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ORIGINAL RESEARCH

Quantitative assessment of caveolin-1 G14713A polymorphism and cancer susceptibility in the Asian population

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Purpose: The relationship between *caveolin-1* (*CAV1*) G14713A polymorphism and cancer susceptibility remains inconclusive. The current meta-analysis was performed on the basis of a systematic search in electronic databases for a more precise estimation of the associations.

Methods: Odds ratio (OR) with 95% confidence interval (CI) was used to estimate the pooled effect.

Results: A total of 12 studies including 4,994 cases and 5,606 controls were involved in this meta-analysis. In the overall analysis, *CAV1* G14713A polymorphism was significantly associated with an increased risk of cancer (A vs G: OR =1.77, 95% CI: 1.49–2.10, $P_{het}<0.01$; [AA + AG] vs GG: OR =2.03, 95% CI: 1.64–2.53, $P_{het}<0.01$; AA vs [AG + GG]: OR =1.72, 95% CI: 1.40–2.12, $P_{het}<0.01$; AA vs GG: OR =2.24, 95% CI: 1.69–2.98, $P_{het}<0.01$; AG vs GG: OR =1.98, 95% CI: 1.62–2.41, $P_{het}<0.01$). Subgroup analysis by cancer type showed that *CAV1* G14713A polymorphism was associated with an increased risk of digestive system cancer and other cancer types.

Conclusion: Our findings suggest that *CAV1* G14713A polymorphisms may modify the risk of cancer, especially digestive system cancer. However, further well-designed studies are warranted to validate this association.

Keywords: caveolin-1, polymorphism, cancer, susceptibility

Introduction

Annual cancer incidence and mortality continue to rise worldwide. There were ~12.7 million new cases and 7.6 million new deaths in 2008.[1] Although the pathogenetic mechanism of cancer has not been fully understood, extensive evidence has indicated the important roles of polymorphisms in the key genes during the process of carcinogenesis.[2–4] Screening and identification of single nucleotide polymorphisms that are related to cancer susceptibility would greatly benefit individuals at high risk of cancer in the early prevention and treatment settings.

Caveolin-1 (CAV1) is a member of the caveolin family of proteins and has been proved to modulate multiple cancer-associated processes, including cellular transformation, tumor growth, cell migration and metastasis, cell death and survival, and angiogenesis in a number of signaling pathways.[5–7] Thus, CAV1 is thought to play an important role in tumor development and progression. The *CAV1* gene is located on the human chromosome 7q31.1 and has some potentially functional polymorphisms identified. Among these polymorphisms, the associations of *CAV1* G14713A polymorphism and cancer susceptibility have been widely investigated; however, results are conflicting.[8–19] For instance, Liu et al reported

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significant positive associations between *CAV1* G14713A polymorphism and the risk of breast cancer.[16] However, Wu et al reported no significant association between *CAV1* G14713A polymorphism and risk of prostate cancer.[14] Based on these observations, we conducted the present meta-analysis to clarify the role of *CAV1* G14713A polymorphism in carcinogenesis.

Methods

Publication search and inclusion criteria

We searched electronic databases containing PubMed, Chinese National Knowledge Infrastructure, and Chinese Biology Medicine up to June 2015, using the following terms: "caveolin-1 or CAV1" AND "genetic polymorphism or polymorphisms or variant" AND "cancer or carcinoma or tumor". Additional studies were identified by hand-searching references of original or review articles on this topic. If data were published in more than one article, only the publication with the largest sample size was included. Studies were selected according to the following criteria: 1) studies should have evaluated the association between *CAV1* G14713A polymorphism and cancer susceptibility; 2) the type of study design should be a case-control study; and 3) studies should have a detailed genotype frequency of cases and controls.

Data extraction

Two investigators independently screened the studies and extracted the following data from the included studies: first author's name, publication year, ethnicity, cancer type, total number of cases and controls, and genotype distributions in cases and controls. Disagreements were resolved through discussion with another investigator.

Statistical analysis

Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated to assess the strength of associations of *CAV1* G14713A polymorphism with cancer susceptibility. ORs were calculated using five genetic models: homozygous (AA vs GG), heterozygous (AG vs GG), dominant ([AA + AG] vs GG), recessive (AA vs [AG + GG]), and allele contrast (A vs G). Subgroup analysis was also conducted according to the type of cancer. Heterogeneity among studies was assessed using the Q-test and I^2 statistics. When heterogeneity was considered significant ($P_{het}<0.05$ or $I^2>50\%$), a random-effect model was used; otherwise, a fixed-effect model was used. Sensitivity analysis was performed by removing the single studies, one at a time and recalculating the summarized ORs. Potential publication bias of the included studies was assessed by Begg's funnel plots and Egger's test. All P-values were two sided, and all analyses were carried out with STATA 12.0 software package (Stata Corporation, College Station, TX, USA).

Results

Characteristics of studies and main results

As shown in Figure 1, we initially extracted 56 articles in relation to the search words. Among them, 12 articles that met the inclusion criteria were included in this study. The principle characteristics of the 12 eligible studies are summarized in Tables 1 and 2. Six studies were conducted on digestive system cancer and six studies on cancer of other systems. The main meta-analysis results and the heterogeneities are shown in Table 3 and Figure 2. In the overall analysis, *CAV1* G14713A polymorphism showed a significant association with increased risk of cancer (A vs G: OR =1.77, 95% CI: 1.49–2.10, $P_{het}<0.01$; [AA + AG] vs GG: OR =2.03, 95% CI: 1.64–2.53, $P_{het}<0.01$; AA vs [AG + GG]: OR =1.72, 95% CI: 1.40–2.12, $P_{het}<0.01$; AA vs GG: OR =2.24, 95% CI: 1.69–2.98, $P_{het}<0.01$; AG vs GG: OR =1.98, 95% CI: 1.62–2.41, $P_{het}<0.01$). In addition, the results of stratified analysis by tumor type suggested that *CAV1* G14713A polymorphism was associated with an increased risk of digestive system cancer (A vs G: OR =2.02, 95% CI: 1.75–2.33, $P_{het}=0.03$; [AA + AG] vs GG: OR =2.40, 95% CI: 1.94–2.98, $P_{het}<0.01$; AA vs [AG + GG]: OR =2.01, 95% CI: 1.68–2.40, $P_{het}=0.83$;

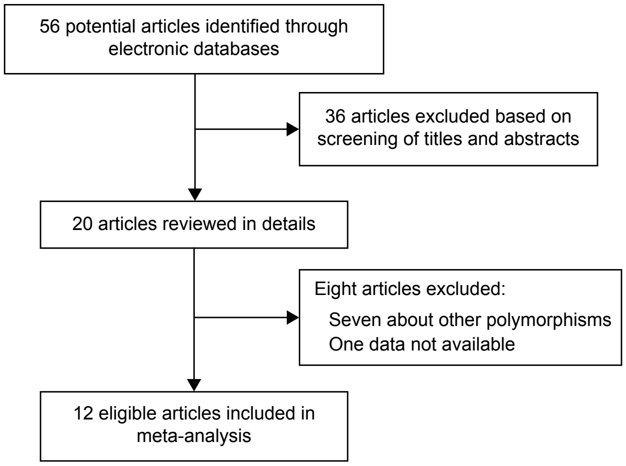


Figure 1 Flow-chart of included studies for this meta-analysis.

Table 1 Main characteristics of included studies

First author	Ethnicity	Cancer type	Case	Control
Wang et al[8]	Asian	Esophageal squamous cell carcinoma (digestive system cancer)	427	427
Zhang et al[9]	Asian	Gastric cancer (digestive system cancer)	412	412
Lin et al[10]	Asian	Gastric cancer (digestive system cancer)	358	358
Wang et al[11]	Asian	Leukemia (other system cancer)	266	266
Hsu et al[12]	Asian	Hepatocellular carcinoma (digestive system cancer)	298	298
Chang et al[13]	Asian	Upper urothelial tract cancer (other system cancer)	218	580
Wu et al[14]	Asian	Prostate cancer (other system cancer)	250	500
Tsou et al[15]	Asian	Nasopharyngeal carcinoma (other system cancer)	176	176
Liu et al[16]	Asian	Breast cancer (other system cancer)	1,232	1,232
Bau et al[17]	Asian	Oral cancer (digestive system cancer)	620	620
Bau et al[18]	Asian	Bladder cancer (other system cancer)	375	375
Yang et al[19]	Asian	Colorectal cancer (digestive system cancer)	362	362

Table 2 Allele frequency and genotype distributions of cases and controls in included studies

First author	Case (G14713A)							Control (G14713A)						
	GG	GA	AA	GA + AA	GG + GA	G	A	GG	GA	AA	GA + AA	GG + GA	G	A
Wang et al[8]	212	168	47	215	380	592	262	281	123	23	146	404	685	169
Zhang et al[9]	148	175	89	264	323	471	353	265	104	43	147	369	634	190
Lin et al[10]	172	136	50	186	308	480	236	235	90	33	123	325	560	156
Wang et al[11]	110	106	50	156	216	326	206	176	67	23	90	243	419	113
Hsu et al[12]	162	96	40	136	258	420	176	196	77	25	102	273	469	127
Chang et al[13]	118	72	28	100	190	308	128	377	146	57	203	523	900	260
Wu et al[14]	151	72	27	99	223	374	126	330	129	41	170	459	789	211
Tsou et al[15]	113	47	16	63	160	273	79	116	45	15	60	161	277	75
Liu et al[16]	704	409	119	528	1,113	1,817	647	801	311	120	431	1,112	1,913	551
Bau et al[17]	238	279	103	382	517	755	485	397	167	56	223	564	961	279
Bau et al[18]	144	160	71	231	304	448	302	245	96	34	130	341	586	164
Yang et al[19]	135	165	62	227	300	435	289	234	96	32	128	330	564	160

Table 3 Meta-analysis of caveolin-1 G14713A polymorphism and cancer susceptibility in Asian population

Variables	Allele contrast (A vs G)				Dominant contrast ([AA + AG] vs GG)				Recessive contrast (AA vs [AG + GG])			
	I^2	P_{het}	P_z	OR (95% CI)	I^2	P_{het}	P_z	OR (95% CI)	I^2	P_{het}	P_z	OR (95% CI)
All	86%	<0.01	<0.01	1.77 (1.49–2.10)	86%	<0.01	<0.01	2.03 (1.64–2.53)	61%	<0.01	<0.01	1.72 (1.40–2.12)
Digestive system cancer	61%	0.03	<0.01	2.02 (1.75–2.33)	71%	<0.01	<0.01	2.40 (1.94–2.98)	0%	0.83	<0.01	2.01 (1.68–2.40)
Other cancer types	88%	<0.01	<0.01	1.55 (1.18–2.03)	86%	<0.01	<0.01	1.72 (1.25–2.36)	70%	0.01	0.02	1.49 (1.06–2.10)
	Homozygous contrast (AA vs GG)				**Heterozygous contrast (AG vs GG)**							
All	78%	<0.01	<0.01	2.24 (1.69–2.98)	79%	<0.01	<0.01	1.98 (1.62–2.41)				
Digestive system cancer	14%	0.32	<0.01	2.84 (2.36–3.42)	68%	0.01	<0.01	2.30 (1.84–2.88)				
Other cancer types	81%	<0.01	0.01	1.81 (1.16–2.84)	78%	<0.01	<0.01	1.69 (1.28–2.24)				

Abbreviations: P_{het}, *P*-value of heterogeneity test; P_Z, *P*-value of *Z*-test; OR, odds ratio; CI, confidence interval.

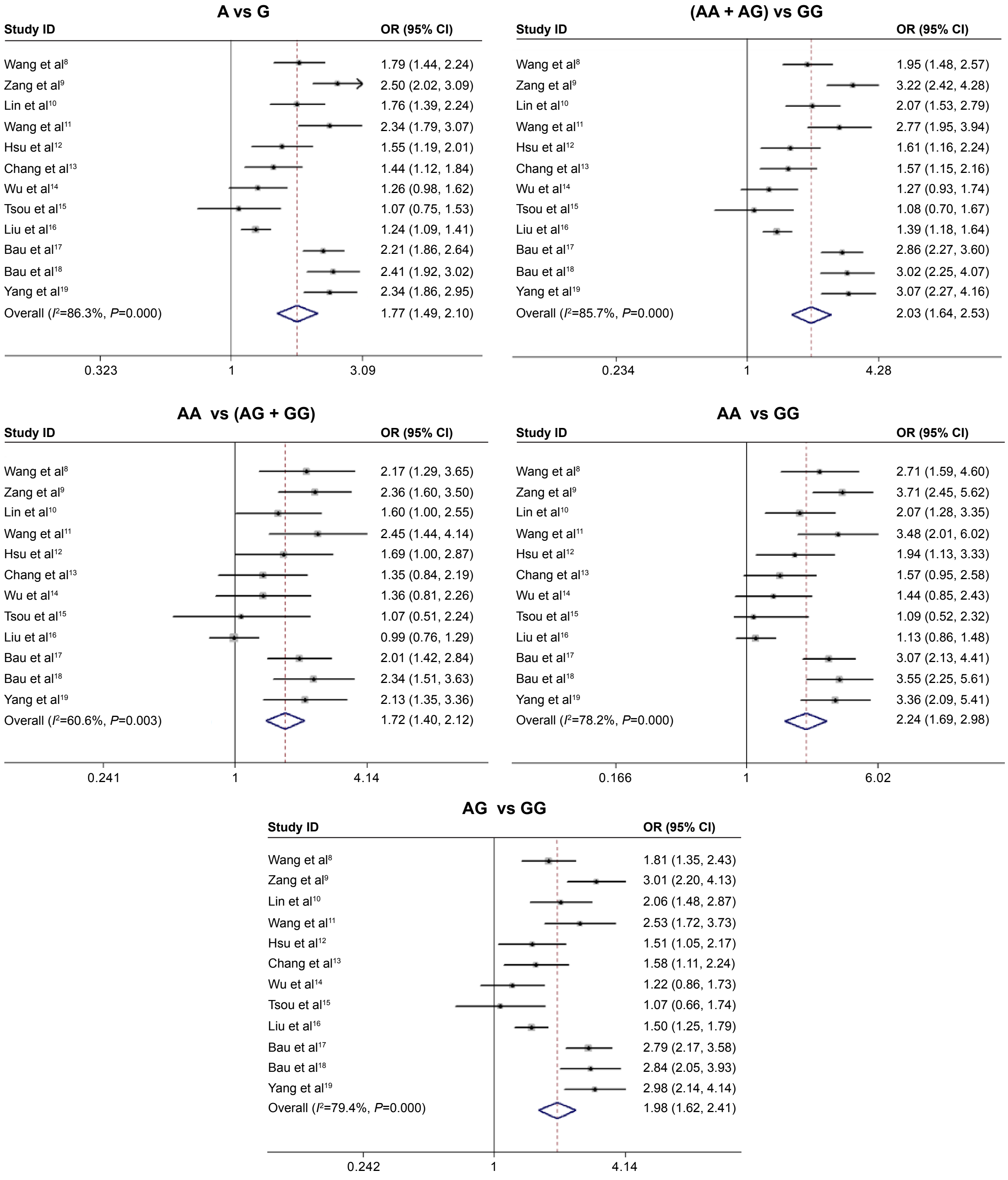
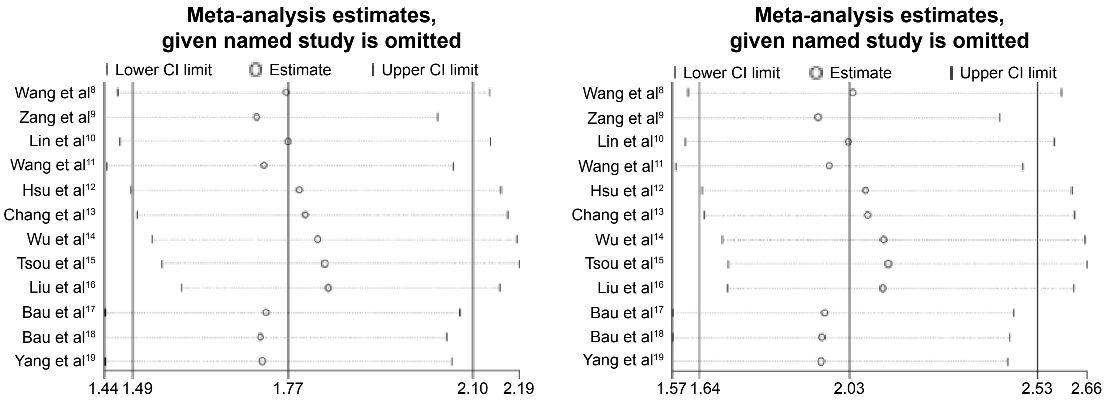


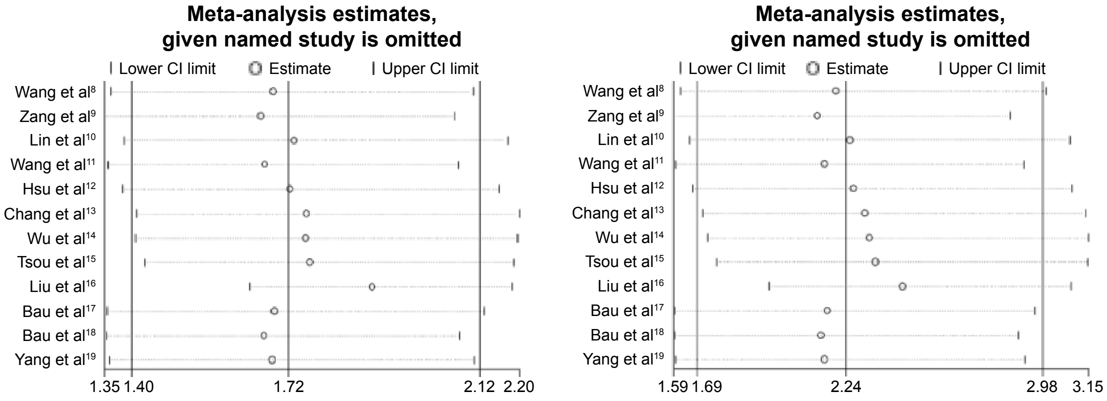
Figure 2 Forest plots representing the pooled results of ORs for the association between *CAV1* G14713A polymorphism and overall cancer risk.
Note: Weights are from random effects analysis.
Abbreviations: OR, odds ratio; CI, confidence interval; *CAV1*, *caveolin-1*.

AA vs GG: OR =2.84, 95% CI: 2.36–3.42, P_{het}=0.32; AG vs GG: OR =2.30, 95% CI: 1.84–2.88, P_{het}=0.01) and cancer of other systems (A vs G: OR =1.55, 95% CI: 1.18–2.03, P_{het}<0.01; [AA + AG] vs GG: OR =1.72, 95% CI: 1.25–2.36, P_{het}<0.01; AA vs [AG + GG]: OR =1.49, 95% CI: 1.06–2.10, P_{het}=0.01; AA vs GG: OR =1.81, 95% CI: 1.16–2.84, P_{het}<0.01; AG vs GG: OR =1.69, 95% CI: 1.28–2.24, P_{het}<0.01).



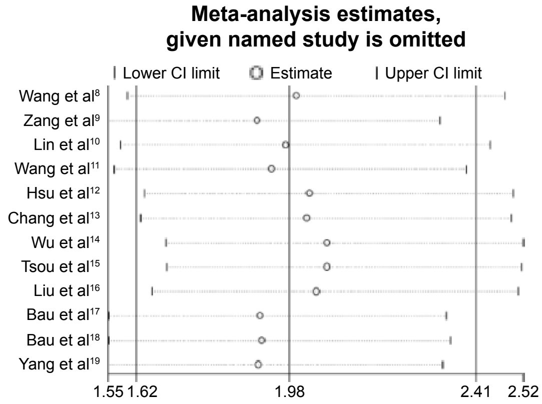
A vs G

(AA + AG) vs GG



AA vs (AG + GG)

AA vs GG



AG vs GG

Figure 3 Sensitivity analysis results of the association between *CAV1* G14713A polymorphism and overall cancer risk.
Abbreviations: CI, confidence interval; OR, odds ratio; *CAV1*, *caveolin-1*.

Sensitivity analysis and publication bias

A sensitivity analysis was performed by omitting every study in turn to check the influence of the removed data. Pooled estimates for all genetic models were insensitive to the removal of individual study, and the corresponding pooled ORs were not substantially altered, suggesting that our results were stable and reliable (Figure 3). Both Begg's funnel plots and Egger's test were performed to examine the underlying publication bias (Figure 4). The symmetrical funnel plots and *P*-value >0.05 for Egger's test indicated no publication bias in this meta-analysis.

Discussion

CAV1 is the major structural protein in caveolae and consists of 178 amino acids; it has been identified as a tumor suppressor in 1989.[20] CAV1 plays an important role in many signaling pathways, molecular transport, and cellular proliferation and differentiation, which are potentially involved in the

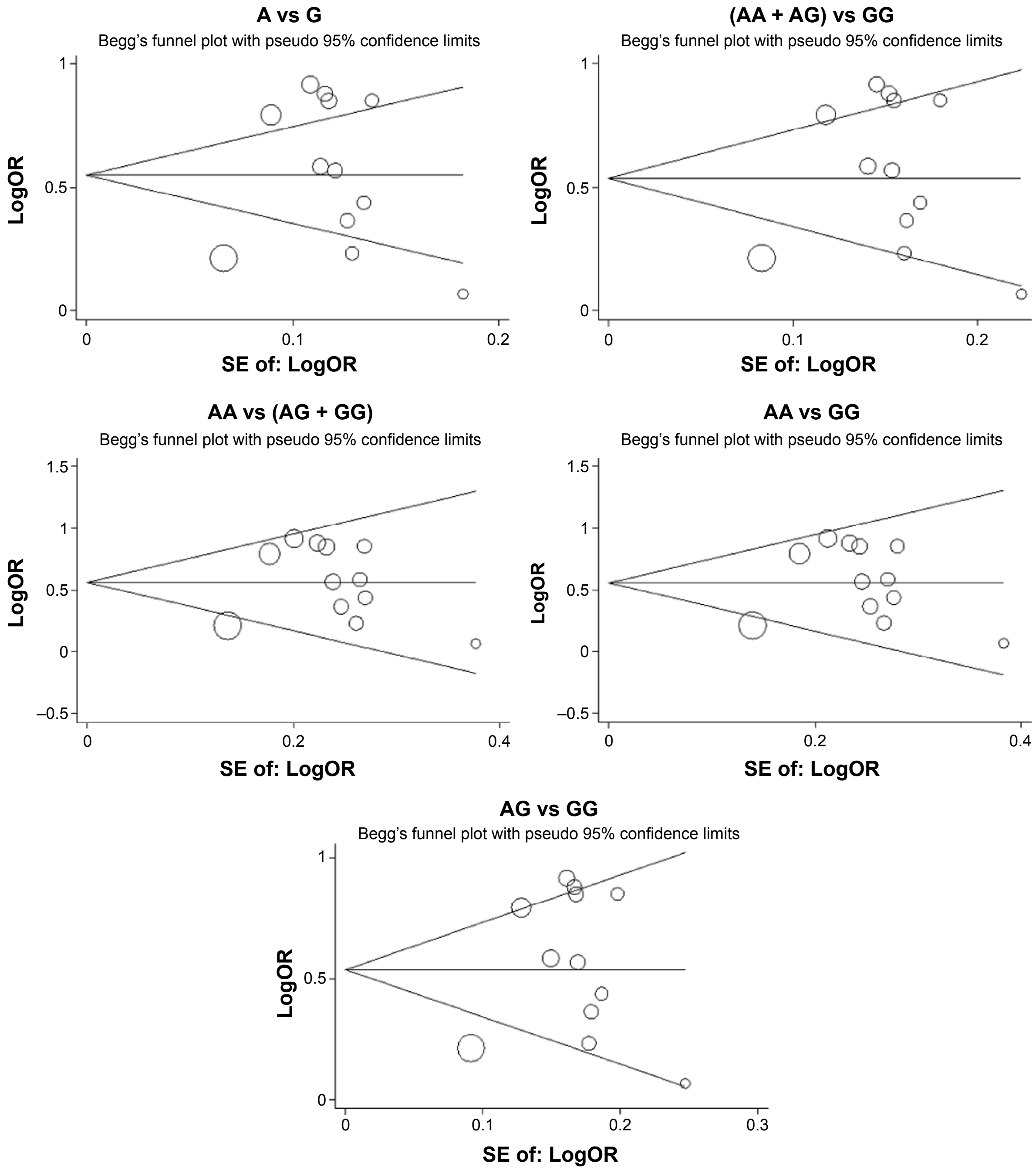


Figure 4 Begg's funnel plots of the association between *CAV1* G14713A polymorphism and overall cancer risk.
Abbreviations: SE, standard error of the logOR; logOR, natural logarithm of the OR; OR, odds ratio; *CAV1*, *caveolin-1*.

development of human cancer.[21] The association of *CAV1* G14713A polymorphism with cancer risk has been widely reported, but results are conflicting. For example, some studies indicated that *CAV1* G14713A polymorphism was associated with cancer risk, such as esophageal squamous cell carcinoma, gastric cancer, hepatocellular carcinoma, and breast cancer.[9,10,12,16] Other studies demonstrated that *CAV1* G14713A polymorphism was not associated with the risk of cancer, including prostate cancer and nasopharyngeal carcinoma.[14,15] To provide a more detailed overview of the association, five genetic models were used in the current meta-analysis. To our knowledge, this is the first meta-analysis of the association between *CAV1* G14713A polymorphism and cancer risk, and the results suggested that *CAV1* G14713A polymorphism increased the risk of cancer. In the subgroup analysis by tumor type, *CAV1* G14713A polymorphism was significantly associated with an increased risk of digestive system cancer and cancer of other systems.

Our meta-analysis had some advantages. For instance, we strictly obeyed the inclusion and exclusion criteria to reduce selection bias. Furthermore, there was no evidence of publication bias in this meta-analysis, and the sensitivity analysis confirmed the reliability and stability of the results. Despite these advantages, limitations should be considered when interpreting our results. First, our results were based on unadjusted estimates. More analyses that are precise can be conducted if individual data, including age and sex, were available. Second, all published studies were based on Asian populations. Therefore, the results of this meta-analysis may be applicable to the specified ethnicity alone.

Conclusion

The present study demonstrated that *CAV1* G14713A polymorphism might contribute to individual susceptibility to cancer. However, further well-designed studies are required to evaluate this association.

Acknowledgment

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Disclosure

The authors report no conflicts of interest in this work.

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