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Original Article

XRCC1 Arg399Gln polymorphism is not associated with breast cancer in Chinese

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Abstract: Background: A number of studies have been conducted to explore the association of XRCC1 polymorphisms with Breast cancer (BC) risk in Asians, but the results have been inconsistent. We therefore performed the present meta-analysis to explore the relationship in detail. Materials and Methods: Reported studies were searched from 1990 to October 15, 2014 in PubMed and Wan fang Med Online. We performed a meta-analysis of 13 published case-control studies fitting our eligibility criteria. These studies involved XRCC1 Arg399Gln polymorphisms in 4984 BC cases and 5744 controls in dominant (ArgArg vs. GlnGln+ArgGln), recessive (ArgGln+ArgArg vs. GlnGln), and co-dominant (ArgArg vs. GlnGln) inheritance models. The total odds Ratio (OR) and 95% CI were calculated and analyzed by Review Manager 5.2 and STATE 12. Results: Overall, significantly increased BC risk was observed in any genetic model (dominant model: odds ration [OR] = 1.31, 95% confidence interval [CI] = [1.08, 1.58]; recessive model: OR = 0.63, 95% CI = [0.50, 0.81]; codominant model: OR = 2.52, 95% CI: [1.38, 4.60]) when all eligible studies were pooled into the meta-analysis. In further stratified analyses, no association was found between Arg399Gln polymorphism and BC risk in Chinese fewer than three hereditary models. Conclusions: Our results suggest that the XRCC1 Arg399Gln polymorphism may be associated with increased Breast cancer risk among Asians, except Chinese population.

Keywords: XRCC1 gene, polymorphism, Arg399Gln, breast cancer

Introduction

Breast cancer is the most common invasive cancer in women, and like other forms of cancer it results from multiple hereditary and environmental modulators, possibly in an interactive manner. Many risk factors such as ionizing radiation and alcohol consumption have been established to account for approximately 30% of breast cancer patients [1]. Base-excision repair (BER) is an important DNA repair pathway that is responsible for the repair of base damage resulting from exposure to X-rays, oxygen radicals, and alkylating agents [2-4]. The X-ray repair cross-complementing group 1 gene (XRCC1) is one of these DNA repair genes in the pathway. XRCC1 acts as a central scaffolding protein by binding to DNA ligase III, DNA polymerase β, and poly (ADP-ribose) polymerase in BER at the site of damaged DNA [5] Masson et al.

Previous epidemiology studies on the association between genetic polymorphisms of XRCC1 and BC have given inconsistent results in Asians. In hospital-based case-control studies conducted among Korean women, Kim et al. and Seoul et al. found the Gln allele was associated with an increased risk of breast cancer [6, 7]. Several studies [8-11] demonstrated that Arg399Gln polymorphism might not play a significant role in the risk of breast cancer among Chinese women. While in other studies, significant association was found between Arg399Gln polymorphism and BC risk in Chinese [12, 13]. For Indians, three studies showed consistent association of Arg399Gln polymorphism and BC risks [14-16].

Based on previously published studies, several meta-analysis have been conducted on the Arg399Gln and breast cancer risk [17-22], but not special in the Asian population or Chinese.

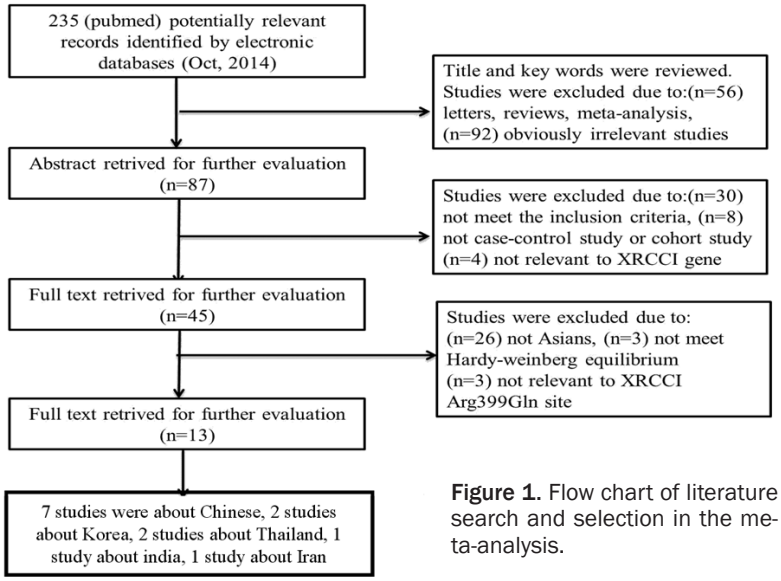

Figure 1. Flow chart of literature search and selection in the meta-analysis.

Maybe due to heterogeneity across different countries and relative few studies in Asians, no conclusion has been drawn yet in the Asian countries. Therefore, we have performed such a meta-analysis on XRCC1 Arg399Gln polymorphism and BC.

Materials and methods

Literature inclusion criteria

(1) The subjects of literature must be Chinese and Indian; (2) Case-control study of the Arg399Gln polymorphism and breast cancer risk; (3) The papers must provide the sample size, the OR information such as genotype frequency that can calculate OR and 95% CI; (4) When more than one paper used the same study population, we included a recent literature.

Literature exclusion criteria

(1) There was no controls; (2) Duplicated data; (3) The articles were reviews; (4) Controls were with other malignancies. PubMed and Wanfang Med Online were searched by using key words: "Arg399Gln"; "rs25487"; "X-ray repair cross-complementing group 1"; "XRCC1"; "breast neoplasms"; "breast cancer"; "polymorphism". The date of the search interval was from 1990 to October 15, 2014 and the scope of the search was all papers consisted of journals and dissertations.

Study selection and data extraction

According to pre-established criteria of inclusion and exclusion, a double-check procedure was carried out to make sure the accuracy of the data entry. The following year, publication language, country, the data of total and exposure number in cases and control groups. A standardized procedure was performed to estimate Odds Ratio of cases and controls. Characteristics of studies were summarized.

Statistical analysis methods

Hardy-Weinberg equilibrium was tested by the chi-square test based on an Excel program. In meta-analysis, we examined the association between allele Arg of Arg399Gln and the risk of breast cancer compare to that of allele Gln, as well as using codominant (Arg/Arg versus Gln/Gln), recessive [(Arg/Gln+Arg/Arg) versus Gln/Gln] and dominant [Arg/Arg versus (Gln/Gln+Arg/Gln)] genetic models. Statistical analysis was done by using Review Manager 5.2 and STATA 12. Adjusted OR value and 95% CI were calculated for each study, and crude OR value should be calculated if adjusted OR value was not available. The Cochrane Q statistics test and I^2 were performed for heterogeneity in this meta-analysis with a $P > 0.10$ and $I^2 < 50\%$, simultaneously, while a random effects model was selected when $P < 0.10$ or $I^2 > 50\%$. The funnel plot was drawn to evaluate publication bias. Egger's test and Begg's test were also done to check the publication bias. All the tests were two-sided, a *P* value of 0.05 for any test or model.

Results

Overview of included studies

According to the search strategy, 13 papers were selected in **Figure 1**. A total of 13 publications with 13 case-control studies of 4984 BC cases and 5744 controls were finally included in this meta-analysis. We had read all the 13 papers. All these 13 studies were conducted in Asian population, among them, 7 studies were

Table 1. General Characteristics of Studies Included in the Meta-analysis

Author	Country	publication language	Year	Genotype distribution						OR (95% CI)	OR (95% CI)	Control X^2 HWE	*P* value
				case			control						
				ArgArg	ArgGln	GlnGln	ArgArg	ArgGln	GlnGln	ArgArg/ (GlnGln+ArgGln)	(ArgGln+ArgArg) /GlnGln		
Shu	China	English	2003	561	442	85	610	498	74	1.00 (0.85-1.18)	0.79 (0.57-1.09)	4.369a	0.037
Jin MJ	China	Chinese	2006	48	27	8	127	97	27	0.88 (0.39-2.03)	1.13 (0.49- 2.59)	1.658	0.198
Qian Y	China	Chinese	2010	349	255	62	412	304	73	1.01 (0.71-1.44)	0.99 (0.70- 1.42)	2.382	0.123
Li Liu	China	English	2011	518	402	84	547	367	81	1.03 (0.75-1.42)	0.97 (0.71- 1.33)	3.014	0.083
Peijian Ding	China	English	2014	318	209	79	347	254	32	2.82 (1.84-4.32)	0.36 (0.23- 0.54)	2.814	0.093
Hao Luo	China	English	2014	83	90	21	137	91	17	1.63 (0.83-3.18)	0.61 (0.31- 1.20)	0.126	0.723
Zhai XJ	China	English	2006	173	101	28	347	240	52	1.15 (0.71-1.87)	0.87 (0.54- 1.40)	1.315	0.251
Hsu	China Taiwan	English	2010	198	149	48	276	202	53	1.25 (0.82-1.89)	0.80 (0.53- 1.21)	3.087	0.079
Sangrajrang	Thailand	English	2008	268	201	38	246	158	20	1.64 (0.94-2.86)	0.61 (0.35- 1.07)	0.715	0.398
IARC-Thai	Thailand	English	2006	241	188	31	228	141	19	1.40 (0.78-2.53)	0.71 (0.40- 1.28)	0.221	0.638
Kim	Korea	English	2002	92	79	34	90	101	14	1.04 (0.70-1.54)	0.37 (0.19-0.71)	4.156a	0.041
Seoul	Korea	English	2006	148	119	41	149	144	21	0.98 (0.71-1.34)	0.47 (0.27- 0.81)	3.139	0.076
Chacko	India	English	2005	56	50	17	79	35	9	2.15 (1.29-3.58)	0.49 (0.21- 1.15)	3.081	0.079
Saadat	Iran	English	2008	83	70	33	81	90	16	0.95 (0.63-1.43)	0.43 (0.23- 0.82)	1.683	0.195
Mitra	India	English	2008	44	52	54	83	107	35	1.41 (0.90-2.19)	0.33 (0.20- 0.54)	0.003	0.958
Syamala	India	English	2009	147	154	58	193	126	48	0.63 (0.47-0.84)	0.78 (0.52-1.18)	12.743a	0.0004

a: The studies are not in HWE.

Table 2. Summary OR and 95% CI of XRCC1 Arg399Gln polymorphism and breast cancer risk

Contrast	N of studies	Population	OR	95% CI	test for overall effect		test for heterogeneity	
					Z	P	I^2	P
ArgArg vs. GlnGln+ArgGln (dominant model)	13	Total	1.31	(1.08-1.58)	2.74	0.006	57%	0.006
	7	Chinese	0.77	(0.57-1.04)	1.71	0.005	68%	0.09
ArgArg+ArgGln vs. GlnGln (recessive model)	13	Overall	0.63	(0.50-0.81)	3.73	7E-04	65%	0.0002
	7	Chinese	1.22	(0.87-1.70)	1.16	0.001	73%	0.25
ArgArg vs. GlnGln (codominant model)	13	Overall	0.63	(0.50-0.80)	3.9	0.004	59%	<0.0001
	7	Chinese	0.76	(0.56-1.03)	1.78	0.009	65%	0.07

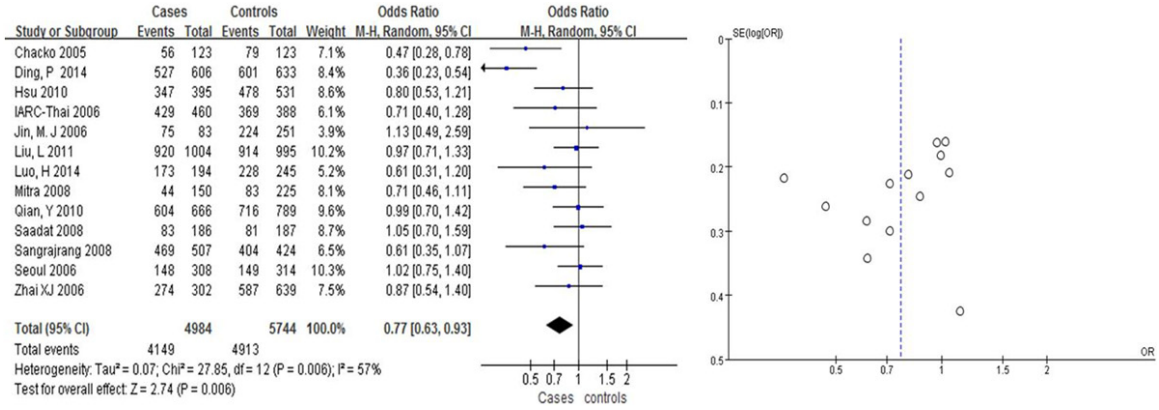

Figure 2. Pooled gene effect for Arg399Gln in relation to breast cancer via a dominant model.

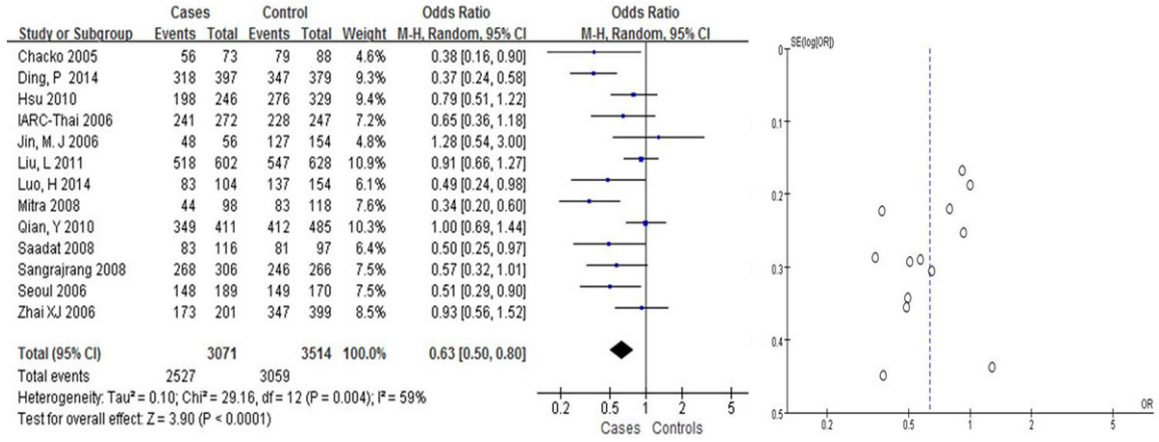

Figure 3. Pooled gene effect for Arg399Gln in relation to breast cancer via a codominant model.

dealing with Chinese people including 3250 BC cases and 4083 controls. The characteristics of individual studies are summarized in **Table 1**.

Meta-analysis results

A summary of our results is shown in **Table 2**. For each study, we investigated the association based on the assumption of different inheritance models of the Arg399Gln allele. In all the three inheritance models of Arg399Gln, there was between-study heterogeneity in the individual studies (all $P < 0.01$ and $I^2 > 25\%$, **Table 2**), so we analyzed the data using the random-effect model.

We found that Arg399Gln had a weak correlation with the risk of BC in Asians (OR = 1.31, 95% CI: [1.08, 1.58] in the dominant model;

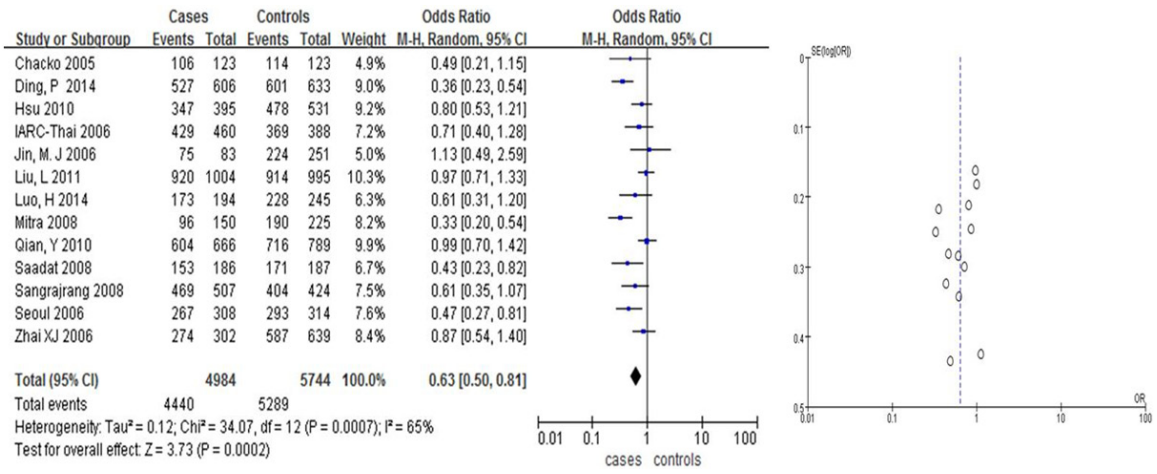

Figure 4. Pooled gene effect for Arg399Gln in relation to breast cancer via a recessive model.

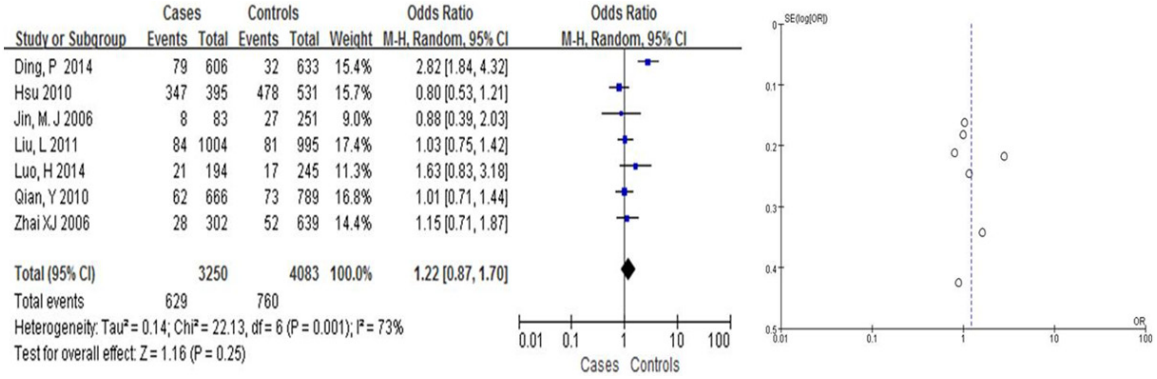

Figure 5. Pooled gene effect for Arg399Gln in relation to breast cancer in Chinese via a recessive model.

and OR = 0.63, 95% CI: [0.50, 0.81] in the recessive model, **Table 2**; **Figures 2**, **3**). Arg399Gln had a strong correlation with the risk of BC in the co-dominant model (OR = 0.63, 95% CI: [0.50, 0.80], **Table 2**; **Figure 4**). However, seven studies dealing with Chinese suggested no associations with BC risk in any hereditary model (OR = 0.77, 95% CI: [0.57, 1.04] in the dominant model (**Figure 6**), OR = 1.22, 95% CI: [0.87, 1.70] in the recessive model (**Figure 5**); and OR = 0.76, 95% CI: [0.56, 1.03] in the codominant model) (**Figure 7**).

Test of heterogeneity

Q test and I^2 were calculated to test the heterogeneity in **Table 2**. *P* value was less than 0.10, so we analyzed the pooled ORs with random effects model. Many factors might lead to heterogeneity. One is the small sample sizes of cases and controls.

Publication bias

Funnel plots was performed to assess the publication bias in **Figures 2**-**4**. In addition, the Egger's test and Begg's test were also selected to test publication bias in **Table 3**. For the comparison of 399Arg versus 399Gln, the *P* value of Begg's test of studies dealing with Chinese was 0.175 > 0.05, so it indicated that there was no publication bias. Sensitivity analysis was performed by sequential omission of individual studies, and the results also indicated that the pooled result was robust.

Discussion

Meta-analysis is a powerful tool for summarizing the different studies. It can not only overcome the problem of small size and inadequate statistical power of genetic studies of complex traits, but also can provide more reliable results

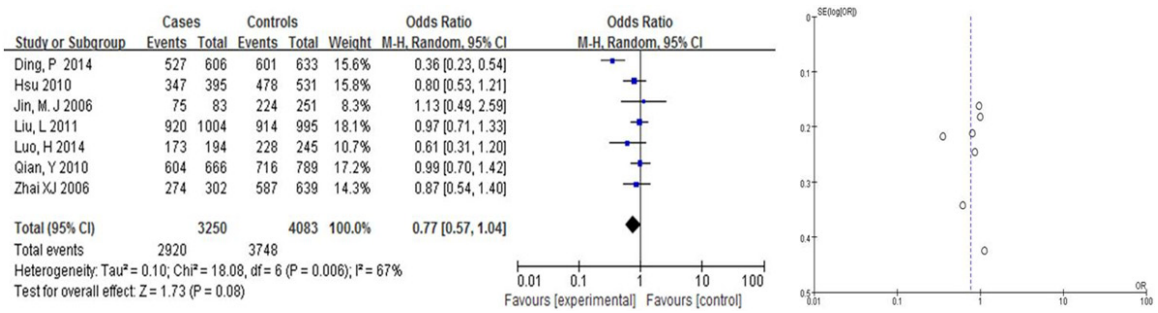

Figure 6. Pooled gene effect for Arg399Gln in relation to breast cancer in Chinese via a dominant model.

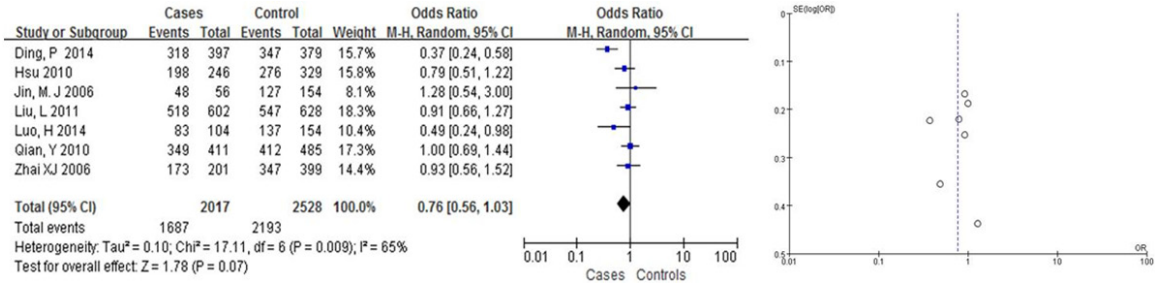

Figure 7. Pooled gene effect for Arg399Gln in relation to breast cancer in Chinese via a codominant model.

Table 3. Publication bias for all analysis

Population	*P* value	
	Egger's test	Begg's Test
Chinese	0.415	0.175
Asians	0.161	0.502

than a single case-control study. In addition, with the much larger sample size from the combined reports, the impact from ethnicity and other factors can be better elucidated. This meta-analysis incorporated 13 studies of 4984 breast cancer cases and 5744 controls, has further increased the sample size and enlarged the statistical power to reflect the precision effect of the Arg399Gln in breast cancer in the Asian population.

Based on our results, individuals who had the Gln allele were more likely to have BC (recessive model: OR = 0.63, 95% CI: [0.50, 0.81]; codominant model: OR = 0.63, 95% CI: [0.50, 0.80]). This is consistent with previous meta-analysis. Huang et al. (Huang, Li, & Yu, 2009) also demonstrated that Arg399Gln polymorphism increased breast cancer risk in Asians [odds ratio (OR) = 1.26, 95% confidence interval (CI): 0.96-1.64]. DNA is continuously damaged by endogenous and exogenous mutagens and carcinogens. The damages are fixed by multiple DNA repair pathways including BER, nucleotide excision repair, mismatch repair, and double-strand break repair [2]. Cells with unrepaired DNA damage undergo either apoptosis or unregulated growth to malignancy. As a DNA repair gene, XRCC1 X-ray Polymorphisms in XRCC1 gene, involving an amino acid change at evolutionarily conserved regions, could alter the XRCC1 function. Codon 399 is located in the poly (adenosine diphosphate-ribose) polymerase-binding domain and within an identified BRCA1 COOH terminus domain [23]. In view of its functional significance, it is biologically possible that the Arg399Gln polymorphism may modulate the risk of breast cancer.

The Arg399Gln variant presented no association with BC risk in Chinese population. Further sensitivity analysis suggested the stability of the current results, by showing similar ORs before and after sequential removal of single study. This result was conflict with the overall result. The power of the test was enough because of 3250 BC cases and 4083 controls. The inconsistence might be due to two main reasons. Firstly, the environment and cultural were different across different countries.

Different countries have different life styles and diet habits. Besides the environmental and cultural divergences, it cannot be totally ruled out that the evolutionary history of linkage disequilibrium patterns will vary significantly across different ethnic populations. Generally, a locus is in close linkage with another nearly causal locus in one ethnic group but not in another [24]. As a consequence, there is a need to construct a database of breast cancer-susceptibility genes or polymorphisms in each racial/ethnic group.

In conclusion, our meta-analyses, under both recessive and dominant models, indicate that the Arg399Gln polymorphism associates with an increased risk of breast cancer in the Asian population, except Chinese population. With the large population size for our analyses, we feel that the results are reliable. However, more comparative studies are needed to evaluate associations in other countries. Furthermore, mechanistic studies need to be conducted to evaluate the underlying reasons for the association. Thirdly, we cannot take environment factors, such as smoking, estrogen level, and other clinic characteristics into account, to analyze the role of gene-environment, which prevented further adjustment in risk estimates and may have overestimated the true effect size.

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Disclosure of conflict of interest

None.

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