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Association of Methylenetetrahydrofolate Reductase, Vitamin D Receptor, and Interleukin-16 Gene Polymorphisms With Renal Cell Carcinoma Risk

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Abstract

In this meta-analysis, we investigated the association of methylenetetrahydrofolate reductase, vitamin D receptor, and interleukin-16 gene polymorphisms with the risk of renal cell carcinoma. We searched the PubMed and Cochrane Library databases up to July 1, 2017, and included 12 eligible case–control studies in our analysis. The vitamin D receptor ApaI A allele, ApaI AA and aa genotypes, BsmI B allele, and Fok1 FF genotype were all associated with the risk of renal cell carcinoma in Asian populations. However, methylenetetrahydrofolate reductase (rs1801133 and rs1801131), vitamin D receptor (TaqI and Fok1), and interleukin-16 (rs4778889 and rs11556218) gene polymorphisms were not associated with the risk of renal cell carcinoma. Our study indicates that the vitamin D receptor ApaI A allele, ApaI AA and aa genotypes, BsmI B allele, and Fok1 FF genotype are associated with renal cell carcinoma risk.

Keywords

renal cell carcinoma, methylenetetrahydrofolate reductase, vitamin D receptor, interleukin-16, gene polymorphism, meta-analysis

Abbreviations

Cis, confidence intervals; *IL-16*, interleukin-16; *MTHFR*, methylenetetrahydrofolate reductase; OR, odds ratio; *VDR*, vitamin D receptor

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Introduction

Renal cell carcinoma, one of the most malignant tumors, is associated with low survival rates because of resistance to conventional cancer therapies such as radiotherapy and chemotherapy as well as high degree of recurrence after curative surgeries because of distant metastases.[1,2] Therefore, there is urgent need for improved diagnostic and prognostic biomarkers that can accurately predict renal cell carcinoma progression. The etiology of renal cell carcinoma is not clear, and risk factors are not well established.

Many studies have shown that genetic polymorphisms in methylenetetrahydrofolate reductase (*MTHFR*), vitamin D receptor (*VDR*), and interleukin-16 (*IL-16*) are associated with the risk of renal cell carcinoma.[3-7] However, some of the findings are contradictory. Arjumand *et al* reported that *VDR* BsmI (rs1544410) was associated with pathogenesis of RCC.[8] But, Yang *et al* showed that there was no correlation between *VDR* BsmI genotypes and RCC.[9] The *MTHFR* rs1801133, *MTHFR* rs1801131, *VDR* ApaI (rs7975232), *VDR* BsmI (rs1544410), *VDR* TaqI (rs731236), *VDR* Fok1 (rs2228570), *IL-16* rs4778889, and *IL-16* rs11556218 are polymorphisms associated with risk of prostate, lung, breast, and ovarian cancer.[10-18]

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Many studies have identified *MTHFR*, *VDR*, and *IL-16* gene polymorphisms in renal cell carcinoma. Therefore, we conducted a comprehensive meta-analysis to investigate whether the polymorphisms in the *MTHFR*, *VDR*, and *IL-16* genes are associated with the risk of renal cell carcinoma.

Materials and Methods

Literature Search Strategy

We identified 73 articles after searching the PubMed, and Cochrane Library databases until July 1, 2017, with the following keywords: *methylenetetrahydrofolate reductase* OR *MTHFR* OR *vitamin D receptor* OR *VDR* OR *interleukin-16* OR *IL-16* and *renal cell carcinoma* OR *renal cell cancer*. Among these, we searched case–control studies that reported renal cell cancer outcomes and provided data regarding *MTHFR*, *VDR*, and *IL-16* genotype distribution for inclusion in our meta-analysis. We excluded articles that were (1) reviews and editorials, (2) case reports, (3) did not report *MTHFR*, *VDR*, and *IL-16* gene polymorphism or renal cell cancer outcomes, and (4) did not investigate the role of *MTHFR*, *VDR*, and *IL-16* gene expression to renal cell cancer. If multiple publications were identified for the same data, we only recruited the latest paper for our final analysis.

Data Extraction

The following information was extracted from each eligible study by 2 independent investigators: first author's surname, publication year, location of the study conducted, ethnicity, control source of the control group, and the number of cases and controls for *MTHFR*, *VDR*, and *IL-16* genotypes. Any disagreements in the 2 sets of data were resolved by discussion.

Statistical Analysis

Statistical analyses were performed with the Cochrane Review Manager Version 5 (Cochrane Library, London, United Kingdom). In most cases, the pooled statistics were analyzed by the fixed effects model (Mantel-Haenszel method), but random effects model (DerSimonian-Laird method) was used to analyze data when $P_{\text{heterogeneity}} < .1$. Data were expressed as odds ratios (ORs) and 95% confidence intervals (CIs) for dichotomous data. $P < .05$ was considered statistically significant for pooled ORs. I^2 was used to test the heterogeneity among the included studies. We conducted subgroup analysis when more than 2 included reports were available for analysis.

Results

Study Characteristics

The literature search yielded 73 studies with 72 from PubMed and 1 from Cochrane Library (Figure 1). Based on inclusion and exclusion criteria, 12 articles were identified for this meta-analysis. As shown in Table 1, 3 included studies reported the relationship between *MTHFR* gene polymorphism and renal cell carcinoma susceptibility.[3,19,20] All 3 studies analyzed *MTHFR* 677C/T rs1801133,[3,19,20] whereas 2 studies assessed *MTHFR* 1298A/C rs1801131.[3,19]

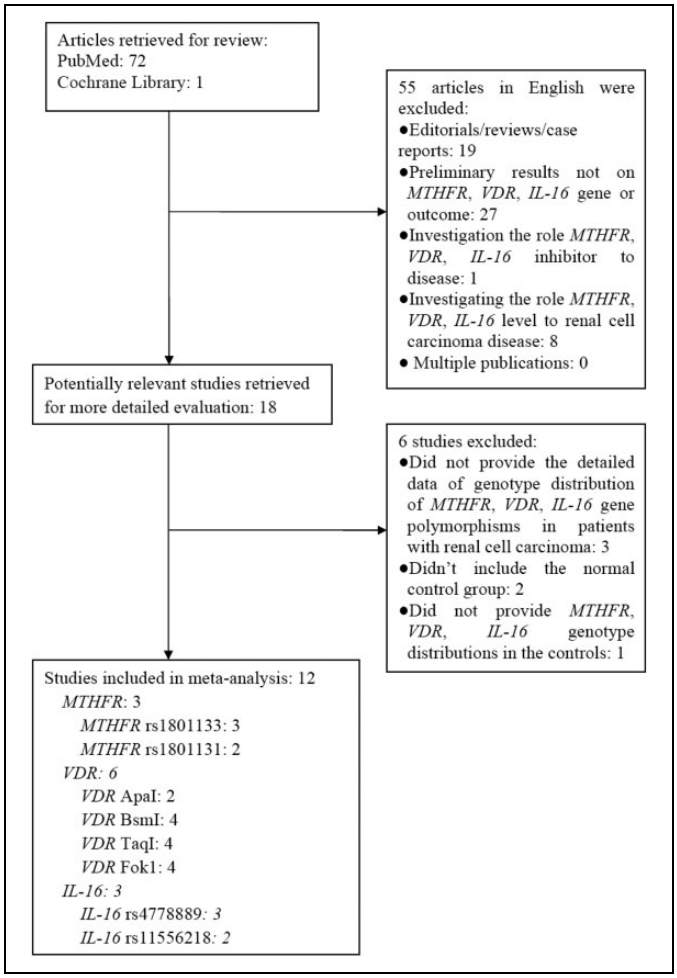

Figure 1. Flow chart of study search and selection.

As shown in Table 2, 6 studies reported the relationship between *VDR* gene polymorphism and the susceptibility of renal cell carcinoma.[4,5,8,9,21,22] Among these, 2 studies analyzed *VDR* ApaI rs7975232,[9,21] whereas 4 studies each reported *VDR* BsmI rs1544410,[5,8,9,21] *VDR* TaqI rs731236,[4,5,9,21] and *VDR* Fok1 rs2228570[5,8,9,22] gene polymorphisms.

As shown in Table 3, 3 studies reported the relationship between *IL-16* gene polymorphism and renal cell carcinoma susceptibility in Chinese population.[6,7,23] Among these, 3 studies reported *IL-16* rs4778889,[6,7,23] whereas 2 studies reported *IL-16* rs11556218[6,23] gene polymorphisms.

Association of MTHFR Gene Polymorphism With Renal Cell Carcinoma Susceptibility

The *MTHFR* rs1801133 (T allele as well as TT and CC genotypes) and rs1801131 (C allele as well as CC and AA genotypes) were not associated with renal cell carcinoma risk (Figure 2 and Table 4).

Table 1. Effects of MTHFR Gene Polymorphism on Renal Cell Carcinoma Risk.

					Case				Control			
Gene Sites	Author, Year	Ethnicity	Country/Subgroup	Source of Control	TT	CT	CC	Total	TT	CT	CC	Total
rs1801133	Moore *et al*, 2008	Caucasian	Europe	Hospital	93	370	355	818	113	419	556	1088
	Ajaz *et al*, 2012	Asian	Pakistan	Population	4	50	108	162	6	50	121	177
	Lv *et al*, 2015	Asian	China	Population	16	32	33	81	23	36	21	80
rs1801131					CC	AC	AA	Total	CC	AC	AA	Total
	Moore *et al*, 2008	Caucasian	Europe	Hospital	85	357	376	818	113	483	491	1087
	Ajaz *et al*, 2012	Asian	Pakistan	Population	19	106	43	168	8	105	59	172

Abbreviation: MTHFR, methylenetetrahydrofolate reductase.

Table 2. Summary of the Effects of VDR Gene Polymorphism on Renal Cell Carcinoma Risk.

					Case				Control			
Restriction Sites	Author, Year	Ethnicity	Country/Subgroup	Source of Control	AA	Aa	aa	Total	AA	Aa	aa	Total
ApaI	Obara *et al*, 2007	Asian	Japan	Population	23	52	60	135	11	71	68	150
	Yang *et al*, 2016	Asian	China	Population	35	153	114	302	18	135	149	302
BsmI					BB	Bb	bb	Total	BB	Bb	bb	Total
	Obara *et al*, 2007	Asian	Japan	Population	0	33	102	135	1	41	108	150
	Karami *et al*, 2008	Caucasian	United States	Hospital	81	370	324	775	112	474	407	993
	Arjumand *et al*, 2012	Asian	Indian	Healthy	50	88	58	196	83	130	37	250
	Yang *et al*, 2016	Asian	China	Population			255	302			265	302
TaqI					tt	Tt	TT	Total	tt	Tt	TT	Total
	Ikuyama *et al*, 2002	Asian	Japan	Hospital	1	19	82	102	8	70	126	204
	Obara *et al*, 2007	Asian	Japan	Population	0	31	104	135	1	37	112	150
	Karami *et al*, 2008	United States	Caucasian	Hospital	97	361	320	778	137	438	402	977
	Yang *et al*, 2016	Asian	China	Population			261	302			272	302
Fok1					ff	Ff	FF	Total	ff	Ff	FF	Total
	Karami *et al*, 2008	Caucasian	United States	Hospital	149	376	286	811	199	492	338	1029
	Arjumand *et al*, 2012	Asian	Indian	Healthy	40	94	62	196	38	98	114	250
	Southard *et al*, 2012	Caucasian	Finland	Healthy	22	66	64	152	48	144	113	305
	Yang *et al*, 2016	Asian	China	Population	61	171	70	302	64	159	79	302

Abbreviation: VDR, vitamin D receptor.

Table 3. Effects of IL-16 Gene Polymorphism on Renal Cell Carcinoma Risk.

				Case				Control			
Restriction Sites	Author, Year	Country/Subgroup	Source of Control	CC	CT	TT	Total	CC	CT	TT	Total
rs4778889	Zhu *et al*, 2010	China	Hospital	14	122	199	335	34	135	171	340
	Wang *et al*, 2015	China	Hospital	22	77	82	181	12	106	160	278
	Yang *et al*, 2016	China	Hospital	28	113	132	273	14	84	176	274
rs11556218				GG	TG	TT	Total	GG	TG	TT	Total
	Wang *et al*, 2015	China	Population	12	75	94	181	15	108	155	278
	Yang *et al*, 2016	China	Hospital	15	110	149	274	12	107	155	274

Abbreviation: IL-16, interleukin-16.

Association Between VDR *Gene Polymorphism and Renal Cell Carcinoma Susceptibility*

The *VDR* ApaI A allele as well as AA and aa genotypes were associated with renal cell carcinoma risk in Asians (A allele: OR = 1.41, 95% CI: 1.15-1.72, $P = .0007$; AA genotype: OR = 2.25, 95% CI: 1.41-3.60, $P = .0007$; aa genotype: OR = 0.72, 95% CI: 0.55-0.94, $P = .01$; Table 4). The *VDR* BsmI alleles and genotypes were not associated with the risk of renal cell carcinoma (B allele: OR = 0.81, 95% CI: 0.60-1.09, $P = .17$; BB genotype: OR = 0.83, 95% CI: 0.65-1.05, $P = .12$; bb genotype: OR = 1.21, 95% CI: 0.79-1.85, $P = .37$; Table 4). In Asian population, B allele was associated with the risk of renal cell carcinoma, but BB genotype and bb genotype were not (B allele: OR = 0.68, 95% CI: 0.54-0.85, $P = .001$; BB genotype:

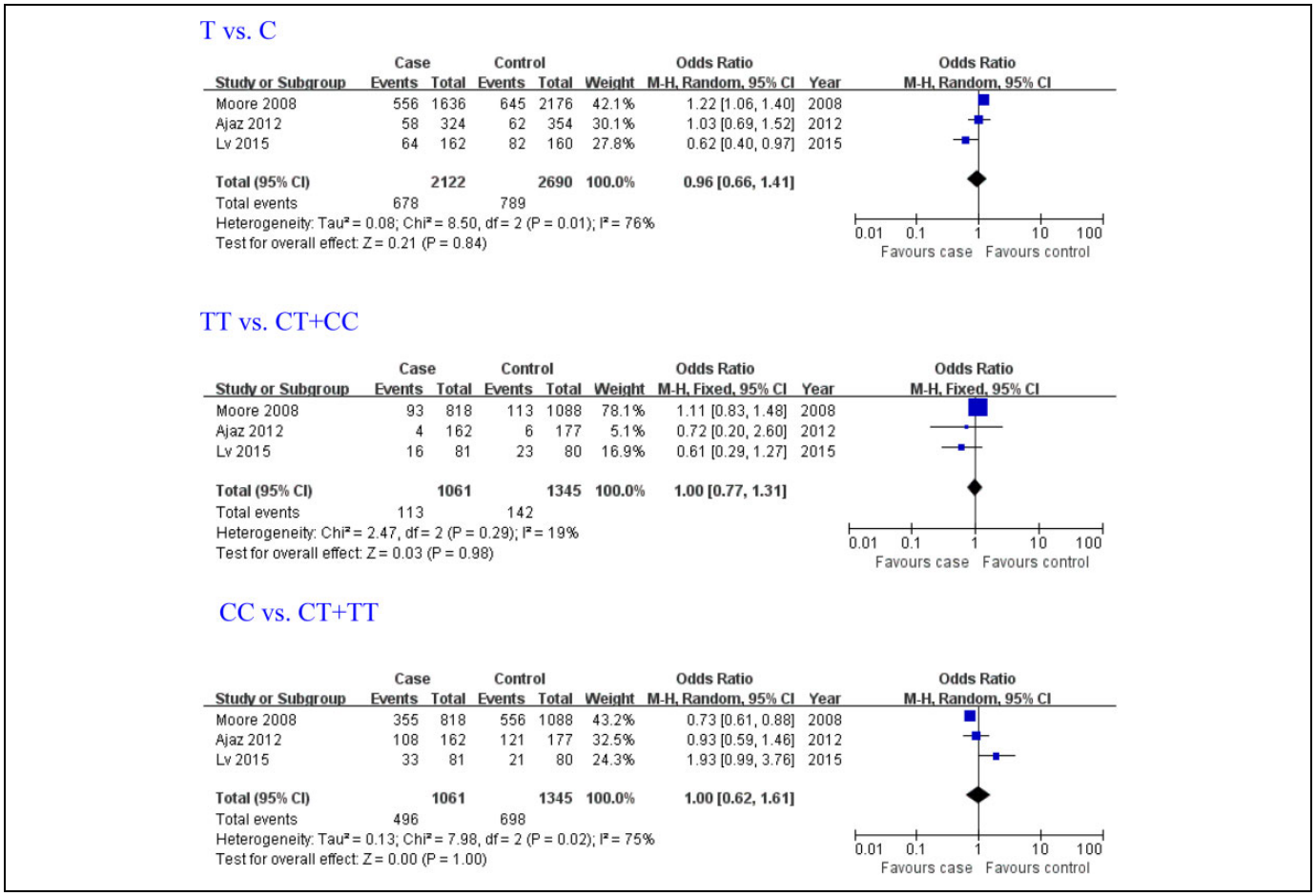

Figure 2. Association of methylenetetrahydrofolate reductase (MTHFR) rs1801133 gene polymorphism with renal cell carcinoma susceptibility.

OR = 0.68, 95% CI: 0.45-1.03, $P = .07$; bb genotype: OR = 1.35, 95% CI: 0.43-4.22, $P = .60$; Table 4).

The *VDR* TaqI allele and genotypes were not associated with the risk of renal cell carcinoma (t allele: OR = 0.74, 95% CI: 0.46-1.19, $P = .21$; tt genotype: OR = 0.84, 95% CI: 0.64-1.10, $P = .20$; TT genotype: OR = 1.16, 95% CI: 0.75-1.78, $P = .50$; Table 4).

The *VDR* Fok1 allele and genotype were not associated with the risk of renal cell carcinoma (f allele: OR = 1.05, 95% CI: 0.85-1.29, $P = .64$; ff genotype: OR = 0.99, 95% CI: 0.83-1.18, $P = .90$; FF genotype: OR = 0.91, 95% CI: 0.66-1.26, $P = .57$; Figure 3 and Table 4). In Asian population, FF genotype was associated with the risk of renal cell carcinoma (Table 4), but F allele and ff genotype were not. Furthermore, *VDR* BsmI f allele as well as ff and FF genotypes were not associated with the risk of renal cell carcinoma in Caucasians (Table 4).

Association of IL-16 *Gene Polymorphism With the Susceptibility of Renal Cell Carcinoma*

The *IL-16* rs4778889 C allele and genotype were not associated with the risk of renal cell carcinoma in Chinese population (C allele: OR = 1.24, 95% CI: 0.66-2.33, $P = .50$; CC genotype: OR = 1.36, 95% CI: 0.38-4.79, $P = .64$; TT genotype: OR = 0.78, 95% CI: 0.40-1.50, $P = .45$; Figure 4; Table 4). Moreover, the *IL-16* rs11556218 G allele, GG and TT genotypes were also not associated with renal cell carcinoma risk in Chinese population (G allele: OR = 1.11, 95% CI: 0.91-1.36, $P = .30$; GG genotype: OR = 1.25, 95% CI: 0.72-2.18, $P = .42$; TT genotype: OR = 0.89, 95% CI: 0.69-1.14, $P = .36$; Table 4).

Discussion

In previous studies, the gene polymorphisms have been associated with increased susceptibility of renal cell carcinoma. Our study indicated that *MTHFR* rs1801133 (T allele, TT and CC genotypes) as well as *MTHFR* rs1801131 (C allele, CC and AA genotypes) were not associated with renal cell carcinoma risk (Table 4). Since the number of included studies were small, further investigations are necessary to confirm these findings. The MTHFR, a central enzyme involved in folate metabolism, plays an important role in DNA synthesis and methylation that are relevant in cancer pathogenesis.[24-26] Our findings suggest that *MTHFR* rs1801133 and rs1801131 gene polymorphisms do not affect DNA synthesis and methylation, and therefore, do not influence the onset of renal cell carcinoma.

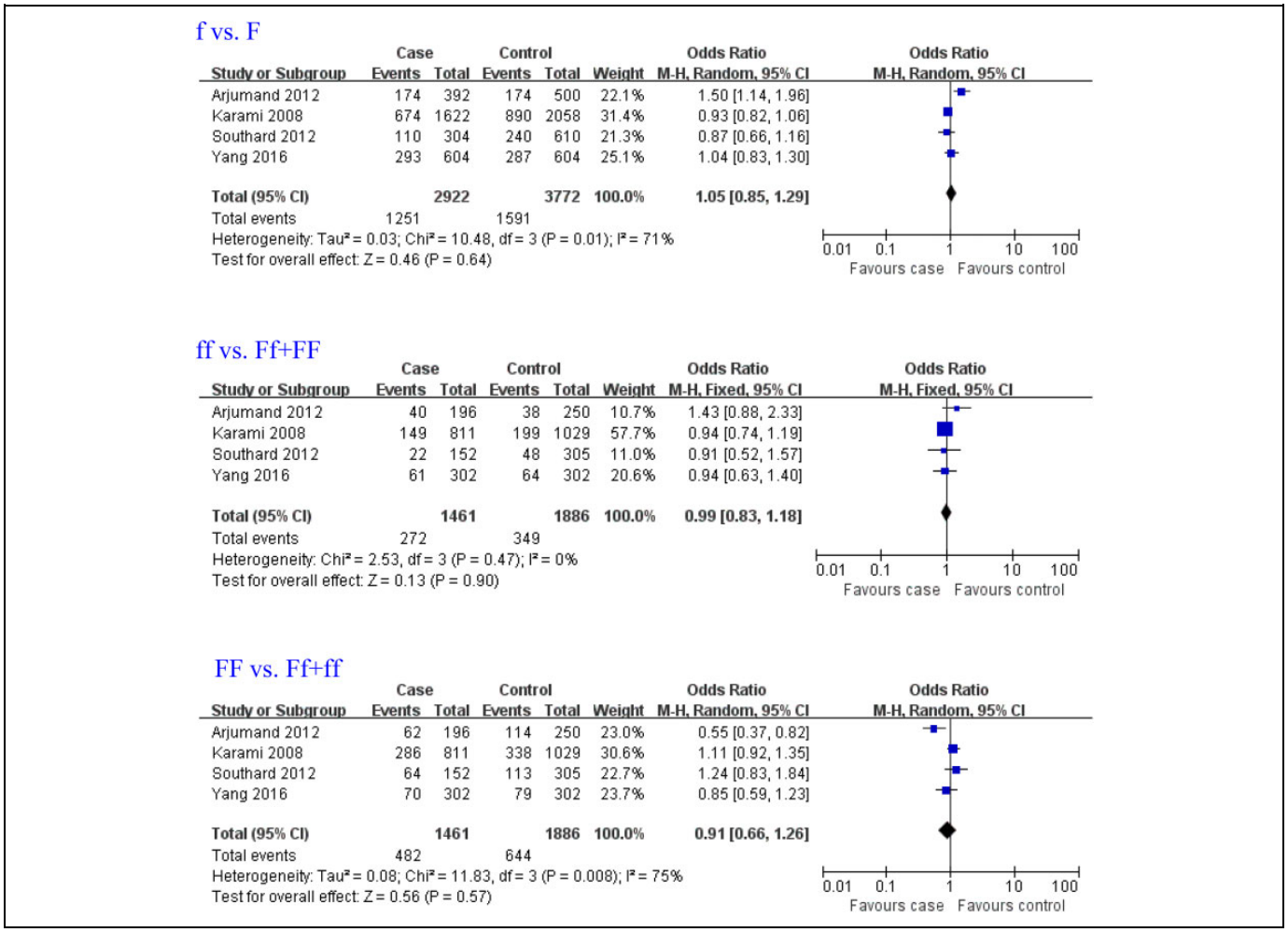

Figure 3. Association of vitamin D receptor (VDR) Fok1 gene polymorphism with renal cell carcinoma susceptibility.

The *VDR* BsmI, TaqI, and Fok1 gene polymorphisms are not associated with renal cell carcinoma risk in overall populations. Interestingly, *VDR* ApaI (A allele, AA and aa genotypes, BsmI B allele, and Fok1 FF genotype are associated with the risk of renal cell carcinoma. Ou *et al* conducted a meta-analysis and demonstrated that the ApaI AA genotype, BsmI BB genotype, Fok1 f allele, and Fok1 FF genotype were associated with renal cell carcinoma risk in Asians.[27] Our study was more robust as it included more studies than Ou *et al.*[27] Vitamin D regulates the cell proliferation, differentiation, and apoptosis in various tissues and plays a protective role in some cancer types.[28,29] We showed that *VDR* ApaI (A allele, AA genotype, aa genotype), BsmI B allele, *and* Fok1 FF genotype are associated with onset of renal cell carcinoma suggesting that these polymorphisms alter the activity of VDR.

Our meta-analysis also showed that *IL-16* rs4778889 (C allele, CC and TT genotypes) as well as rs11556218 (G allele, GG and TT genotypes) gene polymorphisms were not associated with renal cell carcinoma risk in Chinese population. Interleukin-16 is a multifunctional pro-inflammatory cytokine, which is associated with many complex human disorders as it plays a critical role in regulating cellular homoeostasis.[30] Our study demonstrates that IL-16 rs4778889 and rs11556218 gene polymorphisms did not alter IL-16 function and therefore was not involved in the onset of renal cell carcinoma.

Our study demonstrates that the *VDR* ApaI (A allele, AA and aa genotypes), BsmI B allele, and Fok1 FF genotype are potential indicators of renal cell carcinoma risk in Asians. This needs to be confirmed by large-scale studies in future. Furthermore, the association of haplotype blocks of those genes with renal cell carcinoma needs to be investigated.

Gene disfunction could induce the disorders of cell growth and differentiation, and it can lead to the out of control of cell proliferation and apoptosis which affects the susceptibility of RCC. The MTHFR, a critical enzyme in the metabolism of folic acid, converts 5, 10-methylenetetrahydrofolate acid into 5-methyltetrahydrofolate and is a key importance for the homocysteine metabolism.[31,32] The active form of vitamin D acts as a steroid hormone and binds to the VDR. Vitamin D receptor mediates many genomic and nongenomic effects of vitamin D.[33] This receptor is expressed in most cell types including cells in kidney. Interleukin-16, a multifunctional pro-inflammatory cytokine, plays a critical role in regulation of cellular functions such as homoeostasis and affects the

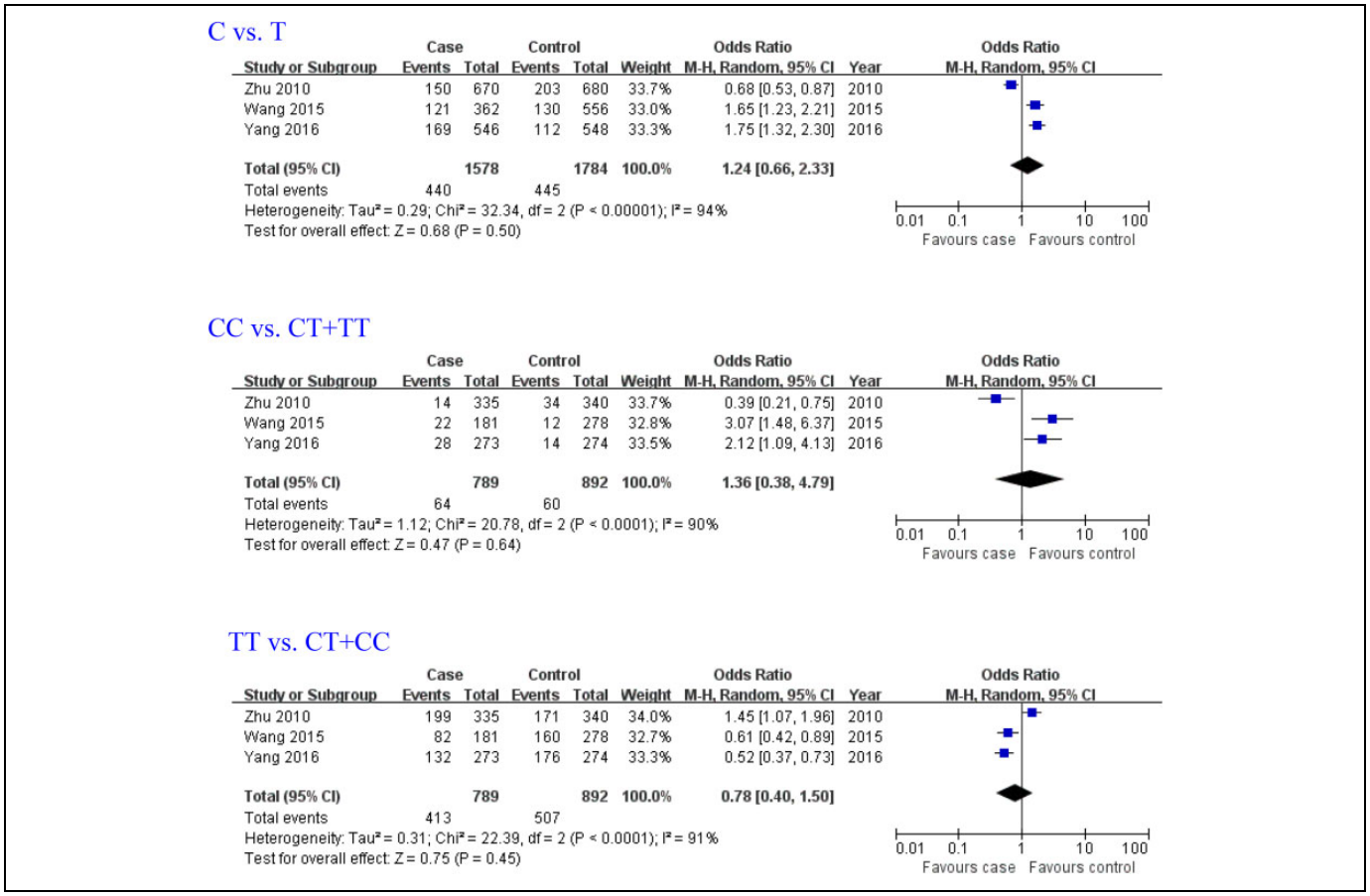

Figure 4. Association of interleukin-16 (IL-16) rs4778889 gene polymorphism with renal cell carcinoma susceptibility.

Table 4. Association of MTHFR, VDR, and IL-16 Gene Polymorphisms With Renal Cell Carcinoma Risk.[a]

Alleles and Genotypes	Group and Subgroups	Studies Number	Q Test *P* Value	Model Selected	OR (95% CI)	*P*
MTHFR rs1801133						
T vs C	Overall	3	.01	Random	0.96 (0.66-1.41)	.84
	Asian	2	.10	Fixed	0.82 (0.61-1.10)	.19
TT vs (CT + CC)	Overall	3	.29	Fixed	1.00 (0.77-1.31)	.98
	Asian	2	.82	Fixed	0.64 (0.34-1.20)	.16
CC vs (CT + TT)	Overall	3	.02	Random	1.00 (0.62-1.61)	1.00
	Asian	2	.07	Random	1.28 (0.63-2.62)	.50
MTHFR rs1801131						
C vs A	Overall	2	.05	Random	1.13 (0.81-1.57)	.46
CC vs (AC + AA)	Overall	2	.29	Fixed	1.48 (0.59-3.74)	.41
AA vs (AC + CC)	Overall	2	.08	Random	0.87 (0.57-1.33)	.52
VDR ApaI						
A vs a	Asian	2	.47	Fixed	1.41 (1.15-1.72)	**.0007**
AA vs Aa + aa	Asian	2	.64	Fixed	2.25 (1.41-3.60)	**.0007**
aa vs AA + Aa	Asian	2	.13	Fixed	0.72 (0.55-0.94)	**.01**
VDR BsmI						
B vs b	Overall	3	.02	Random	0.81 (0.60-1.09)	.17
	Asian	2	.34	Fixed	0.68 (0.54-0.85)	**.001**
BB vs Bb + bb	Overall	3	.49	Fixed	0.83 (0.65-1.05)	.12
	Asian	2	.70	Fixed	0.68 (0.45-1.03)	.07

(continued)

Table 4. (continued)

Alleles and Genotypes	Group and Subgroups	Studies Number	Q Test *P* Value	Model Selected	OR (95% CI)	*P*
bb vs Bb + BB	Overall	4	.003	Random	1.21 (0.79-1.85)	.37
	Asian	3	.0005	Random	1.35 (0.43-4.22)	.60
VDR TaqI						
t vs T	Overall	3	.01	Random	0.74 (0.46-1.19)	.21
	Asian	2	.05	Random	0.61 (0.31-1.22)	.16
tt vs Tt + TT	Overall	3	.43	Fixed	0.84 (0.64-1.10)	.20
	Asian	2	.83	Fixed	0.27 (0.05-1.55)	.14
TT vs Tt + tt	Overall	4	.007	Random	1.16 (0.75-1.78)	.50
	Asian	3	.004	Random	1.25 (0.60-2.61)	.54
VDR Fok1						
f vs F	Overall	4	.01	Random	1.05 (0.85-1.29)	.64
	Asian	2	.04	Random	1.24 (0.87-1.76)	.24
	Caucasian	2	.68	Fixed	0.92 (0.82-1.04)	.19
ff vs Ff + FF	Overall	4	.47	Fixed	0.99 (0.83-1.18)	.90
	Asian	2	.19	Fixed	1.11 (0.82-1.51)	.51
	Caucasian	2	.91	Fixed	0.93 (0.75-1.16)	.53
FF vs Ff + ff	Overall	4	.008	Random	0.91 (0.66-1.26)	.57
	Asian	2	.11	Fixed	0.69 (0.53-0.91)	**.007**
	Caucasian	2	.64	Fixed	1.14 (0.95-1.35)	.15
IL-16 rs4778889						
C vs T	Asian	3	<.00001	Random	1.24 (0.66-2.33)	.50
CC vs CT + TT	Asian	3	<.0001	Random	1.36 (0.38-4.79)	.64
TT vs CT + CC	Asian	3	<.0001	Random	0.78 (0.40-1.50)	.45
IL-16 rs11556218						
G vs T	Asian	2	.84	Fixed	1.11 (0.91-1.36)	.30
GG vs TG + TT	Asian	2	.98	Fixed	1.25 (0.72-2.18)	.42
TT vs TG + GG	Asian	2	.80	Fixed	0.89 (0.69-1.14)	.36

Abbreviations: CI, confidence interval; IL-16, interleukin-16; MTHFR, methylenetetrahydrofolate reductase; OR, odds ratio; VDR, vitamin D receptor.
[a]Bold values were significant.

secretion of tumor-related inflammatory cytokines.[30,34] The current evidences indicated that MTHFR, VDR, and IL-16 take part in the pathogenesis of cancers.

The limitations of our study include small sample size, limited statistical power, heterogeneity of enrolled cases, variable study designs, and various interventions. These may have affected the statistical results and hence need to be regarded cautiously and confirmed in the future.

In conclusion, we demonstrate the association of *VDR* ApaI A allele, AA genotype, aa genotype, BsmI B allele, and Fok1 FF genotype are associated with the risk of renal cell carcinoma in Asians.

Authors' Note

Tianbiao Zhou and Hongyan Li contributed equally to this article.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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