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International Journal of Surgery and Research (IJSR)
ISSN : 2379-156X

Caveolin-1 Polymorphisms and Cancer risk in Asian: A Meta - Analysis

Case Report

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Abstract

Cancer is the leading cause of death in the world. Genetic factors can influence the susceptibility and pathophysiology of cancer. Single nucleotide polymorphisms are the most common genetic variation and have become a focus in cancer research. In recent years, considerable research has indicated the link between CAV-1 polymorphism and cancer susceptibility. However, individual studies are inconsistent. We conducted a meta-analysis to eliminate this inconsistency. We performed a systematic computerized search of PubMed, ISI Web of Knowledge, and Chinese National Knowledge Infrastructure Data using the following keywords: "CAV-1," "Caveolin-1," "polymorphism," "variant," and "cancer". Pooled odds ratios with 95% confidence intervals were used to evaluate the strength of the association between CAV-1 polymorphism and cancer risk. Publication bias was estimated using Begg's funnel plots and Egger's regression test. The study showed that rs3807987 A>G polymorphism increased the risk of cancer in all five comparison models, and rs7804372 A>T polymorphism decreased the risk of cancer. However, no significant association was found in rs1997623, rs12672038, rs3757733, and rs3807992 polymorphisms and cancer. Egger's test results did not indicate any evidence of publication bias in this study. In conclusion, our meta-analysis showed that CAV-1 rs3807987 A>G polymorphism increased the risk of cancer and rs7804372 A>T polymorphism decreased the risk of cancer. Further studies that include different ethnicities and with a large population size should be conducted to reach a comprehensive conclusion.

Introduction

Cancer is the leading cause of death worldwide, both in developed and developed countries. GLOBOCAN estimates of cancer incidence and mortality indicate that 14.1 million new cancer cases and there were 8.2 million deaths in 2012 [1]. Cancer is a complex disease that can be affected by genetic factors [2], which can influence the susceptibility and pathophysiology of cancer [3, 4]. Single nucleotide polymorphisms (SNPs) are the most common genetic variation and have become a focus in cancer research. An increasing number of studies have found that SNPs can predict the risk, prognosis, and effect of drugs on individuals with cancer [5, 6].

Caveolin-1 (CAV-1) is an 18-24 kDa protein located at 7q31.1. The protein has three exons and belongs to the caveolin protein family [7]. It serves as a scaffolding protein in charge of recruiting related signaling molecules to the caveolae and regulating their activity [8]. Studies showed that CAV-1 plays roles in cancer, diabetes, cardiovascular disease, and pulmonary fibrosis [8-11]. In cancer, CAV-1 appears to act as both a tumor suppressor and oncogene. It is downregulated and it inhibits malignant potential of tumor cells in ovarian, colon, and breast cancers [12-14]. However, it is upregulated and promotes malignant potential of tumor cells in bladder and prostate cancer [15, 16].

The potential effect of cancer risk due to the CAV-1 gene, a considerable number of recent studies have indicated the link between CAV-1 polymorphism and cancer susceptibility. More than 20 SNPs in the CAV-1 promoter were detected in different types of cancers, some of which were thought to be genetic risk factors [17, 18]. Six SNPs (rs1997623, rs3807987, rs12672038, rs3757733, rs7804372, and rs3807992) were most frequently studied among Asians. However, individual studies have inconsistent or conflicting findings because of heterogeneity of data collection and inadequate sample sizes. To eliminate this inconsistency, we conducted a meta-analysis of all eligible case-control studies that have been published to date and estimated the cancer risk of six common

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Received: October 14, 2016
Accepted: November 12, 2016
Published: November 15, 2016

Citation: Lin B, Mao W, Kulkarni A, Liu C (2016) Caveolin-1 Polymorphisms and Cancer risk in Asian: A Meta - Analysis. *Int J Surg Res,* S2:001, 1-6.
doi: http://dx.doi.org/10.19070/2379-156X-SI02001

CAV-1 polymorphisms.

Material and Methods

Literature Search

To identify potentially all eligible studies, we performed a systematic computerized search of PubMed, ISI Web of Knowledge, and Chinese National Knowledge Infrastructure (CNKI) Data using the following keywords: "CAV-1," "Caveolin-1," "polymorphism," "variant," and "cancer." The last retrieval date was April 30, 2016. In addition, studies were identified through a manual search of reviews and retrieved studies. The language was restricted to English and Chinese. Studies were included in the analysis if they satisfied the following inclusion criteria: 1) evaluation of the association between CAV-1 polymorphism and cancer susceptibility in Asian; 2) case-control study or cohort studies; and 3) the genotype distribution of the polymorphism in cases and controls was sufficient to estimate the odds ratios (ORs) with a 95% confidence interval (CI) and a P value. The main exclusion criteria were listed as follows: 1) case reports, review articles, and editorials; 2) only case population; 3) duplication of a previous publication; and 4) no available genotype frequency.

Data extraction from published studies were extracted independently by two investigators. Discrepancies were resolved by discussing their findings on every item. For each included study, the following information was collected: first author, year of publication, region, study design, sample size, source of control, genotyping method, allele or genotype frequencies, and P value for Hardy–Weinberg equilibrium (HWE) of controls.

Statistical Analysis

The HWE for each study that describes control subjects was evaluated by a chi-square test. A P value < 0.05 was considered significant disequilibrium. OR with 95% CI was performed to assess the strength of the CAV-1 SNPs and cancer susceptibility. The pooled ORs were performed for allele comparison, dominant and recessive models, homozygote comparison, and heterozygote comparison. The Z test was performed to estimate the significance of the pooled ORs, and $P < 0.05$ was considered statistically significant. The heterogeneity among the studies was verified by the chi-square-based I^2 test and the P value of the Q test. $P > 0.05$ indicated a lack of heterogeneity, $I^2 < 25\%$ indicated low heterogeneity, I^2 of 25–75% indicated moderate heterogeneity, and $I^2 > 75\%$ indicated high heterogeneity. If $P > 0.05$, then pooled ORs were calculated by using a fixed effects model. Otherwise, a random effects model was used. Furthermore, sensitivity analyses were performed by sequentially removing each eligible study. Publication bias of literature was assessed with Begg's funnel plot test. $P < 0.05$ was considered representative of statistically significant publication bias. All P values were two-sided, and statistical analyses were conducted using the STATA software version 12.0 (StataCorp, College Station, TX, USA).

Results

Characteristics of Studies

Following the search strategy, 51 articles in PubMed, 49 articles in ISI Web of Knowledge, and 8 articles in CNKI were identified. After removing duplicates, 69 potential relevant studies were retrieved. Then, 44 articles were excluded after title and abstract screening. Next, 12 articles were excluded after full text reading. In the end, 13 articles were included in this study. Figure 1 presents the detailed process of selecting and excluding studies. In the 13 articles, all studies were case-control studies with the following SNP distribution: 11 articles were about polymorphism rs1997623 [19-29], 11 articles were about rs12672038 [19-29], 10 articles were about rs3757733 [19, 21-29], 12 articles were about rs3807987 [18-29], 9 articles were about rs3807992 [18, 19, 21-29], and 13 articles about rs7804372 [19, 21-30]. The characteristics of the included studies are summarized in Table 1.

Figure 1. Flow chart of Study Indetification.

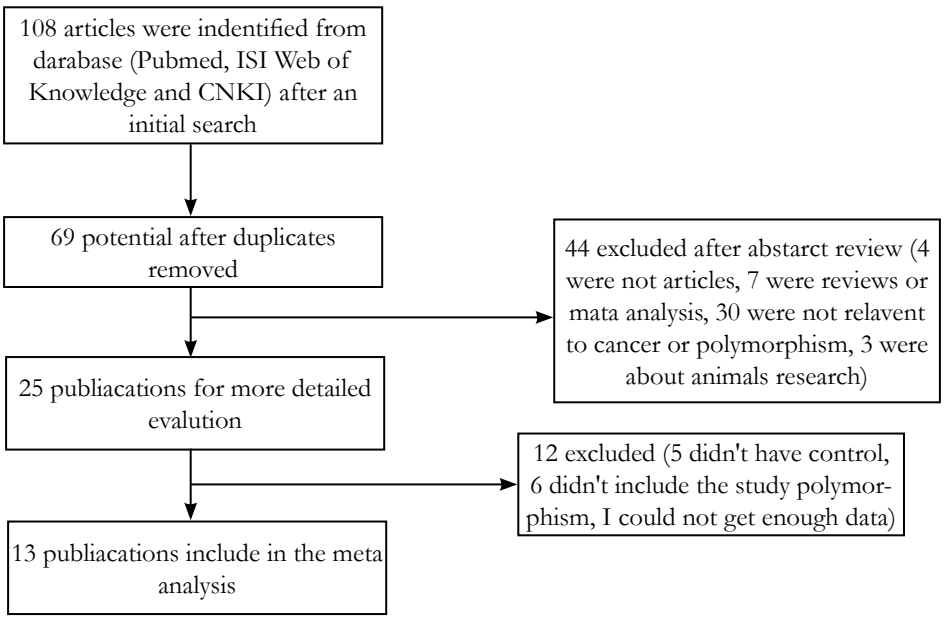


Table 1. Main Characteristics of Included Studies in this Meta - Analysis.

Author	Year	Tumor site	Country /Region	Ethnicity	Case/ Control	Genotyping methods	SNPs
Lin	2014	Gastric	Taiwan	Asian	358/358	PCR-RFLP	rs1997623, rs12672038, rs3757733, rs3807987, rs3807992, rs7804372
Zhang	2014	Gastric	China	Asian	412/412	MALDI-TOF	rs3807987, rs7804372
Wang	2014	esophageal	China	Asian	427/427	PCR-RFLP	rs1997623, rs12672038, rs3807987
Sugie	2013	Prostate	Japan	Asian	134/86	PCR-RFLP	rs7804372
Wang	2013	Leukemia	Taiwan	Asian	266/266	PCR-RFLP	rs1997623, rs12672038, rs3757733, rs3807987, rs3807992, rs7804372
Chang	2013	Upper Urothelial Tract	Taiwan	Asian	218/580	PCR-RFLP	rs1997623, rs12672038, rs3757733, rs3807987,rs3807992, rs7804372
Hsu	2013	Hepatocellular	Taiwan	Asian	298/298	PCR-RFLP	rs1997623, rs12672038, rs3757733, rs3807987, rs3807992, rs7804372
Tsou	2011	Nasopharyngeal	Taiwan	Asian	176/176	PCR-RFLP	rs1997623, rs12672038, rs3757733, rs3807987, rs3807992, rs7804372
Liu	2011	Breast	Taiwan	Asian	1232/1232	PCR-RFLP	rs1997623, rs12672038, rs3757733, rs3807987, rs3807992, rs7804372
Wu	2011	Prostate	Taiwan	Asian	250/500	PCR-RFLP	rs1997623, rs12672038, rs3757733, rs3807987, rs3807992, rs7804372
Bau	2011	Bladder	Taiwan	Asian	375/375	PCR-RFLP	rs1997623, rs12672038, rs3757733, rs3807987, rs3807992, rs7804372
Bau	2011	Oral	Taiwan	Asian	620/620	PCR-RFLP	rs1997623, rs12672038, rs3757733, rs3807987, rs7804372
Yang	2010	colorectal	Taiwan	Asian	362/362	PCR-RFLP	rs1997623, rs12672038, rs3757733, rs3807987, rs3807992, rs7804372

PCR-RFLP: polymerase chain reaction–restriction fragment length polymorphism;
MALDI-TOF: matrix-assisted laser desorption/ionization time-of-flight mass spectrometry platform.

Quantitative Synthesis

Results of CAV-1 rs1997623, rs12672038, rs3757733, rs3807987, rs3807992, and rs7804372 polymorphisms and cancer risk are presented in Table 2. For rs1997623, no significant associations were found using allele comparison (C vs. A: OR=0.921, 95% CI: 0.730–1.160, P=0.484) and recessive models (CC vs. AC+AA: OR=0.922, 95% CI: 0.728–1.169, P=0.504). For rs12672038, rs3757733, and rs3807992, no significant statistic associations were found in allele comparison, dominant and recessive models, homozygote comparison, and heterozygote comparison. The particular data for rs12672038 were as follows: A vs. G: OR=1.034, 95% CI: 0.967–1.104, P=0.329; AA vs. GG: OR=1.086, 95% CI0.932–1.266, P=0.292; AA vs. AG+GG: OR=1.081, 95% CI: 0.930–1.256, P=0.310; AA+AG vs. GG: OR=1.028, 95% CI: 0.947–1.115, P=0.514; AG vs. GG: OR=1.014, 95% CI: 0.930–1.107, P=0.751. For rs3757733, A vs. T: OR=0.964, 95% CI: 0.990–1.032, P=0.289; AA vs. TT: OR=0.921, 95% CI: 0.791–1.073, P=0.292; AA vs. AT+TT: OR=0.928, 95% CI: 0.799–1.077, P=0.326; AA+AT vs. TT: OR=0.968, 95% CI: 0.888–1.054, P=0.449; AT vs.. TT: OR=0.980, 95% CI=0.894–1.075, P=0.670. For rs3807992, A vs. G: OR=1.767, 95% CI: 1.486–2.101, P=0.825; AA vs. GG: OR=0.983, 95% CI: 0.843–1.146, P=0.828; AG vs. GG: OR=1.039, 95% CI: 0.943–1.145, P=0.435; AA vs. AG+GG: OR=0.966, 95% CI: 0.834–1.118, P=0.641; AA+AG vs. GG: OR=1.027, 95% CI: 0.938–1.125, P=0.563. rs3807987 it was significantly associated with an increased risk of cancer in allele comparison (A vs. G: OR=1.767, 95% CI; 1.486–2.101, P=0.000), dominant models (AA+AG vs. GG: OR=2.034, 95% CI=1.639–2.526, P=0.000), recessive models (AA vs. AG+GG: OR=1.724, 95% CI: 1.402–2.119, P=0.000), homozygote comparison (AA vs. GG: OR=2.243, 95% CI: 1.686–2.984, P=0.000), and heterozygote comparison (AG vs. GG: OR=1.976, 95% CI: 1.621–3.410, P=0.000). rs7804372 was significantly associated with a decreased risk of cancer in allele comparison (A vs. T: OR=0.704, 95% CI; 0.645–0.768, P=0.000), dominant models (AA+AT vs. TT: OR=0.706, 95% CI=0.653–0.762, P=0.000), recessive models (AA vs. AT+TT: OR=0.580, 95% CI: 0.508–0.662, P=0.000), homozygote comparison (AA vs. TT: OR=0.528, 95% CI: 0.461–0.604, P=0.000), and heterozygote comparison (AT vs. TT: OR=0.766, 96% CI: 0.705–0.832, P=0.000).(Figure 2)

Heterogeneity and Sensitivity Analysis

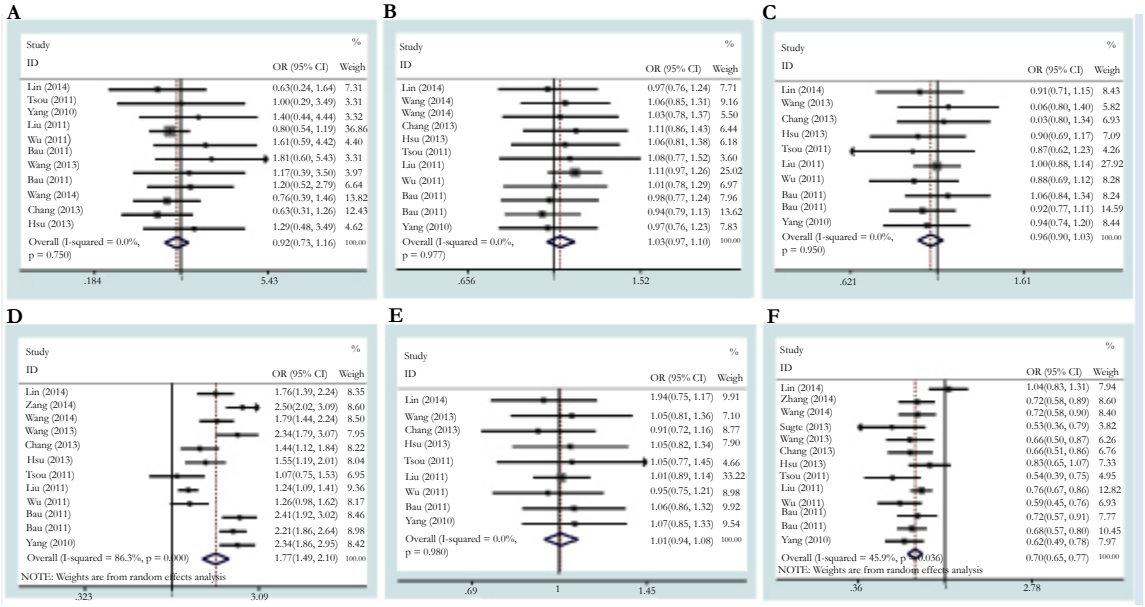
Heterogeneity was evaluated using the chi-square-based I^2 test and Q test. Results showed that heterogeneity existed in the five comparisons of rs3807987 and allele comparison of rs7804372. In the remaining SNPs, no significant heterogeneity was observed (Table 2). Sensitivity analysis was conducted to verify the effect of each study on the overall OR. Each study was omitted time by time. Results showed that the pooled ORs of these six polymorphisms were not materially altered by the contribution of any individual study (Figure3). Thus, the meta-analysis was statistically robust.

Table 2. Meta - Analysis of the Caveolin-1 Polymorphism and Cancer Risk in Asian.

Comparisons		OR(95% CI)	P	Heterogeneity		Mod-el
				P	I^2(%)	
rs1997623	C vs A	0.921(0.730-1.160)	0.484	0.750	N/A	F
	CC vs AC+AA	0.922(0.728-1.169)	0.504	0.767	N/A	F
	CC vs AC	0.926(0.728-1.178)	0.529	0.778	N/A	F
rs12672038	A vs G	1.034(0.967-1.104)	0.329	0.997	N/A	F
	AA vsGG	1.086(0.932-1.266)	0.292	0.972	N/A	F
	AA vs AG+GG	1.081(0.930-1.256)	0.310	0.975	N/A	F
	AA+AG vs GG	1.028(0.947-1.115)	0.514	0.996	N/A	F
	AG vs GG	1.014(0.930-1.107)	0.751	0.999	N/A	F
rs3757733	A vs T	0.964(0.900-1.032)	0.289	0.950	N/A	F
	AA vs TT	0.921(0.791-1.073)	0.292	0.966	N/A	F
	AA vs AT+TT	0.928(0.799-1.077)	0.326	0.980	N/A	F
	AA+AT vs TT	0.968(0.888-1.054)	0.449	0.993	N/A	F
	AT vs TT	0.980(0.894-1.075)	0.670	1.000	N/A	F
rs3807987	A vs G	1.767(1.486-2.101)	0.000	0.000	86.3	R
	AA vs GG	2.243(1.686-2.984)	0.000	0.000	78.2	R
	AA vs AG	1.069(0.993-1.225)	0.336	0.612	N/A	F
	AA vs AG+GG	1.724(1.402-2.119)	0.000	0.003	60.6	R
	AA+AG vs GG	2.034(1.639-2.526)	0.000	0.000	85.7	R
rs3807992	Avs G	1.008(0.940-1.080)	0.825	0.980	N/A	F
	AA vs GG	0.983(0.843-1.146)	0.828	0.990	N/A	F
	AA vs AG	0.946(0.809-1.106)	0.483	0.965	N/A	F
	AA vs AG+GG	0.966(0.834-1.118)	0.641	0.985	N/A	F
	AA+AG vs GG	1.027(0.938-1.125)	0.563	0.952	N/A	F
rs7804372	A vs T	0.704(0.645-0.768)	0.000	0.036	45.9	R
	AA vs TT	0.528(0.461-0.604)	0.000	0.078	38.4	F
	AA vs AT	0.677(0.588-0.781)	0.000	0.475	N/A	F
	AA vs AT+TT	0.580(0.508-0.662)	0.000	0.157	N/A	F
	AA+AT vs TT	0.706(0.653-0.762)	0.000	0.315	12.9	F

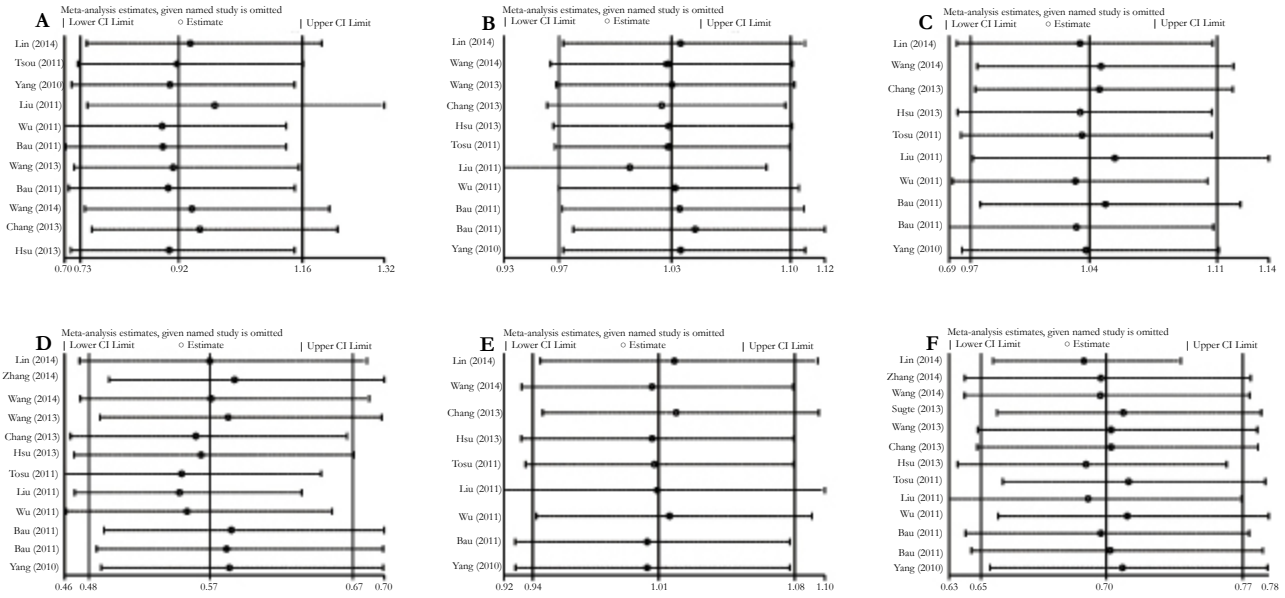
R = random-effect model; F = fixed-effect model; OR = odds ratio; 95% CI = 95% confidence interval; P = P value.

Figure 2. Forest Plot for the Caveolin-1 Polymorphism and Cancer Susceptibility in the Allele Comparison.



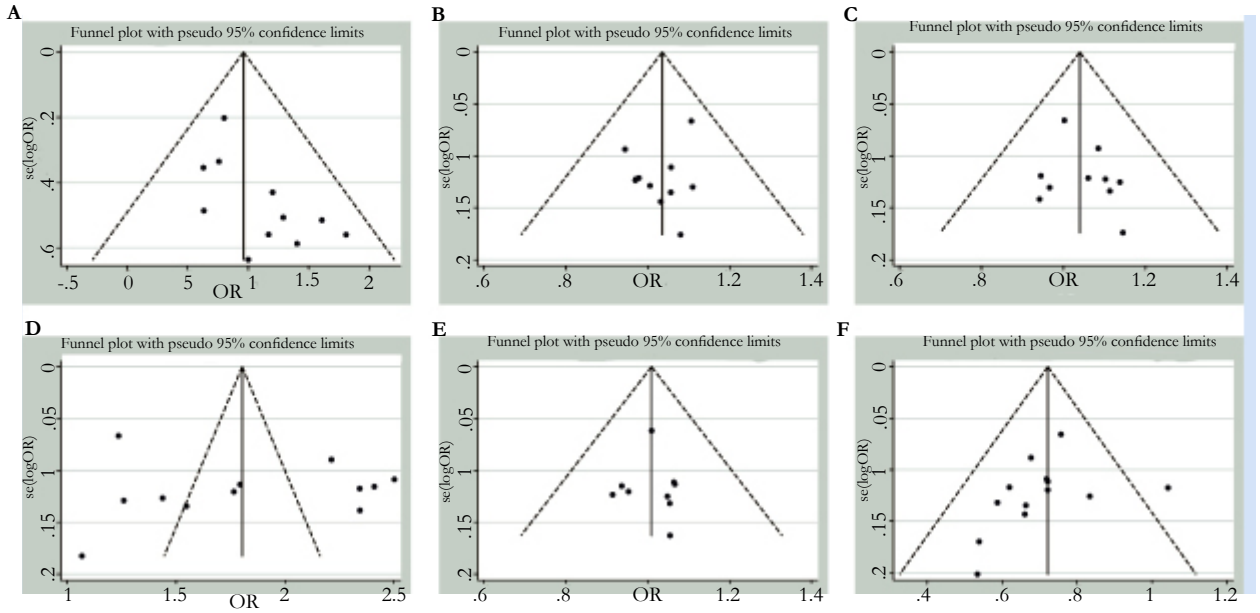
A: rs1997623, C vs A. B:rs12672038, A vs G. C: rs3757733, A vs T. D: rs3807987, A vs G. E : rs3807992 A vs G. F: rs7804372, A vs T.

Figure 3. Sensitivity Analysis of the Influence of Allele Comparison in Cancer Risk.



A: rs1997623. B:rs12672038. C: rs3757733. D: rs3807987. E : rs3807992. F: rs7804372.

Figure 4. Funnel Plot for Publication Bias Test.



A: rs1997623. B:rs12672038. C: rs3757733. D: rs3807987. E : rs3807992. F: rs7804372.

Publication bias

Publication bias in all the studies was assessed by Begg's funnel plot and Egger's test. All the graphical funnel plots were symmetrical for the comparison of the genetic models of every SNP (Figure 4). Egger's test results did not indicate any evidence of publication bias in this study.

Discussion

The overall goal of a meta-analysis is to combine the results of previous studies to obtain an overall conclusion. In this meta-analysis, we detected the associations between CAV-1 rs1997623, rs3807987, rs12672038, rs3757733, rs7804372, and rs3807992 polymorphisms and cancer risk. To our knowledge, this study is the first to use meta-analysis to obtain comprehensive insights into the CAV-1 polymorphism and risk associated with all types of cancer in an Asian population. This study showed that rs3807987 A>G polymorphism increased the risk of cancer in all five comparison models and rs7804372 A>T polymorphism decreased the risk of cancer. However, no significant association was found in rs1997623, rs12672038, rs3757733, and rs3807992 polymorphisms and cancer.

The reasons CAV-1 polymorphisms affect cancer risk were not clearly understood. The polymorphism in the promoter may affect the expression of CAV-1. In non-small cell lung carcinoma, the expression of CAV-1 was statistically correlated with pathologic TNM stage and lymph node metastasis [31] because poly-

morphism affects the binding site of the promoter or changes the methylation site.

Heterogeneities between studies were found in the rs3807987 and rs7804372 polymorphisms in this meta-analysis. This meta-analysis includes only Asian people. However, the heterogeneities due to ethnicity cannot be eliminated. Heterogeneities due to different cancer types must be considered in this study.

This meta-analysis has some limitations. First, the small sample size in the studies may have resulted in low statistical power. Hence, additional detailed and large-scale studies are necessary. Second, the analysis did not consider gene environment interactions because of the lack of sufficient data. Finally, this study mainly focused on an Asian population. Whether the results can be generalized and applied to other populations remains unclear.

Conclusion

Our meta-analysis results showed that CAV-1 rs3807987 A>G polymorphism increased the risk of cancer, and rs7804372 A>T polymorphism decreased the risk of cancer. No significant association was found in rs1997623, rs12672038, rs3757733, and rs3807992 polymorphisms and cancer. Further studies that include different ethnicities and have a large population size should be conducted to obtain a comprehensive conclusion.

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