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Association of rs2279744 and rs117039649 promoter polymorphism with the risk of gynecological cancer

A meta-analysis of case–control studies

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Abstract

Background: Increasing evidence has suggested that rs2279744 is associated with rs117039649 polymorphism, which can increase the risk of gynecological cancers, including cervical, ovarian, breast, and endometrial cancer. The results are inconsistent so that we performed a meta-analysis of current literature to clarify the impacts of these polymorphisms on gynecological cancer.

Methods: Eligible articles were identified through an exhaustive search of relevant databases including PubMed, Embase, Web of science, Springer Link, Chinese National Knowledge Infrastructure (CNKI), and Weipu database for the period up to July 2016. Data about the association between single nucleotide polymorphisms (SNPs) and cancer risk were refined from the selected articles as well as other information about cases and controls, and all of them were extracted by 2 independent researchers and pooled odds ratio with 95% confidence interval was calculated.

Results: This analysis included 24 articles, 27 case–control studies of rs2279744 polymorphism and 3 case–control studies of rs117039649 polymorphism. Significant association with the risk of gynecological cancer was observed for both SNPs. Subgroup analysis by ethnicity and cancer type (cervical, ovarian, breast, and endometrial) also showed a positive relationship between rs2279744 polymorphism and gynecological cancer risk in Caucasian; and there was also a notable association between rs2279744 polymorphism and cervical cancer.

Conclusions: We found that rs2279744 (SNP309) and rs117039649 (SNP285) were both associated with the risk of gynecological cancers. Subgroup analysis showed that rs2279744 (SNP309) was associated with the risk of gynecological cancers in Caucasian and Asian according to the ethnicity and cancer type, especially for endometrial cancer.

Abbreviations: BC = breast cancer, CC = cervical cancer, CI = confidence interval, CNKI = Chinese National Knowledge Infrastructure, EC = endometrial cancer, HWE = Hardy–Weinberg equilibrium, MDM2 = murine double minute 2, NOS = New Castle–Ottawa Quality assessment Scale, OC = ovarian cancer, OR = odds ratio, SNP = single nucleotide polymorphism.

Keywords: gynecological cancer, meta-analysis, polymorphism, rs117039649, rs2279744

1. Introduction

It is well known that the gynecological cancer is the leading cause of cancer-related death in women. And the major cancer types include cervical cancer (CC), ovarian cancer (OC), endometrial cancer (EC), and breast cancer (BC). The BC is the most common cancer, which can be affected by both environmental and genetic factors. However, the mechanism remains unknown.[1,2] We thought that BC must have some resemblance in estrogen regulation with the above 3 types. Hence, here we considered it as gynecological cancer to study together[3]. CC is the 3rd-leading cause of death in women' neoplasis worldwide, and the morbidity of CC has increased recently.[4] It has been reported that human papillomavirus is an important cause for CC.[5,6]

OC is most commonly seen among women who died from gynecological malignancies in China, while EC often occurs in well-developed countries and is also influenced by environmental factors.[7–9] In general, gynecological cancers are threatening the health and lives of women all over the world. However, the therapies for them were absent now. Therefore, further understanding of the mechanism and new method for diagnosis and treatment from genetic perspective are of great significance.

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JZ carried out the entire procedure including the literature search, data extraction, performed the statistical analysis, drafted the manuscript, and revised submitted the manuscript. ZZ conceived of the study, coordinated and participated in the entire process of drafting and revised the manuscript. YZ contributed to statistical analysis and revision the manuscript. JZ and YZ contributed to the revisions of the manuscript. All authors have contributed significantly. All authors read and approved the final manuscript.

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Recent studies have shown that the morbidity of gynecological oncology was controlled by the heredity of genes,[10] and studying on genes to the gynecological oncology is beneficial to analysis the internal mechanism for them. In recent years, the gene fiMDM2 (murine double minute 2), as a proto-oncogene, was found to be an important regulator of P53 through multifarious pathways.[11] Several studies have found that over expression of MDM2 gene can result in excessive inactivation of p53, which can enable damaged cells to escape the cell-cycle checkpoint control and become cancerous.[12,13] Meanwhile, MDM2 results in the degradation of P53 through E3 ubiquitin-ligating enzyme, which decreases the function of P53,[14,15] and leads to the onset and development of various diseases, including cancer.[16,17]

It has been reported that genetic polymorphisms play an important role in gynecological cancer.[18] Research has shown that a T to G change at nucleotide 309 (SNP309) in the first intron of MDM2 gene (rs2279744) increases the affinity of the promoter to the transcription activator Sp1, which leads to the high level of MDM2 mRNA and protein expression that weakens the P53 pathway.[19] It has been reported that MDM2 SNP309 genetic polymorphism could predispose the patient to sporadic cancer risk.[20] For instance, Hong et al[21] found that the MDM2 309GG genotype was associated with an increased risk of esophageal squamous cell carcinoma. Meanwhile, the 309G allele has also been associated with early diagnosis of estrogen receptor-positive BC.[22] In addition, another functional single nucleotide polymorphisms (SNPs) at nucleotide 285 G>C (rs117039649) was also identified in the promoter region located 24 bps from SNP309 in Caucasian,[23] It has been reported that the presence of the 285C allele correlated with a decreased cancer risk for breast, ovarian and EC in patients who harbored 309G allele,[22] which suggested that it may function as a neutralizer to the effect of SNP309 in MDM2.

Several studies reported that the polymorphism of rs2279744 or rs117039649 may be associated with the increased susceptibility to gynecological cancers, and the published articles of meta-analysis nearly included all the types of gynecological cancers, but most of them are single studies, including single type of locus or cancer.[7,24,25] None of the articles analyzed the relationship between the polymorphisms of these 2 SNPs and the overall risk of gynecological cancer. In addition, the studies of specific type of cancer also reported conflicting results, such as the analysis of CC by Meissner et al[26] and Roszak et al.[27] The signal path diagram was shown in Fig. 1.

In our meta-analysis, we aimed to detect the association between rs2279744 or rs117039649 polymorphism and the overall gynecological cancer risk. Meanwhile, the subgroup analysis based on race and cancer types can also help elucidate this association in subgroup of patients and for individual type of cancer.

2. Materials and methods

2.1. Publication research and inclusion criteria

We searched several databases, including PubMed, Embase, Web of science, Springer Link, CNKI and Weipu databases, for genetic association studies of the MDM2 T309G, G285C polymorphisms and gynecological cancer. The keywords used were "MDM2 T309G or MDM2 G285C or rs2279744 or rs117039649" combined with "gynecological cancer or gynecological tumor or gynecology," "GWAS or SNP or polymorphism or allele." All databases were searched from their inception to July, 2016. Only papers published in English or Chinese with English abstract were considered.

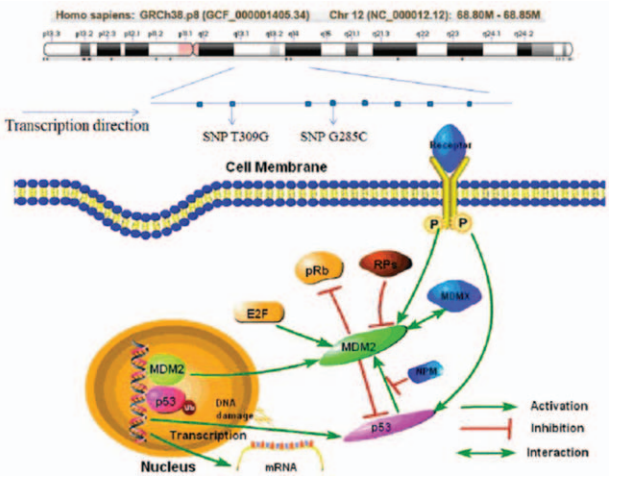

Figure 1. Gene structure and signal path of MDM2. E2F = transcription factor E2F, MDM2 = murine double minute 2, NPM = nucleophosmin, P = phosphorylation, pRb = pro retinoblastoma, Rps = ribosomal protein S, Ub = ubiquitination.

Papers are eligible if they meet the following criteria: publication should be a case–control study with all required data elements available, publication evaluated the association between MDM2 T309G or MDM2 G285C polymorphism with the risk of CC, OC, BC, or EC, publication is a human study. The paper screening was conducted independently by 2 investigators. The same criteria were applied when assessed the quality and data extraction of the publications. And publication bias of all articles was analyzed by the funnel plots, Begg test Pr > |t| value >0.05 indicating no publication bias existed. In addition, we have to claim that no ethical approval and patient consent are required in this paper, because all analyses were based on previous published studies in this article, which does not involve using of tissue, blood, urine, genetic material samples and survey scales.

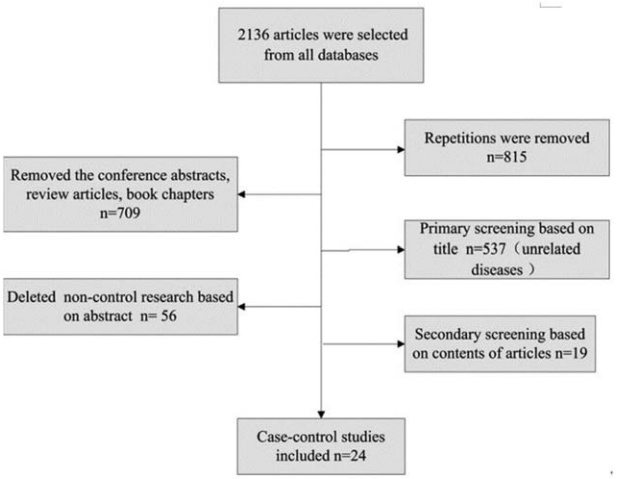

Figure 2. Process of articles selection. n = 24 articles were selected eventually.

2.2. Quality assessment and data extraction

The quality of the identified studies was assessed according to the New Castle–Ottawa Quality assessment Scale (NOS), which measures the quality of a study based on 10 criteria. Publication with a total score of 8 to 9 points were considered to be high-quality, 6 to 7 points were considered moderate quality; and 5 points or lower to be low quality. Two reviewers independently extracted the data using a standard extraction form that includes the following: the first author's name, year of publication; the country of the study, ethnicity of the study subjects, age of the cases and controls, numbers of the cases and controls, cancer type, genotyping methods for MDM2 T309G or MDM2 G285C, and the genotypes' frequency. If a study contained more than 1 cancer type or ethnicity, genotype data were extracted separately according to cancer type or ethnicity for subgroup analysis.

2.3. Statistical analysis

We used the goodness-of-fit test to assess the Hardy–Weinberg equilibrium (HWE). Summary odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were estimated for each polymorphism in different genetic models, including recessive genotype, dominant genotype, heterozygous genotype, homozygote genotype, and allele genotype to assess the association between MDM2 T309G or MDM2 G285C polymorphism and the risk of gynecological cancer. Cochran Q test and Higgins (I^2) test were used to assess the degree of heterogeneity between studies. The pooled ORs were calculated using a fixed-effects ($P > .05$ or $I^2 < 50\%$) or random-effects model ($P < .05$ or $I^2 > 50\%$) based on the level of heterogeneity. The publication bias was also evaluated using the Begg funnel plots ($Pr > |z|$) and Egger test ($Pr > |t|$). All data were analyzed using STATA 12.0 software.

3. Results

3.1. Characteristics and quality of the publications

A total of 24 articles were included in this meta-analysis. The selection process was summarized in Fig. 2, and the characteristics of the 24 studies are showed in Table 1.

Our analysis included 27 case–control studies (1 article reported the study of 2 ethnicity groups,[26] another reported the study of 3 different types of cancer.[28]). All studied rs2279744. Of them, 12 studies were conducted among Caucasians, 14 studies were among Asians and 2 in African American. Only 3 papers reported rs117039649, all in Caucasians. The majority of the studies were not deviated from HWE, only 6 showed genetic disequilibrium ($P < .05$) (Table 2). According to NOS criteria, 2 publications[28,29] were considered high quality (8 or 9 points), 12[1,7,8,30–38] were moderate quality (6 or 7 points), and 10[2,11,20,26,27,39–43] low quality (5 or lower points) (Table 3).

3.2. Analysis of relationship between SNPs and cancer risk

3.2.1. Association between rs2279744 or rs117039649 polymorphism and gynecological cancer risk. The meta-analysis of rs2279744 polymorphism included 6094 cases and 6808 controls from 27 case–control studies. Three studies

Table 1

Characteristics of the studies included in the meta-analysis.

Authors	Year of publication	Country	Ethnicity	Age, y, mean ± SD, or mean (range)		Samples size and type of cancer studied, n			
				Cases	Controls		Cases	Controls	Genotyping
Roszak et al[27]	2015	Poland	Caucasians	48.3 ± 10.8	47.8 ± 9.5	Cervical	456	481	PCR–RFLP
Meissner et al[26]	2007	Brazil	Caucasians	43.6	—	Cervical	26	52	PIRA–PCR
			Negro				46	48	
Kang et al[7]	2009	China	Asian	52.74 ± 10.84	52.69 ± 11.62	Ovarian	257	257	PCR–RFLP
Lang et al[2]	2009	Sweden	Caucasian	34	30	Breast	123	146	PCR–RFLP
Piotrowski et al[30]	2012	Poland	Caucasians	59.4 ± 10.2	58.7 ± 10.5	Breast	468	550	PCR–RFLP
Wang et al[39]	2013	China	Asian	—	—	Breast	600	600	PCR–RFLP
Koh et al[40]	2011	Singapore	Asian	61.3 ± 8	58.8 ± 8.3	Breast	358	614	
Jiang et al[41]	2011	China	Asian	46.8	44.2	Cervical	105	140	PCR–RFLP
Wu et al[1]	2010	China	Asian	49	47	Breast	698	525	PCR–RFLP
Guan et al[11]	2014	China	Asian	50.1	48.7	Breast	305	345	TaqMan assay
Wang et al[31]	2009	China	Asian	52.74 ± 10.84	52.69 ± 11.62	Ovarian	257	257	PCR–RFLP
Terry et al[32]	2008	USA	Caucasians	—	—	Endometrial	122	368	PCR–RFLP
Campbell et al[33]	2006	UK	Caucasians	40	39	Breast	351	258	PCR–RFLP
Walsh et al[20]	2007	USA	Caucasians	—	—	Endometrial	73	79	PCR–RFLP
Cox et al[29]	2007	USA	Caucasians	50	50	Breast	306	607	PCR–RFLP
Singh et al[42]	2008	India	Caucasians	45	45	Breast	104	105	ARMS–PCR
Ashton et al[34]	2009	Australia	Caucasians	—	—	Endometrial	191	291	PCR–RFLP
Ueda et al[28]	2009	Japan	Asian	—	—	Cervical	88	108	PCR
				—	—	Endometrial	119	108	PCR
				—	—	Ovarian	85	108	PCR
Nunobiki et al[8]	2009	Japan	Asian	—	—	Endometrial	102	95	PCR–RFLP
Alshatwi et al[38]	2011	Saudi	Asian	50 ± 5	50 ± 5	Breast	100	100	TaqMan assay
Singhal et al[43]	2012	India	Asian	—	—	Cervical	182	182	PCR–RFLP
Zając et al[35]	2012	Poland	Caucasians	64.9 ± 8.2	54.42 ± 19.22	Endometrial	152	100	PCR–RFLP
Vargastorres et al[36]	2014	Brazil	Negro	37.97 ± 11.69	37.8 ± 10.6	Cervical	293	184	PCR–RFLP
Yadav et al[37]	2016	India	Asian	48.00 ± 12.51	47.81 ± 11.84	Breast	100	100	AS–PCR

ARMS = amplification refractory mutation system, AS = allele specific, PCR = polymerase chain reaction, PIRA = primer introduced restriction analysis, RFLP = restriction fragment length polymorphism, SD = standard deviation.

Table 2

Genotype and allele distribution of MDM2 polymorphisms in cases and controls.

SNP		Case					Control					HWE	
MDM2 309 Rs2279744	Study	T/T	T/G	G/G	T	G	T/T	T/G	G/G	T	G	χ^2	*P*
	Roszak et al[27]	174	204	78	552	360	202	204	75	608	354	3.742026	.053060
	Meissner et al[26]	9	17	0	35	17	22	24	6	68	36	0.019992	.887558
		18	22	6	58	34	12	26	10	50	46	0.348576	.554920
	Kang et al[7]	56	121	80	233	281	77	120	60	274	240	0.989304	.319912
	Lang et al[2]	52	57	14	161	85	68	60	18	196	96	0.692641	.405267
	Piotrowski et al[30]	183	207	78	573	363	233	241	76	707	393	1.158316	.281814
	Wang et al[39]	138	273	189	549	651	191	295	114	677	523	—	—
	Koh et al[40]	77	212	96	366	404	140	300	174	580	648	0.240606	.623768
	Jiang et al[41]	17	50	38	84	126	30	84	26	144	136	5.655036	.017405
	Wu et al[1]	142	372	184	656	740	122	266	137	510	540	0.105283	.745578
	Guan et al[11]	76	132	97	284	326	53	168	124	274	416	0.099527	.752397
	Wang et al[31]	77	120	60	274	240	56	121	80	233	281	0.644601	.422049
	Terry et al[32]	47	54	21	148	96	163	155	50	481	255	1.798645	.179876
	Campbell et al[33]	132	160	59	424	278	105	111	42	321	195	1.862946	.172285
	Walsh et al[20]	28	27	18	83	63	32	38	9	102	56	0.206450	.649563
	Cox et al[29]	137	130	39	404	208	257	273	77	787	427	0.115075	.734438
	Singh et al[42]	25	48	31	98	110	25	47	33	97	113	1.040251	.307762
	Ashton et al[34]	78	84	29	240	142	128	126	37	382	200	0.469263	.493326
	Ueda et al[28]	20	47	21	87	89	20	66	22	106	110	5.353478	.020680
		26	54	39	106	132	20	66	22	106	110	5.353478	.020680
		21	45	19	87	85	20	66	22	106	110	5.353478	.020680
	Nunobiki et al[8]	24	44	34	92	112	17	59	19	93	97	5.593784	.018024
	Alshatwi et al[38]	21	47	32	89	111	33	49	18	115	85	0.000654	.979595
	Singhal et al[43]	63	74	45	200	164	108	52	22	268	96	12.71385	.000362
	Zając et al[35]	24	30	98	78	226	24	48	28	96	104	0.147928	.700522
	Vargastorres et al[36]	146	117	30	409	177	102	69	13	273	95	0.080657	.776408
	Yadav et al[37]	35	46	19	116	84	33	53	14	119	81	0.993991	.318768

		Case					Control						
MDM2 285 Rs117039649	Study	G/G	G/C	C/C	G	C	G/G	G/C	C/C	G	C	χ^2	*P*
	Roszak et al[27]	430	25	1	885	27	431	47	3	909	53	1.819402	.177384
	Piotrowski et al[30]	444	23	1	911	25	494	54	2	1042	58	0.161618	.687670
	Vargastorres et al[36]	288	5	0	581	5	184	0	0	368	0	—	—

HWE = Hardy–Weinberg equilibrium, MDM2 = murine double minute 2, SNP = single nucleotide polymorphism.

containing 1217 cases and 1215 were included for the analysis of rs117039649 polymorphism. The genotypes of rs2279744 polymorphism are listed in Table 2. Based on the heterogeneity test ($P_{het} < .05$), 4 genetic models were analyzed using random-effect models: TT vs TG + GG, GG vs TG + TT, TT vs GG, and T vs G; and TT vs TG model was analyzed using a fixed-effect model. The ORs for GG vs TG + TT, TT vs GG, and T vs G genetic models were 1.32 (95% CI: 1.11, 1.57, $P < .05$), 0.77 (95% CI: 0.63, 0.94, $P < .05$), and 0.86 (95% CI: 0.77, 0.96, $P < .05$) (Fig. 3A–C), respectively. The data indicated that TT and

Table 3

Quality of articles included in the analysis.

Article (authors)	Selection				Comparability		Exposure			Scores
Conditions	1	2	3	4	a	b	1	2	3	10
Roszak et al[27]		*	*	*	*	*				5
Meissner et al[26]	*		*	*		*	*			5
Kang et al[7]	*	*	*	*	*	*	*			7
Lang et al[2]	*	*	*	*		*				5
Piotrowski et al[30]	*	*	*	*	*	*				6
Wang et al[39]		*	*	*	*	*				5
Koh et al[40]		*				*				2
Jiang et al[41]	*	*	*	*		*				5
Wu et al[1]	*	*	*	*	*	*	*			7
Guan et al[11]	*	*				*	*			4
Wang et al[31]	*	*	*	*	*	*				6
Terry et al[32]	*		*	*	*	*		*	*	7
Campbell et al[33]	*	*	*	*	*	*	*			7
Walsh et al[20]	*			*	*	*				4
Cox et al[29]	*	*	*		*	*	*	*	*	8
Singh et al[42]	*		*	*	*	*				5
Ashton et al[34]	*	*	*	*	*	*				6
Ueda et al[28]	*	*	*	*		*	*	*	*	8
Nunobiki et al[8]	*	*	*	*		*	*			6
Alshatwi et al[38]	*	*	*	*	*	*	*			7
Singhal et al[43]	*		*			*	*			4
Zając et al[35]	*	*	*	*	*	*	*			7
Vargastorres et al[36]	*	*	*	*	*	*	*			7
Yadav et al[37]	*	*	*	*	*	*	*			7

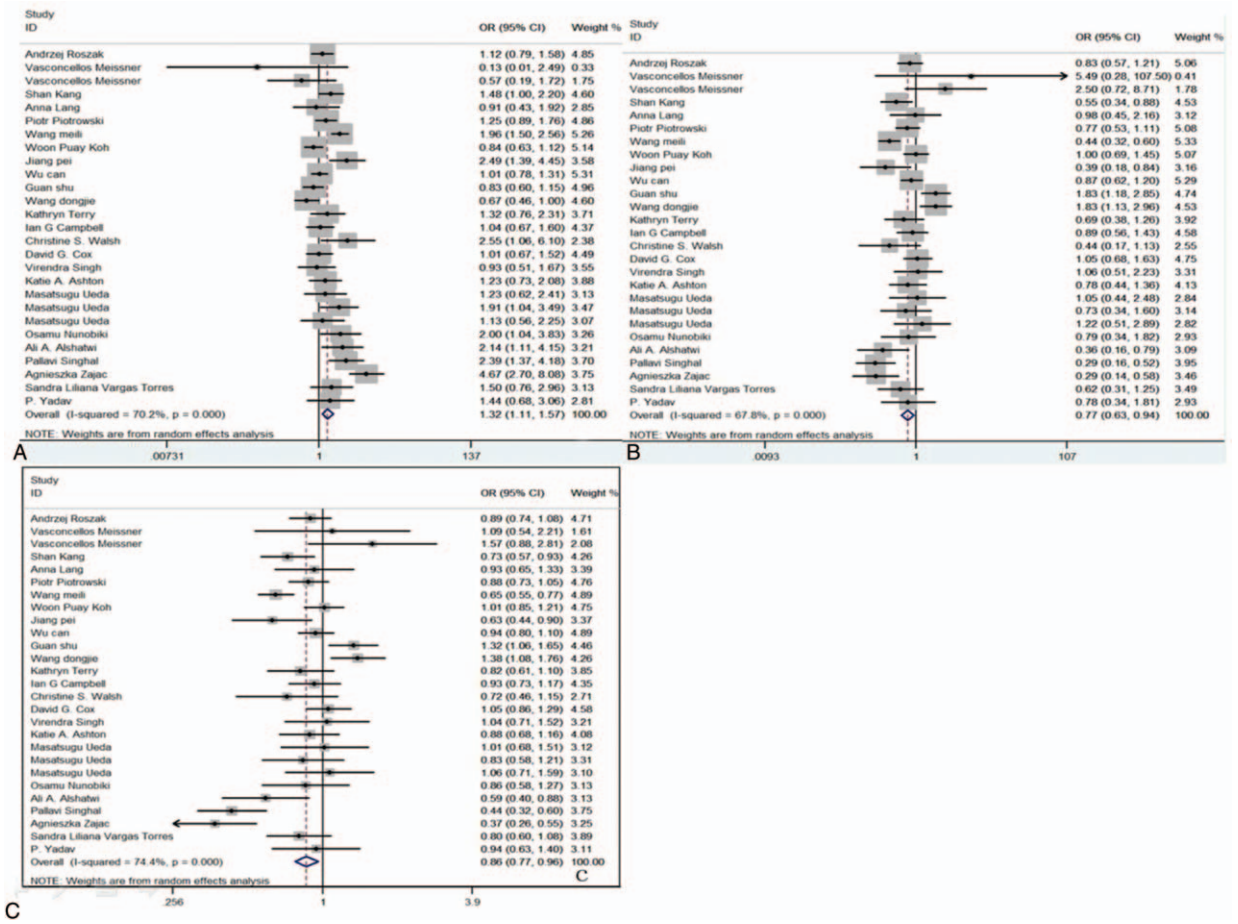

Figure 3. Forest plots of the association between SNP309 polymorphism and risk of gynecological cancers. Left to 1 (solid line in the middle) indicates SNP is associated with a reduced risk of cancer; Right to 1: SNP is associated with an increased risk of cancer. (A) Model GG vs TG + TT; (B) model TT vs GG; (C) model T vs G. CI = confidence interval, OR = odds ratio, SNP = single nucleotide polymorphism.

T (compare with GG, G) genotype is associated with a reduced risk of gynecological cancer while GG genotype (compared with TG + TT) showed an increased risk of gynecological cancer. No significant association between MDM2 T309G polymorphism and gynecological cancer risk was observed in the TT vs TG + GG (OR = 0.89, 95% CI: 0.79, 1.02, $P > .05$) and TT vs TG (OR = 0.93, 95% CI: 0.86, 1.01, $P > .05$) models.

For rs117039649 polymorphism, the heterogeneity was insignificant ($P_{het} > .05$). Thus, the fixed-effects model was used and the pooled ORs for GG vs GC + CC, GC vs GG, and G vs C genetic models were 1.85 (95% CI: 1.32, 2.60, $P < .05$), 0.55 (95% CI: 0.39, 0.77, $P < .05$), and 1.83 (95% CI: 1.32, 2.54, $P < .05$), respectively (Fig. 4A–C), suggesting that GG or G genotype might be associated with an increased risk of gynecological cancer, compared with GC + CC or C, while GC showed a reduced risk when compared with GG.

3.2.2. Subgroup analysis.

3.2.2.1. The association between rs2279744 and rs117039649 polymorphism and gynecological cancer risk by ethnicity. For rs2279744, all 3 subgroups (Caucasian, Asian, and African American) were analyzed. In Caucasian, 3 genetic models including TT vs TG + GG (OR = 0.89, 95% CI: 0.79, 0.99, $P < .05$) (Fig. 5A), TT vs GG (OR = 0.78, 95% CI: 0.63, 0.96, $P < .05$) (Fig. 5B), and T vs G (OR = 0.86, 95% CI: 0.75, 0.98, $P < .05$) (Fig. 5C) were indicated to be significant, suggesting that TT or T polymorphism may be protective for gynecological cancer. In Asian, an increased risk was observed in the GG vs TG + TT model (OR = 1.36, 95% CI: 1.07, 1.74, $P < .05$) (Fig. 5D). However, we did not observe significant association between rs2279744 polymorphism and gynecological cancer risk in African American. These results indicated that rs2279744 polymorphism may be associated with gynecological cancer risk in Caucasian and Asian.

3.2.2.2. The association between rs2279744 or rs117039649 polymorphism and the types of gynecological cancer. Five genetic models were used to investigate the association between rs2279744 polymorphism and the types of gynecological cancer. Our findings indicated that 3 genetic models, including GG vs TG + TT (OR = 2.02, 95% CI: 1.31, 3.11, $P < .05$) (Fig. 6A), TT vs GG (OR = 0.60, 95% CI: 0.43, 0.83, $P < .05$) (Fig. 6B), and T vs G (OR = 0.73, 95% CI: 0.56, 0.94, $P < .05$) (Fig. 6C), had a significant association with the risk of EC, suggesting that TT or T polymorphism might be associated with a decreased risk of EC. No evidence was observed in relation to other 3 types of cancers. We did not conduct the subgroup analysis because of data limitation. All the data are summarized in Table 4.

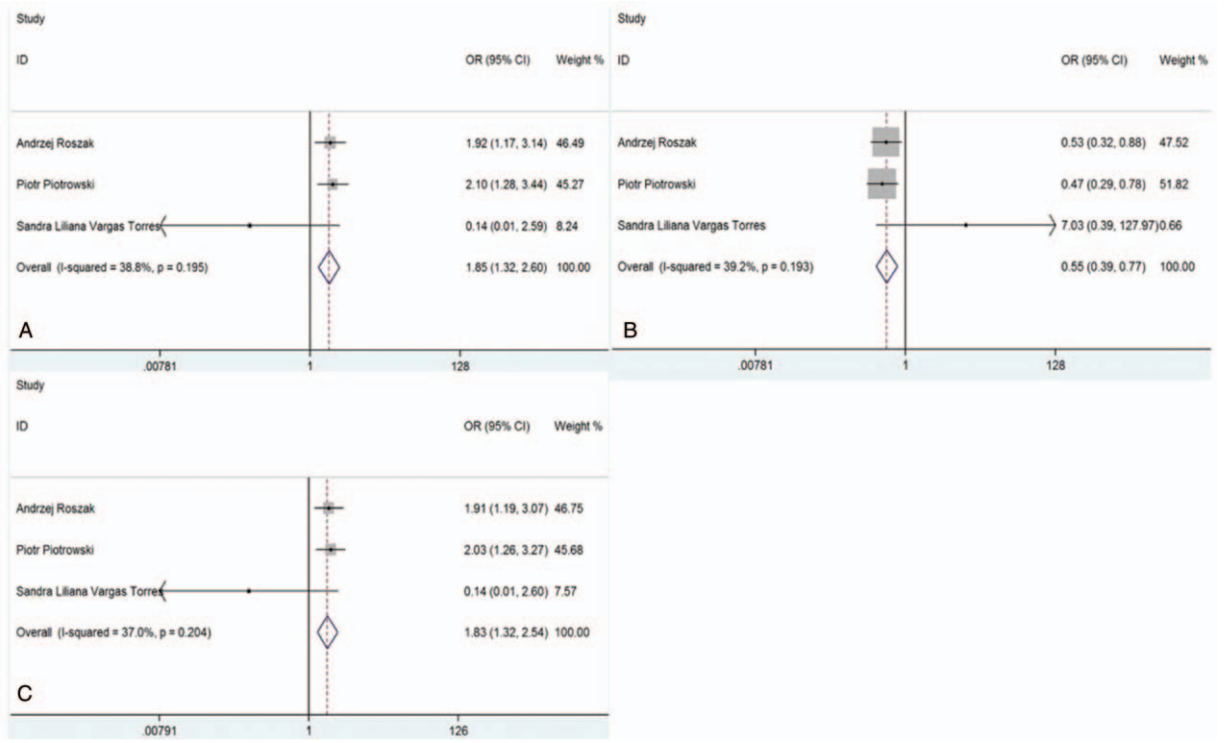

Figure 4. Forest plots of the association between SNP285 polymorphism and risk of gynecological cancers. (A) Model GG vs GC + CC; (B) model GC vs GG; and (C) model G vs C.

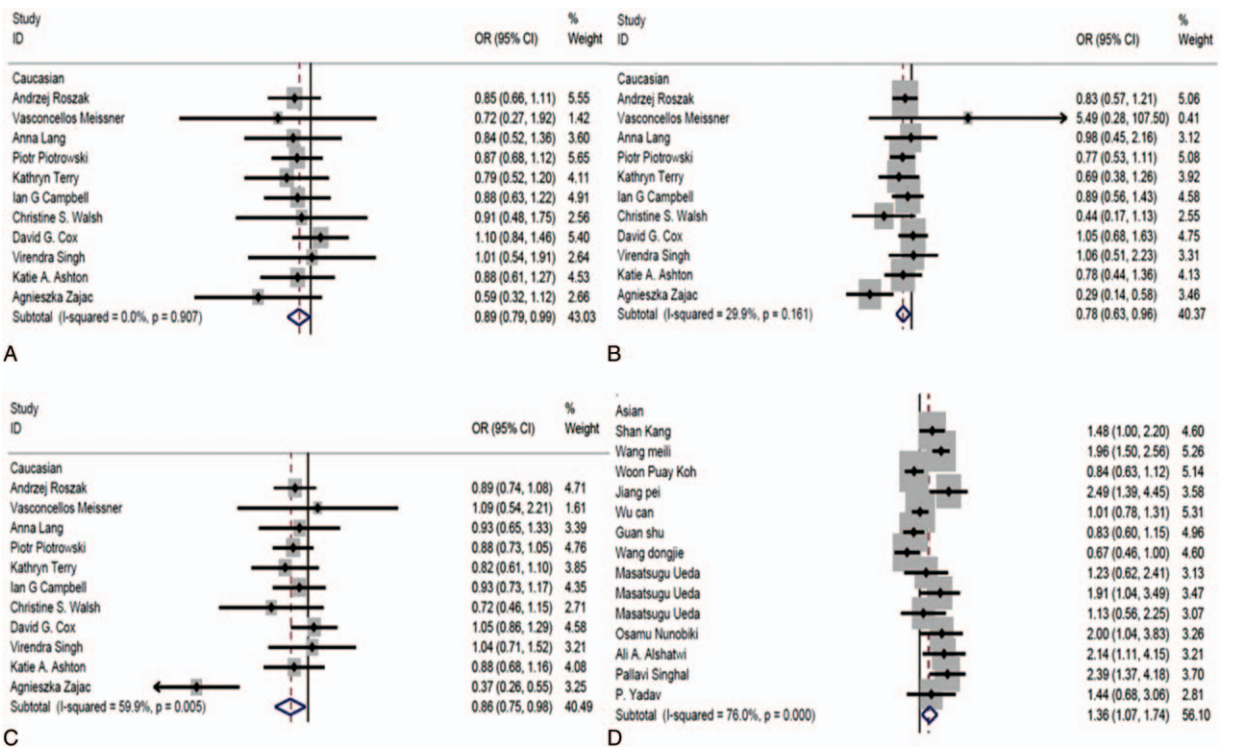

Figure 5. The association between SNP309 polymorphism and risk of gynecological cancer by ethnicity. (A) Model TT vs TG + GG in Caucasian; (B) model TT vs GG in Caucasian; (C) model T vs G in Caucasian; and (D) model GG vs TG + TT in Asian.

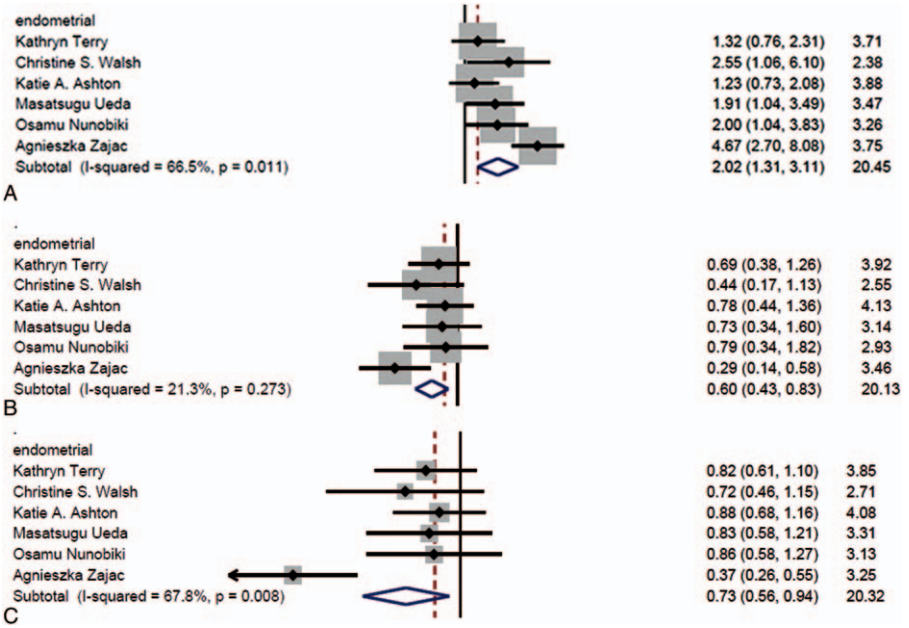

Figure 6. The association between SNP309 polymorphism and risk of gynecological cancer by type. (A) Model GG vs TG + TT in; (B) model TT vs GG; and (C) model T vs G.

3.3. Publication bias

Funnel plots were symmetric in all genetic models, and Begg test did not show significant publication bias ($P > .05$) (Fig. 7), indicating that we random selected the articles with positive and negative outcomes together to a certain extent.

4. Discussion

It has been reported that Sp1 binding to the MDM2 P2 promoter could be influenced by the polymorphism of SNPT309G, resulting in a high-level expression of MDM2 protein.[19] However, MDM2 SNPG285C allele may play a reverse role to SNP309.[25] The status of 309G is associated with an early diagnosis and tumor formation in Li–Fraumeni syndrome and several malignancies according to recent reports.[44,45] Interestingly, the association was only observed in women. So we aimed to explore the association between the polymorphisms at these 2 locus and the risk of gynecological cancers in this analysis.

Recently, Xue et al[23] published a meta-analysis of the association between MDM2 T309G polymorphism and EC, but they only studied the SNPT309G with the EC and the analysis was based on the search of 2 databases. In our meta-analysis, we first analyzed the association between SNPs of MDM2 and the risk of gynecological cancer as a whole. Five genetic models were considered including dominant, recessive, homozygote, heterozygous, and allele genotypes. We found that TT and T allele were associated with a reduced risk of gynecological cancer when compared with GG and G allele in SNP309, suggesting that SNPT309G was a risky mutation to women. Meanwhile, SNPG285C performs an opposite role. When compared with GC + CC, an increased risk for gynecological cancer was observed for GG polymorphism, the same was for G vs C. However, GC was associated with a reduced risk of gynecological cancer when compared with GG. Although only 3 articles were included in the analysis of SNPG285C, the number of subjects was still large: 1117 cases and 1221 controls. Hence, the

Table 4

Results of meta-analysis.

SNP	Genetic model	Subjects	OR (95% CI)	Z	*P*	I^2, %	P_{het}	Effect model	Begg test $P > \|z\|$	Egger test Pr > |t|
MDM2 309	TT vs TG + GG	12,902	0.89 (0.79, 1.02)	1.67	.094	58.80	.000	Random	0.227	0.389
MDM2 309	GG vs TG + TT	12,902	1.32 (1.11, 1.57)	3.16	.002	70.2	.000	Random	—	—
MDM2 309	TT vs TG	10,120	0.93 (0.86, 1.01)	1.66	.097	46.5	.005	Fixed	—	—
MDM2 309	TT vs GG	6921	0.77 (0.63, 0.94)	2.57	.010	67.8	.000	Random	—	—
MDM2 309	T vs G	25,806	0.86 (0.77, 0.96)	2.75	.006	74.4	.000	Random	—	—
MDM2 285	GG vs GC + CC	2432	1.85 (1.32, 2.60)	3.57	.000	38.8	.195	Fixed	—	—
MDM2 285	CC vs GC + GG	2432	1.42 (0.8, 2.52)	0.98	.329	0.00	.759	Fixed	—	—
MDM2 285	GC vs GG	2425	0.55 (0.39, 0.77)	3.44	.001	39.2	.193	Fixed	—	—
MDM2 285	GG vs CC	2278	2.38 (0.46, 12.27)	1.04	.300	0.00	.762	Fixed	—	—
MDM2 285	G vs C	4864	1.83 (1.32, 2.54)	3.63	.000	37.0	.204	Fixed	—	—

CI = confidence interval, MDM2 = murine double minute 2, OR = odds ratio, SNP = single nucleotide polymorphism, Z = Z test.

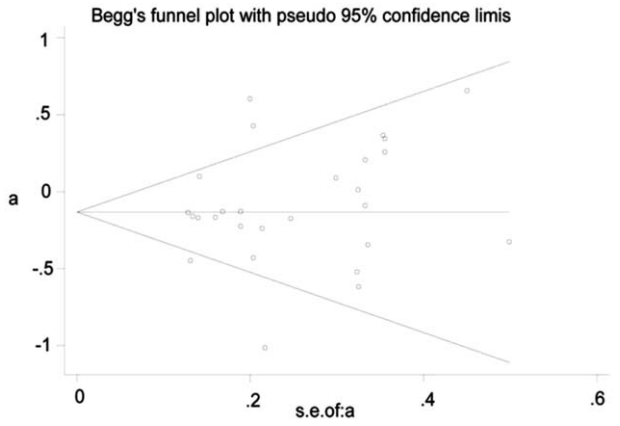

Figure 7. Funnel plots of all articles included in the analysis. a = log OR, s.e. of a = se (log OR).

results should be relatively reliable. Interestingly, we also confirmed that SNP309G and 285C, as 2 locus in MDM2 promoter, had an opposing effects in Caucasians regarding the risk of gynecological cancer. One similar point was observed for both SNPs: the GG and G alleles were all associated with increased risk of gynecological cancer when compared with their corresponding variant alleles. In other words, GG or G allele seems play a protective role in these 2 SNPs. We also speculated that patients have a good prognosis when harbor SNP285C even with SNP309G. In summary, we reported the overall effects of SNPT309G/G285C on the risk of gynecological cancers. To our best knowledge, this has not been reported so far.

Subgroup analysis was conducted in 2 ways. First, we assessed the association between MDM2 T309G polymorphism and gynecological cancer risk by ethnicity. We found that TT or T allele was associated with a decreased cancer risk in dominate, heterozygote and allele models in Caucasian. While in Asian, compared with TG + TT, GG genotype was associated with a significantly increased risk of gynecological cancer. The results were consistent with our overall analysis. No significant association was found in African American, which may be due to the low number of articles (2 articles). Second, we evaluated the association between MDM2 T309G polymorphism and 4 types of gynecological cancer, respectively. Previous articles of meta-analysis were conducted for breast, cervical, ovarian, and ECs individually. Our study found that GG genotype was associated with an increased risk of endometrial tumor, but not breast tumor,[44,46,47] ovarian or cervical tumor. In addition, we found that TT or T allele genotype (compared with GG or G allele) has a significant association with the risk of EC. In a recent report by Xue et al,[24] a significant association between MDM2 T309G polymorphism and EC in the recessive model was identified, which is consistent with our results. However, we also found that SNPT309G is associated with a reduced endometrial risk in TT vs GG and T vs G models (Fig. 6B and C). Of note, the results of previous studies were conflicting. Kang et al reported that SNPT390G polymorphism of MDM2 reduced the risk of ovarian tumor in Chinese,[7] while Knappskog et al concluded that the SNP309 G increased the risk of OC.[48] A subsequent meta-analysis[25] also identified a significant association in Asian population. However, in our analysis, we did not find a significant relationship between G allele or GG genotype and ovarian tumor.

BC was common. From our subgroup analysis, we did not find its relationship with SNP309G. One reason may be that the effects may vary by ethnicity. Our analysis has several limitations. Six articles were considered to have HWE disequilibrium, which could have an influence on our results. Only 2 articles included analysis based on African American, which restricted our analysis in this population. The number of reports studied SNP285C polymorphism was small, limits our conclusion in this analysis. More researches are needed in the future, to address the limitations of this analysis.

5. Conclusion

We found that rs2279744 (SNP309) and rs117039649 (SNP285) were both associated with the risk of gynecological cancers. Subgroup analysis showed that rs2279744 (SNP309) was associated with the risk of gynecological cancers in Caucasian and Asian according to the ethnicity and cancer type, especially for EC.

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