REVIEW

Association of XRCC2 rs3218536 Polymorphism with Susceptibility of Breast and Ovarian Cancer: A Systematic Review and Meta-Analysis

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Abstract

Background: Previous studies have investigated the association of X-Ray Repair Cross-Complementing Group 2 (XRCC2) rs3218536 polymorphism with breast and ovarian cancer. However, this association remains conflicting. Therefore, we have performed the current systematic review and meta-analysis to clarify the association between XRCC2 rs3218536 polymorphism with risk of breast and ovarian cancer. **Methods:** We conducted a search in PubMed, Google Scholar and ISI Web of Science to select relevant studies on the association of XRCC2 rs3218536 polymorphism with breast and ovarian cancer susceptibility. We calculated the odds ratios (OR) and 95% confidence intervals (CI) for five genetic contrasts. In addition, a stratified analysis was conducted cancer type, ethnicity and HWE status. **Results:** A total of 17 studies with 5694 cases and 6450 controls for breast cancer and nine case-control studies with 4464 cases and 6353 controls for ovarian cancer were identified for the analysis of the association with XRCC2 rs3218536 polymorphism. The pooled ORs revealed that XRCC2 rs3218536 polymorphism was associated with breast cancer under the heterozygote contrast (AG vs. GG: OR = 0.929, 95% CI = 0.873-0.987, p=0.018) and ovarian cancer under dominant contrast (AA+AG vs. GG: OR = 0.725, 95% CI = 0.537-0.979, p=0.036) in the overall population. The stratified analysis indicated a significant association of XRCC2 rs3218536 polymorphism with breast and ovarian cancer risk among Caucasians. **Conclusion:** Inconsistent with previous meta-analysis, this meta-analysis shows that the XRCC2 rs3218536 polymorphism was associated with breast and ovarian cancer risk in overall population, especially among Caucasians.

Keywords: Breast cancer- ovarian cancer- XRCC2 rs3218536- polymorphism- meta-analysis

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Introduction

Breast cancer is the most frequently diagnosed cancer among women, which contributed to 25 % of all cancer cases in women worldwide (Shiryazdi et al., 2015; Yazdi et al., 2015). A hereditary component accounts for 10-15% of all breast and ovarian cancer cases. It is estimated that 30% of hereditary breast cancer cases are due to mutations in one of the BRCA1 and BRCA2 genes (Forat-Yazdi et al., 2015; Neamatzadeh et al., 2015). Ovarian cancer is the fifth leading cause of cancer deaths occurring in women and leading cause of mortality from gynecologic cancer (Stewart et al., 2013). It is estimated that familial ovarian cancer accounts for 5-15% of the total cases of ovarian cancer (Lynch et al., 2009). It is known that family history is one of the most important risk factors in ovarian cancer development. A possible genetic contribution to both breast and ovarian cancer risk is indicated by the increased incidence of these cancers among women with a family history (National Comprehensive Cancer Network). The mechanism of breast and ovarian carcinogenesis is still not well understood (Yoneda et al., 2012). It has been reported that several potential genes (with low, medium and high penetrance) and combining with environmental factors may be important in the development of these malignancies (Xu et al., 2014; Yoneda et al., 2012).

The X-Ray Repair Cross-Complementing Group 2 (XRCC2) gene encodes a member of the Rad51 family of related proteins that maintains chromosome stability by participating in homologous recombination and repairs DNA damage. The XRCC2 and XRCC3 are two of the members of RAD51-related proteins (Michalska et al.,

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2016; Sobhan et al., 2017). The XRCC2 gene has roles in the homologous recombination repair (HRR) pathway of double-stranded DNA, which repairs chromosomal fragmentation, deletions and translocations (Kuschel et al., 2002). A significant number of single nucleotide polymorphisms (SNPs) have been identified in the XRCC2 gene such as rs3218536 (Arg188His), rs718282, rs3218384, rs3218550, rs3218408, rs2040639 and rs3218499 (Xu et al., 2014; Sarwar et al., 2016). Of these SNPs, XRCC2 rs3218536 polymorphism is caused by A to G transition in exon 3 and results in Arginine (Arg) in substitution of Histidine (His) at codon 188 of the protein. However, it is thought that the XRCC2 rs3218536 polymorphism associated with a lowered risk for breast cancer and epithelial ovarian cancer. To date, several studies have been conducted to evaluate the association of XRCC2 rs3218536 polymorphism with breast and ovarian cancer. However, the conclusions have been conflicting. Therefore, we performed the current meta-analysis to clarify the association between XRCC2 rs3218536 polymorphism with risk of breast and ovarian cancer.

Materials and Methods

Literature and Search Strategy

We have conducted a systematic literature search using the PubMed, Gene, Google scholar, Web of Science and EMBASE database to find studies assessing the association between XRCC2 rs3218536 polymorphism and two breast and ovarian cancer up to January 20, 2017. We sought publication with the following key words: ‘‘breast cancer’’, ‘‘ovarian cancer’’, ‘‘X-Ray Repair Cross Complementing 2’’, ‘‘DNA repair protein XRCC2’’, ‘‘XRCC2’’, ‘‘rs3218536’’, “single nucleotide polymorphism”, “polymorphism”, “SNP”, “mutation”, and “variation”. In addition, we have identified related studies by hand screening of included studies. The search was limited to human studies were published only in English language.

Inclusion Criteria and Data Extraction

The studies included in the current meta-analysis meet the following criteria: (1) evaluates the associations between XRCC2 rs3218536 polymorphism and breast and ovarian cancer risk; (2) used case–control or prospective cohort design; and (3) containing at least genotype frequencies for estimating an odds ratio (OR) with 95% confidence interval (95% CI). In addition, the exclusion criteria were as the follows: (1) not conducted on human subjects, (2) not breast and ovarian cancer research (3) only included patients or healthy subjects, (4) duplicate of previous publications (completely or partially), and (5) above all, have not sufficient data about frequency of genotypes.

Data extraction

For each study, we have extracted carefully (two authors independently) the following data: First author, publication year, country of origin, ethnicity, number of cases and controls, and Hardy–Weinberg Equilibrium (HWE). Any disagreements were discussed and resolved through consensus with a third investigator. In this meta-analysis the subject’s (cases and controls) ethnicities were categorized as Caucasian, Asian, or African.

Statistical analysis

The strength of association was assessed by calculating the odds ratios and 95% confidence intervals and the Z-test was used to evaluate statistical significance with P-values less than 0.01 considered as statistically significant. Pooled ORs were estimated for five genetic contrast including allele (A vs. G), heterozygote (AG vs. GG), homozygote (AA vs. GG), dominant (AA+AG vs. GG) and recessive (AA vs. AG+GG) contrasts. In the current meta-analysis, the heterogeneity between studies was calculated by X2-based Q test and I2. The heterogeneity were considered significant when p value was less than 0.05 for the Q test or I2>25% in I2 statistics. Moreover, a random effects model using the DerSimonian was utilized to calculate the OR and 95% CI for comparisons with moderate to high heterogeneity (P-value > 0.1 and I2 > 25%) (DerSimonian et al., 1986). Otherwise, a fixed-effects model using the Mantel–Haenszel method was used. Sensitivity analysis was performed by sequential omission of individual studies (leave-one-out analysis) for various genetic models in the overall population and for subgroup analysis by ethnicity and HWE status. We have evaluated publication bias graphically using the Begg’s funnel plot and statistically using the method of Egger’s linear regression test (Egger et al., 1997); P<0.05 indicated that the result was statistically significant. We have used comprehensive meta-analysis (CMA) V2.0 software (Biostat, USA) to perform all the statistical analyses. Two-sided P values < 0.05 were considered statistically significant.

Results

Characteristics of the included studies

Based on the established search criteria, articles were retrieved for the association of XRCC2 rs3218536 polymorphism with breast and ovarian cancer susceptibility. Twenty publications (26 studies) met the inclusion criteria, the characteristics of which are showed in Table 1 and 2. Of these 20 publications, 16 publications (17 studies) with 5694 cases and 6450 controls evaluate the association of XRCC2 rs3218536 polymorphism with breast cancer risk. Two out of the 17 studies were published in Asians (Ding et al., 2014; Qureshi et al., 2014) and the others were in Caucasians (Rafii et al., 2002; Kuschel et al., 2002; Han et al., 2004; Webb et al., 2005; Millikan et al., 2005; Garcia-Closas et al., 2006; Brooks et al., 2008; Loizidou et al., 2008; Pooley et al., 2008; Silva et al., 2010; Jakubowska et al., 2010; Makowska et al., 2012; Smolarz et al., 2014; Shadrina et al., 2014). There were 15 studies of Caucasian descendants (USA, UK, Poland, Australia, Portugal, Russia and Cyprus) and 2 studies of East Asian descendants communities (China and Pakistan). In addition, of these 20 publications, 5 publications (9 case-control studies) with 4464 cases and 6353 controls for association between XRCC2 rs3218536 polymorphism and ovarian cancer. The populations came from different

Table 1. Characteristics of Studies Included in the Meta-Analysis of XRCC2 Rs3218536 Polymorphism and Breast Cancer

First author	Country (Ethnicity)	Case/ Control	Cases					Controls					HWE
			Genotype			Allele		Genotype			Allele		
			GG	AG	AA	G	A	GG	AG	AA	G	A	
Rafii et al. 2002	UK (Caucasian)	519/398	431	82	6	944	94	351	45	2	747	49	0.669
Kuschel et al. 2002	UK (Caucasian)	1725/1811	1,476	234	15	3,186	264	1,538	267	6	3,343	279	0.116
Han et al. 2004	USA (Caucasian)	952/1237	811	134	7	1,756	148	1,066	165	6	2297	177	0.887
Webb et al. 2005	Australia (Caucasian)	1447/783	1,251	187	9	2,689	205	675	101	7	1,451	115	0.144
Millikan et al. 2005a	USA (Caucasian)	765/678	744	21	0	1,509	21	653	25	0	1331	25	0.624
Millikan et al. 2005b	USA (Caucasian)	1268/1134	1,084	176	8	2,344	192	982	145	7	2,109	159	0.515
Garcia-Closas et al. 2006	Poland (Caucasian)	1981/2280	1,763	212	6	3,738	224	1,983	281	16	4,247	313	0.085
Brooks et al. 2008	USA (Caucasian)	602/602	515	83	4	1,113	91	519	78	5	1,116	88	0.283
Loizidou et al. 2008	Cyprus (Caucasian)	1108/1177	972	135	1	2,079	137	999	177	34	2,175	245	<0.001
Pooley et al. 2008	UK (Caucasian)	4232/4384	3,590	610	32	7,790	674	3,639	711	34	7,989	779	0.91
Silva et al. 2010	Portugal (Caucasian)	289/548	243	46	0	532	46	445	103	0	993	103	0.015
Jakubowska et al. 2010	Poland (Caucasian)	314/290	272	42	0	586	42	254	36	0	544	36	0.259
Makowska et al. 2012	Poland (Caucasian)	790/798	212	374	204	798	782	202	406	190	810	786	0.615
Ding et al. 2014	China (Asian)	606/633	166	280	160	612	600	184	305	144	673	593	0.413
Smolarz et al. 2014	Poland (Caucasian)	70/70	12	8	50	32	108	18	40	12	76	64	0.205
Shadrina et al. 2014	Russia (Caucasian)	659/656	594	65	0	1253	65	587	67	2	1241	71	0.952
Qureshi et al. 2014	Pakistan (Asian)	156/150	131	20	5	282	30	137	12	1	286	14	0.216

countries, including UK, Denmark, USA, Australia, Egypt and Poland. There were 8 studies (Auranen et al., 2005; Webb et al., 2005; Beesley et al., 2007; Michalska et al., 2016) of Caucasian descendants and 1 study (Mohamed et al., 2013) of African descendant. Genotype distributions in the controls of two studies for breast cancer (Loizidou et al., 2008; Silva et al., 2010) and two studies for ovarian cancer (Mohamed et al., 2013; Michalska et al., 2016) were not in agreement with HWE ($p < 0.05$).

Meta-analysis

Association of XRCC2 rs3218536 polymorphism and breast cancer

The meta-analysis of a possible association between XRCC2 rs3218536 polymorphism and breast cancer is summarized in Tables 3. Based on the total study population, a strong association was found between of XRCC2 rs3218536 polymorphism and breast cancer under the heterozygote contrast (AG vs. GG: OR = 0.929, 95% CI = 0.873-0.987, p=0.018) in the overall population (Figure 2E). Considering the limited number of qualified studies in the Asian and other descendent population, the stratified analyses was only presented for Caucasians. In the subgroup analyses of ethnicity, the meta-analysis results indicated a strong association between the XRCC2 rs3218536 polymorphism and breast cancer susceptibility among Caucasians only under the heterozygote contrast (AG vs. GG: OR = 0.920, 95% CI = 0.861-0.980, p=0.009). Additionally, significant associations between the XRCC2 rs3218536 polymorphism and breast cancer under the recessive contrast (AG vs. GG: OR = 1.635, 95% CI = 1.109-2.413, p=0.013) was found according to the HWE.

Association of XRCC2 rs3218536 polymorphism and ovarian cancer

The meta-analysis of a possible association between the XRCC2 rs3218536 polymorphism and risk of ovarian

Table 2. Characteristics of Studies Included in the Meta-Analysis of XRCC2 Rs3218536 Polymorphism and Ovarian Cancer

First author	Country (Ethnicity)	Case/Control		Cases					Controls					HWE
				Genotype			Allele		Genotype			Allele		
				GG	AG	AA	G	A	GG	AG	AA	G	A	
Auranen et al. 2005a	UK (Caucasian)	729	842	629	98	2	1356	102	704	129	9	1537	147	0.263
Auranen et al. 2005b	Denmark (Caucasian)	944	404	260	54	1	574	56	331	68	5	730	78	0.481
Auranen et al. 2005c	USA (Caucasian)	269	561	238	31	0	507	31	484	75	2	1043	79	0.614
Auranen et al. 2005d	UK (Caucasian)	275	1811	251	23	1	525	25	1538	267	6	3343	279	0.116
Webb et al. 2005a	Australia (Caucasian)	430	950	364	63	3	791	69	802	140	8	1744	156	0.492
Webb et al. 2005b	Australia (Caucasian)	94	168	87	5	2	179	9	150	16	2	316	20	0.052
Beesley et al. 2007	Australia (Caucasian)	923	817	799	117	7	1715	131	696	115	7	1507	129	0.356
Mohamed et al. 2013	Egypt (African)	100	100	6	58	36	70	130	16	60	24	92	108	0.037
Michalska et al. 2016	Poland (Caucasian)	700	700	120	80	500	320	1080	180	400	120	760	640	0.001

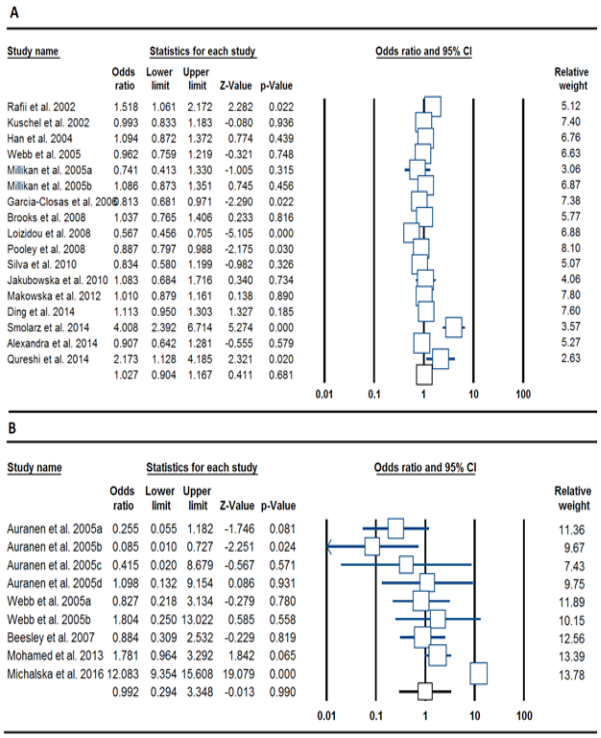

Figure 1. Forest Plot For Association Of XRCC2 Rs3218536 Polymorphism With Breast And Ovarian Cancer Susceptibility. A: breast cancer (allele contrast: A vs. G), B: ovarian cancer (Recessive contrast: AA vs. AG+GG).

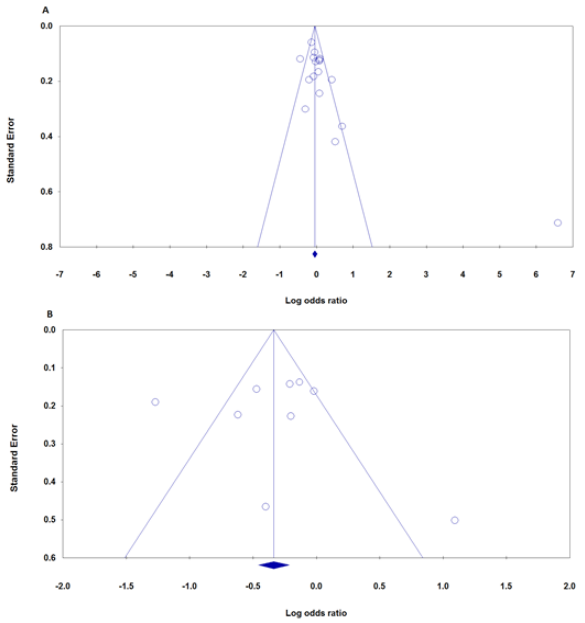

Figure 2. Begg's Funnel Plots for Association of XRCC2 Rs3218536 Polymorphism with Breast and Ovarian Cancer for Publication Bias Test. Each Point Represents A Separate Study For The Indicated Association. A: breast cancer (dominant contrast: AA+AG vs. GG), B: ovarian cancer (dominant contrast: AA+AG vs. GG).

cancer is summarized in Table 4. The pooled analysis for XRCC2 rs3218536 polymorphism and risk of ovarian cancer involved 5 publications (9 case-control studies) with 4,464 cases and 6,353 controls. The pooled ORs revealed that XRCC2 rs3218536 polymorphism was associated with risk of ovarian cancer only under dominant genetic model (AA+AG vs. GG: OR = 0.725, 95% CI = 0.537-0.979, p=0.036) in the overall (Table 4). Stratification analysis by ethnicity showed significant association between XRCC2 rs3218536 polymorphism and ovarian cancer in Caucasian under heterozygote contrast (AG vs. GG: OR = 0.710, 95% CI = 0.517-0.975, p=0.034) and dominant contrast (AA+AG vs. GG: OR = 0.666, 95% CI = 0.502-0.884, p=0.005, Table 2, Figure 2a). And we also observed association between this polymorphism and ovarian cancer according to the HWE under allele contrast (A vs. G: OR = 0.685, 95% CI =

Table 3. Meta-Analysis of the Association of XRCC2 Rs3218536 Polymorphism and Breast Cancer

	Genetic model	Type of model	Heterogeneity		Odds ratio		Publication Bias		
			I^2 (%)	P_H	OR	95% CI	P_{OR}	P_{Beggs}	P_{Eggers}
Overall									
	A vs. G	Random	79.49	<0.001	1.027	0.904-1.167	0.681	0.387	0.142
	AG vs. GG	Fixed	30.49	0.113	0.929	0.873-0.987	0.018	0.592	0.412
	AA vs. GG	Random	66.5	<0.001	1.125	0.770-1.643	0.542	1	0.868
	AA+AG vs. GG	Random	86.39	<0.001	1.118	0.923-1.353	0.255	0.108	0.016
	AA vs. AG+GG	Random	78.06	<0.001	1.443	0.945-2.203	0.089	0.742	0.695
Caucasian									
	A vs. G	Random	79.49	<0.001	0.998	0.872-1.143	0.979	0.552	0.216
	AG vs. GG	Fixed	29.28	0.137	0.92	0.861-0.980	0.009	1	0.779
	AA vs. GG	Random	69.57	<0.001	1.038	0.647-1.665	0.878	0.631	0.76
	AA+AG vs. GG	Random	87.52	<0.001	1.098	0.892-1.352	0.377	0.165	0.033
	AA vs. AG+GG	Random	80.92	<0.001	1.354	0.774-2.371	0.289	0.45	0.856
HWE									
	A vs. G	Random	73.54	<0.001	1.077	0.956-1.213	0.225	0.165	0.033
	AG vs. GG	Fixed	31.58	0.116	0.943	0.885-1.006	0.074	0.428	0.312
	AA vs. GG	Random	54.02	0.01	1.232	0.892-1.701	0.206	0.582	0.555
	AA+AG vs. GG	Random	86.57	<0.001	1.196	0.973-1.471	0.089	0.047	0.009
	AA vs. AG+GG	Random	73.75	<0.001	1.635	1.109-2.413	0.013	0.854	0.28

Table 4. Meta-Analysis of the Association of XRCC2 Rs3218536 Polymorphism and Ovarian Cancer

	Genetic model	Type of model	Heterogeneity		Odds ratio			Publication Bias	
			I^2 (%)	P_H	OR	95% CI	POR	P_{Beggs}	P_{Eggers}
Overall									
	A vs. G	Random	97.33	<0.001	0.922	0.491-1.732	0.801	1	0.046
	AG vs. GG	Random	82.27	<0.001	0.767	0.555-1.059	0.107	0.916	0.798
	AA vs. GG	Random	82.73	<0.001	1.132	0.419-3.059	0.808	0.465	0.002
	AA+AG vs. GG	Random	80.96	<0.001	0.725	0.537-0.979	0.036	1	0.825
	AA vs. AG+GG	Random	92.22	<0.001	0.992	0.294-3.348	0.99	0.916	0.002
Caucasian									
	A vs. G	Random	97.66	<0.001	0.862	0.429-1.730	0.675	1	0.045
	AG vs. GG	Random	82.15	<0.001	0.71	0.517-0.975	0.034	0.386	0.685
	AA vs. GG	Random	84.89	<0.001	0.906	0.277-2.962	0.87	0.901	0.002
	AA+AG vs. GG	Random	79.27	<0.001	0.666	0.502-0.884	0.005	0.386	0.5
	AA vs. AG+GG	Random	91.63	<0.001	0.873	0.189-4.034	0.862	0.901	0.001
HWE									
	A vs. G	Random	82.79	<0.001	0.685	0.496-0.947	0.022	0.367	0.569
	AG vs. GG	Fixed	12.14	0.337	0.855	0.745-0.981	0.026	0.229	0.241
	AA vs. GG	Fixed	0	0.629	0.656	0.357-1.207	0.176	0.548	0.647
	AA+AG vs. GG	Random	81.89	<0.001	0.672	0.481-0.938	0.02	0.367	0.507
	AA vs. AG+GG	Fixed	10.04	0.352	0.627	0.341-1.154	0.134	0.367	0.519

0.496-0.947, p=0.034), heterozygote contrast (AG vs. GG: OR = 0.710, 95% CI = 0.517-0.975, p=0.034) and dominant contrast (AA+AG vs. GG: OR = 0.666, 95% CI = 0.502-0.884, p=0.005, Table 2, Figure 2a).

Test of heterogeneity

For XRCC2 rs3218536 polymorphism and breast cancer, when the data pooled a significant heterogeneity observed in allele (I^2=79.49%, P_h=<0.001), homozygote (I^2=66.50%, P_h=0.042), dominant (I^2=86.39%, P_h=<0.001) and recessive (I^2=78.06%, P_h=<0.001) contrasts (Table 3). After subjects stratified by ethnicity and HWE status, the heterogeneity not disappeared obviously (Table 3). For XRCC2 rs3218536 polymorphism and ovarian cancer, when the data pooled a significant heterogeneity observed in allele (I^2=97.33%, Ph=<0.001), heterozygote (I^2=82.27%, P_h=<0.001), homozygote (I^2=82.73%, P_h=<0.001), dominant (I^2=80.96%, P_h=<0.001) and recessive (I^2=92.22%, P_h=<0.001) contrasts (Table 4). After subjects stratified by ethnicity and HWE status, the heterogeneity not disappeared obviously Caucasian. However, by HWE status the heterogeneity disappeared obviously in heterozygote (I^2=12.14%, P_h=0.337), homozygote (I^2=0.00%, P_h=0.629) and recessive (I^2=10.04%, P_h=0.352) contrasts (Table 4).

Publication bias

Both Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. The shapes of the funnel plots revealed no obvious asymmetry for association of XRCC2 rs3218536 polymorphism with breast cancer in the overall analyses (Figure 2A). However, the results of Egger's regression test provided sufficient evidence for publication bias in dominant contrast ($P_{Begg's}$=0.108, P_{Eggers}=0.016), suggesting that there was obvious publication bias in the genetic contrast. In addition, the publication bias has seen in the meta-analysis XRCC2 rs3218536 polymorphism in Caucasians (dominant contrast: $P_{Begg's}$=0.108, P_{Eggers}=0.016) and by HWE status (allele contrast: $P_{Begg's}$=0.165, P_{Eggers}=0.033; dominant contrast: $P_{Begg's}$=0.047, P_{Eggers}=0.009). Moreover, the results of Egger's regression test provided evidence of publication bias for association of XRCC2 rs3218536 polymorphism with ovarian cancer in allele ($P_{Begg's}$=1.000, P_{Eggers}=0.033), homozygote ($P_{Begg's}$=0.465, P_{Eggers}=0.002) and recessive contrasts ($P_{Begg's}$=0.916, P_{Eggers}=0.002) in overall analysis. In addition, the publication bias has seen in the meta-analysis XRCC2 rs3218536 polymorphism and ovarian cancer in Caucasians (allele: $P_{Begg's}$=1.000, P_{Eggers}=0.045; homozygote: $P_{Begg's}$=0.901, P_{Eggers}=0.002 and recessive contrasts: $P_{Begg's}$=0.901, P_{Eggers}=0.001).

Discussion

In this meta-analysis, we have evaluated the associations of XRCC2 rs3218536 polymorphism with breast and ovarian cancer susceptibility. To the best knowledge, our data suggested a significant association between the XRCC2 rs3218536 polymorphism and increased risk for breast cancer under heterozygote contrast. Additionally, the dominant contrast for the XRCC2 rs3218536 polymorphism indicated increased risk for OC.

Several meta-analyses have estimated the association between XRCC2 rs3218536 polymorphism and breast cancer risk (Yu et al., 2010; He et al., 2014; Kong et al., 2015; Zhang et al., 2016). He et al., (2014) in a meta-analysis of 45 case-control studies from 26

publications with 30868 cases and 38656 controls have evaluated XRCC2 rs3218536 polymorphism association with breast and ovarian cancer risk. According to their results, this polymorphism might be had different roles in development breast and ovarian cancer. Their findings not confer the association between XRCC2 rs3218536 polymorphism and breast cancer. While, they have showed this polymorphism might contribute to decreased ovarian cancer susceptibility. Actually, their findings suggested a protective role of the XRCC2 rs3218536 polymorphism in formation of ovarian cancer. Similarly to the He et al., (2014) results, in another meta-analysis of 16 studies involving 18,341 cases and 19,028 controls, Yu et al., (2010) not found evidence of a significant association between XRCC2 rs3218536 and breast cancer susceptibility in all five genetic contrasts. Also, in the recent meta-analysis by Kong et al., (2015) they have reported the same results to the two meta-analyses. However, inconsistent to the previous meta-analyses, we have found that the XRCC2 rs3218536 polymorphism positively confer the risk of development both breast cancer in the overall population and Caucasians. Interestingly, Zhang et al., (2016) in a meta-analysis of 15 case-control studies with 4,757 cases and 8,431 controls not found a significant association between XRCC2 rs3218536 polymorphism and ovarian cancer risk. In addition, in the stratified analyses by HWE status they have seen that rs3218536 polymorphism was associated with the decreased risk of ovarian cancer. However, in the current meta-analysis, we have found that this polymorphism significantly associated with risk of ovarian cancer in overall and by subgroup analysis in Caucasians and HWE status.

Many factors may contribute to the strong heterogeneity among overall analysis (Mehdinejad et al., 2017; Jafari Nedooshan et al., 2017). In the meta-analysis of XRCC2 rs3218536 polymorphism and breast cancer, the heterogeneity between studies was not significantly reduced in the subgroup analysis by the ethnicity and HWE, which indicating that the effect of XRCC2 rs3218536 in development breast cancer may not be modified by ethnicity and HWE. However, the heterogeneity between studies in the meta-analysis of XRCC2 rs3218536 polymorphism and ovarian cancer was significantly reduced by HWE status.

To the best knowledge, current meta-analysis is by far the most comprehensive and convicting on the association of the XRCC2 rs3218536 polymorphism with breast and ovarian cancer susceptibility to date. This meta-analysis has two strengths compared with previous meta-analysis as follow; first, in this meta-analysis, relatively all eligible studies with large sample sizes were included, which would decrease the risk of random error. Second, the quality of eligible publications included in meta-analysis was more satisfactory and met mostly the inclusion criteria. However, some limitations should be taken into consideration when explaining the results as follow: first, most of the studies included in the meta-analysis were performed in the Caucasian population, the limited number was from Asians (only two publications) and there was no relevant study from Africans. However, most subjects were from Caucasian, but limited to the UK, Poland and USA. Thus, to obtain more precise meta-analysis of XRCC2 rs3218536 polymorphism on breast and ovarian cancer susceptibility, additional studies with larger sample size and involving different ethnicities especially Asians and African are required. Second, because we have included only relevant published articles and written in English language in the meta-analysis, publication bias may have occurred, even though it was not found by making use of statistical tests. Third, the overall outcomes were based on individual unadjusted ORs without adjustment for other risk factors such as age, histological subtypes, clinical stages, menstrual status, environmental and other confounding lifestyle factors. Finally, this meta-analysis could not address the gene-gene and gene-environmental interactions in the association between XRCC2 rs3218536 polymorphism and risk of breast and ovarian cancer. Therefore, future studies that include detailed information on exposures to environmental factors to assess the possible gene-gene and gene-environment interactions in the association between XRCC2 rs3218536 polymorphism and risk of breast and ovarian cancer are required.

In summary, this systematic review and meta-analysis shows that the XRCC2 rs3218536 polymorphism was associated with breast and ovarian cancer susceptibility in overall population and Caucasians. According to the limitations listed above, Asian and African descendent studies should be similarly performed.

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