REVIEW

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Correlation of *VEGF* +405C/G Polymorphism with Gastrointestinal Tract Cancers Risk: An Updated Meta-Analysis

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Abstract

Background: The functional polymorphisms of *VEGF* can affect different cellular processes and play a major role in angiogenesis and tumor development. Several case-control studies have explored the association of *VEGF* +405C/G polymorphism with GIT cancer risk, however, the results were inconsistent. Therefore, the meta-analysis was conducted to clarify the association. **Methods:** Based on the inclusion and exclusion criteria, relevant data were extracted from PubMed, Google Scholar, Web of Science and Science Direct. Twenty three studies comprising 5,656 cases and 6,319 healthy controls were included in the present meta-analysis and the data was analysed by using online MetaGenyo software. **Results:** In the present study, no significant association was found in any of the genetic models in overall analysis as well as when data was stratified according to the ethnicity ($p>0.05$). After performing sub-group analysis on the basis of cancer type, significant association was found with increased risk of developing esophageal cancer under allele contrast, recessive, GG vs. CC and GG vs. GC models ($p<0.05$). Under overdominant model, *VEGF* +405C/G polymorphism was significantly associated with decreased risk of developing esophageal cancer ($p=0.017$) and GG vs. GC model showed a significant association with the risk of developing colorectal cancer ($p=0.047$) and pancreatic cancer ($p=0.010$). However, GC vs. CC model showed that *VEGF* +405C/G polymorphism was significantly associated with reduced risk of pancreatic cancer ($p=0.039$). **Conclusion:** The present updated meta-analysis suggested that *VEGF* +405C/G polymorphism may serve as a biomarker for determining an individual's risk of esophageal, colorectal and pancreatic cancer.

Keywords: Meta-analysis- *VEGF* +405C/G polymorphism- gastrointestinal tract cancers- angiogenesis

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Introduction

Cancer is a multifactorial disease and one of the leading cause of mortality worldwide [1]. Gastrointestinal tract (GIT) cancers accounts for more than 25% of all cancer cases [2]. Both environmental and genetic factors influence the susceptibility to different GIT cancers. Ninety percent of the variability in the human genome is due to single nucleotide polymorphisms (SNPs), which have been shown to affect cancer susceptibility by either increasing or decreasing an individual's risk of developing cancer [3]. SNPs in the untranslated region (UTR) may have functional consequences on mRNA stability and expression, as they change the secondary structure and miRNA target sites within the UTRs [4, 5]. The expression of known genes and signaling pathways involved in cancer are altered by these changes.

VEGF, a heparin-binding glycoprotein, plays a crucial role in endothelial cell proliferation and migration, and increases vascular permeability of tumor cells by the process called angiogenesis [6, 7]. Hypoxia-sensitive regulatory elements are found in the 5' and 3' UTRs which contribute to high variability in *VEGF* production among tissues [8, 9]. *VEGF* +405C/G (*VEGF* -634C/G) polymorphism present in 5′ UTR is situated in the MZF1 transcription factor's potential binding site, it affects the translation efficiency of *VEGF*A and is associated with prognosis of many cancers [10]. It also affects the expression at the post-translation level by changing the activity of the internal ribosomal entry site B, and by promoting the initiation of translation at the AUG codon [11].

Many case-control studies have analyzed the effect of *VEGF* +405C/G polymorphism on different GIT cancers in different populations but the results were inconsistent and contradictory (Table 1). This may be due to the small sample size, ethnic differences, and heterogeneity between study samples. This brings forth the importance of meta-analysis, which provides the accurate estimate of genetic effect by pooling the individual study data [12]. A meta-analysis has already been done to find the association between *VEGF* +405C/G polymorphism and

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GIT cancer risk [13] .This meta-analysis included only 11 studies [14-24], however, it did not include all articles, such as those on esophageal cancer [25], oral cancer [26], gastric cancer [27, 28], hepatocellular carcinoma [29], pancreatic cancer [30, 31] and colorectal cancer [32, 33]. The relationship between *VEGF* +405C/G polymorphism and overall cancer risk was analyzed by another meta-analysis on 70 studies [34]. In this meta-analysis, authors included only 17 studies on GIT cancers, however there are additional studies that have reported the role of *VEGF* +405C/G polymorphism in different GIT cancers but were not included in this meta-analysis like on esophageal cancer [25], gastric cancer [28, 35, 36], hepatocellular carcinoma [29], pancreatic cancer [30, 31], colorectal cancer [33]. Furthermore, many case-control studies on different GIT cancers have been published subsequent to these meta-analyses [36-43]. So, an updated meta-analysis that included all the studies that were left out of earlier meta-analysis is needed. Moreover studies where genotypic distribution of controls was deviated from Hardy Weinberg Equilibrium (HWE) were included in both of these meta-analyses [21-24], which may impact the overall analysis.

Therefore, we carried out an up-to-date meta-analysis of all eligible case-control studies to investigate the relationship between *VEGF* +405C/G polymorphism and GIT cancer risk. Finding the functional biomarkers associated with cancer risk may help in the development of drugs as well as valuable insight into the pathophysiology for particular malignancy. We hypothesized that the *VEGF* +405C/G polymorphism might be associated with altered risk of GIT cancers, and a comprehensive meta-analysis will provide a better understanding of its role in different populations.

The present meta-analysis aims

- To determine the overall association between *VEGF* +405C/G polymorphism and GIT cancer risk,
- To analyze the association of *VEGF* +405C/G polymorphism in different ethnic groups and cancer subtypes,
- To assess the heterogeneity, publication bias among the included studies,
- To examine the impact of individual study on the overall analyses by using sensitivity analysis.

In this meta-analysis, we statistically combine data from previously published case-control studies across different populations that investigated the association between the *VEGF* +405C/G polymorphism and GIT cancer risk.

Search Strategy

A comprehensive literature search was conducted by the three authors: SKW (Research Scholar), KG (Associate Professor and Head of Human Genetics Department) and VS (Professor) to identify relevant case-control studies for the present meta-analysis. For this, all the available literature published till March, 2024 on the association of *VEGF* +405C/G polymorphism with gastrointestinal tract (GIT) cancer risk was retrieved from different online databases such as PubMed, Google Scholar, Web of Science and Science Direct. The keywords and terms used to search the relevant articles were: vascular endothelial growth factor, *VEGF* +405C/G polymorphism, *VEGF* +634C/G polymorphism, rs2010963, GIT cancers risk, case-control studies, genetic association studies. We also identified articles by manually searching the references of different articles, reviews and previous meta-analyses. We included articles that were published in English language only. The selection process used was illustrated as a flow diagram (Figure 1).

Inclusion and Exclusion Criteria

Case-control studies that have evaluated the association of *VEGF* +405C/G polymorphism with different GIT cancers with sufficient genotype data to calculate the odds ratio (OR) and 95% CI were included. However, short/brief reports, animal model studies, case-only studies, and the case-controls studies in which genotypic frequencies were deviated from HWE in controls were not included in the present meta-analysis. The characteristics of the studies includes and excluded have been detailed in Table 1.

Materials and Methods

The present meta-analysis was performed following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [44]. The PICO (Participants, Intervention, Comparison, Outcome) criteria was used to design the study questions [45].

Data Extraction and Quality Assessment

Based on the inclusion and exclusion criteria, relevant data were extracted from the individual publication such as: ethnicity of population, number of cases and controls, genotype distribution among cases and controls, HWE p-value, last name of the first author and year of publication. The New-Castle Ottawa Scale (NOS) was used to evaluate the quality of eligible studies [46]. NOS is based on star scoring system and comprised three parameters:

a. Selection (Is the case defined adequately?, Representativeness of cases, Selection of controls and Definition of controls)

b. Comparability (Comparability of cases and controls on the basis of age, gender, ethnicity etc.)

c. Exposure (Ascertainment of exposure, Same method of ascertainment for cases and controls and Non-Response Rate).

Each publication can receive up to 9 stars and publications that received 5 or more stars are regarded as of high quality. Publications included in the present meta-analysis were of high quality, as indicated by the overall score, which ranged from 6 to 8 (Table 2).

Statistical Analysis

Data analyses in the present meta-analysis were performed by using online statistical software, MetaGenyo [47]. Pooled odds ratio (OR) and 95% confidence intervals (CI) were used to evaluate the association between *VEGF* +405C/G polymorphism and GIT cancer risk.

Table 1. Characteristics of the Published Case-Control Studies on *VEGF* +405C/G Polymorphism in Gastrointestinal Tract Cancers

Cancer	Ethnicity	Country	Cases/Controls	Source of control	Genotype Distribution						HWE in control p-value	Reference	Study included in the meta analysis
					Cases			Controls					
					CC	GC	GG	CC	GC	GG			
Oral	Caucasian	Serbia	114/126	-	11	55	48	16	49	61	0.22	[26]	Yes
	Caucasian	Germany	80/40	-	20	23	37	10	12	18	**0.017**	[23]	No
Esophageal	Asian	India	231/233	PB	17	98	116	20	110	103	0.21	[43]	Yes
	Asian	India	150/141	HB	9	57	84	17	66	58	0.788	[25]	Yes
	Caucasian	USA	308/546	HB	29	124	155	62	251	233	0.65	[17]	Yes
Gastric	Asian	India	180/360	-	16	64	100	28	160	172	0.26	[39]	Yes
	Asian	Korea	151/367	-	28	70	53	59	178	130	0.88	[38]	Yes
	Mixed	Brazil	177/260	HB	27	82	68	29	117	114	0.901	[36]	Yes
	Asian	China	401/403	PB	66	209	126	65	189	149	0.69	[28]	Yes
	Asian	China	150/150	HB	29	47	74	30	44	76	**0.000016**	[24]	No
	Caucasian	USA	171/100	HB	30	72	69	21	28	51	**0.00012**	[22]	No
	Middle East	Oman	130/130	PB	22	59	49	14	54	62	0.66	[20]	Yes
	Asian	China	540/561	PB	92	287	161	97	278	186	0.69	[27]	Yes
	Caucasian	Greece	100/100	PB	19	40	41	9	39	52	0.66	[35]	No
	Caucasian	Greece	100/100	PB	19	40	41	9	39	52	0.66	[15]	Yes
	Asian	Korea	413/413	PB	31	253	129	84	223	106	0.09	[14]	Yes
Hepatocellular	Asian	China	476/526	HB	82	232	162	78	248	200	0.93	[37]	Yes
	Asian	China	92/99	PB	18	40	34	13	52	34	0.31	[29]	Yes
Pancreatic	Asian	India	80/87	HB	10	28	42	9	49	29	0.07	[31]	Yes
	Caucasian	Poland	85/50	-	47	25	13	8	30	12	0.14	[30]	Yes
Colorectal	Asian	Indonesia	40/40	-	5	24	11	12	19	9	0.77	[42]	Yes
	Middle East	Turkey	40/53	PB	8	21	11	14	17	22	**0.01**	[41]	No
	Middle East	Iran	264/344	HB	35	103	126	45	159	140	0.98	[40]	Yes
	Caucasian	Greece	224/263	PB	34	92	98	49	126	88	0.74	[33]	Yes
	Caucasian	Sweden	302/336	PB	37	130	135	32	137	167	0.61	[32]	Yes
	Caucasian	Greece	312/362	HB	59	125	128	76	141	145	**0.00026**	[21]	No
	Caucasian	Italy	301/91	PB	48	135	118	15	46	30	0.71	[19]	Yes
	Asian	Korea	465/413	PB	106	193	166	84	223	106	0.09	[18]	Yes
	Caucasian	Austria	432/430	PB	47	192	193	43	195	192	0.52	[16]	Yes

Significant p-values are highlighted in bold

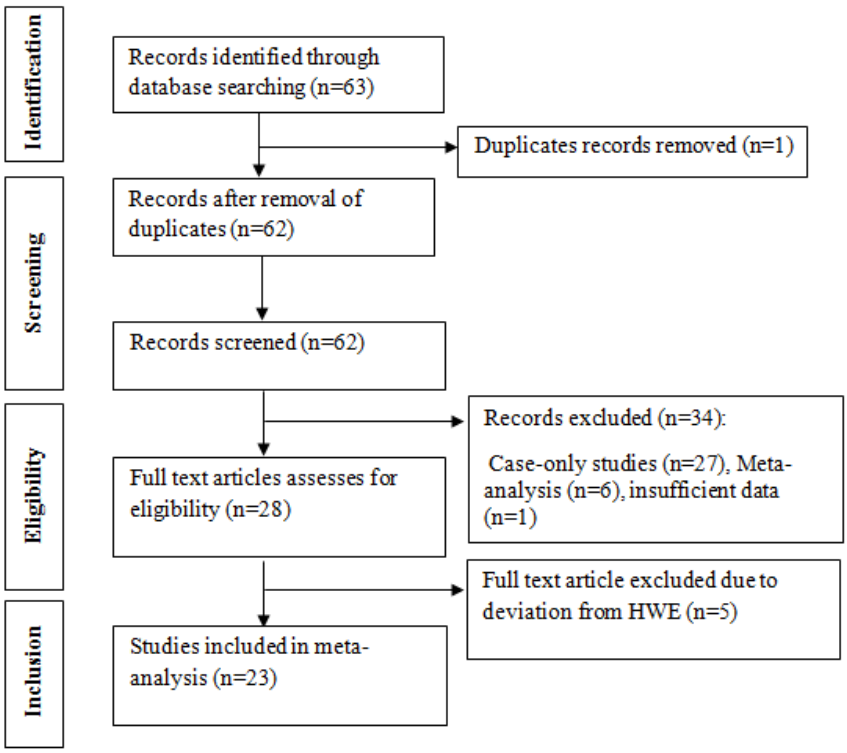


Figure 1. Flow Diagram Showing the Selection Process for Meta-Analysis by Using PRISMA Guidelines

Table 2. The Newcastle-Ottawa Scale (NOS) for the Assessment of Case-Control Studies Included in the Meta-Analysis

Selection				Comparability	Exposure			Total Score	Reference
Case defined adequately	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases/ controls	Ascertainment of exposure	Same selection method of ascertainment of cases-controls	Same Non response rate in cases/ controls		
*	*	*	*	**	*	*	-	8	[43]
*	*	-	*	**	*	*	*	8	[25]
*	*	-	*	**	*	*	-	7	[17]
*	*	-	*	**	*	*	-	7	[26]
*	*	-	*	**	*	*	-	7	[39]
*	*	-	*	**	*	*	-	7	[38]
*	*	-	*	**	*	*	-	7	[36]
*	*	*	*	**	*	*	-	8	[28]
*	*	*	*	**	*	*	-	8	[20]
*	*	*	*	**	*	*	*	8	[27]
*	*	*	*	**	*	*	*	8	[15]
*	*	*	*	**	*	*	-	8	[14]
*	*	-	*	**	*	*	-	7	[37]
*	*	*	*	**	*	*	-	8	[29]
*	*	-	*	**	*	*	-	7	[31]
*	*	-	*	**	*	*	-	7	[30]
*	*	-	*	**	*	*	-	7	[42]
*	*	-	*	**	*	*	-	7	[40]
*	*	*	*	**	*	*	-	8	[33]
*	*	*	*	**	*	*	-	8	[32]
*	*	*	*	-	*	*	-	6	[19]
*	*	*	*	-	*	*	-	6	[18]
*	*	*	*	**	*	*	-	8	[16]

The association was assessed under different genetic models. $p<0.05$ was considered as statistically significant. Cochran's Q-test was used to assess the heterogeneity (I^2) among studies. $p<0.05$ or $I^2 > 50\%$ indicates the presence of heterogeneity and in this case random effect model was selected (Dersimonian-Laird method). If $p\geq0.05$ and $I^2 <50\%$, fixed effect model was used (Mantel-Haenszel method). Publication bias was assessed by Begg's funnel plot [48] and by Egger's linear regression test [49], $p<0.05$ was considered as significant publication bias. In order to find probable outliers, a sensitivity analysis was also carried out by excluding each study at a time and then re-evaluating the results.

Results

Twenty three studies comprising 5656 cases and 6319 healthy controls were included in the present meta-analysis. The characteristics of the included studies have been detailed in Table 1. Out of 23 studies, 7 studies were on colorectal cancer, 3 studies were on esophageal cancer, 8 studies were on gastric cancer, 2 studies were on hepatocellular cancer, 2 studies were on pancreatic cancer and one study was on oral cancer. From 23 studies, 12 studies have evaluated the association of *VEGF* +405C/G polymorphism with the risk of developing GIT cancers in Asian population, 8 studies in Caucasian population, 2 studies with Middle East population and one study with mixed ethnicity.

Pooled Analysis

Analysis was done by using all genetic models in order to find the association between *VEGF* +405C/G polymorphism and GIT cancer risk. Overall no significant association was found in any of the genetic models ($p>0.05$). Stratification analysis on the basis of ethnicity, also revealed no significant association between *VEGF* +405C/G polymorphism and GIT cancer risk in any of the genetic model ($p>0.05$) (Table 3). After performing sub-group analysis on the basis of cancer type, we found a significant association of *VEGF* +405C/G polymorphism with increased risk of developing esophageal cancer under allele contrast (OR=1.29; 95%CI, 1.11-1.51; p=0.001), recessive (OR=1.41; 95%CI, 1.15-1.72; p=0.0008), GG vs. CC (OR=1.56; 95%CI, 1.09-2.24; p=0.016), and GG vs. GC (OR=1.37; 95%CI, 1.11-1.69; p=0.0029) models. Under over dominant model, *VEGF* +405C/G polymorphism was significantly associated with decreased risk of developing esophageal cancer (OR=0.78; 95%CI, 0.64-0.96; p=0.017). GG vs. GC model showed a significant association of *VEGF* +405C/G polymorphism with the risk of developing colorectal cancer (OR=1.26; 95%CI, 1.00-1.58; p=0.047) and pancreatic cancer (OR=2.03; 95%CI, 1.18-3.50; p=0.010). However, GC vs. CC model showed that *VEGF* +405C/G polymorphism was significantly associated with reduced risk of pancreatic cancer (OR=0.26; 95%CI, 0.07-0.94; p=0.039) (Table 4) (Figure 2).

Heterogeneity Analysis

In overall analysis, substantial heterogeneity was observed in all genetic association models ($I^2 >50\%$), so random effect model was used. However, after stratification on basis of ethnicity and cancer type, some did ($I^2 >50\%$), and some did not ($I^2 <50\%$), exhibit heterogeneity (Tables 3, 4).

Publication Bias

No overall publication bias was observed as assessed by symmetrical Begg's funnel plots (Figure 3) and by Egger's test ($p>0.05$). Subgroup analysis on the basis of cancer type revealed publication bias in colorectal cancer under GC vs. CC model (Tables 3, 4).

Sensitivity Analysis

Sensitivity analysis was carried out by removing one study at a time from the pooled analysis in order to examine the impact of individual study on the results. Results demonstrated that removal of any study had no observable impact on the overall analysis (Figure 4).

Discussion

Gastrointestinal tract cancers are among the most common type of cancers which are caused by the combined effect of various factors like environment, genetic and epigenetic modifications. Genetic factors are the most significant contributing factor in the development of cancer. SNPs are the genetic markers that are widely used in the cancer research and identification of SNPs that are significantly associated with cancer risk will be useful for developing therapeutic approaches [50]. The functional polymorphisms of *VEGF* can affect different cellular processes and play a major role in angiogenesis and tumor development [51]. Genetic polymorphisms in *VEGF* may alter *VEGF* production and activity, resulting in variations in tumor development among individuals. *VEGF* +405C/G polymorphism was found to be associated with decreased *VEGF* protein expression and plays a role in the development of tumors [10, 52]. Many case-control studies have detected the effect of *VEGF* +405C/G polymorphism on different GIT cancers however, the results were inconclusive or controversial. So, a comprehensive meta-analysis was conducted to evaluate the association of *VEGF* +405C/G polymorphism with GIT cancer susceptibility. No significant association was found between *VEGF* +405C/G polymorphism and GIT cancers risk in the present meta-analysis. However, stratification analysis on the basis of cancer type showed that *VEGF* +405C/G polymorphism was associated with increased risk of developing colorectal cancer under GG vs. GC model. A meta-analysis conducted on GIT cancers involving 2862 cases and 3028 controls reported a significant association of *VEGF* +405C/G polymorphism with colorectal cancer risk under recessive model [13]. No significant association of *VEGF* +405C/G polymorphism with cancer risk was reported in other meta-analysis [53]. In meta-analysis of 70 case-control studies, including 25,245 cases 28,219 controls reported a significant association with increased cancer risk under the CG vs. GG, dominant, and allele contrast models in African population. An increased risk of urogenital cancers was

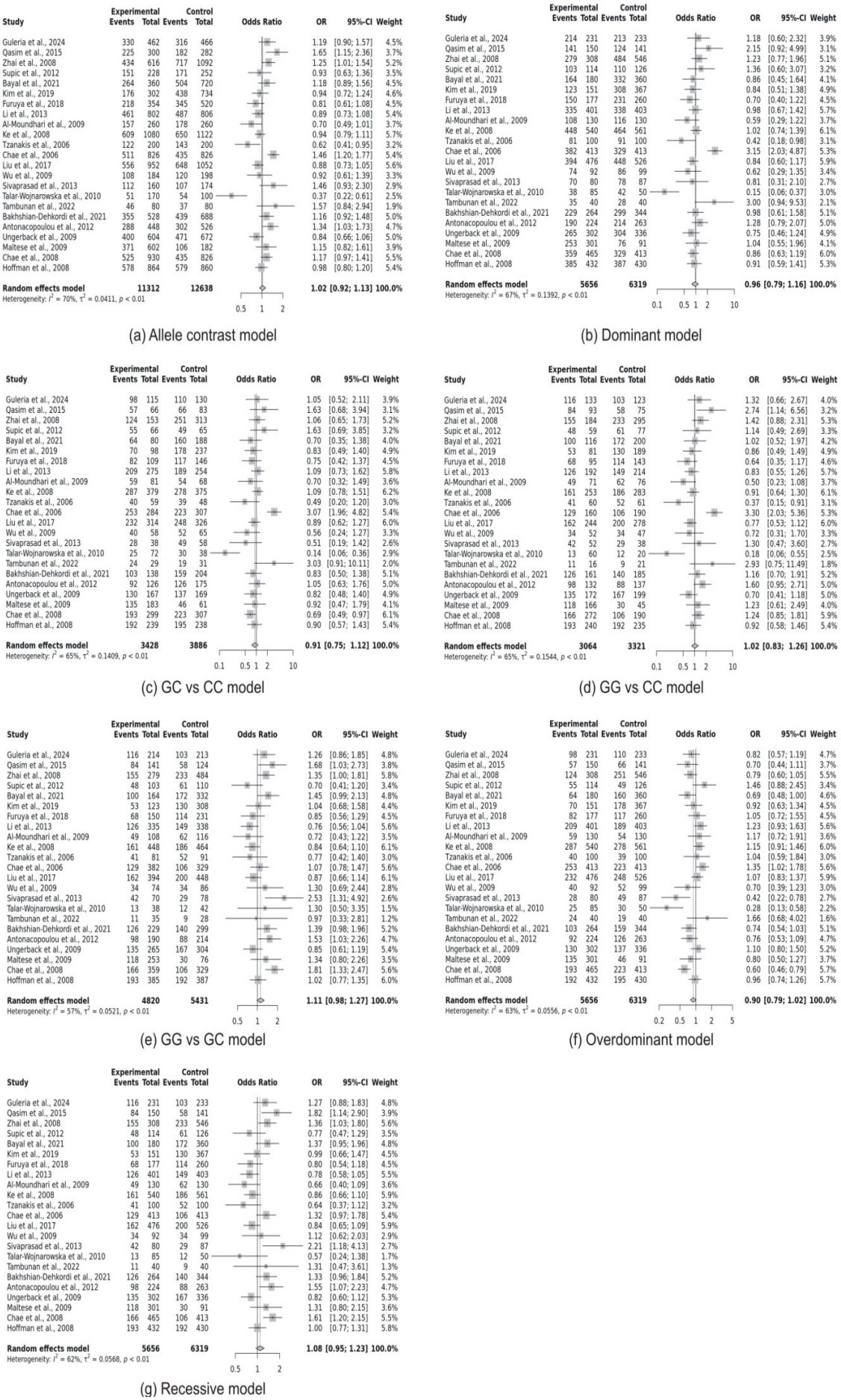


Figure 2. Forest Plots to Identify the Relationship between *VEGF* +405C/G Polymorphism and GIT Cancer Risk Using Different Genetic Models

Table 3. Association of *VEGF* +405C/G Polymorphism with Gastrointestinal Cancer Risk According to Ethnicity

Model	Ethnicity	Number of studies	Test of association				Test of heterogeneity		Publication bias
			OR	95% CI	p-value	Model	p-value	I^2	Egger's test p-value
Allele contrast (G vs. C)	Overall	23	1.02	(0.92- 1.13)	0.67	Random	0	0.7	0.62
	Asian	12	1.11	(0.98- 1.26)	0.09	Random	0.0007	0.66	0.17
	Caucasian	8	0.92	(0.74- 1.14)	0.44	Random	0	0.78	0.09
	Middle East	2	0.92	(0.56- 1.51)	0.74	Random	0.02	0.81	NA
	Mixed	1	0.81	(0.61- 1.08)	0.15	Fixed	NA	NA	NA
Recessive model (GG vs. GC+CC)	Overall	23	1.08	(0.95- 1.23)	0.22	Random	0	0.62	0.87
	Asian	12	1.18	(0.98- 1.42)	0.08	Random	0.0006	0.66	0.12
	Caucasian	8	1.01	(0.81- 1.27)	0.89	Random	0.017	0.59	0.29
	Middle East	2	0.96	(0.49- 1.90)	0.92	Random	0.021	0.81	NA
	Mixed	1	0.79	(0.54- 1.18)	0.26	Fixed	NA	NA	NA
Dominant model (GG+GC vs. CC)	Overall	23	0.96	(0.78- 1.16)	0.65	Random	0	0.67	0.58
	Asian	12	1.11	(0.85- 1.46)	0.43	Random	0.0001	0.7	0.48
	Caucasian	8	0.8	(0.54- 1.19)	0.28	Random	0.0009	0.71	0.12
	Middle East	2	0.84	(0.57- 1.25)	0.4	Fixed	0.248	0.25	NA
	Mixed	1	0.69	(0.39- 1.22)	0.21	Fixed	NA	NA	NA
Overdominant (GC vs. CC +GG)	Overall	23	0.89	(0.79- 1.02)	0.09	Random	0	0.63	0.17
	Asian	12	0.89	(0.74- 1.08)	0.25	Random	0.0001	0.72	0.24
	Caucasian	8	0.87	(0.70- 1.09)	0.23	Random	0.016	0.59	0.46
	Middle East	2	0.85	(0.65- 1.12)	0.26	Fixed	0.132	0.56	NA
	Mixed	1	1.05	(0.72- 1.55)	0.78	Fixed	NA	NA	NA
GG vs. CC	Overall	23	1.01	(0.83- 1.25)	0.86	Random	0	0.65	0.75
	Asian	12	1.2	(0.89- 1.60)	0.21	Random	0.0003	0.68	0.28
	Caucasian	8	0.87	(0.59- 1.29)	0.5	Random	0.0032	0.67	0.1
	Middle East	2	0.8	(0.36- 1.81)	0.59	Random	0.075	0.68	NA
	Mixed	1	0.64	(0.35- 1.17)	0.15	Fixed	NA	NA	NA
GG vs. GC	Overall	23	1.11	(0.98- 1.27)	0.1	Random	0.0004	0.57	0.46
	Asian	12	1.18	(0.97- 1.44)	0.1	Random	0.0004	0.68	0.15
	Caucasian	8	1.09	(0.95- 1.25)	0.23	Fixed	0.11	0.4	0.75

Table 3. Continued

Model	Ethnicity	Number of studies	Test of association			Test of heterogeneity			Publication bias
			OR	95% CI	p-value	Model	p-value	I^2	Egger's test p-value
GG vs. GC	Middle East	2	1.03	(0.55- 1.95)	0.92	Random	0.042	0.76	NA
	Mixed	1	0.85	(0.56- 1.28)	0.44	Fixed	NA	NA	NA
	Overall	23	0.91	(0.75- 1.12)	0.37	Random	0	0.65	0.41
GC vs. CC	Asian	12	1.04	(0.77- 1.39)	0.79	Random	0.0001	0.72	0.86
	Caucasian	8	0.79	(0.54- 1.15)	0.21	Random	0.006	0.65	0.19
	Middle East	2	0.79	(0.52- 1.20)	0.27	Fixed	0.699	0	NA
	Mixed	1	0.75	(0.41- 1.36)	0.35	Fixed	NA	NA	NA

reported under CG vs. GG, CC vs. GG, CC vs. CG, dominant, recessive and allele contrast models. Reduced risk of osteosarcoma was observed under the CC vs. CG model, while an increased risk of osteosarcoma was identified under the overdominant model. A significant association with reduced thyroid cancer risk was reported under the CC vs. GG, recessive, and allele contrast models [34].

Previous studies on the correlation between *VEGF* +405C/G polymorphism and different GIT cancers reported varied results. The GG genotype of *VEGF* +405C/G polymorphism was significantly associated with increased risk of esophageal cancer in patients from Kashmir, North-West India [25]. Similarly, in the present study significant association was found with increased risk of esophageal cancer under allele contrast, recessive, GG vs. CC and GG vs. GC models when data was stratified on the basis of cancer type. No association of *VEGF* +405C/G polymorphism with esophageal cancer risk was reported in Caucasian population [17]. A significant association of *VEGF* +405C/G polymorphism with increased risk of colorectal cancer under GG vs. GC model was observed in the present study. Our findings were different from some previously published studies. CG genotype, combined CG+CC genotypes and C allele of *VEGF* +405C/G polymorphism were associated with decreased risk of colorectal cancer in Italian [19], Korean [18] and Caucasian [33] patients respectively. There was no association of *VEGF* +405C/G polymorphism with colorectal cancer risk in Caucasian [16], Swedish population [32].

Present meta-analysis has many strengths: In the present meta-analysis substantially larger number of studies was included than the previous meta-analysis on *VEGF* +405C/G polymorphism with GIT cancers susceptibility, thus will enhance the statistical power of the study and provide the more precise results. Present meta-analysis included studies in which genotype distribution in controls were in HWE. Moreover, high quality studies as assessed by New-Castle Ottawa scale were included in the present meta-analysis. Additionally, we conducted a sensitivity analysis, which demonstrated that individual study had no impact on the overall outcome.

There are some limitations of the present meta-analysis: Significant heterogeneity was observed, which may influence the interpretation of results. Subgroup analysis on the basis of cancer type showed publication bias in colorectal cancer under GC vs. CC model.

In conclusion, the present updated meta-analysis observed a significant association between *VEGF* +405C/G polymorphism and GIT cancers (esophageal cancer, colorectal cancer, pancreatic cancer). While the present study indicate that *VEGF* +405C/G polymorphism may play a role in susceptibility to GIT cancer, the observed heterogeneity highlights the need for further research to identify the underlying mechanisms and also the interactions with environmental factors.

Author Contribution Statement

KG and VS designed the study. SKW and KG

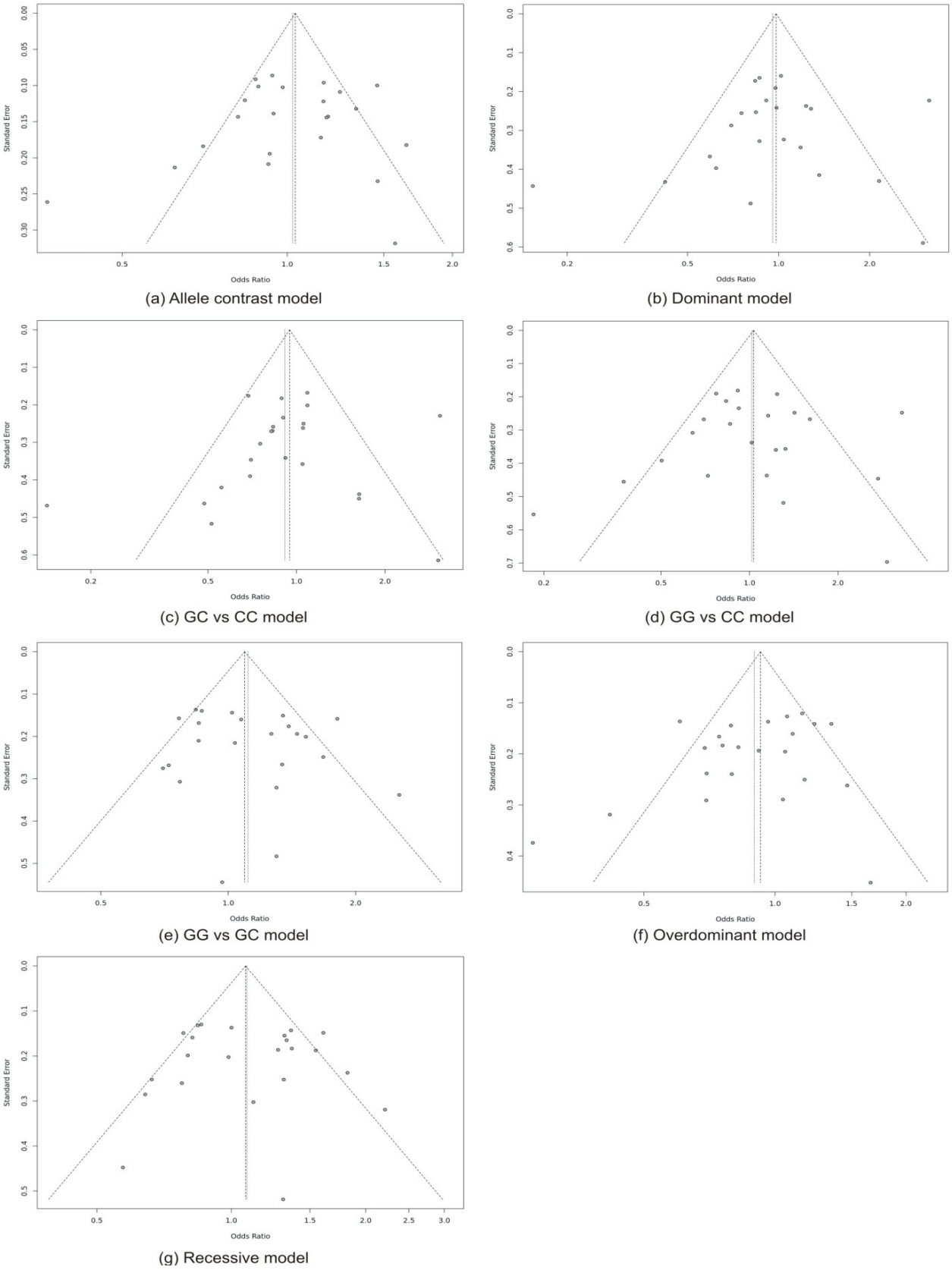


Figure 3. Funnel Plots for Detection of Publication Bias Using Different Genetic Models

Table 4. Association of *VEGF* +405C/G Polymorphism with Gastrointestinal Cancer Risk According to Cancer Type

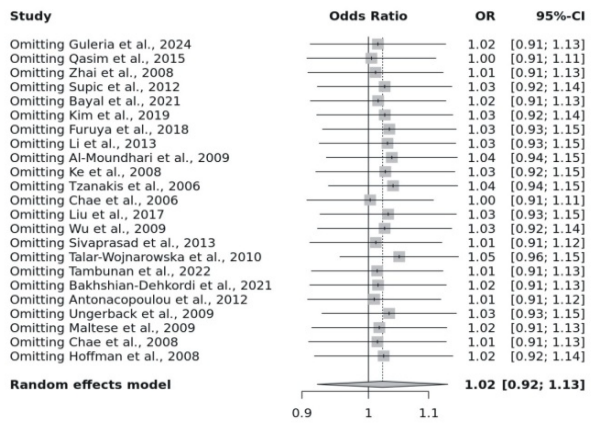
Model	Cancer type	Number of studies	Test of association				Test of heterogeneity		Publication bias
			OR	95% CI	p-value	Model	p-value	I^2	Egger's test p-value
Allele contrast (G vs. C)	Overall	23	1.02	(0.92- 1.13)	0.67	Random	0	0.7	0.62
	Colorectal	7	1.09	(0.99- 1.19)	0.07	Fixed	0.107	0.42	0.39
	Esophageal	3	1.29	(1.11- 1.51)	**0.001**	Fixed	0.326	0.11	0.47
	Gastric	8	0.94	(0.78- 1.12)	0.49	Random	0.0002	0.75	0.22
	Hepatocellular	2	0.88	(0.75- 1.04)	0.14	Fixed	0.813	0	NA
	Oral	1	0.93	(0.63- 1.36)	0.7	Fixed	NA	NA	NA
	Pancreatic	2	0.73	(0.19- 2.86)	0.65	Random	0.0001	0.94	NA
Recessive model (GG vs. GC+CC)	Overall	23	1.08	(0.95- 1.23)	0.22	Random	0	0.62	0.87
	Colorectal	7	1.22	(0.99- 1.51)	0.059	Random	0.032	0.56	0.7
	Esophageal	3	1.41	(1.15- 1.72)	**0.0008**	Fixed	0.46	0	0.5
	Gastric	8	0.92	(0.76- 1.11)	0.39	Random	0.032	0.54	0.49
	Hepatocellular	2	0.88	(0.69- 1.12)	0.29	Fixed	0.384	0	NA
	Oral	1	0.77	(0.46- 1.29)	0.32	Fixed	NA	NA	NA
	Pancreatic	2	1.17	(0.31- 4.38)	0.82	Random	0.014	0.83	NA
Dominant model (GG+GC vs. CC)	Overall	23	0.96	(0.78- 1.16)	0.65	Random	0	0.67	0.58
	Colorectal	7	0.96	(0.81- 1.15)	0.7	Fixed	0.36	0.08	0.06
	Esophageal	3	1.34	(0.94- 1.89)	0.09	Fixed	0.48	0	0.47
	Gastric	8	0.94	(0.63- 1.39)	0.75	Random	0	0.79	0.3
	Hepatocellular	2	0.79	(0.58- 1.09)	0.15	Fixed	0.49	0	NA
	Oral	1	1.36	(0.60- 3.07)	0.46	Fixed	NA	NA	NA
	Pancreatic	2	0.35	(0.07- 1.77)	0.2	Random	0.012	0.84	NA
Overdominant (GC vs. GG +CC)	Overall	23	0.89	(0.79- 1.02)	0.09	Random	0	0.63	0.17
	Colorectal	7	0.84	(0.69- 1.02)	0.075	Random	0.048	0.52	0.38
	Esophageal	3	0.78	(0.64- 0.96)	**0.017**	Fixed	0.851	0	0.54
	Gastric	8	1.1	(0.98- 1.24)	0.106	Fixed	0.19	0.3	0.29
	Hepatocellular	2	0.99	(0.79- 1.25)	0.971	Fixed	0.18	0.45	NA
	Oral	1	1.46	(0.88- 2.45)	0.144	Fixed	NA	NA	NA
	Pancreatic	2	0.35	(0.22- 0.57)	1.67	Fixed	0.407	0	NA

Significant p-values are highlighted in bold

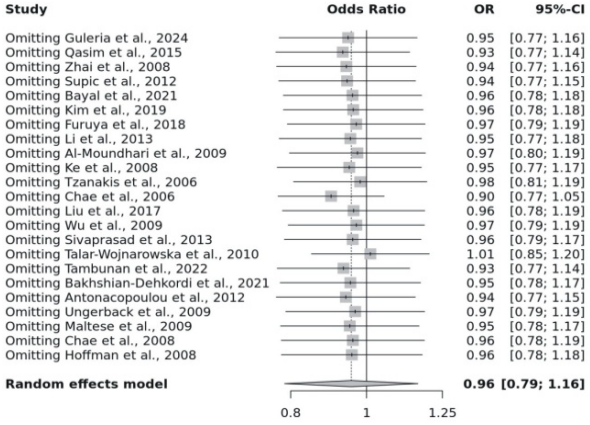
Table 4. Continued

Model	Cancer type	Number of studies	Test of association			Test of heterogeneity			Publication bias
			OR	95% CI	p-value	Model	p-value	I^2	Egger's test p-value
GG vs. CC	Overall	23	1.02	(0.83- 1.25)	0.86	Random	0	0.65	0.75
	Colorectal	7	1.13	(0.93- 1.38)	0.22	Fixed	0.25	0.24	0.4
	Esophageal	3	1.56	(1.09- 2.24)	**0.016**	Fixed	0.38	0	0.49
	Gastric	8	0.89	(0.58- 1.36)	0.58	Random	0	0.79	0.39
	Hepatocellular	2	0.76	(0.54- 1.07)	0.12	Fixed	0.89	0	NA
	Oral	1	1.14	(0.49- 2.69)	0.76	Fixed	NA	NA	NA
	Pancreatic	2	0.49	(0.07- 3.36)	0.47	Random	0.01	0.85	NA
GG vs. GC	Overall	23	1.11	(0.98- 1.27)	0.1	Random	0.0004	0.57	0.46
	Colorectal	7	1.26	(1.00- 1.58)	**0.047**	Random	0.027	0.58	0.97
	Esophageal	3	1.37	(1.11- 1.69)	**0.0029**	Fixed	0.65	0	0.52
	Gastric	8	0.92	(0.81- 1.05)	0.23	Fixed	0.19	0.29	0.94
	Hepatocellular	2	0.92	(0.72- 1.19)	0.53	Fixed	0.24	0.26	NA
	Oral	1	0.7	(0.41- 1.20)	0.19	Fixed	NA	NA	NA
	Pancreatic	2	2.03	(1.18- 3.50)	**0.01**	Fixed	0.26	0.22	NA
GC vs. CC	Overall	23	0.91	(0.75- 1.12)	0.37	Random	0	0.65	0.41
	Colorectal	7	0.85	(0.70- 1.03)	0.1	Fixed	0.36	0.08	0.005
	Esophageal	3	1.13	(0.79- 1.64)	0.49	Fixed	0.68	0	0.42
	Gastric	8	0.98	(0.67- 1.44)	0.93	Random	0.0001	0.76	0.22
	Hepatocellular	2	0.82	(0.59- 1.15)	0.25	Fixed	0.304	0.05	NA
	Oral	1	1.63	(0.69- 3.85)	0.26	Fixed	NA	NA	NA
	Pancreatic	2	0.26	(0.07- 0.94)	**0.039**	Random	0.06	0.71	NA

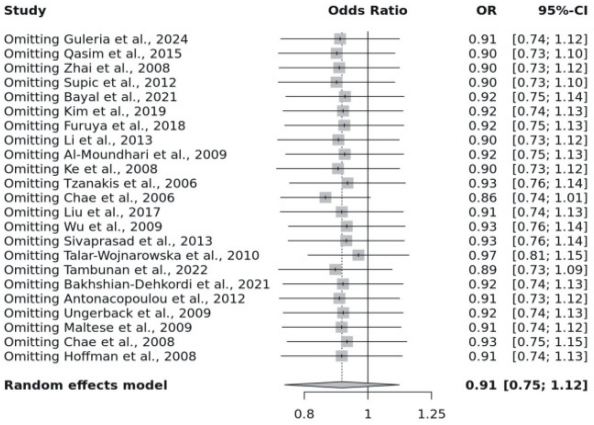
Significant p-values are highlighted in bold



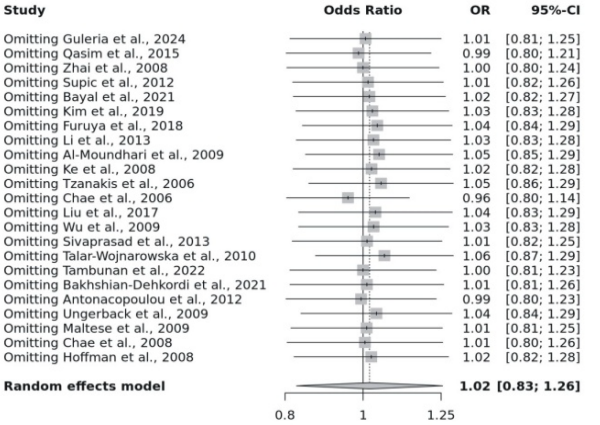
(a) Allele Contrast model



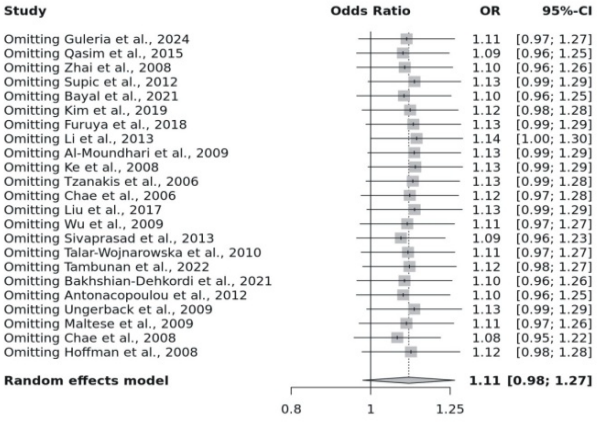
(b) Dominant model



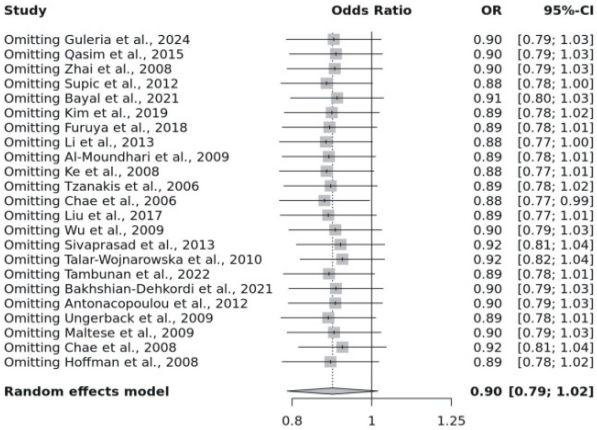
(c) GC vs. CC model



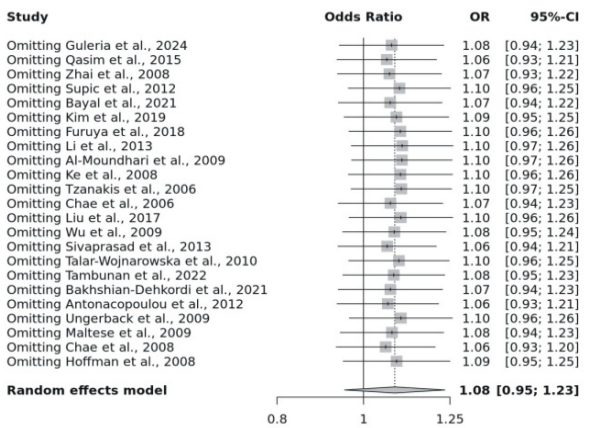
(d) GG vs. CC model



(e) GG vs. GC model



(f) Overdominant model



(e) Recessive model

Figure 4. Sensitivity Analysis by Using Different Genetic Model

prepared the manuscript. All authors read and approved the manuscript.

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Availability of data

All data has been included in the manuscript.

Conflict of interest

All authors declare that they have no conflict of interest.

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