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Original Article

Association of three single nucleotide polymorphisms of *ESR1* with breast cancer susceptibility: a meta-analysis

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Abstract

Expression of estrogen receptors is correlated with breast cancer risk, but inconsistent results have been reported. To clarify potential estrogen receptor (ESR)-related breast cancer risk, we analyzed genetic variants of *ESR1* in association with breast cancer susceptibility. We performed a meta-analysis to investigate the association between rs2234693, rs1801132, and rs2046210 (single nucleotide polymorphisms of *ESR1*), and breast cancer risk. Our analysis included 44 case-control studies. For rs2234693, the CC genotype had a higher risk of breast cancer compared to the TT or CT genotype. For rs2046210, the AA, GA, or GA + GG genotype had a much higher risk compared to the GG genotype. No significant association was found for the rs1801132 polymorphism with breast cancer risk. This meta-analysis demonstrates association between the rs2234693 and rs2046210 polymorphisms of *ESR1* and breast cancer risk. The correlation strength between rs2234693 and breast cancer susceptibility differs in subgroup assessment by ethnicity.

Keywords: breast cancer, estrogen receptor alpha, meta-analysis, single nucleotide polymorphism

Introduction

Breast cancer is one of the leading causes of cancer mortality in women worldwide[1]. Many environmental exposures contribute to breast cancer risk, including exposure to some organic solvents, polycyclic aromatic hydrocarbons (PAHs), organic chlorine compounds, pesticides, and ingestion of food contaminated by fungus, bacteria, and heavy metals, such as cadmium, chromium, lead, and arsenic[2-3]. However, newer genomics technology has also identified genetic variations as risk factors for breast cancer[4]. *BRCA1* was the first gene found to be associated with breast cancer risk[5], although two other well-known genes, *HER2* and *BRCA2*, are also associated with breast cancer risk[6-7].

Khan *et al.* reported that estrogen receptor (ESR) expression is also associated with breast cancer susceptibility[8]. Breast tissue exposed long-term to high levels of estrogen may develop cancer, which can result from ESR stimulation by estrogen-mediated aberrant gene expression[9].

More recently, *ESR1*-induced carcinogenesis in mammary tissues has been explained by epigenetic

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mechanisms. Indeed, *ESR1* methylation may influence activity of normal breast tissue[10]. ESRs have two typical types, ESR-alpha and ESR-beta, which are encoded by *ESR1* and *ESR2*, respectively. *ESR1* (6q25.1) single nucleotide polymorphisms (SNPs) are associated with tumor carcinogenesis, cell proliferation, and metastasis[11]. For example, *Pvu*II (rs2234693) and *Xba*I (rs9340799) polymorphisms located in intron 1 are correlated with breast cancer[12], prostate cancer[13], and systemic lupus erythematosus[14].

However, other studies have found inconsistent results. For example, Li *et al.* found no significant correlation between rs9340799 and breast cancer risk[15]. Zhang *et al.* conducted a meta-analysis of *ESR1* SNPs associated with breast cancer risk, although that study did not include rs2046210, an important novel SNP[16]. Considering the heterogeneous approaches and limited sample sizes of earlier studies, we performed a larger sample size-based meta-analysis of published reports of three of the most studied *ESR1* SNPs: rs2234693, rs1801132, and rs2046210. Our included studies covered reports published in both Chinese and English, since most studies published were conducted by Chinese researchers and the association between rs2046210 and breast cancer risk was first found in China[17].

Materials and methods

Search strategy

We performed a systematic search of English and Chinese databases, including PubMed, Web of Science, Embase, Springer, China National Knowledge Infrastructure (CNKI) (http://www.cnki.net), Wanfang Data (http://www.wanfangdata.com.cn), and VIP (http://www.cqvip.com). We searched these databases by using key terms including "ESR1", "ESR-alpha", "ESR α", "breast cancer risk", and "breast cancer susceptibility". The most recent search was performed on January 1, 2016.

Data extraction

Two researchers, H.X. and J.L., independently extracted information from the literature. Entered data were double-checked to ensure accuracy, and inconsistent data were resolved by discussion. In total, 177 studies were related to the key terms. Data were included in the meta-analysis if they met the following criteria (***Fig. 1***): (i) included recent pathology diagnosed as breast cancer; (ii) reported association between risk of breast cancer and one or more of the four *ESR1* polymorphisms; (iii) included case-control studies; (iv) included adult women as study subjects; (v) results were adjusted for age and body mass index; (vii) genotypes of controls followed Hardy–Weinberg equilibrium. Studies were excluded if: (i) the full article was not accessible; (ii) drugs that may be an interactive factor, such as tamoxifen, were included; (iii) results mainly focused on the mechanism of *ESR1* influencing breast cancer; (iv) the study based on most samples was selected from overlapped ones.

From each study, the following information was

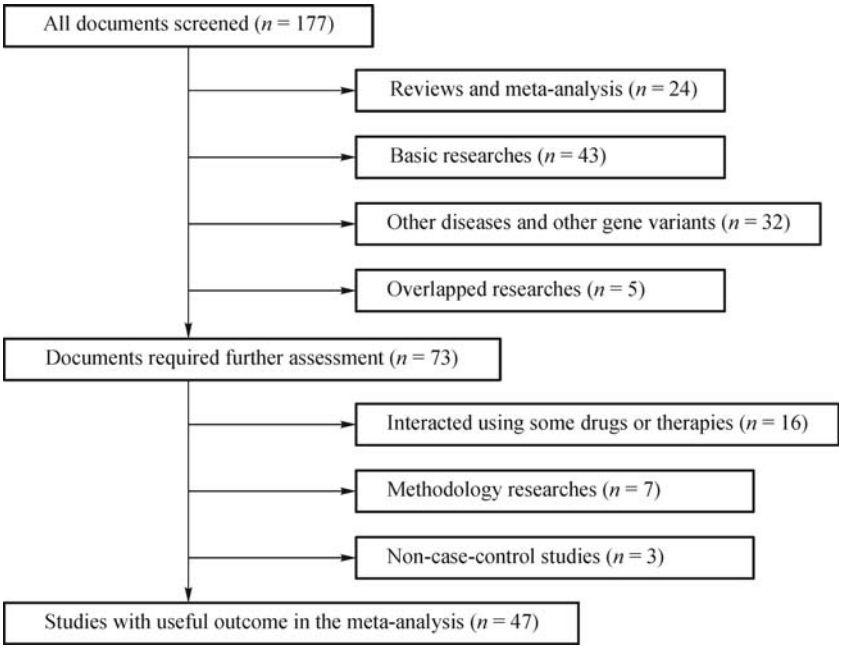

Fig. 1 **Flow diagram of data extraction**

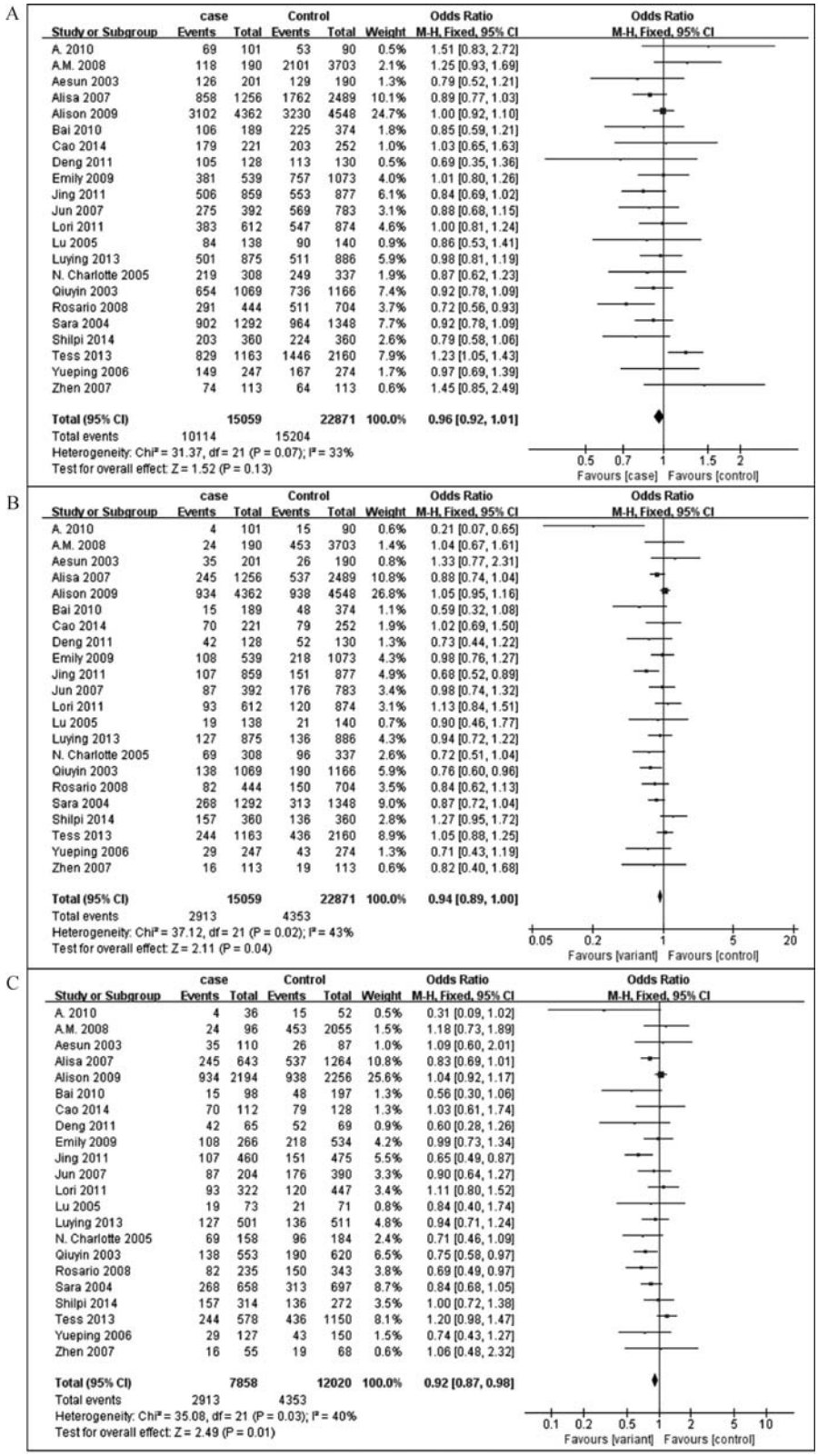

Fig. 2 **Forest plot of the association between breast cancer risk and rs2234693 polymorphism in all population.** A: dominant model (TT + TC *vs*. CC), B: recessive model (TT *vs*. TC + CC), C: homozygous model (TT *vs*. CC).

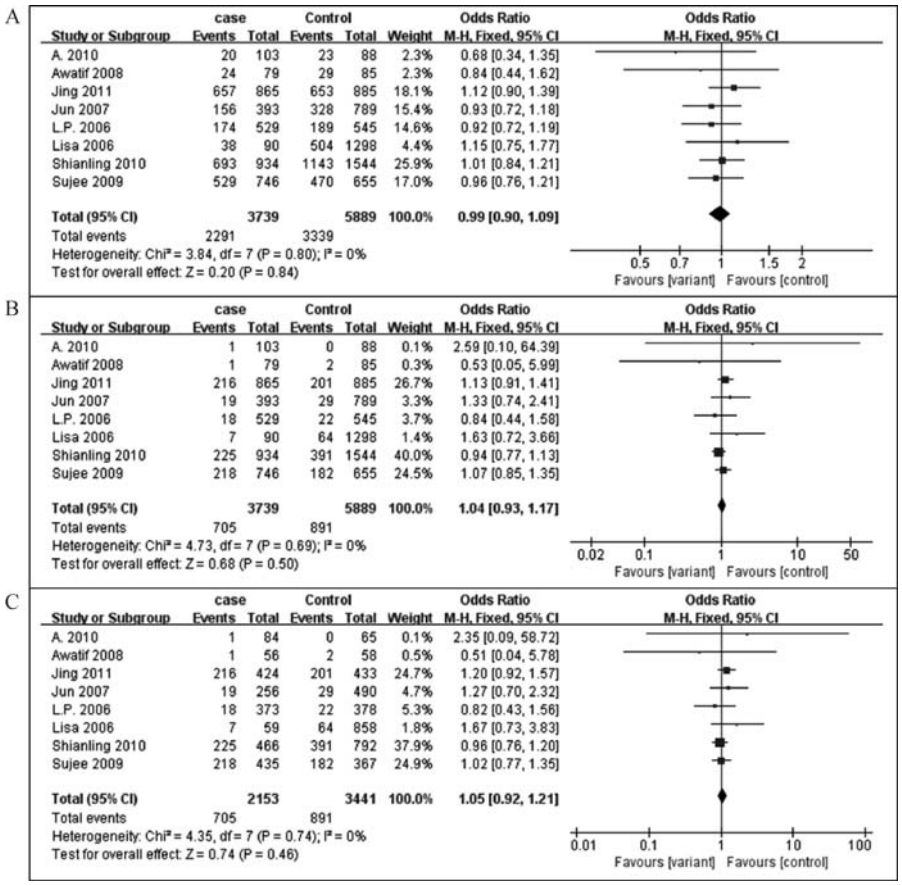

Fig. 3 **Forest plot of the association between breast cancer risk and rs1801132 polymorphism in all population.** A: dominant model (CC + CG *vs*. GG), B: recessive model (CC *vs*. CG + GG), C: homozygous model (CC *vs*. GG).

extracted: first author's name, year of publication, country of origin, ethnicity, matching criteria, number of cases and controls, and odds ratio (OR) values. If any information was not included in the study, the term "mixed" was used.

Statistical analysis

Pooled ORs with 95% confidence intervals (CIs) were calculated to assess risk of breast cancer associated with *ESR1* polymorphisms. The I^2 index was used to measure heterogeneity among included studies. An $I^2 \geqslant 50\%$ indicated heterogeneity among studies and a DerSimonian and Laird random-effects model was used to analyze data. Otherwise, we used a Mantel–Haenszel fixed-effects model to analyze data. For each SNP in *ESR1*, we analyzed three inheritance models (dominant, recessive, and homozygous models) when possible.

To explore whether there were differences in results of the above meta-analysis in different ethnicities, we performed a subgroup-analysis on each SNP by ethnicity. Asians and/or Han Chinese were regarded as subgroup 1, and Europeans and/or Caucasians as subgroup 2. Publication bias was tested with funnel plots and Egger's test, and Forest plots were used to present pooled results. Sensitivity analysis was used to evaluate the stability of results by removing some of the studies, the sizes of which were significantly larger than others or the results were significantly different from other studies. All analyses, except the Egger's test (using Stata V12.0), were performed using Review Manager V5.3.

Results

As shown in ***Fig. 1***, 177 studies were identified and reviewed. After inclusion and exclusion procedures were applied, 47 studies were included in the meta-analysis, comprising 137,451 cases and 145,391 controls. Details of each included study are described in ***Table 1.***

According to I^2 indexes of all three SNPs, we found that heterogeneity existed in dominant (97%), recessive (94%), and homozygous (91%) models of rs2046210, but not in any inheritance models of rs2234693 and rs1801132. Thus, a fixed-effects model was used to analyze studies on rs1801132 and rs2234693. A random-effects model was used for those on rs2046210.

As shown in ***Fig. 2B-C***, we found significant

associations between rs2234693 and breast cancer risk in a recessive model [OR: 0.94, 95%CI (0.89, 0.996)] and homozygous model [OR: 0.92, 95%CI (0.87, 0.98)]. Significant associations were also found for rs2046210 in all three inheritance models (***Fig. 4A-C***). No significant associations were found for rs1801132 (***Fig. 3***).

Funnel plots and Egger's test were used to represent publication bias for the three SNPs (***Fig. 5***). We found no publication bias for any of the three inheritance

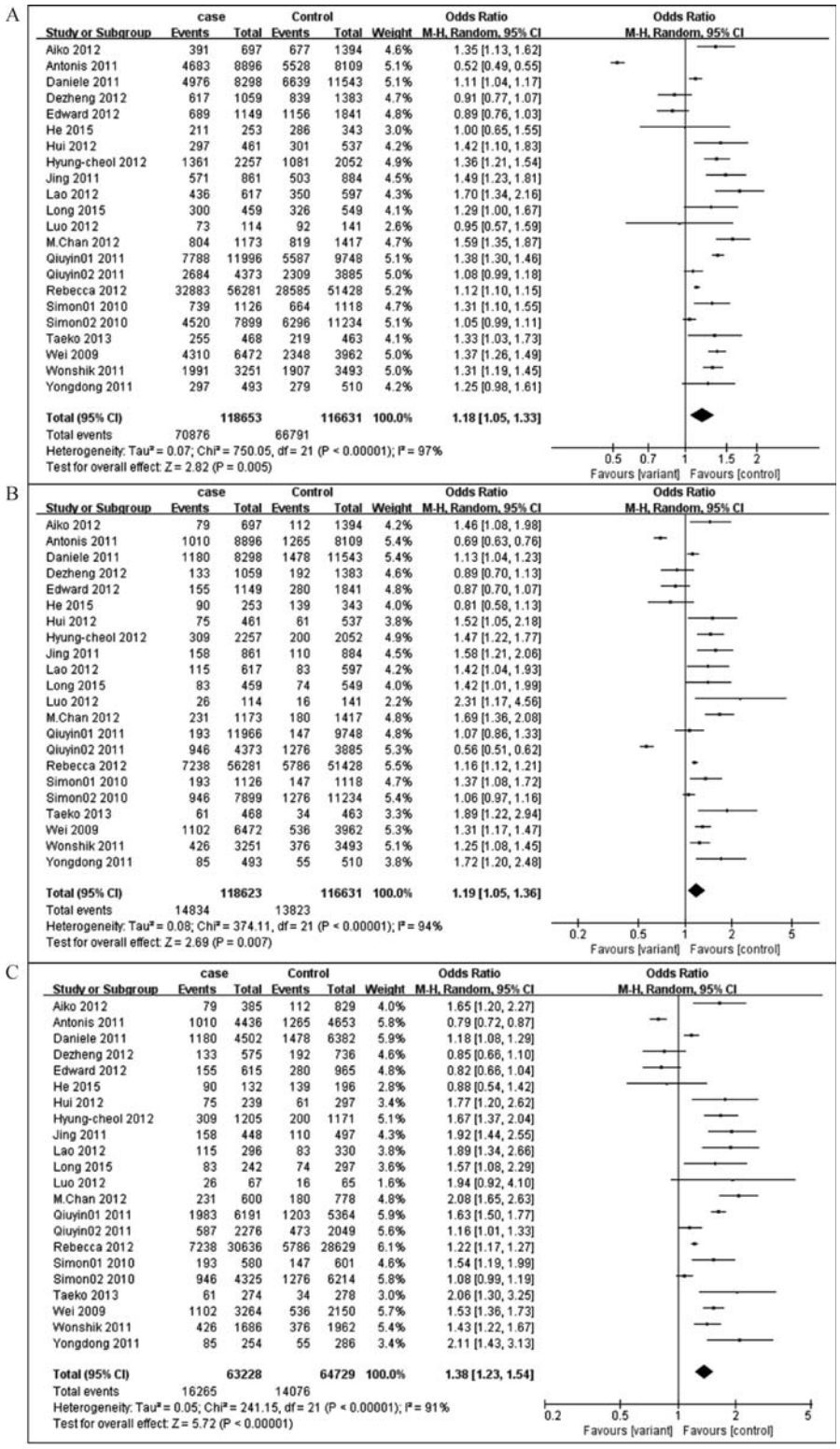

Fig. 4 **Forest plot of the association between breast cancer risk and rs2046210 polymorphism in all population.** A: dominant model (GG + GA *vs*. AA), B: recessive model (GG *vs*. GA + AA), C: homozygous model (GG *vs*. AA).

Table 1 **Characteristics of literatures included in the meta-analysis.**

SNP	Author(ref.)	Year	Country	Ethnicity	Matching Criteria	Sample Size	
						Case	Control
rs2234693	Anghel[18]	2010	Romania	Caucasian	Ethnicity	101	90
	Gonzalez-Zuloeta[19]	2008	Netherlands	Caucasian	Ethnicity	190	3703
	Shin[20]	2003	Korea	Asian	Area	201	190
	Kjaergaard[21]	2007	Denmark	Caucasian	Ethnicity	1256	2489
	Dunning[22]	2009	Mixed	Mixed	Mixed	4548	4362
	Bai[23]	2010	China	Han	Ethnicity	189	374
	Cao[24]	2014	China	Asian	Area	221	252
	Deng[25]	2011	China	Asian	Area	128	130
	Sonestedt[26]	2009	Sweden	Caucasian	Ethnicity	539	1073
	Han[27]	2011	China	Asian	Area	859	877
	Wang[28]	2007	USA	Caucasian	Ethnicity	392	783
	Sakoda[29]	2011	China	Asian	Area	612	874
	Lu[30]	2005	China	Asian	Area	138	140
	Tang[31]	2013	China	Asian	Area	875	886
	Onland-Moret[32]	2005	Netherlands	Caucasian	Ethnicity	308	337
	Cai[33]	2003	China	Asian	Area	1069	1166
	Gonzalez-Mancha[34]	2008	Spain	Caucasian	Ethnicity	444	704
	Wedren [35]	2004	Sweden	Caucasian	Ethnicity	1292	1348
	Chattopadhyay [36]	2014	India	Asian	Area	360	360
	Clendenen[37]	2013	Sweden	Caucasian	Ethnicity	1163	2106
	Shen[38]	2006	China	Asian	Area	247	274
	Hu[39]	2007	China	Asian	Area	113	113
rs1801132	Anghel[18]	2010	Romania	Caucasian	Ethnicity	103	88
	Awatif[40]	2008	Sudan	Caucasian	Ethnicity	79	85
	Han[27]	2011	China	Asian	Area	865	885
	Wang[28]	2007	USA	Caucasian	Ethnicity	393	789
	Fernandez[41]	2006	Spain	Caucasian	Ethnicity	529	545
	Ding[42]	2010	India	Asian	Area	934	1544
	Jeon[43]	2009	Korean	Asian	Area	746	655
	Gallicchio[44]	2006	USA	Caucasian	Ethnicity	90	1298

Table 1 **Characteristics of literatures included in the meta-analysis.** (continued)

SNP	Author(ref.)	Year	Country	Ethnicity	Matching Criteria	Sample Size	
						Case	Control
Rs2046210	Sueta[45]	2012	Japan	Asian	Area	697	1394
	Antoniou[46]	2011	USA	Caucasian	Ethnicity	8896	8109
	Campa[47]	2011	Germany	European	Area	8298	11543
	Huo[48]	2012	USA	African	Ethnicity	1059	1383
	Ruiz-Narvaez[49]	2012	USA	African–American	Ethnicity	1149	1841
	He[50]	2015	China	Asian	Area	253	343
	Guo[51]	2012	China	Han	Ethnicity	461	537
	Kim[52]	2012	Korea	Asian	Area	2257	2052
	Lao[53]	2012	China	Asian	Area	617	597
	Zhou[54]	2015	China	Asian	Area	459	549
	Luo[55]	2012	China	Asian	Area	114	141
	Chan[56]	2012	China	Asian	Area	1173	1417
	Han[27]	2011	China	Asian	Area	861	884
	Cai01[57]	2011	Mixed	Asian	Area	11996	9748
	Cai02[57]	2011	Mixed	European	Area	4373	3885
	Hein[58]	2012	Mixed	Mixed	Ethnicity	56281	51428
	Stacey01[59]	2010	Mixed	Asian	Area	1126	1118
	Stacey02[59]	2010	Mixed	European	Area	7899	11234
	Mizoo[60]	2013	Japan	Asian	Area	468	463
	Zheng[17]	2009	USA	European	Area	6472	3962
	Han[61]	2011	Korea	Asian	Area	3251	3493
	Jiang[62]	2011	China	Asian	Area	493	510

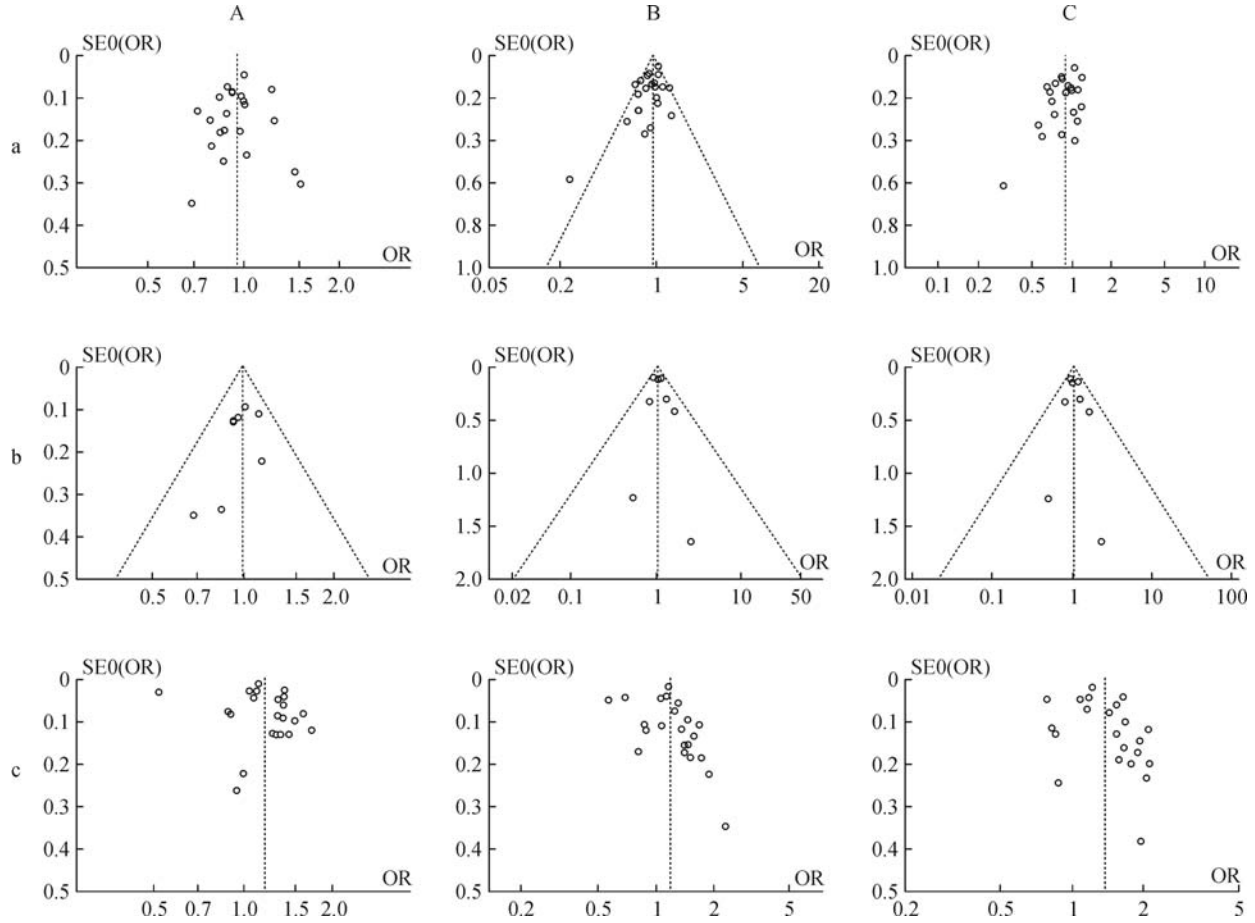

Fig. 5 **Funnel plots of the association between breast cancer risk and all three polymorphisms in all populations.** (A) dominant model, (B) recessive model, (C) homozygous model, (a) rs2234693, (b) rs1801132, (c) rs2046210. Two symmetric oblique dotted lines was used to mark Mantel–Haenszel fixed-effects models.

models of rs1801132 (P = 0.272, 0.493, and 0.631, for dominant, recessive, and homozygous model, respectively) and rs2046210 (P = 0.568, 0.489, and 0.196, respectively). For rs2234693, we observed possible bias in the recessive model (P = 0.553, 0.045, and 0.053, respectively).

Tables 2-4 show the results of our subgroup analyses. For rs2234693, subgroup 1 retained strong association with breast cancer susceptibility, and heterogeneity was low among the studies (three I^2 values were all less than 50%). In subgroup 2, only the homozygous model showed strong association with low heterogeneity (***Table 2***); no significant correlation was shown in the other two groups. In addition, for rs1801132, the results for the two subgroups were negative (***Table 3***); thus, independent of subgroup, the rs1801132 polymorphism might not have significance for breast cancer risk. For rs2046210, the two subgroups both had strong positive results (***Table 4***); thus, correlation between rs2046210 and breast cancer risk was not affected by ethnicity.

Finally, we performed sensitivity analysis to evaluate whether our results were stable. First, we removed the study from Anghel *et al.*[18] for its significant OR values (0.68, 2.59, 2.35, ***Fig. 3***) and re-analyzed the associa-

Table 2 **Subgroup meta-analysis of the association between the rs2234693 polymorphism and breast cancer risk.**

Subgroup[$]	Dominant model			Recessive model			Homozygous model		
	I^2(%)	Ph[*]	OR (95%CI)	I^2(%)	Ph[*]	OR(95%CI)	I^2(%)	Ph[*]	OR(95%CI)
1	0	0.75	0.92 (0.85, 0.99)	11	0.33	0.85 (0.76, 0.95)	43	0.06	0.89 (0.80, 0.99)
2	63	0.006	0.98 (0.86, 1.11)	52	0.03	0.89 (0.77, 1.04)	35	0.14	0.91 (0.84, 0.99)

[*]*P*-value from heterogeneity test; [$]Subgroup 1: Asian and/or Han population, 2: European and/or Caucasian population.

tion between rs1801132 and breast cancer risk in all three models. Still, no significant correlation was found (P = 0.966, 0.514 and 0.474 for the dominant, recessive and homozygous models, respectively). Besides, we also re-analyzed the association between rs2234693 and breast cancer risk in the recessive model by removing the Anghel *et al.* study[18] due to its potential influence on publication bias. The publication bias no longer existed (P = 0.140) and the association between rs2234693 and breast cancer risk in the recessive model was marginally significant [OR: 0.95, 95%CI (0.90, 1.0004)]. Given that the effect size only changed slightly, we concluded that the results of our meta-analysis were stable.

Discussion

The association between *ESR1* polymorphisms and breast cancer risk has attracted increasingly more attention[8-9]. Although there have been several genetic variations reportedly associated with breast cancer risk, our meta-analysis is the first to include these three polymorphisms of *ESR1*. Among the 44 studies included in our meta-analysis, 29 include Asian populations and 17 include Caucasian populations. The meta-analysis found that a variant genotype (AG or AA) of rs2046210 and one (CC) of rs2234693 were associated with increased risk of breast cancer. However, we did not find associations between breast cancer risk and another *ESR1* SNP, rs1801132.

Previous studies have found that variants of *ESR1* are associated with endometriosis, uterine fibroids, breast cancer, and osteoporosis[19–21,63–65]. ESR and progesterone receptor (PR) status is also important for clinicians to determine whether a patient needs adjuvant therapy and, if so, what type is needed[22,66]. The mechanism for this influence of ESR may be through estrogen, which generally stimulates ESR-mediated transcription, thereby increasing the number of errors during DNA replication as well as rate of cell proliferation[23,67].

Rs2234693 is intronic and possibly affects receptor function *via* altered pre-mRNA splicing. Herrington *et al.* found that the C allele of rs2234693 produces a functional binding site for transcription factor B-Myb, significantly increasing transcription of a downstream reporter construct compared to the T allele[24,68], which may explain its high correlation with breast cancer risk.

Rs2046210, located upstream of *ESR1*, is strongly and consistently associated with breast cancer risk in a three-stage genome-wide association study[17]. It should be noted that rs2046210 is also associated with bone mineral density, a trait that is affected by estrogen[25]. In our analysis, rs2046210 was significantly associated with risk of breast cancer in all three models, indicating that variant A carriers have a higher risk of breast cancer compared to GG homozygotes. Stacey *et al.* hypothesized that it was the polymorphism itself or causal variants in linkage disequilibrium that might regulate *ESR1* expression and elevate susceptibility to breast cancer[29,59]. However, direct evidence of whether rs2046210 affects *ESR1* expression is lacking; therefore, further investigations are required[27,70]. Sun *et al.*[28,71] found that SNP rs2046210 may increase expression of *AKAP12*, a functional gene located ~26.8 kb upstream of SNP rs2046210 that is associated with malignancy and metastasis in many cancer types, including breast cancer[29,72], expression in both normal tissues and tumor tissues. This regulation may explain how the genetic variations in this locus play a role in multiple stages of breast cancer development, including initiation, progression, and metastasis.

Table 3 **Subgroup meta-analysis of the association between the rs1801132 polymorphism and breast cancer risk.**

Subgroup[$]	Dominant model			Recessive model			Homozygous model		
	I^2 (%)	Ph[*]	OR (95%CI)	I^2 (%)	Ph[*]	OR (95%CI)	I^2 (%)	Ph[*]	OR (95%CI)
1	0	0.6	1.03 (0.91, 1.16)	0	0.4	1.03 (0.91, 1.16)	0	0.45	1.04 (0.90, 1.21)
2	0	0.77	0.93 (0.80, 1.09)	0	0.64	1.15 (0.79, 1.68)	0	0.63	1.12 (0.77, 1.65)

[*]P-value from heterogeneity test; [$]Subgroup 1: Asian and/or Han population, 2: European and/or Caucasian population.

Table 4 **Subgroup meta-analysis of the association between the rs2046210 polymorphism and breast cancer risk.**

Subgroup[$]	Dominant model			Recessive model			Homozygous model		
	I^2 (%)	Ph[*]	OR (95%CI)	I^2 (%)	Ph[*]	OR (95%CI)	I^2 (%)	Ph[*]	OR (95%CI)
1	73	< 0.00001	1.34 (1.24, 1.44)	66	0.0002	1.37 (1.23, 1.53)	76	< 0.00001	1.62 (1.44, 1.83)
2	90	< 0.00001	1.14 (1.03, 1.27)	65	0.03	1.15 (1.05, 1.25)	85	0.0001	1.22 (1.06, 1.41)

[*]P-value from heterogeneity test; [$]Subgroup 1: Asian and/or Han population, 2: European and/or Caucasian population.

Interestingly, rs1801132 is reported to influence mRNA stability and translation efficiency and predict exonic splicing enhancers[30,73]. However, we found no significant association in this meta-analysis. Hence, it is implied that there are some other unknown metabolisms contributing to the varying influence of different SNPs on ESR1 expression.

Zhang *et al.* performed a meta-analysis on associations between rs2234693 and rs1801132 and breast cancer and found that individuals with a TT + TC or TT genotype in rs2234693 had a higher risk of developing breast cancer than those with a CC genotype[16], which is consistent with our results. However, we also provided a subgroupanalysis with more details. For rs2234693, Caucasian patients were likely to develop breast cancer in a homozygous model, indicating that the association between rs2234693 and breast cancer risk was stronger in Asians, but not non-correlated in Caucasians as previously reported. Our negative result on rs1801132 also gave a further justification to Zhang *et al.* and Sun *et al.* [31,74], but is inconsistent with Li *et al.* [32,75], which may be due to its limited sample sizes and different inclusion or exclusion criteria with ours.

Possible bias was observed for rs2234693 in the recessive model, which may be due to the significantly lower OR value reported by Anghel *et al.* [18]. Through the sensitivity analysis, we found that the upper bound of 95%CI was changed to 1.0004 after removing the study of Anghel *et al.* We concluded that the influence of publication bias was limited as our results are stable.

To the best of our knowledge, this meta-analysis included the most recently published articles reporting the association between *ESR* gene SNPs with breast cancer. We believe that our study provided more evidence supporting further investigation on *ESR* gene. We acknowledge that there were some limitations of our study. For rs1801132, our sample size was limited. However, as most studies did not report smoking, blood pressure, or other environmental factors for subgroups, it was not possible for us to perform stratified analyses.

In conclusion, our meta-analysis demonstrated a link between the rs2234693 and rs2046210 polymorphisms of *ESR1* and breast cancer risk. In addition, the correlation strength between rs2234693 and breast cancer susceptibility differs in subgroup assessment by ethnicity. Based on a much larger sample size, our results gave further justifications and supplements to previous works and clarified the inconsistency of their contradictory results.

Acknowledgements

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