed a meta-analysis of all eligible studies to evaluate the association between these four polymorphisms of the *COX-2* gene and CRC risk.

MATERIALS AND METHODS

Search strategy

A literature research was conducted using PubMed and Web of Science up to December 2012 without language restrictions. Relevant studies were identified using the terms: ('cyclooxygenase-2 or *COX-2* or PTGs2') and ('genetic polymorphism or polymorphisms or single-nucleotide polymorphism') and ('colorectal cancer/neoplasms or colon cancer/neoplasms or rectal cancer/neoplasms'). The search was restricted to humans. Additional studies were identified by a hand search of references of original or review articles on this topic. If data or data subsets were published in more than one article, only the publication with the largest sample size was included.

Inclusion criteria and exclusion criteria

Studies were included if they met the following criteria: 1) studies that evaluated the association between the four polymorphisms (-765G>C, -1195G>A, 8473T>C, and Val511Ala) and CRC, 2) a case-control study design, and 3) had detailed genotype frequency of cases and controls or could be calculated from the article text. The major exclusion criteria were: 1) case-only study, case reports, and review articles, 2) studies without the raw data of the four genotypes of *COX-2*, 3) studies that compared the *COX-2* variants in familial adenomatous polyposis, or colorectal adenoma, and 4) studies that investigated *COX-2* variants as marks for response to therapy.

Data extraction and quality assessment

The two investigators (Wang J and Guo XF) independently extracted data according to the inclusion criteria. Disagreement was resolved by discussion between them. If they could not reach a consensus, an expert (Dong WG) was consulted to resolve the dispute and a final majority decision was made. For each study, the following data was collected: the first author's name, year of publication, country of origin, ethnicity, number of genotyped cases and controls, and minor allele frequency in the controls. Patient ethnicity was categorized as Asian, Caucasian, and African-American.

Statistical analysis

Meta-analysis was performed using the Cochrane Collaboration RevMan 5.0 (Copenhagen, 2008) and STATA package version 9.2 (Stata Corporation, College Station, TX, USA) software. We calculated odd ratios corresponding to a 95% confidence interval (95% CI) to assess the strength of association between the four polymorphisms of the *COX-2* gene and CRC risk. Heterogeneity assumption was checked by a χ^2-based Q test.[24] We also quantified the effect of heterogeneity by I^2 test. When a significant Q test ($p<0.1$) or I^2 >50% indicated heterogeneity across studies, the random effects model was used,[25] or else the fixed effects model was used.[26] Before the effect estimation of *COX-2* polymorphisms in colorectal cancer, we tested whether genotype frequencies of controls were in Hardy-Weinberg equilibrium (HWE) using χ^2 test. Four comparison genetic models were used to assess the association: the dominant model (the combined variant homozygote and heterozygote versus the wild-type homozygote), the recessive model (the variant homozygote versus the combined heterozygote and wild-type homozygote), the heterozygote comparison (heterozygote versus the wild-type homozygote), and the homozygote comparison (variant homozygote versus the wild-type homozygote). Stratification analyses were performed on ethnicity. Analysis of sensitivity was performed to evaluate the stability of the results. Finally, potential publication bias was inves-

tigated using Begg's funnel plot and Egger's regression test.[27,28] $p< 0.05$ was regarded as statistically significant.

RESULTS

Study characteristics

The search strategy retrieved 99 potentially relevant studies. According to the inclusion criteria, 15 studies with full-text were included in this meta-analysis and 84 studies were excluded. The flow chart of study selection in summarized in Fig. 1. As shown in Table 1, there were 11 case-control studies with 3432 cancer cases and 5286 controls concerning -765G>C polymorphism, 5 case-control studies with 1854 cancer cases and 2950 controls concerning -1195G>A, 5

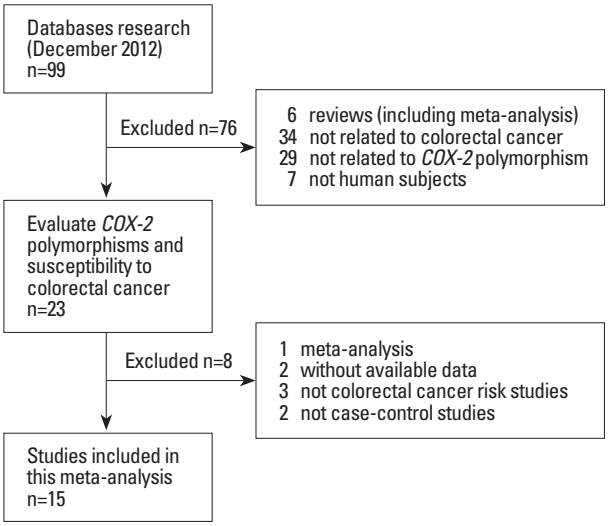


Fig. 1. Flow chart showing study selection procedure.

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

Study	Yrs	Country	Ethnicity	Case			Control				
				WT Ho	Ht	VR Ho	WT Ho	Ht	VR Ho	P_{HWE}	MAF
-765G>C				GG	GC	CC	GG	GC	CC		C freq.
Hamajima, et al.[9]	2001	Japan	Asian	140	8	0	230	11	0	0.716	0.023
Cox, et al.[10]	2004	Spain	Caucasian	150	59	11	170	77	10	0.730	0.189
Koh, et al.[11]	2004	Singapore	Asian	273	37*		1067	110*		NA	NA
Tan, et al.[12]	2007	China	Asian	919	81	0	1237	63	0	0.371	0.024
Xing, et al.[13]	2008	China	Asian	119	17	1	169	29	1	0.838	0.078
Iglesias, et al.[14]	2009	Spain	Caucasian	172	99	13	76	43	4	0.480	0.207
Thompson, et al.[15]	2009	USA	Caucasian	291	119	11	343	121	15	0.286	0.158
Hoff, et al.[16]	2009	Netherlands	Caucasian	241	75	10	249	112	8	0.260	0.173
Andersen, et al.[17]	2009	Denmark	Caucasian	267	83	9	566	186	13	0.609	0.139
Pereira, et al.[18]	2010	Portugal	Caucasian	77	38	2	166	83	7	0.373	0.189
Daraei, et al.[19]	2012	Iran	Asian	38	67	5	53	58	9	0.201	0.317
-1195G>A				GG	GA	AA	GG	GA	AA		A freq.
Siezen, et al.[20]	2006	Denmark	Caucasian	29	191	410	61	354	665	0.130	0.780
Thompson, et al.[15]	2009	USA	Caucasian	9	138	275	15	168	297	0.131	0.794
Hoff, et al.[16]	2009	Netherlands	Caucasian	12	101	213	13	124	232	0.471	0.797
Andersen, et al.[17]	2009	Denmark	Caucasian	13	116	230	25	258	482	0.177	0.799
Pereira, et al.[18]	2010	Portugal	Caucasian	4	43	70	6	73	177	0.634	0.834
8473T>C				TT	TC	CC	TT	TC	CC		C freq.
Cox, et al.[10]	2004	Spain	Caucasian	140	121	29	126	120	25	0.639	0.314
Siezen, et al.[20]	2006	Denmark	Caucasian	97	83	20	190	163	35	0.996	0.282
Thompson, et al.[15]	2009	USA	Caucasian	176	189	56	216	199	65	0.081	0.343
Andersen, et al.[17]	2009	Denmark	Caucasian	147	178	34	315	355	95	0.745	0.356
Pereira, et al.[18]	2010	Portugal	Caucasian	54	51	10	118	114	24	0.638	0.316
Val511Ala				V/V	V/A+A/A		V/V	V/A+A/A			
Lin, et al.[21]	2002	USA	African-Americans	129	9		237	21		NA	NA
Goodman, et al.[22]	2004	USA	African-Americans	109	6		186	14		NA	NA
Sansbury, et al.[23]	2006	USA	African-Americans	223	17		292	34		NA	NA

HWE, Hardy-Weinberg equilibrium; NA, not available; Ht, heterozygote; VR Ho, variant homozygote; WT Ho, wide-type homozygote; MAF, minor allele frequency.

P_{HWE} was calculated by goodness-of fit X^2-test, $P_{HWE}<0.05$ was considered statistically significant.

*Numbers of GC+CC.

case-control studies with 1827 cancer cases and 2853 controls concerning 8473T>C, and 3 case-control studies with 493 cancer cases and 784 controls concerning Val511Ala. Three ethnicities were addressed: five studies focused on Asian populations,[9,11-13,19] seven on Caucasian populations,[10,14-18,20] and three on African-American populations.[21-23] The distribution of genotypes in the controls was consistent with the HWE for all selected studies, except for one study for -765G>C,[11] and three studies for Val511Ala,[21-23] the P_{HWE} of which were not available.

Association between *COX-2* polymorphisms and colorectal cancer

Eleven studies reported the association between *COX-2* -765G>C polymorphism and susceptibility to CRC. Overall, there was no significant difference in *COX-2* -765G>C genotype distribution between CRC and controls [GC+CC vs. GG (OR=1.08, 95% CI: 0.96-1.21, p=0.07); CC vs. GG (OR=1.11, 95% CI: 0.77-1.60, p=0.96); GC vs. GG (OR=1.05, 95% CI: 0.87-1.28, p=0.03); CC vs. GC+GG (OR=1.09, 95% CI: 0.76-1.56, p=0.85)] (Table 2, Fig.2). In the subgroup analysis by ethnicity, results were similar in the Caucasian population, while significantly increased risk was found in those of Asian descent [GC+CC vs. GG (OR=1.41, 95% CI: 1.15-1.75, p=0.39); GC vs. GG (OR=1.48, 95% CI: 1.15-1.90, p=0.24)] (Table 2, Fig.3).

The -1195G>A *COX-2* polymorphism analysis, fitting into five studies, revealed that there was no significant difference in *COX-2* -1195G>A genotype distribution between CRC and controls in the Caucasian population [GA+AA vs. GG (OR=1.11, 95% CI: 0.82-1.51, p=0.78); AA vs. GG (OR=1.14, 95% CI: 0.84-1.56, p=0.69); GA vs. GG (OR=1.05, 95% CI: 0.76-1.44, p=0.91); AA vs. GA+GG (OR=1.08, 95% CI: 0.96-1.22, p=0.27)] (Table 2, Fig. 4A).

Five studies reported an association between *COX-2* 8473T>C polymorphism and susceptibility to CRC, all patients came from Caucasian populations. No association was found between 8473C allele and susceptibility to CRC [TC+CC vs.TT (OR=1.03, 95% CI: 0.89-1.18, p=0.91); CC vs.TT (OR=0.96, 95% CI: 0.76-1.21, p=0.81); TC vs. TT (OR=1.04, 95% CI: 0.90-1.21, p=0.85); CC vs. TC+TT (OR=0.93, 95% CI: 0.75-1.16, p=0.74)] (Table 2, Fig. 4B).

There were three studies that reported an association between *COX-2* Val511Ala polymorphism and susceptibility to CRC, and all patients came from African-American populations. The results showed that no association between 511Ala allele and susceptibility to CRC [Val/Ala+Ala/Ala vs. Val/Val (OR=0.71, 95% CI: 0.46-1.09, p=0.94)] (Table 2, Fig. 4C).

Sensitivity analysis was performed by sequential omission of individual studies. For -765G>C polymorphism, The estimated pooled odd ratio did not change after excluding the study that was not in HWE. For the other polymorphisms, the significance of pooled OR in all individual analyses was not influenced excessively by omitting any single study. The above analysis indicated that the results were stable and statistically robust.

Publication bias

We used Begg's funnel plot and Egger's test to address potential publication bias in the available literature. The publication bias of the meta-analysis on the association between *COX-2* polymorphisms and susceptibility to CRC was detected for all four polymorphisms in a dominant model. The shape of the funnel plots did not reveal any evidence of funnel plot asymmetry. Egger's test also showed that there was

Table 2. Summary of ORs for *COX-2* Polymorphism and Colorectal Cancer Risk

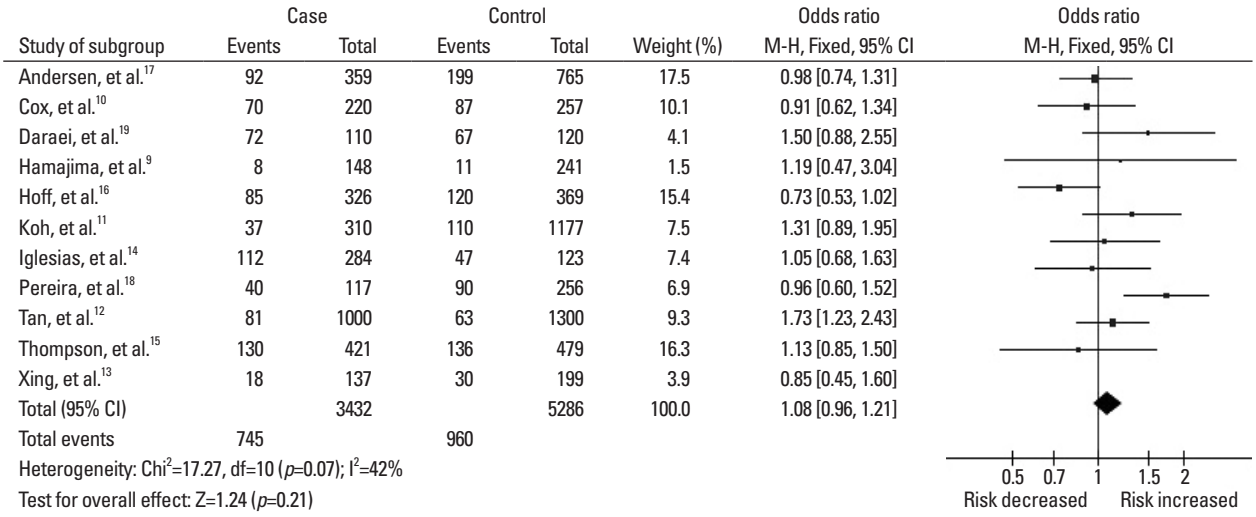
SNP	Ethnicity	Studies	Dominant model		Recessive model		Ht vs. WT Ho		VR Ho vs. WT Ho	
			OR (95% CI)	p value‡	OR (95% CI)	p value‡	OR (95% CI)	p value‡	OR (95% CI)	p value‡
-765G>C	Total	11	1.08 (0.96, 1.21)	0.07	1.09 (0.76, 1.56)	0.85	1.05 (0.87, 1.28)†	0.03	1.11 (0.77, 1.60)	0.96
	Asian	5/4*	1.41 (1.15, 1.75)	0.39	0.67 (0.24, 1.87)	0.55	1.48 (1.15, 1.90)	0.24	0.85 (0.29, 2.48)	0.69
	Caucasian	6	0.96 (0.83, 1.10)	0.54	1.17 (0.79, 1.72)	0.85	0.94 (0.81, 1.09)	0.38	1.15 (0.78, 1.69)	0.90
-1195G>A	Caucasian	5	1.11 (0.82, 1.51)	0.78	1.08 (0.96, 1.22)	0.27	1.05 (0.76, 1.44)	0.91	1.14 (0.84, 1.56)	0.69
8473T>C	Caucasian	5	1.03 (0.89, 1.18)	0.91	0.93 (0.75, 1.16)	0.74	1.04 (0.90, 1.21)	0.85	0.96 (0.76, 1.21)	0.81
Val511Ala	African-Americans	3	0.71 (0.46, 1.09)	0.94	-	-	-	-	-	-

CI, confidence interval; *COX-2*, cyclooxygenase-2; OR, odds ratio; SNP, single-nucleotide polymorphism; Ht+VR vs. WT Ho, dominant model; VR Ho vs. Ht+WT Ho, recessive model.

*There were five studies in the dominant model, four in the other models.

†Random-effects model was used when the p for heterogeneity test was ≤0.05, otherwise the fixed-effect model was used.

‡Test for heterogeneity.



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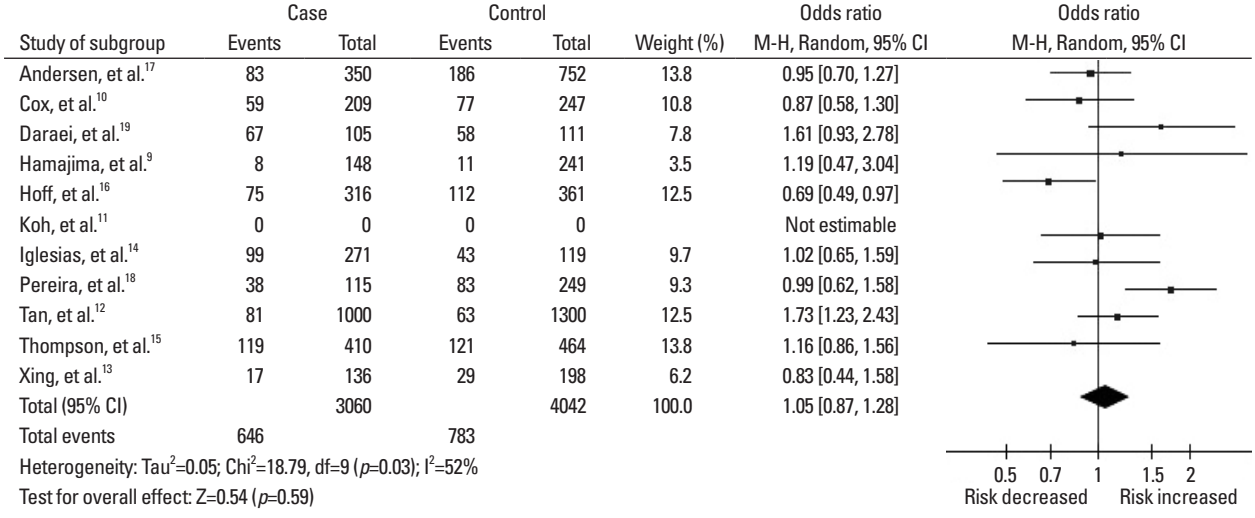

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Fig. 2. Meta-analysis of the association between -765G>C polymorphism and susceptibility to colorectal cancer. (A) Dominant model. (B) GC vs. GG. CI, confidence interval.

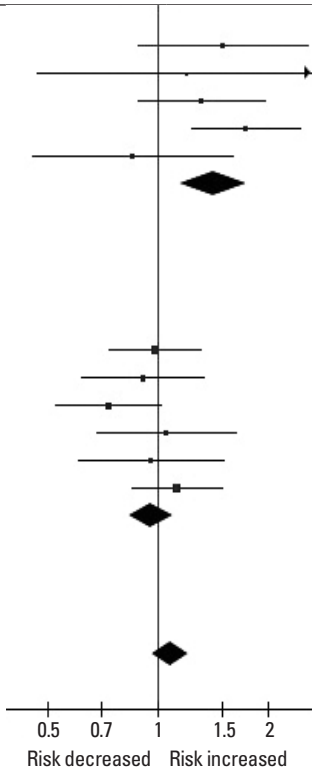
no statistical significance for the evaluation of publication bias ($P_{765G>C}$=0.904, $P_{1195G>A}$=0.136, $P_{8473T>C}$=0.361, $P_{Val511Ala}$=0.485) (Fig. 5).

DISCUSSION

Evidence suggests that *COX-2* plays an important role in carcinogenesis.[29,30] The specific function of *COX-2* in the formation of prostaglandins makes it a strong candidate for increasing susceptibility to common cancers such as colorectal cancer, gastric cancer and other cancers.[31] Eberhart, et al.[32] reported that more than 85% of human colon cancers have elevated levels of *COX-2*. Regular use of *COX-2* inhibitor has been shown to decrease the relation risk of developing colorectal cancer.[33] It is reported that polymorphisms may alter the expression of *COX-2* and thereby modulate the risk for various cancers. Although the exact molecular mechanism is still unclear, several polymorphisms in *COX-2* have been reported previously, and the results are still controversial.

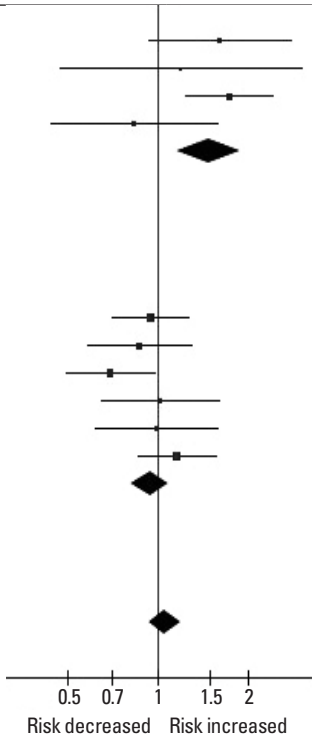
The present meta-analysis included 3432 cancer cases and 5286 controls concerning -765G>C polymorphism, 1854 cancer cases and 2950 controls concerning -1195G>A, 1827 cancer cases and 2853 controls concerning 8473T>C, and 493 cancer cases and 784 controls concerning Val511Ala in the coding regions of *COX-2*. And we explored the role of these four potentially functional polymorphisms of *COX-2* in susceptibility to CRC. The *COX-2* -765G>C polymorphism is within the promoter region, which appears to disrupt a stimulatory protein1 binding site, and leads to a 30% reduction of *COX-2* promoter activity *in vitro*.[34] In this study,

Study of subgroup	Case Events	Case Total	Control Events	Control Total	Weight (%)	Odds ratio M-H, Fixed, 95% CI
2.1.1 Asian						
Daraei, et al.[19]	72	110	67	120	4.1	1.50 [0.88, 2.55]
Hamajima, et al.[9]	8	148	11	241	1.5	1.19 [0.47, 3.04]
Koh, et al.[11]	37	310	110	1177	7.5	1.31 [0.89, 1.95]
Tan, et al.[12]	81	1000	63	1300	9.3	1.73 [1.23, 2.43]
Xing, et al.[13]	18	137	30	199	3.9	0.85 [0.45, 1.60]
Subtotal (95% CI)		1705		3037	26.3	1.41 [1.15, 1.75]
Total events	216		281			
Heterogeneity: Chi^2=4.14, df=4 (p=0.39); I^2=3%						
Test for overall effect: Z=3.23 (p=0.001)						
2.1.2 Caucasian						
Andersen, et al.[17]	92	359	199	765	17.5	0.98 [0.74, 1.31]
Cox, et al.[10]	70	220	87	257	10.1	0.91 [0.62, 1.34]
Hoff, et al.[16]	85	326	120	369	15.4	0.73 [0.53, 1.02]
Iglesias, et al.[14]	112	284	47	123	7.4	1.05 [0.68, 1.63]
Pereira, et al.[18]	40	117	90	256	6.9	0.96 [0.60, 1.52]
Thompson, et al.[15]	130	421	136	479	16.3	1.13 [0.85, 1.50]
Subtotal (95% CI)		1727		2249	73.7	0.96 [0.83, 1.10]
Total events	529		679			
Heterogeneity: Chi^2=4.06, df=5 (p=0.54); I^2=0%						
Test for overall effect: Z=0.62 (p=0.53)						
Total (95% CI)		3432		5286	100.0	1.08 [0.96, 1.21]
Total events	745		960			
Heterogeneity: Chi^2=17.27, df=10 (p=0.07); I^2=42%						
Test for overall effect: Z=1.24 (p=0.21)						
Test for subgroup differences: Chi^2=9.19, df=1 (p=0.002); I^2=89.1%						



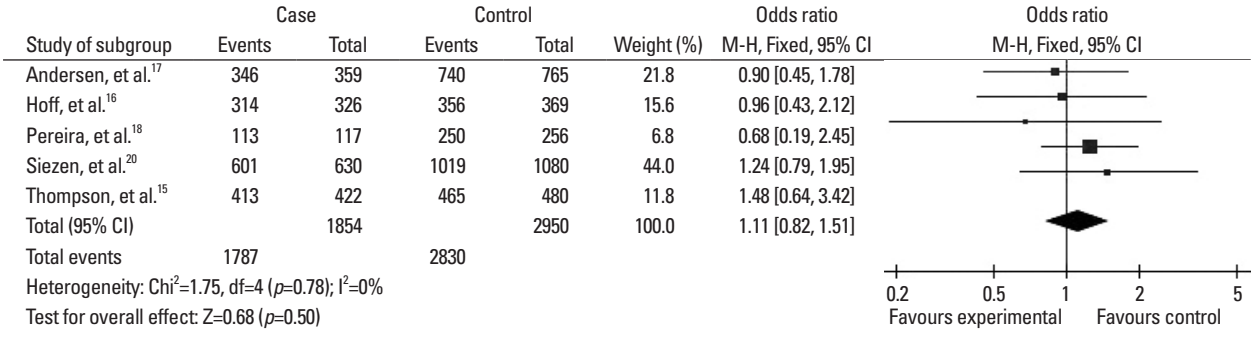
A

Study of subgroup	Case Events	Case Total	Control Events	Control Total	Weight (%)	Odds ratio M-H, Fixed, 95% CI
4.1.1 Asian						
Daraei, et al.[19]	67	105	58	111	4.3	1.61 [0.93, 2.78]
Hamajima, et al.[9]	8	148	11	241	1.7	1.19 [0.47, 3.04]
Tan, et al.[12]	81	1000	63	1300	10.6	1.73 [1.23, 2.43]
Xing, et al.[13]	17	136	29	198	4.4	0.83 [0.44, 1.58]
Subtotal (95% CI)		1389		1850	21.0	1.48 [1.15, 1.90]
Total events	173		161			
Heterogeneity: Chi^2=4.18, df=3 (p=0.24); I^2=28%						
Test for overall effect: Z=3.04 (p=0.002)						
4.1.2 Caucasian						
Andersen, et al.[17]	83	350	186	752	19.0	0.95 [0.70, 1.27]
Cox, et al.[10]	59	209	77	247	10.7	0.87 [0.58, 1.30]
Hoff, et al.[16]	75	316	112	361	16.8	0.69 [0.49, 0.97]
Iglesias, et al.[14]	99	271	43	119	8.0	1.02 [0.65, 1.59]
Pereira, et al.[18]	38	115	83	249	7.4	0.99 [0.62, 1.58]
Thompson, et al.[15]	119	410	121	464	17.0	1.16 [0.86, 1.56]
Subtotal (95% CI)		1671		2192	79.0	0.94 [0.81, 1.09]
Total events	473		622			
Heterogeneity: Chi^2=5.31, df=5 (p=0.38); I^2=6%						
Test for overall effect: Z=0.86 (p=0.39)						
Total (95% CI)		3060		4042	100.0	1.05 [0.93, 1.19]
Total events	646		783			
Heterogeneity: Chi^2=18.79, df=9 (p=0.03); I^2=52%						
Test for overall effect: Z=0.78 (p=0.44)						
Test for subgroup differences: Chi^2=9.36, df=1 (p=0.002); I^2=89.3%						



B

Fig. 3. Subgroup analysis of -765G>C polymorphism by ethnicity. (A) dominant model. (B) GC vs. GG. CI, confidence interval.



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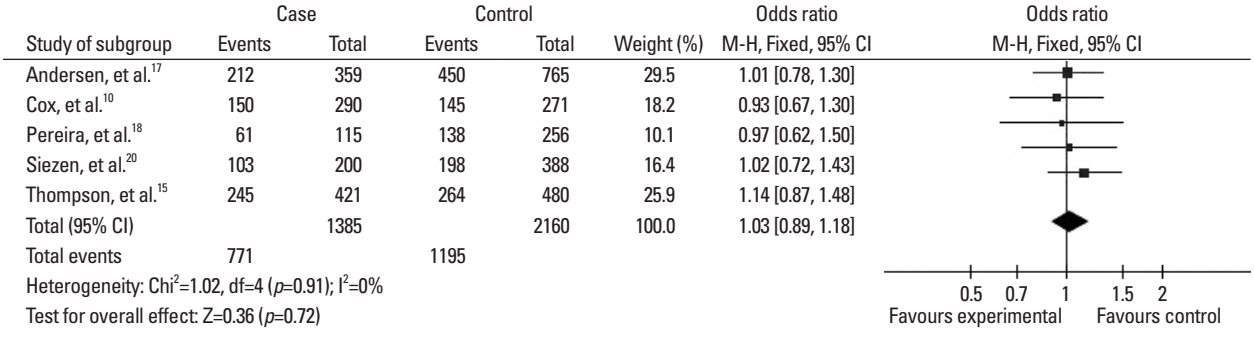

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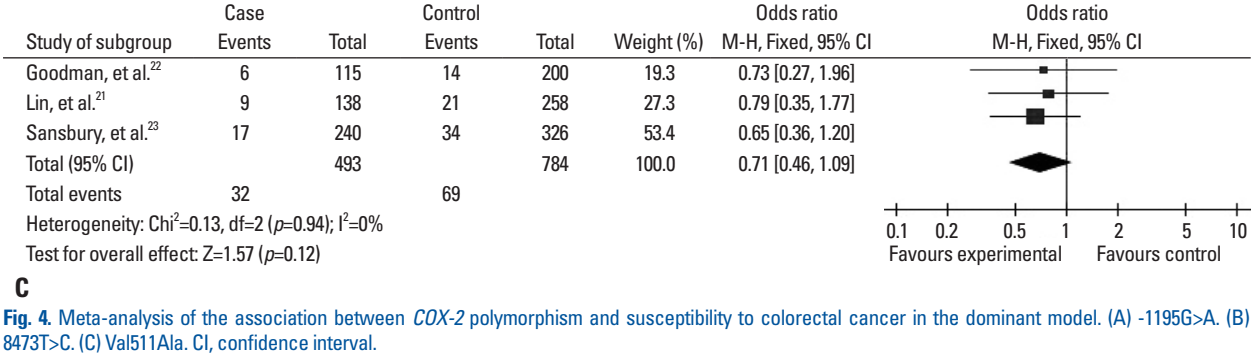

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Fig. 4. Meta-analysis of the association between *COX-2* polymorphism and susceptibility to colorectal cancer in the dominant model. (A) -1195G>A. (B) 8473T>C. (C) Val511Ala. CI, confidence interval.

no significant association between *COX-2* -765G>C and the risk of CRC under all four genetic models in overall comparisons were observed. However, in the subgroup analysis by ethnicity, *COX-2* -765C allele was significantly associated with an increasing risk of CRC in Asian populations, but not for Caucasian populations. The results may due to ethnic differences in genetic backgrounds and the environment in which they lived. The *COX-2* -1195G>A polymorphism, also located in the promoter region, which contains several key cis-acting regulatory elements and may play important roles in the regulation of *COX-2* transcription.[35] This meta-analysis included five studies, all of which came from the Caucasian population, and found that *COX-2* -1195G>A polymorphism was not significantly related to a risk of CRC. The *COX-2* 8473T>C polymorphism is located in the 3'-untranslated region, which contains highly-conserved adenine-uracil-rich elements. This motif is involved in the regulation of *COX-2* production by acting both as an mRNA instability determinant and a translation inhibitory element.[36-38] However, we also found no association between *COX-2* 8473T>C and risk of CRC. The Val511Ala polymorphism, identified only in African-Americans, showed nonsignificant relevance to risk of CRC in this study. In short, the results may be explained by different ethnic groups. Interactions with other genetic variants are possible reasons. In addition, gene-environmental factors may also explain the discrepancies. However, because only few studies on European populations were included, this result should be interpreted with caution, and more studies are needed.

Some limitations of this meta-analysis should be addressed. First, because of incomplete raw data or publication limitations, some relevant studies could not be included in our analysis. Second, the number of published studies

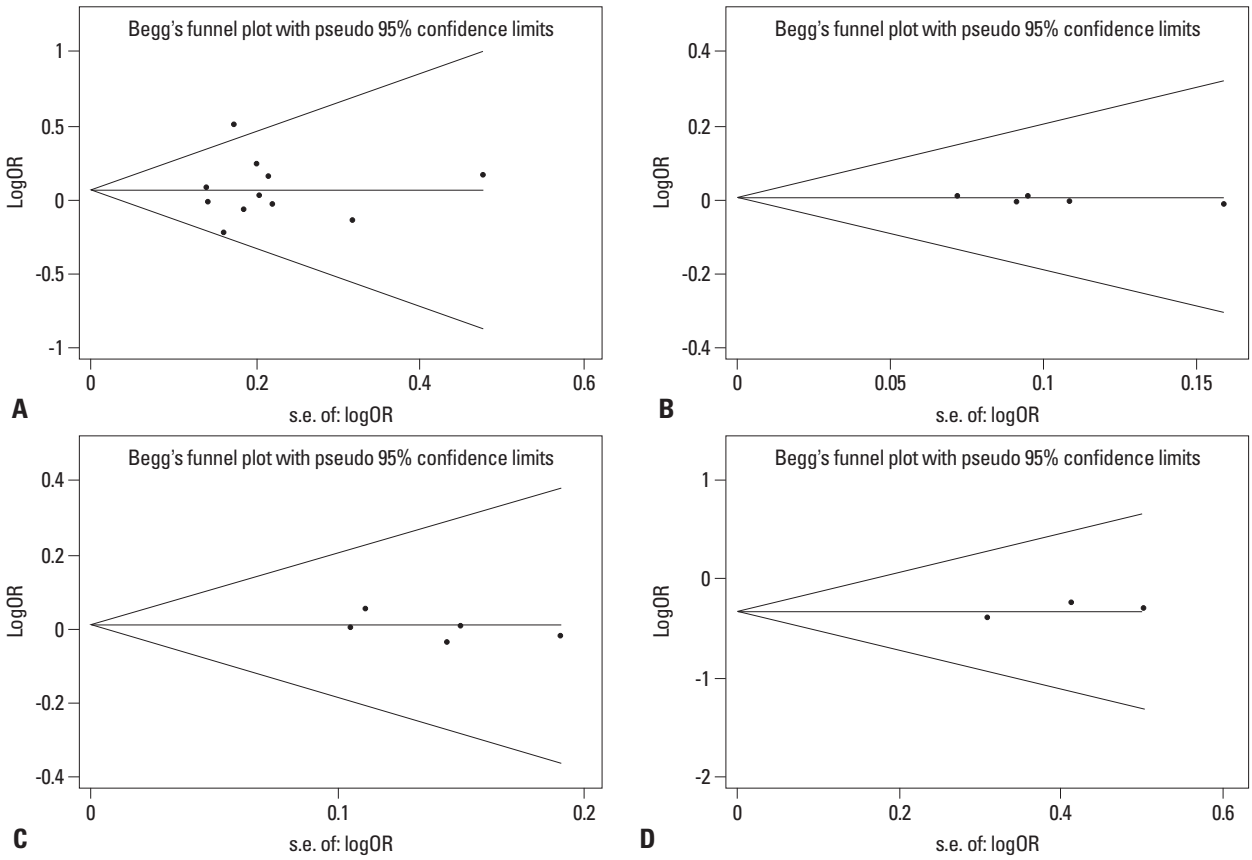

Fig. 5. Begg's funnel plot for publication bias. Each point represents a separate study for the indicated association. Log [OR], natural logarithm of OR. Horizontal line, mean effect size. (A) -765G>C. (B) -1195G>A. (C) 8473T>C. (D) Val511Ala. OR, odds ratio.

was not sufficiently large, and some studies of small size may not have enough statistical power to explore the real association. Third, some misclassifications may be occurred, which would influence our results. Fourth, the overall outcomes were based on unadjusted estimates, and some potentially suspected factors such as age, sex, smoking and environmental factors were not analysis, so the result should be cautiously interpreted.

In summary, this meta-analysis sought to provide evidence for associations between -765G>C, -1195G>A, 8473T>C, and Val511Ala polymorphisms and CRC risk, and discerned that -765G>C may lead to an increased risk in those of Asian descent. However, no evidence indicated that -1195G>A and 8473T>C were associated with susceptibility to CRC in Caucasians, nor was Val511Ala in African-Americans. However, large and well-designed studies are warranted to validate our findings.

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