REVIEW

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Association between *XRCC2* Arg188His Polymorphism and Breast Cancer Susceptibility: A Systematic Review and Meta-Analysis

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Abstract

Breast cancer is one of the most common cancers in the world and leading cause of cancer-related death among women. Several studies indicated that Arg188His (rs3218536) polymorphism of X-ray repair cross-complementing 2 (*XRCC2*) may be associated with breast cancer risk. However, this association remains ambiguous. Thus, we performed a meta-analysis to provide more precise conclusion on this issue. A comprehensive search in PubMed, Google Scholar and ISI Web of Science was performed to select all relevant studies. Odds ratios (OR) with corresponding 95% confidence intervals (CI) were applied to assess the strength of the relationships. A total of 17 studies with 5694 breast cancer cases and 6450 healthy subjects were identified. The pooled data revealed that *XRCC2* Arg188His polymorphism was marginally with susceptibility to breast cancer globally under the heterozygote contrast (OR = 0.929, 95% CI = 0.873-0.987, p=0.018). Moreover, subgroup analysis by ethnicity revealed that this polymorphism was associated with breast cancer risk among Caucasians. On the whole, the present study demonstrates that the *XRCC2* Arg188His polymorphism may contribute to an increased risk of breast cancer.

Keywords: Breast Cancer- *XRCC2*- Arg188His- Polymorphism- Meta-Analysis

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Introduction

Breast cancer is the most common malignancy in women in Europe and the United States and second leading cause of cancer-related death [1-3]. Approximately 320,000 new cases of breast cancer were diagnosed in the United States in 2018, resulting in 41,000 deaths. Moreover, World Health Organization (WHO, 2018) reported that, breast cancer is the most common cancer diagnosed among women in 154 out of 185 countries of the world and it is the leading cause of cancer-related mortality in over 100 countries [4, 5]. Due to the multiformity of the clinical behaviors, it is difficult to predict and diagnosed only with clinical information. Momenimovahed et al., in a review mentioned a numerous risk factors such as demographic factors (gender, age, blood group), reproductive factors (age of menarche, age of menopause, full-term pregnancy, abortion, ovulatory menstrual cycle, pregnancy characteristics), hormonal (hormonal contraceptive methods, ovulation-stimulating drugs, postmenopausal hormone therapy), hereditary (genetic factors and positive family history of breast cancer),breast related (lesser lactation duration, more breast density, benign breast disorder), lifestyle (obesity, alcohol consumption, smoking, coffee, diet, more physical activity, Vitamin D, duration of sleep), which can increase or decrease the possibility of developing breast cancer [6-8]. According to the estimates of the fraction of cases

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of breast cancer, approximate 47% of breast cancer cases and 41% of the pathological in the total USA population can be ascribed to well-established risk factors [9, 10].

The unambiguous cause of carcinogenesis has not yet been established, but several risk factors conducive to the development of breast cancer are known [11, 12]. Genome studies of the breast cancer involve a great range of the genome pieces [13]. According to a recent study about the heritability of the breast cancer, the best predictive breast cancer tests incorporating multiple SNPs and family history have an area under the curve (AUC) in the range 0.7 to 0.8. *BRCA1* and *BRCA2* mutations are inherited in an autosomal dominant fashion [14, 15]. Germline mutations in *BRCA1* have been identified in 15-20% of women with a family history of breast cancer and 60-80% of women with a family history of both breast and ovarian cancer [16-18]. Moreover, genome-wide association studies (GWAS) have identified over 80 loci significantly associated with sporadic breast cancer, which these variants explain only 16 % of breast cancer heritability [19, 10].

The X-ray repair cross-complementing 2 (*XRCC2*) gene, located at 7q36.1, is a member of the RecA/Rad51-related protein family that participates in homologous recombination repair (HRR) to maintain chromosome stability and repair DNA damage [13, 20-23]. Thus, *XRCC2* is a functional candidate for involvement in cancer progression [24-26]. Common variants within *XRCC2*, including Arg188His polymorphism, have been identified as potential cancer susceptibility loci in recent studies, although association results are controversial [27, 28]. The non-synonymous variation (rs3218536) caused due to c.563G>A substitution in exon 3 of *XRCC2* gene results in substitution of Arg to His amino acid at codon 188. This polymorphism has been proposed associated with an increased risk of breast cancer [29]. A number of studies investigated the relationship between *XRCC2* rs3218536 polymorphism and breast cancer susceptibility, but with conflicting results. Thus, we conducted a comprehensive meta-analysis to explore the possible association between *XRCC2* rs3218536 polymorphisms and risk of breast cancer.

Materials and Methods

Search Strategy

The present meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. An elaborate search in the PubMed/MEDLINE, Google Scholar, EMBASE, Cochrane Library database, SciELO, Springer Link, African Journals Online, Academic Search, Bielefeld Academic Search Engine, BioOne, Circumpolar Health Bibliographic Database (CHBD), Cochrane Library, Current Contents, DeepDyve , MedRxiv, Europe PubMed Central (Europe PMC), Indian Citation Index (ICI) , Technology Journal database and Egyptian Knowledge Bank (EKB) Chinese Biomedical Database (CBD), China Biology Medicine disc, China National Knowledge Infrastructure (CNKI), Chinese literature (Wan Fang) and China Science databases was carried out for studies that examined the association of *XRCC2* Arg188His polymorphism with susceptibility to breast cancer up to January 2023. Moreover, a manually screened reference of relevant studies to identify additional studies was carried out by two authors. The following medical subject headings (MeSH) terms and keywords were applied to identify the publications: (''Breast'' OR ''Tumor'' OR ''Cancer'' OR ''Neoplasm'') AND (''X-Ray Repair Cross Complementing 2'' OR ''DNA repair protein *XRCC2*'' OR ''*XRCC2*'' OR ''rs3218536'' OR ''Arg188His'' OR ''R188H'') AND (''Gene'' OR ''Genotype'' OR ''Allele'' OR ''Polymorphism'' OR ''Single Nucleotide Polymorphisms'' OR ''SNPs'' OR ''Variant'' OR ''Variation'' OR ''Single Nucleotide Variations'' OR ''Mutation''). The search was limited to English language articles. In addition, studies were identified by a manual search of references from the original studies. Articles were screened and assessed by two independent authors on the basis of a standard protocol, and any discrepancies were resolved by discussion until a consensus was reached.

Inclusion Criteria

The inclusion criteria for these studies were as follows: 1) studies examined the association of the *XRCC2* Arg188His polymorphism with breast cancer risk; 2) studies with case-control or cohort design published in English; 3) studies reported detailed data for estimation of odds ratio (OR) and 95% confidence interval (CI), as well as available allele genotype frequencies for cases and controls. The exclusion criteria were as follows: 1) Studies did not describe the association of *XRCC2* Arg188His polymorphism with breast cancer risk; 2) studies focusing on animals or in vitro; 3) studies that did not provide sufficient data for pooling data; 4) case only studies or no controls; 5) linkage studies and family based studies (twins and sibling); 6) case reports, abstracts, comments, conference abstracts, editorials, reviews, meta-analysis; and 7) duplicated studies or data. After deliberate searching, we reviewed all papers in accordance with the criteria defined above for further analysis.

Data Extraction

Two authors extracted data independently and in duplicate, and the data was verified by third author. The data was compared, and any disagreement was discussed and resolved with consensus. The following data was extracted from each studies: first author name, year of publication, ethnicity (Asian, Caucasian, African and mixed populations), country of origin, genotyping methods, number of cases and controls for each genotype, frequencies of genotypes in cases and controls, minor allele frequency (MAF) in controls, and Hardy-Weinberg equilibrium (HWE) in controls. If selected articles did not reported necessary data the corresponding authors was contacted by email to request the missing data. Minor allele frequencies and Hardy-Weinberg equilibrium in control groups were calculated by using excel-based Court lab-HW calculator software.

Statistical Analysis

The strength of the association of *XRCC2* Arg188His

(rs3218536) polymorphism with susceptibility to breast cancer was examined by odd ratios (ORs) with 95% confidence intervals (CIs). Z-test was carried out to evaluate the statistical significance of pooled ORs. We used five genetic models, i.e., allele (A vs. G), homozygote (AA vs. GG), heterozygote (AG vs. GG), dominant (AA+AG vs. GG) and recessive (AA vs. AG+GG) to evaluate the association of *XRCC2* Arg188His polymorphism with susceptibility to breast cancer. The heterogeneity between studies was assessed with the chi-squared based Q-test. A significant p value (<0.10) was used to indicate heterogeneity among studies. Moreover, the I^2 statistic was applied to quantify the proportion of the total heterogeneity were used (I^2<25 indicates low heterogeneity, 25% ≤ I^2≤50% indicates moderate heterogeneity, and I^2>50% indicates large heterogeneity). When P<0.10 or I^2>50%, the random-effects model (the DerSimonian-Laird method) was utilized to pool the data. Otherwise, the fixed-effects model (the Mantel-Haenszel method) was used [30-33]. For each study, the distribution of genotypes in controls was calculated for departure from HWE to assess the study quality of genotype data in healthy subjects, in which P<0.05 was considered statistically significant. Stratified analysis by ethnicity was performed to identify the specific effects of heterogeneity. Sensitivity analysis by sequentially omitting the single studies and recounting the pooled ORs and 95% CIs utilized to confirm the stability of our data [34-38]. Moreover, Sensitivity analysis was carried out by excluding those studies deviated from HWE for each polymorphism. The funnel plot was utilized to test the publication bias and Egger's test (linear regression analysis) was used to check the symmetry of funnel plots. An asymmetric plot and the P value of Egger's test or Begg's test less than 0.05 were considered as significant publication bias [11, 39, 40]. The statistical analysis for the current meta-analysis study was performed by using the comprehensive meta-analysis (CMA) version 2.20 software (Biostat, USA). All P-values in the meta-analysis were two-sided, and statistical significance was considered when the P-value was less than 0.05.

Results

Characteristics of the included studies

As shown in Figure 1, our initial search yielded 731 studies, with duplicate studies removed resulting in 419 studies remaining. Among them, 139 studies were excluded based on titles and abstracts. Following the inclusion exclusion criteria 208 studies were excluded. Finally, a total of 17 case-control studies in 16 publications [41-55] with 5694 cases and 6450 controls evaluate the association of *XRCC2* Arg188His polymorphism with breast cancer risk. In terms of ethnicity, 16 studies were performed among Caucasians, ten studies among Asians, and eight studies were conducted among mixed populations. Three genotyping methods including TaqMan, PCR-RFLP, and Ligase Detection Reaction were used to genotype the *XRCC2* Arg188His polymorphism. Genotype distributions in the controls of two studies for breast cancer were not in agreement with HWE (p < 0.05).

Overall and Subgroup Analyses

The pooled association of *XRCC2* Arg188His polymorphism with breast cancer susceptibility is summarized in Table 1. Seventeen case-control studies with 5694 cases and 6450 controls f *XRCC2* Arg188His polymorphism were analyzed. Our pooled data revealed that there was no a significant between *XRCC2* Arg188His polymorphism and breast cancer risk under four genetic models, i.e., allele, homozygote, heterozygote, and dominant. However, there was a significant association between this polymorphism and breast cancer susceptibility under the heterozygote model (AG vs. GG: OR = 0.929, 95% CI = 0.873-0.987, p=0.018) (Figure 2). Stratified analysis by ethnicity revealed that the polymorphism was significantly associated with breast cancer among Caucasians women under the heterozygote contrast (AG vs. GG: OR = 0.920, 95% CI = 0.861-0.980, p=0.009) (Table 2). Considering the limited number of studies among Asian and other descendent population, the stratified analyses was only presented for Caucasians. Moreover, significant association was found positive association after removing HWE violation studies under the recessive contrast (AG vs. GG: OR = 1.635, 95% CI = 1.109-2.413, p=0.013).

Sensitivity analysis and test of heterogeneity

Sensitivity analysis was conducted to estimate the influence of some individual study on pooled results by calculating the ORs before and after exclusion of a single article from meta-analysis in turn. No outlying study was observed to significantly change the pooled ORs after it was removed. There was a significant heterogeneity was observed *XRCC2* Arg188His polymorphism under four genetic models, i.e., 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) in our meta-analysis (Table 2). Therefore, a meta-regression analysis was carried out to observe the source of heterogeneity in the general variables. However, our results showed that the ethnicity and HWE status were not all associated with the large heterogeneity

Publication bias

The Egger's test and Begg's funnel plot were used to assess the publication bias of the studies involved in this meta-analysis. The results showed that there was statistically significant evidence of publication bias under dominant genetic model ($P_{Begg's}$=0.108, P_{Eggers}=0.016, Figure 3 and 4). Therefore, we used the Duval and Tweedie non-parametric ''trim and fill'' method to the publication bias. The results showed that the current meta-analysis with and without ''trim and fill'' did not draw different results, indicating that our results were statistically reliable.

Discussion

Although there have been tremendous advances in elucidating genetic risk factors underlying both familial and sporadic breast cancer, much of the genetic contribution to breast cancer etiology remains unknown

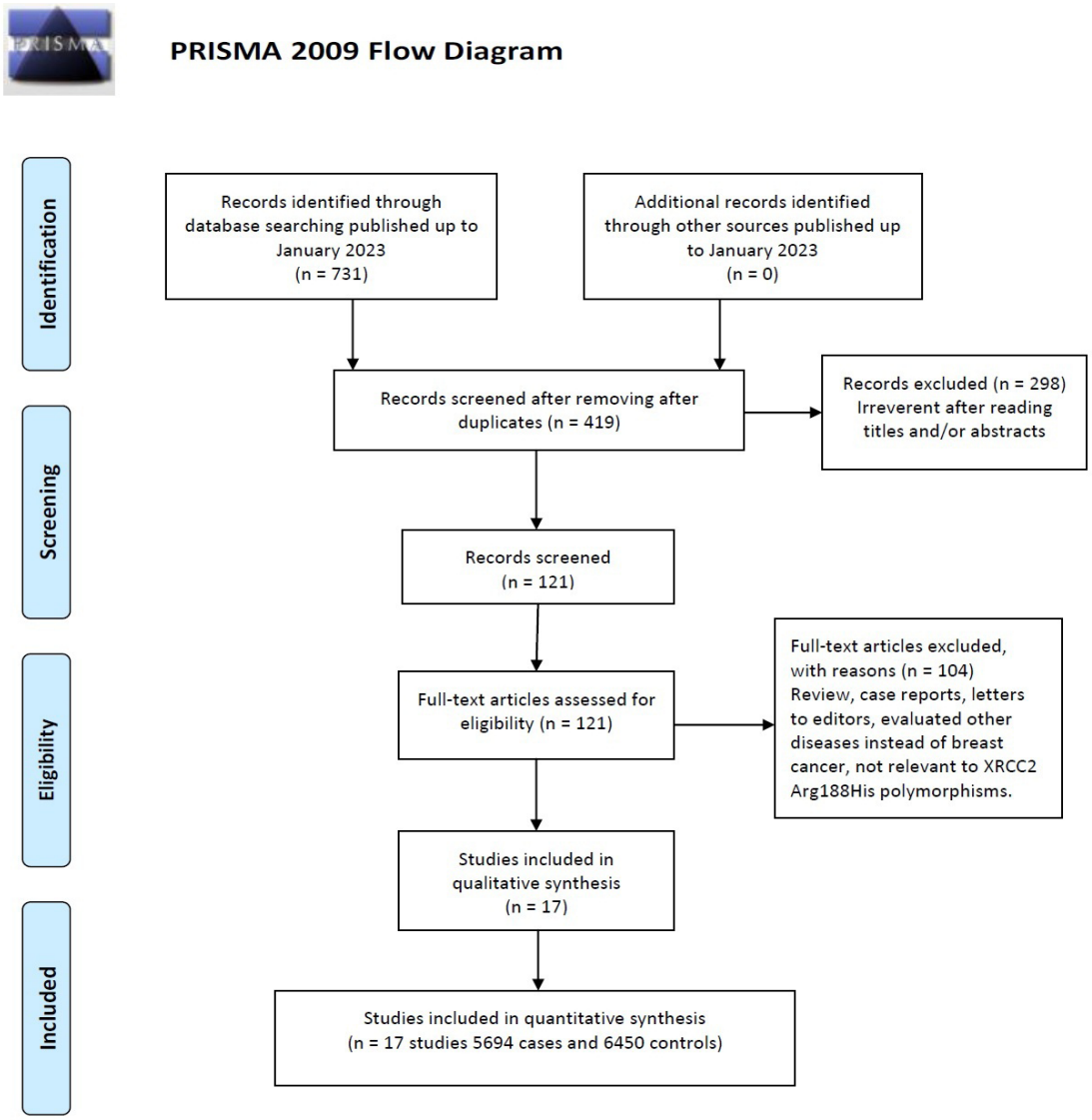

Figure 1. Flow Diagram of Selecting Eligible Studies for the Meta-Analysis

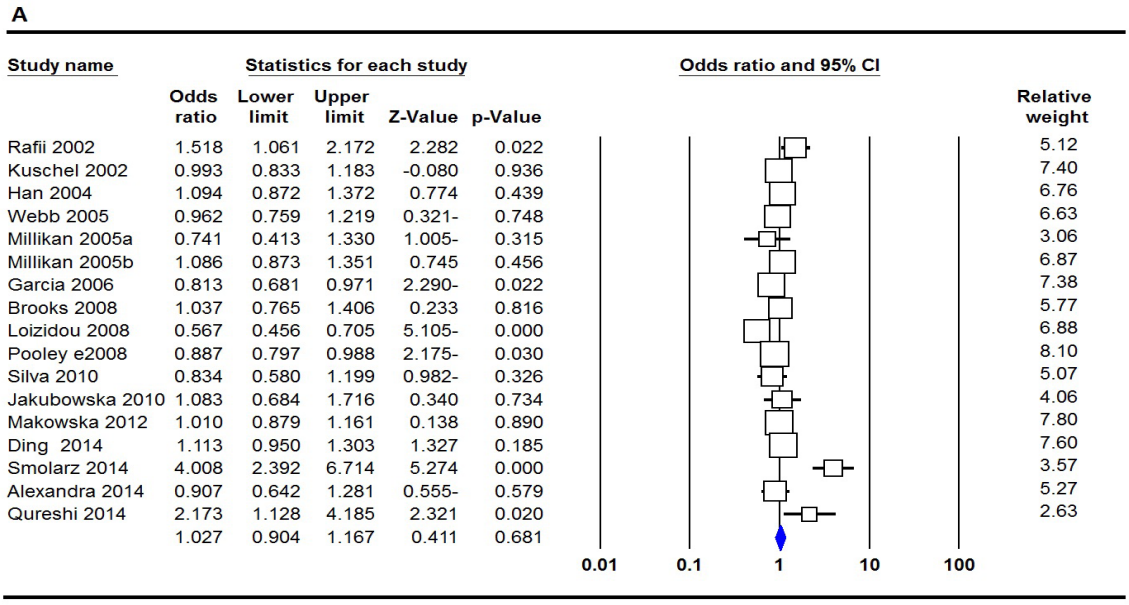

Figure 2. Forest Plots for Association of X *XRCC2* Arg188His (rs3218536) Polymorphism with Susceptibility to Breast Cancer. A) Allele (A vs. G)

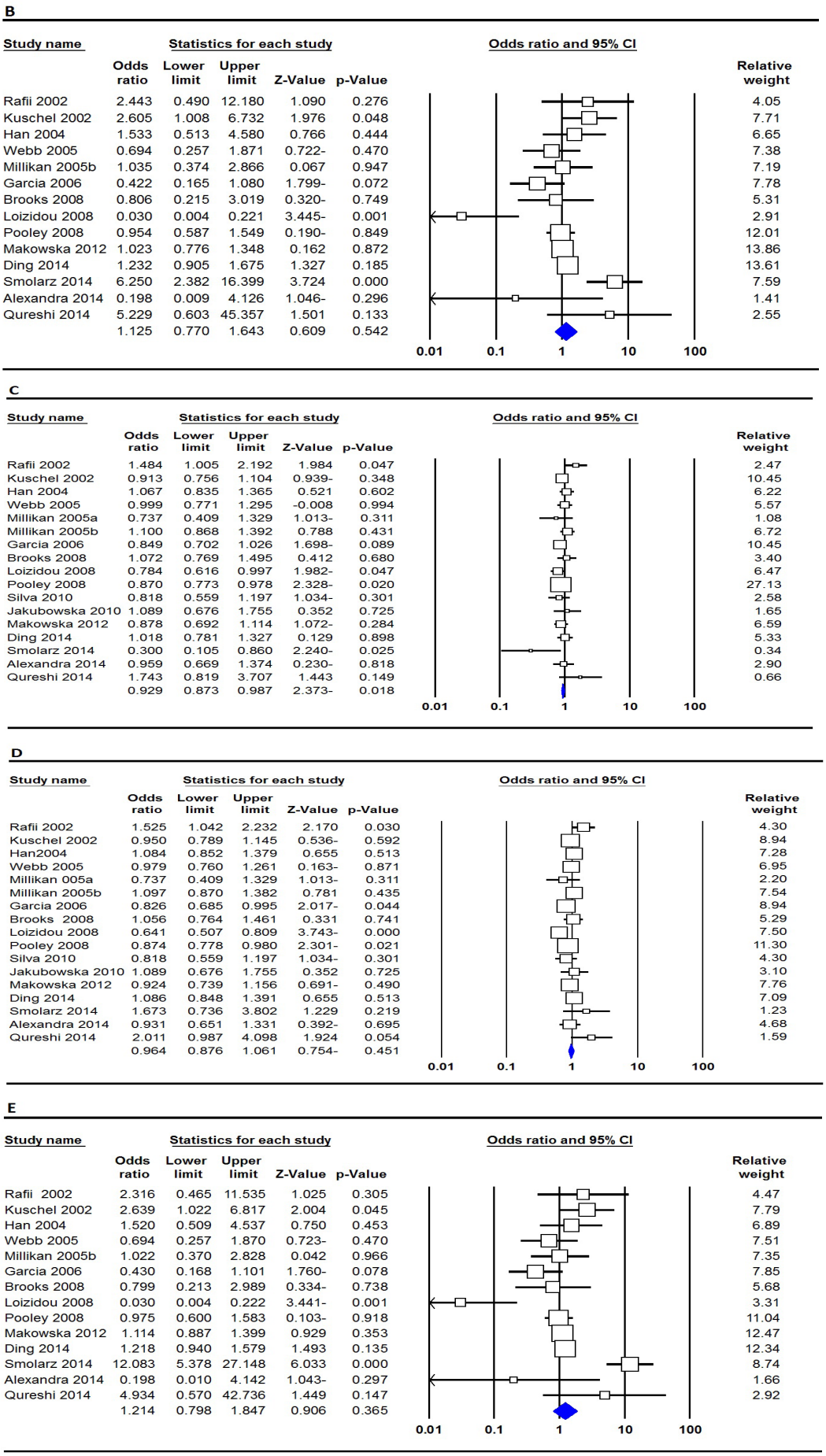

Figure 2. Forest Plots for Association of X XRCC2 Arg188His (rs3218536) Polymorphism with Susceptibility to Breast Cancer. B) homozygote (AA vs. GG); C) heterozygote (AG vs. GG); D) dominant (AA+AG vs. GG); E) and recessive (AA vs. AG+GG).

Table 1. Characteristics of Studies Included in the Meta-Analysis of *XRCC2* Arg188His Polymorphism and Breast Cancer

First author	Country (Ethnicity)	Source of Controls	Genotyping methods	Case/Control	Cases					Controls					HWE	MAF
					Genotype			Allele		Genotype			Allele			
					GG	AG	AA	G	A	GG	AG	AA	G	A		
Rafii 2002	UK(Caucasian)	HB	TaqMan	519/398	431	82	6	944	94	351	45	2	747	49	0.669	0.062
Kuschel 2002	UK(Caucasian)	PB	TaqMan	1725/1811	1476	234	15	3186	264	1538	267	6	3343	279	0.116	0.077
Han 2004	USA(Caucasian)	PB	TaqMan	952/1237	811	134	7	1756	148	1066	165	6	2297	177	0.887	0.072
Webb 2005	Australia(Caucasian)	PB	TaqMan	1447/783	1251	187	9	2689	205	675	101	7	1451	115	0.144	0.073
Millikan 2005a	USA(Caucasian)	PB	TaqMan	765/678	744	21	0	1509	21	653	25	0	1331	25	0.624	0.018
Millikan 2005b	USA(Caucasian)	HB	TaqMan	1268/1134	1084	176	8	2344	192	982	145	7	2109	159	0.515	0.07
Garcia-Closas 2006	Poland(Caucasian)	PB	NA	1981/2280	1763	212	6	3738	224	1983	281	16	4247	313	0.085	0.069
Brooks 2008	USA(Caucasian)	NA	PCR-RFLP	602/602	515	83	4	1113	91	519	78	5	1116	88	0.283	0.073
Loizidou 2008	Cyprus(Caucasian)	PB	PCR-RFLP	1108/1177	972	135	1	2079	137	999	177	34	2175	245	<0.001	0.101
Pooley 2008	UK(Caucasian)	PB	TaqMan	4232/4384	3590	610	32	7790	674	3639	711	34	7989	779	0.91	0.089
Silva 2010	Portugal(Caucasian)	HB	TaqMan	289/548	243	46	0	532	46	445	103	0	993	103	0.015	0.094
Jakubowska 2010	Poland (Caucasian)	NA	PCR-RFLP	314/290	272	42	0	586	42	254	36	0	544	36	0.259	0.062
Makowska 2012	Poland(Caucasian)	NA	PCR-RFLP	790/798	212	374	204	798	782	202	406	190	810	786	0.615	0.492
Ding 2014	China(Asian)	PB	LDR	606/633	166	280	160	612	600	184	305	144	673	593	0.413	0.468
Smolarz 2014	Poland(Caucasian)	PB	PCR-RFLP	70/70	12	8	50	32	108	18	40	12	76	64	0.205	0.457
Shadrina 2014	Russia(Caucasian)	HB	PCR-RFLP	659/656	594	65	0	1253	65	587	67	2	1241	71	0.952	0.054
Qureshi 2014	Pakistan (Asian)	PB	PCR-RFLP	156/150	131	20	5	282	30	137	12	1	286	14	0.216	0.047

HB, Hospital based; PB, Population based; PCR-RFLP, Polymerase chain reaction-restriction fragment length polymorphism; LDR: Ligase Detection Reaction HWE, Hardy-Weinberg equilibrium; MAF: minor allele frequency.

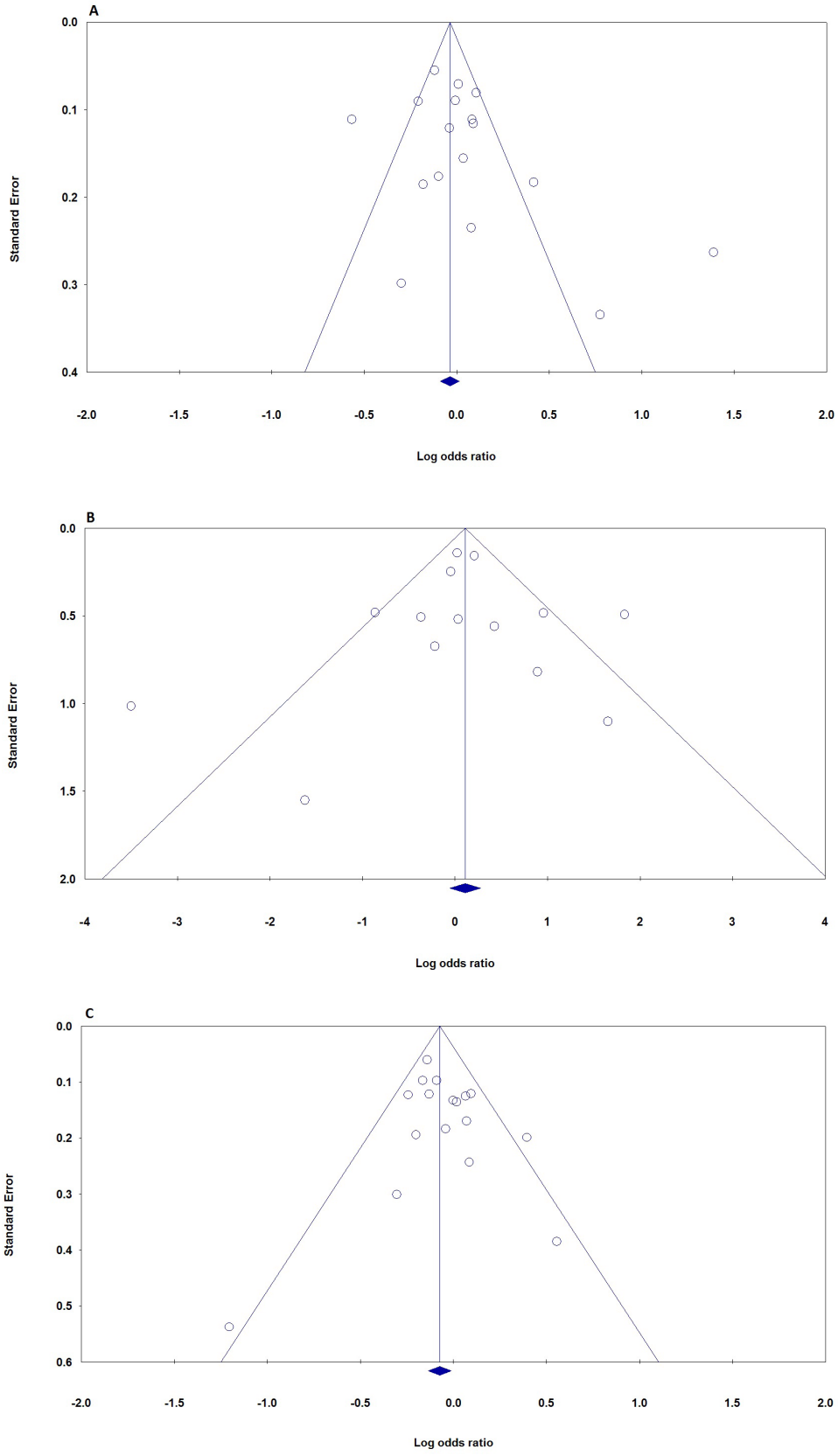

Figure 3. Begg's Funnel Plot of Publication Bias Test for association of X *XRCC2* Arg188His (rs3218536) Polymorphism with Susceptibility to Breast Cancer. A) Allele (A vs. G); B) homozygote (AA vs. GG); C) heterozygote (AG vs. GG)

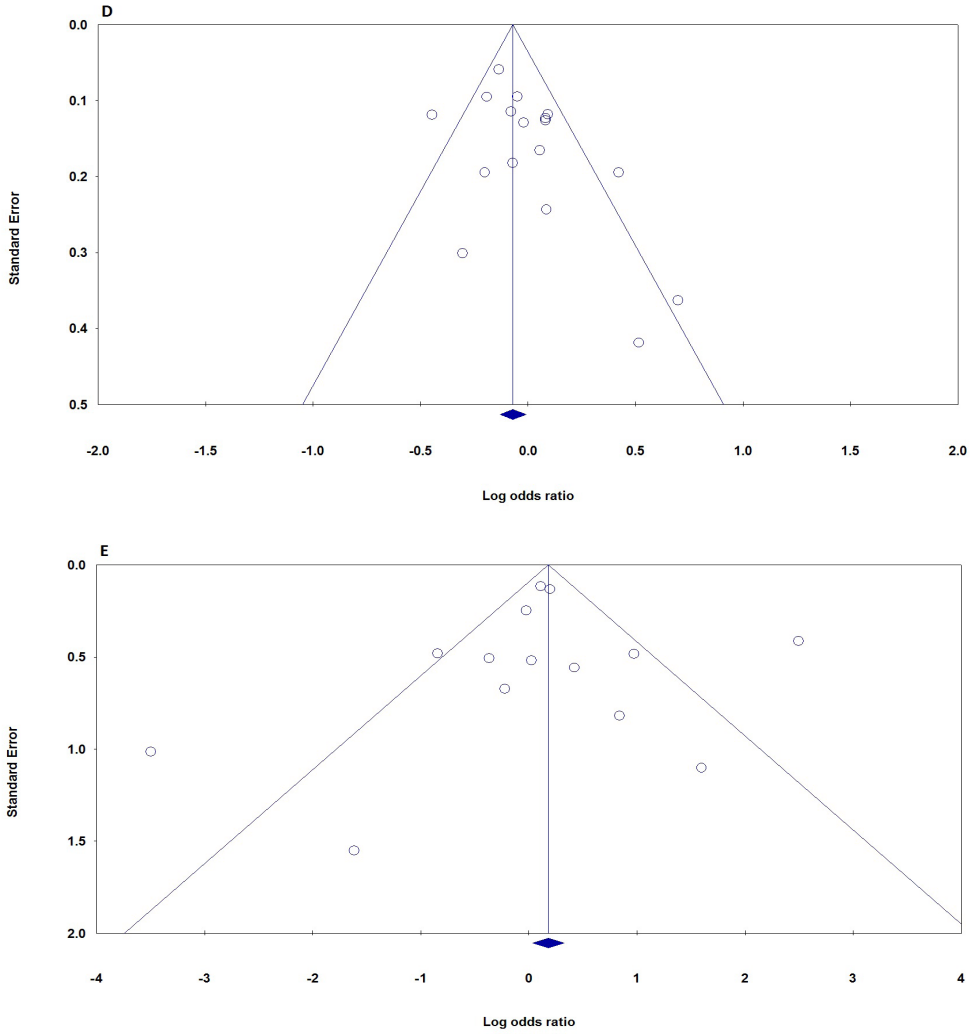

Figure 3. Begg's Funnel Plot of Publication Bias Test for association of X *XRCC2* Arg188His (rs3218536) Polymorphism with Susceptibility to Breast Cancer. D) dominant (AA+AG vs. GG); E) and recessive (AA vs. AG+GG).

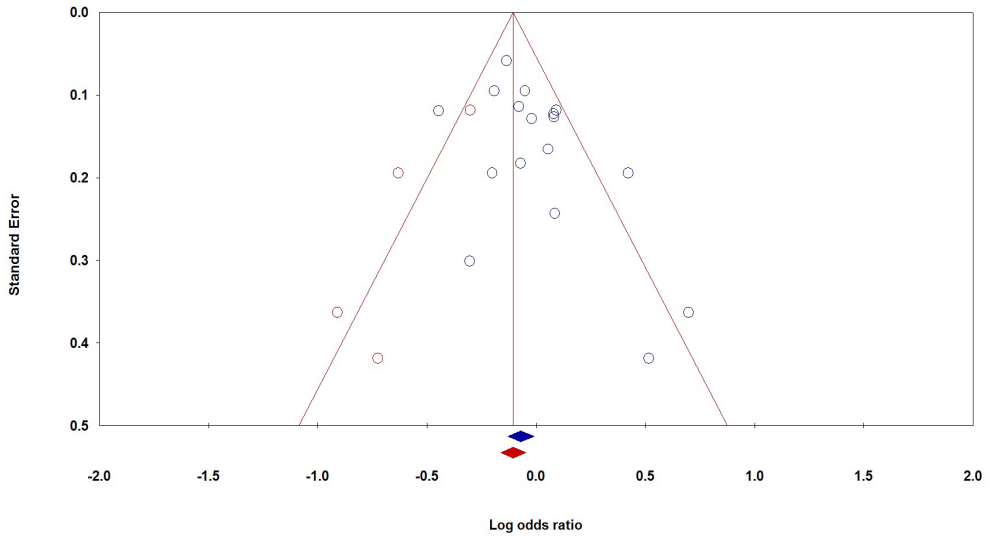

Figure 4. Begg's Funnel Plot of Publication Bias Test before (Blue) and after (Red) Trim-and-Fill Method for association of X *XRCC2* Arg188His (rs3218536) Polymorphism with Susceptibility to Breast Cancer under the Dominant Model (AA+AG vs. GG).

Table 2. Meta-Analysis of the association of *XRCC2* Arg188His 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
	AA vs. GG	Random	66.5	<0.001	1.125	0.770-1.643	0.542	1	0.868
	AG vs. GG	Fixed	30.49	0.113	0.929	0.873-0.987	0.018	0.592	0.412
	AA+AG vs. GG	Random	86.39	<0.001	0.964	0.876-1.061	0.451	0.108	0.016
	AA vs. AG+GG	Random	78.06	<0.001	1.214	0.798-1.847	0.365	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
	AA vs. GG	Random	69.57	<0.001	1.038	0.647-1.665	0.878	0.631	0.76
	AG vs. GG	Fixed	29.28	0.137	0.92	0.861-0.980	0.009	1	0.779
	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
	AA vs. GG	Random	54.02	0.01	1.232	0.892-1.701	0.206	0.582	0.555
	AG vs. GG	Fixed	31.58	0.116	0.943	0.885-1.006	0.074	0.428	0.312
	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

[56-58]. Several meta-analyses have evaluated the association of *XRCC2* Arg188His polymorphism with susceptibility to breast cancer [59, 60, 28, 35, 21]. We performed a meta-analysis of case-control studies to resolve the controversial results reported in previous studies. Seventeen case-control studies with 5694 cases and 6450 controls f *XRCC2* Arg188His polymorphism were analyzed. Overall, the polymorphism was found to be significantly associated with breast cancer susceptibility under the heterozygote genetic model. In 2006, García-Closas et al., in a two population-based studies in USA and Poland, and meta-analyses examined the association of 19 polymorphisms at seven genes (*XRCC2*, XRCC3, *BRCA2*, ZNF350, BRIP1, XRCC4, LIG4) with susceptibility to breast cancer in two population-based studies in USA (3,368 cases and 2,880 controls) and Poland (1,995 cases and 2,296 controls). Their results showed that the polymorphisms at these genes are unlikely to have a substantial overall association with breast cancer risk; however, weak associations are possible for XRCC3 (T241M and IVS7-14A>G), *BRCA2* N372H, and ZNF350 S472P [45]. In 2007, Breast Cancer Association Consortium (BCAC) in a meta-analysis evaluated risk of breast cancer using data from up to 12 studies on*ADH1C I350V, AURKA F31I, BRCA2 N372H, CASP8 D302H, ERCC2 D312N, IGFBP3 -202 c>a, LIG4 D501D, PGR V660L, SOD2 V16A, TGFB1 L10P, TP53 R72P, XRCC1 R399Q, XRCC2 R188H, XRCC3 T241M, XRCC3 5' UTR*, and *XRCC3* IVS7-14 polymorphisms. The pooled data showed a borderline significant association for five polymorphisms (CASP8 D302H, IGFBP3 -202 c>a, PGR V660L, SOD2 V16A, and TGFB1 L10P). however, there was not association with breast cancer risk foe remaining polymorphism [27]. He et al. in a meta-analysis of 45 case-control studies from 26 publications with 30868 cases and 38656 controls have evaluated *XRCC2* Arg188His polymorphism relation with cancer risk. Their pooled data showed that there was no a significant association between the *XRCC2* Arg188His polymorphism and risk of breast cancer [60]. Yu et al., in a meta-analysis based on 16 studies with 18,341 cases and 19,028 controls revealed that there was no a significant association between *XRCC2* Arg188His and risk of breast cancer susceptibility under all five genetic models [28]. Lin et al., genotyped 12 *XRCC2* tagging single nucleotide polymorphisms (SNPs) in 1131 breast cancer cases and 1148 healthy subjects from the Sheffield Breast Cancer Study (SBCS), and examined their associations with breast cancer risk and survival by estimating ORs and HRs, and their corresponding 95% CIs. Their results showed a significant association with breast cancer risk in the SBCS dataset was the *XRCC2* Arg188His polymorphism [61].

The presence of heterogeneity might distort the results of a meta-analysis [62-64]. Many factors may contribute to the strong heterogeneity among overall analysis. The heterogeneity might be explained by sampling errors and the small number of samples in some studies or chance or real differences in populations or in interactions with other risk factors [65-68]. To explore the sources of heterogeneity in this meta-analysis, a subgroup analysis by ethnicity and HWE was performed. Stratified analyses revealed that the heterogeneity was not significantly reduced or disappeared, which indicated that ethnicity and HWE status could not partly explain the source of heterogeneity. However, these results indicated that the effect of *XRCC2* Arg188His may not be modified by ethnicity and HWE.

To our knowledge, this is the most comprehensive

meta-analysis which has first investigated the association between the *XRCC2* Arg188His polymorphism and susceptibility of breast cancer. However, several limitations should be taken into consideration when explaining the results: First, most of the studies included in this study were carried out among Caucasians and the number of included studies was relatively small in Asians. Therefore, the association *XRCC2* Arg188His polymorphism with risk of breast cancer in other ethnicity remained unclear. Thus, to obtain more precise results, further studies with larger sample size and involving different ethnicities especially Asians and African are necessary. Second, only studies published in English were included, so relevant articles published in other languages were possibly missed, and this may have resulted in the relatively small sample size and causing a language bias. Moreover, this meta-analysis enrolled published articles only, while some related articles may remain unpublished, possibly resulting in publication bias. Third, several important confounding factors, such as age, smoking, drinking, family history of breast cancer, environmental exposures and lifestyle, were not considered for stratification analysis because relevant data was insufficient in the primary reports. Finally, this meta-analysis could not address the gene-gene and gene-environmental interactions in the association of *XRCC2* Arg188His polymorphism with breast cancer risk. 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* Arg188His polymorphism and risk of breast and ovarian cancer are required.

In summary, our pooled data revealed that the *XRCC2* Arg188His (rs3218536) polymorphism was associated with increased risk of breast cancer risk globally and among Caucasian women. Additional large studies with high methodological quality especially among other descendent should be included in future meta-analyses to validate the association between the *XRCC2* Arg188His (rs3218536) polymorphism with breast cancer.

Author Contribution Statement

Conceptualization: Seye Alireza Dastgheib, Soheila Sayad, Sepideh Azizi; Data curation: Nazanin Hajizadeh, Fatemeh Asadian; Formal analysis: Seyed Alireza Dastgheib, Hossein Neamatzadeh; Investigation: Kazem Aghili, Maedeh Barahman; Methodology: Mojgan Karimi-Zarchi, Maedeh Barahman; Supervision: Mohammad Manzourolhojeh, Amirmasoud Shiri; Validation: Seye Alireza Dastgheib, Mojgan Karimi-Zarchi; Writing – original draft: Soheila Sayad, Maedeh Barahman; Writing – review & editing: Soheila Sayad, Hossein Neamatzadeh.

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Conflicts of interest/Competing interests

The authors declare that they have no conflict of interest.

Ethics approval

This article does not contain any studies with human participants or animals performed by any of the authors. An ethical approval was not necessary as this study was a meta-analysis based on previous studies.

Consent to participate

Not applicable for this manuscript.

Data availability

The dataset used and/or analyzed during this study is available from the corresponding author on a reasonable request.

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