Association of XRCC3 18067 C>T (Thr241Met) polymorphism with risk of cervical and ovarian cancers: A systematic review and meta-analysis

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Abstract: The 18067 C>T polymorphism of *XRCC3* gene has been considered to be implicated in the development of cervical and ovarian cancers, but the results are inconsistent. Thus, we conducted a meta-analysis to assess the association of XRCC3 18067 C>T polymorphism with risk of cervical and ovarian cancers. All studies on the association of XRCC3 18067 C>T polymorphism with cervical and ovarian cancers risk were retrieved. Finally, a total of 17 studies including 10 studies with 5,637 cases and 10,057 controls on ovarian cancer and 7 studies with 1,112 cases and 1,233 controls on cervical cancer were selected. Overall, pooled results showed that the XRCC3 18067 C>T polymorphism was significantly associated with increased risk of ovarian cancer (TC vs. CC: OR = 0.904, 95% CI = 0.841–0.972, $p = 0.006$; TT + TC vs. CC: OR = 0.914, 95% CI = 0.853–0.979, $p = 0.010$) and cervical cancer (TC vs. CC: OR = 1.00, 95% CI = 1.066–1.585, $p = 0.009$). Further subgroup analysis by ethnicity revealed an increased risk of cervical and ovarian cancer in Asians and Caucasians, respectively. The present meta-analysis inconsistent with the previous meta-analysis suggests that the XRCC3 18067 C>T polymorphism might be implicated in the pathogenesis of cervical and ovarian cancers.

Keywords: cervical cancer, ovarian cancer, *XRCC3* gene, polymorphism, meta-analysis

Introduction

Cervical and ovarian cancers remain two of the leading cause of cancer mortality worldwide among women and the most common site in several low-income countries [1, 2]. It is widely accepted that certain oncogenic types of human papilloma virus (HPV) are essential cause of cervical cancer development [3]. Almost 100% of women with a diagnosis of cervical cancer have been found to have had an HPV infection [4]. Ovarian cancer is characterized by few early symptoms, presentation at an advanced stage, and poor survival [5, 6]. The exact causes of ovarian cancer are not known. Relatively few risk factors for ovarian cancer have been identified, including age, parity, oral contraceptive use, lifestyle factors, and family history of breast or ovarian cancer, many of these are not easily modifiable on the population level [4, 7].

Genome-wide association studies have been extremely successful at finding susceptibility loci for cervical and ovarian cancers [8]. Molecular epidemiological studies have been conducted with the candidate gene approach to identify susceptibility genes for cervical and ovarian cancers, many of which have showed inconsistent result [9]. DNA repair plays an important role in the maintenance of genomic integrity by correcting DNA alterations caused by endogenous and exogenous genotoxic agents [10]. At present, several DNA repair genes (e.g., *XPD, XPF, ERCC1, XRCC1, XRCC3, XPA, XPB, XPC*, and *hOGG1*) have been reported to be associated with cervical and ovarian cancers, and the X-ray cross-complementing group 3 (*XRCC3*) gene has received an increasing attention [11, 12].

The human *XRCC3* gene (MIM: 600675) is localized on chromosomes 14q32.3 [13]. It is involved in the homologous recombination repair (HR) pathway, responsible for DNA double-strand breaks [14]. *XRCC3* is a polymorphic gene where many SNPs have been already described. Several polymorphisms in the *XRCC3* gene have been described to affect the enzyme function and/or its interaction with other proteins involved in DNA damage and repair [13, 14]. Of these, C18607T transition (rs861539) at exon 7 resulting in an amino acid change at codon 241 (Thr241Met) has been studied frequently [13]. This polymorphism has been reported to be associated with the development of some cancers, such as bladder, skin, breast, lung, and colorectal cancers [15].

Several epidemiological studies were conducted in recent years to evaluate the association of the XRCC3 18067 C>T polymorphism with cervical and ovarian cancers [16, 17]. Some studies have shown a significant statistical correlation of this polymorphism with cervical and ovarian cancers, whereas others did not find any such association. Thus, these inconsistent results fail to clarify this complicated genetic relationship, presumably due to small sample size in each published study, various genetic backgrounds, and possible selection bias. To reliably demonstrate the effect of XRCC3 18067 C>T polymorphism on cervical and ovarian cancer risks, we performed a comprehensive systematic review and meta-analysis of all eligible studies to resolve this pivotal issue.

Materials and Methods

Study identification and selection

This meta-analysis conformed to the Preferred Reporting Items for Systematic Reviews and Meta-analyses criteria. Two investigators independently searched the MEDLINE (PubMed), Google Scholar, Web of Science (Thomson-Reuters), Scientific Information Database (SID), Chinese National Knowledge Infrastructure (CNKI), the Chinese Wanfang, and the Chinese VIP databases for eligible articles examined the association of XRCC3 18067 C>T polymorphism with cervical and ovarian cancer risks published up to January 30, 2019. The following terms were utilized: ("ovarian cancer" OR "cervical cancer") AND ("X-ray repair cross complementing 3" OR "XRCC3") AND ("XRCC3 18067 C>T" OR "Thr241Met" OR "rs861539") AND ("polymorphism", OR "mutation" OR "variant" OR "gene" OR "genotype" OR "SNP" OR "allele"). The search was performed without any restrictions on language and was focused on studies that had been conducted in humans. In addition, manual searching of the references of eligible studies, reviews and related meta-analyses, and the abstracts presented at relevant conferences were performed to identify potentially relevant studies. If there were multiple reports of the same study or overlapping data, only the study with the largest sample sizes or the most recent one should be in the final analysis.

Data extraction

Information was carefully extracted from all eligible studies independently by two investigators according to the inclusion criteria listed above, and potential disagreements were resolved by consensus. The following data were collected from each study: name of first author, publication year, country where the study was conducted, racial descent (categorized as Asian, Caucasian, or mixed descent), polymorphisms, genotypic testing method, number of cases and controls, genotype frequency of cases and controls, minor allele frequencies in control subjects, and result of Hardy–Weinberg equilibrium (HWE) test in control subjects. In this meta-analysis, ethnicity was categorized as: Caucasian, Asian, and Mixed.

Inclusion and exclusion criteria

To be included in the meta-analysis, studies had to meet all the criteria: (1) use a case–control or cohort design; (2) assess the association of the XRCC3 18067 C>T polymorphism with ovarian and cervical cancers; and (3) provide sufficient data for estimating odds ratios (ORs) with 95% confidence intervals (CIs). The exclusion criteria were: (1) studies that could not offer the number of cases and controls or other essential information; (2) case only or studies without control group; (3) family based or linkage studies; (4) case reports, reviews, and studies; and (5) overlapping data. In the case of multiple studies by the same researchers involving the same or overlapping data sets, the most recent study with the largest number of participants was included in the meta-analysis.

Statistical analyses

The strength of association of the XRCC3 18067 C>T polymorphism with ovarian and cervical cancers susceptibility was assessed by OR with the corresponding 95% CI. The *Z*-test was performed to determine the significance of the pooled OR, with $p < 0.05$ defined as the significance threshold. The pooled ORs were calculated for the risk associated with the XRCC3 18067 C>T polymorphism in the allele model (T vs. C), homozygote model (TT vs. CC), heterozygote model (TC vs. CC), dominant model (TT + TC vs. CC), and recessive model (TT + TC vs. CC). The between-studies heterogeneity was tested using the *Q* statistic. If $p < 0.10$, the heterogeneity was considered statistically significant. Venice criteria for the I^2 test included: $I^2 < 25\%$ represents no heterogeneity, $I^2 = 25\%$–50% represents moderate heterogeneity, $I^2 = 50\%$–75% represents large heterogeneity, and $I^2 > 75\%$ represents extreme heterogeneity. The *p* value of <0.05 for the *Q*-test indicated a lack of heterogeneity among studies, so that the pooled OR estimate of each study was calculated by the fixed-effects model (the Mantel–Haenszel method), otherwise the random effects model (the DerSimonian–Laird method) was utilized. Furthermore, to explore the source of between-study heterogeneity, the subgroup analyses were performed. The one-way sensitivity analyses were performed to survey the stability of the results, namely, a single study in the meta-analysis was omitted each time to reflect the influence of the individual data set to the pooled OR. Publication bias was assessed by visually examining the asymmetry of a funnel plot in which the log estimates were plotted against their standard errors. Furthermore, we also employed an Egger's regression test in our analysis to calculate two-tailed *p* values for quantifying publication bias. A HWE test of the VDR gene polymorphisms in healthy subjects was examined using χ^2 test. If *p* value > 0.05, the genotype distribution of the control group conformed to HWE. All the statistical analyses were performed by comprehensive meta-analysis version 2.0 software (Biostat, USA). All the *p* values were two sides and less than 0.05 were considered significant.

Results

Study selection and characteristics

A flow diagram schematizing the inclusion and exclusion process of identified articles with the inclusion criteria is presented in *Fig. 1*. After a comprehensive search, a total of 126 literatures were identified. Of these studies, the first screening excluded 47 were considered as duplicates or not relevant, leaving 79 studies for further selection. Finally, a total of 17 case–control studies (in 14 publications) were included in this meta-analysis [18–31]. Of these, there were seven studies with 1,112 cases and 1,233 controls on cervical cancer [18–24] and 10 studies with 5,637 cases and 9,267 controls on ovarian cancer [25, 27–31]. The main characteristics of studies included in the present meta-analysis are presented in *Table I*. Of all the eligible studies, four were conducted in Asian, two were in Caucasians, and one was in mixed for cervical cancer; eight were conducted in Caucasians and two were in mixed for ovarian cancer. Twelve studies were population-based and four were hospital-based studies. One study in the present meta-analysis did not state the source of controls. Four genotyping methods were used, including AS-PCR, PCR-RFLP, Pyrosequencing™, and TaqMan assay. The genotype distributions among the controls in two studies were not consistent with HWE on ovarian cancer *(Table I)*.

Quantitative synthesis

Table II listed the main results of the meta-analysis of XRCC3 18067 C>T polymorphism with cervical and ovarian cancers risk. When all the eligible studies were pooled into meta-analysis, the results showed that XRCC3 18067 C>T polymorphism was not significantly associated with increased risk of cervical and ovarian cancers under all genetic models genetic models, i.e., allele (T vs. C: OR = 1.014, 95% CI = 0.930–1.106, $p = 0.745$), homozygote (TT vs. CC: OR = 1.010, 95% = CI 0.855–1.194, $p = 0.906$), heterozygote (TC vs. CC: OR = 0.967, 95% CI = 0.876–1.067, $p = 0.530$), dominant (TT + TC vs. CC: OR = 0.993, 95% CI = 0.889–1.108, $p = 0.897$), and recessive (TT vs. TC + CC: OR = 1.028, 95% CI = 0.894–1.183, $p = 0.700$).

The studies were further stratified by cancer type and ethnicity. When stratified by cancer, there was a significant association between XRCC3 18067 C>T polymorphism and increased risk of cervical cancer under the heterozygote model (TC vs. CC: OR = 1.00, 95% CI = 1.066–1.585, $p = 0.009$; *Fig. 2A*). Moreover, the XRCC3 18067 C>T polymorphism was significantly associated with increased risk of ovarian cancer under two genetic models, i.e., heterozygote (TC vs. CC: OR = 0.904, 95% CI = 0.841–0.972, $p = 0.006$) and dominant (TT + TC vs. CC: OR = 0.914, 95% CI = 0.853–0.979, $p = 0.010$; *Fig. 2B*).

Subgroup analysis by ethnicity showed that there was a significant association between XRCC3 18067 C>T polymorphism and cervical cancer in Asian under three genetic models, i.e., model (T vs. C: OR = 1.302, 95% CI = 1.076–1.576, $p = 0.007$), heterozygote (TC vs. CC: OR = 1.441, 95% CI = 1.113–1.867, $p = 0.006$) and dominant (TT + TC vs. CC: OR = 1.469, 95% CI = 1.148–1.880, $p = 0.002$), but not in Caucasians. Moreover, subgroup analysis showed that there was a

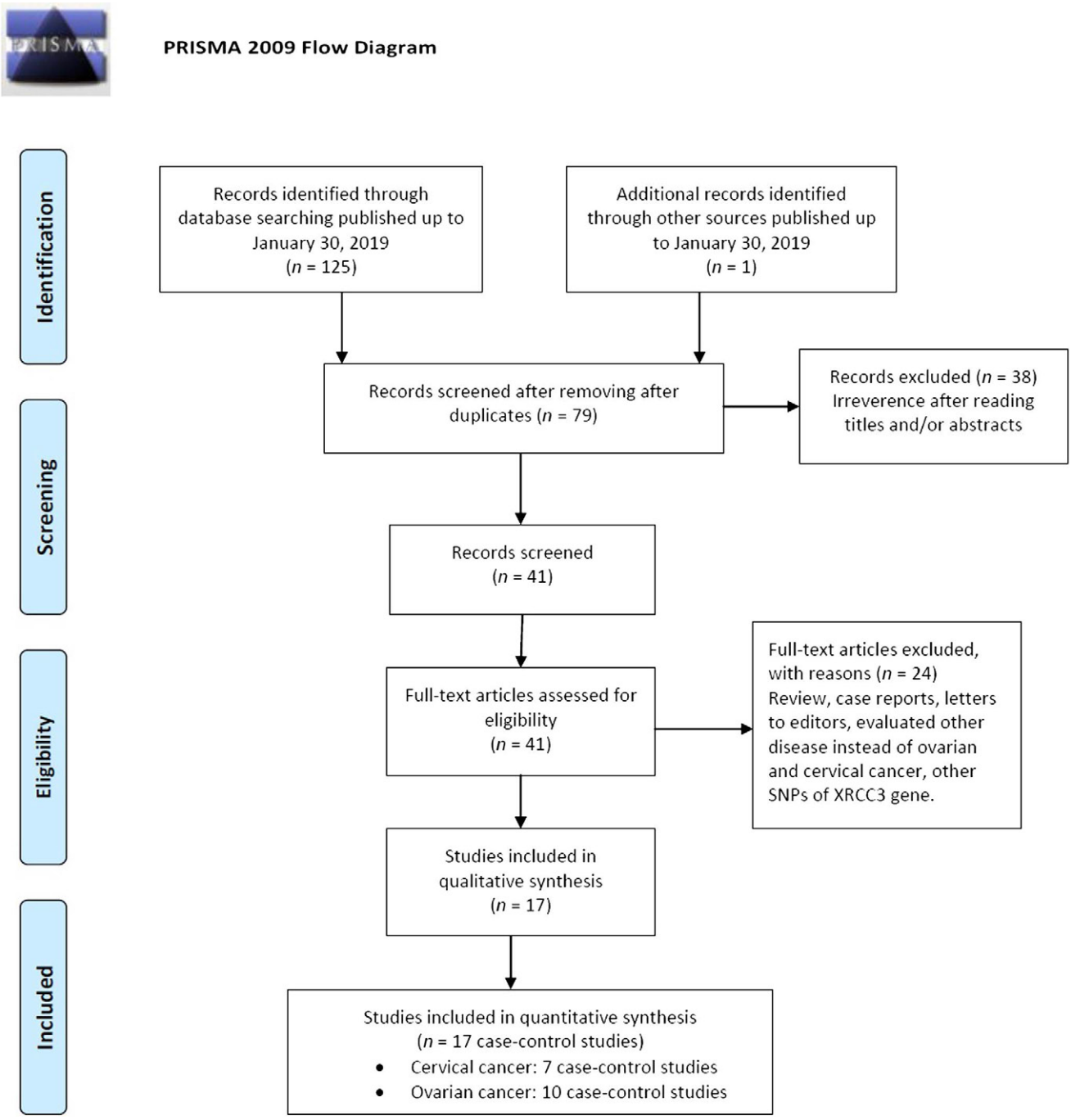

Fig. 1. Flow diagram of selection of studies included in the current meta-analysis

significant association between XRCC3 18067 C>T polymorphism and increased risk of ovarian cancer in Caucasians under two genetic models, i.e., heterozygote (TC vs. CC: OR = 0.898, 95% CI = 0.834–0.967, $p = 0.004$) and dominant (TT + TC vs. CC: OR = 0.905, 95% CI= 0.844–0.970, $p = 0.005$). In the subgroup analyses by ethnicity, no studies were performed for ovarian cancer in Asians suggesting that our results might be not applicable for these populations.

Test of heterogeneity and sensitivity analyses

For cervical cancer, statistical significant heterogeneity among studies under four genetic models was observed when all eligible studies were pooled into the meta-analysis. However, the heterogeneity test showed that there was no significant heterogeneity in terms of the XRCC3 18067 C>T polymorphism association with ovarian cancer. Therefore, to explore the potential

Table I. Characteristics of studies included in the meta-analysis

First author (year)	Country (ethnicity)	SOC	Genotyping technique	Case/control	Cases					Controls					MAFs	HWE
					Genotypes			Alleles		Genotypes			Alleles			
					CC	CT	TT	C	T	CC	CT	TT	C	T		
Cervical cancer																
He (2008)	China (Asian)	PB	AS-PCR	200/200	177	19	4	373	27	182	17	1	381	19	0.047	0.391
Xiao (2010)	China (Asian)	PB	PCR-RFLP	158/164	82	59	17	223	93	115	41	8	271	57	0.173	0.097
Settheetham-Ishida (2011)	Thailand (Asian)	PB	PCR-RFLP	111/118	101	10	0	212	10	106	12	0	224	12	0.050	0.560
Pérez (2013)	Argentina (Caucasian)	PB	Sequencing	117/205	50	56	11	156	78	78	95	32	251	159	0.387	0.730
Djansugurova (2013)	Kazakhstan (Caucasian)	PB	AS-PCR	217/160	140	57	20	337	97	124	32	4	280	40	0.125	0.278
Colacino-Silva (2017)	Brazil (Mixed)	HB	PCR-RFLP	77/73	43	28	6	114	40	36	30	7	102	44	0.301	0.837
Al-Harbi (2017)	Saudi Arabia (Asian)	NS	PCR-RFLP	232/313	79	126	27	284	180	126	145	42	397	229	0.365	0.977
Ovarian cancer																
Auranen (2005a)	UK (Caucasian)	PB	TaqMan	1039/2614	427	468	144	1322	756	1046	1231	337	3336	1892	0.361	0.394
Auranen (2005b)	USA (Caucasian)	PB	TaqMan	270/344	125	114	31	364	176	130	174	40	434	254	0.369	0.110
Auranen (2005c)	Danish (Caucasian)	PB	TaqMan	361/891	144	168	49	456	266	358	394	139	1110	672	0.377	0.079
Webb (2005)	Australia (Caucasian)	HB	PCR	543/1125	229	238	76	696	390	438	538	149	1416	834	0.371	0.420
Beesley (2007a)	Australia (Caucasian)	PB	PCR-RFLP	504/972	207	223	74	637	371	370	471	131	1211	733	0.377	0.326
Beesley (2007b)	Australia (Caucasian)	PB	PCR-RFLP	731/747	291	339	101	921	541	288	351	108	927	567	0.379	0.949
Quaye (2009)	UK-USA-DK (Caucasian)	PB	Sequencing	1332/2024	545	612	175	1702	962	784	958	282	2526	1522	0.376	0.695
Gonzalez-Hormazaba (2012)	Chile (Mixed)	PB	TaqMan	87/570	45	32	10	122	52	335	209	23	879	261	0.224	0.171
Monteiro (2014)	Brazil (Mixed)	HB	PCR-RFLP	70/70	32	33	5	97	43	32	33	5	97	43	0.307	0.023
Michalska (2016)	Poland (Caucasian)	HB	PCR-RFLP	700/700	180	340	180	700	700	150	350	200	650	750	0.535	0.892

SOC: source of control; PB: population-based; HB: hospital-based; NA: not stated; PCR: polymerase chain reaction; ASPCR: allele-specific PCR; RFLP: restriction fragment length polymorphism; MAF: minor allele frequency; HWE: Hardy–Weinberg equilibrium

Table II Results of the association of XRCC3 18067 C>T polymorphism with cervical and ovarian cancer risks

			Heterogeneity		OR			Publication bias		
Subgroup	Genetic model	Type of model	I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
Overall	T vs. C	Random	61.03	0.001	1.014	0.930–1.106	0.326	0.745	0.091	0.112
	TT vs. CC	Random	51.70	0.009	1.010	0.855–1.194	0.118	0.906	0.162	0.079
	TC vs. CC	Random	39.28	0.049	0.967	0.876–1.067	−0.670	0.530	0.232	0.151
	TT + TC vs. CC	Random	54.91	0.003	0.993	0.889–1.108	−0.129	0.897	0.232	0.140
	TT vs. TC + CC	Random	43.09	0.034	1.028	0.894–1.183	0.385	0.700	0.224	0.099
Cervical cancer	T vs. C	Random	73.82	0.001	1.223	0.897–1.669	1.272	0.203	1.000	0.901
	TT vs. CC	Random	68.44	0.007	1.456	0.723–2.932	1.053	0.292	0.707	0.376
	TC vs. CC	Fixed	26.84	0.224	1.300	1.066–1.585	2.596	0.009	0.548	0.242
	TT + TC vs. CC	Random	58.55	0.025	1.270	0.935–1.726	1.530	0.126	0.763	0.452
	TT vs. TC + CC	Random	64.54	0.015	1.309	0.693–2.470	0.829	0.407	0.452	0.225
Asian	T vs. C	Fixed	60.39	0.056	1.302	1.076–1.576	2.716	0.007	1.000	0.862
	TT vs. CC	Fixed	58.94	0.088	1.457	0.918–2.314	1.595	0.111	1.000	0.446
	TC vs. CC	Fixed	14.62	0.319	1.441	1.113–1.867	2.768	0.006	0.308	0.474
	TT + TC vs. CC	Fixed	36.18	0.195	1.469	1.148–1.880	3.055	0.002	0.734	0.666
	TT vs. TC + CC	Fixed	61.31	0.075	1.165	0.754–1.801	0.689	0.491	1.000	0.375
Caucasians	T vs. C	Random	91.87	0.00	1.253	0.500–3.138	0.481	0.630	NA	NA
	TT vs. CC	Random	89.45	0.002	1.484	0.188–11.730	0.374	0.708	NA	NA
	TC vs. CC	Fixed	45.46	0.176	1.234	0.873–1.743	1.193	0.233	NA	NA
	TT + TC vs. CC	Random	83.94	0.013	1.248	0.551–2.826	0.532	0.595	NA	NA
	TT vs. TC + CC	Random	88.24	0.004	1.425	0.210–9.655	0.363	0.716	NA	NA
Ovarian cancer	T vs. C	Fixed	4.19	0.402	0.956	0.910–1.003	−1.830	0.067	0.210	0.554
	TT vs. CC	Fixed	31.26	0.158	0.942	0.850–1.045	−1.130	0.259	0.591	0.313
	TC vs. CC	Fixed	0.00	0.662	0.904	0.841–0.972	−2.725	0.006	1.000	0.929
	TT + TC vs. CC	Fixed	0.00	0.504	0.914	0.853–0.979	−2.569	0.010	1.000	0.849
	TT vs. TC + CC	Fixed	25.21	0.211	1.010	0.994–1.092	−0.133	0.894	0.371	0.209
Caucasians	T vs. C	Fixed	0.00	0.763	0.948	0.902–0.996	−2.137	0.033	1.000	0.171
	TT vs. CC	Fixed	0.00	0.791	0.922	0.831–1.024	−1.514	0.130	0.901	0.445
	TC vs. CC	Fixed	0.00	0.567	0.898	0.834–0.967	−2.853	0.004	0.386	0.221
	TT + TC vs. CC	Fixed	0.00	0.638	0.905	0.844–0.970	−2.818	0.005	0.386	0.133
	TT vs. TC + CC	Fixed	0.00	0.804	0.977	0.888–1.074	−0.480	0.631	0.901	0.963

OR: odds ratio; CI: confidence interval; NA: not applicable

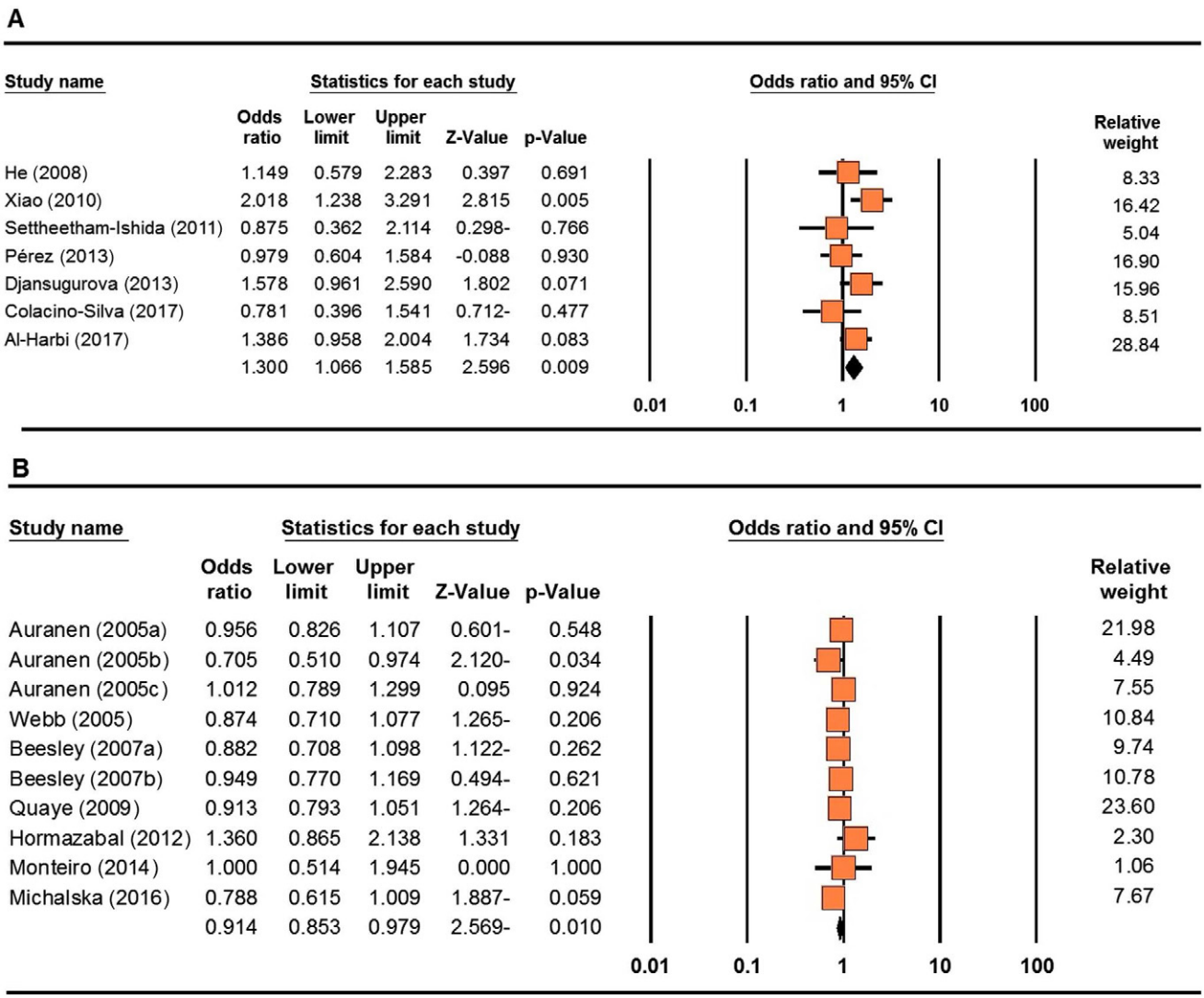

Fig. 2. Forest plots for association of XRCC3 Thr241Met polymorphism with cervical cancer and ovarian cancer. A: cervical cancer (heterozygote model: TC vs. CC); B: ovarian cancer (dominant model: TT + TC vs. CC)

sources of heterogeneity across studies, we performed subgroup analysis under all models. To explore the sources of heterogeneity, we conducted subgroup analyses by ethnicity, genotyping methods, and source of controls. Subgroup analyses by ethnicity showed that the heterogeneity was still significant in Caucasians populations, indicating that ethnicity was the major source that contributed to heterogeneity for cervical cancer. In addition, we have performed sensitivity analyses to assess the influence of each individual study on the pooled ORs by sequential omission of individual studies. The results suggested that the sequential omission of individual studies did not significantly affect the pooled ORs for the XRCC3 18067 C>T polymorphism, the stability of the current meta-analysis results. For ovarian cancer, sensitivity analysis was further performed by excluded one HWE-violating study. However, the XRCC3 18067 C>T polymorphism association with ovarian cancer risk was not influenced by omitting the study.

Publication bias

Both Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures in all genetic models and by ethnicity. The shape of the funnel plot did not reveal any evidence of obvious asymmetry in overall and by cancer type *(Fig. 3)*. Then, we used the Egger's test to provide statistical evidence of funnel plot symmetry. The results still did not suggest any evidence of publication bias in overall, by cancer type and ethnicity *(Table II)*.

Discussion

The *XRCC3* gene is one of the major genes involved in the restoration phase of DNA damage [14]. More than 300 validated single nucleotide polymorphisms in the *XRCC3* gene were reported in the dbSNP database

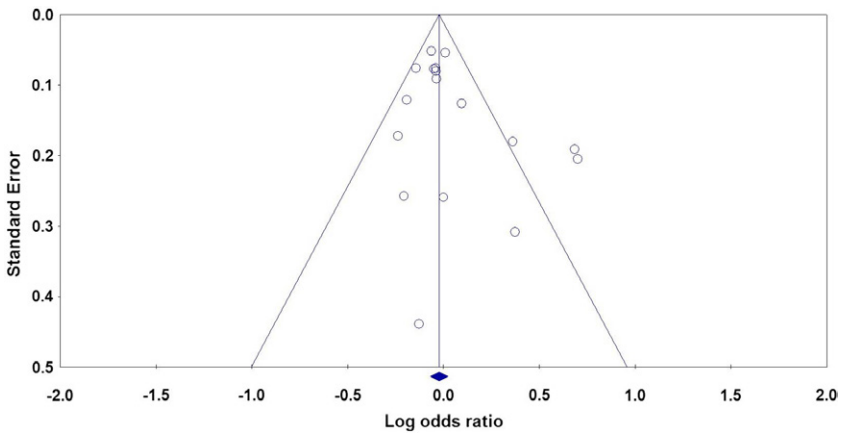

Fig. 3. Begg's funnel plot of publication bias test for XRCC3 Thr241Met polymorphism in overall under the allele model (A vs. G)

among them, 18067 C>T (rs861539) in *XRCC3* codon 241 (Thr241Met) was the most extensively studied in different malignancies [16, 17]. There is evidence that XRCC3 18067 C>T polymorphism is a functional variant with potential to affect the capacity of DNA repair activity [15]. The association of this polymorphism with cervical and ovarian cancer risk has been assessed in several studies, which showed inconclusive results.

In the present meta-analysis, we examined the association of XRCC3 18067 C>T polymorphism with cervical and ovarian cancers risk. We found that the XRCC3 18067 C>T polymorphism was significantly associated with ovarian cancer risk. We also observed a significant relationship between the XRCC3 18067 C>T polymorphism and ovarian cancer in Caucasians. However, our results were inconsistent with previous meta-analysis. Yan et al. [16] in a meta-analysis of seven studies with 3,635 cases and 5,473 controls suggested that the XRCC3 18067 C>T polymorphism may not be associated with ovarian cancer in all five genetic models in overall and Caucasians population. In 2013, Qin et al. [17] in a meta-analysis of five case–control studies with a total of 806 cervical cancer cases and 850 controls estimated the association between XRCC3 18067 C>T polymorphism and cervical cancer risk. The results showed a significant association that XRCC3 18067 C>T polymorphism may contribute to the susceptibility of cervical cancer only under heterozygote model. The association was also confirmed by our meta-analysis, which involved seven studies with 1,112 cases and 1,233 controls only in the heterozygote model. Moreover, the previous [16] and the current meta-analyses findings confirmed that XRCC3 18067 C>T polymorphism is associated with the risk of cervical cancer among Asians, but not among Caucasians, suggesting that this polymorphism may modify the risk of cervical cancer in different ethnicities. Compared to the previous meta-analyses, the included studies to the current meta-analysis are most precise and comprehensive attributing to the largest sample size and accumulative meta-analysis method. Hence, our results are more precise and comprehensive on the association of XRCC3 18067 C>T polymorphism with cervical and ovarian cancers.

The heterogeneity plays an important role when performing meta-analysis and finding the source of heterogeneity is very important for the final result of meta-analysis. There were several sources bringing in heterogeneity, such as study design, age, sex distribution, sample size, genotyping methods, and ethnicity. Obviously, there was potential to moderate level heterogeneity in the current meta-analysis. Thus, we have performed meta-regression analysis to find source of heterogeneity. The heterogeneity between our studies was significantly reduced in the analysis of the cancer type and by ethnicity subgroups, indicating that the effect of XRCC3 18067 C>T polymorphism may be modified by cancer etiology and ethnicity backgrounds.

The main advantage of our meta-analysis that publication bias was not observed, which indicates that the whole pooled results, may be unbiased. However, several limitations in this meta-analysis should be addressed. First, the included studies only provided data toward Asians and Caucasians. The data regarding other ethnicities such as Africans were not found. Therefore, we cannot generalize these findings to every ethnic group. Second, there were only seven studies with a total of 1,112 cases and 1,233 controls that were finally included into the meta-analysis for cervical cancer. The number of included studies was relatively limited, which may increase the risk of bias in the meta-analysis, especially in the subgroup analysis by ethnicity. Thus, more studies with a larger sample size from different ethnicities should be performed in the future. Third, we have included only published studies in the meta-analysis, and non-significant or negative findings may be unpublished. Hence, any preexisting publication bias will be reflected in the findings; however, the statistical data may not show it. Fifth, the summary ORs were based on individual

unadjusted estimates, while a more precise analysis might be performed if detailed individual data were available, which could allow for an adjusted estimation by age, obesity, hormone replacement therapy, reproductive history and infertility, gynecologic surgery, and environment factors. Lack of information for data analysis may cause serious confounding bias. Finally, gene–gene and gene–environment interactions may have influenced our findings, as ovarian and cervical cancers are mainly caused by genetic and environmental factors. However, these interactions were not tested in the current meta-analysis because of the lack of sufficient data.

In summary, our meta-analysis demonstrated that the XRCC3 18067 C>T polymorphism may be associated with increased risk of cervical and ovarian cancers. Moreover, the XRCC3 18067 C>T polymorphism might be a potential risk factor for cervical cancer among Asians and for ovarian cancer among Caucasians. However, to validate this association and our findings further, large and well-designed epidemiological studies are warranted.

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