Association of four genetic polymorphisms in the vascular endothelial growth factor-A gene and development of ovarian cancer: a meta-analysis

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ABSTRACT

This study meta-analyzed the literature on possible association of four polymorphisms (+936C/T, -460C/T, -2578C/A and -1154G/A) in the vascular endothelial growth factor (VEGF)-A gene with risk of ovarian cancer. Meta-analysis of 7 case-control studies involving +936C/T, 4 studies involving -460C/T, 4 studies involving -2578C/A and 2 studies involving -1154G/A showed significant association between -460C/T and ovarian cancer risk. This risk was observed in the total population (allelic model, OR 1.80, 95% CI 1.26-2.59, *P* = 0.001; recessive model, OR 1.84, 95% CI 1.13-2.98, *P* = 0.01; dominant model, OR 0.51, 95% CI 0.39-0.67, *P* < 0.001; homozygous model, OR 2.48, 95% CI 1.72-3.56, *P* < 0.001; heterozygous model, OR 1.67, 95% CI 1.26-2.21, *P* < 0.001) and in the subgroup of Asian study participants. The CA genotype at -2578C/A was a risk factor in the total population, while the CT genotype at +936C/T was a protective factor in Caucasians. None of the five genetic models suggested a significant association between -1154G/A and ovarian cancer risk in the entire study population, or between +936C/T and risk in Asian or Chinese participants. These findings should be verified in large, well-designed studies.

INTRODUCTION

Ovarian cancer is a major cause of cancer-related death in females worldwide [1, 2]. Although treatment can significantly improve quality of life, the 5-year survival rate for patients with advanced ovarian cancer remains below 30%, mainly due to high rates of recurrence and metastasis [3, 4]. Development of ovarian cancer has been linked to numerous environmental and lifestyle factors, including age, early menarche, late menopause, non-childbearing, high-fat diet, exposure to talcum powder and asbestos, and long-term hormone supplementation [5, 6]. Ovarian cancer has also been linked to several genetic polymorphisms [7–9].

Angiogenesis, which refers to the formation of new capillary blood vessels from preexisting ones, is an important factor in the development and spread of cancer, including ovarian cancer [10–12]. A key mediator of angiogenesis is vascular endothelial growth factors (VEGFs) [13], which are expressed at higher levels in malignant ovarian tumor tissues than in benign tumor tissues or tissue of low malignant potential [14–16]. This implicates VEGFs in the pathological angiogenesis of ovarian cancer. Indeed, prognosis and overall survival of ovarian cancer patients correlate with serum and/or tumor levels of VEGFs [17–21]. These findings suggest that genetic factors affecting VEGF expression or activity may influence ovarian cancer development and progression.

The founding member of the VEGF family, VEGF-A, is encoded by a gene on chromosome 6p12 that comprises a 14-kb coding region of eight exons and exhibits alternate splicing to form a family of proteins. [22]. Several single-nucleotide polymorphisms (SNPs) in this gene correlate with VEGF expression [23–25]. Numerous case-control studies [26–32] have investigated whether polymorphisms in the VEGF-A gene at positions +936C/T (rs3025039), -460C/T (rs833061), -2578C/A (rs699947) or -1154G/A (rs1570360) influence ovarian cancer risk. Results have been inconclusive and contradictory, prompting us to perform this comprehensive

meta-analysis of all available evidence on these potential associations. To the best of our knowledge, this is the first meta-analysis concerning all four of these previously analyzed polymorphisms and ovarian cancer risk.

RESULTS

Description of studies

A total of 104 potentially relevant publications published in English or Chinese up to April 12, 2017 were systematically identified in PubMed, EMBASE, Google Scholar and Chinese National Knowledge Infrastructure databases (Figure 1). We excluded 83 studies based on review of the titles and abstracts, because they did not analyze the target polymorphisms in the VEGF-A gene or because they did not examine ovarian cancer risk. We excluded another 8 studies because they were not casecontrol studies, 3 studies because they were review articles and 1 study because it did not report precise genotypes. Another 2 studies were excluded because they analyzed overlapping patient populations. In the end, 7 studies were included in the final meta-analysis [26–32] (Table 1).

All 7 studies evaluated the association between the +936C/T polymorphism and ovarian cancer risk (1,345 cases and 1,671 controls). Four studies [26, 29, 31, 32] evaluated the association between the -460C/T polymorphism and

ovarian cancer risk (813 cases and 905 controls); 4 studies [28, 29, 31, 32], the association between the -2578C/A polymorphism and ovarian cancer risk (1,022 cases and 1,228 controls); and 2 studies [29, 31], the association between the -2578C/A polymorphism and ovarian cancer risk (602 cases and 623 controls). The distribution of genotypes in controls was consistent with Hardy-Weinberg equilibrium (HWE, P > 0.05) in all but one study [32] involving the -460C/T polymorphism.

All studies in the meta-analysis received a score of at least 6 on the Newcastle–Ottawa Scale [34], indicating that they were all of good quality. The mean score for all included studies was 7 (Table 2).

Meta-analysis of studies on the +936C/T (rs3025039) polymorphism

Meta-analysis of a possible association between +936C/T polymorphism and ovarian cancer risk is summarized in Table 3. Based on the total study population involving 1,345 cases and 1,751 controls, none of the five genetic models indicated a significant association: allelic model, OR 1.17, 95% CI 0.79–1.72, P = 0.44 (Figure 2A); recessive model, OR 1.25, 95% CI 0.82–1.88, P = 0.30 (Figure 2B); dominant model, OR 0.89, 95% CI 0.55–1.45, P = 0.65 (Figure 2C); homozygous model, OR 1.24, 95% CI 0.76–2.03, P = 0.39

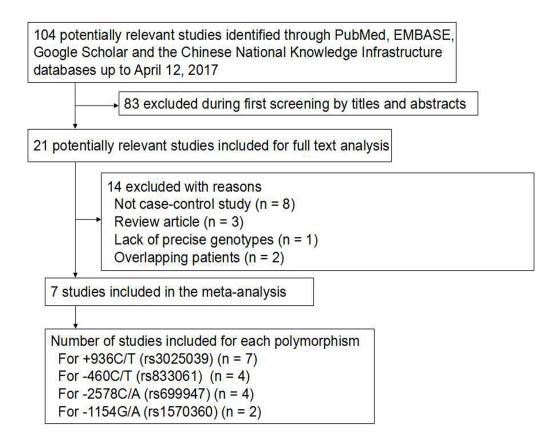


Figure 1: Flowchart of study selection.

First author	Year	Ethnicity	Country	Genotyping method	Type of controls	P for HWE	Cases/ Controls	No. of	cases		Allele free cases, n, (%)	quencies of)	No. of	f contro	ols	Allele fre controls, n,	equencies o (%)
+936C/T (rs30	025039)							CC	СТ	TT	С	Т	СС	СТ	TT	С	Т
Konac [26]	2007	Caucasian	Turkey	PCR-RFLP	PB	0.156	47/106	1	13	33	15 (16.0)	79 (84.0)	1	34	71	36 (17.0)	176 (83.0)
Jakubowska [27]	2008	Caucasian	Poland	PCR-RFLP	HB	0.863	145/280	108	33	4	249 (85.9)	41 (14.1)	196	77	7	469 (83.8)	91 (16.2)
Jia [28]	2009	Asian	China	PCR-RFLP	HB	0.729	256/329	174	77	5	425 (83.0)	87 (17.0)	229	92	8	550 (83.6)	108 (16.4)
Li [29]	2010	Asian	China	PCR-RFLP	HB	0.443	303/303	211	86	6	508 (83.8)	98 (16.2)	201	94	8	496 (81.8)	110 (18.2)
RinckJunior [30]	2015	Caucasian	Brazil	PCR-RFLP	HB	0.343	131/137	111	16	4	238 (90.8)	24 (91.6)	103	33	1	239 (87.2)	35 (12.8)
Janardhan [31]	2015	Asian	India	PCR-RFLP	PB	0.625	300/320	232	64	4	528 (88.0)	72 (12.0)	303	17	0	623 (97.3)	17 (2.7)
Zhang[32]	2016	Asian	China	PCR-RFLP	HB	0.616	163/276	109	46	8	264 (81.0)	62 (19.0)	192	75	9	459 (83.1)	93 (16.9)
-460C/T (rs83	3061)							CC	СТ	TT	С	Т	CC	СТ	TT	С	Т
Konac [26]	2007	Caucasian	Turkey	PCR-RFLP	РВ	0.156	47/106	5	21	21	15 (16.0)	79 (84.0)	13	58	35	84 (39.6)	128 (60.4)
Li [29]	2010	Asian	China	PCR-RFLP	HB	0.262	303/303	12	93	198	117 (19.3)	489 (80.7)	17	95	191	129 (21.3)	477 (78.7)
Janardhan [31]	2015	Asian	India	PCR-RFLP	РВ	0.945	300/320	96	152	52	344 (57.3)	256 (42.7)	167	128	25	462 (72.2)	178 (27.8)
Zhang[32]	2016	Asian	China	PCR-RFLP	HB	0.002	163/176	13	63	87	89 (27.3)	237 (72.7)	19	104	53	142 (40.3)	210 (59.7)
-2578C/A (rs6	99947)							CC	CA	AA	С	А	CC	CA	AA	С	А
Jia [28]	2009	Asian	China	PCR-RFLP	HB	0.155	256/329	140	99	17	379 (74.0)	133 (26.0)	191	113	25	495 (75.2)	163 (24.8)
Li [29]	2010	Asian	China	PCR-RFLP	HB	0.807	303/303	166	117	20	449 (74.1)	157 (25.9)	183	104	16	470 (77.6)	136 (22.4)
Janardhan [31]	2015	Asian	India	PCR-RFLP	РВ	0.886	300/320	116	142	42	374 (62.3)	226 (37.7)	117	154	49	388 (60.6)	252 (39.4)
Zhang[32]	2016	Asian	China	PCR-RFLP	HB	0.257	163/276	90	58	15	238 (73.0)	88 (27.0)	200	67	9	467 (84.6)	85 (15.4)
-1154G/A (rs1	570360)							GG	GA	AA	G	А	GG	GA	AA	G	А
Li [29]	2010	Asian	China	PCR-RFLP	HB	0.952	302/303	244	54	4	542 (89.7)	62 (10.3)	217	79	7	513 (84.7)	93 (15.3)
[anardhan [31]	2015	Asian	India	PCR-RFLP	РВ	0.425	300/320	166	113	21	445 (74.2)	155 (25.8)	239	77	4	555 (86.7)	85 (13.3)

Table 1: Characteristics of studies in the meta-analysis

PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; HWE, Hardy-Weinberg equilibrium; PB, population-based; HB, hospital-based.

Table 2: Methodological quality of case-control studies in our meta-analyses, based on the Newcastle–Ottawa Scale

		Selection (sco	re)		Comparability (score)		Exposure (score)		
Study	Adequate definition of patient cases	Representativeness of patients/cases	Selection of controls	Definition of controls	Control for important factor or additional factor	Ascertainment of exposure (blinding)	Same method of ascertainment for participants	Non- response rate ^a	Total score ^b
Konac [26]	1	1	1	1	2	0	1	1	8
Jakubowska [27]	1	1	0	1	2	0	1	1	7
Jia [28]	1	1	0	1	1	0	1	1	6
Li [29]	1	1	0	1	1	0	1	1	6
Rinck-Junior [30]	1	1	0	1	1	0	1	1	6
Janardhan [31]	1	1	1	1	2	0	1	1	8
Zhang [32]	1	1	1	1	2	0	1	1	8

^a One point was awarded when there was no significant difference in the response rate between groups, based on the chi-squared test (P > 0.05).

^bCalculated by adding up the points awarded for each item.

(Figure 2D); and heterozygous model, OR 1.07, 95% CI 0.65–1.76, P = 0.79 (Figure 2E).

We also meta-analyzed data for ethnic subgroups. Meta-analysis of 4 studies [28, 29, 31, 32] involving 1,022 Asian cases and 1,228 Asian controls showed no evidence of a significant association between the +936C/T polymorphism and ovarian risk risk for any of the five genetic models (Table 3): allelic, OR 1.47, 95% CI 0.81–2.67, P = 0.21; recessive model, OR 1.19, 95% CI 0.68–2.11, P = 0.54; dominant, OR 0.67, 95% CI 0.35– 1.29, P = 0.23; homozygous, OR 1.22, 95% CI 0.69–2.16, P = 0.50; and heterozygous, OR 1.46, 95% CI 0.77–

Genotype comparison and	OD 105 %/ CU	7 (D	Hete	rogeneity of stu design	udy	Analysis
genetic model	OR [95 % CI]	Z (P value)	χ^2	df (<i>P</i> value)	I ² (%)	model
+936C/T (rs3025039) in total po	opulation from 7 case	control studies (1,345 case	es and 1,751 cor	ntrols)	
Allelic (T-allele vs. C-allele)	1.17 [0.79, 1.72]	0.78 (0.44)	37.23	6 (< 0.001)	84	Random
Recessive (TT vs. CT + CC)	1.25 [0.82, 1.88]	1.04 (0.30)	4.82	6 (0.57)	0	Fixed
Dominant (CC vs. CT + TT)	0.89 [0.55, 1.45]	0.45(0.65)	39.45	6 (< 0.001)	85	Random
Homozygous (TT vs. CC)	1.24 [0.76, 2.03]	0.87 (0.39)	5.50	6 (0.48)	0	Fixed
Heterozygous (CT vs. CC)	1.07 [0.65, 1.76]	0.27 (0.79)	38.83	6 (< 0.001)	85	Random
+936C/T (rs3025039) in Asian p	oopulation from 4 case	e-control studies	(1,022 cas	ses and 1,228 co	ontrols)	
Allelic (T-allele vs. C-allele)	1.47 [0.81, 2.67]	1.25 (0.21)	33.47	3 (< 0.001)	91	Random
Recessive (TT vs. CT + CC)	1.19 [0.68, 2.11]	0.61 (0.54)	3.46	3 (0.33)	13	Fixed
Dominant (CC vs. CT + TT)	0.67 [0.35, 1.29]	1.19 (0.23)	30.92	3 (< 0.001)	90	Random
Homozygous (TT vs. CC)	1.22 [0.69, 2.16]	0.68 (0.50)	3.96	3 (0.27)	24	Fixed
Heterozygous (CT vs. CC)	1.46 [0.77, 2.75]	1.16 (0.24)	27.99	3 (< 0.001)	89	Random
+936C/T (rs3025039) in Caucas	ian population from .	3 case-control stu	udies (323	cases and 523	controls)	1
Allelic (T-allele vs. C-allele)	0.84 [0.63, 1.12]	1.19 (0.23)	1.05	2 (0.59)	0	Fixed
Recessive (TT vs. CT + CC)	1.31 [0.71, 2.39]	0.87 (0.38)	1.28	2 (0.53)	0	Fixed
Dominant (CC vs. CT + TT)	1.44 [1.00, 2.07]	1.98 (0.05)	1.07	2 (0.59)	0	Fixed
Homozygous (TT vs. CC)	1.31 [0.50, 3.44]	0.55 (0.58)	1.51	2 (0.47)	0	Fixed
Heterozygous (CT vs. CC)	0.64 [0.44, 0.93]	2.33 (0.02)	1.90	2 (0.39)	0	Fixed
+936C/T (rs3025039) in Chines	e population from 3 c	ase-control studi	ies (722 ca	ses and 908 cor	ntrols)	
Allelic (T-allele vs. C-allele)	1.00 [0.83, 1.20]	0.01 (0.99)	1.57	2 (0.46)	0	Fixed
Recessive (TT vs. CT + CC)	1.00 [0.55, 1.83]	0.00 (1.00)	1.18	2 (0.55)	0	Fixed
Dominant (CC vs. CT + TT)	1.00 [0.81, 1.23]	0.01 (0.99)	1.28	2 (0.53)	0	Fixed
Homozygous (TT vs. CC)	1.00 [0.55, 1.84]	0.01 (1.00)	1.29	2 (0.52)	0	Fixed
Heterozygous (CT vs. CC)	1.00 [0.81, 1.24]	0.01 (0.99)	0.99	2 (0.61)	0	Fixed

Table 3: Overall meta-analysis of the association between the +936C/T (rs3025039) and risk of ovarian cancer

OR, odds ratio; 95% CI, 95% confidence interval.

2.75, P = 0.24. Similarly, no evidence of an association was identified in meta-analysis of 3 studies [26, 27, 30] involving 323 Caucasian cases and 523 Caucasian controls in four genetic models: allelic, OR 0.84, 95% CI 0.63–

1.12, P = 0.23; recessive, OR 1.31, 95% CI 0.71–2.39, P = 0.38; dominant, OR 1.44, 95% CI 1.00–2.07, P = 0.05; and homozygous, OR 1.31, 95% CI 0.50–3.44, P = 0.58. In contrast, the CT genotype at +936C/T was found to be a

A Study or Subgroup	Case Events		Contro Events		Weight	Odds Ratio M-H, Random, 95% Cl		M-H, Ra	ds Ratio ndom, 9		
Jakubowska 2008	41	290	91	560	14.9%	0.85 [0.57, 1.27]		m-ng rua	- -	570 01	
Janardhan 2015	72	600	17	640	13.1%	5.00 [2.91, 8.58]			-	-	
Jia 2009	87	512	108	658	15.9%	1.04 [0.77, 1.42]			+		
Konac 2007	79	94	176	212	11.7%	1.08 [0.56, 2.08]			_		
Li 2010	98	606	110	606	16.0%	0.87 [0.65, 1.17]			+		
RinckJunior 2015	24	262	35	274	13.0%	0.69 [0.40, 1.19]		-	-		
Zhang 2016	62	326	93	552	15.4%	1.16 [0.81, 1.65]			+		
-											
Total (95% CI)		2690		3502	100.0%	1.17 [0.79, 1.72]			•		
Total events	463		630								
Heterogeneity: Tau ² = Test for overall effect:				(P < 0.1	00001); P	= 84%	0.01	0.1	1	10	10
	Z= 0.78 (F = 0.4	4)								
3	Case		Contr			Odds Ratio			ls Ratio		
Study or Subgroup						M-H, Fixed, 95% Cl		M-H, Fi	xed, 95	% CI	
Jakubowska 2008	4	145	7	280	11.6%	1.11 [0.32, 3.84]			-	-	
Janardhan 2015	4	300	0	320	1.2%	9.73 [0.52, 181.47]					
Jia 2009	5	256	8	329	17.1%	0.80 [0.26, 2.47]			-		
Konac 2007	33	47	71	106	32.4%	1.16 [0.55, 2.45]		2	-		
Li 2010	6	303	8	303	19.5%	0.74 [0.26, 2.17]			•		
RinckJunior 2015	4	131	1	137	2.4%			-		-	_
Zhang 2016	8	163	9	276					+	-	
			-								
Total (95% CI)		1345		1751	100.0%	1.25 [0.82, 1.88]					
Total events	64	a (5	104	~~			ī.				
Heterogeneity: Chi ² = Test for overall effect				= 0%			0.01	0.1	1	10	10
		(F = 0.,	50)								
	Case		Contro			Odds Ratio			ds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Ra	<u>ndom, 9</u>	95% CI	
Jakubowska 2008	108	145	196	280	16.3%	1.25 [0.80, 1.97]			+-		
Janardhan 2015	232	300	303	320	15.2%	0.19 [0.11, 0.33]					
Jia 2009	174	256	229	329	17.3%	0.93 [0.65, 1.32]			+		
Konac 2007	1	47	1	106	2.6%	2.28 [0.14, 37.29]					_
Li 2010	211	303	201	303	17.4%	1.16 [0.83, 1.64]			+-		
RinckJunior 2015	111	131	103	137	14.6%	1.83 [0.99, 3.39]					
Zhang 2016	109	163	192	276	16.7%	0.88 [0.58, 1.34]			+		
T-4-1 (05% CI)		4245		4754	400.0%	0.0010.55 4.451			-		
Total (95% CI)	046	1345	1005	1751	100.0%	0.89 [0.55, 1.45]			•		
Total events	946 - 0.32: Chi		1225 5 df = 6				⊢		•		
	= 0.32; Chi	²= 39.4	5, df = 6				⊢ 0.01		◆		1(
Total events Heterogeneity: Tau ² = Test for overall effect:	= 0.32; Chi Z = 0.45 (² = 39.4 P = 0.6	5, df = 6 5)	(P < 0.1		= 85%	⊢ 0.01				11
Total events Heterogeneity: Tau ² = Test for overall effect:)	: 0.32; Chi Z = 0.45 (Case	² = 39.4 P = 0.6 s	5, df = 6 5) Contro	(P < 0.1	00001); I²	= 85% Odds Ratio	⊢ 0.01	Odd	ls Ratio		11
Total events Heterogeneity: Tau ² = Test for overall effect:) <u>Study or Subgroup</u>	: 0.32; Chi Z = 0.45 (Case Events	² = 39.4 P = 0.6 s <u>Total</u>	5, df = 6 5) Contro <u>Events</u>	(P < 0.1 Is Total	00001); I² Weight	= 85% Odds Ratio M-H, Fixed, 95% Cl	0.01	Odd			1(
Total events Heterogeneity: Tau ² = Test for overall effect:) Study or Subgroup Jakubowska 2008	0.32; Chi Z = 0.45 (Case <u>Events</u> 4	² = 39.4 P = 0.6 s <u>Total</u> 112	5, df = 6 5) Contro <u>Events</u> 7	(P < 0.1 Is <u>Total</u> 203	00001); I² <u>Weight</u> 16.9%	= 85% Odds Ratio <u>M-H, Fixed, 95% Cl</u> 1.04 [0.30, 3.62]	0.01	Odd	ls Ratio		1
Total events Heterogeneity: Tau ² = Test for overall effect:) Study or Subgroup Jakubowska 2008 Janardhan 2015	= 0.32; Chi Z = 0.45 (Case Events 4 4	² = 39.4 P = 0.6 s <u>Total</u> 112 236	5, df = 6 5) Contro <u>Events</u> 7 0	(P < 0.1 Is 203 303	00001); I² <u>Weight</u> 16.9% 1.5%	= 85% Odds Ratio <u>M-H, Fixed, 95% CI</u> 1.04 [0.30, 3.62] 11.75 [0.63, 219.30]	0.01	Odd	ls Ratio		1
Total events Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Jakubowska 2008 Janardhan 2015 Jia 2009	: 0.32; Chi Z = 0.45 (Case <u>Events</u> 4 4 5	² = 39.4 P = 0.6 s <u>Total</u> 112 236 179	5, df = 6 5) <u>Contro</u> <u>Events</u> 7 0 8	(P < 0.1 Is 203 303 237	00001); I ² <u>Weight</u> 16.9% 1.5% 23.6%	= 85% Odds Ratio <u>M-H, Fixed, 95% CI</u> 1.04 [0.30, 3.62] 11.75 [0.63, 219.30] 0.82 [0.26, 2.56]	0.01	Odd	ls Ratio		11
Total events Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Jakubowska 2008 Janardhan 2015 Jia 2009 Konac 2007	: 0.32; Chi Z = 0.45 (Case <u>Events</u> 4 4 5 33	² = 39.4 P = 0.6 s <u>Total</u> 112 236 179 34	5, df = 6 5) <u>Contro</u> <u>Events</u> 7 0 8 71	(P < 0.1 Is 203 303 237 72	00001); I² <u>Weight</u> 16.9% 1.5% 23.6% 4.7%	= 85% Odds Ratio <u>M-H, Fixed, 95% Cl</u> 1.04 (0.30, 3.62) 11.75 (0.63, 219.30) 0.82 (0.26, 2.56) 0.46 (0.03, 7.66)	0.01	Odd	ls Ratio		11
Total events Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Jakubowska 2008 Janardhan 2015 Jia 2009 Konac 2007 Li 2010	: 0.32; Chi Z = 0.45 (Case <u>Events</u> 4 4 5 33 6	² = 39.4 P = 0.6 s <u>Total</u> 112 236 179 34 217	5, df = 6 5) Eventro 7 0 8 71 8	(P < 0.1 Is <u>Total</u> 203 303 237 72 209	00001); I ² <u>Weight</u> 16.9% 1.5% 23.6% 4.7% 27.9%	= 85% Odds Ratio <u>M-H, Fixed, 95% Cl</u> 1.04 [0.30, 3.62] 11.75 [0.63, 219.30] 0.82 [0.26, 2.56] 0.46 [0.03, 7.66] 0.71 [0.24, 2.10]	0.01	Odd	ls Ratio		11
Total events Heterogeneity: Tau ² = Test for overall effect:) Study or Subgroup Jakubowska 2008 Janardhan 2015 Jia 2009 Konac 2007 Li 2010 RinckJunior 2015	= 0.32; Chi Z = 0.45 (Case <u>Events</u> 4 4 5 33 6 4	² = 39.4 P = 0.6 s 112 236 179 34 217 115	5, df = 6 5) <u>Contro Events</u> 7 0 8 71 8 1	(P < 0.1 Is 203 203 203 237 72 209 104	00001); I ² <u>Weight</u> 16.9% 1.5% 23.6% 4.7% 27.9% 3.6%	= 85% Odds Ratio <u>M-H, Fixed, 95% CI</u> 1.04 [0.30, 3.62] 11.75 [0.63, 219.30] 0.82 [0.26, 2.56] 0.46 [0.03, 7.66] 0.71 [0.24, 2.10] 3.71 [0.24, 2.13]	0.01	Odd	ls Ratio		1
Total events Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Jakubowska 2008 Janardhan 2015 Jia 2009	: 0.32; Chi Z = 0.45 (Case <u>Events</u> 4 4 5 33 6	² = 39.4 P = 0.6 s <u>Total</u> 112 236 179 34 217	5, df = 6 5) Eventro 7 0 8 71 8	(P < 0.1 Is <u>Total</u> 203 303 237 72 209	00001); I ² <u>Weight</u> 16.9% 1.5% 23.6% 4.7% 27.9%	= 85% Odds Ratio <u>M-H, Fixed, 95% Cl</u> 1.04 [0.30, 3.62] 11.75 [0.63, 219.30] 0.82 [0.26, 2.56] 0.46 [0.03, 7.66] 0.71 [0.24, 2.10]	0.01	Odd	ls Ratio		
Total events Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Jakubowska 2008 Janardhan 2015 Jia 2009 Konac 2007 Li 2010 RinckJunior 2015 Zhang 2016 Total (95% CI)	: 0.32; Chi Z = 0.45 (Case <u>Events</u> 4 4 5 33 6 4 8	² = 39.4 P = 0.6 s 112 236 179 34 217 115	5, df = 6 5) Events 7 0 8 71 8 71 8 1 9	(P < 0.1 Is Total 203 303 237 72 209 104 201	00001); I ² <u>Weight</u> 16.9% 1.5% 23.6% 4.7% 27.9% 3.6%	= 85% Odds Ratio <u>M-H, Fixed, 95% CI</u> 1.04 [0.30, 3.62] 11.75 [0.63, 219.30] 0.82 [0.26, 2.56] 0.46 [0.03, 7.66] 0.71 [0.24, 2.10] 3.71 [0.24, 2.13]	0.01	Odd	ls Ratio		
Total events Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Jakubowska 2008 Janardhan 2015 Jia 2009 Konac 2007 Li 2010 RinckJunior 2015 Zhang 2016 Total (95% CI) Total events	: 0.32; Chi Z = 0.45 (Case <u>Events</u> 4 4 5 33 6 4 8 8	² = 39.4 P = 0.6 s 112 236 179 34 217 115 117 1010	5, df = 6 5) Events 7 0 8 71 8 71 8 1 9	(P < 0.1 Is 203 203 237 72 209 104 201 1329	00001); ² <u>Weight</u> 16.9% 1.5% 23.6% 4.7% 27.9% 3.6% 21.7%	= 85% Odds Ratio <u>M-H, Fixed, 95% CI</u> 1.04 [0.30, 3.62] 11.75 [0.63, 219.30] 0.82 [0.26, 2.56] 0.46 [0.03, 7.66] 0.71 [0.24, 2.10] 3.71 [0.41, 33.76] 1.57 [0.59, 4.18] 1.24 [0.76, 2.03]		Odd	ls Ratio		
Total events Heterogeneity: Tau ² = Test for overall effect:) Study or Subgroup Jakubowska 2008 Janardhan 2015 Jia 2009 Konac 2007 Li 2010 RinckJunior 2015 Zhang 2016 Total (95% CI) Total events Heterogeneity: Chi ² =	: 0.32; Chi Z = 0.45 (Case <u>Events</u> 4 4 5 33 6 4 8 8 64 5.50, df=	² = 39.4 P = 0.6 s 112 236 179 34 217 115 117 1010 6 (P = 1	5, df = 6 5) Contro Events 7 0 8 71 8 7 1 8 1 9 104 0.48); I² =	(P < 0.1 Is 203 203 237 72 209 104 201 1329	00001); ² <u>Weight</u> 16.9% 1.5% 23.6% 4.7% 27.9% 3.6% 21.7%	= 85% Odds Ratio <u>M-H, Fixed, 95% CI</u> 1.04 [0.30, 3.62] 11.75 [0.63, 219.30] 0.82 [0.26, 2.56] 0.46 [0.03, 7.66] 0.71 [0.24, 2.10] 3.71 [0.41, 33.76] 1.57 [0.59, 4.18] 1.24 [0.76, 2.03]	0.01	Odd	ls Ratio		_
Total events Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Jakubowska 2008 Janardhan 2015 Jia 2009 Konac 2007 Li 2010 RinckJunior 2015 Zhang 2016 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect:	: 0.32; Chi Z = 0.45 (Case <u>Events</u> 4 4 5 33 6 4 8 8 64 5.50, df=	² = 39.4 P = 0.6 s 112 236 179 34 217 115 117 1010 6 (P = 1	i5, df = 6 5) Contro Events 7 0 8 71 8 7 1 8 1 9 104 0.48); I² =	(P < 0.1 Is 203 203 237 72 209 104 201 1329	00001); ² <u>Weight</u> 16.9% 1.5% 23.6% 4.7% 27.9% 3.6% 21.7%	= 85% Odds Ratio <u>M-H, Fixed, 95% CI</u> 1.04 [0.30, 3.62] 11.75 [0.63, 219.30] 0.82 [0.26, 2.56] 0.46 [0.03, 7.66] 0.71 [0.24, 2.10] 3.71 [0.41, 33.76] 1.57 [0.59, 4.18] 1.24 [0.76, 2.03]		Odc <u>M-H, Fiz</u>	ls Ratio	% CI	_
Total events Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Jakubowska 2008 Janardhan 2015 Jia 2009 Konac 2007 Li 2010 RinckJunior 2015 Zhang 2016 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect:	: 0.32; Chi Z = 0.45 (Case <u>Events</u> 4 4 4 5 33 6 4 8 6 4 5.50, df= Z = 0.87 (Case	<pre>P = 0.6 P = 0.6 S Total 112 236 179 34 217 115 117 1010 6 (P = 0.3 s</pre>	5, df = 6 5) <u>Contro Events</u> 7 0 8 71 8 71 8 1 9 104 0.48); l ² = 9) Contro	(P < 0.1 Is Total 203 303 237 72 209 104 201 1329 0% Is	Weight 16.9% 1.5% 23.6% 4.7% 27.9% 3.6% 21.7% 100.0%	= 85% Odds Ratio <u>M-H, Fixed, 95% CI</u> 1.04 [0.30, 3.62] 11.75 [0.63, 219.30] 0.82 [0.26, 2.56] 0.46 [0.03, 7.66] 0.71 [0.24, 2.10] 3.71 [0.41, 33.76] 1.57 [0.59, 4.18] 1.24 [0.76, 2.03] Odds Ratio	 D.01	Odc <u>M-H, Fb</u> 	Is Ratio	% CI 10 ⊳	_
Total events Heterogeneity: Tau ² = Test for overall effect: J Study or Subgroup Jakubowska 2008 Janardhan 2015 Jia 2009 Konac 2007 Li 2010 RinckJunior 2015 Zhang 2016 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup	: 0.32; Chi Z = 0.45 (Case <u>Events</u> 4 4 4 5 33 6 4 8 6 4 5.50, df= Z = 0.87 (Case	<pre>P = 0.6 P = 0.6 S Total 112 236 179 34 217 115 117 1010 6 (P = 0.3 s</pre>	5, df = 6 5) <u>Contro Events</u> 7 0 8 71 8 71 8 1 9 104 0.48); l ² = 9) Contro	(P < 0.1 Is Total 203 303 237 72 209 104 201 1329 0% Is	Weight 16.9% 1.5% 23.6% 4.7% 27.9% 3.6% 21.7% 100.0%	 85% Odds Ratio M-H, Fixed, 95% CI 1.04 [0.30, 3.62] 11.75 [0.63, 219.30] 0.82 [0.26, 2.56] 0.46 [0.03, 7.66] 0.71 [0.24, 2.10] 3.71 [0.41, 33.76] 1.57 [0.59, 4.18] 1.24 [0.76, 2.03] Odds Ratio M-H, Random, 95% CI 	 D.01	Odc <u>M-H, Fi</u> 2 	Is Ratio	% CI 10 ⊳	-
Total events Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Jakubowska 2008 Janardhan 2015 Jia 2009 Konac 2007 Li 2010 RinckJunior 2015 Zhang 2016 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect:	: 0.32; Chi Z = 0.45 (Case <u>Events</u> 4 4 4 5 33 6 4 8 6 4 5.50, df= Z = 0.87 (Case	<pre>P = 0.6 P = 0.6 S Total 112 236 179 34 217 115 117 1010 6 (P = 0.3 s</pre>	5, df = 6 5) <u>Contro Events</u> 7 0 8 71 8 71 8 1 9 104 0.48); l ² = 9) Contro	(P < 0.1 Is Total 203 303 237 72 209 104 201 1329 0% Is	Weight 16.9% 1.5% 23.6% 4.7% 27.9% 3.6% 21.7% 100.0%	= 85% Odds Ratio <u>M-H, Fixed, 95% CI</u> 1.04 [0.30, 3.62] 11.75 [0.63, 219.30] 0.82 [0.26, 2.56] 0.46 [0.03, 7.66] 0.71 [0.24, 2.10] 3.71 [0.41, 33.76] 1.57 [0.59, 4.18] 1.24 [0.76, 2.03] Odds Ratio	 D.01	Odc <u>M-H, Fb</u> 	Is Ratio	% CI 10 ⊳	_
Total events Heterogeneity: Tau ² = Test for overall effect: Jakubowska 2008 Janardhan 2015 Jia 2009 Konac 2007 Li 2010 RinckJunior 2015 Zhang 2016 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup	: 0.32; Chi Z = 0.45 (Case <u>Events</u> 4 4 5 33 6 4 8 64 5.50, df= Z = 0.87 (Case <u>Events</u>	* = 39.4 P = 0.6 s Total 112 236 179 34 217 115 117 1010 6 (P = 1) P = 0.3 s Total	5, df = 6 5) Contro Events 7 0 8 71 8 71 8 71 9 104 0.48); ² = 9) Contro Events	(P < 0.1 Is Total 203 303 237 72 209 104 201 1329 0% Is Total	200001); ² 16.9% 1.5% 23.6% 4.7% 27.9% 3.6% 21.7% 100.0% Weight	 85% Odds Ratio M-H, Fixed, 95% CI 1.04 [0.30, 3.62] 11.75 [0.63, 219.30] 0.82 [0.26, 2.56] 0.46 [0.03, 7.66] 0.71 [0.24, 2.10] 3.71 [0.41, 33.76] 1.57 [0.59, 4.18] 1.24 [0.76, 2.03] Odds Ratio M-H, Random, 95% CI 	 D.01	Odc <u>M-H, Fb</u> 	Is Ratio	% CI 10 ⊳	_
Total events Heterogeneity: Tau ² = Test for overall effect: Jakubowska 2008 Janardhan 2015 Jia 2009 Konac 2007 Li 2010 RinckJunior 2015 Zhang 2016 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: <u>Study or Subgroup</u> Jakubowska 2008 Janardhan 2015	: 0.32; Chi Z = 0.45 (Case <u>Events</u> 4 4 5 33 6 4 8 64 5.50, df= Z = 0.87 (Case <u>Events</u> 33	² = 39.4 P = 0.6 s 112 236 179 34 217 115 117 1010 6 (P = 1 P = 0.3 s <u>Total</u> 141	5, df = 6 5) Contro Events 7 7 0 8 71 8 71 8 71 8 1 9 9 104 0.48); ² = 9) Contro Events 77	(P < 0.1 Is Total 203 303 237 72 209 104 201 1329 0% Is Total 273	00001); I ² 16.9% 1.5% 23.6% 27.9% 3.6% 21.7% 100.0% Weight 16.3%	= 85% Odds Ratio <u>M-H, Fixed, 95% CI</u> 1.04 [0.30, 3.62] 11.75 [0.63, 219, 30] 0.82 (0.26, 2.66] 0.46 (0.03, 7.66] 0.71 [0.24, 2.10] 3.71 [0.24, 2.10] 3.71 [0.41, 33.76] 1.57 [0.59, 4.18] 1.24 [0.76, 2.03] Odds Ratio <u>M-H, Random, 95% CI</u> 0.78 [0.49, 1.25] 4.92 [2.80, 8.62]	 D.01	Odc <u>M-H, Fb</u> 	Is Ratio	% CI 10 ⊳	_
Total events Heterogeneity: Tau ² = Test for overall effect: Jakubowska 2008 Janardhan 2015 Jia 2009 Konac 2007 Li 2010 RinckJunior 2015 Zhang 2016 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: <u>Study or Subgroup</u> Jakubowska 2008	: 0.32; Chi Z = 0.45 (Case <u>Events</u> 4 4 5 33 6 4 8 6 4 5.50, df= Z = 0.87 (Case <u>Events</u> 33 64 77	² = 39.4 P = 0.6 s 112 236 179 34 217 115 117 1010 6 (P = 1 P = 0.3 s Total 296 251	5, df = 6 5) Contro Events 7 0 8 71 8 1 9 104 0.48); I [≠] = 9) Contro Events 77 17 92	(P < 0.1 Is Total 203 303 237 72 209 104 201 1329 0% Is Total 273 320 321	Weight 16.9% 1.5% 23.6% 27.9% 3.6% 21.7% 100.0% Weight 16.3% 15.3% 17.3%	= 85% Odds Ratio <u>M-H, Fixed, 95% CI</u> 1.04 [0.30, 3.62] 11.75 [0.63, 219.30] 0.82 [0.26, 2.56] 0.46 [0.03, 7.66] 0.71 [0.41, 33.76] 1.57 [0.59, 4.18] 1.24 [0.76, 2.03] Odds Ratio <u>M-H, Random, 95% CI</u> 0.78 [0.49, 1.26] 4.92 [2.80, 8.62] 1.10 [0.77, 1.58]	 D.01	Odc <u>M-H, Fb</u> 	Is Ratio	% CI 10 ⊳	_
Total events Heterogeneity: Tau ² = Test for overall effect: Jatubowska 2008 Janardhan 2015 Jia 2009 Konac 2007 Li 2010 RinckJunior 2015 Zhang 2016 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: <u>Study or Subgroup</u> Jakubowska 2008 Janardhan 2015 Jia 2009 Konac 2007	: 0.32; Chi Z = 0.45 (Case <u>Events</u> 4 4 4 5 33 6 4 8 6 4 5.50, df= Z = 0.87 (Case <u>Events</u> 33 64 77 13	*= 39.4 P = 0.6 s Total 112 236 179 34 217 115 117 1010 6 (P = 0.3 s Total 296 291 291 291 291 14	5, df = 6 5) Contro Events 7 0 8 71 8 1 9 104 0.48); l ² = 9) Contro Events 77 77 77 17 92 34	(P < 0.1 Is Total 203 303 237 72 209 104 201 1329 0% Is Total 273 320 321 321 35	Weight 16.9% 1.5% 23.6% 4.7% 27.9% 3.6% 21.7% 100.0% Weight 16.3% 15.3% 17.3% 2.6%	= 85% Odds Ratio <u>M-H, Fixed, 95% CI</u> 1.04 [0.30, 3.62] 11.75 [0.63, 219.30] 0.82 [0.26, 2.56] 0.46 [0.03, 7.66] 0.71 [0.24, 2.10] 3.71 [0.41, 33.76] 1.57 [0.59, 4.18] 1.24 [0.76, 2.03] Odds Ratio <u>M-H, Random, 95% CI</u> 0.78 [0.49, 1.25] 4.92 [2.80, 8.62] 1.10 [0.77, 1.58] 0.38 [0.02, 6.57]	 D.01	Odc <u>M-H, Fb</u> 	Is Ratio	% CI 10 ⊳	_
Total events Heterogeneity: Tau ² = Test for overall effect: Jatuby or Subgroup Jakubowska 2008 Janardhan 2015 Jia 2009 Konac 2007 Li 2010 RinckJunior 2015 Zhang 2016 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: Jatubowska 2008 Janardhan 2015 Jia 2009 Konac 2007 Li 2010	: 0.32; Chi Z = 0.45 (Case <u>Events</u> 4 4 4 5 33 6 4 8 6 4 5.50, df= Z = 0.87 (Case <u>Events</u> 33 64 77 7 13 86	*= 39.4 P = 0.6 s Total 112 236 179 34 217 115 117 1010 6 (P = 1 141 296 251 14 297	5, df = 6 5) Contro Events 7 0 8 71 8 104 0.48); l ² = 9) Contro Events 77 17 92 34 94	(P < 0.1 Is Total 203 303 237 72 209 104 201 1329 0% Is Total 273 320 0% Is Total 320 321 322 322 321 322 321 322 321 323 323	Weight 16.9% 1.5% 23.6% 4.7% 27.9% 21.7% 100.0% Weight 16.3% 15.3% 17.3% 2.6% 17.4%	= 85% Odds Ratio <u>M-H, Fixed, 95% CI</u> 1.04 [0.30, 3.62] 11.75 [0.63, 219.30] 0.82 [0.26, 2.56] 0.46 [0.03, 7.66] 0.71 [0.24, 2.10] 3.71 [0.41, 33.76] 1.57 [0.59, 4.18] 1.24 [0.76, 2.03] Odds Ratio <u>M-H, Random, 95% CI</u> 0.78 [0.49, 1.26] 4.92 [2.80, 8.62] 1.10 [0.77, 1.58] 0.38 [0.02, 6.57] 0.87 [0.61, 1.24]	 D.01	Odc <u>M-H, Fb</u> 	Is Ratio	% CI 10 ⊳	_
Total events Heterogeneity: Tau ² = Test for overall effect: Jakubowska 2008 Janardhan 2015 Jia 2009 Konac 2007 Li 2010 RinckJunior 2015 Zhang 2016 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: Jakubowska 2008 Janardhan 2015 Jia 2009 Konac 2007 Li 2010 RinckJunior 2015	: 0.32; Chi Z = 0.45 (Case <u>Events</u> 4 4 5 33 6 4 8 64 5.50, df= Z = 0.87 (Case <u>Events</u> 33 64 77 13 86 16	*= 39.4 P = 0.6 s Total 112 236 179 34 217 117 1010 6 (P = 1 P = 0.3 s Total 296 251 14 297 127	5, df = 6 5) Contro Events 7 0 8 71 8 1 9 104 0.48); I² = 9) Contro Events 77 17 92 34 94 33	(P < 0.) Is Total 203 303 237 72 209 104 201 1329 0% Is Total 273 320 0% Is Total 273 320 321 352 295 136	Weight 16.9% 1.5% 23.6% 4.7% 27.9% 3.6% 21.7% 100.0% Weight 16.3% 17.3% 17.4% 14.3%	= 85% Odds Ratio <u>M-H, Fixed, 95% CI</u> 1.04 [0.30, 3.62] 11.75 [0.63, 219.30] 0.82 [0.26, 2.56] 0.46 [0.03, 7.66] 0.71 [0.24, 2.10] 3.71 [0.41, 33.76] 1.57 [0.59, 4.18] 1.24 [0.76, 2.03] Odds Ratio <u>M-H, Random, 95% CI</u> 0.78 [0.49, 1.25] 4.92 [2.80, 8.62] 1.10 [0.77, 1.58] 0.38 [0.02, 6.57] 0.87 [0.61, 1.24] 0.45 [0.23, 0.87]	 D.01	Odc <u>M-H, Fb</u> 	Is Ratio	% CI 10 ⊳	_
Total events Heterogeneity: Tau ² = Test for overall effect: Jatuby or Subgroup Jakubowska 2008 Janardhan 2015 Jia 2009 Konac 2007 Li 2010 RinckJunior 2015 Zhang 2016 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: Jatubowska 2008 Janardhan 2015 Jia 2009 Konac 2007 Li 2010	: 0.32; Chi Z = 0.45 (Case <u>Events</u> 4 4 4 5 33 6 4 8 6 4 5.50, df= Z = 0.87 (Case <u>Events</u> 33 64 77 7 13 86	*= 39.4 P = 0.6 s Total 112 236 179 34 217 115 117 1010 6 (P = 1 141 296 251 14 297	5, df = 6 5) Contro Events 7 0 8 71 8 104 0.48); l ² = 9) Contro Events 77 17 92 34 94	(P < 0.1 Is Total 203 303 237 72 209 104 201 1329 0% Is Total 273 320 0% Is Total 320 321 322 322 321 322 321 322 321 323 323	Weight 16.9% 1.5% 23.6% 4.7% 27.9% 21.7% 100.0% Weight 16.3% 15.3% 17.3% 2.6% 17.4%	= 85% Odds Ratio <u>M-H, Fixed, 95% CI</u> 1.04 [0.30, 3.62] 11.75 [0.63, 219.30] 0.82 [0.26, 2.56] 0.46 [0.03, 7.66] 0.71 [0.24, 2.10] 3.71 [0.41, 33.76] 1.57 [0.59, 4.18] 1.24 [0.76, 2.03] Odds Ratio <u>M-H, Random, 95% CI</u> 0.78 [0.49, 1.26] 4.92 [2.80, 8.62] 1.10 [0.77, 1.58] 0.38 [0.02, 6.57] 0.87 [0.61, 1.24]	 D.01	Odc <u>M-H, Fb</u> 	Is Ratio	% CI 10 ⊳	_
Total events Heterogeneity: Tau ² = Test for overall effect: Jatubowska 2008 Janardhan 2015 Jia 2009 Konac 2007 Li 2010 RinckJunior 2015 Zhang 2016 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: Jakubowska 2008 Janardhan 2015 Jia 2009 Konac 2007 Li 2010 RinckJunior 2015 Zhang 2016 Total (95% CI)	: 0.32; Chi Z = 0.45 (Case <u>Events</u> 4 4 5 33 6 4 8 6 4 5.50, df= Z = 0.87 (Case <u>Events</u> 33 64 77 13 86 16 16 46	*= 39.4 P = 0.6 s Total 112 236 179 34 217 117 1010 6 (P = 1 P = 0.3 s Total 296 251 14 297 127	5, df = 6 5) Contro Events 7 0 8 71 8 1 9 104 0.48); l ² = 9) Contro Events 77 17 77 17 792 34 94 33 75	(P < 0. Is Total 203 203 209 104 201 1329 0% Is Total 273 320 321 35 295 136 267	Weight 16.9% 1.5% 23.6% 4.7% 27.9% 3.6% 21.7% 100.0% Weight 16.3% 17.3% 17.4% 14.3%	= 85% Odds Ratio <u>M-H, Fixed, 95% CI</u> 1.04 [0.30, 3.62] 11.75 [0.63, 219.30] 0.82 [0.26, 2.56] 0.46 [0.03, 7.66] 0.71 [0.24, 2.10] 3.71 [0.41, 33.76] 1.57 [0.59, 4.18] 1.24 [0.76, 2.03] Odds Ratio <u>M-H, Random, 95% CI</u> 0.78 [0.49, 1.25] 4.92 [2.80, 8.62] 1.10 [0.77, 1.58] 0.38 [0.02, 6.57] 0.87 [0.61, 1.24] 0.45 [0.23, 0.87]	 D.01	Odc <u>M-H, Fb</u> 	Is Ratio	% CI 10 ⊳	_
Total events Heterogeneity: Tau ² = Test for overall effect: Jakubowska 2008 Janardhan 2015 Jia 2009 Konac 2007 Li 2010 RinckJunior 2015 Zhang 2016 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: Jakubowska 2008 Janardhan 2015 Jia 2009 Konac 2007 Li 2010 RinckJunior 2015 Zhang 2016	: 0.32; Chi Z = 0.45 (Case <u>Events</u> 4 4 4 5 33 6 4 8 6 4 5.50, df= Z = 0.87 (Case <u>Events</u> 33 64 777 13 86 16 46 335	*= 39.4 P = 0.6 s Total 112 236 179 34 217 115 117 1010 6 (P = 0.3 s Total 296 251 141 297 127 155 1281	5, df = 6 5) Contro Events 7 0 8 71 8 104 0.48); l ² = 9) Contro Events 77 17 92 34 94 33 75 422	(P < 0. Is Total 203 303 237 72 209 104 201 1329 0% Is Total 273 320 321 35 295 136 267 1647	Weight 16.9% 1.5% 23.6% 4.7% 27.9% 21.7% 100.0% Weight 16.3% 17.3% 2.6% 17.3% 16.6% 100.0%	 = 85% Odds Ratio M-H, Fixed, 95% CI 1.04 [0.30, 3.62] 11.75 [0.63, 219.30] 0.82 [0.26, 2.56] 0.46 [0.03, 7.66] 0.71 [0.41, 33.76] 1.57 [0.59, 4.18] 1.24 [0.76, 2.03] Odds Ratio M-H, Random, 95% CI 0.78 [0.49, 1.26] 4.92 [2.80, 8.62] 1.10 [0.77, 1.58] 0.38 [0.02, 6.57] 0.87 [0.61, 1.24] 0.45 [0.23, 0.87] 1.08 [0.70, 1.67] 1.07 [0.65, 1.76] 	 D.01	Odc <u>M-H, Fb</u> 	Is Ratio	% CI 10 ⊳	_

Figure 2: Forest plot describing the association between the +936C/T polymorphism (rs3025039) and risk of ovarian cancer across all study participants according to five genetic models. (A) allelic (T-allele vs. C-allele), (B) recessive (TT vs. CT + CC), (C) dominant (CC vs. CT + TT), (D) homozygous (TT vs. CC) and (E) heterozygous (CT vs. CC).

Genotype comparison and	OD 105 9/ CU	7 (Develope)	Hetero	geneity of study	y design	Analysis
genetic model	OR [95 % CI]	Z (P value)	χ^2	df (<i>P</i> value)	I ² (%)	model
-460C/T (rs833061) in total pop	oulation from 4 case-	control studies (8	13 cases	and 905 contro	ls)	
Allelic (T-allele vs. C-allele)	1.80 [1.26, 2.59]	3.20 (0.001)	14.46	3 (0.002)	79	Random
Recessive (TT vs. CT + CC)	1.84 [1.13, 2.98]	2.47 (0.01)	12.41	3 (0.006)	76	Random
Dominant (CC vs. CT + TT)	0.51 [0.39, 0.67]	4.87 (< 0.001)	3.30	3 (0.35)	9	Fixed
Homozygous (TT vs. CC)	2.48 [1.72, 3.56]	4.90 (< 0.001)	4.30	3 (0.23)	30	Fixed
Heterozygous (CT vs. CC)	1.67 [1.26, 2.21]	3.35 (< 0.001)	5.24	3 (0.16)	43	Fixed
–460C/T (rs833061) in Asian po	pulation from 3 case	e-control studies (766 cases	and 799 control	ols)	
Allelic (T-allele vs. C-allele)	1.58 [1.13, 2.22]	2.65 (0.008)	8.85	2 (0.01)	77	Random
Recessive (TT vs. CT + CC)	1.90 [1.03, 3.49]	2.06 (0.04)	12.40	2 (0.002)	84	Random
Dominant (CC vs. CT + TT)	0.49 [0.37, 0.65]	4.97 (< 0.001)	2.41	2 (0.30)	17	Fixed
Homozygous (TT vs. CC)	2.61 [1.78, 3.82]	4.93 (< 0.001)	3.62	2 (0.16)	45	Fixed
Heterozygous (CT vs. CC)	1.73 [1.29, 2.32]	3.69 (< 0.001)	4.21	2 (0.12)	53	Fixed

Table 4: Overall meta-analysis of the association between the -460C/T (rs833061) and risk of ovarian cancer

OR, odds ratio; 95% CI, 95% confidence interval.

protective factor in the heterozygous model (OR 0.64, 95% CI 0.44–0.93, P = 0.02; Table 3). Lastly, meta-analysis of 3 studies [28, 29, 32] involving 722 Chinese cases and 908 Chinese controls showed no evidence of a significant association between the +936C/T polymorphism and ovarian risk for any of the five genetic models (Table 3): allelic, OR 1.00, 95% CI 0.83–1.20, P = 0.99; recessive, OR 1.00, 95% CI 0.55–1.83, P = 1.00; dominant, OR 1.00, 95% CI 0.81–1.23, P = 0.99; homozygous, OR 1.00, 95% CI 0.55–1.84, P = 1.00; and heterozygous, OR 1.00, 95% CI 0.81–1.24, P = 0.99.

Meta-analysis of studies on the -460C/T (rs833061) polymorphism

The meta-analysis of a possible association between the -460C/T polymorphism and ovarian risk is summarized in Table 4. Based on the total study population involving 813 cases and 905 controls, a significant association between the -460C/T polymorphism and ovarian risk was demonstrated across the total population according to five genetic models: allelic, OR 1.80, 95% CI 1.26– 2.59, P = 0.001 (Figure 3A); recessive, OR 1.84, 95% CI 1.13–2.98, P = 0.01 (Figure 3B); dominant, OR 0.51, 95% CI 0.39–0.67, P < 0.001 (Figure 3C); homozygous, OR 2.48, 95% CI 1.72–3.56, P < 0.001 (Figure 3D); and heterozygous, OR 1.67, 95% CI 1.26–2.21, P < 0.001(Figure 3E).

A significant association was also observed in the subgroup of 766 Asian cases and 799 Asian controls in 3 studies [29–32] according to five genetic models (Table 4):

allelic, OR 1.58, 95% CI 1.13–2.22, *P* = 0.008; recessive, OR 1.90, 95% CI 1.03–3.49, *P* = 0.04; dominant, OR 0.49, 95% CI 0.37–0.65, *P* < 0.001; homozygous, OR 2.61, 95% CI 1.78–3.82, *P* < 0.001; and heterozygous, OR 1.73, 95% CI 1.29–2.32, *P* < 0.001.

Meta-analysis of studies on the -2578C/A (rs699947) polymorphism

The meta-analysis of a possible association between the -2578C/A polymorphism and ovarian cancer risk is summarized in Table 5. Based on the total study population (exclusively Asian) involving 1,022 cases and 1,228 controls, no evidence of an association was identified in four genetic models: allelic, OR 1.23, 95% CI 0.91–1.66, P = 0.18 (Figure 4A); recessive, OR 1.11, 95% CI 0.83– 1.50, P = 0.48 (Figure 4B); dominant, OR 0.78, 95% CI 0.57–1.08, P = 0.14 (Figure 4C); and homozygous, OR 1.33, 95% CI 0.75–2.35, P = 0.33 (Figure 4D). In contrast, the CA genotype at -2578C/A was found to be a risk factor in the heterozygous model (OR 1.22, 95% CI 1.02–1.46, P = 0.03; Figure 4E).

Meta-analysis of studies on the -1154G/A (rs1570360) polymorphism

The meta-analysis of a possible association between the -1154G/A polymorphism and ovarian cancer risk is summarized in Table 6. Based on the total study population (exclusively Asian) involving 602 cases and 623 controls, none of the five genetic models indicated a significant

A	Cases		Contro			Odds Ratio		-	dds Ratio		
Study or Subgroup						M-H, Random, 95% Cl		M-H, Ra	andom, 95	% CI	
Janardhan 2015	256	600	178	640	29.1%	1.93 [1.52, 2.45]			•		
Konac 2007	79	94	128	212	16.9%	3.46 [1.87, 6.40]			-		
Li 2010	489	606	477	606	27.7%	1.13 [0.85, 1.50]			+		
Zhang 2016	237	326	210	352	26.3%	1.80 [1.30, 2.49]			+		
Total (95% CI)		1626		1810	100.0%	1.80 [1.26, 2.59]			•		
Total events	1061		993								
Heterogeneity: Tau ² =	0.10: Chi ^a	2 = 14.4	6 df = 3	(P = 0.0)02): I ² = 7	9%	<u> </u>	-			
Test for overall effect:							0.01	0.1	1	10	100
3	Cases	2	Contro	le		Odds Ratio		0	dds Ratio		
Study or Subgroup					Weight I	M-H, Random, 95% Cl			andom, 95	% CI	
Janardhan 2015	52	300	25	320	24.7%	2.47 [1.49, 4.10]		111-11610		70 01	
Konac 2007	21	47	35	106	19.7%	1.64 [0.81, 3.31]			1		
Li 2010	198	303	191	303	29.2%	1.11 [0.79, 1.54]			T		
Zhang 2016	87	163	53	176	26.3%	2.66 [1.70, 4.15]			1		
Total (95% CI)		813		905	100.0%	1.84 [1.13, 2.98]			•		
Total events	358		304								
Heterogeneity: Tau ² =	0.18; Chi	²= 12.4	1, df = 3 i	(P = 0.0)06); I² = 7	6%		-		+	
Test for overall effect:							0.01	0.1	1	10	100
C	C	_	Canto	- 1-		O dela Datia		0.	lde Detie		
-	Case		Contr		Mojaht	Odds Ratio			lds Ratio ixed, 95%	CI	
Study or Subgroup						M-H, Fixed, 95% Cl		<u>IVI-FI, F</u>	1xeu, 95%	u	
Janardhan 2015	96	300	167	320		0.43 [0.31, 0.60]		_			
Konac 2007	5	47	13	106		0.85 [0.29, 2.54]					
Li 2010	12	303	17	303		0.69 [0.33, 1.48]					
Zhang 2016	13	163	19	176	11.2%	0.72 [0.34, 1.50]					
Total (95% CI)		813		905	100.0%	0.51 [0.39, 0.67]			•		
Total events	126		216								
Listerenensity Ohiz-	2.20 46-	3 (P =	0.35); [?:	= 9%			—			+	
Helefobeneily Chr=	: 3 .3U_DI=			w / v			0.01	0.1	1	10	100
Heterogeneity: Chi ² = Test for overall effect:							0.01	0.1			
Test for overall effect:	Z = 4.87	(P < 0.0	00001)			Oddo Datia	0.01				
Test for overall effect:	Z = 4.87 (Case	(P≺0.(s	00001) Contr		Mainlet	Odds Ratio	0.01	Od	lds Ratio		
Test for overall effect) Study or Subgroup	Z = 4.87 Case Events	(P < 0.(s <u>Total</u>	Contr Events	Total		M-H, Fixed, 95% Cl		Od	lds Ratio ixed, 95%	CI	
Test for overall effect: <u> Study or Subgroup</u> Janardhan 2015	Z = 4.87 Case Events 52	(P < 0.0 s <u>Total</u> 148	Contr Events 25	<u>Total</u> 192	37.3%	M-H, Fixed, 95% Cl 3.62 [2.11, 6.20]		Od	lds Ratio	CI	
Test for overall effect: <u>Study or Subgroup</u> Janardhan 2015 Konac 2007	Z = 4.87 Case Events 52 21	(P < 0.0 s <u>Total</u> 148 26	00001) Contr <u>Events</u> 25 35	<u>Total</u> 192 48	37.3% 12.5%	M-H, Fixed, 95% Cl 3.62 [2.11, 6.20] 1.56 [0.49, 5.00]		Od	lds Ratio ixed, 95%	CI	
Test for overall effect: <u>Study or Subgroup</u> Janardhan 2015 Konac 2007 Li 2010	Z = 4.87 (Case <u>Events</u> 52 21 198	(P < 0.0 s <u>Total</u> 148 26 210	00001) Contr <u>Events</u> 25 35 191	Total 192 48 208	37.3% 12.5% 29.0%	<u>M-H, Fixed, 95% Cl</u> 3.62 [2.11, 6.20] 1.56 [0.49, 5.00] 1.47 [0.68, 3.16]		Od	lds Ratio ixed, 95%	CI	
Test for overall effect: Study or Subgroup Janardhan 2015 Konac 2007	Z = 4.87 (Case <u>Events</u> 52 21 198	(P < 0.0 s <u>Total</u> 148 26	00001) Contr <u>Events</u> 25 35 191	Total 192 48 208	37.3% 12.5%	M-H, Fixed, 95% Cl 3.62 [2.11, 6.20] 1.56 [0.49, 5.00]		Od	lds Ratio ixed, 95%	CI	
Test for overall effect: <u>Study or Subgroup</u> Janardhan 2015 Konac 2007 Li 2010	Z = 4.87 (Case <u>Events</u> 52 21 198	(P < 0.0 s <u>Total</u> 148 26 210	00001) Contr <u>Events</u> 25 35 191	Total 192 48 208 72	37.3% 12.5% 29.0%	<u>M-H, Fixed, 95% Cl</u> 3.62 [2.11, 6.20] 1.56 [0.49, 5.00] 1.47 [0.68, 3.16]		Od	lds Ratio ixed, 95%	CI	
Test for overall effect: Study or Subgroup Janardhan 2015 Konac 2007 Li 2010 Zhang 2016	Z = 4.87 (Case <u>Events</u> 52 21 198	(P < 0.0 s <u>Total</u> 148 26 210 100	00001) Contr <u>Events</u> 25 35 191	Total 192 48 208 72	37.3% 12.5% 29.0% 21.2%	<u>M-H, Fixed, 95% C1</u> 3.62 [2.11, 6.20] 1.56 [0.49, 5.00] 1.47 [0.68, 3.16] 2.40 [1.10, 5.25]		Od	lds Ratio ixed, 95%	CI	
Test for overall effect: D Study or Subgroup Janardhan 2015 Konac 2007 Li 2010 Zhang 2016 Total (95% CI) Total events	Z = 4.87 (Case <u>Events</u> 52 21 198 87 358	(P < 0.0 s <u>Total</u> 148 26 210 100 484	Contr Events 25 35 191 53 304	Total 192 48 208 72 520	37.3% 12.5% 29.0% 21.2%	<u>M-H, Fixed, 95% C1</u> 3.62 [2.11, 6.20] 1.56 [0.49, 5.00] 1.47 [0.68, 3.16] 2.40 [1.10, 5.25]		Ос <u>М-Н, F</u>	Ids Ratio ixed, 95%	<u>CI</u>	
Test for overall effect: <u>Study or Subgroup</u> Janardhan 2015 Konac 2007 Li 2010 Zhang 2016 Total (95% CI)	: Z = 4.87 (Case <u>Events</u> 52 21 198 87 358 : 4.30, df =	(P < 0.(s <u>Total</u> 148 26 210 100 484 3 (P =	00001) Contr Events 25 35 191 53 304 0.23); I ² :	Total 192 48 208 72 520	37.3% 12.5% 29.0% 21.2%	<u>M-H, Fixed, 95% C1</u> 3.62 [2.11, 6.20] 1.56 [0.49, 5.00] 1.47 [0.68, 3.16] 2.40 [1.10, 5.25]	0.01	Od	lds Ratio ixed, 95%	CI	100
Test for overall effect: <u>Study or Subgroup</u> Janardhan 2015 Konac 2007 Li 2010 Zhang 2016 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect:	: Z = 4.87 (Case <u>Events</u> 52 21 198 87 358 4.30, df = : Z = 4.90 ((P < 0.(s <u>Total</u> 148 26 210 100 484 3 (P = (P < 0.(00001) Contr Events 25 35 191 53 304 0.23); I ² : 00001)	<u>Total</u> 192 48 208 72 520 = 30%	37.3% 12.5% 29.0% 21.2%	M-H, Fixed, 95% CI 3.62 [2.11, 6.20] 1.56 [0.49, 5.00] 1.47 [0.68, 3.16] 2.40 [1.10, 5.25] 2.48 [1.72, 3.56]		Od <u>M-H, F</u> 0.1	Ids Ratio	<u>CI</u>	100
Test for overall effect: D Study or Subgroup Janardhan 2015 Konac 2007 Li 2010 Zhang 2016 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: E	: Z = 4.87 (Case <u>Events</u> 52 21 198 87 358 : 4.30, df = : Z = 4.90 (Case	(P < 0.0 s <u>Total</u> 148 26 210 100 484 3 (P = (P < 0.0 s	00001) Contr Events 25 35 191 53 304 0.23); I²: 00001) Contr	<u>Total</u> 192 48 208 72 520 = 30%	37.3% 12.5% 29.0% 21.2% 100.0 %	M-H, Fixed, 95% Cl 3.62 [2.11, 6.20] 1.56 [0.49, 5.00] 1.47 [0.68, 3.16] 2.40 [1.10, 5.25] 2.48 [1.72, 3.56] Odds Ratio		Oc <u>M-H, F</u> 0.1 Oc	Ids Ratio	<u>ci</u> - -	100
Test for overall effect: Study or Subgroup Janardhan 2015 Konac 2007 Li 2010 Zhang 2016 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: E Study or Subgroup	: Z = 4.87 (Case <u>Events</u> 52 21 198 87 358 : 4.30, df = : Z = 4.90 (Case <u>Events</u>	(P < 0.0 s <u>Total</u> 148 26 210 100 484 3 (P = (P < 0.0 s <u>Total</u>	00001) Contr Events 25 35 191 53 304 0.23); I ² : 00001) Contr Events	<u>Total</u> 192 48 208 72 520 = 30% = 30%	37.3% 12.5% 29.0% 21.2% 100.0% Weight	M-H, Fixed, 95% Cl 3.62 [2.11, 6.20] 1.56 [0.49, 5.00] 1.47 [0.68, 3.16] 2.40 [1.10, 5.25] 2.48 [1.72, 3.56] Odds Ratio M-H, Fixed, 95% Cl		Oc <u>M-H, F</u> 0.1 Oc	Ids Ratio	<u>ci</u> - -	100
Test for overall effect: Study or Subgroup Janardhan 2015 Konac 2007 Li 2010 Zhang 2016 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: E <u>Study or Subgroup</u> Janardhan 2015	: Z = 4.87 (Case <u>Events</u> 52 21 198 87 358 4.30, df = : Z = 4.90 (Case <u>Events</u> 152	(P < 0.0 s <u>Total</u> 148 26 210 100 484 3 (P = (P < 0.0 s <u>Total</u> 248	00001) Contr Events 25 35 191 53 304 0.23); I ² : 00001) Contr Events 128	<u>Total</u> 192 48 208 72 520 = 30% ols <u>Total</u> 295	37.3% 12.5% 29.0% 21.2% 100.0% <u>Weight</u> 60.1%	M-H, Fixed, 95% Cl 3.62 [2.11, 6.20] 1.56 [0.49, 5.00] 1.47 [0.68, 3.16] 2.40 [1.10, 5.25] 2.48 [1.72, 3.56] Odds Ratio <u>M-H, Fixed, 95% Cl</u> 2.07 [1.46, 2.91]		Oc <u>M-H, F</u> 0.1 Oc	Ids Ratio ixed, 95%	- - 10	100
Test for overall effect: Study or Subgroup Janardhan 2015 Konac 2007 Li 2010 Zhang 2016 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: E <u>Study or Subgroup</u> Janardhan 2015 Konac 2007	: Z = 4.87 (Case <u>Events</u> 52 21 198 87 358 4.30, df = : Z = 4.90 (Case <u>Events</u> 152 21	(P < 0.0 s <u>Total</u> 148 26 210 100 484 3 (P = (P < 0.0 s <u>Total</u> 248 26	00001) Contr Events 25 35 191 53 304 0.23); I ² : 00001) Contr Events 128 58	<u>Total</u> 192 48 208 72 520 520 = 30% ols <u>Total</u> 295 71	37.3% 12.5% 29.0% 21.2% 100.0% <u>Weight</u> 60.1% 7.9%	M-H, Fixed, 95% CI 3.62 [2.11, 6.20] 1.56 [0.49, 5.00] 1.47 [0.68, 3.16] 2.40 [1.10, 5.25] 2.48 [1.72, 3.56] Odds Ratio M-H, Fixed, 95% CI 2.07 [1.46, 2.91] 0.94 [0.30, 2.96]		Oc <u>M-H, F</u> 0.1 Oc	Ids Ratio ixed, 95%	- - 10	100
Test for overall effect: Study or Subgroup Janardhan 2015 Konac 2007 Li 2010 Zhang 2016 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: E <u>Study or Subgroup</u> Janardhan 2015 Konac 2007 Li 2010	: Z = 4.87 (Case <u>Events</u> 21 198 87 358 : 4.30, df = : Z = 4.90 (Case <u>Events</u> 152 21 93	(P < 0.0 s <u>Total</u> 148 26 210 100 484 3 (P = (P < 0.0 s <u>Total</u> 248 26 105	00001) Contr Events 25 35 191 53 304 0.23); I ² : 00001) Contr Events 128 58 95	Total 192 48 208 72 520 = 30% ols Total 295 71 112	37.3% 12.5% 29.0% 21.2% 100.0% <u>Weight</u> 60.1% 7.9% 13.9%	M-H, Fixed, 95% CI 3.62 [2.11, 6.20] 1.56 [0.49, 5.00] 1.47 [0.68, 3.16] 2.40 [1.10, 5.25] 2.48 [1.72, 3.56] Odds Ratio M-H, Fixed, 95% CI 2.07 [1.46, 2.91] 0.94 [0.30, 2.96] 1.39 [0.63, 3.06]		Oc <u>M-H, F</u> 0.1 Oc	Ids Ratio ixed, 95%	- - 10	100
Test for overall effect: Study or Subgroup Janardhan 2015 Konac 2007 Li 2010 Zhang 2016 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: E <u>Study or Subgroup</u> Janardhan 2015 Konac 2007	: Z = 4.87 (Case <u>Events</u> 52 21 198 87 358 4.30, df = : Z = 4.90 (Case <u>Events</u> 152 21	(P < 0.0 s <u>Total</u> 148 26 210 100 484 3 (P = (P < 0.0 s <u>Total</u> 248 26	00001) Contr Events 25 35 191 53 304 0.23); I ² : 00001) Contr Events 128 58	<u>Total</u> 192 48 208 72 520 520 = 30% ols <u>Total</u> 295 71	37.3% 12.5% 29.0% 21.2% 100.0% <u>Weight</u> 60.1% 7.9% 13.9%	M-H, Fixed, 95% CI 3.62 [2.11, 6.20] 1.56 [0.49, 5.00] 1.47 [0.68, 3.16] 2.40 [1.10, 5.25] 2.48 [1.72, 3.56] Odds Ratio M-H, Fixed, 95% CI 2.07 [1.46, 2.91] 0.94 [0.30, 2.96]		Oc <u>M-H, F</u> 0.1 Oc	Ids Ratio ixed, 95%	- - 10	100
Test for overall effect: Study or Subgroup Janardhan 2015 Konac 2007 Li 2010 Zhang 2016 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: E <u>Study or Subgroup</u> Janardhan 2015 Konac 2007 Li 2010	: Z = 4.87 (Case <u>Events</u> 21 198 87 358 : 4.30, df = : Z = 4.90 (Case <u>Events</u> 152 21 93	(P < 0.0 s <u>Total</u> 148 26 210 100 484 3 (P = (P < 0.0 s <u>Total</u> 248 26 105	00001) Contr Events 25 35 191 53 304 0.23); I ² : 00001) Contr Events 128 58 95	<u>Total</u> 192 48 208 72 520 = 30% ols <u>Total</u> 295 71 112 123	37.3% 12.5% 29.0% 21.2% 100.0% <u>Weight</u> 60.1% 7.9% 13.9%	M-H, Fixed, 95% CI 3.62 [2.11, 6.20] 1.56 [0.49, 5.00] 1.47 [0.68, 3.16] 2.40 [1.10, 5.25] 2.48 [1.72, 3.56] Odds Ratio M-H, Fixed, 95% CI 2.07 [1.46, 2.91] 0.94 [0.30, 2.96] 1.39 [0.63, 3.06] 0.89 [0.41, 1.92]		Oc <u>M-H, F</u> 0.1 Oc	Ids Ratio ixed, 95%	- - 10	100
Test for overall effect: Study or Subgroup Janardhan 2015 Konac 2007 Li 2010 Zhang 2016 Total (95% Cl) Total events Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Janardhan 2015 Konac 2007 Li 2010 Zhang 2016 Total (95% Cl)	Z = 4.87 (Case <u>Events</u> 21 198 87 358 4.30, df= Z = 4.90 (Case <u>Events</u> 152 21 93 63	(P < 0.0 s <u>Total</u> 148 26 210 100 484 3 (P = (P < 0.0 s <u>Total</u> 248 26 105 76	00001) Contr Events 25 35 191 53 304 0.23); I ² : 00001) Contr Events 128 58 95 104	<u>Total</u> 192 48 208 72 520 = 30% ols <u>Total</u> 295 71 112 123	37.3% 12.5% 29.0% 21.2% 100.0% <u>Weight</u> 60.1% 7.9% 13.9% 18.0%	M-H, Fixed, 95% CI 3.62 [2.11, 6.20] 1.56 [0.49, 5.00] 1.47 [0.68, 3.16] 2.40 [1.10, 5.25] 2.48 [1.72, 3.56] Odds Ratio M-H, Fixed, 95% CI 2.07 [1.46, 2.91] 0.94 [0.30, 2.96] 1.39 [0.63, 3.06]		Oc <u>M-H, F</u> 0.1 Oc	Ids Ratio ixed, 95%	- - 10	100
Test for overall effect: Study or Subgroup Janardhan 2015 Konac 2007 Li 2010 Zhang 2016 Total (95% Cl) Total events Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Janardhan 2015 Konac 2007 Li 2010 Zhang 2016	Z = 4.87 (Case <u>Events</u> 52 21 198 87 358 4.30, df= Z = 4.90 (Case <u>Events</u> 152 21 93 63	(P < 0.0 s <u>Total</u> 148 26 210 100 484 3 (P = (P < 0.0 s <u>Total</u> 248 26 100 484 484 105 76 455	00001) Contr Events 25 35 191 53 304 0.23); I ² : 00001) Contr Events 128 58 95 104 385	Total 192 48 208 72 520 = 30% ols Total 295 71 112 123 601	37.3% 12.5% 29.0% 21.2% 100.0% <u>Weight</u> 60.1% 7.9% 13.9% 18.0%	M-H, Fixed, 95% CI 3.62 [2.11, 6.20] 1.56 [0.49, 5.00] 1.47 [0.68, 3.16] 2.40 [1.10, 5.25] 2.48 [1.72, 3.56] Odds Ratio M-H, Fixed, 95% CI 2.07 [1.46, 2.91] 0.94 [0.30, 2.96] 1.39 [0.63, 3.06] 0.89 [0.41, 1.92]		Oc <u>M-H, F</u> 0.1 Oc	Ids Ratio ixed, 95%	- - 10	100

Figure 3: Forest plot describing the association between the -460C/T polymorphism (rs833061) and risk of ovarian cancer across all study participants according to five genetic models. (A) allelic (T-allele vs. C-allele), (B) recessive (TT vs. CT + CC), (C) dominant (CC vs. CT + TT), (D) homozygous (TT vs. CC) and (E) heterozygous (CT vs. CC).

Genotype comparison and	OR [95 % CI]	Z (P value)	Hete	Analysis		
genetic model	OK [95 76 CI]	L (F value)	χ^2	df (<i>P</i> value)	I ² (%)	model
-2578C/A (rs699947) in total p	oopulation from 4 cas	e-control studie	s (1,022 c	ases and 1,22	28 controls)	
Allelic (A-allele vs. C-allele)	1.23 [0.91, 1.66]	1.34 (0.18)	14.70	3 (0.002)	80	Random
Recessive (AA vs. CA + CC)	1.11 [0.83, 1.50]	0.71 (0.48)	6.85	3 (0.08)	56	Fixed
Dominant (CC vs. CA+AA)	0.78 [0.57, 1.08]	1.48 (0.14)	10.46	3 (0.02)	71	Random
Homozygous (AA vs. CC)	1.33 [0.75, 2.35]	0.97 (0.33)	9.04	3 (0.03)	67	Random
Heterozygous (CA vs. CC)	1.22 [1.02, 1.46]	2.20 (0.03)	6.72	3 (0.08)	55	Fixed

Table 5: Overall meta-analysis of the association between the -2578C/A (rs699947) and risk of ovarian cancer

OR, odds ratio; 95% CI, 95% confidence interval.

association: allelic, OR 1.20, 95% CI 0.34–4.22, P = 0.77(Figure 5A); recessive, OR 1.87, 95% CI 0.19–18.93, P = 0.59 (Figure 5B); dominant, OR 0.83, 95% CI 0.22– 3.22, P = 0.79 (Figure 5C); homozygous, OR 1.99, 95% CI 0.14–28.35, P = 0.61 (Figure 5D); and heterozygous, OR 1.14, 95% CI 0.34–3.85, P = 0.84 (Figure 5E).

Sensitivity analysis

The robustness of the meta-analysis of 4 studies [26, 29, 31, 32] examining a possible association between the -460C/T polymorphism and ovarian cancer risk was assessed by repeating the meta-analysis after excluding a study by Zhang et al. [32] in which the *P* value associated with HWE was less than 0.05. Deleting these data from the meta-analysis did not alter the results except in the recessive model, the results of which should therefore be interpreted with caution.

Publication bias

Potential publication bias in this meta-analysis was assessed using Begg's funnel plot. No obvious asymmetry was observed in Begg's funnel plots of allelic modeling of the polymorphisms +936C/T (Figure 6), -460C/T (Figure 7) or -2578C/A (Figure 8). P values for Begg's test were greater than 0.05 for the +936C/T results based on all the genetic models: allelic, P = 0.230; recessive, P = 0.230; dominant, P = 1.000; homozygous, P =0.368; and heterozygous, P = 0.764. Similarly, P values were greater than 0.05 for the -460C/T results (allelic, P = 0.734; recessive, P = 1.000; dominant, P = 0.734; homozygous, P = 0.734; heterozygous, P = 0.734) and for the -2578C/A results (allelic, P = 0.308; recessive, P = 0.089; dominant, P = 0.734; homozygous, P = 0.089; heterozygous, P = 0.734). These results suggest no potential publication bias in the included data on +936C/T, -460C/T and -2578C/A polymorphisms. Begg's test was not applied to data on the -1154G/A polymorphism because of the small number of publications.

DISCUSSION

The number of case-control studies exploring the influence of VEGF-A polymorphisms on ovarian cancer risk has grown in recent years [26-32]. Limited sample size and ethnic differences among the various populations examined have contributed to a lack of consensus in this literature, so we conducted this comprehensive metaanalysis to evaluate the association of ovarian cancer risk with four polymorphisms in the VEGF-A gene (+936C/T, -460C/T, -2578C/A and -1154G/A). Our meta-analysis suggests that the -460C/T polymorphism is significantly associated with ovarian cancer risk across the total population as well as the Asian population. In contrast, none of the five genetic models suggested a significant association between the + 936C/T polymorphism and ovarian cancer risk in Asian populations in general or in Chinese populations specifically. None of the five genetic models suggested a significant association between the -1154G/A polymorphism and ovarian cancer risk across the entire study population.

While the present meta-analysis was being conducted, Zhang et al. [33] published a meta-analysis of the relationship between ovarian cancer risk and the three polymorphisms +936C/T, -460C/T, and -2578C/A. Similar to their results, we found that the CT genotype at +936C/T may act as a protective factor in Caucasian populations. On the other hand, our meta-analysis contrasts with the previous one because we found the -460C/T polymorphism to be significantly associated with ovarian cancer risk across the total population as well as the Asian subpopulation, and the CA genotype at -2578C/A to be associated with cancer risk across the total population, whereas that previous meta-analysis did not report either association. This discrepancy

A	Case		Contro			Odds Ratio		s Ratio	
Study or Subgroup						M-H, Random, 95% (<u>dom, 95% Cl</u>	
Janardhan 2015	226	600	252	640		0.93 [0.74, 1.1]		1	
Jia 2009	133	512	163	658		1.07 [0.82, 1.39		Ť.	
Li 2010	157	606	136	606	25.4%	1.21 (0.93, 1.5)	7]	†	
Zhang 2016	88	326	85	552	22.6%	2.03 [1.45, 2.84	4]	+	
Total (95% CI)		2044		2456	100.0%	1.23 [0.91, 1.66	51	•	
Total events	604		636				.1		
Heterogeneity: Tau ² =		2 - 14		(P – 0	002):12-	90%	⊢ − − −	+ +	
Test for overall effect:				(i – 0.	.002),1 =	00.0	0.01 0.1	1 10	10
В	Case	•	Contro	alo		Odds Ratio	Odds R	otio	
					Moight		M-H, Fixed		
Study or Subgroup						M-H, Fixed, 95% Cl	м-п, rixeu	95% CI	
Janardhan 2015	42	300	49	320	49.6%	0.90 [0.58, 1.41]		_	
Jia 2009	17	256	25	329	24.8%	0.86 [0.46, 1.64]		-	
Li 2010	20	303	16	303	18.2%	1.27 [0.64, 2.50]	-	_	
Zhang 2016	15	163	9	276	7.4%	3.01 [1.28, 7.04]	-		
Total (95% CI)		1022		1228	100.0%	1.11 [0.83, 1.50]	•		
Total events	94		99			• • •			
Heterogeneity: Chi ² =	6.85 df=	3 (P =	0.08); 12 =	= 56%					
Test for overall effect:							0.01 0.1 1	10	100
C									
С	Case		Contro			Odds Ratio		s Ratio	
Study or Subgroup						M-H, Random, 95% (<u>dom, 95% Cl</u>	
Janardhan 2015	116	300	117	320	25.9%	1.09 (0.79, 1.51	•	†	
Jia 2009	140	256	191	329	25.7%	0.87 (0.63, 1.21	1]	•	
Li 2010	166	303	183	303	26.0%	0.79 [0.58, 1.10)j -	•	
Zhang 2016	90	163	200	276	22.5%	0.47 (0.31, 0.7)	0] 🗕 🗕	·	
Total (95% CI)		1022		1228	100.0%	0.78 [0.57, 1.08	8]	•	
Total events	512		691						
Heterogeneity: Tau ² =	0.08; Chi	² = 10.	46, df = 3	(P = 0.	.02); I ² = 7	'1%		+ +	
Test for overall effect:							0.01 0.1	i 10	10
D	6	_	Contra	-1-		Odda Datia	0.11	- D-ti-	
D	Case	-	Contro		14/	Odds Ratio		s Ratio	
Study or Subgroup						M-H, Random, 95% (dom, 95% Cl	
Janardhan 2015	42	158	49	166	29.8%	0.86 [0.53, 1.40			
Jia 2009	17	157	25	216	25.4%	0.93 [0.48, 1.78	•		
Li 2010	20	186	16	199		1.38 [0.69, 2.7			
Zhang 2016	15	105	9	209	20.3%	3.70 [1.56, 8.78	3]		
Total (95% CI)		606		790	100.0%	1.33 [0.75, 2.35	5]	•	
Total events	94		99						
Heterogeneity: Tau² =				P = 0.0	13); I² = 67	%	0.01 0.1	1 10	10
Test for overall effect:	Z = 0.97 (P = 0.3	33)				0.01 0.1	1 10	10
Е	Case	s	Contro	ols		Odds Ratio	Odds R	atio	
Study or Subgroup					Weight	M-H, Fixed, 95% Cl	M-H, Fixed		
Janardhan 2015	142	258	154	271	31.3%	0.93 [0.66, 1.31]		00// 01	
Jia 2009	99	238	104	304	27.0%		1	-	
						1.20 [0.84, 1.69]		_	
Li 2010	117	283	104	287	28.1%	1.24 [0.88, 1.74]		_	
Zhang 2016	58	148	67	267	13.5%	1.92 [1.25, 2.96]		-	
Total (95% CI)		928		1129	100.0%	1.22 [1.02, 1.46]	•		
Total events	416		438			. ,			
Heterogeneity: Chi ² =		3 (P =		= 55%					
Test for overall effect:				0070			0.01 0.1 1	10	100
restrat oronan onoot.		. 0.0	-,						

Figure 4: Forest plot describing the association between the -2578C/A polymorphism (rs699947) and risk of ovarian cancer across all study participants according to five genetic models. (A) allelic (A-allele vs. C-allele), (B) recessive (AA vs. CA + CC), (C) dominant (CC vs. CA + AA), (D) homozygous (AA vs. CC) and (E) heterozygous (CA vs. CC).

Table 6: Overall meta-analysis of the association between the -1154G/A (rs1570360) and risk of ovarian cancer

Genotype comparison and	OD 105 0/ CU	$\mathcal{T}(\mathbf{D}_{\mathrm{real}})$	Hetero	geneity of stud	y design	A malauria madal
genetic model	OR [95 % CI]	Z (P value)	χ^2	df (P value)	I ² (%)	Analysis model
-1154G/A (rs1570360) in total	population from 2	case-control st	tudies (6	02 cases and 62	3 controls)
Allelic (A-allele vs. G-allele)	1.20 [0.34, 4.22]	0.29 (0.77)	31.05	1 (< 0.001)	97	Random
Recessive (AA vs. GC + GG)	1.87 [0.19, 18.93]	0.53 (0.59)	7.91	1 (0.005)	87	Random
Dominant (GG vs. GA + AA)	0.83 [0.22, 3.22]	0.26 (0.79)	28.14	1 (< 0.001)	96	Random
Homozygous (AA vs. GG)	1.99 [0.14, 28.35]	0.51 (0.61)	10.34	1 (0.001)	90	Random
Heterozygous (GA vs. GG)	1.14 [0.34, 3.85]	0.21 (0.84)	21.58	1 (< 0.001)	95	Random

OR, odds ratio; 95% CI, 95% confidence interval.

may reflect the fact that we included two large case-control studies involving all four VEGF-A polymorphisms absent from the previous meta-analysis, leading to much larger sample sizes for meta-analysis of 2578C/A and -460C/T polymorphisms in our work. In addition, we meta-analyzed the relationship between -1154G/A polymorphism and ovarian risk, which was not examined in that previous meta-analysis. Therefore, our meta-analysis provides new evidence for the important role of VEGF-A polymorphisms in ovarian cancer development. To the best of our knowledge, the present study is the most comprehensive and robust meta-analysis of these genetic polymorphisms and ovarian cancer.

Despite the potential insights it offers, the present study has several limitations that may affect interpretation of the results. First, the P value for HWE was less than 0.05 in the case-control study by Zhang et al. [32] on the -460C/ T polymorphism. These results suggest that this study population may not be representative of the broader target population. Nevertheless, sensitivity analyses showed that deleting these data from the meta-analysis did not alter the results except in the recessive model, which is unlikely to significantly affect the observed significant relationship between -460C/T polymorphism and ovarian cancer risk. Second, our exclusion of unpublished data and of papers published in languages other than English and Chinese may have biased our results. Third, the studies may be subject to performance bias, attrition bias and reporting bias, although Newcastle-Ottawa scores were at least 6 for all 7 studies, indicating high quality. Lastly, the results may be affected by additional confounding factors, such as age, obesity, type of cancer, or other factors, and we could not take this into account in the meta-analyses because studies either did not report these baseline data or they aggregated the data in different ways. Thus, these conclusions should be verified in large, well-designed studies.

In conclusion, this meta-analysis indicates that there may be a significant association between the -460C/T polymorphism and ovarian cancer risk. The

CA genotype at -2578C/A may be a risk factor in the total population, while the CT genotype at +936C/T may be a protective factor in the Caucasian population. The -1154G/A polymorphism may not be related to ovarian cancer risk.

MATERIALS AND METHODS

Search strategy

PubMed, EMBASE, Google Scholar and the Chinese National Knowledge Infrastructure databases were systematically searched up to April 12, 2017 for clinical and experimental case-control studies published in English or Chinese that assessed potential associations of ovarian cancer risk with at least one of the following polymorphisms in the VEGF-A gene: +936C/T (rs3025039), -460C/T (rs833061), -2578C/A (rs699947), and -1154G/A (rs1570360). The following search strings were used: *vascular endothelial growth factor* +936C/T, vascular endothelial growth factor -460C/T, vascular endothelial growth factor -2578C/A, vascular endothelial growth factor -1154G/A, rs3025039, rs833061, rs699947, and rs1570360. Searches were also conducted with each of these eight terms AND each of the following terms: polymorphism, polymorphisms, SNP, variant, variants, variation, genotype, genetic or mutation. Lastly, searches were conducted with each of the above terms AND each of the following: ovarian cancer, ovarian carcinoma or OC. Reference lists in identified articles and reviews were also searched manually to identify additional eligible studies.

This literature and meta-analysis were performed in accordance with the guidelines and recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Supplementary Table 1) [34].

Inclusion criteria

To be included in our review and meta-analysis, studies had to satisfy the following criteria: (1) a case-

А	Case	-	Contro			Odds Ratio		Odds Ratio		
Study or Subgroup						M-H, Random, 95% Cl		M-H, Random, 9)5% CI	
Janardhan 2015	155	600	85	640	50.3%	2.27 [1.70, 3.05]		_ 1		
Li 2010	62	604	93	606	49.7%	0.63 [0.45, 0.89]		•		
Total (95% CI)		1204		1246	100.0%	1.20 [0.34, 4.22]		•		
Total events	217		178					.		
Heterogeneity: Tau² =				(P < 0.	00001); F	²= 97%	0.01	0.1 1	10	100
Test for overall effect:	Z = 0.29 (P = 0.7	7)				0.01	0.1	10	100
В	Case	s	Contro	ols		Odds Ratio		Odds Ratio	0	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random, 9	5% CI	
Janardhan 2015	21	300	4	320	50.9%	5.95 [2.02, 17.53]		-	-	
Li 2010	4	302	7	303	49.1%	0.57 [0.16, 1.96]				
Total (95% CI)		602		623	100.0%	1.87 [0.19, 18.93]				
Total events	25		11							
Heterogeneity: Tau ² =		² = 7.9 ⁴		P = 0.0	05): I ² = 8	7%	<u> </u>			
Test for overall effect:				0.0	00/,1		0.01	0.1 1	10	100
	2 - 0.00 (1 - 0.0	•/							
С	Case	s	Contro	ols		Odds Ratio		Odds Ratio	0	
Study or Subgroup	Events	Total			Weight	M-H, Random, 95% Cl		M-H, Random, 9		
Janardhan 2015	166	300	239	320	50.2%	0.42 (0.30, 0.59)				
Li 2010	244	302	217	303	49.8%	1.67 [1.14, 2.44]		-		
2.2010	2.11	002	2		10.070					
Total (95% CI)		602		623	100.0%	0.83 [0.22, 3.22]		-		
Total events	410		456			• • •				
Heterogeneity: Tau ² =		2 - 20	14 df=1	(P < 0	000043-8	² = 96%	—		_	1
meleioueneily, i au -	: 0.92; Chi	-= Zŏ.	14. ui – i		00001).1			- · · · ·		
				ų · · •.	00001),1	- 55 %	0.01	0.1 1	10	100
Test for overall effect:				ų · 0.	00001),1		0.01	0.1 1	10	100
		P = 0.7			00001),1	Odds Ratio	0.01	0.1 1 Odds Ratio		100
	Z = 0.26 (Case	P = 0.7 s	9) Contro	ols			0.01		0	100
Test for overall effect:	Z = 0.26 (Case	P = 0.7 s	9) Contro	ols		Odds Ratio	0.01	Odds Ratio	0	100
Test for overall effect: D <u>Study or Subgroup</u>	Z = 0.26 (Case Events	P = 0.7 s <u>Total</u>	9) Contro <u>Events</u>	ols Total	Weight	Odds Ratio M-H, Random, 95% Cl	0.01	Odds Ratio	0	100
Test for overall effect: D <u>Study or Subgroup</u> Janardhan 2015	Z = 0.26 (Case Events 21	P = 0.7 s <u>Total</u> 187	9) Contro <u>Events</u> 4	ols <u>Total</u> 243	Weight 50.6%	Odds Ratio <u>M-H, Random, 95% Cl</u> 7.56 (2.55, 22.42)	0.01	Odds Ratio	0	100
Test for overall effect: D <u>Study or Subgroup</u> Janardhan 2015	Z = 0.26 (Case Events 21	P = 0.7 s <u>Total</u> 187	9) Contro <u>Events</u> 4	b is <u>Total</u> 243 224	Weight 50.6%	Odds Ratio <u>M-H, Random, 95% Cl</u> 7.56 (2.55, 22.42)	0.01	Odds Ratio	0	100
Test for overall effect: D <u>Study or Subgroup</u> Janardhan 2015 Li 2010	Z = 0.26 (Case Events 21	P = 0.7 s <u>Total</u> 187 248	9) Contro <u>Events</u> 4	b is <u>Total</u> 243 224	<u>Weight</u> 50.6% 49.4%	Odds Ratio <u>M-H, Random, 95% Cl</u> 7.56 (2.55, 22.42) 0.51 (0.15, 1.76)	0.01	Odds Ratio	0	100
Test for overall effect: D <u>Study or Subgroup</u> Janardhan 2015 Li 2010 Total (95% CI)	Z = 0.26 (Case <u>Events</u> 21 4 25	P = 0.7 s <u>Total</u> 187 248 435	9) Contro <u>Events</u> 4 7	bls <u>Total</u> 243 224 467	<u>Weight</u> 50.6% 49.4% 100.0 %	Odds Ratio <u>M-H, Random, 95% CI</u> 7.56 (2.55, 22.42) 0.51 (0.15, 1.76) 1.99 (0.14, 28.35)		Odds Ratio	0 05% CI	
Test for overall effect: D <u>Study or Subgroup</u> Janardhan 2015 Li 2010 Total (95% CI) Total events	Z = 0.26 (Case <u>Events</u> 21 4 25 3.31; Chi	P = 0.7 s <u>Total</u> 187 248 435 ² = 10.7	9) Contro <u>Events</u> 4 7 11 34, df = 1	bls <u>Total</u> 243 224 467	<u>Weight</u> 50.6% 49.4% 100.0 %	Odds Ratio <u>M-H, Random, 95% CI</u> 7.56 (2.55, 22.42) 0.51 (0.15, 1.76) 1.99 (0.14, 28.35)	0.01 L	Odds Ratio	0	100
Test for overall effect: D <u>Study or Subgroup</u> Janardhan 2015 Li 2010 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect:	Z = 0.26 (Case <u>Events</u> 21 4 25 3.31; Chi Z = 0.51 (P = 0.7 s <u>Total</u> 187 248 435 ² = 10.0 P = 0.6	9) Contro <u>Events</u> 4 7 11 34, df = 1 1)	Dis <u>Total</u> 243 224 467 (P = 0.	<u>Weight</u> 50.6% 49.4% 100.0 %	Odds Ratio <u>M-H, Random, 95% Cl</u> 7.56 [2.55, 22.42] 0.51 [0.15, 1.76] 1.99 [0.14, 28.35] 90%		Odds Ratio	0 05% CI 10	
Test for overall effect: D <u>Study or Subgroup</u> Janardhan 2015 Li 2010 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: E	Z = 0.26 (Case Events 21 4 25 3.31; Chi Z = 0.51 (Case	P = 0.7 s <u>Total</u> 187 248 435 7 = 10.2 P = 0.8 s	9) Contro <u>Events</u> 4 7 11 34, df = 1 1) Contro	Dis <u>Total</u> 243 224 467 (P = 0.	<u>Weight</u> 50.6% 49.4% 100.0% 001); I ² =	Odds Ratio <u>M-H, Random, 95% Cl</u> 7.56 [2.55, 22.42] 0.51 [0.15, 1.76] 1.99 [0.14, 28.35] 90% Odds Ratio		Odds Ratio	0 05% CI 10	
Test for overall effect: D <u>Study or Subgroup</u> Janardhan 2015 Li 2010 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: <u>E</u> <u>Study or Subgroup</u>	Z = 0.26 (Case <u>Events</u> 21 4 25 3.31; Chi Z = 0.51 (Case <u>Events</u>	P = 0.7 s <u>Total</u> 187 248 435 ² = 10. ² P = 0.8 s <u>Total</u>	9) Contro <u>Events</u> 4 7 11 34, df = 1 1) Contro <u>Events</u>	bls <u>Total</u> 243 224 467 (P = 0. (P = 0.	<u>Weight</u> 50.6% 49.4% 100.0 % 001); I ² = <u>Weight</u>	Odds Ratio <u>M-H, Random, 95% Cl</u> 7.56 [2.55, 22.42] 0.51 [0.15, 1.76] 1.99 [0.14, 28.35] 90% Odds Ratio <u>M-H, Random, 95% Cl</u>		Odds Ratio	0 05% CI 10	
Test for overall effect: D <u>Study or Subgroup</u> Janardhan 2015 Li 2010 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: <u>E</u> <u>Study or Subgroup</u> Janardhan 2015	Z = 0.26 (Case <u>Events</u> 21 4 25 3.31; Chi Z = 0.51 (Case <u>Events</u> 113	P = 0.7 s <u>Total</u> 187 248 435 248 435 248 435 P = 0.8 s <u>Total</u> 279	9) Contro <u>Events</u> 4 7 11 34, df = 1 1) Contro <u>Events</u> 77	Dis <u>Total</u> 243 224 467 (P = 0. (P = 0. Dis <u>Total</u> 316	<u>Weight</u> 50.6% 49.4% 100.0% 001); I ² = <u>Weight</u> 50.3%	Odds Ratio <u>M-H, Random, 95% Cl</u> 7.56 [2.55, 22.42] 0.51 [0.15, 1.76] 1.99 [0.14, 28.35] 90% Odds Ratio <u>M-H, Random, 95% Cl</u> 2.11 [1.49, 3.00]		Odds Ratio	0 05% CI 10	
Test for overall effect: D <u>Study or Subgroup</u> Janardhan 2015 Li 2010 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: <u>E</u> <u>Study or Subgroup</u>	Z = 0.26 (Case <u>Events</u> 21 4 25 3.31; Chi Z = 0.51 (Case <u>Events</u>	P = 0.7 s <u>Total</u> 187 248 435 ² = 10. ² P = 0.8 s <u>Total</u>	9) Contro <u>Events</u> 4 7 11 34, df = 1 1) Contro <u>Events</u>	bls <u>Total</u> 243 224 467 (P = 0. (P = 0.	<u>Weight</u> 50.6% 49.4% 100.0 % 001); I ² = <u>Weight</u>	Odds Ratio <u>M-H, Random, 95% Cl</u> 7.56 [2.55, 22.42] 0.51 [0.15, 1.76] 1.99 [0.14, 28.35] 90% Odds Ratio <u>M-H, Random, 95% Cl</u>		Odds Ratio	0 05% CI 10	
Test for overall effect: D <u>Study or Subgroup</u> Janardhan 2015 Li 2010 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: <u>E</u> <u>Study or Subgroup</u> Janardhan 2015 Li 2010	Z = 0.26 (Case <u>Events</u> 21 4 25 3.31; Chi Z = 0.51 (Case <u>Events</u> 113	P = 0.7 s <u>Total</u> 187 248 435 248 435 248 435 P = 0.8 s <u>Total</u> 279 298	9) Contro <u>Events</u> 4 7 11 34, df = 1 1) Contro <u>Events</u> 77	Is 10tal 243 224 467 (P = 0. ols Total 316 296	Weight 50.6% 49.4% 100.0% 001); I ² = <u>Weight</u> 50.3% 49.7%	Odds Ratio <u>M-H, Random, 95% Cl</u> 7.56 [2.55, 22.42] 0.51 [0.15, 1.76] 1.99 [0.14, 28.35] 90% Odds Ratio <u>M-H, Random, 95% Cl</u> 2.11 [1.49, 3.00] 0.61 [0.41, 0.90]		Odds Ratio	0 05% CI 10	
Test for overall effect: D <u>Study or Subgroup</u> Janardhan 2015 Li 2010 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: <u>E</u> <u>Study or Subgroup</u> Janardhan 2015 Li 2010 Total (95% CI)	Z = 0.26 (Case Events 21 4 25 3.31; Chi Z = 0.51 (Case Events 113 54	P = 0.7 s <u>Total</u> 187 248 435 248 435 248 435 P = 0.8 s <u>Total</u> 279	9) Contro <u>Events</u> 4 7 11 34, df = 1 1) Contro <u>Events</u> 77 79	Is 10tal 243 224 467 (P = 0. ols Total 316 296	<u>Weight</u> 50.6% 49.4% 100.0% 001); I ² = <u>Weight</u> 50.3%	Odds Ratio <u>M-H, Random, 95% Cl</u> 7.56 [2.55, 22.42] 0.51 [0.15, 1.76] 1.99 [0.14, 28.35] 90% Odds Ratio <u>M-H, Random, 95% Cl</u> 2.11 [1.49, 3.00]		Odds Ratio	0 05% CI 10	
Test for overall effect: D <u>Study or Subgroup</u> Janardhan 2015 Li 2010 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: <u>E</u> <u>Study or Subgroup</u> Janardhan 2015 Li 2010 Total (95% CI) Total events	Z = 0.26 (Case <u>Events</u> 21 4 25 3.31; Chi Z = 0.51 (Case <u>Events</u> 113 54 167	P = 0.7 s <u>Total</u> 187 248 435 * = 10.2 * P = 0.6 s <u>Total</u> 279 298 577	9) Contro <u>Events</u> 4 7 11 34, df = 1 1) Contro <u>Events</u> 77 79 156	Total 243 224 467 (P = 0. ols Total 316 296 612	<u>Weight</u> 50.6% 49.4% 100.0% 001); I ² = <u>Weight</u> 50.3% 49.7% 100.0 %	Odds Ratio <u>M-H, Random, 95% Cl</u> 7.56 [2.55, 22.42] 0.51 [0.15, 1.76] 1.99 [0.14, 28.35] 90% Odds Ratio <u>M-H, Random, 95% Cl</u> 2.11 [1.49, 3.00] 0.61 [0.41, 0.90] 1.14 [0.34, 3.85]		Odds Ratio	0 05% CI 10	
Test for overall effect: D <u>Study or Subgroup</u> Janardhan 2015 Li 2010 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: <u>E</u> <u>Study or Subgroup</u> Janardhan 2015 Li 2010 Total (95% CI)	Z = 0.26 (Case Events 21 4 25 3.31; Chi Z = 0.51 (Case Events 113 54 167 0.74; Chi	P = 0.7 s <u>Total</u> 187 248 435 ² = 10.2 s <u>Total</u> 279 298 577 ² = 21.2	9) Contro <u>Events</u> 4 7 11 34, df = 1 1) Contro <u>Events</u> 77 79 156 58, df = 1	Total 243 224 467 (P = 0. ols Total 316 296 612	<u>Weight</u> 50.6% 49.4% 100.0% 001); I ² = <u>Weight</u> 50.3% 49.7% 100.0 %	Odds Ratio <u>M-H, Random, 95% Cl</u> 7.56 [2.55, 22.42] 0.51 [0.15, 1.76] 1.99 [0.14, 28.35] 90% Odds Ratio <u>M-H, Random, 95% Cl</u> 2.11 [1.49, 3.00] 0.61 [0.41, 0.90] 1.14 [0.34, 3.85]		Odds Ratio	0 05% CI 10	

Figure 5: Forest plot describing the association between the -1154G/A polymorphism (rs1570360) and risk of ovarian cancer across all study participants according to five genetic models. (A) allelic (A-allele vs. G-allele), (B) recessive (AA vs. GC + GG), (C) dominant (GG vs. GA + AA), (D) homozygous (AA vs. GG) and (E) heterozygous (GA vs. GG).

control design was used to assess the association of at least one of the four target polymorphisms with ovarian cancer risk in humans; (2) full text was available, and sufficient data were reported to estimate an odds ratio (OR) with 95% confidence interval (CI); and (3) genotype frequencies were reported. If multiple publications from the same research group appeared to report data for the same cases and controls, we included only the most recent publication in our meta-analysis.

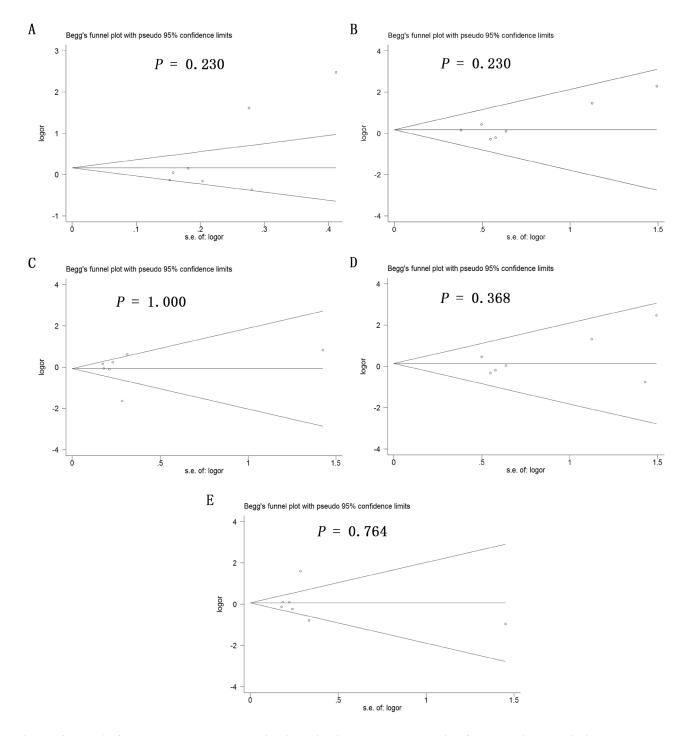


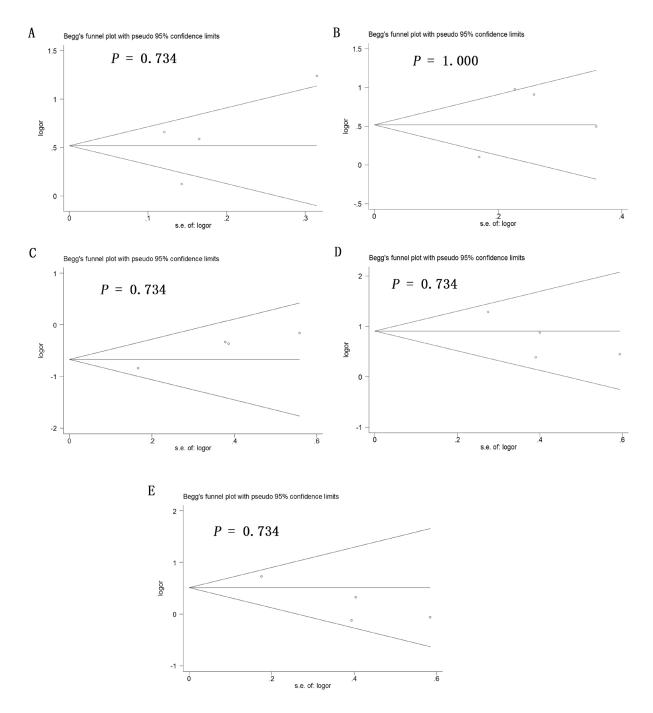
Figure 6: Begg's funnel plot to assess publication bias in the meta-analysis of a potential association between the +936C/T polymorphism (rs3025039) and risk of ovarian cancer across all study participants according to five genetic **models.** (A) allelic (T-allele vs. C-allele), (B) recessive (TT vs. CT + CC), (C) dominant (CC vs. CT + TT), (D) homozygous (TT vs. CC) and (E) heterozygous (CT vs. CC).

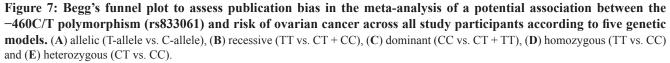
Data extraction

Two authors (CHX and ZHH) independently extracted the following data from included studies: first author's family name, year of publication, ethnicity, country of origin, testing methods, type of controls, *P* value for HWE in controls, numbers and genotypes of cases and controls, frequencies of genotypes in cases and controls. Discrepancies were resolved by consensus.

Assessment of methodological quality

The quality of the included studies was assessed independently by two authors (CHX and ZHH) according to the Newcastle–Ottawa Scale [35]. This scale awards





a maximum of 9 points to a study, with higher scores indicating better quality. Differences in quality score outcomes between the two assessors were solved by consensus. If consensus was not reached, a third assessor (HX) was consulted for the final decision.

Statistical analysis

Unadjusted odds ratios (ORs) with 95% confidence intervals (95% CI) were used to assess the strength of the association of each of the four target polymorphisms

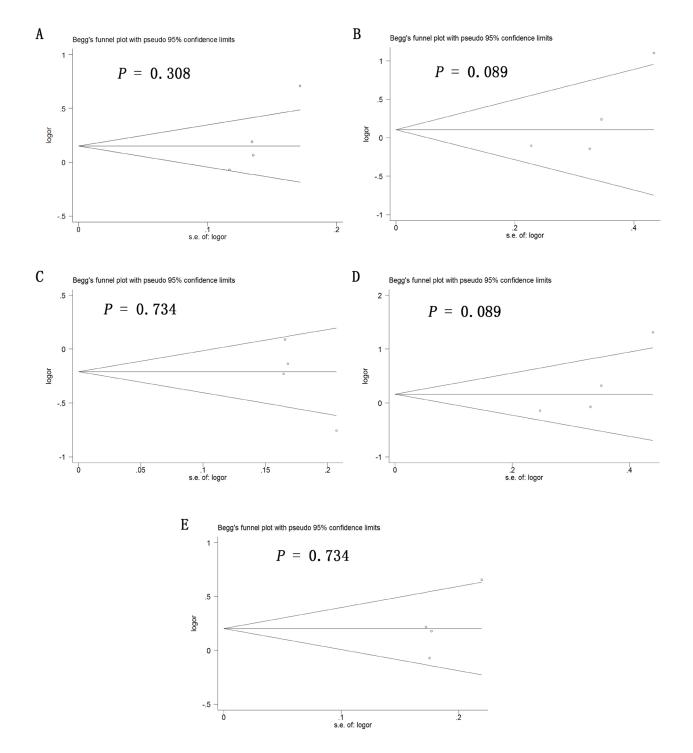


Figure 8: Begg's funnel plot to assess publication bias in the meta-analysis of a potential association between the -2578C/A polymorphism (rs699947) and risk of ovarian cancer across all study participants according to five genetic models. (A) allelic (A-allele vs. C-allele), (B) recessive (AA vs. CA + CC), (C) dominant (CC vs. CA + AA), (D) homozygous (AA vs. CC) and (E) heterozygous (CA vs. CC). with ovarian cancer risk, based on genotype frequencies in cases and controls. The significance of pooled ORs was determined using the *Z* test, with P < 0.05 defined as the significance threshold. Meta-analysis was conducted using a fixed-effect model when P > 0.10 for the *Q* test, indicating lack of heterogeneity among studies; otherwise, a random-effect model was used. All statistical tests for meta-analyses were performed using Review Manager 5.2 (Cochrane Collaboration). Publication bias was assessed using Begg's funnel plot Stata 14.0 (Stata Corp, College Station, TX, USA), with P < 0.05 considered statistically significant.

Author contributions

Designed the study: Hong Xu and Chao-Huan Xu. Searched databases and collected full-text papers: Chao-Huan Xu. Extracted and analyzed the data: Chao-Huan Xu and Zhong-Hui He. Statistical analyses: Chao-Huan Xu and Zhong-Hui He. Wrote the manuscript: Chao-Huan Xu. All authors reviewed the manuscript.

CONFLICTS OF INTEREST

The authors declare no competing financial interests.

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