RESEARCH COMMUNICATION

XRCC1 Arg399Gln Gene Polymorphism and Breast Cancer Risk: a Meta-analysis Based on Case-control Studies

Kusheng Wu[1]*, Daisi Su[2], Kun Lin[1], Jiayi Luo[1], William W Au[1]

Abstract

Background: The Arg399Gln polymorphism in the XRCC1 DNA repair gene is likely to be involved with the development of breast cancer (BC). However, there have been inconsistent reports of association. The objective of this study was to systematically evaluate the published papers. Methods: We performed a meta-analysis of 44 published case-control studies fitting our eligibility criteria. These studies involved XRCC1 Arg399Gln polymorphisms in 20,841 BC cases and 22,688 controls in dominant (GlnGln+ArgGln vs. ArgArg), recessive (GlnGln vs. ArgGln+ArgArg), and co-dominant (GlnGln vs. ArgArg) inheritance models. Analyses of Asian, African and Caucasian ethnic subgroups was also conducted. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of associations. Results: Our overall analyses indicated Arg399Gln to be associated with a trend of increased BC risk when using recessive (OR=1.15, 95%CI: 1.05–1.27), and co-dominant models (OR=1.15, 95%CI: 1.04-1.27) to analyze the data. In ethnic subgroups, Arg399Gln significantly increased BC risk in Asians (OR=1.54, 95%CI: 1.18–2.01) when using recessive model analysis, in Africans (OR=1.30, 95%CI: 1.07–1.60) when using dominant model analysis, and in Asians (OR=1.50, 95%CI: 1.15–1.97) and Africans (OR=1.80, 95%CI: 1.08-3.02) when using the co-dominant model analysis. Conclusions: From our meta-analysis of data from 44 publications, we conclude that XRCC1 Arg399Gln allele is a risk factor for the development breast cancer, especially among Asian and African populations.

Key words: XRCC1 gene polymorphism - Arg399Gln - breast cancer

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Introduction

Genetic variation in DNA repair genes can cause alteration in DNA repair function, resulting in the accumulation of DNA damage and gene mutations, and the development of health consequences such as cancer (Harms et al., 2004). 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 (Goode et al., 2002; Hoeijmakers, 2001; Wood et al., 2001). 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 (Cappelli et al., 1997; Masson et al., 1998). Like most genes, XRCC1has numerous genetic variations (Goode et al., 2002). These variations, such as Arg399Gln, can alter the DNA repair function of the gene and therefore health outcomes (Duell et al., 2002).

Case–control study is a well-accepted method to investigate the association between diseases and specific genes, e.g. XRCC1 Arg399Gln polymorphism and BC. However, previous studies regarding the relationships have provided inconsistent results. For example, Saadat et al. (2008) reported that 399Gln allele acted as a recessive allele and increased the BC risk (Gln/Gln vs. Arg/Arg+Arg/Gln, OR=2.31, 95%CI: 1.21–4.35). However, Costa et al. (2007) reported that women with XRCC1 399Gln genotypes were protected against BC (OR=0.54, 95%= CI: 0.35–0.84). It has also been suggested that the relationship between XRCC1 Arg399Gln and BC risk might be modified by ethnicity of the population and/or family history (Li et al., 2009). Among other studies Thyagarajan et al. (2006) concluded that there was no significant association between BC and the polymorphism.

There can be many reasons for the discrepancy in the publications. One is the small sample sizes of cases and controls. The other is the complication by the use and comparison of different ethnic populations. So, a

*[1]Faculty of Preventive Medicine, [2]Master of Public Health Education Center, Shantou University Medical College, Shantou, Guangdong, China *For correspondence: kswu@stu.edu.cn*

systematic meta-analysis of the available studies can provide more definitive answers. In addition, with the much larger sample size from the combined reports, the impact from ethnicity and other factors can be better elucidated. Therefore, we have performed such a meta-analysis on XRCC1 Arg399Gln polymorphism and BC.

Materials and Methods

Search strategy

All the case–control studies were identified by literature searches in the PubMed, CNKI, SpringerLink, Ovid, EBSCO and ScienceDirect database (prior to February 2011) using the following words and terms: 'XRCC1', 'polymorphism', 'Arg399Gln' and 'breast cancer'. References of the retrieved publications were also screened. Only research articles were included and the language of publication was restricted to English and Chinese. Studies had to be based on an unrelated case–control design, so pedigree data were excluded. The genotype distribution of the control population of the studies had to be in Hardy–Weinberg equilibrium (HWE) (P>0.05). All selected studies had to fulfill the following four criteria: (1) case–control study of the Arg399Gln polymorphism and breast cancer risk; (2) sufficient published data for estimating an odds ratio with 95% confidence interval; (3) when multiple publications reported on the same or overlapping data, we selected the largest or most recent publication, as recommended by Little et al. (2002) and (4) clear description of ethnic background of study populations.

Data extraction

The information was extracted from each publication: the first author's name, journals or publication data, year of publications, country origin, sources of controls, ethnic descent of the study population (categorized as Asian, Caucasian, and African), genotyping method, and number of different genotype in all subjects.

Statistical analysis

We examined the association between Arg399Gln polymorphism and the risk of BC, using codominant (Gln/Gln versus Arg/Arg), recessive (Gln/Gln versus Arg/Gln+Arg/Arg) and dominant (GlnGln+ArgGln versus ArgArg) genetic models. In our study, both Mantel–Haenszel's fixed-effects method and DerSimonian and Laird's random-effects method were used. A chi-square based Q test and an I2 test were both performed to evaluate the between-study heterogeneity of the studies. Venice criteria (Ioannidis et al., 2008) 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'. So in this study if P <0.10 or I^2 >25%, the between-study heterogeneity was therefore considered to be significant, we chose the random-effects model to calculate the OR. If not, the fixed effects model was performed. RevMan 5.0 software was employed to estimate summary OR and 95% CI by weighting each study result by a factor of within- and between-study variance. A Z test was performed to determine the significance of the pooled OR. For each genetic comparison, subgroup analysis was performed according to ethnic descent status: Asian, African or Caucasian. Funnel plots were used to access publication bias by the method of Begg's test (Begg and Mazumdar, 1994) and Egger's test (Egger et al., 1997). An asymmetric plot suggested possible publication bias (P ≥0.05 suggests no bias). Hardy–Weinberg equilibrium was tested by the chi-square test based on an Excel programme. Analyses were performed by SPSS 15.0 for Windows (SPSS Inc.) and RevMan 5.0 software.

Results

Study characteristics

There were 40 publications based on case-control studies that met the inclusion criteria (Listed alphabetically: Ali et al., 2008; BCAC, 2006; Brewster et al., 2006; Bu et al., 2006; Chacko et al., 2005; Costa et al., 2007; Deligezer and Dalay, 2004; Duell et al., 2001; Dufloth et al., 2005; Figueiredo et al., 2004; Forsti et al., 2004; Han et al., 2003; Hsu et al., 2010; Hussien et al., 2011; Jelonek et al., 2010; Jin et al., 2006; Kim et al., 2002; Kipikasova et al., 2008; Liu et al., 2011; Loizidou et al., 2008; Metsola et al., 2005; Mitra et al., 2008; Moullan et al., 2003; Pachkowski et al., 2006; Patel et al., 2005; Saadat et al., 2008; Sangrajrang et al., 2008; Santos et al., 2010; Shen et al., 2005; Shu et al., 2003; Silva et al., 2007; Smith et al., 2008; Smith et al., 2003a; Smith et al., 2003b; Sterpone et al., 2010; Syamala et al., 2009; Thyagarajan et al., 2006; Zhai et al., 2006; Zhang et al., 2006; Zipprich et al., 2010). Each subpopulation in these articles was treated as a separate study in our meta-analysis. One combined analysis (BCAC, 2006) included nine individual case–control studies, two of which (studies PBSC and US 3-state) were also reported by Zhang et al. (2006) with more cases being included. Thus, our meta-analysis started with 49 studies from 40 publications (Table 1). We extracted the eligible data and rejected data where HWE was doubtful. Five studies were not in agreement with the equilibrium of the Arg399Gln in the controls (Table 1), for this reason they were not included in the final meta-analysis. As a result, 44 case–control studies including 20 841 cases and 22 688 controls for Arg399Gln polymorphism were identified for this meta-analysis. Populations were divided into three ethnic categories: Caucasian, Asian, and African.

Meta-analysis result of Arg399Gln and breast cancer

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

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

First author	Year	Country	Ethnicity	Control source	Case			Control			in controls†
					ArgArg	ArgGln	GlnGln	ArgArg	ArgGln	GlnGln	
Duell	2001	USA	African	Population	164	82	7	198	64	4	0.221
Duell	2001	USA	Caucasian	Population	162	175	49	164	158	59	3.998*
Kim	2002	Korea	Korean	Hospital	92	79	34	90	101	14	4.156*
Shu	2003	China	Chinese	Population	561	442	85	610	498	74	4.365*
Smith	2003a	USA	Caucasian	Hospital	99	122	30	115	123	29	0.207
Moullan	2003	France	French	Population	109	113	32	127	146	39	0.087
Smith	2003b	USA	Caucasian	Hospital	70	72	20	119	150	31	2.659
Han	2003	USA	Caucasian	Population	391	460	135	545	616	176	0.009
Deligezer	2004	Turkey	Turkish	Unknown	58	68	25	50	66	17	0.442
Figueiredo	2004	Canada	Caucasian	Population	168	179	55	160	185	57	0.089
Forsti	2004	Finland	Finnish	Population	100	103	20	138	129	31	0.011
Dufloth	2005	Brazil	Brazilian	Population	46	33	7	118	100	20	0.017
Patel	2005	USA	Caucasian	Population	196	195	61	280	202	56	0.092
Chacko	2005	India	Indian	Hospital	56	50	17	79	35	9	3.081
Shen	2005	USA	Caucasian	Population	412	539	116	444	536	130	2.75
Metsola	2005	Finland	Finnish	Hospital	237	196	46	256	185	37	0.193
Thyagarajan	2006	USA	Caucasian	Population	57	76	60	135	140	47	1.175
Zhai	2006	China	Chinese	Hospital	173	101	28	347	240	52	1.313
Brewster	2006	USA	Caucasian	Population	108	159	38	126	135	49	1.585
Zhang	2006	USA	Caucasian	Population	1214	1433	392	1054	1173	360	0.936
Pachkowski	2006	USA	African	Population	536	203	22	493	172	11	0.834
Pachkowski	2006	USA	Caucasian	Population	504	581	159	480	494	148	1.369
Jin	2006	China	Chinese	Population	48	27	8	127	97	27	1.658
Bu	2006	USA	Caucasian	Hospital	84	84	22	42	43	10	1.846
IARC-Thai‡	2006	Thailand	Thai	Hospital	241	188	31	228	141	19	0.23
Seoul‡	2006	Korea	Korean	Hospital	148	119	41	149	144	21	3.139
ABCFs‡	2006	Australia	Caucasian	Population	609	669	194	328	391	109	0.196
GENICA‡	2006	Germany	Caucasian	Population	254	290	58	252	299	74	1.055
LSHTM‡	2006	UK	Caucasian	Population	251	251	83	256	274	68	0.174
Madrid‡	2006	Spain	Caucasian	Hospital	354	350	104	309	353	108	0.201
USRTS‡	2006	USA	Caucasian	Population	314	307	86	425	499	127	1.123
Saadat	2007	Iran	Iranian	Population	83	70	33	81	90	16	1.683
Silva	2007	Portugal	Caucasian	Hospital	112	104	25	191	212	53	0.251
Costa	2007	Portugal	Caucasian	Population	112	109	65	228	338	95	2.866
Sangrajrang	2008	Thailand	Thai	Hospital	268	201	38	246	158	20	0.715
Loizidou	2008	Cyprus	Caucasian	Population	506	479	122	520	516	140	0.484
Ali	2008	USA	Mixed	Hospital	11	16	13	21	20	7	0.382
Smith	2008	USA	Caucasian	Hospital	135	141	36	179	181	46	0.0006
Smith	2008	USA	African	Hospital	38	13	1	58	15	1	0.0007
Kipikasova	2008	Slovak	Slovak	Population	15	50	49	17	43	53	2.644
Mitra	2008	India	Indian	Population	44	52	54	83	107	35	0.003
Syamala	2009	India	Indian	Hospital	147	154	58	193	126	48	12.743**
Hsu	2010	Taiwan	Chinese	Hospital	198	149	48	276	202	53	3.087
Jelonek	2010	Poland	Polish	Population	41	40	13	206	276	69	2.535
Sterpone	2010	Italia	Italian	Population	8	24	11	16	10	5	2.126
Santas	2010	Brazil	Brazilian	Population	24	39	2	24	53	8	7.291**
Zipprich	2010	USA	Caucasian	Population	126	115	30	139	141	43	0.579
Hussien	2011	Egypt	Egyptian	Clinics	37	51	12	50	40	10	0.227
Lin	2011	China	Chinese	Population	547	367	81	518	402	84	0.231

†$\chi 2$ for testing Hady-Weinberg equilibrium; ‡The seven studies come from the same publication: BCAC, 2006
*P<0.05; **P<0.01

399Gln 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%), so we analyzed the data using the random-effect model. We found that 399Gln had a weak correlation with the risk of BC (OR =1.15, 95% CI: 1.05–1.27 in the recessive model; and OR =1.15, 95% CI: 1.04–1.27 in the codominant model, Table 2, Figure 1, Figure 2).

We analyzed the relationship of Arg399Gln polymorphisms and BC in different ethnic subgroups: Caucasians, Asians, and Africans. In the recessive model, ten studies dealing with Asians had between-study heterogeneity (P= 0.008 and I^2=60%), so we analyzed the data using the random-effect model and found that 399Gln (GlnGln vs. ArgGln+ArgArg) increased the risk of BC in Asians (OR=1.54, 95%CI:

Table 2. Summary OR and 95%CI of XRCC1 Arg399Gln Polymorphism and Breast Cancer Risk

Contrast	N of studies	Ethnicity	OR	95%CI	test for overall effect		test for heterogeneity		
					Z	P	χ^2	P	I^2
GlnGln vs. ArgArg	44	Total	1.15	1.04-1.27	2.80**	0.005	82.05	<0.001	48%
(codominant model)	10	Asian	1.50	1.15-1.97	2.95**	0.003	21.3	0.01	58%
	4	African	1.80	1.08-3.02	2.24*	0.03	0.13	0.99	0%
	30	Caucasian	1.05	0.95-1.16	1.01	0.31	46.16	0.02	37%
GlnGln +ArgGln vs. ArgArg	44	Total	1.04	0.98-1.10	1.34	0.18	76.94	0.001	44%
(dominant model)	10	Asian	1.08	0.93-1.25	0.98	0.33	20.83	0.01	57%
	4	African	1.30	1.07-1.60	2.59*	0.009	3.3	0.35	9%
	30	Caucasian	1.01	0.95-1.07	0.29	0.77	46.14	0.02	37%
GlnGln vs. ArgArg +ArgGln	44	Total	1.15	1.05-1.27	2.93**	<0.001	87.61	<0.001	51%
(recessive model)	10	Asian	1.54	1.18-2.01	3.17**	0.002	22.42	0.008	60%
	4	African	1.59	0.96-2.63	1.79	0.07	0.5	0.92	0%
	30	Caucasian	1.05	0.96-1.15	1.12	0.26	47.5	0.02	39%

* P<0.05; **P<0.01

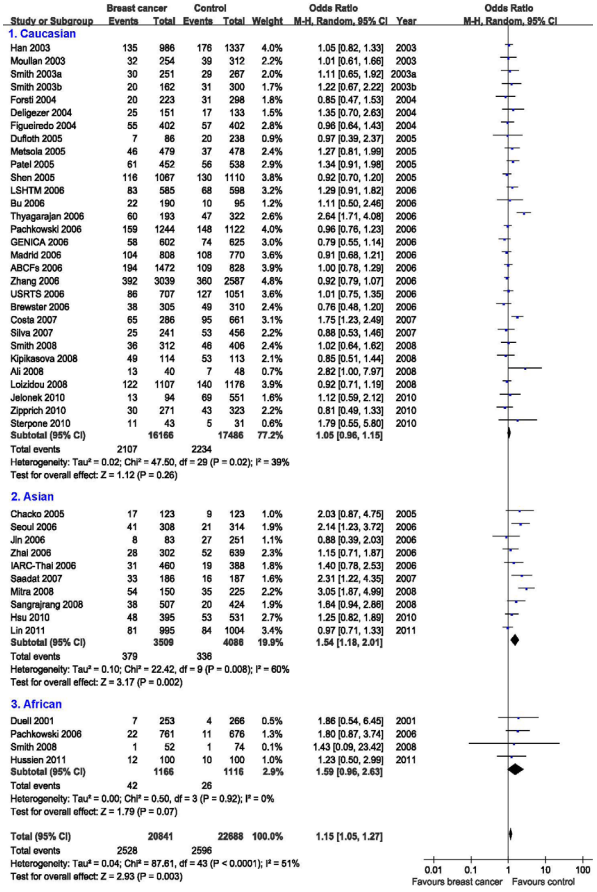

Figure 1. Pooled Gene Effect for Arg399Gln in Relation to Breast Cancer via a Recessive Model among Ethnic Subgroups

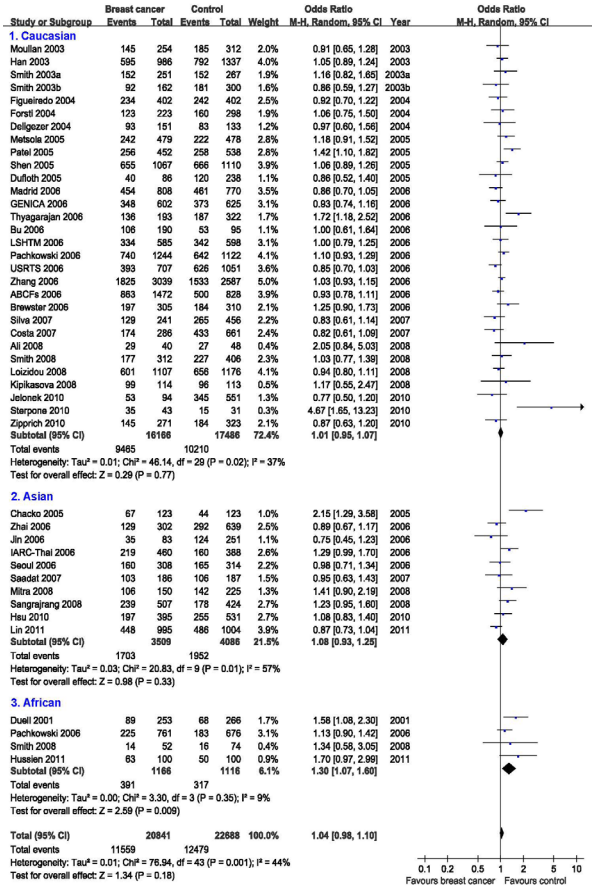

Figure 2. Pooled Gene Effect for Arg399Gln in Relation to Breast Cancer via a Codominant Model among Ethnic Subgroups

1.18–2.01, Table 2, Figure 1). Four articles dealing with Africans had no between-study heterogeneity (P=0.35 and I2=9%) in the dominant model, and in the fixed-effect model meta-analysis, 399Gln (GlnGln+ArgGln vs. ArgArg) was also related with the occurrence of BC (OR =1.30, 95%CI: 1.07–1.60, Table 2, Figure 3).

Thirty studies dealing with Caucasians suggested no associations with BC risk in any of the three inherence models. In the codominant model analysis of stratified subgroups, there were associations both in Asians (OR=1.50, 95%CI: 1.15-1.97) and in Africans (OR=1.80, 95%CI: 1.08-3.02, Table 2, Figure 2).

Publication bias

The data included in the present study suggested that there might be a publication bias for the comparison of 399Gln versus 399Arg in the dominant and co-dominant models used. However, when we stratified 399Gln versus 399Arg according to different ethnic groups, there was no publication bias in the subgroups or alternatively the publication bias decreased markedly (Figure 4).

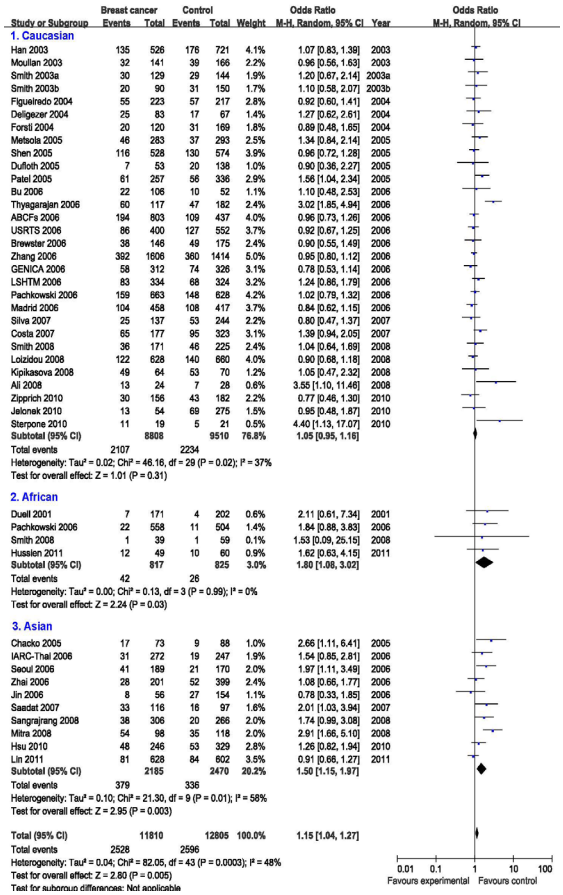

Figure 3. Pooled Gene Effect for Arg399Gln in Relation to Breast Cancer via a Dominant Model among Ethnic Subgroups

Discussion

BC is a multifactorial disease that results from the complex interactions between genetic and environmental factors. From our meta-analysis of the combined 44 studies, XRCC1 Arg399Gln was associated with a trend of increased BC risk. Based on our results, individuals who had the Gln allele were more likely to have BC (recessive model: OR =1.15, 95% CI: 1.05–1.27; codominant model: OR =1.15, 95% CI: 1.04–1.27). This is biologically plausible because 399Gln is located at the carboxylic acid terminal side of the polyadenosine diphosphate-ribose polymerase interacting domain and has been shown to reduce DNA repair capacity (Duell et al., 2000), and somatic glycophorin A mutations were significantly higher in 399Gln homozygotes than in heterozygotes (Lunn et al., 1999). Furthermore, in the recessive model analysis of stratified subgroups, Arg399Gln had a higher risk correlation with BC in Asians (OR =1.54, 95% CI: 1.18–2.01) and Africans (OR =1.59, 95% CI: 0.96–2.63) than in Caucasians (OR =1.05, 95% CI: 0.96–1.15). Considering the lower frequency of Gln/Gln, the population-attributable risk was limited among Asians.

There is an obvious publication bias of studies for the comparison of 399Gln versus 399Arg, but when we stratified the studies into different ethnic subgroups, the publication bias disappeared or decreased. Moreover, though there was moderate heterogeneity between the combined studies of XRCC1 Codon399, when we analyzed the Arg399Gln polymorphism in different ethnic subgroups, the between-study heterogeneity decreased markedly. These results suggest that the publication bias and heterogeneity may be partly due to the variable effects of stratified ethnic subgroups, and some genetic polymorphisms may be associated with risk of some diseases in a specific ethnic subgroup.

XRCC1 is very important for efficient base excision and single-strand break repair. The interactions of XRCC1 and its substrate result in assembly of the repair complex at the site of damage and regulate the activity of several repair enzymes, particularly poly (ADP-ribose) polymerase 1 (PARP1), ligase III and polynucleotide kinase 3'-phosphatase (Caldecott et al., 1996). Cells of rodents lacking XRCC1 are very sensitive to genetoxins and show increased genetic instability (Caldecott et al., 1994; 1996). XRCC1 has two BRCA1 carboxyl-terminal (BRCT) domains (BRCT1 and BRCT2), located centrally and at the C-terminal end, respectively. The centre of BRCT1 domain binds to and down-regulates the single-strand breaks and gaps recognition protein PARP1 and is required for efficient SSBR during both G1 and S/G2 phases of the cell cycle. The mechanism by which XRCC1 399Gln may contribute to BC is, however, unknown. Since XRCC1 is a recruiting protein for BER, the possibility exists that 399Gln acts by modifying the interactions with other BER proteins. In particular, APE1 and PARP1 are candidates, because they interact with XRCC1 through the BRCT1 domain that contains codon 399 (Masson

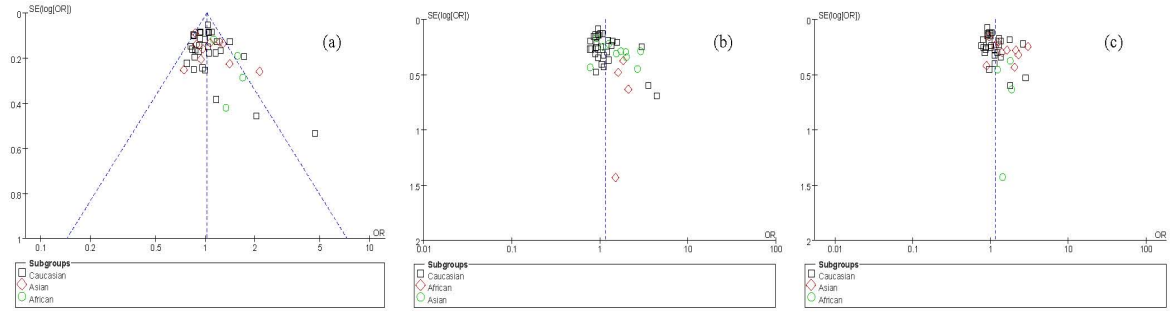

Figure 4. Funnel Plot of Comparison for Publication Bias in Arg399Gln Ethnicity Subgroup Analysis via (a) Recessive Model, (b) Codominant Model, and (c) Dominant Model

et al., 1998; Marsin et al., 2003). The polymorphism Arg399Gln is located close to BRCT1's C-terminal boundary. The mutation in this domain will change XRCC1's structure and maybe disrupt the combination of BRCT1 and PARP1. Finally, the involvement of DNA repair defects in the development of BC is relevant. This is because mutations in the two well-known BC genes (BRCA1 and BRCA2) contribute to DNA repair deficiency (Novak et al., 2009), as well as their interacting proteins. Furthermore, XRCC1 probably interacts with the breast cancer gene proteins because it has two BRCA1 carboxyl-terminal (BRCT) domains.

In conclusion, our meta-analyses, under both recessive and dominant models, indicate that the Arg399Gln polymorphism associates with an increased risk of breast cancer, especially in the Asian 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 ethnic groups. Furthermore, mechanistic studies need to be conducted to evaluate the underlying reasons for the association.

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