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META-ANALYSIS

Association between COX-2 -1195G>A polymorphism and gastrointestinal cancer risk: A meta-analysis

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Abstract

AIM

To perform a meta-analysis to investigate the association between cyclooxygenase-2 (COX-2) -1195G>A gene polymorphism and gastrointestinal cancers.

METHODS

Publications related to the COX-2 -1195G>A gene polymorphism and gastrointestinal cancers published before July 2016 were retrieved from PubMed, EMBASE, Web of Science, China Biological Medicine Database, China National Knowledge Infrastructure, and CQVIP Database. Meta-analysis was performed using Stata11.0 software. The strength of the association was evaluated by calculating the combined odds ratios (ORs) and the corresponding 95%CIs. The retrieved publications were excluded or included one by one for sensitivity analysis. In addition, the funnel plot, Begg's rank correlation test, and Egger's linear regression method were applied to analyse whether the included publications had publication bias.

RESULTS

A total of 24 publications related to the COX-2 -1195G>A gene polymorphism were included, including 28 studies involving 11043 cases and 18008 controls. The meta-analysis results showed that the COX-2 -1195G>A gene polymorphism significantly correlated with an increased risk of gastrointestinal cancers, particularly gastric cancer (A *vs* G: OR = 1.35; AA/AG *vs* GG: OR = 1.54; AA *vs* GG/AG: OR = 1.43; AA *vs* GG: OR = 1.80; AG *vs* GG: OR = 1.35). Compared to the Caucasian population in America and Europe, the COX-2 -1195G>A gene polymorphism in the Asian population (A *vs* G: OR = 1.30; AA/AG *vs* GG: OR

= 1.50; AA *vs* GG/AG: OR = 1.35; AA *vs* GG: OR = 1.71; AG *vs* GG: OR = 1.37) significantly increased gastrointestinal cancer risk. The sensitivity analysis ($P < 0.05$) and the false positive report probability ($P < 0.2$) confirmed the reliability of the results.

CONCLUSION

The results showed that the COX-2 -1195G>A gene polymorphism might be a potential risk factor for gastrointestinal cancers. Further validation by a large homogeneous study is warranted.

Key words: COX-2; -1195G>A; Polymorphism; Meta-analysis; Gastrointestinal cancer

Core tip: To explore the association of the cyclooxygenase-2 (COX-2) (-1195G>A) polymorphism with gastrointestinal cancers, we conducted this retrospective study. According to this meta-analysis, we discovered that the COX-2 (-1195G>A) polymorphism may be a risk factor for gastrointestinal cancers and may increase the risk of gastrointestinal cancers in the Asian population. Furthermore, we applied a false-positive report probability to make the results more credible. Our findings indicated that focusing on the COX-2 (-1195G>A) polymorphism to prevent gastrointestinal cancers may be viable.

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INTRODUCTION

Gastrointestinal cancers have high morbidity and mortality worldwide, with most cases being gastric cancer and colorectal cancer[1,2]. Because currently there is still no effective early diagnosis method, patients are often diagnosed at a middle or late stage; even after treatment, their quality of life and survival time are still significantly affected[3]. Improving the early diagnosis and treatment of gastric cancer and colorectal cancer has important significance in the prognosis of patients[4,5]. Therefore, studying pathogenic mechanisms of tumours, clarifying the molecular mechanism, discovering "key" molecular markers of tumours, and predicting cancer risk in a timely fashion are key to the prevention, diagnosis, and molecular targeted therapy of gastric cancer and colorectal cancer.

Previous studies have shown that cyclooxygenase-2 (COX-2) is a rate-limiting enzyme of prostaglandin synthesis[6] and is closely associated with the development of malignant tumours[7]. COX-2 is localized in the nuclear membrane under physiological conditions and can be expressed in the cytoplasm and nucleus of corresponding tissues after inflammatory stimulation to participate in inflammatory reactions and promote the formation of a tumour inflammatory microenvironment[8]. A larger amount of literature confirmed that a high COX-2 expression level was present in many malignant tumours, including breast cancer, lung cancer, liver cancer, and nasopharyngeal carcinoma. The high COX-2 expression level was not only an early event of the development of malignant tumours but was also directly correlated with the infiltration degree, lymph node metastasis, TNM stage, and patient prognosis[9-11]. Further studies indicated that the intracellular localizations of COX-2 in tumour cells of different tissues types were different[12]. COX-2 was highly expressed in gastric cancer and colorectal cancer cells; in addition, COX-2 was expressed in macrophages and fibroblasts in tumour tissues[13]. These results indicated that COX-2 expression gradually increases during the process of malignant transformation of precancerous lesions into malignant tumours, suggesting that COX-2 is involved in the developmental process of gastric cancer and colorectal cancer; however, the specific mechanism is still not clear.

The COX-2 gene is localized at q25.2-25.3 of chromosome 1 and contains 10 exons and 9 introns with a total length of approximately 8.3 kb. COX-2 is a rapid-response gene to various factors, such as inflammatory factors, tumourigenic factors, injury, and growth factors, all of which can induce its rapid expression[14,15]. There have been already many published studies on the association between COX-2 gene polymorphisms and susceptibility to gastrointestinal cancers. It is generally considered that COX-2 -765G>C and COX-2 -8473T>C gene mutations are closely associated with the development of gastrointestinal cancers[16,17]. However, the association between COX-2 -1195G>A and gastric and colorectal cancers is still unclear. Because the COX-2 gene has larger distribution differences in populations of different ethnicities and different regions and the sample size in a single study is limited, this association cannot be entirely explained. Given the current controversial study results, we aimed to perform a meta-analysis to confirm the association between the COX-2 -1195G>A polymorphism and susceptibility to gastric and colorectal cancers.

MATERIALS AND METHODS

Retrieval strategy

We performed retrieval using the MeSH terms of (COX-2 -1195G>A or COX-2 -1195G>A) and (gastrointestinal or colorectal or colon or rectal or stomach or gastric) and (cancer or tumour or carcinoma) and (polymorphism or

Table 1 Quality evaluation scale of the included literature

Criterion	Score
Representativeness of cases	
Selected from population or cancer registry	3
Selected from hospital	2
Selected from pathology archives, but without description	1
Not described	0
Source of controls	
Population-based	3
Blood donors or volunteers	2
Hospital-based (cancer-free patients)	1
Not described	0
Case-control match	
Matched by age and gender	3
Not matched by age and gender	0
Specimens used for determining genotypes	
White blood cells or normal tissues	3
Tumor tissues or exfoliated cells of tissue	0
Hardy-Weinberg equilibrium (HWE)	
Hardy-Weinberg equilibrium in control subjects	3
Hardy-Weinberg disequilibrium in control subjects	0
Total sample size	
> 1000	3
> 500 and < 1000	2
> 200 and < 500	1
< 200	0

SNP or variant or mutation) in the following databases: PubMed, EMBASE, Web of Science, China Biological Medicine Database, China National Knowledge Infrastructure, and CQVIP Database. The relevant studies in China and other countries were retrieved. The retrieval period was between the establishment of the databases and July 2016. Relevant conference papers were manually retrieved from the journal database of the Third Military Medical University library.

Inclusion criteria

The included literature in this study met the following criteria: (1) studies about the COX-2 -1195G>A gene polymorphism and susceptibility to gastrointestinal cancers; (2) case-controlled or cohort studies; (3) gastrointestinal cancer patients as the case group; and (4) enough genotype data to calculate odds ratios (ORs) and corresponding 95% confidence internals (CIs).

Exclusion criteria

The exclusion criteria were as follows: (1) the study topic of the article was not about the COX-2 -1195G>A gene polymorphism and susceptibility to gastrointestinal cancers; (2) the studies were not case-controlled or cohort studies; (3) abstracts, reviews, case reports, or repetitively published articles; and (4) the study data were not complete or the raw data could not be obtained.

Data extraction and quality evaluation

The data were independently extracted by two researchers (Xiao-Wei Zhang, Jun Li) using the unified data table. The major extracted data included the following information: first author, publication year, country, tumour type, sources of the control group, matching criteria, genotyping method, genotype distribution in the case group and the control group, and the Hardy-Weinberg equilibrium (HWE) examination result of the control group. If the data extraction results were inconsistent, a third party was consulted to reach a consensus.

The included publications were scored using the predetermined criteria[18,19]. These criteria were extracted and modified from previous studies (Table 1). The quality evaluation scale was used to evaluate the included studies from six aspects: representativeness of cases, source of controls, case-control match, specimens used for determining genotypes, HWE, and total sample size. The scores ranged from the lowest, 0 points, to the highest, 18 points. Publications with a score < 12 were classified as "low quality" and publications with a score $\geqslant$ 12 were classified as "high quality."

Statistical analysis

The OR and 95%CI were used as the effective index of the study. $P < 0.05$ indicated that the difference was statistically significant. Five genetic models, including allele model (A *vs* G), dominant model (AA/AG *vs* GG), recessive model (AA *vs* GG/AG), homozygous model (AA *vs* GG), and heterozygous model (AG *vs* GG), were compared. The statistical significance of combined OR values were examined using the Z test, and the significance level was set at 0.05 (bilateral). The χ^2 test was used to evaluate whether the genotypes in the control group conformed to HWE. The Cochrane *Q* test was performed to analyse the heterogeneity among studies[20]. $P < 0.10$ was considered significantly different. In addition, the I^2 value was combined to quantitatively evaluate the level of heterogeneity. The I^2 values were between 0% and 100%; when the value was larger, the heterogeneity was higher. When the heterogeneity examination result showed $P < 0.10$ or $I^2 > 50\%$, the random effects model (DerSimonian-Laird method)[21] was used to perform the analysis; otherwise, the fixed effects model (Mantel-Haenszel method)[22] was used. The included studies were deleted one by one to perform sensitivity analysis to examine the effect of a single study on the total combined effect size. Whether the included literature had publication bias was analysed through the funnel plot[23], Egger's linear regression method[24], and Begg's rank correlation test[25]. The meta-analysis was performed using Stata11.0 software.

The method reported by Wacholder *et al*[26] was used to analyse the false positive report probability (FPRP) of each significant correlation. A prior probability of 0.001 was set to detect an OR of 1.5. When the FPRP value was lower than 0.2, the correlation was noteworthy. The statistical power and FPRP value were calculated using

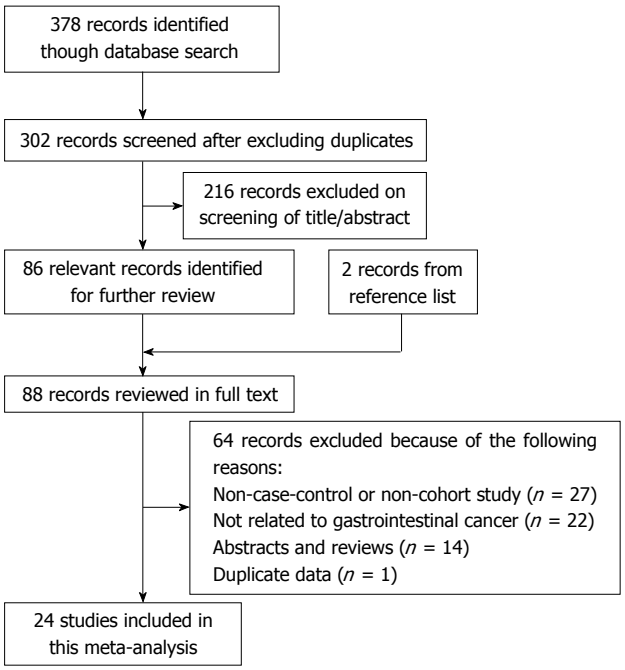

Figure 1 Flow chart of literature inclusion and exclusion.

the Excel spreadsheet provided by Wacholder *et al*[26].

RESULTS

Literature retrieval results

A total of 378 relevant publications were retrieved. After repetitive publications were excluded, there were 302 publications. Literature screening was performed according to the inclusion and exclusion criteria. Based on titles and abstracts, 216 publications that were irrelevant to the study topic were excluded. After abstracts and the full texts were further carefully read, 64 publications were excluded (27 publications of non-case-controlled and cohort studies, 22 publications irrelevant to gastrointestinal cancers, 14 publications of abstracts and reviews, and 1 repeatedly published article). Based on the references of the included literature, 2 more publications were obtained. A total of 24 publications were finally included, involving 11,043 cases and 18,008 controls (Figure 1).

Characteristics of the included studies

Among the 24 included publications (Table 2[27-49]), 11 were reports on gastric cancer and 13 on colorectal cancer; 14 were studies in Asian populations, 8 in Caucasian populations, and 2 in mixed populations. The HWE examination results of the distribution of genotypes in the control group are shown in Table 2. Among the 24 publications, the distribution of genotypes in the control groups of 19 publications conformed to HWE. The quality score of a single study ranged from 7 to 18. There were 19 publications of high quality studies ($\geq$ 12).

Meta-analysis results

The ORs of different comparisons and the heterogeneity examination results are shown in Table 3. The results showed that COX-2 -1195G>A gene polymorphism in all of the genetic models (A *vs* G: OR = 1.54; AA/AG *vs* GG: OR = 1.24; AA *vs* GG/AG: OR = 1.16; AA *vs* GG: OR = 1.31; AG *vs* GG: OR = 1.18) had a significant correlation with susceptibility to gastrointestinal cancers. However, when the predetermined prior probability was below 0.001, all of the FPRP values were higher than 0.2. This result indicated that the association was not noteworthy.

The subgroup analysis was performed based on tumour types (Figure 2). In the gastric cancer group (A *vs* G: OR = 1.35; AA/AG *vs* GG: OR = 1.54; AA *vs* GG/AG: OR = 1.43; AA *vs* GG: OR = 1.80; AG *vs* GG: OR = 1.35), the results showed that the COX-2 -1195G>A gene polymorphism was significantly correlated with cancer susceptibility. Analysis of FPRP in the gastric group showed that the value in the AA *vs* GG/AG model (FPR*P* = 0.174) was lower than 0.2, indicating that the result was noteworthy. However, the COX-2 -1195G>A gene polymorphism was not significantly correlated with susceptibility to colorectal cancer.

When subgrouping based on ethnicity (Figure 3), in the Asian population (A *vs* G: OR = 1.30; AA/AG *vs* GG: OR = 1.50; AA *vs* GG/AG: OR = 1.35; AA *vs* GG: OR = 1.71; AG *vs* GG: OR = 1.37), COX-2 -1195G>A could significantly increase the risk of developing gastrointestinal cancers. In addition, in the A *vs* G model (FPR*P* = 0.069), AA/AG *vs* GG model (FPRP = 0.167) and AA *vs* GG model (FPR*P* = 0.093), the FPRP values were lower than 0.2, indicating that the analytic results were stable and reliable. The results did not show a significant correlation between the COX-2 -1195G>A gene polymorphism and gastrointestinal cancer susceptibility in the Caucasian and mixed populations.

The subgroup analysis based on the sources of the control group showed that, in the studies based on populations from communities (A *vs* G: OR = 1.16; AA/AG *vs* GG: OR = 1.26; AA *vs* GG/AG: OR = 1.19; AA *vs* GG: OR = 1.35; AG *vs* GG: OR = 1.19), the COX-2 -1195G>A gene polymorphism significantly correlated with gastrointestinal susceptibility. The FPRP value in the A *vs* G model was lower than 0.2, indicating that the correlation was noteworthy. For studies based on populations from hospitals, none of the genetic models showed a correlation with intestinal cancers.

The subgroup analysis using the quality evaluation scores showed that, in the high quality studies (A *vs* G: OR = 1.15; AA/AG *vs* GG: OR = 1.25; AA *vs* GG/AG: OR = 1.19; AA *vs* GG: OR = 1.34; AG *vs* GG: OR = 1.19), the COX-2 -1195G>A gene polymorphism correlated with susceptibility to the development of

Table 2 Baseline information of the included studies

Ref.	Year	Country	Type of cancer	Source of controls	Matching criteria	Genotyping method	Cases			Controls			HWE	Quality score
							AA	AG	GG	AA	AG	GG		
Liu *et al*[27]	2006	China	Gastric cancer	PB	NA	DHPLC	88	116	44	375	771	377	0.626	14
Siezen *et al*[28]	2006	Netherland	Colorectal cancer	PB	Age, sex, center	PCR-RFLP	127	59	10	243	128	20	0.558	17
Siezen *et al*[28]	2006	Netherland	Colorectal cancer	PB	Age, sex, center	PCR-RFLP	283	132	19	422	226	41	0.149	18
Jiang *et al*[29]	2007	China	Gastric cancer	PB	Age, sex	PCR-RFLP	74	132	48	79	163	62	0.187	16
Tan *et al*[30]	2007	China	Colorectal cancer	PB	Age, sex	PCR-RFLP	320	502	178	308	692	300	0.020	14
Andersen *et al*[31]	2009	Denmark	Colorectal cancer	PB	Sex	Taqman	230	116	13	482	258	25	0.177	15
Hoff *et al*[32]	2009	Netherland	Colorectal cancer	HB	Age, sex	PCR-RFLP	213	101	12	232	124	13	0.471	14
Thompson *et al*[33]	2009	United States	Colorectal cancer	PB	NA	Taqman	275	138	9	297	168	15	0.131	14
Pereira *et al*[34]	2010	Portugal	Colorectal cancer	HB	NA	PCR-RFLP	70	43	4	177	73	6	0.634	10
Zhang *et al*[35]	2011	China	Gastric cancer	PB	Age, sex	PCR-RFLP	107	184	32	256	513	175	0.004	14
Zhang *et al*[36]	2011	China	Gastric cancer	PB	Age, sex	PCR-RFLP	113	175	69	241	527	217	0.027	14
Jing *et al*[37]	2012	China	Gastric cancer	PB	Age, sex	PCR-RFLP	49	87	19	51	133	53	0.059	15
Li *et al*[38]	2012	China	Gastric cancer	PB	NA	PCR-RFLP	98	145	53	73	166	80	0.461	14
Shin *et al*[39]	2012	Korea	Gastric cancer	PB	NA	PCR-RFLP	32	54	14	37	41	22	0.107	12
Zhang *et al*[40]	2012	China	Colorectal cancer	PB	NA	PCR-RFLP	77	216	50	62	184	94	0.09	12
Andersen *et al*[41]	2013	Denmark	Colorectal cancer	PB	NA	KASP™ genotyping	587	313	47	1126	560	61	0.397	15
Li *et al*[42]	2013	China	Colorectal cancer	HB	NA	PCR-RFLP	116	248	87	179	336	114	0.045	9
Makar *et al*[43]	2013	United States	Colorectal cancer	PB	Age, location, sex	Taqman	910	455	57	1198	509	67	0.162	17
Makar *et al*[43]	2013	United States	Colorectal cancer	PB	Age, location, sex	Taqman	619	287	33	958	496	63	0.905	17
Makar *et al*[43]	2013	United States	Colorectal cancer	PB	Age, location, sex	Taqman	376	185	20	509	237	29	0.829	17
Makar *et al*[43]	2013	United States	Colorectal cancer	PB	Age, location, sex	Taqman	338	138	21	558	249	20	0.206	17
Ruan *et al*[44]	2013	China	Colorectal cancer	PB	NA	PCR-RFLP	34	67	29	39	53	28	0.232	12
Pereira *et al*[45]	2014	Portugal	Colorectal cancer	HB	NA	Taqman	143	85	15	323	133	16	0.614	11
Vogel *et al*[46]	2014	Norseland	Colorectal cancer	PB	NA	KBioscience	110	24	2	209	114	11	0.337	12
Gao *et al*[47]	2015	China	Gastric cancer	PB	Age, sex	Taqman	86	137	55	74	137	57	0.664	16
Lu *et al*[17]	2015	China	Gastric cancer	HB	NA	PCR-RFLP	69	39	25	27	35	72	0.000	7
Tao *et al*[48]	2015	China	Gastric cancer	PB	Age, sex	PCR-RFLP	39	71	26	31	65	25	0.397	15
Zamudio *et al*[49]	2016	Peru	Gastric cancer	HB	NA	Taqman	85	103	32	106	139	43	0.815	9

HWE: Hardy-Weinberg equilibrium; PB: Population-based; HB: Hospital-based; DHPLC: Denaturing high performance liquid chromatography; PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism; NA: Not available.

gastrointestinal cancers. However, the FPRP analytic values were all higher than 0.2, indicating that the analytic results were not stable. In low quality studies, the COX-2 -1195G>A gene polymorphism did not have a significant correlation with gastrointestinal cancers.

Furthermore, the subgroup analysis based on different genotyping methods showed that, in the studies using the Restriction Fragment Length Polymorphism Analysis of PCR-Amplified Fragments (PCR-RFLP) genotyping method (A *vs* G: OR = 1.23; AA/AG *vs* GG: OR = 1.46; AA *vs* GG/AG: OR = 1.24; AA *vs* GG: OR = 1.58; AG *vs* GG: OR = 1.35), the COX-2 -1195G>A gene polymorphism significantly correlated with gastrointestinal cancer susceptibility. However, the FPRP analysis showed that the evidence of the real correlation of positive results was not sufficient. For genotyping using Taqman and other technologies, the COX-2 -1195G>A gene polymorphism in none of the genetic models was significantly correlated with intestinal cancers.

Table 3 Stratified analyses of the COX-2 -1195G>A polymorphism with risk of gastrointestinal cancers

	n	Allele model (A *vs* G)			Dominant model (AA/AG *vs* GG)			Recessive model (AA *vs* GG/AG)			Homozygous comparison (AA *vs* GG)			Heterozygous comparison (AG *vs* GG)		
		OR (95%CI)	Ph	FPRP	OR (95%CI)	Ph	FPRP	OR (95%CI)	Ph	FPRP	OR (95%CI)	Ph	FPRP	OR (95% CI)	Ph	FPRP
Total	28	1.15 (1.04, 1.26)[1]	0.000	0.73	1.24 (1.06, 1.45)[1]	0	0.876	1.16 (1.04, 1.30)[1]	0.000	0.914	1.31 (1.08, 1.59)[1]	0.000	0.873	1.18 (1.04, 1.34)[1]	0.007	0.915
Type of cancer																
Gastric cancer	11	1.35 (1.14, 1.59)[1]	0.000	0.266	1.54 (1.20, 1.96)[1]	0.000	0.519	1.43 (1.18, 1.72)[1]	0.002	0.174	1.80 (1.36, 2.39)[1]	0.000	0.318	1.35 (1.11, 1.65)[1]	0.038	0.799
Colorectal cancer	17	1.04 (0.94, 1.15)	0.000	0.998	1.05 (0.87, 1.28)	0.002	0.998	1.04 (0.93, 1.18)	0.000	0.998	1.05 (0.83, 1.32)	0.000	0.999	1.06 (0.90, 1.25)	0.060	0.998
Ethnicity																
Asian	14	1.30 (1.14, 1.48)[1]	0.000	0.069	1.50 (1.23, 1.84)[1]	0.000	0.167	1.35 (1.14, 1.60)[1]	0.000	0.376	1.71 (1.33, 2.18)[1]	0.000	0.093	1.37 (1.15, 1.62)[1]	0.007	0.213
Caucasian	12	1.00 (0.89, 1.11)	0.000	0.999	0.91 (0.76, 1.08)	0.360	0.996	1.01 (0.89, 1.15)	0.000	0.999	0.91 (0.74, 1.11)	0.186	0.997	0.92 (0.77, 1.09)	0.749	0.997
Mixed	2	1.10 (0.93, 1.31)	0.612	0.997	1.13 (0.74, 1.73)	0.466	0.998	1.13 (0.91, 1.40)	0.781	0.996	1.20 (0.76, 1.88)	0.482	0.998	1.09 (0.69, 1.70)	0.534	0.999
Source of controls																
PB	22	1.16 (1.06, 1.25)[1]	0.000	0.09	1.26 (1.09, 1.45)[1]	0.003	0.559	1.19 (1.07, 1.33)[1]	0.000	0.685	1.35 (1.13, 1.61)[1]	0.000	0.488	1.19 (1.04, 1.36)[1]	0.031	0.914
HB	6	1.12 (0.75, 1.67)	0.000	0.998	1.14 (0.60, 2.15)	0.000	0.999	1.08 (0.72, 1.63)	0.000	0.999	1.15 (0.54, 2.45)	0.000	0.999	1.12 (0.73, 1.71)	0.021	0.998
Study quality																
High (> 9)	23	1.15 (1.06, 1.25)[1]	0.000	0.504	1.25 (1.09, 1.44)[1]	0.004	0.667	1.19 (1.07, 1.32)[1]	0.000	0.502	1.34 (1.12, 1.59)[1]	0.000	0.469	1.19 (1.04, 1.35)[1]	0.038	0.873
Low (≤ 9)	5	1.13 (0.68, 1.86)	0.000	0.999	1.17 (0.56, 2.45)	0.000	0.999	1.09 (0.65, 1.81)	0.000	0.999	1.17 (0.48, 2.88)	0.000	0.999	1.16 (0.71, 1.90)	0.011	0.998
Genotyping method																
PCR-RFLP	16	1.23 (1.08, 1.40)[1]	0.000	0.633	1.46 (1.19, 1.78)[1]	0.000	0.231	1.24 (1.06, 1.46)[1]	0.000	0.909	1.58 (1.23, 2.02)[1]	0.000	0.436	1.35 (1.14, 1.60)[1]	0.014	0.376
Taqman	9	0.99 (0.90, 1.08)	0.049	0.999	0.97 (0.82, 1.15)	0.428	0.999	0.99 (0.89, 1.11)	0.063	0.999	0.97 (0.79, 1.19)	0.268	0.999	0.98 (0.82, 1.17)	0.669	0.999
Other technologies	3	1.36 (0.86, 2.17)	0.000	0.997	1.16 (0.58, 2.31)	0.008	0.999	1.52 (0.84, 2.75)	0.000	0.997	1.40 (0.55, 3.53)	0.000	0.999	0.99 (0.62, 1.57)	0.118	0.999

[1]OR with statistical significance. *n*: Number of studies included; Ph: *P* value for heterogeneity; FPRP: False positive report probability.

Sensitivity analysis and cumulative analysis

The present study performed sensitivity analysis through gradual deletion of the included studies one by one. The OR value of the combined effect did not have a significant change, indicating that the analytic results were stable and reliable (Figure 4). A cumulative analysis based on the chronological order showed that the OR point estimate value and the corresponding CI trended to become stable and showed a good changing trend (Figure 5).

Publication bias

The funnel plot, Begg's rank correlation test, and Egger's linear correlation were used to evaluate publication bias. The funnel plots of all of the models with a correlation between the COX-2 -1195G>A gene polymorphism and gastrointestinal cancers did not have significant asymmetry. In the AA/AG *vs* GG model, the Begg's rank correlation test showed $P = 0.489$ and the Egger's linear correlation methods showed $P = 0.690$; they both suggested that there was no significant publication bias (Figure 6).

DISCUSSION

In addition to environmental factors, the risk of cancer is also closely associated with the genetic susceptibility of an individual. Previous genetic studies indicated that gene mutations of some inducible enzymes were closely associated with various diseases, including malignant tumours and congenital malformations. These inducible enzymes change the gene expression levels and interfere with signal transduction pathways to inhibit protein synthesis and cause mRNA instability, thus achieving the purpose of changing the encoded proteins and inducing the presence of disease events. Currently, the influences of genes and genetics on the occurrence and development of gastrointestinal cancers are similar to other important factors, such as smoking, drinking, eating habits and geographical environment. Genes and

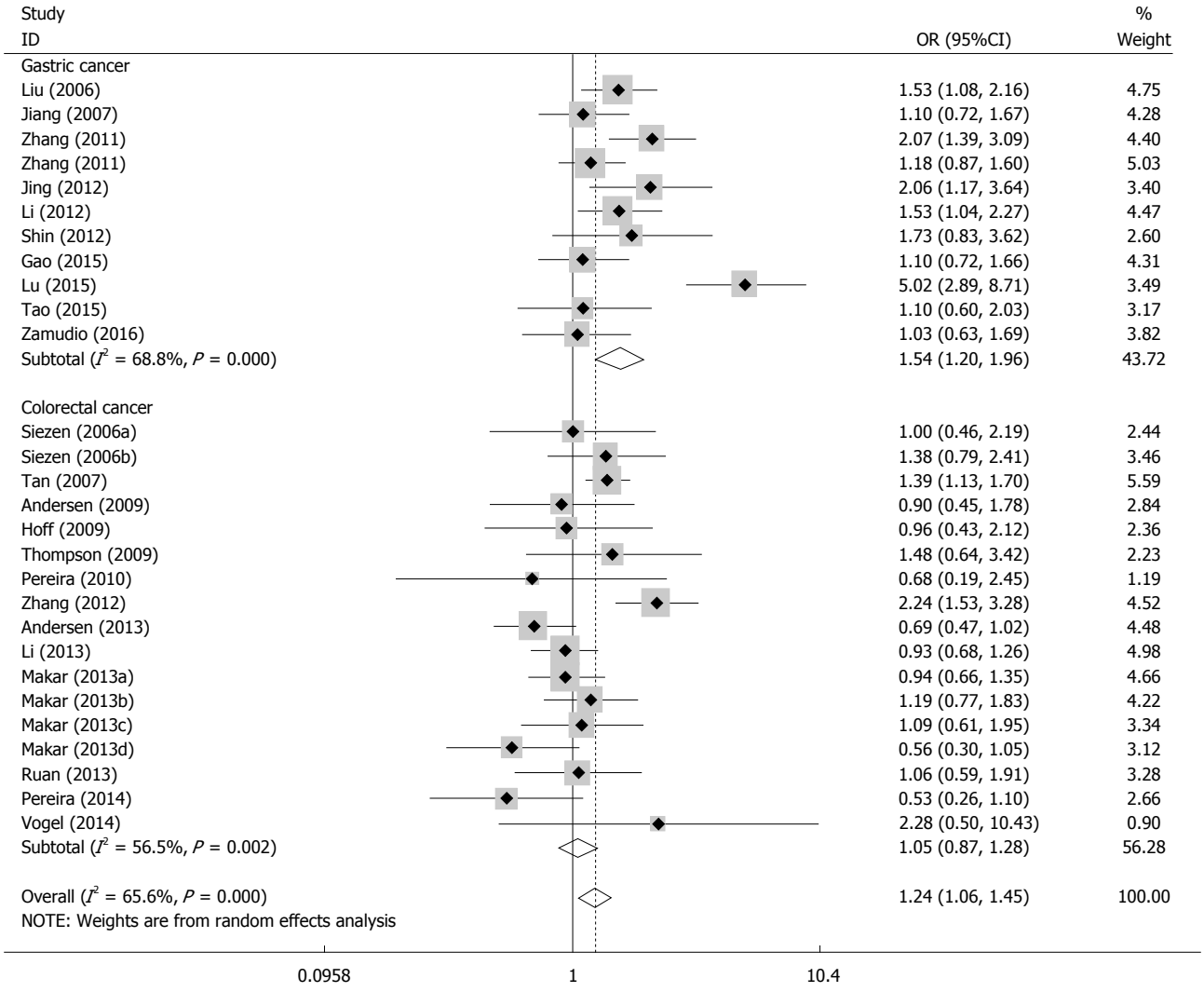

Figure 2 Forest plot of the stratified analysis of the COX-2 -1195G>A dominant model (AA/AG *vs* GG) and susceptibility to gastrointestinal cancers in different tumour types.

genetics have gradually become the hotspots of studies on the pathogenic mechanism of gastrointestinal cancers[50,51].

COX-2 overexpression can influence the tumourigenic gene features of tumour cells, including induction of anti-apoptosis, regulation of extracellular matrix adhesion, promotion of angiogenesis, increase of metastatic potential, and influence of anti-tumour effects[52-54]. Recent studies showed that the COX-2 -1195G>A gene polymorphism generated a c-MYB binding site, thus increasing the transcription activity of the COX-2 gene. c-MYB is an active transcription factor in the haematopoietic system and gastrointestinal tract. c-MYB functions on many genes to regulate the exquisite balance between cell division, differentiation and survival[55], which further confirms that the COX-2 -1195G>A polymorphism might increase susceptibility of individuals to gastrointestinal cancers. However, there were also reports showing that this polymorphism could reduce the risk of developing gastric cancer and colorectal cancer[32]. To clarify this association, we included all case-controlled or cohort studies that met the inclusion criteria to evaluate the correlation using a meta-analysis.

Our study included 24 publications, including 11 gastric cancer publications and 13 colorectal cancer publications. A total of 11,043 cases in the case group and 18,008 cases in the control group were included. The overall meta-analysis results showed that the COX-2 -1195G>A gene in all of the genetic models (A *vs* G: OR = 1.54, 95%CI: 1.04-1.26, P < 0.001; AA/AG *vs* GG: OR = 1.24, 95%CI: 1.06-1.45, P < 0.001; AA *vs* GG/AG: OR = 1.16, 95%CI: 1.04-1.30, P < 0.001; AA *vs* GG: OR = 1.31, 95%CI: 1.08-1.59, P < 0.001; AG *vs* GG: OR = 1.18, 95%CI: 1.04-1.34, P = 0.007) was associated with a high risk of developing gastrointestinal cancers. The results of the publication bias and sensitivity analysis also increased the reliability of the association.

The differences in ethnicity, sources of the control population, environmental factors, and the tumour types can all change the risk of developing

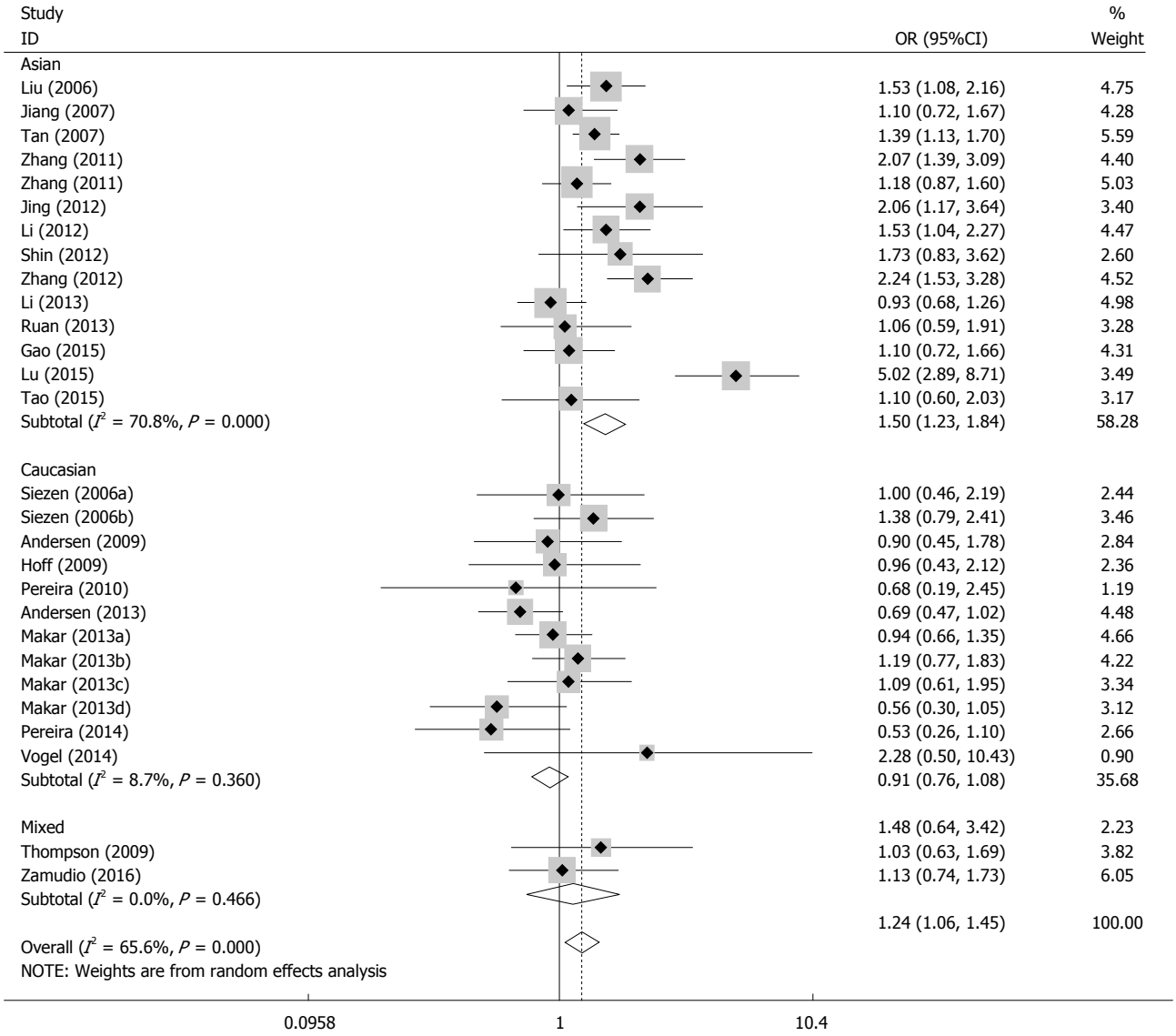

Figure 3 Forest plot of stratified analysis of the COX-2 -1195G>A dominant model (AA/AG *vs* GG) and gastrointestinal cancer susceptibility in different populations.

gastrointestinal diseases through the gene-environment interaction. Therefore, the present study performed subgroup analysis based on the different specific conditions of all of the studies. In the classification of tumour types, the results showed that the COX-2 -1195G>A gene in the AA/AG *vs* GG model had a clear correlation with the gastric cancer susceptibility but did not have a significant correlation with colorectal cancer, suggesting that this genotype might be a very important predisposing factor for gastric cancer. This result was also similar to the reported results in some literature. In addition, the subgroup analysis based on the ethnicity of the study population showed that the mutation frequency of this polymorphism in the Asian gastrointestinal cancer population was higher than that in the Caucasian population in America and Europe, suggesting that the presence of the COX-2 -1195G>A gene polymorphism might greatly increase susceptibility of the Asian population, as represented by Chinese and Korean populations, to gastrointestinal cancers. For the mixed population from America, there were only two reports on its association with gastrointestinal cancers. This result was not sufficient to explain the issue, and studies with a larger sample size are needed to confirm its reliability. The subgroup analysis based on the sources of the control population showed that an increase in the risk of developing gastrointestinal cancers in the population from communities had a statistical correlation with the COX-2 -1195G>A polymorphism; however, this correlation in the population from hospitals was not statistically significant. These results suggested that, in the selection of the sources of controls, the hospital population was restricted by their diseases and medications; therefore, the genotyping results might be affected. Thus, samples from the community population were more representative than those from hospitals and relevant studies should

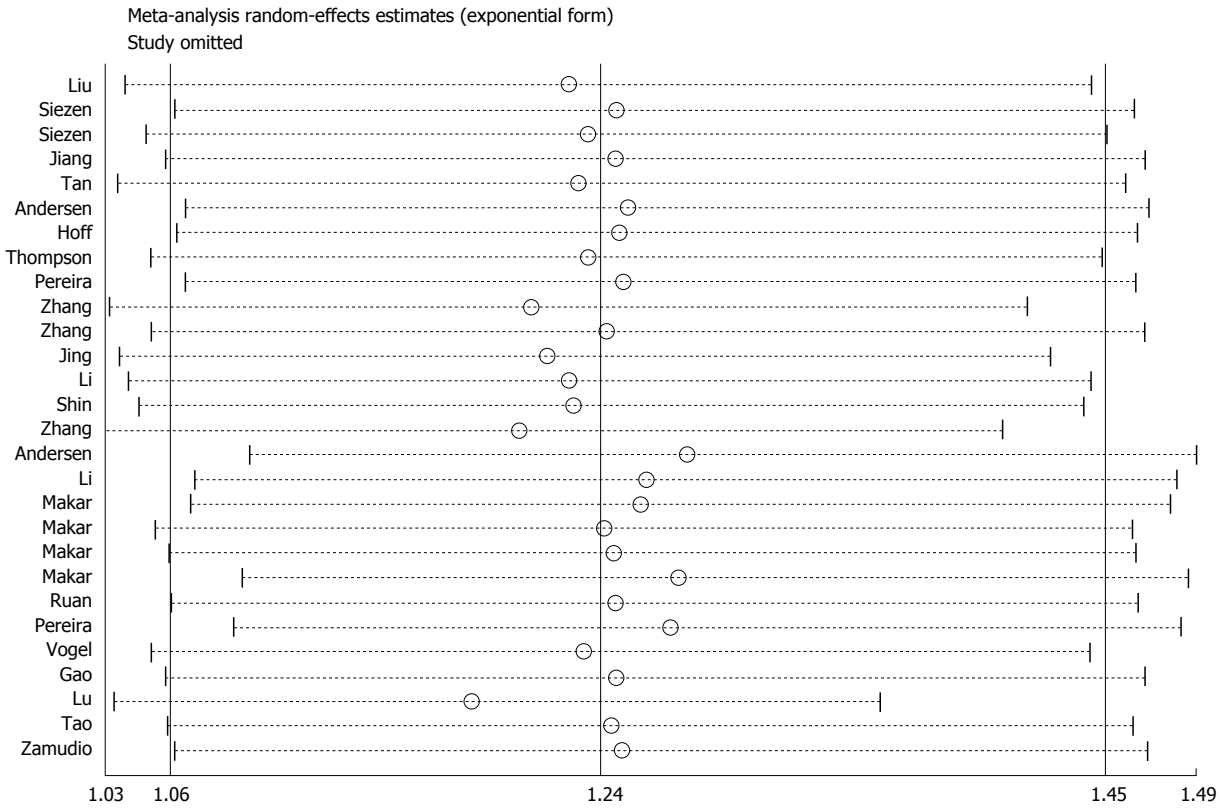

Figure 4 Analysis of the influence of a single study on the total combined OR in the dominant model (AA/AG *vs* GG).

try to select those from the community population as a control group. Furthermore, we also performed subgroup analysis based on genotyping methods and found that the statistical results among subgroups had clear differences. The differences might be because the different detection methods had different theoretical bases. To make the positive rate of our analytic results more real and reliable, we performed FPRP and found that the correlation of the COX-2 -1195G>A polymorphism in the gastric cancer recessive model (FPR*P* = 0.174), the allele model of the Asian population (FPR*P* = 0.069) and the linear model (FPRP) all passed the FPRP test. These results suggested that the correlation of these two aspects had very strong reliability and the authenticity was further confirmed.

The present study had some limitations. First, during overall and subgroup analyses, we found that there was moderate heterogeneity among samples. Although we tried to resolve this issue and used FPRP to increase the reliability of the study results, the exact source of the heterogeneity still could not be completely explained. The present study also revealed that the heterogeneity was not from a single study. The differences in the distribution of the gene polymorphism frequency among ethnic groups and other unknown factors might be the real sources of the heterogeneity. Because gastrointestinal cancers are influenced by many factors, comprehensive study and analysis should be performed in the future by combining these factors, such as diet, living habits, and environmental exposure. Next, due to the restriction of the sample size and disease types in the included literature, we did not retrieve similar literature reports on other gastrointestinal cancers other than gastric cancer and colorectal cancer, and their association with the COX-2 -1195G>A gene polymorphism could not be clarified. Third, the present study is a meta-analysis based on the reported data of the included literature. The unreasonable data in the original studies could not be corrected and possible potential confounding factors, such as age, gender, ethnicity, specific living habits, and smoking and drinking habits, might be present. Fourth, all of the included literature was published in Chinese or English; relevant studies written in other languages may have been missed. Only including Chinese and English literature was also a reason that the sample size was not large enough, which might result in the presence of false-negative results. In addition, this meta-analysis only included published literature, and there are some relevant, important unpublished studies, which might cause a potential publication bias.

In summary, we demonstrate that the AA genotype in the COX-2 -1195G>A gene polymorphism might be an important predisposing factor for gastrointestinal cancers compared to the AG or GG phenotypes, especially for gastric cancer. In addition, compared to the included studies on American and European Caucasian populations, COX-2 -1195G>A increased susceptibility of the Asian population to gastrointestinal

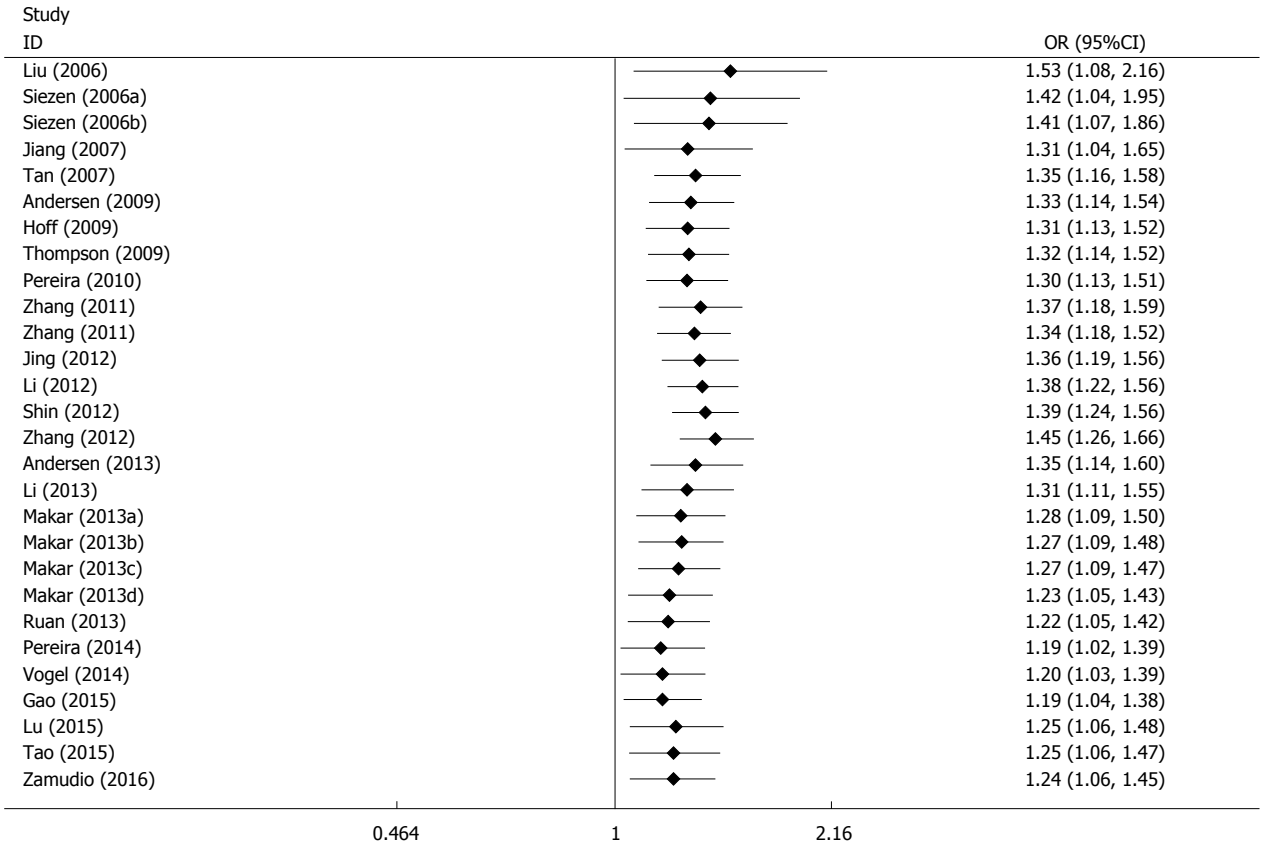

Figure 5 Cumulative meta-analysis of the COX-2 -1195G>A polymorphism and gastrointestinal cancer susceptibility in the dominant model (AA/AG *vs* GG).

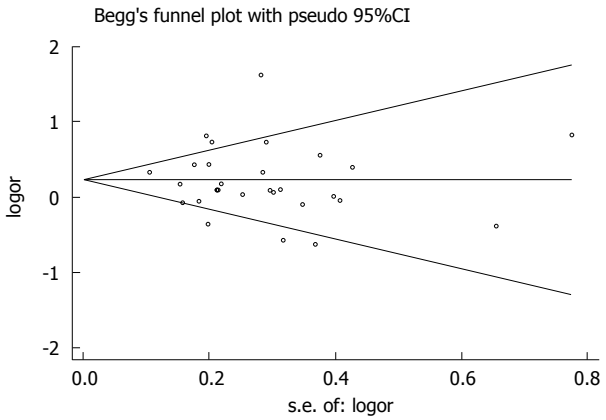

Figure 6 Begg's funnel plot of the publication bias in the COX-2 -1195G>A dominant model (AA/AG *vs* GG).

cancer. In the future, studies with larger sample sizes, more rational design, and more disease types should be performed to validate our conclusion, which can more clearly clarify the association between the COX-2 -1195G>A gene polymorphism and gastrointestinal cancers.

COMMENTS

Background

Cyclooxygenase-2 (COX-2) is closely associated with the development of malignant tumours and is highly expressed in gastric cancer and colorectal cancer cells. Many studies have investigated the association between the COX-2 -1195G>A gene polymorphism and gastrointestinal cancers; however, the results are inconsistent.

Research frontiers

The COX-2 gene is a very important tumour-related gene with multiple SNPs. The expression level of this gene and the function of its encoded protein will be affected by some polymorphic sites, thus increasing or decreasing tumour susceptibility.

Innovations and breakthroughs

In the present study, the authors explored the COX-2 -1195G>A gene polymorphisms associated with susceptibility to gastrointestinal cancers and used an FPRP-based criterion to evaluate whether the study finding was noteworthy.

Applications

This report may present a novel site for the prevention, diagnosis, and molecular targeted therapy of gastric cancer and colorectal cancer.

Terminology

The false positive report probability (FPRP), which is the probability of no true association between a genetic variant and disease given a statistically significant finding, depends not only on the observed *P*-value but also on both the prior probability and the statistical power of the test.

Peer-review

The authors performed a meta-analysis of the association between the COX-2 -1195G>A polymorphism and gastrointestinal cancer risk, which has been extensively investigated.

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