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Association between insulin-like growth factor 1 gene rs35767 polymorphisms and cancer risk
A meta-analysis

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Abstract

Background: Several studies have been conducted on the relationship between insulin-like growth factor 1 gene (IGF-1) rs35767 polymorphisms and cancer risk, but the results are conflicting. We performed a meta-analysis to investigate the relationship between IGF-1 rs35767 polymorphisms and cancer risk.

Methods: Eight studies (5 for IGF-1 rs35767 C>T and 3 for IGF-1 rs35767 A>G) with a total of 11,257 cases and 16,213 controls were included. The studies were about the association between IGF-1 rs35767 polymorphisms and cancer risk and acquired by searching PubMed, Embase, and Web of Science databases for articles published before January 20, 2019. STATA software was used to analyze the data and identify the strength of the association by using pooled-odds ratios (ORs) with corresponding 95% confidence intervals (CIs).

Results: No significant associations were observed between the IGF-1 rs35767 C>T polymorphism and cancer risk in all genetic models. However, the IGF-1 rs35767 A>G polymorphism was significantly associated with increased cancer risk for all genetic models (G vs A: OR = 1.087, 95% CI: 1.036–1.141, P_h = .338; GG vs AA: OR = 1.272, 95% CI: 1.121–1.442, P_h = .359; AG vs AA: OR = 1.187, 95% CI: 1.043–1.351, P_h = .695; AG+GG vs AA: OR = 1.187, 95% CI: 1.043–1.351, P_h = .695; GG vs AA+AG: OR = 1.086, 95% CI: 1.025–1.151, P_h = .275). Begg and Egger tests showed that no publication bias existed.

Conclusion: Our findings indicated that the IGF-1 rs35767 A>G polymorphism might be a risk factor for cancer development. However, additional well-designed studies with sample sizes larger than ours need to be conducted in the future to verify our findings.

Abbreviations: ALL = acute lymphoblastic leukemia, BC = breast cancer, CC = colorectal cancer, 95% CI = 95% confidence interval, HWE = Hardy–Weinberg equilibrium, IGF = insulin-like growth factor, OR = odds ratio, PC = prostste cancer, SNP = single-nucleotide polymorphism, TGCT = testicular germ-cell tumors.

Keywords: insulin-like growth factor 1 gene rs35767, polymorphisms, cancer, meta-analysis

1. Introduction

Cancer has become a major global public health problem due to the global increase in the incidence and mortality of this disease. Approximately 18.1 million new cancer cases and 9.6 million cancer deaths were recorded in 2018.[1] The causes of cancer vary and have not been elucidated completely, but the consensus is that the endless proliferation of cells is central to the carcinogenic process, which is closely related to many signals that control cell growth and death.[2] Therefore, the hormone that regulates cell proliferation has become a hot topic in research on cancer etiology.

Compared with lifestyle and the environment, genetics accounts for a larger proportion of the causation of cancer. Genetic research on the etiology of cancer has recently become a popular research field; single-nucleotide polymorphisms (SNPs) are markers of many complex diseases and the most common and effective type of genetic variations studied in association with disease susceptibility.[3] Many studies have shown that gene polymorphism is associated with cancer risk.

The insulin-like growth factor (IGF) signaling pathway regulates and controls cell proliferation and is essential for the growth and development of mammalians. IGFs have the properties of tissue growth factors, but they also possess additional well-recognized functions similar to those of hormones that regulate growth and energy metabolism at the organism level.[4,5] IGF-1 is a member of the IGF family. IGF-1 is bound principally by the type 1 IGF receptor, which plays a crucial role in cell proliferation, differentiation, and apoptosis, and exerts a recognized effect on tumor growth.[6–8] IGF-1 is also a potent mitogen, and through this pathway, the genes that

encode such proteins may be involved in cell proliferation.[9] Numerous factors affect the serum levels of IGF-1, and genetic predisposition is one of the most important ones.

Several studies have investigated the association between IGF-1 rs35767 polymorphisms and cancer risk.[10–17] However, the results of these studies are inconsistent. Therefore, we performed a comprehensive meta-analysis to obtain a precise estimation of the relationship between IGF-1 rs35767 polymorphisms and cancer risk.

2. Materials and methods

2.1. Publication search

To identify all articles that examined the association between IGF-1 rs35767 polymorphisms and cancer, we searched PubMed, Embase, and Web of Science databases for relevant articles (published before January 20, 2019) by using the following keywords: "IGF1 or IGF-1 or insulin-like growth factor 1," "polymorphism or genetic variant or SNPs," and "cancer or tumour or carcinoma." The references of the retrieved articles were also screened.

2.2. Inclusion and exclusion criteria

Studies included in this meta-analysis needed to satisfy the following criteria:

1. Investigates the relationship between IGF-1 polymorphisms and cancer risk

2. Has a case–control or cohort study design
3. Published in English
4. Contains sufficient genotype data

The exclusion criteria were as follows:

1. Lacking in case–control or cohort study design
2. Meta-analyses or reviews
3. Case reports, comments, reviews, or animal studies
4. Insufficient genotype data

2.3. Data extraction

Data extraction from eligible studies was independently performed by 2 authors. The extracted data included the 1st author, year of publication, country, type of cancer, number of cases and controls, genotyping methods, allele or genotype frequency, and Hardy–Weinberg equilibrium (HWE) in the control group. Any disagreements were resolved by a consensus achieved with a 3rd author.

2.4. Statistical analysis

The odds ratio (OR) and its 95% confidence interval (CI) were used to assess the strength of the association between IGF-1 polymorphisms and cancer risk in 5 genetic models, namely, allele, homozygote, heterozygote, dominant, and recessive. The significance of the combined OR was determined via a Z test ($P < .05$ suggests a significant OR). A test of heterogeneity was
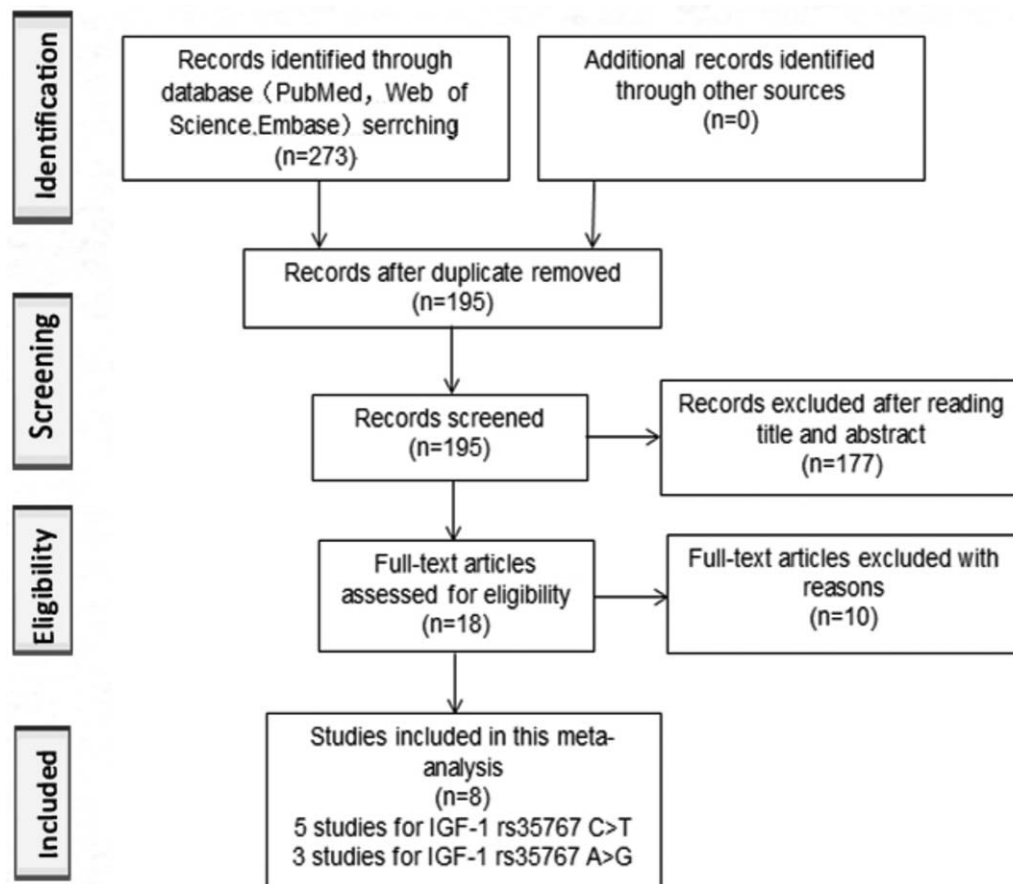

Figure 1. The flow diagram of included/excluded studies. IGF-1 = insulin-like growth factor 1 gene.

conducted using Cochran Q test and Higgins I^2 statistic. I^2 values >50% indicated heterogeneity among studies. A random-effects model was applied when heterogeneity was observed ($I^2 > 50\%$, $P < .05$). Otherwise, the fixed-effects model was used.[18,19] A Chi-squared test was performed to calculate HWE in the controls. The stability of the results was evaluated via a sensitivity analysis, that is, a study was omitted from each round of meta-analysis to reflect the effect of a single data set on the pooled results. Then, Begg and Egger tests were performed to evaluate the publication bias of the eligible literature.[20–22] All statistical analyses were performed with STATA software (Version 12.0; Stata Corporation, College Station, TX), and $P < .05$ was considered statistically significant.

2.5. Ethical consideration

Ethical approval was not required for this study.

3. Results

3.1. Literature search and characteristics of eligible studies

The study selection procedure is shown in Figure 1. A total of 273 publications from PubMed, Embase, and Web of Science databases were reviewed. After the 1st scan, 78 duplicated records were rejected. Among the remaining 195 potentially relevant articles, 177 were considered improper after their titles

Table 1

Characteristics of studies included in IGF-1 rs35767 polymorphism and cancer risk.

Study	Year	Country	Cancer	Genotyping method	Case/control	P_{HWE}	SNP
Feik	2010	Austria	CC	Tqaman	121/1730	0.446(Y)	C>T
Qian	2014	China	PC	Tqaman	664/702	0.213(Y)	C>T
Mao	2017	China	Osteosarcoma	Tqaman	173/175	0.990(Y)	C>T
Pechlivanis	2007	Germany	CC	Tqaman	643/563	0.872(Y)	C>T
Canzian	2006	Caucasian	BC	Tqaman	772/1510	0.064(Y)	C>T
Chia	2007	America	TGCT	Tqaman	574/696	0.718(Y)	A>G
Ollberding	2012	America	CC	Tqaman	1953/2587	0.001(N)	A>G
Patel	2008	America	BC	Tqaman	6357/8250	<0.001(N)	A>G

BC = breast cancer, CC = colorectal cancer, HWE = Hardy–Weinberg equilibrium, IGF-1 = insulin-like growth factor 1, PC = prostste cancer, TGCT = testicular germ-cell tumors.

Table 2

Genotype distributions of insulin-like growth factor 1 rs35767 C>T polymorphism of enrolled studies.

Study	Case			Control			Case		Control	
	CC	CT	TT	CC	CT	TT	C	T	C	T
Feik	79	40	2	1208	470	52	198	44	2886	574
Qian	242	323	99	304	327	71	807	521	935	469
Mao	63	86	24	66	83	26	212	134	215	135
Pechlivanis	440	185	18	391	157	15	1065	221	939	187
Canzian	549	201	22	1016	432	62	1229	245	2464	556

Table 3

Genotype distributions of insulin-like growth factor 1 rs35767 A>G polymorphism of enrolled studies.

Study	Case			Control			Case		Control	
	AA	AG	GG	AA	AG	GG	A	G	A	G
Chia	16	151	407	21	192	483	183	965	234	1158
Ollberding	173	768	1012	301	1053	1233	1114	2792	1655	3519
Patel	251	1876	4230	378	2468	5359	2378	10336	3224	13186

Table 4

Results of the meta-analysis on insulin-like growth factor 1 rs35767 C>T polymorphism and cancer risk.

Genetic model	Type of model	Heterogeneity		Odds ratio				Publication bias	
		I^2, %	P_h	OR	95% CI	Z test	P_{OR}	P_{Begg}	P_{Egger}
T vs C	Random	71.6	.007	1.046	0.870–1.256	0.48	.634	1.000	.861
TT vs CC	Random	65.6	.020	1.019	0.638–1.626	0.08	.938	.624	.220
CT vs CC	Fixed	43.6	.131	1.042	0.926–1.172	0.69	.491	.624	.490
TT+CT vs CC	Random	63.1	.028	1.047	0.879–1.311	0.70	.486	.624	.670
TT vs CT+CC	Random	56.4	.057	0.997	0.669–1.486	0.01	.989	.624	.172

Table 5

Results of the meta-analysis on insulin-like growth factor 1 rs35767 A>G polymorphism and cancer risk.

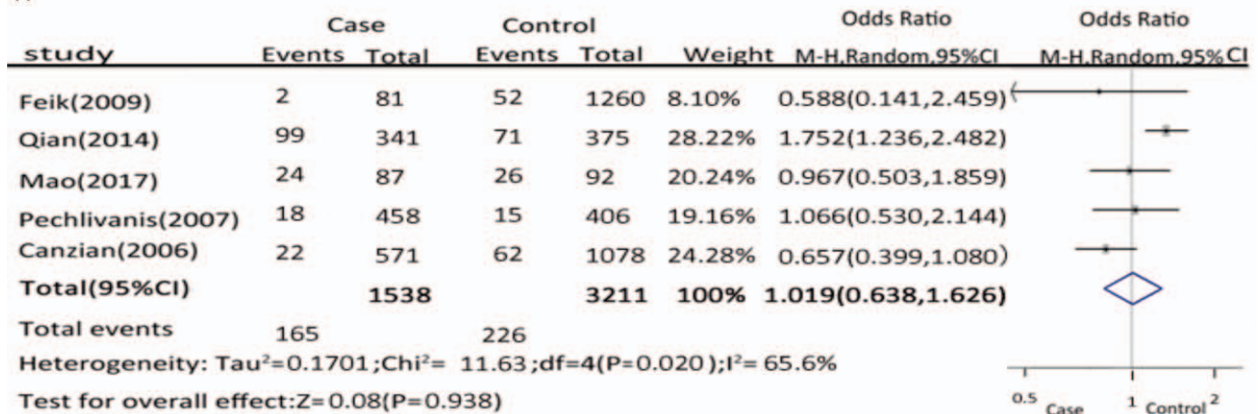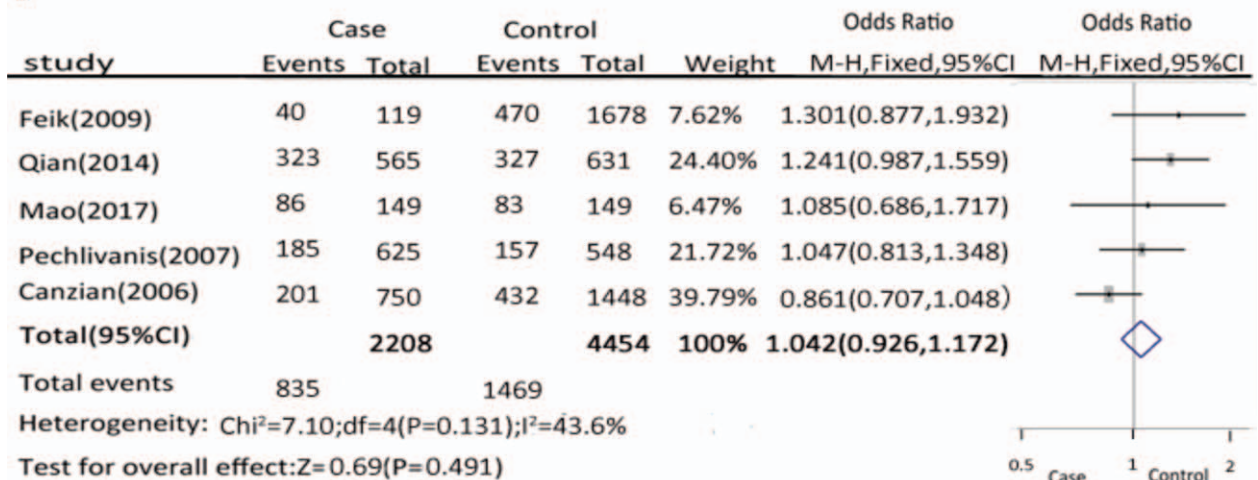| Genetic model	Tylpe of model	Heterogeneity		Odds ratio				Publication bias	
		I^2, %	P_h	OR	95% CI	Z test	P_{OR}	P_{Begg}	P_{Egger}
G vs A	Fixed	42.4	.338	1.087	1.036–1.141	3.41	.001	.602	.668
GG vs AA	Fixed	2.10	.359	1.272	1.121–1.442	3.74	.000	.602	.447
AG vs AA	Fixed	0.00	.695	1.187	1.043–1.351	2.59	.010	.602	.352
AG+GG vs AA	Fixed	0.00	.508	1.240	1.096–1.402	3.41	.001	.602	.393
GG vs AA+AG	Fixed	22.6	.275	1.086	1.025–1.151	2.80	.005	.602	.767
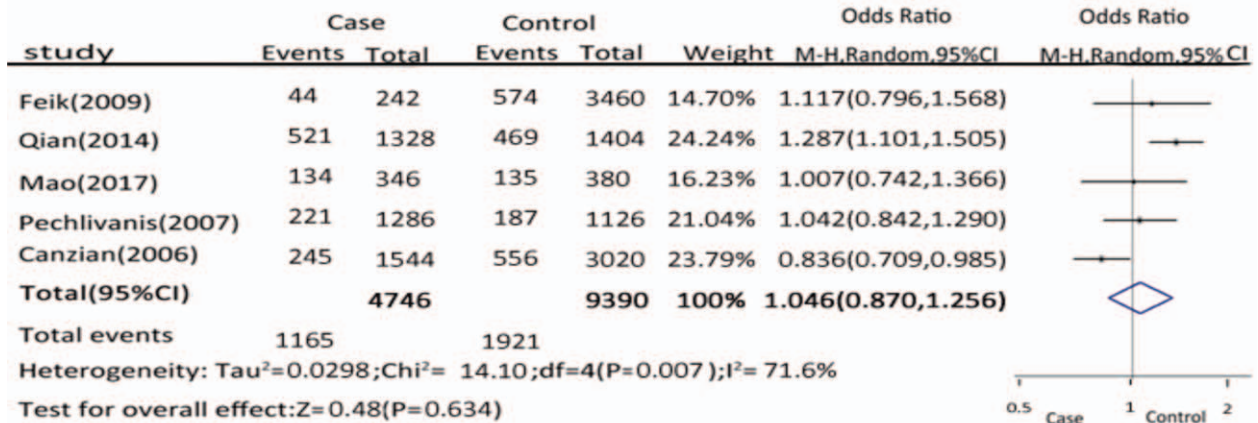
Figure 2. Forest plots in the meta-analysis of the association between the IGF-1 polymorphism (rs35767 C>T) and cancer risk. (A) T vs C. (B) TT vs CC. (C) CT vs CC. (D) TT+CT vs CC. (E) TT vs CT+CC. CI = confidence interval.

and abstracts were read. Amongst the remaining 18 records for full-text assessment, 10 unrelated articles were eliminated in accordance with the predetermined inclusion and exclusion criteria. Ultimately, 8 studies (5 for rs35767 C>T and 3 for rs35767 A>G) with 11,257 cases and 16,213 controls were included in this meta-analysis. The types of cancer included in these studies were colorectal, prostate, and breast cancers; testicular germ-cell tumors; and osteosarcoma. The important characteristics of the selected articles are systematically listed in Table 1. Genotype distributions of IGF-1 rs35767 C>T and IGF-1 rs35767 A>G polymorphism of enrolled studies are showed in Tables 2 and 3 separately.

3.2. Meta-analysis

The results of the meta-analysis are shown in Tables 4 and 5. In addition to the heterozygote model, 4 other genetic models of IGF-1 rs35767 C>T satisfied the criteria for significant heterogeneity, and the random-effects model was used for the analysis. The results revealed no significant associations between the IGF-1 rs35767 C>T polymorphism and cancer risk for all genetic models (T vs C: OR=1.046, 95% CI: 0.870–1.256, P_h=.007; TT vs CC: OR=1.019, 95% CI: 0.638–1.626,

P_h=.020; CT vs CC: OR=0.1.042, 95% CI: 0.926–1.172, P_h=0.131; TT+CT vs CC: OR=1.047, 95% CI: 0.0879–1.311, P_h=0.028; TT vs CT+CC: OR=0.997, 95% CI: 0.669–1.486, P_h=0.057) (Fig. 2). However, fixed-effects models were used for the 5 genetic models of IGF-1 rs35767 A>G. The results suggested that the IGF-1 rs35767 A>G polymorphism was significantly associated with increased cancer risk for all genetic models (G vs A: OR=1.087, 95% CI: 1.036–1.141, P_h=.338; GG vs AA: OR=1.272, 95% CI: 1.121–1.442, P_h=.359; AG vs AA: OR=1.187, 95% CI: 1.043–1.351, P_h=.695; AG+GG vs AA: OR=1.187, 95% CI: 1.043–1.351, P_h=.695; GG vs AA+AG: OR=1.086, 95% CI: 1.025–1.151, P_h=.275) (Fig. 3).

3.3. Sensitivity analysis and publication bias

Sensitivity was evaluated by deleting each study 1 at a time. The result showed that no individual study significantly affected the pooled OR, suggesting the stability of this meta-analysis. The sensitivity analysis of the association between the IGF-1 rs35767 A>G polymorphism and cancer risk is shown in Figure 4.

Begg and Egger tests were performed to determine the publication biases of the studies, as shown in Figure 5. The results are presented in Tables 4 and 5. No statistical evidence of
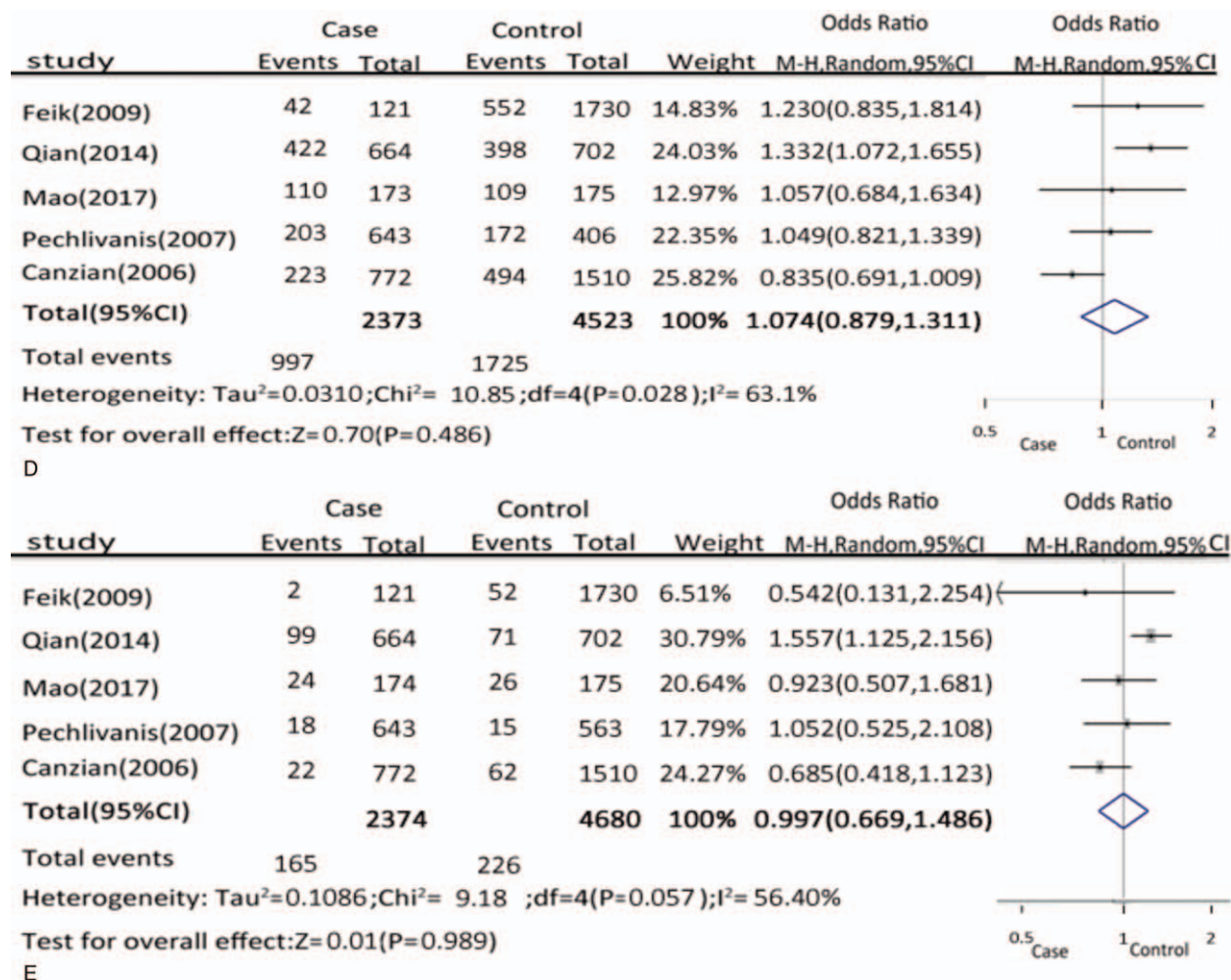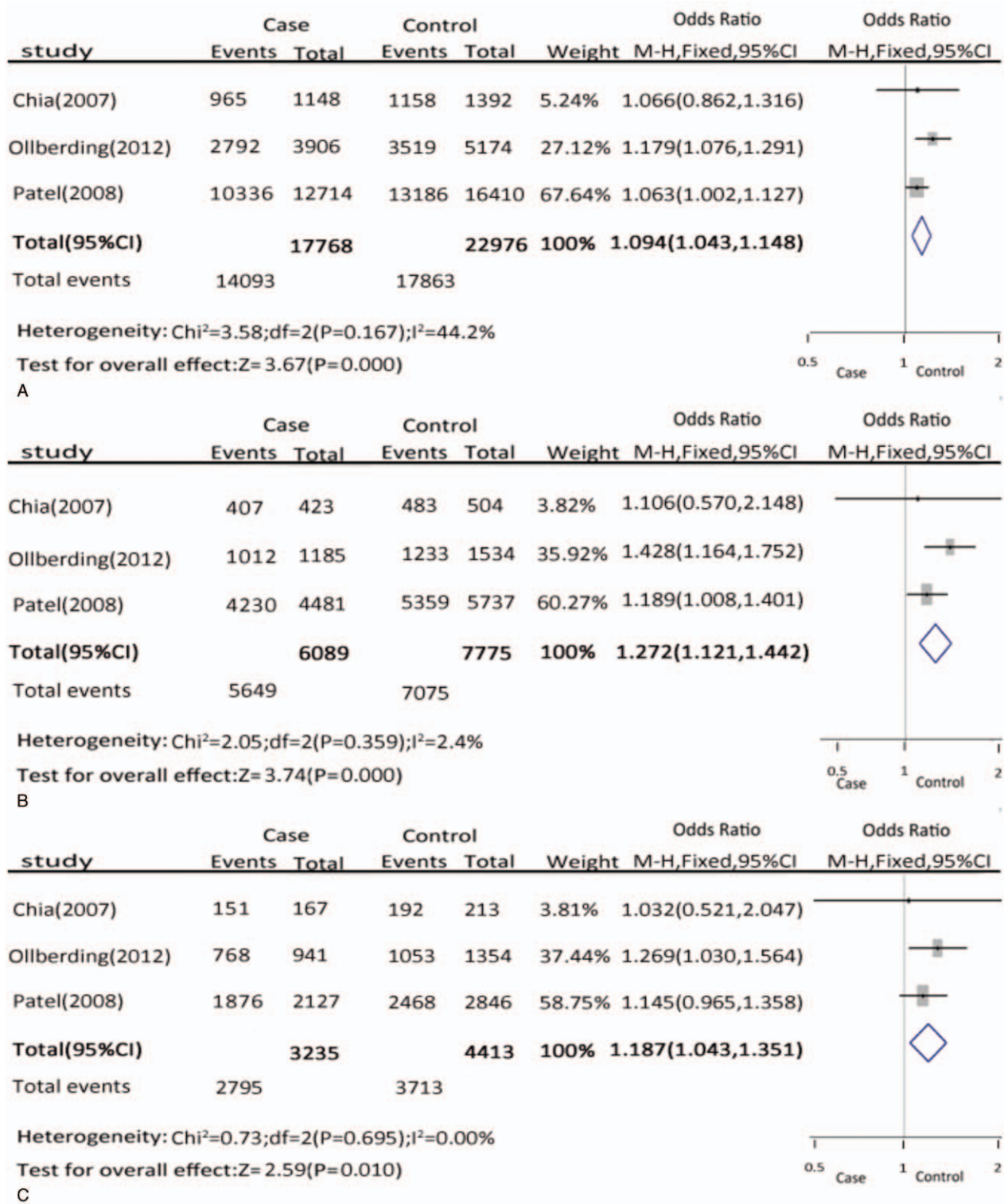

Figure 2. Continued.

Figure 3. Forest plots in the meta-analysis of the association between the insulin-like growth factor 1 gene polymorphism (rs35767 A>G) and cancer risk. (A) G vs A. (B) GG vs AA. (C) AG vs AA. (D) AG+GG vs AA. (E) GG vs AA+AG.
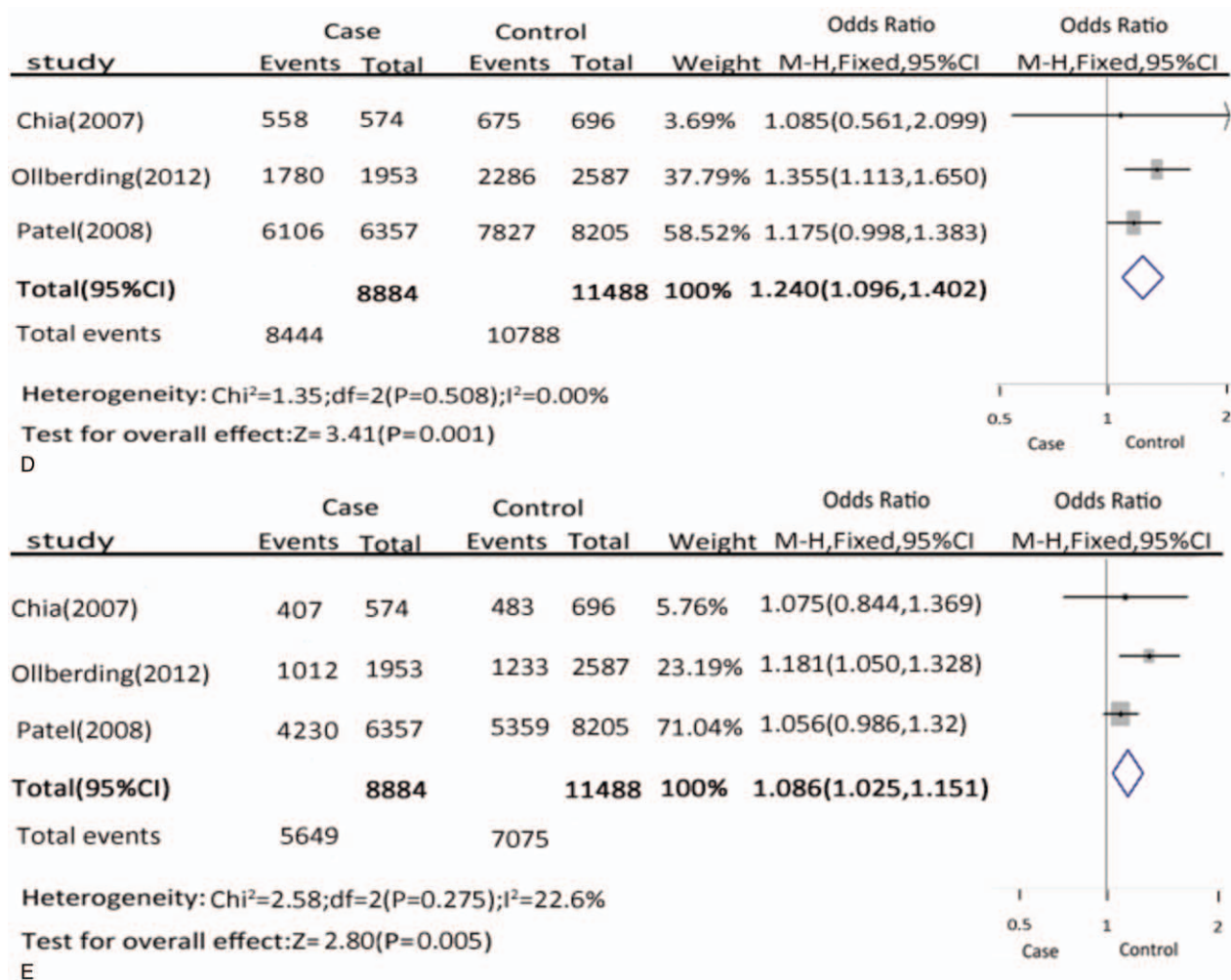
study	Case Events	Total	Control Events	Total	Weight	Odds Ratio M-H,Fixed,95%CI	Odds Ratio M-H,Fixed,95%CI
Chia(2007)	558	574	675	696	3.69%	1.085(0.561,2.099)	
Ollberding(2012)	1780	1953	2286	2587	37.79%	1.355(1.113,1.650)	
Patel(2008)	6106	6357	7827	8205	58.52%	1.175(0.998,1.383)	
Total(95%CI)		8884		11488	100%	1.240(1.096,1.402)	
Total events	8444		10788				

Heterogeneity: Chi²=1.35;df=2(P=0.508);I²=0.00%

Test for overall effect:Z= 3.41(P=0.001)

D

study	Case Events	Total	Control Events	Total	Weight	Odds Ratio M-H,Fixed,95%CI	Odds Ratio M-H,Fixed,95%CI
Chia(2007)	407	574	483	696	5.76%	1.075(0.844,1.369)	
Ollberding(2012)	1012	1953	1233	2587	23.19%	1.181(1.050,1.328)	
Patel(2008)	4230	6357	5359	8205	71.04%	1.056(0.986,1.32)	
Total(95%CI)		8884		11488	100%	1.086(1.025,1.151)	
Total events	5649		7075				

Heterogeneity: Chi²=2.58;df=2(P=0.275);I²=22.6%

Test for overall effect:Z= 2.80(P=0.005)

E

Figure 3. Continued

publication bias was observed in all of the genetic models for IGF-1 rs35767 C>T and IGF-1 rs35767 A>G.

## 4. Discussion

The SNP is a single-nucleotide variation at the genomic level that appears in coding or noncoding sequences.[23] SNP analysis is useful in genomic DNA screening. Exploring the association between genes and diseases is a hot topic because susceptibility genes can affect biologic processes and provide linkages during the investigation of complex diseases, such as cancer.[24] Many SNPs are associated with cancer susceptibility and may thus serve as biomarkers for clinical diagnosis. Understanding of the relationship between genes and cancer can provide a basis for the clinical diagnosis and treatment of cancer. Several IGF-1 SNPs, including rs1520220, rs6214, rs6220, and rs5742612, are associated with cancer susceptibility. Rs35767 SNPs are located in the promoter region of the IGF-1 gene, which is significantly associated with increased susceptibility to childhood acute lymphoblastic leukemia.[25]

The IGF-1 is a potent mitogen that plays a crucial role in metastatic and antiapoptotic functions in many cancers.[9,26]

Changes in the expression of IGF-1 may cause unlimited cell proliferation and division, which in turn may result in cancers because cancers could be produced from an unusual accelerated rate of proliferation.[27] Several studies have suggested that elevated serum levels of IGF-1 increase the risk of acquiring colorectal, prostate, and breast cancer.[28–39] The mature IGF-1 polypeptide is encoded by exons 3 and 4 of the IGF-1 gene, which comprises 6 exons.[40] At the biologic level, IGF-1 is produced by the liver mainly in response to growth hormone stimulation. IGF-1 is also produced in an autocrine and paracrine manner. At the cellular level, IGF-1 combines with the IGF-1 receptor under the influence of IGF-binding proteins then via the RAS–mitogen-activated protein kinase signaling pathway to promote cell proliferation.[41,42] IGF-1 can also serve as an effective antiapoptotic molecule by activating the phosphatidylinositol 3-kinase-AKT pathway to slow down apoptosis.[5,43,44] For both reasons, it may be related to the occurrence and development of cancer.

A series of studies have investigated the association between IGF-1 rs35767 polymorphisms and cancer, but their results are conflicting. To date, no robust evidence on this association is available. With the limited sample size of individual studies,
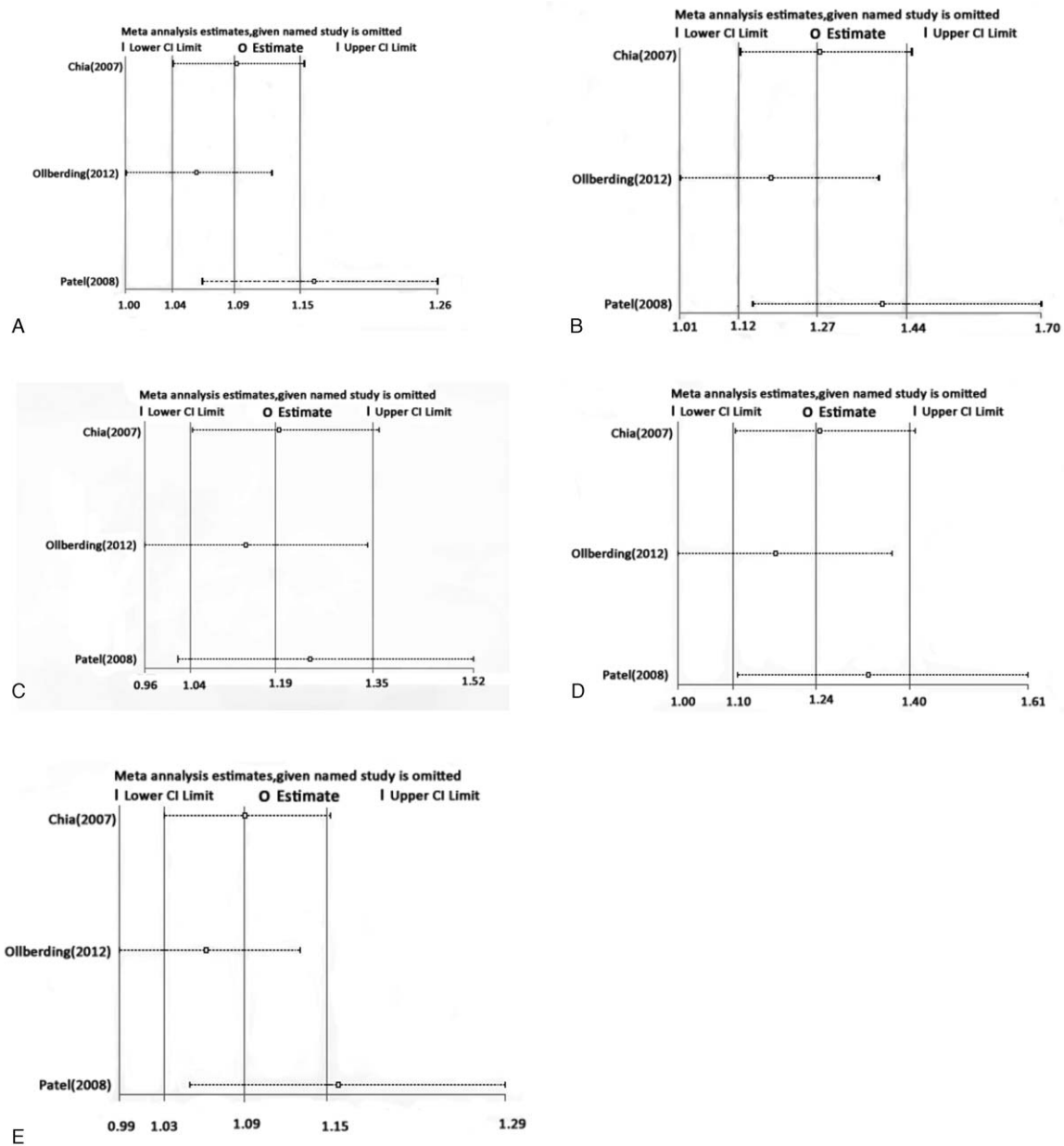
Figure 4. Sensitivity analysis of the meta-analysis of the association between the insulin-like growth factor 1 gene polymorphism (rs35767 A>G) and cancer risk. (A) G vs A. (B) GG vs AA. (C) AG vs AA. (D) AG+GG vs AA. (E) GG vs AA+AG.

drawing a convincing conclusion is difficult because of low statistical validity. A systematic review and meta-analysis can overcome this drawback.[45] We performed this meta-analysis to explore the association between IGF-1 rs35767 polymorphisms and cancer risk.

To our knowledge, this meta-analysis is the 1st to assess the association between IGF-1 rs35767 polymorphisms and cancer risk. In this meta-analysis, we systematically searched for literature on IGF-1 SNPs and cancer in three important databases (PubMed, Embase, and Web of Science). Eight case–control studies were included (5 for IGF-1 rs35767 C>T and 3 for IGF-1 rs35767 A>G). The results showed no significant associations between the IGF-1 rs35767 C>T polymorphism and cancer risk

for all the genetic models. However, the IGF-1 rs35767 A>G polymorphism was significantly associated with increased cancer risk for all the genetic models. Sensitivity analysis showed that no individual study significantly affected the pooled OR, suggesting the stability of this meta-analysis. Begg and Egger tests were performed to determine the publication biases of the studies. No statistical evidence of publication bias was observed in all of the genetic models for IGF-1 rs35767 C>T and rs35767 A>G.

The results of this meta-analysis should be interpreted with caution because of several limitations. Firstly, the number of included studies was small, and all data were from case–control studies. The obtained information may not be enough to estimate the association between IGF-I rs35767 polymorphisms and
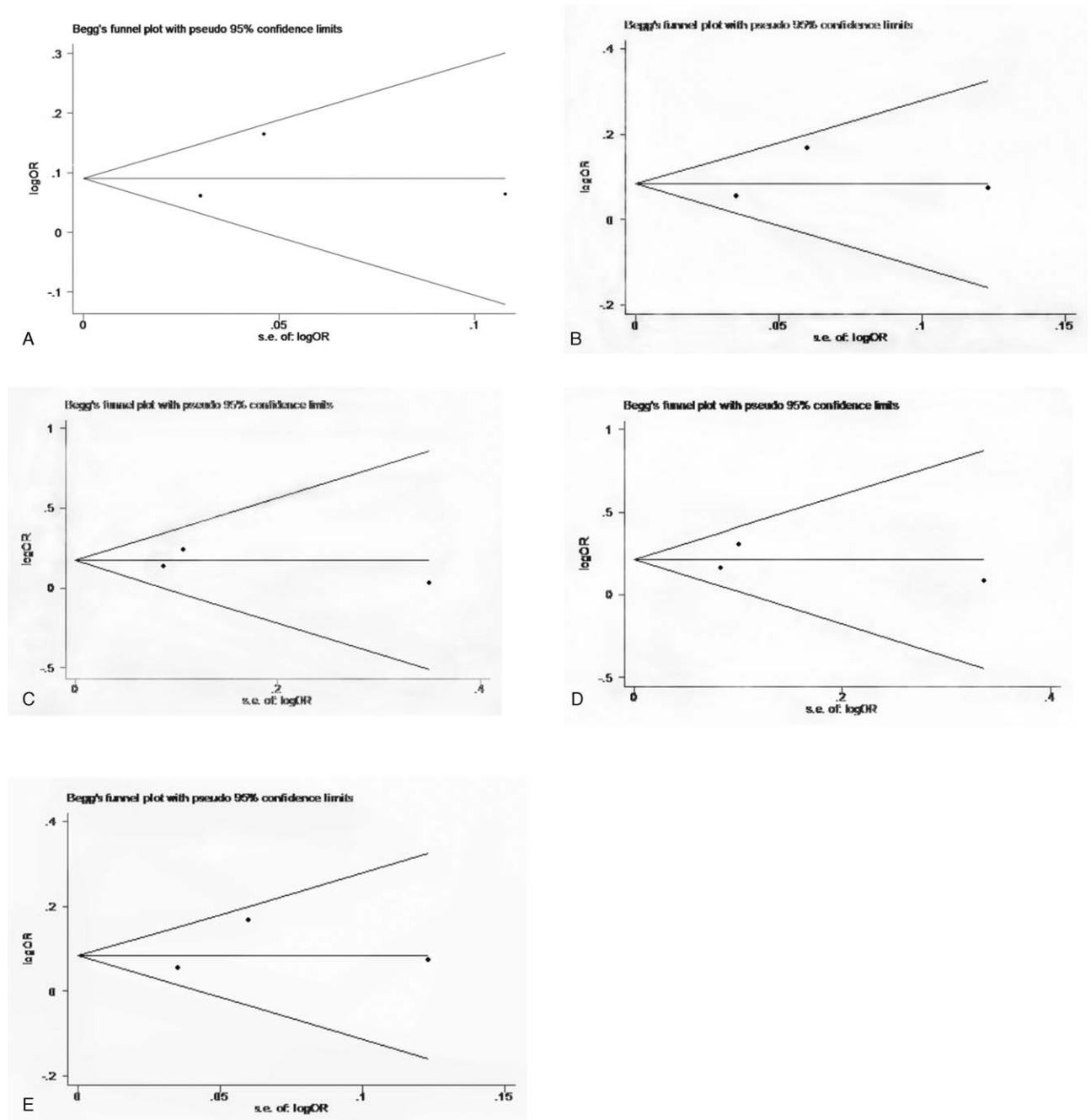
Figure 5. Funnel plots in the meta-analysis of the association between the insulin-like growth factor 1 gene polymorphism (rs35767 A>G) and cancer risk. (A) G vs A. (B) GG vs AA. (C) AG vs AA. (D) AG+GG vs AA. (E) GG vs AA+AG.

cancer risk. Secondly, the results were based on single-factor estimates without any adjustment for other risk factors, including age, body mass index, ethnic groups, smoking and drinking status, and environmental factors. Thirdly, the studies on IGF-1 rs35767 C>T showed relatively evident heterogeneity, which might be a result of the difference in country, ethnicity, and source of controls. Lastly, potential publication bias might exist in our results because studies that report positive findings are more likely to be published than those reporting negative results.

In conclusion, we systematically reviewed and meta-analyzed the relationship between IGF-1 rs35767 polymorphisms and cancer risk for the 1st time. The results of this meta-analysis reveal no significant associations between the IGF-1 rs35767 C>T and cancer risk for all genetic models. However, IGF-1 rs35767 A>G was significantly associated with increased cancer risk for all genetic models. Further experimental validations are necessary to confirm the results.

Author contributions

Conceptualization: Lei Qin, Jiawen Zhao.
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Methodology: Jiawen Zhao, Mingbin Xu.
Project administration: Chengyang Li.
Resources: Lei Qin, Cankun Chen.
Software: Jiawen Zhao.
Validation: Jiwen Cheng, Chengyang Li.
Visualization: Cankun Chen, Jiwen Cheng.
Writing – original draft: Jiawen Zhao.
Writing – review & editing: Jiwen Cheng.

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