RESEARCH ARTICLE

XRCC1 Gene Polymorphisms and Breast Cancer Risk: A Systematic Review and Meta- analysis Study

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Abstract

Breast cancer risk assessment has developed during years and evaluation of genetic factor affecting risk of breast cancer is an important component of this risk assessment. The aim of this meta-analysis was to investigate the role of XRCC1 polymorphisms (Arg194Trp, Arg280His and Arg399Gln) in risk of breast cancer among different population and categories of menopausal status.PubMed, Medline, Web of Science, and PubMed Central were systematically searched to identify studies evaluating association between breast cancer and XRCC1 gene polymorphisms (Arg194Trp, Arg280His and Arg399Gln). Two authors independently extracted required information. Odds Ratios were pooled for four genetic inheritance models using both fixed and the DerSimonian and Laird random-effect models. Egger's test and contour-enhanced funnel plot was used to evaluate publication bias and small study effect. Additional subgroup analysis was performed for menopausal status, ethnicity, and source of controls. After evaluation and applying inclusion criteria on extracted studies, fifty three studies were included in this meta-analysis. For polymorphisms of Arg194Trp and Arg280His, no significant association was observed in all genetic models. Arg194Trp had a protective effect in post-menopausal status only in homozygote model (OR=0.57 [0.37-0.88]). Arg399Gln showed significant association with breast cancer in homozygote (OR=1.21 [1.10-1.34]), dominant (OR=1.09 [1.03-1.15]) and recessive (OR=1.21 [1.09-1.35]) genetic models. Arg399Gln was associated with higher risk in post-menopausal status for homozygote and heterozygote models. Our findings suggest that XRCC1 gene polymorphisms modify breast cancer risk in different populations and different categories of menopausal status.

Keywords: XRCC1 - polymorphism - breast cancer - meta-analysis

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Introduction

Breast cancer accounts as the leading type of cancer among women and is the second most common cause of cancer related death (Siegel et al., 2014). Although breast cancer incidence is less in developing countries, but it is increasing (Key et al., 2001). Studies identified many risk factors for breast cancer including earlier age at menarche, nulliparity, menopause at late age, oral contraceptives, hormonal therapy for the menopause, exogenous hormone, family of breast cancer, high fat diet, alcohol and smoking (Key et al., 2001). Some increase in breast cancer risk is attributable to hereditary factors. Nevertheless, high-risk mutations only explain 5% of breast cancer incidence (Lichtenstein et al., 2000). BRCA1 and BRCA2 with function of DNA repair are known as susceptibility genes for breast cancer (Bertwistle and Ashworth, 1998). Evaluation of breast cancer patients and their relatives demonstrated Defect in DNA repair (Patel et al., 1997).

Base excision repair (BER) is a recovery pathway for localized damage to DNA due to oxidative stress and ionizing radiation. The gene XRCC1 (X-ray repair cross-complementing group 1) is a component involved in DNA BER. Three distinct domains of XRCC1 are sites for interaction with DNA polymerase b, poly(ADP-ribose) polymerase, and DNA ligase III (Silva et al., 2007a). Three known polymorphisms of the XRCC1 gene included codons 194 (Arg to Trp), 280 (Arg to His), and 399 (Arg to Gln) (Shen et al., 1998).

Many attempts have been accomplished to clarify

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association of breast cancer and XRCC1 polymorphism. Despite many studies showed no association between breast cancer and XRCC1 gene polymorphisms (Thyagarajan et al., 2006; Smith et al., 2008; Liu et al., 2011b), some demonstrated increase in risk of breast cancer (Przybylowska-Sygut et al., 2013a; Shadrina et al., 2014b) or even decrease of breast cancer risk (Patel et al., 2005a).

Breast cancer risk assessment has developed during years and evaluation of breast cancer is important for decision making by physicians (Armstrong et al., 2000). In order to clear association of breast cancer with XRCC1 gene polymorphisms (Arg194Trp, Arg280His and Arg399Gln) we conducted this systematic review and meta-analysis.

Material and Methods

Search strategy

To retrieve all relevant studies, a systematic search of databases (PubMed/Medline, ISI web of knowledge/ Thompson Reuters and PubMed central) was conducted from their commencement to April 2015. Search terms were applied were terms related to breast cancer combined to term polymorphism with balloon AND. further assessment was performed with hand search of references of eligible studies and meta-analyses. Full detail of search strategy is available in supplementary Appendix (contact author).

Selection criteria

Studies evaluating association between breast cancer and XRCC1 gene polymorphisms (Arg194Trp, Arg280His and Arg399Gln) were included in this meta-analysis. Studies were excluded if 1) had no control group, 2) were all type of letters articles, comments, and editorial, animal studies, case reports and case series studies, 3) evaluate different polymorphisms of XRCC1 gene and 4) reported occurrence of benign breast diseases, secondary/metastatic BC or all-cause mortality as the main outcome. List of excluded studies and reason of exclusion is provided in supplementary appendix (contact author).

Data extraction

Two authors, applying the priori inclusion and exclusion criteria, screened all citations and abstracts and extract all needed information from included literatures, independently. When conflicting results was seen between reviewers, a third author (senior researcher) discussed about disagreement. EndNote X7 software was used to manage review and organize screening. The following information and data was extracted: name of first author, publication date, study design, source of controls (population based or hospital based), considered confounders in each models, genotyping methods, population ethnicity, total number of cases and controls, menopausal status of cases and controls, number of cases and controls according to menopausal status, mean age of cases and controls, minor allele frequency and (odds ratio) OR and their reported 95% confidence interval (CI) for homozygote, heterozygote and other inheritance models.. Finally, senior author rechecked all information of final stage table. For clarifications and more information (or unavailable full texts), we contacted with first and corresponding author to provide additional data.

Literature quality assessment

For qualification of finally identified studies, five items were considered: 1) source of control group, 2) ethnicity, 3) Hardy Weinberg Equilibrium among controls, 4) menopausal status, and 5) sample size. Detailed study qualification is presented in the supplementary appendix (contact author).

Statistical analysis

Observed frequencies of the XRCC genotype was assessed for Hardy–Weinberg equilibrium using chi-square statistic. Maximally adjusted ORs and 95 % confidence intervals (CIs) were used to combine as the measure of association. The pooled OR were estimated using both fixed and the DerSimonian and Laird random-effect model. Heterogeneity was assessed using Cochran's Q test and inconsistency index (I2). An I2 value above 75% at a significance level of < 0.1 was determined as presence of heterogeneity. Sensitivity analysis was performed by sequential omission of individual studies. Publication bias (small study effect) was assessed with the Egger's regression and contour-enhanced funnel plot. The contour-enhanced funnel plot makes it easier to assess the statistical significance of the hypothetical missing studies. If the region where missing studies exist includes both low and high statistical significance (P-value lower than 1% to greater than 10%, this mean that studies showing XRCC1 as a non-significantly and significantly less effective factor may be missed. Pooled ORs were estimated for all genetic inheritance models including homozygote, heterozygote, recessive and dominant, as well as subgroup analysis were performed for considered variables. The menopausal status stratified to post-menopause and pre menopause. The ethnicity subgroup was defined based on what was exactly mentioned in studies. Subgrouping included population based (those reported a population based case control) and hospital based (those reported a hospital based case control). All analyses were performed using Stata version 14 (Stata Corp LP, College Station, TX, USA).

Results

Through a detailed search of databases, 53 literatures were identified for further evaluation (Figure 1) (Kim et al., 2002b; Han et al., 2003; Moullan et al., 2003; Shu et al., 2003; Smith et al., 2003a; Smith et al., 2003b; Deligezer and Dalay, 2004; Figueiredo et al., 2004; Försti et al., 2004; Huang et al., 2004; Chacko et al., 2005; Dufloth et al., 2005; Metsola et al., 2005; Patel et al., 2005b; Shen et al., 2005; 2006; Brewster et al., 2006; Bu et al., 2006; Pachkowski et al., 2006b; Thyagarajan et al., 2006; Zhai et al., 2006; Zhang et al., 2006b; Costa et al., 2007; Silva et al., 2007b; Ali et al., 2008; Kipikasova et al., 2008; Loizidou et al., 2008; Mitra et al., 2008; Saadat et al., 2008; Sangrajrang et al., 2008; Smith et al., 2008; Sobczuk et al., 2009a; Syamala et al., 2009; Jakubowska

Table 1. Subgroup Meta-Analysis of XRCC1 Arg194Trp Polymorphism and Breast Cancer Risk.

Subgroup		Homozygote						Heterozygote						Dominant						Recessive					
		Studies No.	Fixed model OR (95% CI)	Random model OR (95% CI)	Ph	I2	T2	Studies No.	Fixed model OR (95% CI)	Random model OR (95% CI)	Ph	I2	T2	Studies No.	Fixed model OR (95% CI)	Random model OR (95% CI)	Ph	I2	T2	Studies No.	Fixed model OR (95% CI)	Random model OR (95% CI)	Ph	I2	T2
Overal		20	1.05 (0.89-1.24)	1.05 (0.88-1.25)	0.38	6	0.01	29	1.04 (0.97-1.12)	1.08 (0.96-1.22)	0	58.5	0.05	31	1.04 (0.97-1.10)	1.06 (0.95-1.18)	0	58.5	0.05	19	1.03 (0.88-1.21)	1.03 (0.88-1.21)	0.8	0	0
Menopausal status	pre	5	0.93 (0.56-1.55)	0.86 (0.41-1.81)	0.22	31.4	0.17	4	1.22 (0.95-1.56)	1.22 (0.95-1.56)	0.95	0	0	6	1.12 (0.93-1.35)	1.12 (0.93-1.35)	0.95	0	0	3	0.88 (0.53-1.48)	0.88 (0.53-1.48)	0.99	0	0
	post	4	0.57 (0.37-0.88)	0.57 (0.37-0.88)	0.93	0	0	4	0.84 (0.69-1.02)	0.84 (0.69-1.02)	0.87	0	0	8	0.88 (0.76-1.02)	0.89 (0.72-1.11)	0.06	48.7	0.04	4	0.78 (0.52-1.16)	0.78 (0.52-1.16)	0.58	0	0
Ethnicity	Caucasian	4	0.73 (0.34-1.55)	1.00 (0.28-2.53)	0.1	52.4	0.84	8	1.02 (0.88-1.19)	1.10 (0.81-1.50)	0	66.3	0.12	7	1.03 (0.88-1.20)	1.06 (0.77-1.45)	0	69.1	0.12	3	0.79 (0.33-1.93)	1.10 (0.20-5.90)	0.07	63.1	1.3
	African-American	1						2	0.96 (0.71-1.30)	0.86 (0.46-1.60)	0.23	29.4	0.1	2	0.99 (0.73-1.34)	0.99 (0.73-1.34)	0.76	0	0	1					
	White	1						1						1						1					
	Han Chinese	2	1.09 (0.85-1.40)	1.09 (0.85-1.40)	0.55	0	0	2	1.08 (0.94-1.26)	1.06 (0.84-1.35)	0.11	60.3	0.02	2	1.09 (0.95-1.25)	1.07 (0.85-1.35)	0.11	63.1	0.02	2	1.06 (0.83-1.34)	1.06 (0.83-1.34)	0.85	0	0
	Greek Cypriot	1						1						1						1					
	Mix	1						1						4	0.85 (0.73-1.00)	0.85 (0.72-1.01)	0.29	19.6	0.01	1					
	NS	10	1.07 (0.84-1.36)	1.10 (0.82-1.49)	0.2	26	0.06	14	1.17 (1.02-1.33)	1.22 (0.96-1.55)	0	61.7	0.11	14	1.18 (1.04-1.34)	1.24 (1.00-1.55)	0	62.3	0.1	10	1.03 (0.82-1.30)	1.03 (0.82-1.30)	0.67	0	0
Control source	Hospital based	9	1.09 (0.87-1.36)	1.18 (0.84-1.67)	0.08	44	0.1	13	1.15 (1.02-1.30)	1.26 (1.01-1.56)	0	59.9	0.08	13	1.17 (1.04-1.32)	1.32 (1.06-1.64)	0	61.4	0.08	8	1.06 (0.85-1.31)	1.09 (0.83-1.43)	0.22	25.9	0.04
	Population based	7	1.05 (0.80-1.39)	1.05 (0.80-1.39)	0.81	0	0	10	1.02 (0.93-1.13)	1.05 (0.90-1.24)	0.03	51.2	0.03	13	1.00 (0.92-1.09)	1.00 (0.87-1.12)	0.07	40.2	0.02	7	1.01 (0.76-1.34)	1.01 (0.76-1.34)	0.91	0	0
	Volunteer	2	0.76 (0.33-1.75)	0.76 (0.33-1.75)	0.38	0	0	3	0.92 (0.75-1.14)	0.78 (0.33-1.83)	0.01	80.8	0.42	2	0.89 (0.72-1.11)	0.62 (0.22-1.77)	0	90.4	0.51	2	0.82 (0.31-2.17)	0.82 (0.31-2.17)	0.59	0	0
	NS	2	0.99 (0.57-1.72)	0.99 (0.51-1.95)	0.23	32.2	0.08	3	0.87 (0.65-1.18)	0.79 (0.49-1.25)	0.19	39.8	0.07	3	0.92 (0.62-1.22)	0.83 (0.54-1.28)	0.2	38.5	0.06	2	1.00 (0.62-1.63)	1.00 (0.62-1.63)	0.38	0	0
Continent	Europe	5	0.86 (0.52-1.40)	0.86 (0.52-1.40)	0.95	0	0	9	1.08 (0.92-1.27)	1.07 (0.82-1.39)	0.06	47.3	0.07	7	1.08 (0.91-1.27)	1.05 (0.79-1.40)	0.05	52.7	0.07	4	0.97 (0.63-1.50)	0.97 (0.63-1.50)	0.92	0	0
	America	7	1.03 (0.65-1.64)	1.03 (0.62-1.72)	0.36	9.7	0.05	11	0.96 (0.86-1.07)	0.97 (0.86-1.10)	0.31	13.7	0.01	15	0.96 (0.88-1.06)	0.96 (0.88-1.06)	0.46	0	0	7	1.05 (0.63-1.77)	1.05 (0.62-1.78)	0.41	1.5	0.01
	Asia	7	1.06 (0.88-1.27)	1.05 (0.82-1.33)	0.22	27.3	0.03	8	1.09 (0.97-1.21)	1.09 (0.86-1.37)	0	70.2	0.07	8	1.08 (0.98-1.21)	1.09 (0.86-1.39)	0	74.1	0.08	7	1.02 (0.85-1.23)	1.02 (0.85-1.23)	0.5	0	0
	Africa	1						1						1						1					
Adjustment	Adjusted	13	1.10 (0.90-1.34)	1.11 (0.84-1.48)	0.15	29	0.06	15	1.09 (1.00-1.19)	1.14 (0.99-1.31)	0.02	49.2	0.03	16	1.04 (0.96-1.13)	1.11 (0.96-1.28)	0	63	0.05	2	1.09 (0.76-1.56)	2.23 (0.30-16.44)	0.06	71.4	1.6
	Unadjusted	7	0.96 (0.72-1.27)	0.96 (0.72-1.27)	0.85	0	0	16	0.97 (0.87-1.08)	0.99 (0.79-1.24)	0	65.1	0.09	15	1.00 (0.90-1.11)	1.00 (0.83-1.19)	0.01	55	0.06	17	1.01 (0.85-1.21)	1.01 (0.85-1.21)	0.9	0	0

OR, Odds Ratio; CI, Confidence Intervals; Ph, P values of Q-test for Heterogeneity test; I2, I-Square; T2, Tau-Square; NS, Not Stated

Table 2. Subgroup Meta-Analysis of XRCC1 Arg280His Polymorphism and Breast Cancer Risk

Subgroup		Homozygote						Heterozygote						Dominant						Recessive					
		Studies No.	Fixed model OR (95% CI)	Random model OR (95% CI)	Ph	I2	T2	Studies No.	Fixed model OR (95% CI)	Random model OR (95% CI)	Ph	I2	T2	Studies No.	Fixed model OR (95% CI)	Random model OR (95% CI)	Ph	I2	T2	Studies No.	Fixed model OR (95% CI)	Random model OR (95% CI)	Ph	I2	T2
Overal		5	0.97 (0.52-1.78)	1.18 (0.49-2.84)	0.15	40.4	0.39	10	1.03 (0.93-1.15)	1.04 (0.90-1.20)	0.12	36.5	0.02	11	1.05 (0.95-1.17)	1.06 (0.93-1.21)	0.16	29.4	0.01	6	0.92 (0.47-1.83)	0.92 (0.47-1.83)	0.43	0	0
Meno-pausal status	pre	1						1						3	1.01 (0.74-1.37)	1.01 (0.74-1.37)	0.7	0	0	1					
	post	1						1						3	1.09 (0.82-1.46)	0.88 (0.39-1.99)	0	82	0.41	1					
Ethnic-ity	Caucasian	1						3	1.04 (0.85-1.27)	1.03 (0.82-1.29)	0.32	12.7		3	1.05 (0.86-1.28)	1.04 (0.82-1.31)	0.29	19.5	0.01	2	1.02 (0.26-4.04)	1.02 (0.26-4.04)	0.97	0	0
	African-American	1						2	1.23 (0.79-1.91)	1.23 (0.79-1.91)	0.41	0		1						1					
	White	1						1						1											
	Han Chinese	1						1						1						1					
	Greek Cypriot	1						1						1						1					
	NS	1						2	1.09 (0.72-1.65)	1.01 (0.32-3.22)	0.01	87.1		4	1.17 (0.90-1.53)	1.10 (0.70-1.74)	0.05	60.8	0.13	1					
Control source	Hospital based	1						3	0.65 (0.44-0.95)	0.65 (0.44-0.95)	0.81	0		3	0.94 (0.71-1.24)	0.86 (0.52-1.41)	0.06	64.7	0.12	1					
	Popula-tion based	3	0.62 (0.30-1.28)	0.62 (0.30-1.28)	0.67	0	0	6	1.14 (1.00-1.30)	1.14 (1.00-1.30)	0.53	0		7	1.12 (0.99-1.27)	1.12 (0.99-1.27)	0.48	0	0	4	0.64 (0.29-1.39)	0.64 (0.29-1.39)	0.87	0	0
	Volunteer	1						1						1						1					
Conti-nent	Europe	1						3	1.02 (0.85-1.22)	1.14 (0.80-1.63)	0.05	66.3		3	1.05 (0.88-1.26)	1.16 (0.82-1.64)	0.07	63.4	0.06	2	2.27 (0.56-9.14)	2.25 (0.48-10.49)	0.27	18	0.22
	America	2	1.03 (0.27-3.84)	1.03 (0.27-3.84)	0.95	0	0	5	1.10 (0.93-1.31)	1.10 (0.93-1.31)	0.43	0		5	1.10 (0.94-1.30)	1.10 (0.94-1.30)	0.42	0	0	2	1.02 (0.18-5.75)	1.02 (0.18-5.75)	0.95	0	0
	Asia	2	0.63 (0.29-1.38)	0.72 (0.24-2.13)	0.22	33.1	0.25	2	0.95 (0.77-1.18)	0.81 (0.45-1.45)	0.07	69		3	1.00 (0.83-1.20)	0.98 (0.71-1.35)	0.12	53.1	0.04	2	0.63 (0.26-1.52)	0.70 (0.22-2.27)	0.25	23.5	0.23
Adjust-ment	Adjusted	4	0.72 (0.37-1.40)	0.72 (0.37-1.40)	0.6	0	0	8	1.07 (0.94-1.22)	1.06 (0.88-1.28)	0.1	41.2		7	1.08 (0.95-1.24)	1.09 (0.94-1.25)	0.37	8.2	0						
	Unad-justed	1						2	0.95 (0.78-1.15)	0.96 (0.77-1.19)	0.12	36.5		4	1.01 (0.87-1.19)	1.04 (0.79-1.37)	0.06	58.8	0.04	6	0.92 (0.47-1.83)	0.92 (0.47-1.83)	0.43	0	0

OR, Odds Ratio; CI, Confidence Intervals; Ph, P values of Q-test for Heterogeneity Test; I2, I-square; T2: Tau-Square; NS, Not Stated

Table 3. Subgroup Meta-Analysis of XRCC1 Arg399Gln Polymorphism and Breast Cancer Risk

Subgroup		Homozygote						Heterozygote						Dominant						Recessive					
		Studies No.	Fixed model OR (95% CI)	Random model OR (95% CI)	Ph	I2	T2	Studies No.	Fixed model OR (95% CI)	Random model OR (95% CI)	Ph	I2	T2	Studies No.	Fixed model OR (95% CI)	Random model OR (95% CI)	Ph	I2	T2	Studies No.	Fixed model OR (95% CI)	Random model OR (95% CI)	Ph	I2	T2
Overal		52	1.14 (1.07-1.21)	1.21 (1.10-1.34)	0	49.8	0.05	52	1.03 (0.99-1.07)	1.04 (0.98-1.10)	0	38.3	0.01	54	1.07 (1.03-1.11)	1.09 (1.03-1.15)	0	41.9	0.01	47	1.11 (1.04-1.18)	1.21 (1.09-1.35)	0	59.2	0.07
Meno-pausal status	pre	10	1.09 (0.93-1.27)	1.14 (0.91-1.43)	0.09	40.3	0.05	10	1.10 (1.01-1.20)	1.08 (0.94-1.24)	0.04	49.7	0.02	12	1.02 (0.93-1.12)	1.09 (0.91-1.31)	0	66	0.06	8	1.08 (0.84-1.39)	1.08 (0.84-1.39)	0.07	47.2	0.05
	post	12	1.20 (1.06-1.35)	1.22 (1.05-1.42)	0.27	17.8	0.01	12	1.11 (1.02-1.20)	1.10 (0.98-1.24)	0.08	39.2	0.02	14	1.08 (1.00-1.16)	1.06 (0.95-1.18)	0.04	44.9	0.02	11	1.07 (0.96-1.20)	1.10 (0.96-1.27)	0.23	22.4	0.01
Ethnicity	Caucasian	13	1.19 (1.06-1.33)	1.23 (1.01-1.49)	0.03	48.5	0.05	13	1.08 (1.00-1.17)	1.06 (0.94-1.20)	0.09	37	0.02	14	1.07 (1.00-1.14)	1.08 (0.98-1.18)	0.11	33.3	0.01	10	1.06 (0.96-1.17)	1.20 (0.97-1.48)	0	66.1	0.06
	African-American	2	1.82 (0.85-3.88)	1.82 (0.85-3.88)	0.91	0	0	2	1.10 (0.86-1.41)	1.10 (0.86-1.41)	0.96	0	0	2	1.20 (0.89-1.61)	1.20 (0.89-1.61)	0.97	0	0	2	1.76 (0.78-3.55)	1.73 (0.78-3.84)	0.67	0	0
	White	2	0.99 (0.82-1.19)	0.99 (0.82-1.19)	0.87	0	0	2	1.09 (0.96-1.24)	1.09 (0.96-1.24)	0.89	0	0	2	1.08 (0.95-1.22)	1.08 (0.95-1.22)	0.77	0	0	2	0.87 (0.73-1.03)	0.88 (0.73-1.06)	0.77	0	0
	Han Chinese	5	1.28 (1.06-1.54)	1.40 (0.93-2.11)	0	76.6	0.16	5	0.91 (0.82-1.01)	0.92 (0.80-1.06)	0.14	42.2	0.01	5	0.99 (0.90-1.09)	1.02 (0.86-1.21)	0.03	63.2	0.02	4	1.35 (1.11-1.63)	1.40 (0.89-2.20)	0	80.9	0.17
	Greek Cypriot	1						1						1						1					
	Persian Muslim	1						1						1						1					
	Mix	3	1.09 (0.86-1.38)	1.09 (0.86-1.38)	0.76	0	0	3	1.06 (0.90-1.24)	1.06 (0.90-1.24)	0.95	0	0	4	1.03 (0.91-1.16)	1.03 (0.91-1.16)	0.98	0	0	3	1.06 (0.86-1.31)	1.06 (0.86-1.31)	0.97	0	0
	NS	24	1.25 (1.10-1.42)	1.25 (1.03-1.52)	0	49.7	0.11	24	1.09 (1.00-1.18)	1.08 (0.96-1.22)	0.01	46.1	0.04	25	1.17 (1.08-1.26)	1.15 (1.03-1.30)	0	51.5	0.04	24	1.23 (1.09-1.38)	1.25 (1.04-1.50)	0	52.3	0.1
Control source	Hospital based	19	1.54 (1.33-1.77)	1.51 (1.25-1.82)	0.09	32	0.05	19	1.11 (1.01-1.21)	1.13 (1.00-1.28)	0.03	41.5	0.03	20	1.17 (1.07-1.26)	1.18 (1.05-1.32)	0.02	45.2	0.03	15	1.54 (1.32-1.79)	1.53 (1.26-1.85)	0.16	26.9	0.04
	Popula-tion based	20	1.02 (0.96-1.10)	1.05 (0.97-1.14)	0.79	0	0	20	1.03 (0.98-1.09)	1.02 (0.95-1.10)	0.03	41.5	0.01	22	1.05 (1.00-1.10)	1.05 (0.99-1.12)	0.08	31.1	0.01	20	1.01 (0.94-1.08)	1.03 (0.93-1.13)	0.08	33.2	0.01
	Volunteer	6	1.12 (0.89-1.41)	1.27 (0.66-2.44)	0	75.7	0.43	6	0.97 (0.84-1.13)	1.03 (0.77-1.39)	0.1	46.1	0.06	6	1.00 (0.86-1.15)	1.09 (0.79-1.49)	0.04	58	0.08	6	1.15 (0.92-1.43)	1.26 (0.69-2.32)	0	73.1	0.34
	NS	6	1.51 (1.15-1.99)	1.49 (0.91-2.43)	0.01	68.9	0.26	6	0.97 (0.81-1.15)	0.96 (0.80-1.16)	0.38	6.1	0	6	1.08 (0.92-1.27)	1.07 (0.86-1.33)	0.14	39.5	0.03	6	1.40 (1.10-1.79)	1.49 (0.92-2.39)	0	73.3	0.26
Continent	Europe	13	1.02 (0.87-1.18)	1.05 (0.85-1.29)	0.07	39	0.05	13	0.97 (0.88-1.07)	0.99 (0.85-1.15)	0.02	49	0.03	14	1.07 (0.99-1.15)	1.08 (0.95-1.24)	0.01	56	0.03	12	1.01 (0.90-1.13)	1.01 (0.87-1.18)	0.22	22.4	0.01
	America	21	1.08 (0.99-1.18)	1.08 (0.96-1.21)	0.2	20.2	0.01	21	1.08 (1.02-1.14)	1.08 (1.02-1.14)	0.77	0	0	22	1.05 (0.99-1.11)	1.05 (0.99-1.11)	0.57	0	0	20	1.00 (0.92-1.09)	1.01 (0.92-1.23)	0.01	49.7	0.04
	Asia	15	1.49 (1.31-1.70)	1.58 (1.29-1.94)	0.01	52.3	0.08	15	1.00 (0.93-1.08)	1.04 (0.92-1.17)	0.01	52.1	0.03	16	1.09 (1.02-1.17)	1.13 (1.01-1.27)	0.01	54.2	0.03	15	1.53 (1.35-1.74)	1.61 (1.32-1.97)	0.01	55	0.08
	Africa	2	2.34 (1.10-1.72)	2.46 (0.92-6.57)	0.2	37.9	0.2	2	2.05 (1.28-3.28)	2.05 (1.28-3.28)	0.36	0	0	2	2.07 (1.30-3.29)	2.09 (1.26-3.47)	0	43.2	0.02	2	1.52 (0.72-3.23)	1.52 (0.72-3.23)	0.51	0	0
Adjust-ment	Adjusted	30	1.12 (1.04-1.21)	1.14 (1.03-1.26)	0.01	38.7	0.02	30	1.06 (1.01-1.11)	1.06 (0.99-1.13)	0.01	40.5	0.01	31	1.08 (1.02-1.14)	1.09 (1.00-1.19)	0	50.2	0.02	6	1.60 (1.32-1.94)	1.62 (1.18-2.38)	0	71	0.15
	Unad-justed	21	1.33 (1.16-1.52)	1.39 (1.09-1.77)	0	61.1	0.17	21	0.99 (0.91-1.08)	1.00 (0.89-1.13)	0.06	34.6	0.02	23	1.07 (1.02-1.12)	1.08 (1.01-1.16)	0.03	35.5	0.01	41	1.07 (1.00-1.14)	1.15 (1.03-1.27)	0	50.2	0.05

OR, Odds Ratio; CI, Confidence Intervals; Ph, P values of Q-test for Heterogeneity Test; I2, I-square; T2, Tau-Square; NS, Not stated

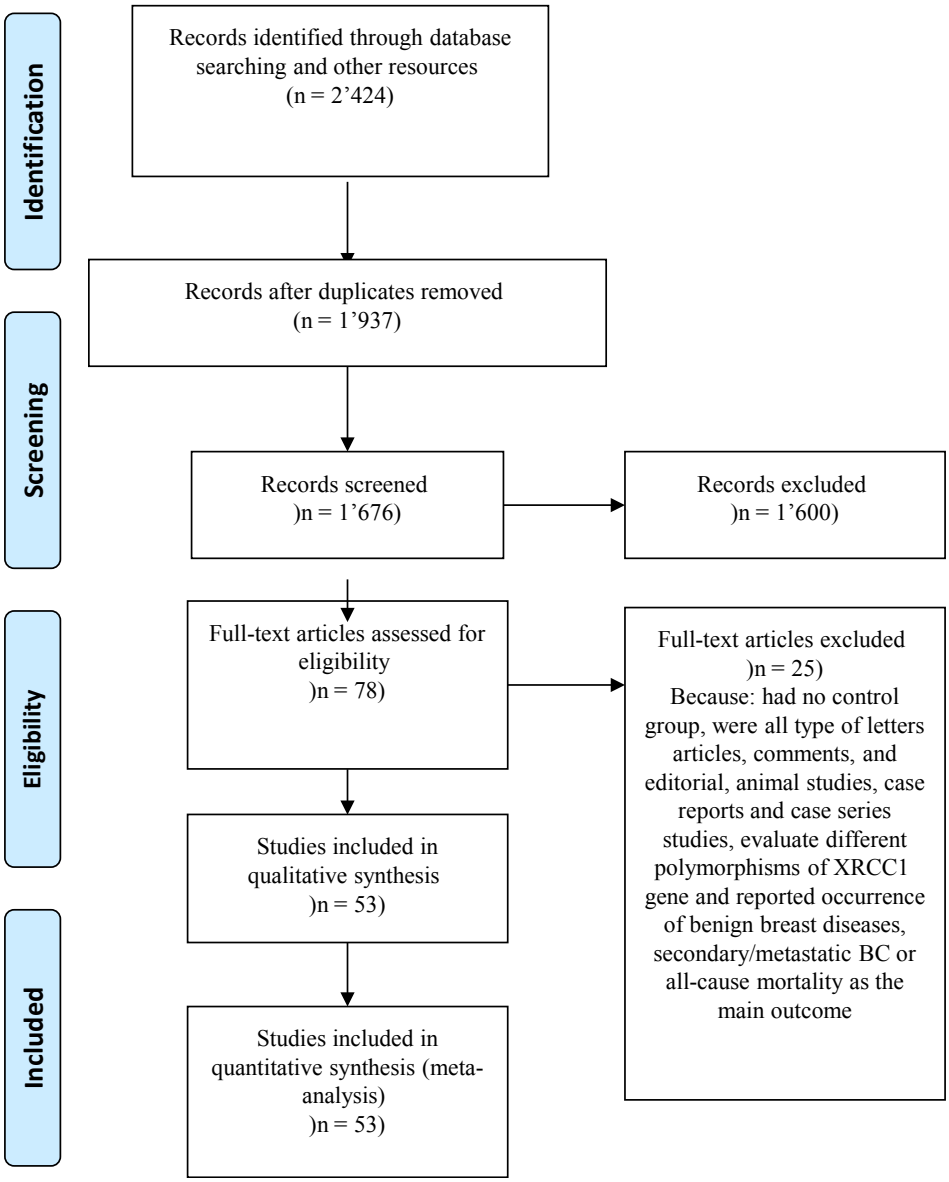

Figure 1. Flowchart of Reviewing Process for Inclusion of Eligible Studies in Meta-Analysis

et al., 2010; Jelonek et al., 2010; Ming-Shiean et al., 2010; Romanowicz et al., 2010; Santos et al., 2010; Sterpone et al., 2010b; Zipprich et al., 2010; Liu et al., 2011a; Roberts et al., 2011; Hussien et al., 2012; Al Mutairi et al., 2013; Przybylowska-Sygut et al., 2013b; Ding et al., 2014; Luo et al., 2014; McCullough et al., 2014; Ramadan et al., 2014; Sapkota et al., 2014; Shadrina et al., 2014a; Smolarz et al., 2014; Macias-Gomez et al., 2015). Thirty-one studies for Arg194Trp (14,381 cases and 15.036 controls), 10 for Arg280His (7,716 cases and 7,370 controls) and 52 for Arg399Gln (31,036cases and 35,994 controls) included in this meta-analysis. several studies (Duell et al., 2001; Romanowicz-Makowska et al., 2007; Sterpone et al., 2010a; Smith et al., 2011; Lee et al., 2014) were excluded because of common studied population with some others (Pachkowski et al., 2006a; Smith et al., 2008; Sobczuk et al., 2009b; Sterpone et al., 2010c). One publication (Consortium, 2006) carried out analysis of nine different studies. Of these nine studies, PBSC and US 3-state had common studied population with Zhang et al (2006a), and Seoul had common studied population with Kim et al (2002a). Because detailed characteristic of nine studies was not available, the single measure of association reported by the Breast Cancer Association Consortium for homozygote and heterozygote genetic models was considered for analysis. Given that, no reported measure of association for dominant and recessive genetic model as well as post/pre-menopause status in the Breast Cancer Association Consortium study, OR of mentioned models was recruited from Zhang and Kim's studies. Detailed characteristics of included studies are presented in supplementary appendix (contact author).

Arg194Trp

Overall, no significant association was detected between Arg194Trp polymorphism of XRCC1 gene and breast cancer in four genetic models. Based on menopausal status, results showed a protective effect of polymorphism on risk of breast cancer in post-menopauses only homozygote model (Trp/Trp vs. Arg/Arg: OR=0.57 [0.37-0.88]) (Figure 2). In subgroup analysis, studies with hospital source of control showed significant association

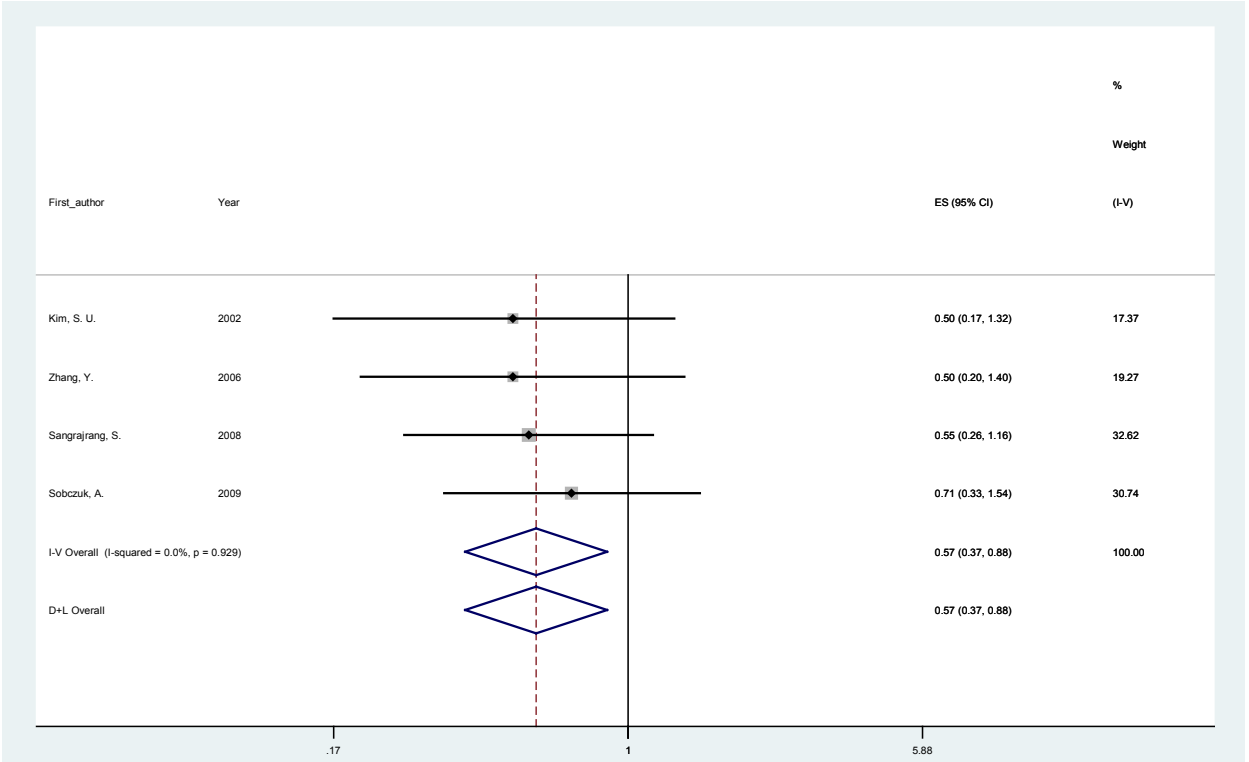

Figure 2. Fixed and Random Effect Model Meta-Analysis of XRCC1 Arg194Trp Polymorphism for Trp/Trp vs. Arg/Arg (Homozygote) Genetic Models and Risk of Breast Cancer in Postmenopausal Woman. The Effect Size is Odds Ratio.

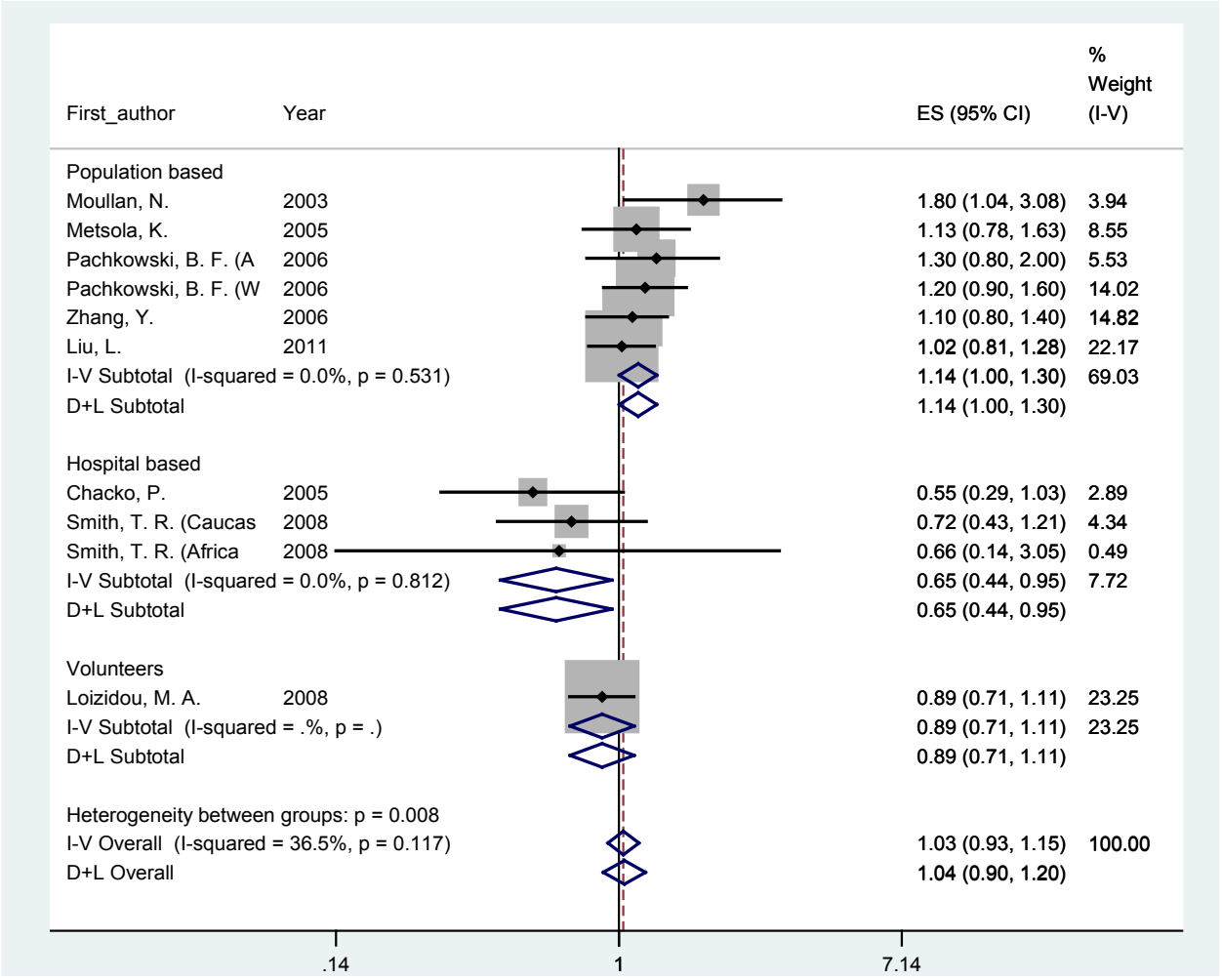

Figure 3. Fixed and Random Effect Model Meta-Analysis of XRCC1 Arg280His Polymorphism for His/Arg vs. Arg/Arg (Heterozygote) Genetic Models and Risk of Breast Cancer Stratified by Source of Control. The Effect Size is Odds Ratio.

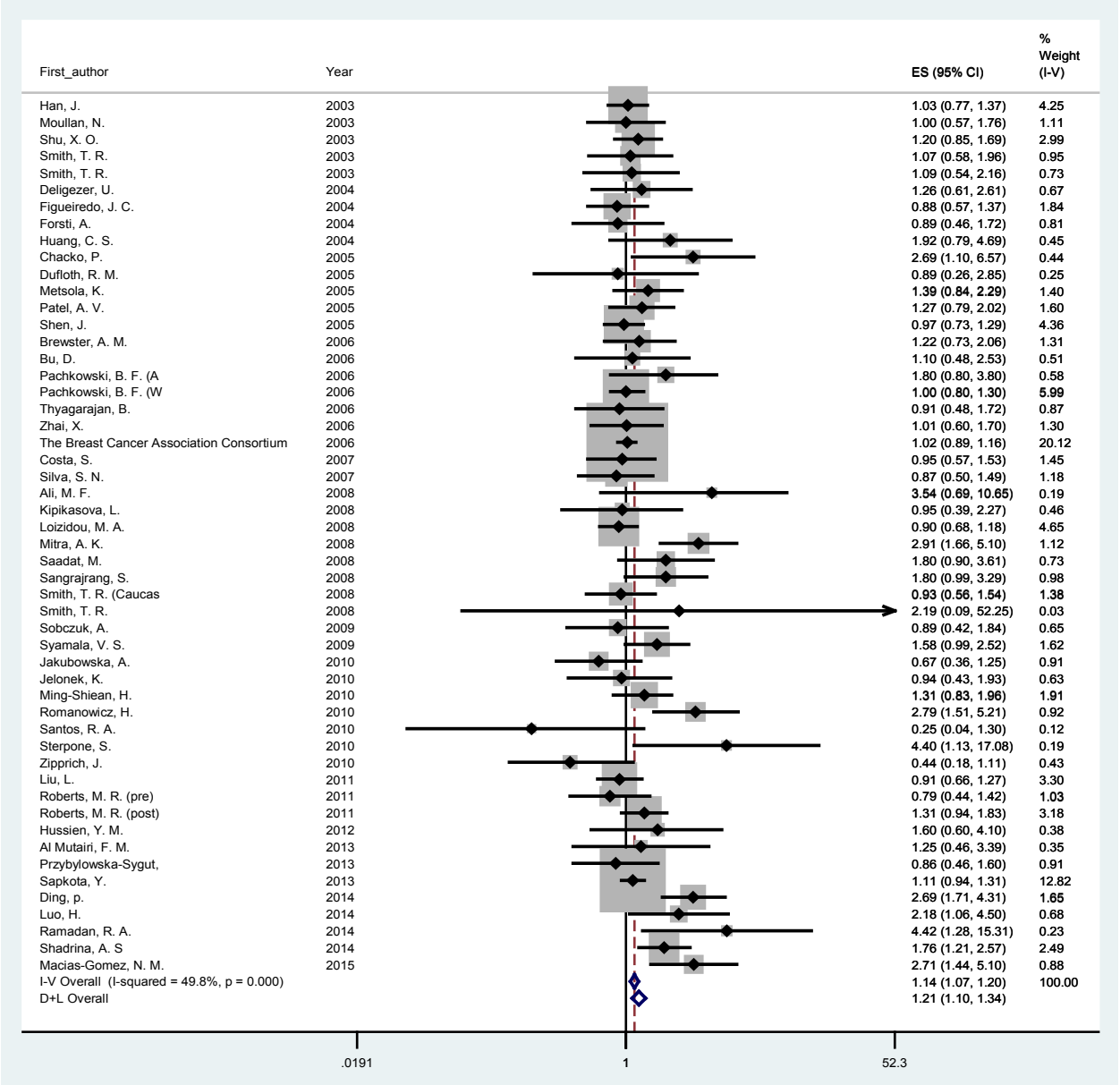

Figure 4. Fixed and Random Effect Model Meta-Analysis of XRCC1 Arg399Gln Polymorphism for Gln/Gln vs. Arg/Arg (Homozygote) Genetic Models and Risk of Breast Cancer. The Effect Size is Odds Ratio.

in heterozygote and dominant models. Results of analysis for Arg194Trp polymorphism are provided in Table 1.

Arg280His

Results display no association between Arg280His polymorphism and breast cancer in general analysis and pre/post-menopausal women. The only relationship found in subgroup analysis was detected in studies with population-based source of control in heterozygote model (Figure 3). Table 2 present pooled ORs for relationship between Arg280His polymorphism and breast cancer.

Arg399Gln

In overall analysis, there was significant association of Arg399Gln polymorphism with breast cancer in homozygote (Gln/Gln vs. Arg/Arg: OR=1.21 [1.10-1.34]) , dominant (Gln/Gln and Gln/Arg vs. Arg/Arg: OR=1.09 [1.03-1.15]) and recessive (Gln/Gln vs. Gln/Arg and Arg/Arg: OR=1.21 [1.09-1.35]) genetic models (Figure 4-6). Stratification analysis base on menopausal status revealed association only in post-menopauses in homo and heterozygote models. Subgroup analysis showed significant association in Caucasians, studies with hospital-based source of control and, Asian and American (only heterozygote model) populations. Detailed pooled ORs are presented in Table 3. No ppublication bias was detected using Egger's regression test. Figures 7 to 9 present the funnel plots for Arg280His, Arg194Trp and Arg399Gln.

Discussion

Our study demonstrated that certain categories of women have higher risk of breast cancer when they carry one of the XRCC1 gene polymorphism (Arg399Gln, Arg280His, or Arg194Trp). The Arg399Gln gene polymorphism has been associated with breast cancer in many studies with different magnitude of risk in different population or categories of patients. As we pooled all the

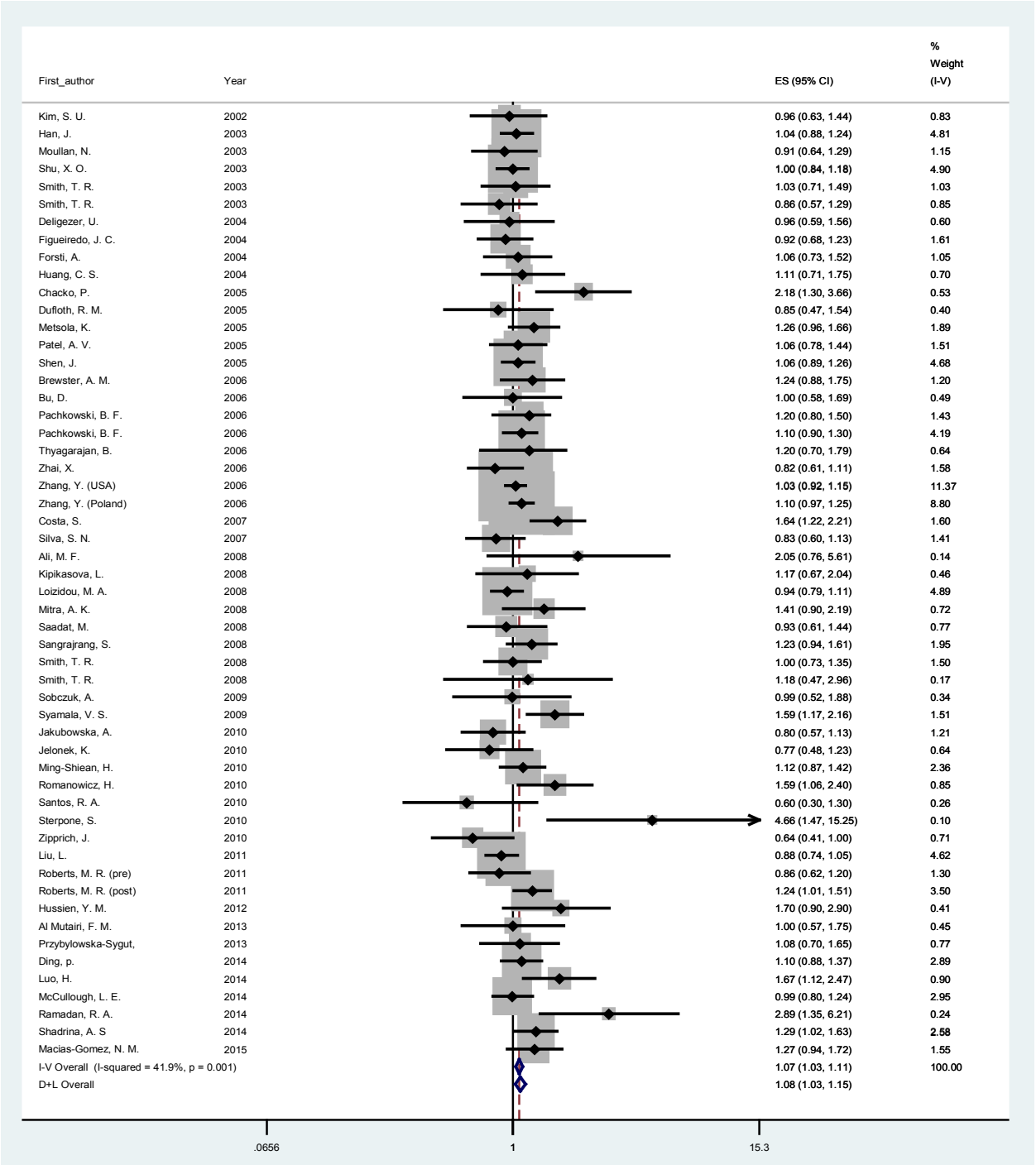

Figure 5. Fixed and Random Effect Model Meta-Analysis of XRCC1 Arg399Gln Polymorphism for Gln/Gln and Gln/Arg vs. Arg/Arg (Dominant) Genetic Models and Risk of Breast Cancer. The Effect Size is Odds Ratio.

individual studies, we compare our result with previous meta-analysis. The last metal analysis of Arg399Gln and risk of breast cancer was done by Bu et al (2014) that included 18 case control studies and just pooled the studies for American population.Their results were similar to our result except that they were able to detect statistically significant association just for certain genetic model (dominant and additive). Another meta-analysis by Wu K. included 44 case and control studies and their finding was similar to our study (they report association under recessive and dominant model) (Wu et al., 2011).

Meta-analysis of the Arg280His gene polymorphism has already been reported in the literature. The more recent meta-analysis reporting on Arg280His polymorphism and breast cancer was published in 2009 (Huang et al., 2009). The study included 37 case controls and examined all genetic models. Their find is consistent with our study result as general (no association) however, in our finding we observed case of association when subgroup analysis were done and when the subgroup included studies that that the source of controls was population based. The discrepancy seen between our result and Huang et al (2009) may be the fact that they did not performed subgroup analysis based on the source of control.

For the Arg194Trp Polymorphism of XRCC1 gene we found two previous meta-analyses one by Huang et al

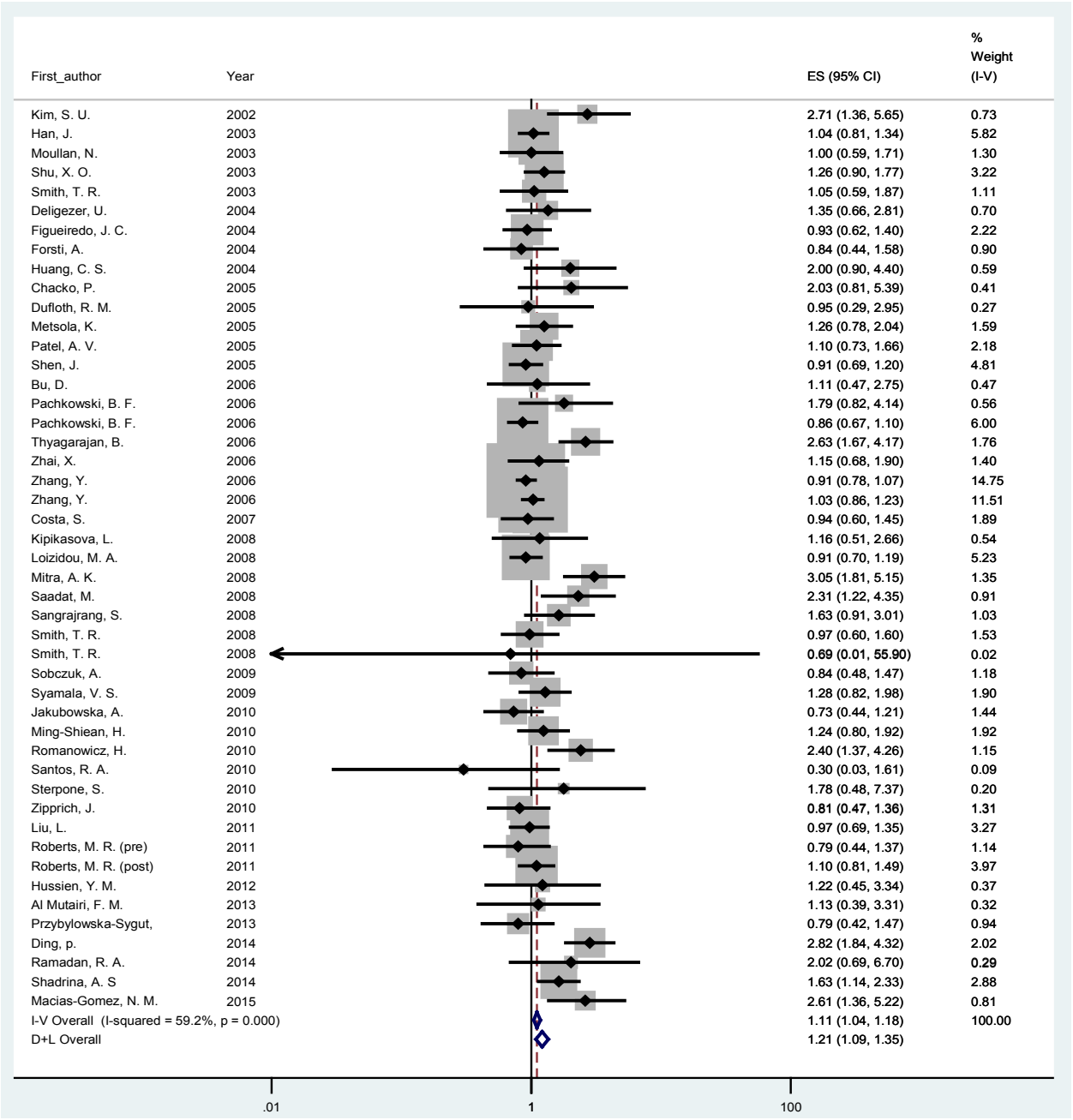

Figure 6. Fixed and Random Effect Model Meta-Analysis of XRCC1 Arg399Gln Polymorphism for Gln/Gln vs. Gln/Arg and Arg/Arg (Recessive) Genetic Models and Risk of Breast Cancer. The Effect Size is Odds Ratio.

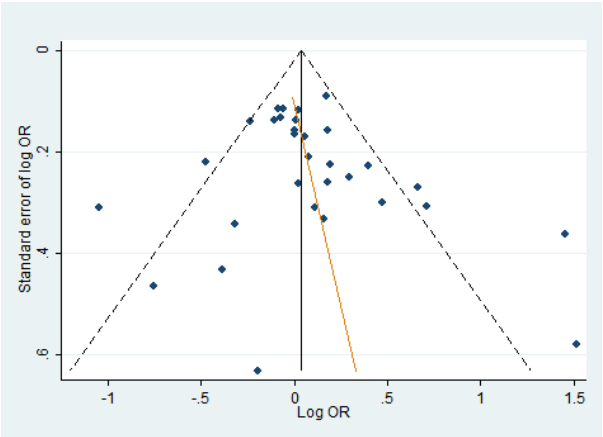

Figure 7. Funnel Plot of Arg194Trp Polymorphism for Trp/Trp and Arg/Trp vs. Arg/Arg (Dominant) Genetic Models with Regression Line Corresponding to the Egger's Regression Test for Funnel-Plot Asymmetry.

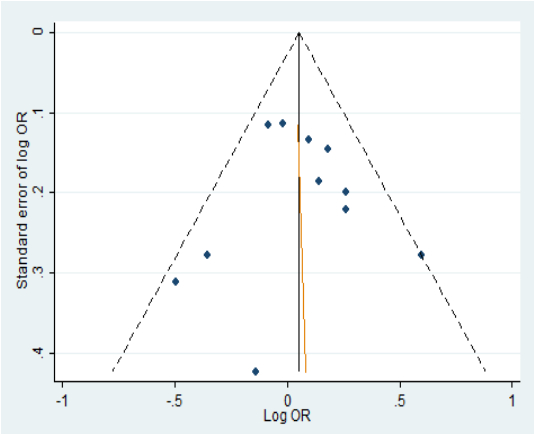

Figure 8. Funnel Plot of XRCC1 Arg280His Polymorphism for His/His and His/Arg vs. Arg/Arg for (Dominant) Genetic Models with Regression Line Corresponding to the Egger's Regression Test for Funnel-Plot Asymmetry.

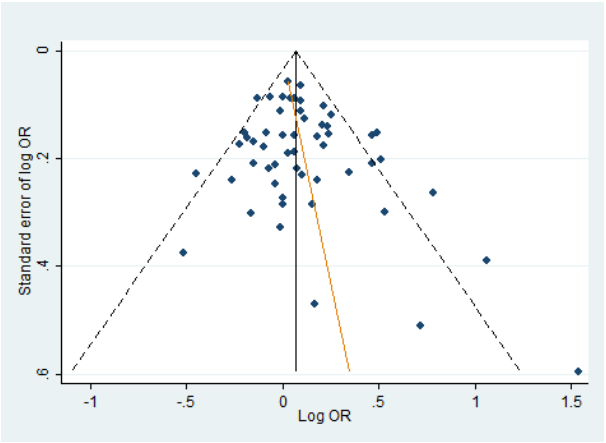

Figure 9. Funnel Plot of XRCC1 Arg399Gln Polymorphism for Gln/Gln and Gln/Arg vs. Arg/Arg (Dominant) Genetic Models with Regression Line Corresponding to the Egger's Regression Test for Funnel-Plot Asymmetry.

(2009) that showed no association between the Arg194Trp polymorphism and risk of breast cancer and the other one by Feng et al (2014) who pooled the studies for cancer as whole and did not report on breast cancer alone. Feng et al (2014) reported elevated risk of cancer among carriers of this polymorphism. Our result is consistent with Huang Y (2009) when it compares the overall results (no association) however, in subgroup analysis; we found increased risk of breast cancer for carrier of this polymorphism among hospital based case control studies.

In conclusions, the XRCC1 polymorphisms (Arg399Gln, Arg280His, or Arg194Trp) act as background risk for people who are carrier of these polymorphisms. Further individual genetic association studies are needed to further our understanding of breast cancer risk among carrier of these polymorphisms.

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