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Association between MDM2 SNP309 and endometrial cancer risk

A PRISMA-compliant meta-analysis

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Abstract

Background: Murine double minute 2 homolog (MDM2) plays an important role in the downregulation of P53 tumor suppressor gene. MDM2 inhibits P53 transcriptional activity and thereby results in accelerated tumor formation. Overexpression of MDM2 has been found in several cancer types including endometrial cancer. SNP309 is located in the promoter region of MDM2 and contributes to the overexpression of MDM2. The association between MDM2 SNP309 polymorphism and endometrial cancer risk has been investigated in several studies; however, the conclusion remains controversial.

Objectives: We performed the present meta-analysis to give a comprehensive conclusion of the association between MDM2 SNP309 polymorphism and endometrial cancer susceptibility.

Methods: We conducted a literature research on PubMed, Embase, Cochrane Library, OVID, Web of Science, Wan Fang, CNKI, and CQVIP databases up to July 31, 2018. Newcastle–Ottawa scale was used to assess the quality of studies. We evaluated the strength of association by combining odds ratios (ORs) and 95% confidence intervals (CIs) in 5 different genetic models under a fixed-effect model or random-effect model. We further conducted subgroup analysis by ethnicity, source of control, histological type, clinical type, grade, and stage of tumor. Sensitivity analysis and publication bias were also performed.

Results: Nine eligible studies were finally included in our meta-analysis. We found MDM2 SNP309 polymorphism increased the risk of endometrial cancer under allele model (OR: 1.23, 95% CI: 1.06–1.41, $P = .005$), homozygote model (OR: 1.43, 95% CI: 1.13–1.81, $P = .003$) and recessive model (OR: 1.55, 95% CI: 1.17-2.04, $P = .002$). Subgroup analysis suggested a similar elevated risk in both Asians and Caucasians. We identified a strong association of enhanced susceptibility to endometrial cancer in endometrioid group (OR: 2.13, 95% CI: 1.28–3.54, $P = .004$) and Type I group (OR: 1.89, 95% CI: 1.25–2.86, $P = .002$) under dominant model. We identified no significant publication bias according to Egger's test.

Conclusions: Our meta-analysis suggested that MDM2 SNP309 polymorphism increased the risk of endometrial cancer significantly, especially in endometrioid and Type I endometrial cancer, indicating MDM2 could serve as a potential diagnostic factor marker for endometrial cancer.

Abbreviations: CI = confidence interval, HB = hospital-based, HWE = Hardy–Weinberg equilibrium, MDM2 = murine double minute 2, NOS = Newcastle–Ottawa scale, ORs = odds ratios, PB = population-based, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RAF = risk allele frequency, SNP = single nucleotide polymorphism.

Keywords: endometial cancer, MDM2, meta-analysis, polymorphism, SNP309

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XZ and YZ contributed equally to this work.

The study was designed by XZ, JZ, and YC. XZ, and YZ did the literature search, study quality assessment, and data extraction. XZ, YZ, LZ, and JL performed the statistical analysis and drafted the tables and figures. XZ wrote the first draft of this analysis, and YZ, CZ, and QC helped to finish the final version. All authors approved the conclusions of our study.

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1. Introduction

Endometrial cancer is one of the most common gynecologic carcinoma worldwide.[1,2] Its incidence rate has been increasing during last decades, especially in developed countries.[2] The etiology of endometrial cancer remains unclear due to complex mechanisms of pathogenesis. It has been reported that environmental factors such as hormone exposure and obesity may contribute to the carcinogensis of endometrial carcinoma.[3,4] Genetic predisposition has also been confirmed to be involved in the etiology.[5,6]

Murine double minute 2 homolog (MDM2) is located in chromosome 12q13-14 and plays a key role in the down-regulation of P53 tumor suppressor gene.[7] P53 is a crucial component that regulates the cell-cycle arrest and apoptosis in response to DNA damage or oncogene expression. It was reported that MDM2 inhibited P53 transcriptional activity through ubiquitination and degradation, thereby resulted in accelerated tumor formation.[8] Overexpression of MDM2 has been found in several cancers, including lung, breast, prostate, bladder, gastric, colorectal, hepatocellular, and endometrial cancer.[9–12] A functional single nucleotide polymorphism located in 309 bp downstream from intron 1 in the promoter region of MDM2 (a change from T to G) was identified and is referred to as SNP309.[7,13] The G variant allele was found to enhance the affinity of MDM2 to SP1 transcription factor and leading to MDM2 overexpression.[7] Several studies have also revealed that G allele of SNP309 is associated with an elevated susceptibility to cancer.[14–16]

So far, the relationship between MDM2 SNP309 polymorphism and endometrial cancer risk has been investigated in several studies, but the conclusions remain inconsistent. Due to the relatively small sample size of each individual study and the conflict results, we performed the present meta-analysis with 9 eligible studies[17–25] to give a more accurate and comprehensive estimation of the association between MDM2 SNP309 and the susceptibility to endometrial carcinoma.

2. Methods

We performed our meta-analysis based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[26]

2.1. Search strategy

We performed a comprehensive literature search for relevant studies in PubMed, Embase, Cochrane Library, OVID, Web of Science, Wan Fang, CNKI, and CQVIP databases up to July 31, 2018. We combined the following items in our search strategy: Polymorphism* or SNP* or mutant or mutation or variation; MDM 2 or MDM-2 or MDM2 or Mouse double minute 2 or Mouse double minute-2 or Mouse double minute2 or Murine double minute 2 or Murine double minute-2 or Murine double minute2; (Endometrial or Endometrium) and (cancer* or neoplasm* or carcinoma*). Furthermore, references of previous articles were manually searched for potential studies.

2.2. Inclusion and exclusion criteria

The inclusion criteria were: studies with case–control or cohort designs; studies investigating the potential association between MDM2 SNP309 polymorphism and endometrial cancer risk; studies with sufficient original data to calculate odds ratios (ORs) and 95% confidence interval (95% CI). When overlapping data appeared in multiple publications, only the study containing largest sample size was included in our meta-analysis.

The exclusion criteria were: reviews, letters, meta-analysis, case reports, meeting abstracts, articles without controls, and articles with different designs.

2.3. Data extraction and quality assessment

Two authors (XZ and YZ) individually reviewed the eligible articles and extracted all useful data from them. Conflicts among the extraction were resolved by discussion with a third investigator (YC). The information extracted from each study was as follows: the last name of the first author, publication year, country and ethnicity of the participants, number of cases and controls, source of controls, and genotypes distribution. We evaluated the quality of studies according to 9-point Newcastle–Ottawa scale (NOS).[27]

2.4. Statistical analysis

Hardy–Weinberg equilibrium (HWE) tests were conducted in each involved study to assess the deviation of genotype distribution from population. The strength of association between MDM2 SNP309 polymorphism and endometrial cancer risk was measured by combined ORs with 95%CI under fixed-effect model or random-effect model according to the heterogeneity among studies. We quantified the heterogeneity by I^2 test which ranges from 0% to 100% to represent the degree of heterogeneity. It indicated significant heterogeneity when $I^2 >$ 50% and a random-effect model (Der Simonian and Laird method) should be adopted for pooled ORs,[28] otherwise the fixed-effect model (Mantel–Haenszel method) was used.[29] To investigate the origin of heterogeneity, we further performed subgroup analysis stratified by ethnicity, source of control, histological type, clinical type, grade and stage of tumor. The overall and subgroup analysis categorized by ethnicity and source of control were performed under five genetic models: allele model (G vs T), homozygote model (GG vs TT), heterozygote model (GT vs TT), dominant model (GG+GT vs TT), and recessive model (GG vs GT+TT), respectively. However, only dominant model was used in the subgroup analysis stratified by histological type, clinical type, grade and stage of tumor because the majority of included researches only provided the data of GG+GT versus TT for these subgroups. Sensitivity analysis was also performed by combining ORs with the removal of each single involved study to investigate the potential subversion of the results. Egger's test and Begg's funnel plot were used to estimate publication bias. $P < .05$ was considered as identification of statistically significant bias of publication.[30] All the data were processed by STATA version12 (Stata Corporation, College Station, TX).

2.5. Ethical approval

Since meta-analysis belonged to secondary analysis based on the studies published previously, the patients' informed consent and the ethical approval were not necessary.

3. Results

3.1. Study characteristics

We identified 171 records in total in primary search from 8 databases with our criterion. There remained 139 studies for screening after the duplicated records were eliminated and 124

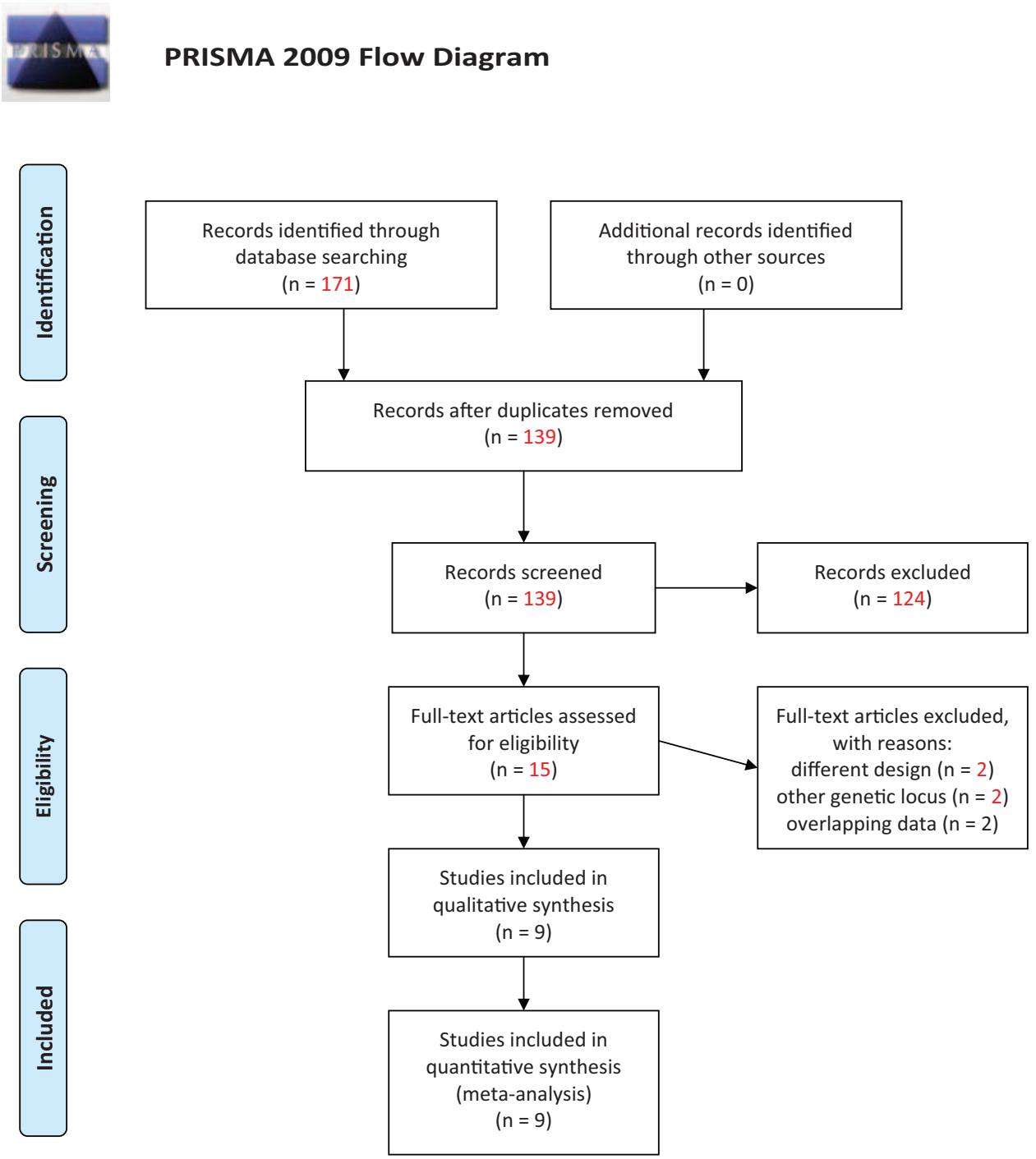

Figure 1. The PRISMA flow diagram of the study inclusion and exclusion. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses,

studies were excluded after skimming the titles and abstracts. Among the 13 studies read by full text, 6 were excluded because 2 offered overlapping data, 2 discussed other genetic locus of MDM2, and 2 designed differently. The intact procedures of inclusion and exclusion are shown in Figure 1. Eventually, there were 9 studies containing 3535 cases and 6476 controls eligible for our meta-analysis.[17–25] One of them involved data from 2 different ethnic groups, so we treated it as 2 separate groups.[18] Table 1 demonstrates the main characteristics of the studies involved. The eligible researches were performed in different

Table 1

Characteristics of the studies included for meta-analysis.

First author	Year	Country	Ethnicity	Source of controls	Sample size		HWE test
					Case	Control	
Walsh[17]	2007	America	Mixed	HB	73	79	0.65
Terry-NHS[18]	2008	America	Caucasian	PB	394	948	0.64
Terry-WHS[18]	2008	America	Caucasian	PB	122	368	0.18
Ashton[19]	2009	Australia	Caucasian	PB	191	291	0.49
Ueda[20]	2009	Japan	Asian	HB	119	108	0.02
Knappskog[21]	2012	Norway	Caucasian	HB	910	2465	0.41
Zajac[22]	2012	Poland	Caucasian	HB	152	100	0.70
Yoneda[23]	2013	Japan	Asian	PB	125	200	0.91
Okamoto[24]	2015	Japan	Asian	HB	45	45	0.63
Gansmo[25]	2017	Norway	Caucasian	PB	1404	1872	0.80

Case–control design was used in all the included studies.

HWE = Hardy–Weinberg equilibrium, HB = hospital-based, PB = population-based, year = publication year.

Table 2

The results of Newcastle–Ottawa scale.

First author	Selection	Comparability	Exposure
Walsh[17]	★★	★★	★★★
Terry[18]	★★★★	★★	★★
Ashton[19]	★★★★	★★	★★★
Ueda[20]	★★	★★	★★★
Knappskog[21]	★★★	★★	★★★
Zajac[22]	★★	★★	★★★
Yoneda[23]	★★★★	★★	★★★
Okamoto[24]	★★	★★	★★★
Gansmo[25]	★★★★	★★	★★★

ethnic lines including Caucasian (n = 6), Asian (n = 3), and mixed group (n = 1). Five studies were population based and five were hospital based. Table 1 also listed the results of HWE test and all studies included were consistent with HWE except one.[20] Table 2 shows the result of NOS for all the included studies. It represented a good quality of included studies that the NOS score of each study was more than 6 points. Table 3 shows the genotype distribution and allele frequency of MDM2 SNP309 of each study.

3.2. Quantitative synthesis

In overall analysis, the results indicated that MDM2 SNP309 polymorphism significantly increased the risk of endometrial carcinoma under allele model (OR: 1.23, 95% CI: 1.06–1.41, $P = .005$, $I^2 = 72.2\%$, $P_{\text{heterogeneity}} = .00$), homozygote model (OR: 1.43, 95% CI: 1.13–1.81, $P = .003$, $I^2 = 56.4\%$, $P_{\text{heterogeneity}} = .01$) and recessive model (OR: 1.55, 95% CI: 1.17–2.04, $P = .002$, $I^2 = 75.5\%$, $P_{\text{heterogeneity}} = .00$) (Fig. 2). However, no statistical association was identified under heterozygote model (OR: 1.02, 95% CI: 0.93–1.12, $P = .69$, $I^2 = 3.6\%$, $P_{\text{heterogeneity}} = .41$) and dominant model (OR: 1.08, 95% CI: 0.99–1.17, $P = .09$, $I^2 = 6.7\%$, $P_{\text{heterogeneity}} = .38$) (Fig. 2).

We further performed subgroup analysis to investigate the source of high heterogeneity among studies. In subgroup analysis stratified by ethnicity, significant association of an elevated cancer risk was found in Asians under recessive model (OR: 1.58, 95% CI: 1.10–2.29, $P = .02$, $I^2 = 0.0\%$, $P_{\text{heterogeneity}} = .67$) and in Caucasians under allele model (OR: 1.23, 95% CI: 1.03–1.47, $P = .02$, $I^2 = 83.2\%$, $P_{\text{heterogeneity}} = .00$), homozygote model (OR: 1.40, 95% CI: 1.05–1.88, $P = .02$, $I^2 = 71.5\%$, $P_{\text{heterogeneity}} = .00$) and recessive model (OR: 1.49, 95% CI: 1.05–2.13, $P = .03$, $I^2 = 84.4\%$, $P_{\text{heterogeneity}} = .00$). When classified according to source of control, the significantly heightened risk was only identified in hospital-based group under homozygote model (OR: 1.65, 95%

Table 3

SNP309 polymorphism of MDM2 genotype distribution and allele frequency in cases and controls.

First author	Genotype (N)								Allele frequency (N, %)					
	Cases				Controls				Cases			Controls		
	Total	GG	TG	TT	Total	GG	TG	TT	G	T	RAF	G	T	RAF
Walsh[17]	73	18	27	28	79	9	38	32	63	83	0.43	56	102	0.35
Terry-NHS[18]	394	63	162	169	948	95	420	433	288	500	0.37	610	1286	0.32
Terry-WHS[18]	122	21	54	47	368	50	155	163	96	148	0.39	255	481	0.35
Ashton[19]	191	29	84	78	291	37	126	128	142	240	0.37	200	382	0.34
Ueda[20]	119	39	54	26	108	22	66	20	132	106	0.55	110	106	0.51
Knappskog[21]	910	123	426	361	2465	300	1093	1072	672	1148	0.37	1693	3237	0.34
Zajac[22]	152	98	30	24	100	28	48	24	226	78	0.74	104	96	0.52
Yoneda[23]	125	34	61	30	200	40	98	62	129	121	0.52	178	222	0.45
Okamoto[24]	45	10	21	14	45	9	24	12	41	49	0.46	42	48	0.47
Gansmo[25]	1404	186	642	576	1872	254	878	740	1014	1794	0.36	1386	2358	0.37

Case–control design was used in all the included studies.

MDM2 = murine double minute 2, RAF = risk allele frequency, risk allele = G allele, SNP = single nucleotide polymorphism.

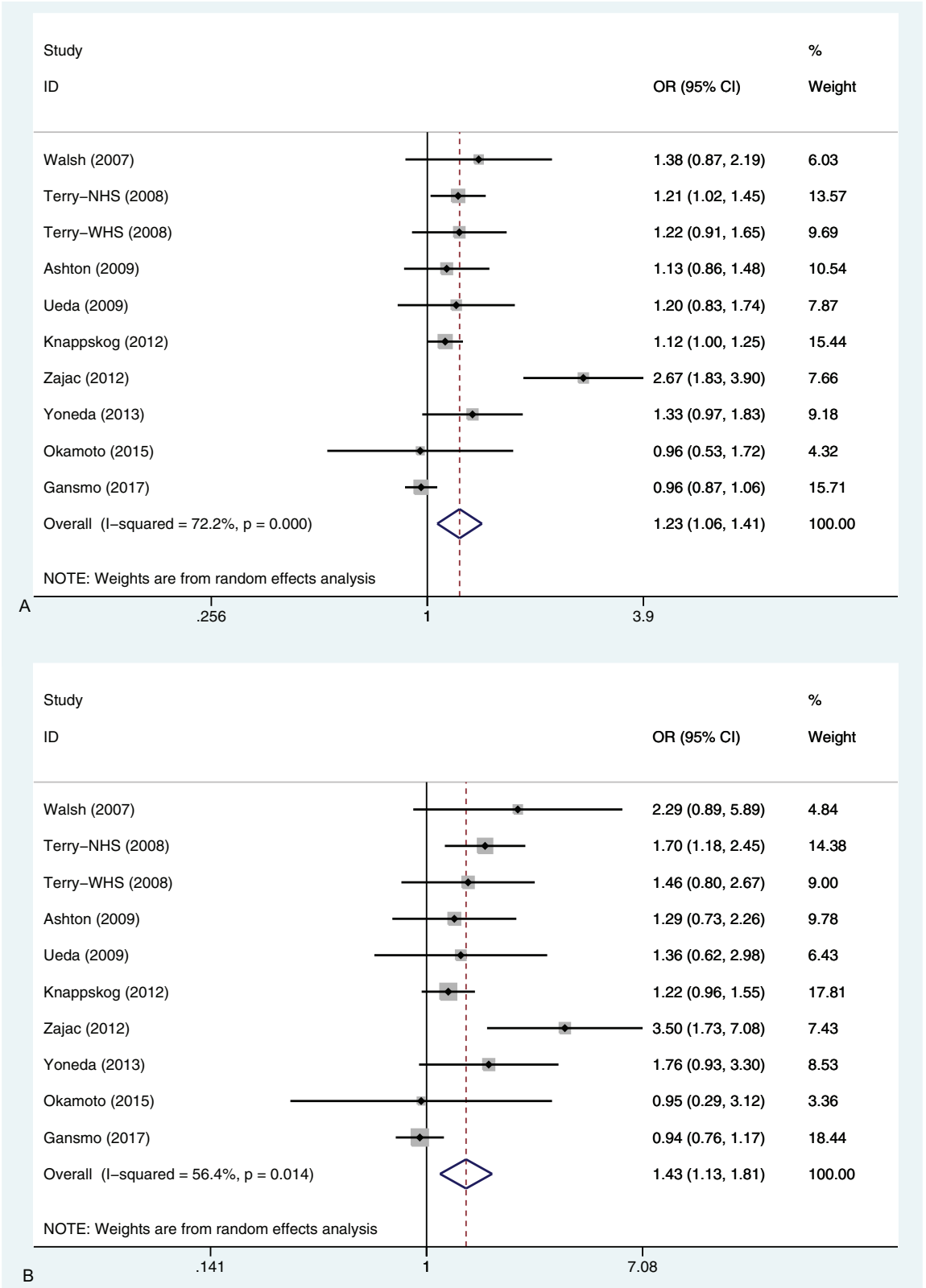

Figure 2. Forest plot for association between MDM2 SNP309 polymorphism and endometrial cancer risk under (A) allele model (G vs T); (B) homozygote model (GG vs TT); (C) heterozygote model (GT vs TT); (D) dominant model (GG + GT vs TT); (E) recessive model (GG vs GT + TT). CI = confidence interval, MDM2 = murine double minute 2, OR = odds ratio, SNP = single nucleotide polymorphism.

CI: 1.04–2.63, $P = .04$, $I^2 = 56.5\%$, $P_{heterogeneity} = .06$), dominant model (OR: 1.16, 95% CI: 1.01–1.33, $P = .04$, $I^2 = 0.0\%$, $P_{heterogeneity} = .54$) and recessive model (OR: 1.97, 95% CI: 1.05–3.70, $P = .04$, $I^2 = 83.9\%$, $P_{heterogeneity} = .00$), but not in population-based group. Furthermore, we attempted to conduct stratified analysis by various clinicopathological characteristics

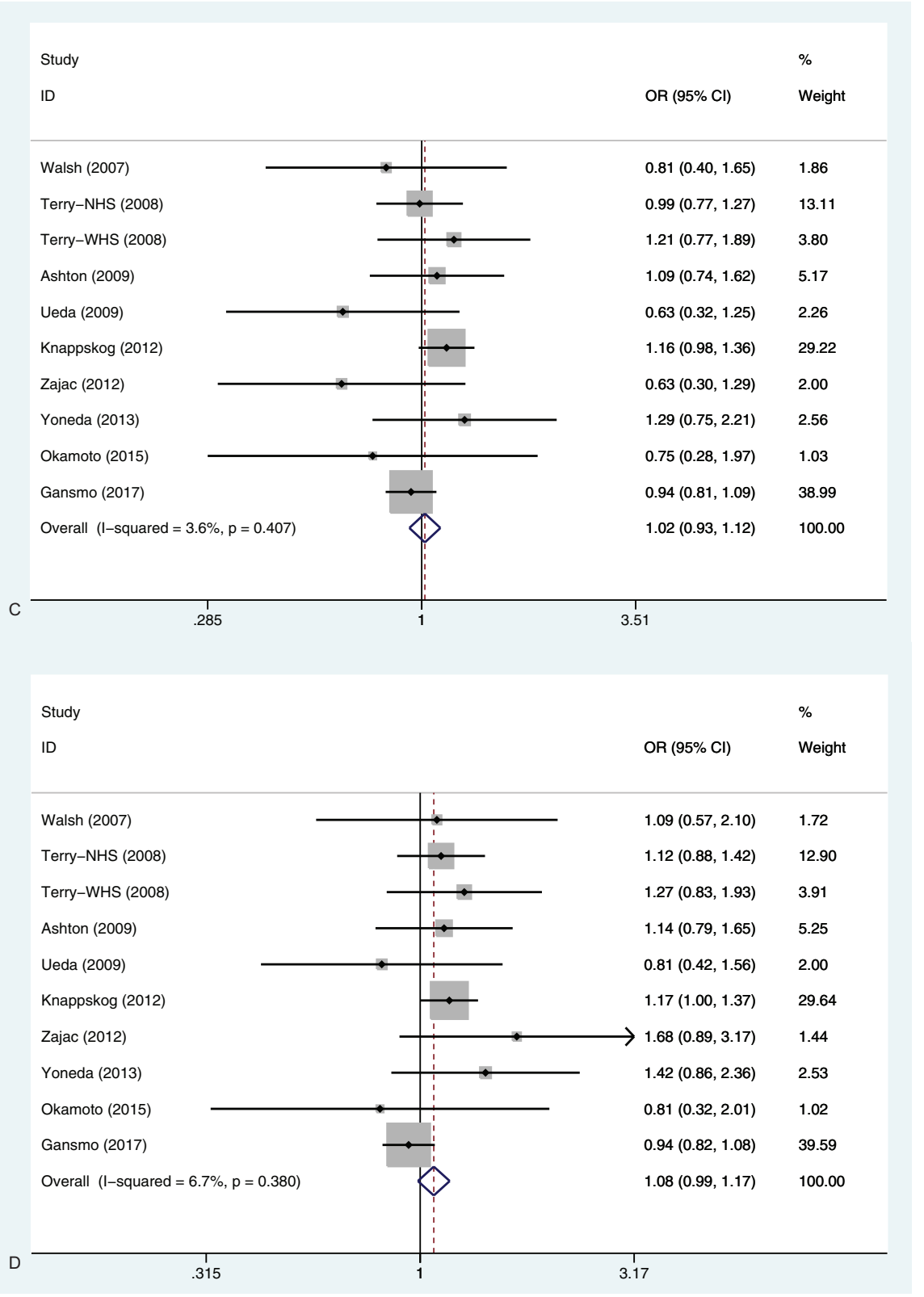

Figure 2. Continued.

including histological and clinical type, grade and stage of endometrial cancer. We accidentally found a stronger correlation with higher ORs in endometrioid (OR: 2.13, 95% CI: 1.28–3.54, $P=.004$, $I^2=0.0\%$, $P_{\text{heterogeneity}}=.87$) and Type I endometrial carcinoma (OR: 1.89, 95% CI: 1.25–2.86, $P=.002$, $I^2=0.0\%$, $P_{\text{heterogeneity}}=.36$) under dominant model, but no association was found in nonendometriod and Type II groups. In subgroup analysis by grade, there found no statistical relationship between

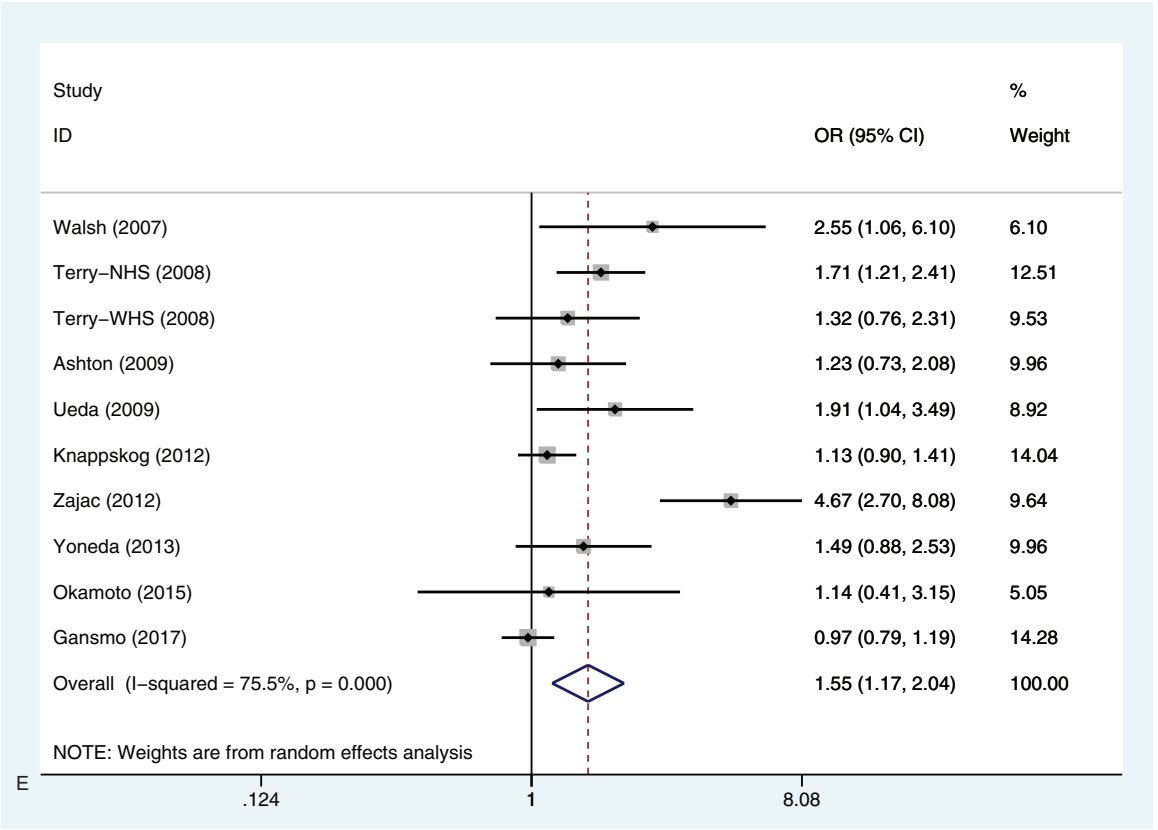

Figure 2. Continued.

all three grades of endometrial cancer and MDM2 SNP309 polymorphism. But when categorized by stage, we identified a distinct increased risk with ORs even higher than endometrioid and Type I group in stage I and III endometrial cancer. The complete results of subgroup analysis are shown in Table 4.

3.3. Sensitivity analysis

We performed sensitivity analysis to investigate whether the absence of each study will alter the result of our meta-analysis. As Figure 3 indicates, no results were subverted when each study was excluded individually, which manifested the stability and reliability of our conclusion (Fig. 3).

3.4. Publication bias

Egger's test and Begg's funnel plot were conducted to evaluate the publication bias. The Begg's funnel plot appeared to be symmetrical visually (Fig. 4), which suggested no evidence of publication bias (Egger's test: $P = .06$).

4. Discussion

So far, investigation of association between MDM2 SNP309 and risk of endometrial cancer has been reported in several researches, but the results remain controversial. Among all included studies, 4 studies revealed an increased risk of MDM2 SNP309 polymorphism in endometrial cancer,[17,18,20,22] 2 studies suggested no statistical significance,[19,23] one reported a suspicious relationship,[21] and the rest 2 did not mention the association between them in their articles.[24,25] Due to the conflicting results from the studies with relatively small sample size, we conducted the present meta-analysis to seek a comprehensive conclusion.

Nine included studies with 10 groups of data were consolidated to seek the connection of MDM2 SNP309 gene polymorphism and endometrial cancer susceptibility. One research conducted by Nunobiki et al[31] from Japan was excluded because the data is overlapped with another study and the sample size is smaller than it. The overall analysis revealed that MDM2 SNP309 significantly enhanced the risk of endometrial cancer. MDM2 is a negative regulator of P53 and plays a crucial role in P53 tumor suppressor pathway.[32] Previous studies showed that MDM2 could bind to P53 protein directly to inhibit its activity via ubiquitination and degradation.[33] The overexpression of MDM2 was reported as a carcinogenic factor by reduction of P53 levels, which attenuated P53 apoptosis response to DNA damage and other cellular stresses, and subsequently resulted in accumulation of genetic errors, leading to accelerated cancer formation.[13,34–38] MDM2 was also reported to facilitate tumor growth in a P53-independent way.[39] The polymorphism of SNP309, which located in MDM2 promoter region, was reported to upregulate the MDM2 expression.[7] This may account for the increased risk of endometrial cancer caused by MDM2 SNP309 polymorphism.

Subgroup analysis was performed to investigate the source of interstudy heterogeneity. The subgroup analysis by ethnicity indicated an elevated susceptibility to endometrial carcinoma in Asians under recessive model and in Caucasians under allele, homozygote and recessive model, which means MDM2 SNP309 polymorphism may contribute to endometrial cancer carcino-

Table 4

Subgroup analyses of association between MDM2 SNP309 polymorphism and endometrial cancer.

Subgroup		Number	ORs	95% CI	*P*	I^2 (%)	Pooling model
Source of control							
Allele model	HB	5	1.37	(0.98,1.92)	.06	79.7	Random-effects model
	PB	5	1.13	(0.98,1.30)	.09	55.3	Random-effects model
Homozygote model	HB	5	1.65	(1.04,2.63)	.04	56.5	Random-effects model
	PB	5	1.33	(0.98,1.81)	.07	60.2	Random-effects model
Heterozygote model	HB	5	1.07	(0.92,1.24)	.40	37.4	Fixed-effects model
	PB	5	0.99	(0.88,1.11)	.89	0.0	Fixed-effects model
Dominant model	HB	5	1.16	(1.01,1.33)	.04	0.0	Fixed-effects model
	PB	5	1.03	(0.93,1.15)	.58	18.1	Fixed-effects model
Recessive model	HB	5	1.97	(1.05,3.70)	.04	83.9	Random-effects model
	PB	5	1.29	(0.99,1.67)	.06	55.2	Random-effects model
Ethnicity							
Allele model	Asian	3	1.22	(0.98,1.53)	.08	0.0	Fixed-effects model
	Caucasian	6	1.23	(1.03,1.47)	.02	83.2	Random-effects model
	Mixed	1	1.38	(0.87,2.20)	.17	—	—
Homozygote model	Asian	3	1.47	(0.94,2.32)	.09	0.0	Fixed-effects model
	Caucasian	6	1.40	(1.05,1.88)	.02	71.5	Random-effects model
	Mixed	1	2.29	(0.89,5.90)	.09	—	—
Heterozygote model	Asian	3	0.94	(0.64,1.38)	.74	29.1	Fixed-effects model
	Caucasian	6	1.03	(0.94,1.13)	.56	15.4	Fixed-effects model
	Mixed	1	0.81	(0.40,1.65)	.56	—	—
Dominant model	Asian	3	1.09	(0.76,1.57)	.64	11.3	Fixed-effects model
	Caucasian	6	1.08	(0.98,1.18)	.11	32.3	Fixed-effects model
	Mixed	1	1.09	(0.57,2.10)	.79	—	—
Recessive model	Asian	3	1.58	(1.10,2.29)	.02	0.0	Fixed-effects model
	Caucasian	6	1.49	(1.05,2.13)	.03	84.4	Random-effects model
	Mixed	1	2.55	(1.06,6.10)	.04	—	—
Histological type							
Dominant model	Endometrioid	2	2.13	(1.28,3.54)	.004	0.0	Fixed-effects model
	Nonendometriod	2	1.94	(0.35,10.87)	.45	62.1	Random-effects model
Clinical type							
Dominant model	Type I	2	1.89	(1.25,2.86)	.002	0.0	Fixed-effects model
	Type II	2	0.90	(0.41,1.96)	.79	0.0	Fixed-effects model
Grade							
Dominant model	Grade 1	2	1.79	(0.92,3.50)	.09	0.0	Fixed-effects model
	Grade 2	2	1.84	(0.96,3.52)	.07	0.0	Fixed-effects model
	Grade 3	2	2.28	(0.63,8.28)	.21	62.6	Random-effects model
Stage							
Dominant model	I	2	4.40	(2.60,7.45)	< .001	49.8	Fixed-effects model
	II	2	3.36	(0.93,12.06)	.06	56.3	Random-effects model
	III	2	4.31	(1.08,17.18)	.04	56.1	Random-effects model
	IV	1	1.11	(0.12,10.10)	.93	—	Fixed-effects model

95% CI = 95% confidence interval, HB = hospital based, ORs = odds ratios, PB = population based, SNP = single nucleotide polymorphism.

genesis in both ethnic populations, but the association is stronger in Caucasians than in Asians. Since cancer is a disease with complicated multigenetic effect, the similarity and difference between races may be responsible for the results. When stratified by source of control, significant association of similar enhanced susceptibility to endometrial cancer could only be found in hospital-based group. This result may reveal potential selection bias among these studies when recruiting participants for matched control groups.

We further performed subgroup analysis categorized by several clinicopathological characteristics including histological and clinical type, grade, and stage of endometrial cancer. We identified a strong association of increased risk of endometrial cancer in endometrioid group and Type I group. Endometrial cancer is classified into 2 clinical types: Type I and II. Type I is estrogen-dependent endometrial cancer and belongs to endometrioid type histologically. It is associated with endometrial hyperplasia. Estrogen receptors are commonly expressed in Type I tumor cells. Type II endometrial carcinoma is estrogen-independent and encompasses nonendometrioid type. It is related to atrophic endometrium and the tumor cells scarcely express estrogen receptors.[40,41] Previous researches indicated that MDM2 overexpression is strongly concerned with estrogen receptor.[34,42] The expression of MDM2 is mediated through the interaction of estrogen receptor with a promoter region of MDM2 where SNP309 located.[43] In addition, it is reported that the GG genotype of SNP309 increases the affinity of MDM2 promoter to the transcription factor SP1.[7] SP1 is known as a co-transcriptional activator of estrogen receptor[44] and contributes to estrogen-mediated gene transcription.[45,46] Therefore, MDM2 SNP309 polymorphism may enhance the susceptibility to estrogen-related Type I endometrial carcinoma, which is in accordance with the result of our subgroup analysis. No statistical association was found between all three grades of

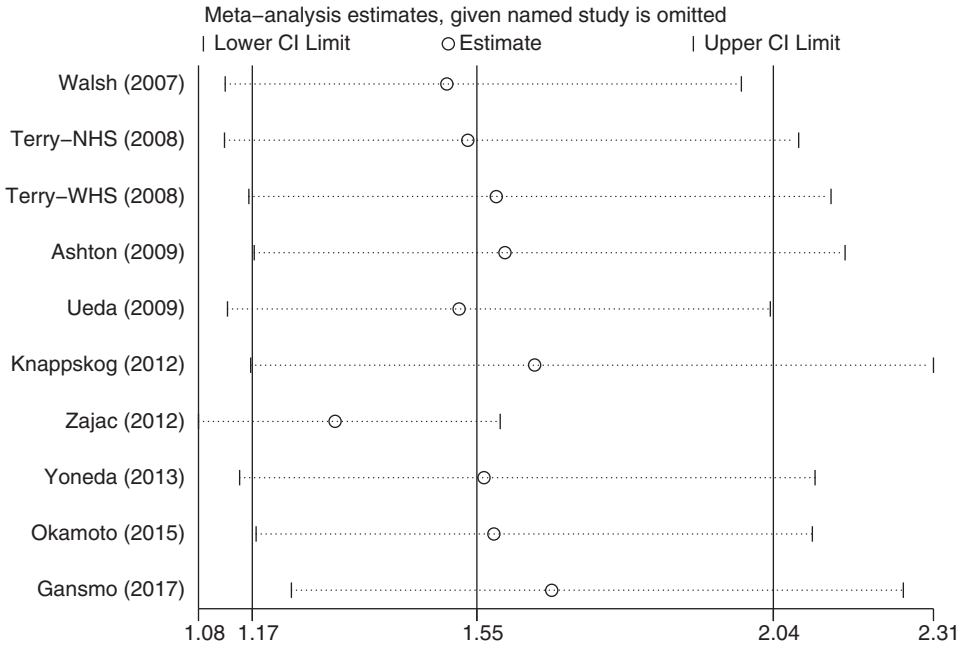

Figure 3. Sensitivity analysis of MDM2 SNP309 polymorphism under recessive model. CI = confidence interval. MDM2 = murine double minute 2, SNP = single nucleotide polymorphism.

endometrial cancer and MDM2 SNP309 polymorphism. When stratified by stage of tumor, our analysis revealed a markedly elevated risk of endometrial cancer in stage I and III group, but not in stage II and IV. Small sample size may be responsible for the dubious result because only 2 studies provided the data of genotype concerned with different stage of carcinoma containing 129 stage I, 42 stage II, 46 stage III and 8 stage IV patients in total. It is noteworthy that the results of the subgroup analysis categorized by various clinicopathological characteristics should be concluded and generalized with caution considering the limited number of relevant studies.

Although one studies included in our analysis deviated from HWE in controls, the conclusions were not subverted when removing the study during sensitivity analysis. Also, we recognized no publication bias in our meta-analysis.

Several limitations of our meta-analysis should be admitted. Firstly, one study is not consistent with the HWE in controls; despite the conclusions did not alter after it was excluded.

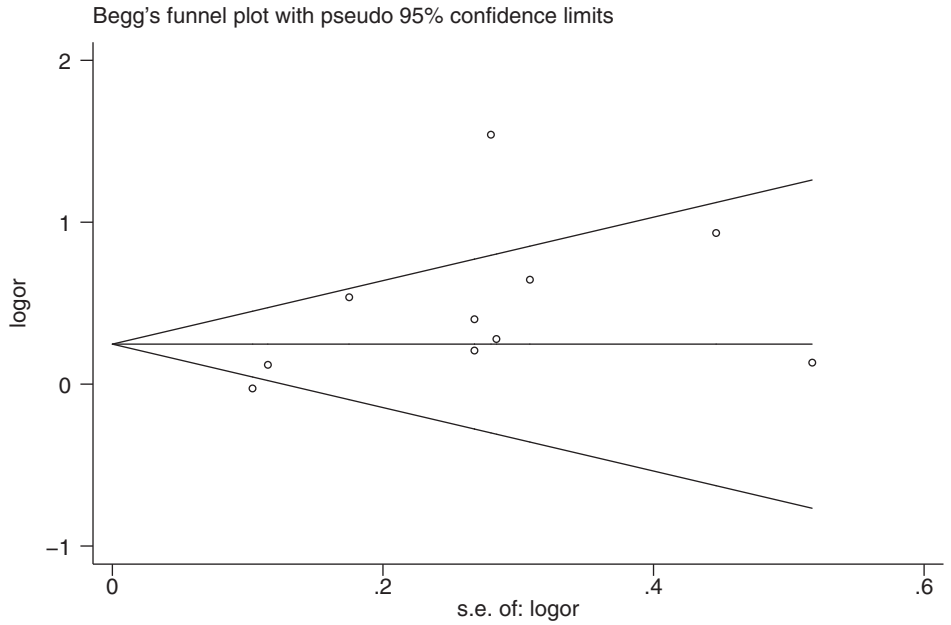

Figure 4. Begg's funnel plot with pseudo 95% confidence limits for MDM2 SNP309 polymorphism under recessive model. MDM2 = murine double minute 2, SNP = single nucleotide polymorphism.

Secondly, data of Africans were not involved because no involved studies mentioned it, which may lead to selection bias. Thirdly, we did not perform subgroup analysis by age, obesity, menstrual status, hypertention history, diabetes history and family history because of insufficient data. Finally, interaction of several gene polymorphisms may also influence endometrial cancer risk, which was not involved in our analysis.

Gene targeting therapy has played an important role in the treatment of several cancers such as lung cancer, breast cancer, chronic myeloid leukemia and so on, but it is still not widely conducted in gynecological tumor. The very first step is to identify the association between gene mutation and endometrial cancer susceptibility, as well as the mechanism of it. Our meta-analysis showed that MDM2 SNP309 polymorphism increased the risk of endometrial cancer significantly both in Asians and Caucasians, but the strength of association may be stronger in Caucasians than in Asians. Also, we identified that SNP309 polymorphism elevated the Type I and endometrioid type endometrial carcinoma significantly. Our result revealed that MDM2 SNP309 polymorphism could serve as a potential prognostic marker for endometrial cancer and may further possibly guide genetic targeted therapy and even prevention strategies. Still, further evidences from future studies with standardized genotyping methods, multiple populations and pathological types are needed to corroborate our conclusions and provide a more comprehensive and precise understanding of association between MDM2 SNP309 polymorphism and endometrial cancer.

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