Association Between ESR1 Pvull, XbaI, and P325P Polymorphisms and Breast Cancer Susceptibility: A Meta-Analysis

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Background: Breast cancer is one of the leading causes of cancer-related deaths for women. Numerous studies have shown that single-nucleotide polymorphisms (SNPs) on the ESR1 gene are associated to this disease. However, data and conclusions are inconsistent and controversial.

Material/Methods: To investigate the association between Pvull (rs2234693), XbaI (rs9340799) and P325P (rs1801132) polymorphisms of ESR1 gene with the risk of breast cancer under different population categorizations, we searched multiple databases for data collection, and performed the meta-analysis on a total of 25 case-control studies. Three different comparison models – dominant model, recessive model, and homozygote comparison model – were applied to evaluate the association.

Results: Our results indicated that people with TT+TC or TT genotype were at a greater risk of developing breast cancer than those with CC genotype in the Pvull polymorphism. While for XbaI and P325P polymorphisms, no significance was found using any of the 3 models. Furthermore, the data were also stratified into different subgroups according to the ethnicity (white or Asian) and source of controls (hospital-based or population-based), and separate analyses were conducted to assess the association. The ethnicity subgroup assessment showed that the higher risk of breast cancer for TT genotype of Pvull polymorphism than CC genotype only occurred in Asian people, but not in white populations. For the source-stratified subgroup analysis, significant association suggested that people with TT + TC genotype were at a greater risk of developing breast cancer than those with CC genotype in the hospital-based subgroup.

Conclusions: Thus, this meta-analysis clarified the inconsistent conclusions from previous studies, conducted analyses for the entire population as well as for different subgroups using diverse population categorization strategies, and has the potential to help provide a personalized risk estimate for breast cancer susceptibility.

MeSH Keywords: Estrogen Receptor Modulators • Meta-Analysis • Polymorphism, Genetic

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Breast cancer (BC) is the most common malignant tumor for women worldwide [1]. Similar to other cancer types, genetic factors play a central role in the development and progression of breast cancer [2]. Studies show that excessive estrogen from the exogenous source can have pathological consequences in human cell, and result in the alteration of tumors, including the occurrence of breast cancer [3]. Two major types of estrogen receptors (ESRs), named as ESR1 and ESR2, act as the key regulators in controlling the actions of estrogen. The ESR1 gene encodes a transcription factor with an estrogen-binding domain, an activation domain, and an estrogen response element (ERE) DNA-binding domain. By regulating the cell proliferation and differentiation via paracrine mechanism, ESR1 is believed to be tightly associated with breast cancer [4]. Therefore, genetic variations in the ESR1 gene, which can lead to disordered estrogen activity, become a potential risk for breast cancer. Single-nucleotide polymorphisms (SNPs) of ESR1 have been studied in numerous clinical studies. Many association studies on this gene have been confined to 2 SNPs (originally detected with the restriction enzymes PvuII and XbaI [5]), which are located in the first intron of ESR1. The ESR1 PvuII and XbaI polymorphisms have been associated to tumorigenesis and many other diseases [6], involving heterogeneous conclusions. The meta-analysis conducted by Li et al. concluded that the PvuII polymorphism of ESR1 was a risk factor for prostate cancer development [7], while the meta-analysis conducted by Gu et al. found no association between frequencies of the PvuII (C>T) polymorphism and prostate cancer susceptibility, but found a positive correlation between XbaI (A>G) polymorphism and the risk of prostate cancer [8]. A recent study showed that the ESR1 PvuII CC/CT and XbaI GG/GA genotypes could increase susceptibility to systemic lupus erythematosus (SLE) [9]. Several other meta-analyses suggested that the PvuII variant, instead of XbaI, was negatively associated with Alzheimer’s disease (AD) in white populations, especially in southern European people, but not in Asian populations [7,10]. The risk of idiopathic scoliosis was not obviously associated with the ESR1 PvuII or XbaI polymorphism [11]. It has been also frequently reported that the PvuII and XbaI polymorphisms of the ESR1 gene are related to breast cancer [12,13]. Li and Xu reported that ESR1 PvuII (C>T) polymorphism placed pre-menopausal women at risk for breast cancer, but XbaI (A>G) polymorphism is not associated with the risk of breast cancer [14]. P325P polymorphism in the exon 4 of ESR1 gene has been found to be associated with bone mineral density in post-menopausal women [15]. Korean women carrying both the ESR1 P325P CC and CDK7 Ex2-28C>T (rs2972388) TT genotypes have been shown to be at increased breast cancer risk [16]. However, because of the heterogeneous of data sources and analysis methods, the conclusions in many of these studies were inconsistent and controversial. Although 2 studies have been conducted on this issue, both of them have some drawbacks. Specifically, Li et al. narrowed the population to Asian women [14]. Hu et al. focused on some of SNPs in ESR1, but SNPs like P325P, which is also associated with the risk of breast cancer, was not included in their articles [17]. In this study, we performed an updated meta-analysis by involving as many data as possible from published studies, to provide a more precise estimation of the potential association between ESR1 PvuII, XbaI, and P325P polymorphisms and the risk of breast cancer. We collected all related studies from online databases to assess the association between 3 SNPs on ESR1 and breast cancer susceptibility. In addition, the analyses were conducted for the entire population, as well as for different subgroups using diverse population categorization strategies.

Material and Methods

Search strategy

We performed an online search of PubMed, Elsevier, Science Direct, Karger, Web of Science, Wiley Online Library, and Springer databases for eligible studies on the association between ESR1 PvuII, XbaI, and P325P polymorphisms with breast cancer susceptibility. The related terms, including “ESR1”, “rs2234693”, “rs9340799”, “rs1801132”, “polymorphism”, “breast cancer” and “BC” were used for searching. The literature search was updated on September 2014.

Data collection

A total of 91 results were found in the literature search. Among these studies, only ones which meet the following criteria were included in our meta-analysis: (i) case-control study that focused on breast cancer and ESR1 gene polymorphisms; (ii) ethnicity and source information was available for case and control; (iii) the diagnosis of breast cancer was confirmed by pathological or histological examination; (v) were published in English language. Studies were excluded when they were: (i) irrelevant articles, duplicated articles; (ii) not case-control study; (iii) genotype frequency information was not accessible; and (iv) meta-analysis, letters, reviews, or editorial articles. As a result, 25 articles were eventually included in the meta-analysis. In our data collection procedure we restricted the time frame from Jan. 2000 to Sept. 2014. Since there was no eligible study prior 2003, all included studies were published later than 2003. For each article, the following data were collected: the first author’s last name, year of publication, country of origin, ethnicity, source of controls, and the number and frequency of ESR1 PvuII, XbaI, and P325P polymorphisms of cases or controls.

Statistical methods

We used STATA software (version 12.0) for all analyses. The strength of the association between ESR1 polymorphisms and
breast cancer susceptibility was assessed using all databases by pooled odds ratios (ORs) with 95% confidence intervals (Cis). Three models were used to evaluate the association: dominant model, recessive model, and homoygote comparison model. We also performed subgroup analyses by ethnicity (white or Asian) and source of controls (hospital-based or population-based). The heterogeneity assumption was assessed by I² index. Higher I² indicates more significant heterogeneity. I²<50% represents the dividing point between low and high heterogeneity. When I²≤50%, we assumed that there was no significant heterogeneity between pooled data. Correspondingly, I²>50 was treated as significant heterogeneity. Moreover, based on the I² index, we chose a different model in analysis: Mantel-Haenszel (M-H) fixed-effects model was used to analyze datasets without significant heterogeneity and DerSimonian and Laird (D-L) random-effects model was used to analyze datasets showing obvious heterogeneity. In our meta-analysis, we used M-H fixed-effects model to test the heterogeneity first, and then chose different models based on the testing results. ORs were calculated with each model within 95% confidence intervals. Forest plots were generated to summarize the results. Potential publication bias was assessed by the Begg’s funnel plots and the Egger’s test. All reported P values were for a two-tailed test.

Results

We performed an online search of multiple databases for eligible studies on the association between ESR1 polymorphisms and breast cancer susceptibility. The procedure of article collection is shown in Figure 1. By excluding irrelevant articles, duplicated articles, and articles not focused on ESR1 polymorphisms and breast cancer, we found a total of 25 case-control studies covering 24 740 cases, and 38 866 controls were eligible [12,13,16–38], main characteristics of which are shown in Table 1. For the ethnicity distribution, there were 8 studies of Asians and 15 studies of whites. For the source of controls, 14 studies used population-based controls and 11 studies used hospital-based controls.

To choose a proper model for the study, we first used the I² indexes to evaluate the heterogeneity of the data for all 3 SNPs. As shown in Table 2, for PvuII, the I² indexes ranged from 36% to 48%, and for XbaI and P325P, the I² values were mostly equal to 0% in all 3 tested genetic models. Statistically significant heterogeneities were only observed for PvuII in dominant model TT vs. (TC+CC) and homoygote model (TT vs. CC). The PvuII polymorphism showed a relative higher I² index than the other 2 SNPs mainly because more studies were included in the PvuII analysis. Nevertheless, all of the I² indexes were smaller than 50%, which can be still considered as non-significant heterogeneity. Therefore, the statistical power was still acceptable in our study. Since the I² indexes were smaller than 50%, M-H fixed-effects models were used for all of the 3 SNPs. The forest plots for PvuII, XbaI, and P325P are shown in Figures 2–4, respectively. Overall, we found significant associations between ESR1 PvuII polymorphism and breast cancer susceptibility in both recessive model (TT+TC) vs. CC: OR=1.08, 95% CI (1.02–1.14), p=0.01, Figure 2B) and homoygote model (TT vs. CC: OR=1.10, 95% CI (1.03–1.18), p=0.03, Figure 2C), but not in dominant model (TT vs. (TC+CC): OR=1.05, 95% CI (1.00–1.10), p=0.05, Figure 2A). These results indicated that the people with TT or TC genotype were at a greater risk of developing breast cancer than those with CC genotype in the ESR1 PvuII polymorphism. On the other hand, for XbaI and P325P, no significance was found for all 3 models (GG vs. GA+AA: OR=1.05, 95% CI (0.94–1.18), p=0.37, Figure 3A; GG+GA vs. AA: OR=1.05, 95% CI (0.98–1.12), p=0.15, Figure 3B; GG vs. AA: OR=1.08, 95% CI (0.96–1.21), p=0.22, Figure 3C; CC vs. CC+GG: OR=1.01, 95% CI (0.91–1.11), p=0.90, Figure 4A; CC+CG vs. GG: OR=0.97, 95% CI (0.86–1.09), p=0.60, Figure 4B; CC vs. CC: OR=0.96, 95% CI (0.84–1.10), p=0.56, Figure 4C). We found that there was no significant publication bias based on funnel plot for all 3 SNPs (Figures 5–7). Egger’s and Begg’s tests also indicated that there was no obvious bias for publications investigating the relationship of ESR1 polymorphisms with breast cancer risk, as shown in Table 2.

Figure 1. Flow diagram of studies included in the meta-analysis.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]
Table 1. Characteristics of literatures included in the meta-analysis.

| Author         | Year | Case  | Control  | Country | Ethnicity | Source* | Age | Genotyping method | Premeno-pausal proportion |
|----------------|------|-------|----------|---------|-----------|---------|-----|------------------|---------------------------|
| Madeira        | 2014 | 9     | 49       | 6       | 64        | Brazil  | 72  | PCR-RFLP         | Median: 55                |
| Chattpoadhyay  | 2014 | 39    | 164      | 157     | 360       | India   | 360 | PCR-RFLP         | <50: 44%                  |
| Tang           | 2013 | 127   | 374      | 293     | 875       | China   | 866 | MALDI-TOF        | Mean: 49                  |
| Lu             | 2013 | 57    | 228      | 227     | 542       | China   | 1016| PCR-RFLP         | Mean: 49                  |
| Sakoda         | 2011 | 93    | 290      | 229     | 612       | China   | 876 | PCR-RFLP         | <50: 51.7% SNaPshot assays |
| Han            | 2011 | 107   | 399      | 353     | 859       | China   | 877 | TaqMan           | Mean: 51                  |
| Sonestedt      | 2009 | 108   | 273      | 158     | 539       | Sweden  | 1073| SEQUENOM         | Mean: 57                  |
| Dunning        | 2009 | 938   | 2164     | 1260    | 4362      | UK      | 1518| PCR-RFLP         | N/A                       |
| Ladd           | 2008 | 24    | 94       | 72      | 190       | Netherlands | 3703| Mean: 70        | N/A                       |
| Gonzalez-Mancha| 2008 | 82    | 209      | 153     | 444       | Spain   | 704  | PCR-RFLP         | Mean: 58                  |
| Wang           | 2007 | 87    | 188      | 117     | 392       | USA     | 783  | PCR-MPLA         | Mean: 57                  |
| Kjaergaard     | 2007 | 245   | 613      | 398     | 1256      | Denmark | 2489| TaqMan           | 25%                      |
| Hu             | 2007 | 16    | 58       | 39      | 113       | China   | 113  | PCR-RFLP         | <50: 73%                  |
| Shen           | 2006 | 29    | 120      | 98      | 247       | China   | 274  | PCR-RFLP         | <50: 79%                  |
| Onland-Moret   | 2005 | 69    | 150      | 89      | 308       | Netherlands | 337 | Mean: 57        | PCR-RFLP                 |
| Modugno        | 2005 | 80    | 115      | 53      | 248       | USA     | 3901 | PCR-MPLA         | Mean: 71                  |
| Wedren         | 2004 | 268   | 634      | 390     | 1292      | Sweden  | 1348| PCR-RFLP         | 0%                       |
| Shin           | 2003 | 35    | 91       | 75      | 201       | Korea   | 190  | PCR-RFLP         | 50-74                    |
| Cai            | 2003 | 138   | 516      | 415     | 1069      | China   | 1166| PCR-RFLP         | Mean: 47                  |

| Author         | Year | Case  | Control  | Country | Ethnicity | Source* | Age | Genotyping method |
|----------------|------|-------|----------|---------|-----------|---------|-----|------------------|
| Madeira        | 2014 | 12    | 47       | 5       | 64        | Brazil  | 72  | PCR-RFLP         | Median: 55                |
| Sakoda         | 2011 | 22    | 197      | 395     | 614       | China   | 876 | SNaPshot assays  | <50: 51.7%                |
| Dunning        | 2009 | 521   | 1967     | 1682    | 4170      | UK      | 4447| PCR-RFLP         | N/A                       |
| Wang           | 2007 | 19    | 137      | 237     | 393       | USA     | 789  | PCR-MPLA         | Mean: 57                  |
| Slattery       | 2007 | 52    | 235      | 287     | 574       | USA     | 725  | PCR-RFLP         | Mean: 47                  |
Furthermore, we performed subgroup analysis, and results are shown in Tables 3–5. For the subgroup analysis by ethnicity, the $I^2$ indexes for Pvull were larger than 50% in both dominant model and homozygote model for white subgroups, indicating a high heterogeneity in these 2 genetic models (Table 3). Correspondingly, we used the random-effects model for assessing the association in these high-heterogeneity cases, and used the fixed-effects model in other cases. Although the above analysis showed that TT genotype of Pvull had higher risk of breast cancer than CC genotype in all populations, further subgroup assessment demonstrated that only Asians followed this trend (TT vs. CC: OR=1.18, 95% CI (1.04–1.33), $p=0.01$), while whites did not (TT vs. CC: OR=1.13, 95% CI (0.98–1.29), $p=0.09$). For the source-stratified subgroup analysis, significant
Figure 2. Forest plot of the association between breast cancer risk and ESR1 PvuII polymorphism in all population with respect to (A) dominant model (TT vs. TC+CC), (B) recessive model (TT+TC vs. CC), and (C) homozygote model (TT vs. CC).
META-ANALYSIS

Numerous studies have been conducted to investigate the association between breast cancer susceptibility with 3 SNPs on ESR1: PvuII, XbaI, and P325P. However, because of the heterogeneous of data and methods, the conclusions in these studies are inconsistent and controversial. For example, some studies concluded that the PvuII CC and CT genotype significantly increased the risk of breast cancer [12,13]. Some studies claimed that T allele of PvuII conferred a high risk of breast cancer [18,24,32]. Other studies showed that ESR1 PvuII polymorphism did not have any significant effect on breast cancer [19,21,25,27,28]. Given these results, it is necessary to perform a meta-analysis to clarify this issue, which can rapidly and effectively increase sample size by combining data of association studies, thus enhancing the statistical power of analysis to estimate the genetic effects. Pooling data from different studies also has the advantage of reducing random errors. With the accumulation of the studies over the years, we performed an updated meta-analysis, by including 3 SNPs of ESR1 and by involving as many data as possible from published studies, to provide a more comprehensive and reliable estimation of the potential association correlation between ESR1 PvuII, XbaI, and P325P polymorphisms and the risk of breast cancer. In the present study, our results showed that genotype TT+TC or TT in ESR1 PvuII were significantly associated with increased breast cancer risk in overall population compared to AA, but no obvious association was found between breast cancer risk and ESR1 XbaI and P325P polymorphism in all population with respect to (A) dominant model (GG vs. GA+AA), (B) recessive model (GG+GA vs. AA) and (C) homozygote model (GG vs. AA).

Discussion

In recent years, the association of genetic susceptibility to cancers has drawn more and more attention to the study of polymorphisms of genes involved in tumorigenesis and other diseases. Numerous studies have been conducted to investigate the association between breast cancer risk and ESR1 XbaI polymorphism in all population with respect to (A) dominant model (GG vs. GA+AA), (B) recessive model (GG+GA vs. AA) and (C) homozygote model (GG vs. AA).
with CC genotype. The ESR1 PvuII polymorphism is intronic and possibly affects receptor function by changing ESR1 expression levels or altering its pre-mRNA splicing. Herrington et al. found that the C allele of PvuII produced a functional binding site for a transcription factor B-Myb, which resulted in significantly increasing transcription of a downstream reporter construct compared to the T allele [39]. This indicates that CC genotype correlates with a higher ESR1 transcriptional level and may explain our observation that TT+TC or TT genotypes were associated with higher breast cancer risk than was CC genotype, but further functional studies are needed to investigate the functions of these alleles.

It is likely that the tumorigenesis of breast cancer is affected by many factors such as age, ethnicity, environment, and other variables. We therefore performed subgroup analysis...
Table 3. Subgroup meta-analysis of the association between ESR1 PvuII polymorphisms and breast cancer risk.

| Subgroup | TT vs. TC+CC | TT+TC vs. CC | TT vs. CC |
|----------|--------------|--------------|-----------|
|          | i² (%) | ph* | OR (95%CI) | pOR* | i² (%) | ph* | OR (95%CI) | pOR* | i² (%) | ph* | OR (95%CI) | pOR* |
| Ethnicity |        |    |           |       |        |    |           |       |        |    |           |       |
| Caucasian | 58.5   | 0.01 | 1.06 (0.95–1.18) | 0.28 | 31.9   | 0.14 | 1.05 (0.98–1.12) | 0.16 | 56.1   | 0.01 | 1.13 (0.98–1.29) | 0.09 |
| Asian    | 10.0   | 0.35 | 1.05 (0.97–1.14) | 0.24 | 38.0   | 0.01 | 1.17 (1.04–1.31) | 0.12 | 33.8   | 0.16 | 1.18 (1.04–1.33) | 0.01 |
| Source   |        |    |           |       |        |    |           |       |        |    |           |       |
| HB       | 74.6   | <0.01 | 1.02 (0.83–1.26) | 0.83 | 15.0   | 0.32 | 1.15 (1.03–1.28) | 0.02 | 58.9   | 0.02 | 1.13 (0.90–1.43) | 0.28 |
| PB       | 0.0    | 0.77 | 1.04 (0.98–1.10) | 0.23 | 44.2   | 0.05 | 1.05 (0.99–1.12) | 0.13 | 81.3   | <0.01 | 0.78 (0.64–0.94) | 0.01 |

* P-value from heterogeneity test; * P-value from OR test.

based on ethnicity of samples. We found only Asians with TT genotype of ESR1 PvuII polymorphism had a higher risk of breast cancer than people with CC genotype, while whites did not show this trend. This may be attributable to genetic heterogeneity among different populations. We could not rule out the possibility of gene-gene interactions or the possibility of linkage disequilibrium between polymorphisms. Further studies of multiple polymorphisms in ESR1 [40,41] or different genes or gene regulators such as microRNAs [42–44] are needed to address this question. In addition, it is also possible...
that differences in environment and lifestyle between different populations may affect the tumorigenesis of breast cancer.

The heterogeneity between studies could also be from the heterogeneous controls. Therefore, we also conducted a source-stratified subgroup analysis on 14 studies of population-based controls and 11 studies of hospital-based controls, and found significant association in the recessive model of the hospital-based subgroup. Interestingly, we also noticed that TT genotype of ESR1 PvuII polymorphism in the population-based subgroup decreased the risk of breast cancer more than CC genotype. The inconsistent results between different subgroups could come from the possible non-differential misclassification bias because the hospital-based controls might develop more breast cancer than healthy populations in subsequent years. For P325P, only 2 studies were included in subgroup analysis for PB. Given this small sample size, the statistical power is limited. More studies should be conducted to provide a more precise result.

### Table 4. Subgroup meta-analysis of the association between ESR1 XbaI polymorphisms and breast cancer risk.

| Subgroup                  | GG vs. GA+AA | GG+GA vs. AA | GG vs. AA |
|---------------------------|--------------|--------------|-----------|
|                           | I² (%)       | p OR         | I² (%)     | p OR         | I² (%)     | p OR         |
| *Ethnicity*               |              |              |           |              |           |              |
| Caucasian                 | 11.9         | 0.33         | 1.09 (0.96–1.22) | 0.17       | 0.0        | 0.51 (0.97–1.13) | 0.27       | 0.0        | 0.41 (0.98–1.26) | 0.10       |
| Asian                     | 0.0          | 0.67         | 0.85 (0.62–1.16) | 0.30       | 0.0        | 0.89 (0.94–1.20) | 0.34       | 0.0        | 0.73 (0.86–1.20) | 0.42       |
| *Source*                  |              |              |           |              |           |              |
| PB                        | 0.0          | 0.66         | 1.04 (0.93–1.17) | 0.46       | 0.0        | 0.76 (0.98–1.12) | 0.15       | 0.0        | 0.75 (0.95–1.20) | 0.27       |

* P-value from heterogeneity test; * P-value from OR test; ** Analysis on HB is not performed due to the lack of study.

### Table 5. Subgroup meta-analysis of the association between ESR1 P325P polymorphisms and breast cancer risk.

| Subgroup                  | CC vs. CG+GG | CC+CG vs. GG | CC vs. GG |
|---------------------------|--------------|--------------|-----------|
|                           | I² (%)       | p OR         | I² (%)     | p OR         | I² (%)     | p OR         |
| *Ethnicity*               |              |              |           |              |           |              |
| Caucasian                 | 0.0          | 0.81         | 1.06 (0.90–1.24) | 0.50       | 0.0        | 0.51 (0.88 (0.60–1.29) | 0.52       | 0.0        | 0.50 (0.61–1.33) | 0.60       |
| Asian                     | 0.0          | 0.51         | 0.98 (0.87–1.10) | 0.70       | 0.0        | 0.43 (0.87–1.11) | 0.73       | 0.0        | 0.42 (0.84–1.12) | 0.67       |
| *Source*                  |              |              |           |              |           |              |
| HB                        | 0.0          | 0.72         | 1.00 (0.90–1.12) | 0.98       | 0.0        | 0.67 (0.99 (0.88–1.11) | 0.83       | 0.0        | 0.64 (0.85–1.13) | 0.81       |
| PB                        | 0.0          | 0.39         | 1.03 (0.83–1.27) | 0.82       | 0.0        | 0.70 (0.71 (0.44–1.14) | 0.16       | 0.0        | 0.60 (0.72 (0.44–1.18) | 0.19       |

* P-value from heterogeneity test; * P-value from OR test.

### Conclusions

Our study provided a systematic review and updated meta-analysis of genetic association between ESR1 PvuII, XbaI and P325P polymorphisms and the risk of human breast cancer. Using 3 models (dominant model, recessive model, and homozygote comparison model), we confirmed that only PvuII polymorphism was a risk factor for breast cancer susceptibility in the overall population, but not XbaI and P325P SNPs. Moreover, our results suggest that subgroup assessment by ethnicity of samples and source of controls yields results that are different from those using the overall population. Thus, we believe our study clarifies the inconsistent conclusions from previous studies, and will shed some light on future breast cancer-related research.

### Conflict of interest statement

No conflict of interest.
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