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Association of Vascular Endothelial Growth Factor Gene Polymorphism With Renal Cell Carcinoma Risk

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Abstract

The conclusion of the relationship between vascular endothelial growth factor gene polymorphism and renal cell carcinoma risk was inconsistent. This study was performed to assess the relationship between vascular endothelial growth factor gene polymorphism and renal cell carcinoma risk using meta-analysis. The association studies were identified from PubMed, Embase, and Web of Science, and eligible studies were included and calculated. Ten studies were included for this meta-analysis. vascular endothelial growth factor (VEGF) +405G > CC allele and GG genotype were associated with renal cell carcinoma risk for overall populations in this meta-analysis (C allele: odds ratio = 1.18, 95% confidence interval: 1.05-1.33, $P = .004$; CC genotype: odds ratio = 1.20, 95% confidence interval: 0.96-1.50, $P = .12$; GG genotype: odds ratio = 0.79, 95% confidence interval: 0.67-0.93, $P = .004$). Furthermore, VEGF +936C>T gene polymorphism and VEGF −2578 C>A gene polymorphism were associated with renal cell carcinoma risk for overall populations (+936C>T: T allele: odds ratio = 1.16, 95% confidence interval: 1.05-1.29, $P = .004$; TT genotype: odds ratio = 1.25, 95% confidence interval: 1.02-1.52, $P = .03$; CC genotype: odds ratio = 0.86, 95% confidence interval: 0.75-0.98, $P = .03$; −2578 C>A: A allele: odds ratio = 1.26, 95% confidence interval: 1.15-1.38, $P < .00001$; AA genotype: odds ratio = 1.39, 95% confidence interval: 1.16-1.67, $P = .0004$; CC genotype: odds ratio = 0.75, 95% confidence interval: 0.61-0.92, $P = .006$). However, VEGF −634G>C, VEGF −460T>C, VEGF −1154 G>A, and VEGF +1612 G>A gene polymorphisms were not associated with renal cell carcinoma risk. In conclusion, VEGF +405G>CC allele and GG genotype, VEGF +936C>T gene polymorphism, and VEGF −2578 C>A gene polymorphism were associated with renal cell carcinoma risk for overall populations. However, more studies should be performed to assess this relationship in the future.

Keywords

renal cell carcinoma, vascular endothelial growth factor, gene polymorphism, meta-analysis

Abbreviations

BC, breast cancer; cSCC, cutaneous squamous cell carcinoma; CI, confidence interval; HWE, Hardy-Weinberg equilibrium; OR, odds ratio; PTC, papillary thyroid carcinoma; VEGF, vascular endothelial growth factor.

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Introduction

Renal cell carcinoma, one of the most malignant tumors, affects men more frequently than women and constitutes nearly 90% of all kidney tumors.[1] The incidence of renal cell carcinoma varies geographically: the highest level is recorded in Europe, North America, and Australia, the lowest in Africa, India, China, and Japan.[1] Diagnosis of renal cell carcinoma at an early stage is challenging, but it can provide the best chance for cure.[2] Renal cell carcinoma, a metabolic disease, being characterized by the dysregulation of metabolic pathways involved in oxygen sensing Von Hippel-Lindau/hypoxia inducible factor (VHL/HIF pathway alterations and the subsequent upregulation of HIF-responsive genes, such as vascular endothelial growth factor [VEGF]).[3]

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Vascular endothelial growth factor, an important signaling proteins involved in angiogenesis, can influence on the development of physiological and pathological tissue.[4] Angiogenesis is an essential physiological process, and it is an important factor in disease pathogenesis. Vascular endothelial growth factor pathway is reported to play a conspicuous role in the growth and progression of human cancers, such as renal cell carcinoma.[5-7] VEGF +405G>C, VEGF −634G>C, VEGF −460T>C, VEGF +936C>T, VEGF −2578 C>A, VEGF −1154 G>A, VEGF +1612 G>A gene polymorphisms were the important gene types for VEGF. The current evidences indicate that VEGF +405G>C, VEGF −634G>C, VEGF −460T>C, VEGF +936C>T, VEGF −2578 C>A, VEGF −1154 G>A, and VEGF +1612 G>A gene polymorphisms might take part in the pathogenesis of carcinogenesis. This meta-analysis was performed to assess the relationship between VEGF +405G>C, VEGF −634G>C, VEGF −460T>C, VEGF +936C>T, VEGF −2578 C>A, VEGF −1154 G>A, VEGF +1612 G>A gene polymorphisms and renal cell carcinoma risk.

Materials and Methods

Search Strategy

The relevant investigation were searched and included from the databases of PubMed, Embase, and Web of Science, on July 1, 2016. The retrieval strategy of "(vascular endothelial growth factor OR VEGF) AND (renal cell carcinoma OR renal carcinoma) AND (polymorphism OR polymorphisms)" was entered into these databases mentioned above. The additional reports were identified through references cited in recruited articles.

Inclusion and Exclusion Criteria

Inclusion criteria. (1) The outcome must be renal cell carcinoma, (2) the study included 2 comparison groups (renal cell carcinoma group vs control group), and (3) report should give the data of VEGF genotype distribution.

Exclusion criteria. (1) Case reports, review articles, and editorials; (2) preliminary result not on VEGF gene polymorphism or renal cell carcinoma; (3) investigating the role of VEGF gene expression to renal cell carcinoma.

Data Extraction

The following information from each eligible investigation was extracted by 2 investigators independently: first author's surname, year of publication, ethnicity, control source of the control group, and the number of cases and controls for VEGF genotypes. Frequencies of allele of VEGF were calculated for renal cell carcinoma group and control group. When the disagreement was occurred, the results would be resolved by discussion.

Statistical Analysis

Cochrane Review Manager Version 5 (Cochrane Library, United Kingdom) was used in this meta-analysis to calculate the extracted data from each report. The pooled statistic was counted using the fixed effects model. However, a random effects model was conducted when the P value of heterogeneity test was less than.1. Results were expressed using odds ratios (OR) for dichotomous data. Ninety-five percent confidence intervals (CIs) were also calculated. $P < .05$ was required for the pooled OR to be statistically significant, and I^2 was used to test the heterogeneity among the included studies. A χ^2 test using a web-based program was applied to determine whether the genotype distribution of the control population reported for VEGF +936C>T conformed to Hardy-Weinberg equilibrium (HWE; $P < .05$ was considered significant). Sensitivity analysis was performed if HWE disequilibrium existed.

Results

Association of VEGF +405G>C Gene Polymorphism With Renal Cell Carcinoma Risk

Three studies[8-10] for the relationship between VEGF +405G>C gene polymorphism and renal cell carcinoma risk were included in this meta-analysis, and the extracted data were shown in Table 1. We found that VEGF +405G>CC allele and GG genotype were associated with renal cell carcinoma risk in overall populations, but not in CC genotype (C allele: OR = 1.18, 95% CI: 1.05-1.33, $P = .004$; CC genotype: OR = 1.20, 95% CI: 0.96-1.50, $P = .12$; GG genotype: OR = 0.79, 95% CI: 0.67-0.93, $P = .004$; Table 2).

In the subgroup analysis by ethnicity, this meta-analysis indicated that VEGF +405G>CC allele and GG genotype were associated with renal cell carcinoma risk in Asian population but not in CC genotype (Table 2). However, VEGF +405G>C gene polymorphism was not associated with renal cell carcinoma susceptibility in Caucasian population (Table 2).

Association of VEGF −634G>C Gene Polymorphism With Renal Cell Carcinoma Risk

Four studies[11-14] for the relationship between VEGF −634G>C gene polymorphism and renal cell carcinoma risk were included in this meta-analysis, and all studies were performed in Asian population (Table 1). We found that VEGF −634G>C gene polymorphism was not associated with renal cell carcinoma risk in Asian population (Table 2).

Association of VEGF −460C >T Gene Polymorphism With Renal Cell Carcinoma Risk

Three studies[8,9,11] for the relationship between VEGF −460C>T gene polymorphism and renal cell carcinoma risk were included in this meta-analysis, and the extracted data were shown in Table 1. We found that VEGF −460C>T gene

Table 1. General Characteristics of the Included Studies in This Meta-Analysis for VEGF Gene Polymorphism With Renal Cell Carcinoma Risk.

First Author, Year	Country/District	Ethnicity	Case				Control			
VEGF +405G>C			CC	GC	GG	Total	CC	GC	GG	Total
Bruyere, 2010	France	Caucasian	8	25	15	48	20	92	86	198
Saenz-Lopez, 2013	Spain	Caucasian	20	93	101	214	32	118	129	279
Qin, 2014	China	Asian	146	391	287	824	144	429	410	983
VEGF −634G>C			CC	GC	GG	Total	CC	GC	GG	Total
Lu, 2015	China	Asian	79	194	139	412	148	377	299	824
Shen, 2015	China	Asian	69	170	121	360	63	163	134	360
Xian, 2015	China	Asian	104	132	30	266	227	256	49	532
Yang, 2015	Taiwan	Asian	39	90	62	191	67	173	136	376
VEGF −460T>C			TT	TC	CC	Total	TT	TC	CC	Total
Bruyere, 2010	France	Caucasian	19	29	1	49	47	109	46	202
Saenz-Lopez, 2013	Spain	Caucasian	56	111	49	216	77	138	58	273
Lu, 2015	China	Asian	228	93	91	412	513	168	143	824
VEGF +936C>T			TT	TC	CC	Total	TT	TC	CC	Total
Abe, 2002	Japan	Asian	7	41	97	145	3	52	90	145
Bruyere, 2010	France	Caucasian	1	17	29	47	2	53	141	196
Saenz-Lopez, 2013	Spain	Caucasian	2	57	156	215	7	73	200	280
Xian, 2015	China	Asian	69	127	70	266	100	236	196	532
Yang, 2015	Taiwan	Asian	10	59	122	191	22	121	232	375
Shen, 2015	China	Asian	55	81	224	360	46	73	240	359
Lu, 2015	China	Asian	59	91	262	412	105	166	554	825
VEGF −2578 C>A			AA	CA	CC	Total	AA	CA	CC	Total
Ajaz, 2011	Pakistan	Asian	32	81	30	143	21	41	44	106
Saenz-Lopez, 2013	Spain	Caucasian	48	114	54	216	53	142	77	272
Yang, 2015	Taiwan	Asian	10	75	106	191	23	153	200	376
Lu, 2015	China	Asian	67	174	171	412	95	332	397	824
Shen, 2015	China	Asian	61	149	150	360	41	141	178	360
Xian, 2015	China	Asian	48	119	99	266	64	225	243	532
VEGF −1154 G>A			AA	AG	GG	Total	AA	AG	GG	Total
Ricketts, 2009	Polish	Caucasian	47	143	134	324	38	130	146	314
Bruyere, 2010	France	Caucasian	5	17	27	49	25	83	94	202
Yang, 2015	Taiwan	Asian	8	52	131	191	21	99	256	376
VEGF +1612 G>A			AA	AG	GG	Total	AA	AG	GG	Total
Abe, 2002	Japan	Asian	1	31	113	145	3	33	109	145
Lu, 2015	China	Asian	49	191	172	412	85	375	365	825
Shen, 2015	China	Asian	39	170	152	361	30	164	166	360
Xian, 2015	China	Asian	30	123	113	266	41	243	248	532

Abbreviation: VEGF, vascular endothelial growth factor.

polymorphism was not associated with renal cell carcinoma risk in overall populations (Table 2).

In the subgroup analysis by ethnicity, this meta-analysis indicated that, in Asian population, VEGF −460C>TT allele and TT genotype were associated with renal cell carcinoma risk but not in CC genotype (Table 2). However, VEGF −460C>T gene polymorphism was not associated with renal cell carcinoma risk in Caucasian population (Table 2).

Association of VEGF +936C>T Gene Polymorphism With Renal Cell Carcinoma Risk

Seven studies[8,9,11-15] for the relationship between VEGF +936C>T gene polymorphism and renal cell carcinoma risk were included in this meta-analysis, and the extracted data were shown in Table 1. We found that VEGF +936C>T gene polymorphism was associated with renal cell carcinoma risk in

Table 2. Meta-Analysis of the Association of VEGF Gene Polymorphism With Renal Cell Carcinoma Risk.

Genetic Contrasts	Group and Subgroups	Studies Number	Q Test *P* Value	Model Selected	OR (95% CI)	*P* Value
VEGF +405G>C						
C vs G	Overall	3	.11	Fixed	1.18 (1.05-1.33)	.004
	Asian	1	–	Fixed	1.23 (1.08-1.41)	.002
	Caucasian	2	.08	Random	1.14 (0.72-1.79)	.58
CC vs GC+GG	Overall	3	.25	Fixed	1.20 (0.96-1.50)	.12
	Asian	1	–	Fixed	1.25 (0.98-1.61)	.08
	Caucasian	2	.14	Fixed	1.00 (0.61-1.63)	.99
GG vs GC+CC	Overall	3	.19	Fixed	0.79 (0.67-0.93)	.004
	Asian	1	–	Fixed	0.75 (0.62-0.90)	.003
	Caucasian	2	.15	Fixed	0.91 (0.67-1.25)	.57
VEGF −634G>C						
C vs G	Asian	4	.35	Fixed	1.05 (0.95-1.16)	.35
CC vs GC+GG	Asian	4	.57	Fixed	1.03 (0.86-1.22)	.77
GG vs GC+CC	Asian	4	.57	Fixed	0.91 (0.77-1.07)	.23
VEGF −460T>C						
T vs C	Overall	3	.0003	Random	1.09 (0.69-1.72)	.72
	Asian	1	–	Fixed	0.76 (0.63-0.91)	.003
	Caucasian	2	.002	Random	1.38 (0.61-3.12)	.44
TT vs TC+CC	Overall	3	.02	Random	1.02 (0.63-1.65)	.93
	Asian	1	–	Fixed	0.75 (0.59-0.95)	.02
	Caucasian	2	.03	Random	1.31 (0.57-3.00)	.53
CC vs TC+TT	Overall	3	.01	Random	0.93 (0.47-1.84)	.83
	Asian	1	–	Fixed	1.35 (1.01-1.81)	.05
	Caucasian	2	.005	Random	0.32 (0.02-5.65)	.44
VEGF +936C>T						
T vs C	Overall	7	.13	Fixed	1.16 (1.05-1.29)	.004
	Asian	5	.13	Fixed	1.18 (1.06-1.32)	.003
	Caucasian	2	.14	Fixed	1.02 (0.76-1.39)	.87
TT vs TC+CC	Overall	7	.48	Fixed	1.25 (1.02-1.52)	.03
	Asian	5	.56	Fixed	1.27 (1.04-1.56)	.02
	Caucasian	2	.23	Fixed	0.56 (0.15-2.05)	.38
CC vs TC+TT	Overall	7	.12	Fixed	0.86 (0.75-0.98)	.03
	Asian	5	.09	Random	0.87 (0.70-1.07)	.18
	Caucasian	2	.19	Fixed	0.93 (0.66-1.30)	.66
VEGF −2578 C>A						
A vs C	Overall	6	.15	Fixed	1.26 (1.15-1.38)	<.00001
	Asian	5	.12	Fixed	1.28 (1.16-1.42)	<.00001
	Caucasian	1	–	Fixed	1.13 (0.88-1.45)	.35
AA vs CA+CC	Overall	6	.63	Fixed	1.39 (1.16-1.67)	.0004
	Asian	5	.59	Fixed	1.44 (1.18-1.76)	.0004
	Caucasian	1	–	Fixed	1.18 (0.76-1.83)	.46
CC vs CA+AA	Overall	6	.05	Random	0.75 (0.61-0.92)	.006
	Asian	5	.03	Random	0.73 (0.58-0.93)	.01
	Caucasian	1	–	Fixed	0.84 (0.56-1.27)	.41
VEGF −1154 G>A						
A vs G	Overall	3	.23	Fixed	1.04 (0.88-1.24)	.63
	Asian	1	–	Fixed	0.94 (0.68-1.29)	.70
	Caucasian	2	.13	Fixed	1.09 (0.89-1.34)	.41
AA vs GA+GG	Overall	3	.49	Fixed	1.04 (0.72-1.51)	.82
	Asian	1	–	Fixed	0.74 (0.32-1.70)	.48
	Caucasian	2	.45	Fixed	1.14 (0.76-1.73)	.53
GG vs GA+AA	Overall	3	.27	Fixed	0.95 (0.76-1.18)	.63
	Asian	1	–	Fixed	1.02 (0.70-1.49)	.90
	Caucasian	2	.12	Fixed	0.91 (0.69-1.20)	.49
VEGF +1612 G>A						
A vs G	Asian	4	.59	Fixed	1.12 (1.00-1.25)	.05
AA vs GA+GG	Asian	4	.56	Fixed	1.27 (0.99-1.64)	.06
GG vs GA+AA	Asian	4	.76	Fixed	0.89 (0.77-1.04)	.14

Abbreviations: OR, odds ratio; VEGF, vascular endothelial growth factor.

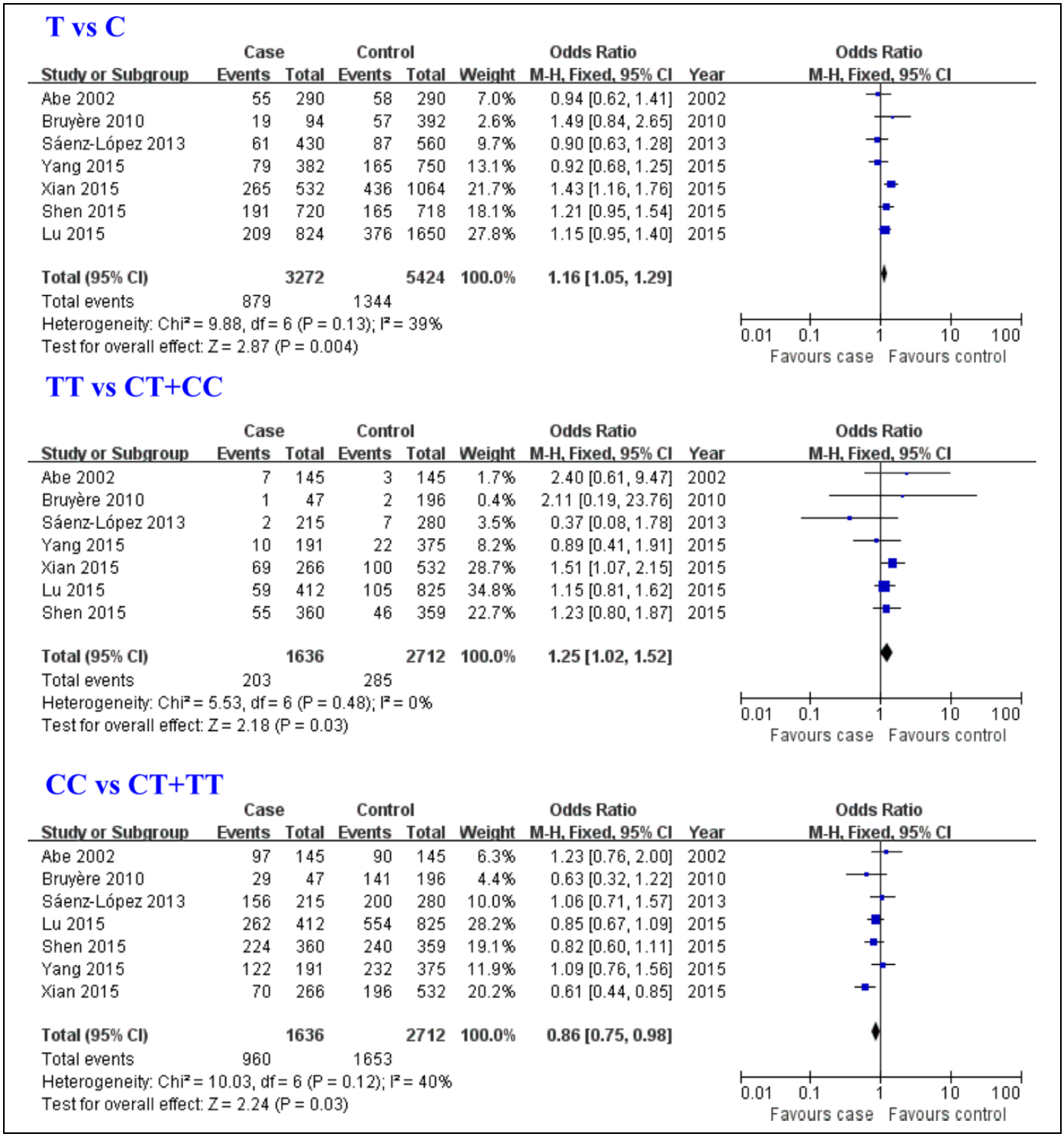

Figure 1. Association between VEGF +936C>T gene polymorphism and renal cell carcinoma risk (overall populations).

overall populations (T allele: OR = 1.16, 95% CI: 1.05-1.29, $P = .004$; TT genotype: OR = 1.25, 95% CI: 1.02-1.52, $P = .03$; CC genotype: OR = 0.86, 95% CI: 0.75-0.98, $P = .03$; Figure 1 and Table 2).

In the subgroup analysis by ethnicity, this meta-analysis indicated that, in Asian population, VEGF +936C>TT allele and TT genotype were associated with renal cell carcinoma risk but not in CC genotype (Table 2). However, VEGF +936C>T gene polymorphism was not associated with renal cell carcinoma risk in Caucasian population (Table 2).

Sensitivity analysis according to genotype distribution of the control population reported for VEGF +936C>T gene polymorphism conformed to HWE for the relationship

between VEGF +936C>T gene polymorphism and renal cell carcinoma risk was performed. Two studies[11,12] were not in HWE. We found that T allele, TT genotype, and CC genotype were not associated with renal cell carcinoma risk (T allele: OR = 1.15, 95% CI: 1.00-1.32, $P = .05$; TT genotype: OR = 1.34, 95% CI: 0.99-1.80, $P = .05$; CC genotype: OR = 0.89, 95% CI: 0.76-1.05, $P = .17$). The results from sensitivity analysis according to HWE were not same as those from nonsensitivity analysis.

Association of VEGF −2578 C>A Gene Polymorphism With Renal Cell Carcinoma Risk

Six studies[9,11-14,16] for the relationship between VEGF −2578 C>A gene polymorphism and renal cell carcinoma risk were included in this meta-analysis, and the extracted data were shown in Table 1. We found that VEGF −2578 C>A gene polymorphism was associated with renal cell carcinoma risk in overall populations (A allele: OR = 1.26, 95% CI: 1.15-1.38, $P > .00001$; AA genotype: OR = 1.39, 95% CI: 1.16-1.67, $P = .0004$; CC genotype: OR = 0.75, 95% CI: 0.61-0.92, $P = .006$; Figure 2 and Table 2).

In the subgroup analysis by ethnicity, this meta-analysis indicated that, in Asian population, VEGF −2578 C>A gene polymorphism was associated with renal cell carcinoma risk (Table 2). However, VEGF −2578 C>A gene polymorphism was not associated with renal cell carcinoma risk in Caucasian population (Table 2).

Association of VEGF −1154 G>A Gene Polymorphism With Renal Cell Carcinoma Risk

Three studies[8,14,17] for the relationship between VEGF −1154 G>A gene polymorphism and renal cell carcinoma risk were included in this meta-analysis, and the extracted data were shown in Table 1. We found that VEGF −1154 G>A gene polymorphism was not associated with renal cell carcinoma risk in overall populations (Table 2).

In the subgroup analysis by ethnicity, this meta-analysis indicated that, in Asian population, VEGF −1154 G>A gene polymorphism was not associated with renal cell carcinoma risk (Table 2). Furthermore, VEGF −1154 G>A gene polymorphism was also not associated with renal cell carcinoma risk in Caucasian population (Table 2).

Association of VEGF +1612 G>A Gene Polymorphism With Renal Cell Carcinoma Risk

Four studies[11-13,15] for the relationship between VEGF +1612 G>A gene polymorphism and renal cell carcinoma risk were included in this meta-analysis, and all studies were performed in Asian population (Table 1). We found that VEGF +1612 G>A gene polymorphism was not associated with renal cell carcinoma risk in Asian population (Table 2).

Discussion

In this meta-analysis, we found that VEGF +405G>CC allele and GG genotype were associated with renal cell carcinoma risk, but CC genotype not in Asian population and in overall populations. However, VEGF +405G>C gene polymorphism was not associated with renal cell carcinoma risk in Caucasians. However, there were only 3 included studies for this meta-analysis (1 for Asians and 2 for Caucasians). The results for the relationship between VEGF +405G>C gene polymorphism and renal cell carcinoma risk might be less robust. More studies should be performed in the future.

In the meta-analysis for the relationship between VEGF −460T>C gene polymorphism and renal cell carcinoma risk, we found that VEGF −460T>C gene polymorphism was associated with renal cell carcinoma risk in Asian population. But, there was only one included studies for Asians, and the results might be less robust. However, VEGF −460T>C gene polymorphism was associated with renal cell carcinoma risk in Caucasians and in overall populations.

Interestingly, VEGF +936C>TT allele and TT genotype were found to be associated with renal cell carcinoma risk in Asians and in overall populations, and CC genotype was associated with renal cell carcinoma risk in overall populations. The sample size for overall populations was 7 studies, and the sample size for Asians was 5 studies. We also tested the publication bias for Asians and overall populations and found there was no publication bias for Asians or for overall populations (data not shown). However, VEGF +936C>T gene polymorphism was not associated with renal cell carcinoma risk in Caucasians, and there were only 2 included studies for the meta-analysis in Caucasians. The results for Caucasians should be confirmed in the future.

Furthermore, we also found that VEGF −2578 C>A gene polymorphism was associated with renal cell carcinoma risk in Asians and in overall populations. The sample size for overall populations was 6 studies, and the sample size for Asians was 5 studies. We also tested the publication bias for Asians and overall populations and also found there was no publication bias for Asians or for overall populations (data not shown). However, VEGF −2578 C>A gene polymorphism was not associated with renal cell carcinoma risk in Caucasians, and there was only one included study for the meta-analysis in Caucasians. The results for Caucasians should be retested in further.

This meta-analysis also indicated that VEGF −634G>C gene polymorphism and VEGF +1612 G>A gene polymorphism were not associated with renal cell carcinoma risk in Asians. Furthermore, VEGF −1154 G>A gene polymorphism was not associated with renal cell carcinoma risk in Asians, in Caucasians, and in overall populations. The sample sizes for VEGF −634G>C gene polymorphism and VEGF +1612 G>A gene polymorphism were 4, and the sample size for VEGF −1154 G>A gene polymorphism was 3. More studies should be conducted in the future.

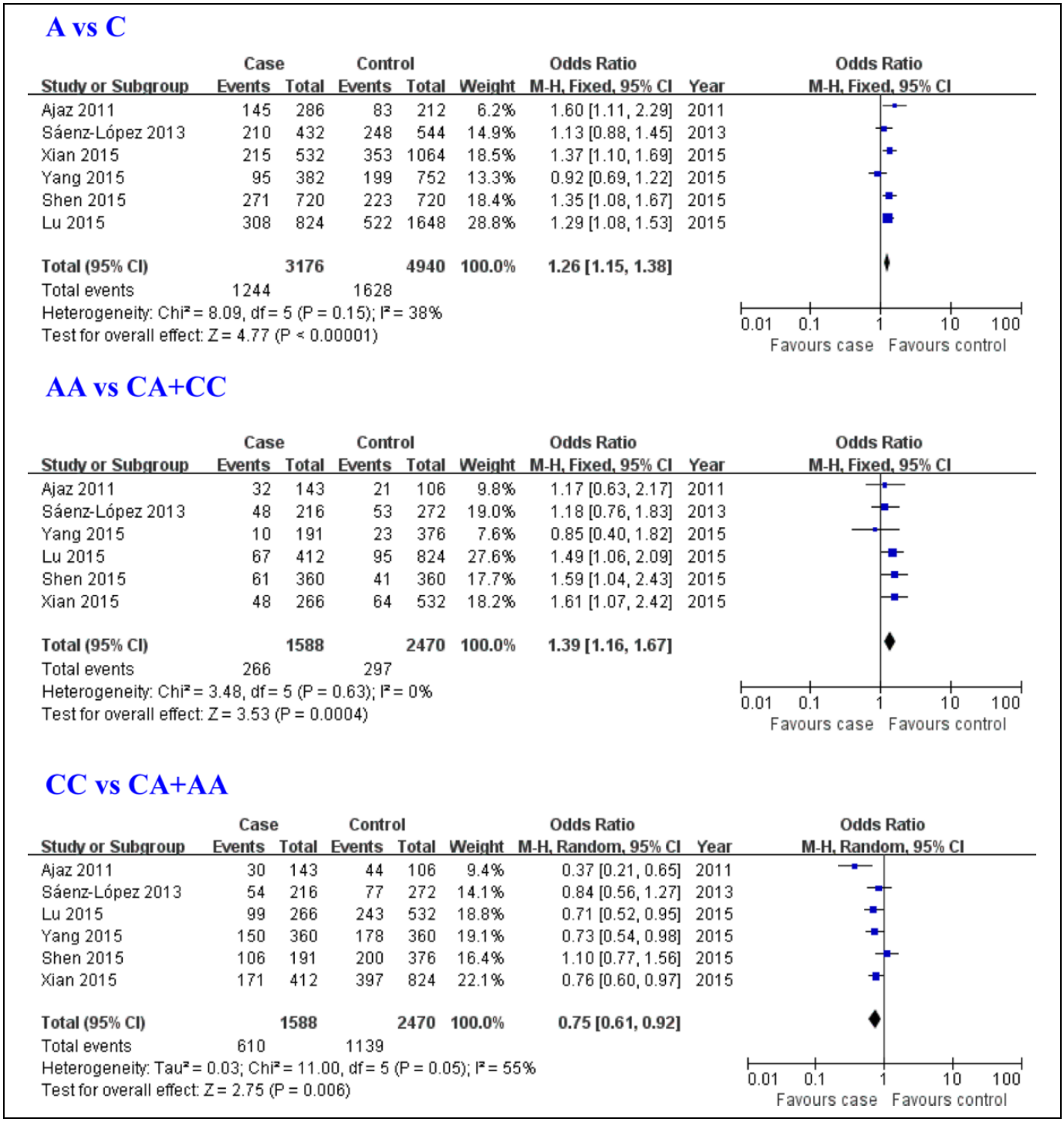

Figure 2. Association between VEGF −2578 C>A gene polymorphism and renal cell carcinoma risk (overall populations).

In previous, Zhang *et al*[18] performed a meta-analysis including 5 studies and indicated that the VEGF +936C>T (including 3 studies), +1612 G>A (including 1 study), −1154 G>A (including 2 studies), −460T>C (including 2 studies), and +405G>C (including 2 studies) gene polymorphisms were not associated with the risk of renal cell carcinoma, and −2578 C>A gene polymorphism might be associated with an increased risk of renal cell carcinoma (including 2 studies). The sample sizes in our meta-analysis were larger than those for Zhang *et al*.[18] The results from our meta-analysis might be more robust. Furthermore, we first conducted the meta-analysis for the relationship between VEGF −634G>C gene polymorphism and the risk of renal cell carcinoma (including 4 studies) and reported that VEGF

−634G>C gene polymorphism was not associated with renal cell carcinoma risk in Asians.

Nie *et al*[19] performed a hospital-based case–control study, analyzed peripheral venous blood collected from 100 patients with cutaneous squamous cell carcinoma (cSCC) and 124 healthy controls, and reported that VEGF gene −460 C>T polymorphism and −1154 G>A polymorphism may serve as potential genetic markers for the risk and prognosis of cSCC. Rezaei *et al*[20] performed a study aimed to evaluate the impact of VEGF rs3025039 (+936C>T), rs2010963 (+405C>G), rs833061 (−460T>C), rs699947 (−2578C>A), and rs35569394 (18-bp I/D) polymorphisms on breast cancer (BC) risk in an Iranian population in southeast of Iran and reported that VEGF rs699947 polymorphism may increase the risk of BC development. Bingül *et al*[21] isolated the DNA from peripheral blood leukocytes of 127 patients with papillary thyroid carcinoma (PTC) and 203 healthy controls and reported that VEGF G+405C polymorphism is associated with an increased risk of PTC. In different cancers, the relationship might be different.

However, there were some limitations in our meta-analyses, due to the lack of heterogeneity analysis, sensitivity analysis, and publication bias of the pooling OR. For the result that the sample size of included studies was small, and it was difficult to state that different cancers have different incidence in different population, have you ever considered the prevalence and ethnics.

In conclusion, VEGF +405G>CC allele, +405G>C GG genotype, VEGF −2578 C>A gene polymorphism, VEGF +936C>TT allele, and VEGF +936C>T TT genotype were associated with renal cell carcinoma risk in Asian population and in overall populations. Furthermore, VEGF −460T>C gene polymorphism was associated with renal cell carcinoma risk in Asian population, and CC genotype was associated with renal cell carcinoma risk in overall populations. However, more association studies are required to clarify this relationship further.

Declaration of Conflicting Interests

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