Association of three single nucleotide polymorphisms of \textit{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 \textit{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 \textit{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 \textit{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\textsuperscript{[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\textsuperscript{[2-3]}. However, newer genomics technology has also identified genetic variations as risk factors for breast cancer\textsuperscript{[4]}. \textit{BRCA1} was the first gene found to be associated with breast cancer risk\textsuperscript{[5]}, although two other well-known genes, \textit{HER2} and \textit{BRCA2}, are also associated with breast cancer risk\textsuperscript{[6-7]}.

Khan \textit{et al.} reported that estrogen receptor (ESR) expression is also associated with breast cancer susceptibility\textsuperscript{[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\textsuperscript{[9]}

More recently, \textit{ESR1}-induced carcinogenesis in mammary tissues has been explained by epigenetic
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 alpha", "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; (vi) 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...
**ESR1** polymorphisms and breast cancer risk

**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).
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 $I^2 \geq 50\%$ 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
| SNP  | Author(ref.) | Year  | Country   | Ethnicity | Matching Criteria | Sample Size |
|------|--------------|-------|-----------|-----------|-------------------|-------------|
|      |              |       |           |           |                   |             |
| 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   |
|       | Bar[23]      | 2010  | China     | Han       | Ethnicity         | 189 374     |
|       | Cad[24]      | 2014  | China     | Asian     | Area              | 221 252     |
|       | Deng[25]     | 2011  | China     | Asian     | Area              | 128 130     |
|       | Sonested[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     |
|       | Ca[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     | Caucasian | Ethnicity         | 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     |
|       | Anghel[40]   | 2010  | Romania   | Caucasian | Ethnicity         | 103 88      |
|       | Awatif[41]   | 2008  | Sudan     | Caucasian | Ethnicity         | 79 85       |
|       | Han[42]      | 2011  | China     | Asian     | Area              | 865 885     |
|       | Wang[43]     | 2007  | USA       | Caucasian | Ethnicity         | 393 789     |
|       | Fernandez[44] | 2006  | Spain     | Caucasian | Ethnicity         | 829 545     |
|       | Ding[45]     | 2010  | India     | Asian     | Area              | 934 1544    |
|       | Jeon[46]     | 2009  | Korean    | Asian     | Area              | 746 655     |
|       | Gallicchio[47] | 2006  | USA       | Caucasian | Ethnicity         | 90 1298     |
| 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-Narvae[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  |
| Charn[56] | 2012     | China | Asian Area |                   |                   | 1173        | 1417 |
| Han[57] | 2011         | China | Asian Area |                   |                   | 861         | 884  |
| Ca01[58] | 2011       | Mixed | Asian Area |                   |                   | 11996       | 9748 |
| Ca02[59] | 2011       | Mixed | European Area |                   |                   | 4373        | 3885 |
| Heng[60] | 2012       | Mixed | Mixed Ethnicity |           |                   | 56281       | 51428|
| Stacey01[61] | 2010   | Mixed | Asian Area |                   |                   | 1126        | 1118 |
| Stacey02[62] | 2010   | Mixed | European Area |       |                   | 7899        | 11234|
| Mizoe[63] | 2013       | Japan  | Asian Area |                   |                   | 468         | 463  |
| Zheng[64] | 2009      | USA    | European Area |             |                   | 6472        | 3962 |
| Han[65] | 2011       | Korea  | Asian Area |                   |                   | 3251        | 3493 |
| Jiang[66] | 2011       | China  | Asian Area |                   |                   | 493         | 510  |
models of rs1801132 ($P = 0.272, 0.493, \text{ and } 0.631$, for dominant, recessive, and homozygous model, respectively) and rs2046210 ($P = 0.568, 0.489, \text{ and } 0.196$, respectively). For rs2234693, we observed possible bias in the recessive model ($P = 0.553, 0.045, \text{ and } 0.053$, 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.\cite{18} for its significant OR values (0.68, 2.59, 2.35, Fig. 3) and re-analyzed the associa-

![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.](image)

| Subgroup\(^a\) | 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             | 0.75 | 0.92 (0.85, 0.99) | 0.33 | 0.85 (0.76, 0.95) | 0.06 | 0.89 (0.80, 0.99) |
| 2             | 0.006 | 0.98 (0.86, 1.11) | 0.03 | 0.89 (0.77, 1.04) | 0.14 | 0.91 (0.84, 0.99) |

$^a$P-value from heterogeneity test; $^b$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 \( (P = 0.966, 0.514 \text{ and } 0.474 \text{ for the dominant, recessive and homozygous models, respectively}) \). Besides, we also re-analyzed the association between rs2234693 and breast cancer risk in the recessive model by removing the Anghel \textit{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 \[\text{OR: 0.95, 95\%CI (0.90, 1.0004)}\]. Given that the effect size only changed slightly, we concluded that the results of our meta-analysis were stable.

**Discussion**

The association between \textit{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 \textit{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 \textit{ESR1} SNP, rs1801132.

Previous studies have found that variants of \textit{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 \textit{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 \textit{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 \textit{et al.} hypothesized that it was the polymorphism itself or causal variants in linkage disequilibrium that might regulate \textit{ESR1} expression and elevate susceptibility to breast cancer\[^{29,59}\]. However, direct evidence of whether rs2046210 affects \textit{ESR1} expression is lacking; therefore, further investigations are required\[^{27,70}\]. Sun \textit{et al.}\[^{28,71}\] found that SNP rs2046210 may increase expression of \textit{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 \( a \) | 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         | 0.93 (0.80, 1.09) | 0 0.4 | 1.03 (0.91, 1.16) | 0 0.4 | 1.03 (0.91, 1.16) | 0 0.45 | 1.15 (0.79, 1.68) | 0 0.6 | 1.12 (0.77, 1.65) |
| 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; \( A \)-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 \( a \) | 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) | 0.66 < 0.00001 | 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) | 0.03 | 1.15 (1.05, 1.25) | 85 0.0001 | 1.22 (1.06, 1.41) |

\( P \)-value from heterogeneity test; \( A \)-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\cite{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\cite{16}, which is consistent with our results. However, we also provided a subgroup analysis 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.\cite{31,74}, but is inconsistent with Li et al.\cite{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.\cite{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.

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