Association of PARP1 rs4653734, rs907187 and rs1136410 variants with breast cancer risk among Iranian women

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ABSTRACT

Background: Breast cancer (BC) is the highest cause of mortality among female cancer patients. In some cases, BC is due to Poly [ADP-ribose] polymerase 1 (PARP1) gene dysregulation, which has been involved in various important cellular processes. Among Iranian women, the association between PARP1 polymorphisms and BC was never studied before so in this case-control study, the genetic association of three SNPs (rs1136410, rs907187 and rs4653734) was analyzed with susceptibility to BC.

Methods: The study subjects were 386 Iranian females divided into 186 patients and 200 healthy controls. The genotypes of PARP1 variants were detected using ARMS and a combined ARMS-RFLP PCR method.

Results: The results showed that Carriers of CG and GG genotypes of the variant rs4653734 were at higher risk of BC compared with wild-type carriers (CC) and this variant was statistically significant under a recessive model of inheritance. Moreover, rs907187 was related to increased BC risk in the CC and GG genotypes under dominant and recessive models of inheritance. The G allele frequency of rs4653734 and rs907187 was higher in breast cancer patients than in normal subjects. No association was detected between rs1136410 and susceptibility to BC among studied groups. Furthermore, A-G-C haplotype was linked to an increased BC risk, whereas A-C-C and A-C-G haplotypes were related to a decreased risk of BC. In Silico predictions suggested that rs907187 affects E2F and E2F-4 transcription factors binding site.

Conclusions: The current study suggests that rs907187 and rs4653734 have remarkable associations with BC risk among Iranian women.

1. Introduction

Breast cancer (BC) is the most common and Lethal type of diagnosed cancer among women (DeSantis et al., 2015). Statistics showed that almost 3 million women suffered from BC in 2015 in the United States (McGuire et al., 2015). Also it had been estimated that 252,710 new cases of invasive BC would be diagnosed among women in 2017 in the United States (https://www.cancer.org/cancer/breast-cancer.html). Among the overall cancer deaths worldwide, almost 60% of deaths occur in developing countries including Iran (Torre et al., 2015). Risk factors correlated with breast cancer in women include genetic susceptibility, unhealthy lifestyles, and other medical conditions (Anothaisintawee et al., 2013; Pharoah et al., 2002).

DNA repair pathways play important roles in maintaining genomic stability and influence carcinogenesis and tumor biology (Lord and Ashworth, 2012). Poly[ADP-ribose] polymerase (PARP) is not only a key DNA repair enzyme which is essential for DNA single-strand break (SSB) repair—a sub-pathway related to base excision repair, but also has been demonstrated to play a crucial role in non-homologous end joining (NHEJ) (Amé et al., 2004; Burkle, 2001; Krishnakumar and Kraus, 2010; Schreiber et al., 2006). PARP proteins also have been involved in various cellular processes including cell survival and death, transcriptional and chromatin structure regulations, telomere integrity, and cell division (D’Amours et al., 1999; Hassa and Hottiger, 2008). PARP1 is an enzyme responsible for about 90% of the ADP-ribosyl transferase activity in human cells (D’Amours et al., 1999). Dysregulation of PARP1 expression has been reported in a variety of human cancers, including breast, melanoma, colorectal, head and neck cancers (Gonçalves et al., 2011; Nosho et al., 2006; Staibano et al., 2005). Furthermore, some defects in PARP1 are enhancing cancer risk (Ossovskaya et al., 2010).

Several studies have demonstrated the association of PARP1 gene variants with the incidence risk of breast cancer. However, the findings
of these studies are still controversial and inconclusive (Alanazi et al., 2013a; Alanazi et al., 2013b; Cao et al., 2007; Smith et al., 2008; Tang et al., 2013). Therefore, the aim of this study was to investigate the association of breast cancer occurrence with three Single Nucleotide Polymorphisms (SNP) of PARP1. The association of two SNPs (rs907187 and rs4653734) at promoter region and a missense mutation (rs1136410) at active site of PARP1 and their haplotypes with BC risk were analyzed among Iranian women. To the best of our knowledge, this study is the first investigation on rs1136410 and rs907187 in Iranian population and the first association study of rs4653734 with BC in the world.

2. Material and methods

2.1. Sampling and genotyping

The present study included a total of 186 patients with histopathological and surgical conformation of BC and 200 healthy individuals. The current study was conducted in accordance with the tenets of the Declaration of Helsinki. All of the subjects were consented to participate in the study. All volunteers, who met the inclusion criteria for participating in this study, were Iranian females who resided in Guilan province. The study subjects’ ages ranged from 35 to 75 years, with an average of 58.4 years. Individuals who had a history of breast tumor or antecedents of malignancy were excluded from the control group. The control group consisted of 100 age- and ethnicity-matched healthy women.

Genomic DNA was extracted from the peripheral blood through Triton X-100 technique. For this purpose, 2 ml of venous blood from each case and control subjects were collected in EDTA-containing tubes. The purified DNA was analyzed by electrophoresis on 1% agarose gel stained with safe stain. Final DNA concentration was determined using Nanodrop (ND-1000, ABI).

Three variants of PARP1 gene (rs4653734, rs907187 and rs1136410) were selected for genotyping. Genotyping assay of rs1136410 was performed using ARMS-PCR protocol (initial denaturation at 94 °C for 5 min, followed by 32 cycles at 94 °C for 45 s, 57.5 °C for 45 s and 72 °C for 45 s and final extension for 5 min at 72 °C). The PCR primers were: Forward 1: 5′-GATGTCCAGCAGGTTGTCAAGCATTTCAG-3′; Forward 2: 5′-GATGTCCAGCAGGTTGTCAAGCATTTCAG-3′; Reverse: 5′-GTTCCTCCACCTGTAACCTGCCC-3′. For genotyping of rs907187 and rs4653734, combined ARMS-RFLP PCR method was applied that two SNPs investigated in one step (Jawaheer et al., 1993). The primer sequences of rs4653734 were designed as bellow:

For ARMS primers designation for genotype rs4653734 and rs907187, combined ARMS-RFLP PCR method was applied that two SNPs investigated in one step (Jawaheer et al., 1993). The procedure included an ARMS primers designation for genotype rs4653734 and genotyping of rs907187 was determined using RFLP-PCR method. More specifically, PCR products were digested by rs4653734 and genotyping of rs907187 was determined using RFLP technique after 2 h incubation. The ARMS-RFLP PCR technique protocol was as follow: 94 °C pre-denaturation for 5 min, 30 cycles of denaturing at 94 °C for 45 s and annealing/extension at 65 °C for 45 s and 72 °C for 45 s and final extension for 5 min at 72 °C. The primer sequences of rs4653734 were designed as bellow:

F1 (5′-GGCGGGGGCATTACGGCC3′) and R (5′-CGGCGGTGAGGACGCGA3′). PCR procedure was carried out using approximately 30 ng genomic DNA, 0.1 mM deoxyribonucleoside triphosphates (dNTPs), 10 × PCR buffer (10 mM Tris–HCl, 50 mM KCl and 0.1% Triton X-100), 1.5 mM MgCl2, 0.5 unit of Taq DNA polymerase and 2 pmol of each primer for a final reaction volume of 25 μl.

2.2. Linkage disequilibrium (LD) analysis

Pairwise LD coefficients of |D'| for three SNPs (rs907187, rs4653734 and rs1136410) from PARP1 were assessed using SNPAlalyze version 8.1.1 software (DYNACOM, Japan). This analysis was done according to Hardy–Weinberg equilibrium model.

2.3. Haplotype analysis

In order to estimate the multi-locus association of PARP1 variants with BC dependence, haplotype analysis was performed on rs907187, rs4653734 and rs1136410. Five haplotypes were predicted with frequencies higher than 0.5%. Haplotype analyses among case and control groups were performed based on the maximum-likelihood method with an expectation-maximization algorithm. Permutation p-values were calculated by comparing haplotype frequencies between control and case groups on the basis of 10,000 replications.

2.4. Bioinformatics analysis

To obtain the potential functions of SNPs located in the regulatory regions and determine the effects of rs4653734 and rs907187 on transcription factor (TF) binding sites, the promoter sequences of two aforementioned SNPs were analyzed by Genomatix (https://www.genomatix.de), Regulome DB (http://www.regulomedb.org/) and TFBIND (http://tfbind.hgc.jp/). Genomatix and TFBIND servers were used to identify TFs which their binding sites can be significantly affected by a given SNP. Also Regulome DB tool applied to verify TF bound to intended nucleotide sequence of the gene promoter. Interestingly, as rs907187 or rs4653734 were in CpG island, the present study investigated the likelihood of these two SNPs as putative CpG-SNPs by MethPrimer tool for further investigations.

2.5. Statistical analysis

To determine whether any significant differences in SNP frequencies occurred between the case and control groups, allele and genotype frequencies were compared using the chi-square method by SNPAlalyze (ver. 8.1.1), SPSS (ver. 20) and MedCalc (ver. 14.8). Odds ratio (OR) and 95% confidence intervals (CI) were calculated to determine the risk of BC associated with a given PARP1 genotype. P-value of < 0.05 was considered as the statistical significance.

3. Results

3.1. Association analysis of PARP1 SNPs in BC patients and healthy individuals

In this study, to perform the association of PARP1 studied SNPs with the prevalence of BC, 186 BCE patients and 200 healthy donors were genotyped. The distributions of allele and genotype frequencies of studied SNPs in both study groups are shown in Table 1. All the genotypic frequencies were in Hardy–Weinberg equilibrium (p > 0.05).

Genotype frequencies of rs1136410 in BC patients and healthy controls were as follows: AA 67 and 69%, AG 32 and 27%, and GG 1 and 4%, respectively. The rs1136410 showed no significant association with BC incidence in any models of inheritance. Additionally, the genotype frequencies of rs4653734 in the two study groups, BC patients and healthy individuals were CC 23 and 23%, CG 1 and 55%, and GG 76 and 22%, respectively. A significant variation was observed in the genotype frequencies of rs4653734 in the two study groups, BC patients and healthy individuals were CC 23 and 23%, CG 1 and 55%, and GG 76 and 22%, respectively. A significant variation was observed in the prevalence of BC, 186 BCE patients and 200 healthy donors were genotyped. The distributions of allele and genotype frequencies of studied SNPs in both study groups are shown in Table 1. All the genotypic frequencies were in Hardy–Weinberg equilibrium (p > 0.05).

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rs907187 was related to increased BC risk in the CC and GG genotypes, dominant, and Recessive models (CG vs. CC: OR=0.37, 95%CI=0.06–0.37, P < 0.0001; GG vs. CC: OR=0.15, 95%CI=0.06–0.37, P < 0.0001; GG vs. CC+CG: OR=0.20, 95%CI=0.08–0.50, P = 0.0006). The G allele frequency for rs907187 was higher in breast cancer patients (OR = 0.33, 95% CI = 0.23–0.47; P < 0.0001).

3.2. Linkage disequilibrium results

Analyses indicated that all three SNPs had a minor allele frequency higher than 5%. The linkage disequilibrium plot of the studied SNPs was represented in Fig. 1. The pairwise linkage disequilibrium is given for each pair of SNPs showing pairwise D’ values (Fig. 2). The observed pairwise D’ values showed that rs4653734 and rs907187 were in strong linkage disequilibrium. Rs4653734 and rs907187 indicated 100% linkage disequilibrium. Also, rs1136410 and rs4653734 were at 66% of linkage disequilibrium.

3.3. Comparison of haplotype frequencies in BC patients and healthy controls

Haplotype analysis was performed among the haplotypes including three SNPs (rs1136410, rs4653734, and rs907187) using SNPAlzye software (Table 2). There were five haplotypes with frequencies higher than 5%. It was found that A-G-C is the most frequent haplotype in both control and cases groups (26.69% and 65.76%, respectively), followed by A-C-C (27.92% and 10.87%, respectively), then A-G-G and G-G-A in control group (16.94 and 6.37%) and case groups (10.32 and 10.32%). Data revealed that the distribution frequency of haplotype A-G-C in the patient group was significantly higher than in the control group (P < 0.0001). Whereas the frequencies of the other two haplotypes (A-C-C and A-C-G) were significantly higher in control group compared to the case group (P < 0.0001 and P = 0.015, respectively).

Table 1

<table>
<thead>
<tr>
<th>SNP</th>
<th>Model</th>
<th>Genotype</th>
<th>Control (n = 200)</th>
<th>BC (n = 186)</th>
<th>OR (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1136410</td>
<td>Co-dominant</td>
<td>AA</td>
<td>138(0.69)</td>
<td>124(0.67)</td>
<td>1.00</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>AG</td>
<td>54(0.27)</td>
<td>60(0.32)</td>
<td>1.23(0.79-1.92)</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GG</td>
<td>8(0.04)</td>
<td>20(0.10)</td>
<td>0.27(0.05-1.33)</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>Dominant</td>
<td>AA</td>
<td>138(0.69)</td>
<td>124(0.67)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AG + GG</td>
<td>62(0.31)</td>
<td>62(0.33)</td>
<td>1.11(0.72-1.70)</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>Recessive</td>
<td>AA + AG</td>
<td>192(0.96)</td>
<td>184(0.99)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>GG</td>
<td>8(0.04)</td>
<td>20(0.10)</td>
<td>0.26(0.54-1.24)</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Allele</td>
<td>A</td>
<td>330(0.82)</td>
<td>308(0.83)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>G</td>
<td>70(0.18)</td>
<td>64(0.17)</td>
<td>0.97(0.67-1.42)</td>
<td>0.91</td>
</tr>
<tr>
<td>rs4653734</td>
<td>Co-dominant</td>
<td>CC</td>
<td>46 (0.23)</td>
<td>42(0.23)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CG</td>
<td>110(0.55)</td>
<td>20(0.10)</td>
<td>0.02(0.004-0.08)</td>
<td>&lt; 0.0001**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GG</td>
<td>44(0.22)</td>
<td>142(0.76)</td>
<td>3.53(2.06-6.05)</td>
<td>&lt; 0.0001**</td>
</tr>
<tr>
<td></td>
<td>Dominant</td>
<td>CC</td>
<td>46(0.23)</td>
<td>42(0.23)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CG + GG</td>
<td>154(0.77)</td>
<td>144(0.77)</td>
<td>1.02(0.63-1.64)</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>Recessive</td>
<td>CC + CG</td>
<td>156(0.78)</td>
<td>44(0.24)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>GG</td>
<td>44(0.22)</td>
<td>142(0.76)</td>
<td>11.44(7.1-18.4)</td>
<td>&lt; 0.0001**</td>
</tr>
<tr>
<td></td>
<td>Allele</td>
<td>C</td>
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<td>86(0.23)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>G</td>
<td>198(0.49)</td>
<td>286(0.77)</td>
<td>3.39(2.48-4.62)</td>
<td>&lt; 0.0001**</td>
</tr>
<tr>
<td>rs907187</td>
<td>Co-dominant</td>
<td>CC</td>
<td>100(0.50)</td>
<td>142(0.77)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CG</td>
<td>72(0.36)</td>
<td>38(0.20)</td>
<td>0.37(0.23-0.59)</td>
<td>&lt; 0.0001**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GG</td>
<td>28(0.14)</td>
<td>6(0.03)</td>
<td>0.15(0.06-0.37)</td>
<td>0.0001**</td>
</tr>
<tr>
<td></td>
<td>Dominant</td>
<td>CC</td>
<td>100(0.50)</td>
<td>142(0.76)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CG + GG</td>
<td>100(0.50)</td>
<td>44(0.24)</td>
<td>0.30(0.20-0.48)</td>
<td>&lt; 0.0001**</td>
</tr>
<tr>
<td></td>
<td>Recessive</td>
<td>CC + GG</td>
<td>172(0.86)</td>
<td>180(0.96)</td>
<td>1.00</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>GG</td>
<td>28(0.14)</td>
<td>6(0.04)</td>
<td>0.20(0.08-0.50)</td>
<td>0.0006*</td>
</tr>
<tr>
<td></td>
<td>Allele</td>
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<td>272(0.68)</td>
<td>322(0.87)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>G</td>
<td>128(0.32)</td>
<td>50(0.13)</td>
<td>0.33(0.23-0.47)</td>
<td>&lt; 0.0001**</td>
</tr>
</tbody>
</table>

* and ** represent statistical significance at p < 0.001 and p < 0.0001, respectively. BC, breast cancer; OR, odds ratio; CI, confidence intervals

3.4. Genotypes and clinical data

Among 186 patients with BC, the clinical characteristics of 86 individuals were completely available. Out of 86 patients, 44 individuals had invasive ductal carcinoma (IDC), 42 patients had invasive lobular carcinoma (ILC), 12 individuals had Lobular Carcinoma in Situ (LCIS) and 8 patients had ductal carcinoma in situ (DCIS). Among 44 patients with IDC, all were stage 3, and the cancer had spread to lung (16 patients), bone (10 patients), liver (4 patients), spleen (2 patients), and in 12 patients BC metastasized to more than a location.

Among 42 patients with ILC, 4 patients were at stage 4 and 38 patients were at stage 3. The location of metastases in these 42 patients was lung (12 patients) and bone (12 patients). Also in 18 patients BC spread to two or more tissues. The characteristics of the 86 patients (ILC and IDC) presented in Table 3.

3.5. Bioinformatics results

TFBIND, Genomatix and Regulome DB softwares were applied to predict TF binding sites and the analyses revealed that the single-nucleotide alterations in rs4653734 (C/G) and rs907187 (C/G) regions possibly modifies the TF binding site. To determine the relationships between the identified SNPs and regulatory sequences, the list of regulatory elements containing binding sites were obtained from Regulome DB. Online servers predicted that E2F and E2F-4 TFs bind to C allele of rs907187; however, these bindings sites were not predicted in the presence of the mutant allele (G). Previous studies reported that E2F-1 and E2F-4 are involved in the expression of PARP1. In addition, it has been predicted that SHARP1 bound to wild allele (C) of rs4653734 whereas, mutant allele (G) didn't bound to this TF. These basic helix-loop-helix TFs have oncogenic or tumor suppressor role in development of various cancers. Another bioinformatics sub-analysis was performed for rs4653734 site as a putative CpG-SNP through MethPrimer tool. Results indicated that rs4653734 and rs907187 were in a CpG island of PARP1 promoter region; based on this, substituting the wild-type alleles of rs4653734 and rs907187 with mutant alleles (C allele with G allele for both of them) revealed that rs4653734 in mutant form can make a
Fig. 1. Linkage disequilibrium structure across the studied PARP1 SNPs rs1136410, rs4653734 and rs907187.

Fig. 2. Schematic visualization of CpG islands in the PARP1 promoter including rs907187 and rs4653734 SNPs using Methprimer tool. Schematic map of the CpG islands indicated two SNPs in wild type (a) and mutant (b) forms. The map extended form 100 bp upstream to 100 bp downstream of two polymorphisms.
In a case–control investigation, Cao et al. observed no correlation between rs1136410 (Val762Ala) at linkage disequilibrium. Cases. Moreover, rs4653734 and rs907187 were in strong linkage disequilibrium among BC patients rather than healthy controls. On the other hand, A-C-C and A-C-G haplotypes were more frequent in controls than patients. SNPs play critical roles in different types of cancers (Amir et al., 2010). SNPs in PARP1 investigated the association of rs907187, rs4653734 and rs1136410 with susceptibility to BC among Iranian women. Also Smith et al. examined the relationship between BC risk and the A762V (rs1136410) which was significantly associated with BC risk (Smith et al., 2008). In the present study, data do not support any association between Val762Ala and breast cancer risk in Iran population. Results were consistent with the reports of Cao et al. and Tang et al. and inconsistent with Alanci et al. and Smith et al. studies. Interestingly, the current findings confirmed the results of a meta-analysis including 21 studies concerning the association between the V762A and the overall risk of cancer which reported no significant association between V762A and breast cancer risk in Iran population. Results were consistent with the reports of Cao et al. and Tang et al. and inconsistent with Alanci et al. and Smith et al. studies. Previously studies have reported controversial results about the association of rs1136410 (Val762Ala) at PARP1 with susceptibility to BC. In a case–control investigation, Cao et al. observed no correlation between Val762Ala and BC in French population (Cao et al., 2007). In turn, Tang et al. conducted a research to explore the modification effects of PARP1 rs1136410 on the correlation between passive smokers and BC risk among pre- and post-menopausal women among Chinese women, although similar differential associations were shown, the interactions were not significant (Tang et al., 2013). However, Alanci et al. found that Val762Ala may play an important role in BC progression in Saudi population (Alanci et al., 2013a). Also Smith et al. examined the relationship between BC risk and the A762V (rs1136410) which was significantly associated with BC risk (Smith et al., 2008). In the present study, data do not support any association between Val762Ala and breast cancer risk in Iran population. Results were consistent with the reports of Cao et al. and Tang et al. and inconsistent with Alanci et al. and Smith et al. studies. Interestingly, the current findings confirmed the results of a meta-analysis including 21 studies concerning the association between the V762A and the overall risk of cancer which reported no significant association between V762A and susceptibility to cancer (Yu et al., 2012). These discrepancies may reflect the differences in ethnic populations, suggesting further studies on the other populations.

In conclusion, the present study suggests association of SNPs in the PARP1 gene with susceptibility to BC. To the best of our knowledge, this is the first study to examine the distribution of rs4653734 and its possible relation to BC development. Clinical data indicate that lung metastasis was one of the most frequent breast metastasis of IDC. Moreover, lung and bone were the most common site of breast metastasis of ILC. The results suggested PARP1 SNPs as SNP markers in prognosis of BC among Iranian women. Also A-G-C haplotype was found more frequently among BC patients rather than healthy controls. On the other hand, A-C-C and A-C-G haplotypes were more frequent in controls than cases. Moreover, rs4653734 and rs907187 were in strong linkage disequilibrium.

Previous studies have reported controversial results about the association of rs1136410 (Val762Ala) at PARP1 with susceptibility to BC. In a case–control investigation, Cao et al. observed no correlation between Val762Ala and BC in French population (Cao et al., 2007). In turn, Tang et al. conducted a research to explore the modification effects of PARP1 rs1136410 on the correlation between passive smokers and BC risk among post-menopausal women among Chinese women, although similar differential associations were shown, the interactions were not significant (Tang et al., 2013). However, Alanci et al. found that Val762Ala may play an important role in BC progression in Saudi population (Alanci et al., 2013a). Also Smith et al. examined the relationship between BC risk and the A762V (rs1136410) which was significantly associated with BC risk (Smith et al., 2008). In the present study, data do not support any association between Val762Ala and breast cancer risk in Iran population. Results were consistent with the reports of Cao et al. and Tang et al. and inconsistent with Alanci et al. and Smith et al. studies. Interestingly, the current findings confirmed the results of a meta-analysis including 21 studies concerning the association between the V762A and the overall risk of cancer which reported no significant association between V762A and susceptibility to cancer (Yu et al., 2012). These discrepancies may reflect the differences in ethnic populations, suggesting further studies on the other populations.

Promoter sequences are potential sources of potential SNPs which might have crucial impacts on gene expression. A body of studies has verified association between the SNP at promoter region and BC risk. Earlier reports by Cao et al. and Zhai et al. failed to find any correlation between rs907187 and breast cancer risk in French and Chinese population, respectively (Cao et al., 2007; Zhai et al., 2015). In contrast, the present analyses indicated that rs907187 was associated with the risk of BC incidence. These challenging results possibly are due to the differences in genetic background and sample sizes. SNPs in the upstream region of a gene can control gene expression by affecting on TF binding sites; data demonstrated that rs907187 was associated with transcriptional Regulation so that the allele substitution in the rs907187 site alters the putative binding site of E2F and E2F-4 Transcription factors. Analysis revealed that G allele of rs907187 might eliminate the binding site of TFs, compared with the wild-type C allele. Therefore, rs907187SNP may control the expression of PARP1 gene. The E2F transcription factor family have been characterized as regulators of the cell cycle (Attwood et al., 2004). A prior study demonstrated that the E2Fs in human cancers are important regulators of apoptosis and proliferation (Hallstrom et al., 2008). Furthermore, an investigation showed that E2Fs also play a role in relapse-free survival time in human BC (Fujii et al., 2011).

In silico analysis disclosed that mutant allele of rs4653734 can create a new CpG site in a CpG island of PARP1 promoter. In other words, carriers of G allele might undergo a new methylation process rather than the wild-type allele. CpG dinucleotides are possible sites of DNA methylation and it have been verified that PARP1 mRNA expression decreased due to methylation of its promoter (Gao et al., 2010). CpG-SNPs may provide a possible molecular mechanism which can affect local DNA methylation and in turn influence the expression of a gene by allowing or preventing the binding of CpG methyl-binding proteins. In this case Taqi et al. suggested that CpG-SNPs probably affect the expression level of target genes by preventing the binding of certain proteins (Taqi et al., 2011).

In conclusion, the present study suggests association of SNPs in the studied regulatory region of PARP1 with susceptibility to BC among.
Iranian women. These findings may serve the identification of high-risk breast cancer patients for further treatment and provide a close follow-up by SNP markers such as rs4653734 and rs907187. To understand the etiology of BC, ethnic background, and more epigenetic effects of PARP1 and BC incidence risk, larger sample sizes in other populations and more SNPs of PARP1 are highly recommended.

Declaration of Competing Interest

The authors declare that they have no conflict of interest to disclose.

References


