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# Association of Polymorphisms in Genes Involved in DNA Repair and Cell Cycle Arrest with Breast Cancer in a Vietnamese Case-Control Cohort

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**Abstract**—Breast cancer (BC) is the most common cancer diagnosis in women worldwide. Among causative BC genes, *MRE11*, *ERCC1*, *TNRC9* (*TOX3*), and *CASC16* play an important role in DNA damage repair; *FGFR2*, *CCNE1*, *ZMIZ1*, and *LSP1* involve in cell cycle checkpoint. A functional polymorphism of these genes may alter DNA repair capacity and genomic stability. Single Nucleotide Polymorphisms (SNPs) can modify the risk of cancer, and thus, SNPs may be considered as potential markers of carcinogenesis. Among them, eight SNPs (rs2981582, rs569550, rs3218035, rs704010, rs2155209, rs3212986, rs12443621 and rs4784227) are significantly associated with BC risk in various populations. This study was conducted to investigate the genetic susceptibility of these SNPs in the development of BC in Vietnamese women. *MRE11* rs2155209 and *CASC162* rs4784227 were found to be associated with BC risk (CC vs. CT + TT: OR = 0.57, 95% CI 0.34 to 0.97, $P = 0.03$ and CT vs. CC + TT: OR = 1.43, 95% CI 1.03 to 1.97, $P = 0.03$; respectively). These findings suggest that SNPs involved in DNA repair genes may affect the susceptibility of BC in Vietnamese women.

**Keywords:** breast cancer, single nucleotide polymorphism, *MRE11*, *rs2155209*, *CASC16*, *rs4784227*.

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## INTRODUCTION

Breast cancer (BC) is one of the most common cancers diagnosed in females worldwide and is a polygenic disease in which inherent factors play a joint role in disease etiology. Several low-frequency, high-penetrance BC predisposition genes have been identified, including *BRCA1* and *BRCA2*. However, most of BC cannot be explained by the above genes (Couch et al., 2014). As a common complex disease, there are some indications of a potential contribution of low-penetrance BC predisposition genes, including genes involved in DNA damage repair and cell cycle arrest.

DNA damage repair and cell-cycle checkpoints avoid genetic instability and mutagenesis. In response to DNA damage, BRCA1 has been found to interact with many DNA repair proteins, including the MRE11 complex (Greenberg et al., 2006), which has an impact on the activator of homologous recombination repair (HRR) pathway. During homologous recombination, *ERCC1* complex, a highly conserved structure-specific endonuclease, is required when DNA double-strand break (DSB) ends are blocked by nonhomologous sequences or secondary structures (Gao and Ge, 2019). *TNRC9* (*TOX3*) was proved to downregulate *BRCA1* by altering the methylation status of its promoter (Shan et al., 2013). Furthermore, variants in *TOX3* may lead to a change in *TOX3* expression, which can eventually affect the risk of BC.

For promoting the cell cycle, the Cdk/cyclin complexes take the primary responsibility. It is also proved that the altering of *CCNE1* expression induces BC (Shaye et al., 2009). Most of the critical positive cell cycle regulators, including Cdks, cyclins, and E2F transcription factors, are encoded by genes induced by *C-MYC* (Bretones et al., 2015), which is regulated by *ZMIZ1* (Rakowski et al., 2013). Other cyclins involved in cell cycle arrest, cyclin D1, is inhibited by *LSP1* (Zhang et al., 2016). All the above pathways are primarily involved in activation through fibroblast growth factors (FGFs) and their receptors (*FGFRs2*).

High-frequency variants in these genes may modulate a predisposition to BC. So far, SNPs have been

**Table 1.** Primer sequences for selected SNPs genotyped using PCR–HRM analysis and the optimal annealing temperature

| Genes | SNPs | Forward primer sequence (5'-3') | Reverse primer sequence (5'-3') | $T_a$ (°C) |
|---|---|---|---|---|
| *MRE11* | rs2155209 | ACCTTGTGGCAAAAG TAGGAGC | GTCCTGGATGCCCAT TATATTGTTT | 62 |
| *ERCC1* | rs3212986 | GCTCCCACAGGCCGG GACAAG | AGTTTCCCGGGGGCA GACTACAC | 62 |
| *TOX3* | rs12443621 | GTTTTATATGCATTAG GCCTGG | CAGTATTCTGATTCC CTTAGAA | 62 |
| *CASC16* | rs4784227 | AGCCAACTCTTTGGG GAGGAAAA | TGAAATTGGTCATGA TGGGAGTATTT | 58 |
| *FGFR2* | rs2981582 | GGTTCCTAAAGCCAG GCAGGCAC | TCCCAGCACTCATCG CCACTTAAT | 62 |
| *CCNE1* | rs3218035 | TCCAGAGATTAATGG CGACAGAT | GCTCCATACATAGAC AGCTAATG | 57 |
| *ZMIZ1* | rs704010 | TGGAGACCTGAGACC TGACCTGAAAA | GCCTACTGCCACGTC TTACAACCT | 66 |
| *LSP1* | rs569550 | GATCCTGGGCACCCTT CAGTCAC | CCGGTAAGCTCAGCC CAAAGTTC | 63 |

identified to be correlated with BC in different populations. Among them, eight SNPs (rs2981582 on *FGFR2*, rs569550 on *LSP1*, rs3218035 on *CCNE1*, rs704010 on *ZMIZ1,* rs2155209 on *MRE11*, rs3212986 on *ERCC1*, rs12443621 *TOX3* and rs4784227 in *CASC16*) have been strongly confirmed to have an association with BC risk in not only Asians but also Europeans and Caucasians (Chen et al., 2015; Chen et al., 2016; Han et al., 2012; Han et al., 2015; Jiang et al., 2016; Kim et al., 2012; Li et al., 2016; Lin et al., 2014; Pei et al., 2014; Shu et al., 2019; Tajbakhsh et al., 2019; Wu et al., 2015; Zhang et al., 2017; Zhao and Ying, 2016; Zuo et al., 2020).

However, these SNPs have not yet been evaluated in the Vietnamese population. In this study, we initially analyzed the association of these eight SNPs with BC susceptibility in the Vietnamese Kinh population, the largest ethnic group in Vietnam.

## MATERIALS AND METHODS

This population-based study is part of an ongoing study, the goal of which is to determine potential SNPs associated with BC susceptibility in Vietnamese Kinh Women. The full sample set in this study included 300 BC female patients and 300 healthy female controls. All cases were diagnosed with breast tumors. The control group consisted of individuals who were healthy blood donors without BC. The age of participants was a range from 40–65 yr and belonged to Kinh ethnic, Vietnam.

Genomic DNA was extracted from whole blood using a salting-out method following Hue et al.'s protocol with some modifications (Hue, 2012). The extracted DNA was stored at –20°C until analysis. The genotyping for eight candidate SNPs was performed by Polymerase chain reaction—High Resolution Melting (PCR-HRM) method. The sets of primers for genotyping were shown in Table 1.

The SNP genotyping assays were executed by LightCycler 480 High-Resolution Melting Master (Roche Diagnostics, Germany) and a LightCycler 96 Instrument with a 96-well thermal block (Roche Diagnostics). The PCR-HRM analysis was performed in a reaction containing 1X LightCycler 480 High-Resolution Melting Dye, 0.2 μM forward and reversed primers, 3.5 mM $MgCl_2$, 10–20 ng of genomic DNA and PCR-grade water. The PCR thermal cycling was as follows: initial denaturation at 95°C for 15 min followed by 40 cycles of 95°C for 30 s an annealing step at the optimal annealing temperature for each SNP for 30s (Table 1), and an elongation step at 72°C for 30 s. HRM analysis was then carried out as the default. One negative control and three positive controls (genotypes confirmed by Sanger sequencing) were included in each run. In other to identify the genotype of a sample, four criteria based on amplification curves, normalized melting curves, normalized melting peaks, and different plots were taken into consideration. Typical genotyping results for eight SNPs are shown in Fig. 1.

In other to determine the potential polymorphisms associated with BC risk, all SNPs were initially genotyped in the primary sample set comprising 100 BC cases and 100 healthy controls that were randomly selected from the full sample set (300 cases and 300 controls). Further validation for potential related SNPs was then

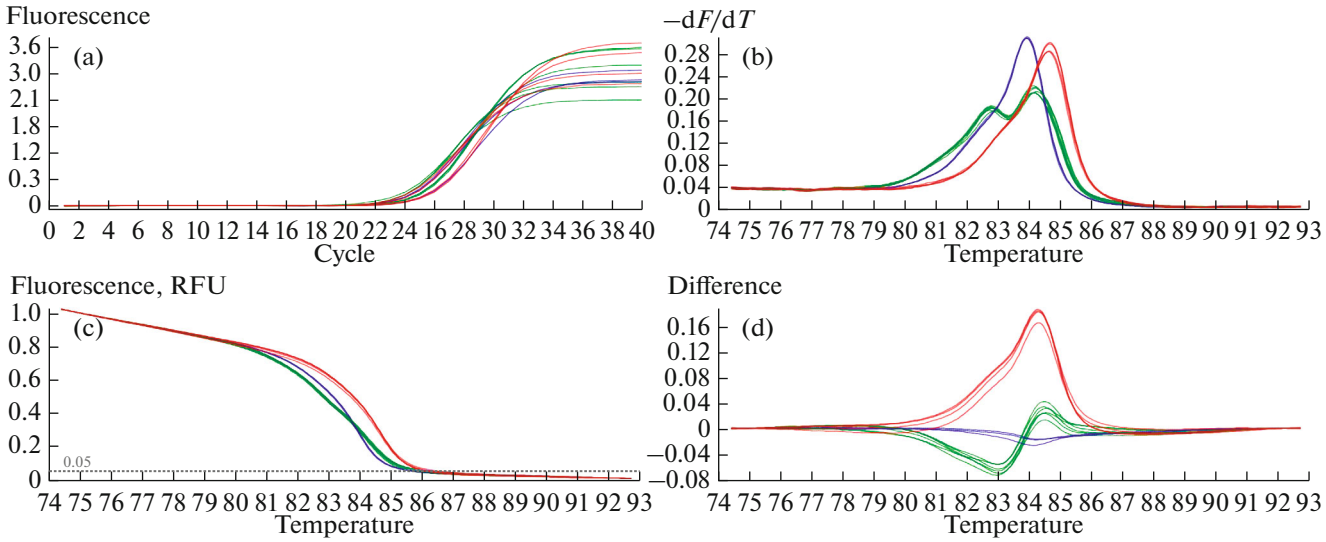


**Fig. 1.** Example of PCR-HRM genotyping results for rs2981582 (T/C) (a) Amplification curves. The Ct value must be lower than 30. (b) Normalized melting peaks. The AT of the two homozygotes must be higher than 0.05. (c) Normalized melting curves. The heterozygote curve cuts the homozygote with the lower $T_m$ in the middle and does not cut the other homozygote curve. (d) Difference plots. The lower-$T_m$ homozygote is set as the baseline, and the heterozygote curve must divide into two sides of the baseline. The homozygote with the higher Tm curve must be on the upper side. Red, blue, and green represent CC, TT and CT genotypes, respectively.

performed in the remaining samples to make up the full set.

Genotype and allele frequencies of each SNP in the population were calculated as percentages. All statistical analysis was undertaken using RStudio Version 1.2.1335. The genotype frequencies of each SNP were tested for deviation from the Hardy–Weinberg equilibrium (HWE) in both cases and controls. Further analysis, including the genetic model association, was carried out using the "SNPassoc" package. The ORs and 95% CIs were calculated to assess BC risk. The threshold to determine a statistically significant association was set at $P = 0.05$.

## RESULTS AND DISCUSSION

In this study, eight SNPs in seven genes engaged in DNA repair and cell cycle checkpoint were investigated the relationships with BC risk. To our knowledge, this is the first case-control study of these SNPs with BC in the Vietnamese population.

In the primary sample set, the genotype and allele frequency of all SNPs are summarized in Table 2. All SNPs were highly variable polymorphisms, with the minor allele frequencies ranging from 12 to 48%. The genotype frequencies of eight polymorphisms were all in agreement with the HWE in cases and controls (data not shown), indicating the research sample represented the Vietnamese population, and the genotyping for these SNPs was reliable.

The association analysis for the primary set indicated that there were no statistically significant differences between 100 cases and 100 controls in genotype and allele frequencies of four variants involved in cell cycle arrest genes, rs2981582, rs3218035, rs704010, and rs569550; and two variants in DNA repair-related genes, rs3212986 and rs12443621. These results indicated that six SNPs rs2981582, rs3218035, rs704010, rs569550, rs3212986, and rs12443621 had low potential to become markers for BC risk in Vietnamese population; therefore there was no further analysis in the bigger sample size.

In the literature, four SNPs in cell cycle checkpoint genes, rs3218035, rs569550, rs704010, and rs2981582, were showed the effect on BC risk in different populations. The TT genotype of rs3218035 has only been discovered to be an increased effect on BC risk in Chinese Han women (Han et al., 2012). LSP1 rs569550 has only been examined in the Chinese population and first found that the TT genotype and T allele could significantly increase the risk of BC (Chen et al., 2015). rs704010 of *ZMIZ1* was found to be associated with BC in Caucasians and Asians populations (Zhang et al., 2017), especially in the Chinese population (Li et al., 2016). The TT and TC genotype of rs2981582 was shown to be significantly correlated with BC development in an Asian population (Shu et al., 2019).

The role of two SNPs in genes involved in DNA damage repair, rs3212986, and rs12443621, in BC development, was inconsistent. *ERCC1* rs3212986 was reported not to be associated with BC risk in Chinese and Taiwanese (Tsai et al., 2018; Yang et al., 2013). *TOX3* rs12443621 was also found no significant asso-

**Table 2.** Allele and genotype frequency distribution and logistic regression analysis of the SNPs obtained from the primary sample set

| Gene SNP | Allele/ Genotype | Genotypes no. (%) | | *P* value | OR | (95%CI) |
|---|---|---|---|---|---|---|
| | | control ($n = 100$) | case ($n = 100$) | | | |
| *MRE11* rs2155209 | T | 152 (76) | 106 (53) | | 1 | |
| | C | 48 (24) | 94 (47) | **0.02** | 1.80 | 1.11–2.91 |
| | TT | 54 | 32 | | 1 | |
| | CT | 44 | 42 | 0.26 | 1.40 | 0.77–2.53 |
| | CC | 2 | 26 | **0.02** | 6.54 | 1.35–31.57 |
| *ERCC1* rs3212986 | G | 114 (57) | 130 (65) | | 1 | |
| | T | 86 (43) | 70 (35) | 0.09 | 1.42 | 0.94–2.16 |
| | GG | 32 | 42 | | 1 | |
| | GT | 50 | 47 | 0.31 | 0.72 | 0.39–1.35 |
| | TT | 18 | 11 | 0.10 | 0.47 | 0.18–1.14 |
| *TOX3* rs12443621 | A | 104 (52) | 104 (52) | | 1 | |
| | G | 96 (48) | 96 (48) | 0.93 | 1.02 | 0.67–1.55 |
| | AA | 26 | 23 | | 1 | |
| | AG | 53 | 57 | 0.64 | 1.17 | 0.6–2.32 |
| | GG | 21 | 20 | 1 | 1.02 | 0.44–2.37 |
| *CASC16* rs4784227 | C | 154 (77) | 138 (69) | | 1 | |
| | T | 46 (23) | 62 (31) | 0.06 | 1.50 | 0.98–2.30 |
| | CC | 63 | 49 | | 1 | |
| | CT | 29 | 40 | 0.31 | 1.77 | 0.99–3.16 |
| | TT | 8 | 11 | 0.06 | 1.62 | 0.64–4.14 |
| | CT + TT | | | **0.04** | 1.74 | 1.05–2.98 |
| *FGFR2* rs2981582 | T | 122 (61) | 106 (53) | | 1 | |
| | C | 78 (39) | 94 (47) | 0.13 | 1.34 | 0.90–1.98 |
| | CC | 37 | 32 | | 1 | |
| | CT | 48 | 42 | 0.94 | 0.97 | 0.51–1.86 |
| | TT | 15 | 26 | 0.11 | 1.96 | 0.87–4.43 |
| *CCNE1* rs3218035 | T | 168 (84) | 176 (88) | | 1 | |
| | C | 32 (16) | 24 (12) | 0.29 | 0.73 | 0.42–1.30 |
| | CC | 70 | 79 | | 1 | |
| | CT | 28 | 18 | 0.11 | 0.57 | 0.29–1.14 |
| | TT | 2 | 3 | 0.74 | 1.36 | 0.22–8.39 |
| *ZMIZ1* rs704010 | T | 128 (64) | 130 (65) | | 1 | |
| | C | 72 (36) | 70 (35) | 0.94 | 0.99 | 0.66–1.47 |
| | CC | 42 | 45 | | 1 | |
| | CT | 44 | 40 | 0.80 | 0.84 | 0.46–1.56 |
| | TT | 14 | 15 | 0.58 | 0.84 | 0.46–1.56 |
| *LSP1* rs569550 | T | 130 (65) | 136 (68) | | 1 | |
| | G | 70 (35) | 64 (32) | 0.54 | 0.88 | 0.59–1.31 |
| | GG | 46 | 50 | | 1 | |
| | GT | 38 | 36 | 0.66 | 0.87 | 0.47–1.62 |
| | TT | 16 | 14 | 0.56 | 0.78 | 0.33–1.81 |

ciation existed between this SNP and the risk of BC in Chinese women (He et al., 2014). Furthermore, rs12443621 was observed to be correlated with increased risk of BC in Caucasians, but not Asian (Gao and Ge, 2019; Zhang and Long, 2015). In this study, rs3212986 and rs12443621 were also found not to be associated with BC risk in the Vietnamese population. Meanwhile, rs3212986 and rs12443621 were found the association with BC risk in other studies in the Chinese population (Chen et al., 2016; Jiang et al., 2016; Pei et al., 2014; Zhao and Ying, 2016). The differences in ethnicity and other genetic and environmental factors could partially explain observed heterogeneities between studies.

In contrast, the remaining two polymorphisms in DNA damage repair genes, rs2155209 and rs4784227, showed a significant association with BC risk in the primary sample set. The logistic regression analysis revealed that the C allele at rs2155209 was significantly more prevalent in cases compared to the controls (OR = 1.80, 95% CI 1.11 to 2.91, $P = 0.02$). The rs2155209 CC were significantly increased among BC patients compared to the rs2155209 TT (rs2155209 CC vs. TT: OR = 6.54, 95% CI 1.35–31.57, $P = 0.02$). Despite no differences in the frequencies of T and C alleles at rs4784227 between cases and controls, the significant association was found between the *TOX3* rs4784227 polymorphism and BC risk under the dominant genetic model (CT + TT vs. CC: OR = 1.74, 95% CI 1.05–2.98, $P = 0.04$). As a significant association between rs2155209 and rs4784227, these two SNPs were considered for further analysis in the remaining sample to make up about 300 cases and 300 controls.

The allelic and genotypic frequencies of rs2155209 and rs4784227 in the full sample set of 300 cases and 300 controls were assessed (Table 3). 1–3% of total 600 tested samples were failed to identify genotypes, which is an acceptable error rate. It have been concluded that the error rate could range between 0.5 and 30% reported in present publications (Dorak, 2017). The association analysis of genetic models showed that a BC risk association was again observed in the recessive model for rs2155209 and codominant, dominant, and overdominant models for rs4784227 (Table 3). In the recessive model of rs2155209, the presence of the homozygous CC genotype decreased the risk of the disease by 0.57-fold compared to the combination of CT and TT genotype (CC vs. CT + TT: OR = 0.57, 95% CI 0.34–0.97, $P = 0.03$). For rs4784227, the CT genotype appears to be associated with increased BC risk by 1.48 and 1.44-fold compared to CC genotype in codominant and dominant genetic model, respectively (CT vs. CC: OR = 1.48, 95% CI 1.06–2.06, $P = 0.02$; CT + TT vs. CC: OR = 1.44, 95% CI 1.05–1.97, $P = 0.02$). Furthermore, comparing to two homozygous genotypes in over dominant, the rs4784227 CT genotype still significantly increased the risk (CT vs. CC + TT: OR = 1.43, 95% CI 1.03–1.97, $P = 0.03$).

*MRE11A* is involved in *MRE11A/RAD50/NBS1* nuclease complex (*MRN* complex) which plays a vital role in the Homologous Recombination Repair pathway (Paull and Deshpande, 2014). The polymorphisms of gene encoding *MRE11A* protein may lead to genomic instability and cancer susceptibility (Heikkinen et al., 2006). SNP rs2155209 is located in the 3' UTR of *MRE11*, on the miRNA-binding site region of hsa-miR-2196, suggesting that the appearance of this SNP can affect the binding ability of miR-2196, thus modulate the expression of the *MRE11* protein (Naccarati et al., 2016) and contribute to genomic instability and cancer susceptibility. In 2015, Wu and colleagues first found an association for the SNP rs2155209 with BC risk in 450 BC cases and 450 cancer-free controls from Chinese. The C allele of rs2155209 was shown to increase the risk of BC (C vs. T: OR = 1.25, 95% CI = 1.02–1.54, $P = 0.03$). Further analysis showed that individuals with TC (TC vs. TT: OR = 1.87; 95% CI = 1.23–2.86, $P = < 0.001$) and TC + CC (TC + CC vs. TT: OR = 1.86, 95% CI = 1.23–2.80, $P = < 0.001$) genotype also showed increased risk to BC (Wu et al., 2015). The association with BC risk of rs2155209 has been secondly reported in this study. The CC genotype of rs2155209 was associated with a decreased risk of BC in the Vietnamese population. These shreds of evidence suggested that this miRNA-binding-site SNP in an HRR pathway gene might play crucial roles in the development of BC.

*TOX3* is a high mobility group-box domain that can modify chromatin structure (O'Flaherty and Kaye, 2003). It was indicated *TOX3* negatively regulated *BRCA1* expression and the high expression of *TOX3* increased breast cancer cell proliferation, migration, and survival (Shan et al., 2013). SNP rs4784227 located on the long arm of chromosome 16 (16q12.1) at 18.4 Kb from the *TOX3* gene in the upstream region (Cowper-Sal lari et al., 2012). This position may disrupt enhancer function by FOXA1-binding affinity-modulation therefore can change *TOX3* expression (Cowper-Sal lari et al., 2012; Meyer and Carroll, 2012). A GWAS in Korean women was conducted and found that the T allele of rs4784227 was significantly associated with BC risk (T vs. C: OR = 1.24, 95% CI = 1.20–1.29, $P = 1 \times 10^{-28}$) (Kim et al., 2012). The T allele of rs4784227 was observed to be significantly related to an increased susceptibility to BC in different Chinese case-control studies (T vs. C: OR = 1.24, 95%CI = 1.06–1.45 (Lin et al., 2014); OR = 1.31, 95% CI = 1.10–1.57 (He et al., 2014); T vs. C: OR 1.22, 95% CI = 1.03–1.45, $P = 0.022$ (Zuo et al., 2020)). Furthermore, the BC association of this SNP was also reported outside Asia. The T allele of rs4784227 was found to be associated with BC risk in studies of European descent (T vs. C: 1.26, 95% CI = 1.12–1.42, $P = 9.7 \times 10^{-5}$) (Han et al., 2015) and Iranian population (T vs. C: OR = 1.5, 95% CI = 1.20–1.87, $P = 0.0001$) (Tajbakhsh et al., 2019). In the Vietnamese population, the CT and CT + TT genotype of

**Table 3.** Logistic regression analysis of the associations of rs2155209 and rs4784227 with BC in the full sample set

| Gene SNP | Genetic models | Genotypes no. (%) | | *P* value | OR | (95%CI) |
|---|---|---|---|---|---|---|
| | | control ($n = 296$) | case ($n = 282$) | | | |
| *MRE11* rs2155209 | T | 396 (66.9) | 398 (70.6) | | 1 | |
| | C | 196 (33.1) | 166 (29.4) | 0.20 | 0.85 | 0.67–1.09 |
| | TT | 143 (48.3) | 141 (50.0) | | 1 | |
| | CT | 110 (37.3) | 116 (41.1) | 0.09 | 1.07 | 0.75–1.52 |
| | CC | 43 (14.5) | 25 (8.9) | 0.09 | 0.59 | 0.34–1.02 |
| | TT + CT | | | | 1 | |
| | CC | | | **0.03** | 0.57 | 0.34–0.97 |
| Gene SNP | Genetic models | Genotypes no. (%) | | *P* value | OR | (95%CI) |
| | | control ($n = 331$) | case ($n = 294$) | | | |
| *CASC16* rs4784227 | C | 496 (75.0) | 412 (70.0) | | 1 | |
| | T | 166 (25.0) | 176 (30.0) | 0.06 | 1.26 | 0.99–1.61 |
| | CC | 192 (58.0) | 144 (49.0) | | 1 | |
| | CT | 112 (33.8) | 124 (42.2) | **0.02** | 1.48 | 1.06–2.06 |
| | TT | 27 (8.2) | 26 (8.8) | 0.40 | 1.28 | 0.72–2.29 |
| | CT + TT | | | **0.02** | 1.44 | 1.05–1.97 |
| | CC + TT | | | | 1 | |
| | CT | | | **0.03** | 1.43 | 1.03–1.97 |

rs4784227 were found to be associated with an increased BC risk. This result is in line with other studies supporting rs4784227 that may lead to a change in *TOX3* expression and eventually affect the risk of BC.

## CONCLUSIONS

As the first study to investigate the association between polymorphisms in *MRE11*, *ERCC1*, *TNRC9* (*TOX3*), *CASC16*, *FGFR2*, *CCNE1*, *ZMIZ1*, *LSP1* genes and the risk of BC in a Vietnamese population, it demonstrated that *MRE11* rs2155209 and *CASC16* rs4784227 are associated with BC risk and can be served as potential biomarkers for BC.

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## COMPLIANCE WITH ETHICAL STANDARDS

*Conflict of interests.* The authors declare no competing interests

*Statement of compliance with standards of research involving humans as subjects.* The study was approved by the ethical committee in the Oncology Hospital of Ho Chi Minh City under the decision no. 177/HDDD-CDT. All patients provided appropriate consent.

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