Original article

Association between ABCB1, ABCG2 carrier protein and COX-2 enzyme gene polymorphisms and breast cancer risk in a Turkish population

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A B S T R A C T

Aim: Breast cancer is the most common cancer and the second leading cause of cancer-related deaths among women. Several genetic and environmental factors are known to be involved in breast cancer pathogenesis, but the exact etiology of this disease is complicated and not completely understood. We aimed to investigate whether the gene polymorphisms of ABCB1 and ABCG2 carrier proteins and COX-2 enzyme affect breast cancer risk.

Method: ABCG2 C421A (rs2231142), ABCB1 C3435T (rs1045642), COX-2 T8473C (rs5275) and COX-2 G306C (rs5277) were genotyped 104 breast cancer patients and 90 healthy controls using a real-time PCR for breast cancer susceptibility.

Results: Patients carrying ABCG2 C421A, the CC genotype, had a higher risk of disease compared with patients carrying any A allele (OR = 3.06; 95% CI = 1.49–6.25, p = 0.0019). The other variants showed no association with breast cancer (p > 0.05). Comparing the pathological parameters with the variants, only, the frequency of C allele of ABCB1 C3435T was significantly lower in the estrogen receptor-α (ERα) (OR = 2.25; 95% CI: 0.75–6.76; p = 0.041) and progesterone receptor (PgR) (OR = 3.67; 95% CI: 1.34–10.03; p = 0.008) positive breast cancer patients. Conclusion: ABCB1 C3435T and ABCG2 C421A might represent a potential risk factor for breast cancer for Turkish women.

1. Introduction

Breast cancer is the most frequent cancer, 30% of all new cancer diagnoses, in women, and is responsible for roughly half a million total deaths each year worldwide (Siegel et al., 2019). According to latest cancer report of Turkey Ministry of Health (2017), the rate of breast cancer is 24.9% in adult Turkish women. Some risk factors influence of developing breast cancer are menstrual history, reproductive factors, hormone use, genetics, family history, diet and exercise (Torre et al., 2017). The loss or inhibition of various ATP-binding cassette (ABC) transporters has been observed to influence tumor cell phenotypes closely associated with malignant potential, including proliferation, differentiation, migration and invasion; these observations have been made across multiple cancer types (Fletcher et al., 2016).

Multi Drug Resistance (P-glycoprotein, P-gp, ABCB1, MDR1) and Breast Cancer Resistance (BCRP, ABCG2, MXR, ABCP) ABC transporter proteins limit the intracellular concentration of the substrates via energy-dependent (active) pumping out of the cell. ABCB1 and ABCG2 protect the body against endogenous and exogenous xenobiotics with their important roles in intestinal absorption and secretion, hepato- and urinary elimination, and barrier through the placenta, testis and brain (DeGorter et al., 2012; Klaassen and Aleksunes, 2010; Robey et al., 2009). The single nucleotide polymorphism (SNP) of ABCB1, C3435T (rs1045642), occurs in exon 26, and the T allele appears to be associated with markedly lower P-gp expression compared with the C allele (Hoffmeyer et al., 2000). The SNP has been shown to be correlated with the development of various type of cancer such as colorectal...
acute lymphoblastic leukemia (Yaya et al., 2014), glioma (Miller et al., 2005) and renal epithelial tumors (Haensch et al., 2007). ABCB1 C3435T might reduce protection for cells and potentially contribute to the development of breast cancer (George et al., 2009; Wang et al., 2013). However, the results have been contradictory (Wang et al., 2012). The ABCG2 C421A (rs2231142) in exon 5 is one of the most important genetic variations and results in lower expression levels in the cellular membrane compared with the wild-type protein (Hira and Terada, 2018). BCRP is also expressed from the apical membrane of alveolar epithelial cells in breast tissue at during pregnancy and lactation and plays a role in the expulsion of accumulated toxins and carcinogens to a woman’s milk (DeGorter et al., 2012; Klaassen and Aleksunes, 2010; van Herwaarden and Schinkel, 2006).

To date, studies have investigated the association between ABCG2 gene polymorphisms and susceptibility to carcinoma such as non-papillary renal cell carcinoma (Korenaga et al., 2005), B cell lymphoma (Campa et al., 2012) and prostate cancer (Hahn et al., 2006). However, the association between ABCG2 gene polymorphisms and breast carcinoma risk has been evaluated in only a few studies (Wu et al., 2015; Ghafoori et al., 2016; Li et al., 2017).

Prostaglandins play a role in carcinogenesis via the suppression of immune responses, and the inhibition of apoptosis, angiogenesis, tumor cell invasion and metastasis pathways (Brasky et al., 2011; Lala et al., 2018). Prostaglandin-endoperoxide synthase 2 (COX-2) is an inducible enzyme that plays a major role in the inflammatory response by converting arachidonic acid to prostaglandins. Overexpression of COX-2 has been found in a variety of cancers; thyroid (Ucan et al., 2017); colorectal (Eberhart et al., 1994), gastric (Ristikimaki et al., 1997) and breast (Liu and Rose, 1996). In recent studies, COX-2 T8473C (rs5275), G898C (rs20417) and G306C (rs5277) have been shown to cause an increase in the level of COX-2 expression (Abraham et al., 2009; Brasky et al., 2011; Yu et al., 2010; Li et al., 2009). The variants have also been investigated for their role in contributing to breast cancer risk (Li et al., 2015). However, the results have been inconclusive.

Overexpression of COX-2 can result the over-production of prostaglandins, which are substrates for P-gp and BCRP. The dysfunction or reduced function of P-gp and BCRP proteins can cause carcinogenesis via xenobiotics and the accumulation of inflammatory agents in cells (Andersen et al., 2015). Knowledge of ethnic and individual genetic differences is very important for understanding personal reactions in the case of exposure to xenobiotics/drugs (Ishikawa et al., 2012; DeGorter et al., 2012). We accordingly investigated whether the single nucleotide polymorphisms (SNPs) of ABCB1 and ABCG2 carrier proteins and COX-2 enzyme affect breast cancer risk since these genetic differences have not been clarified in Turkish population. We believe that the preliminary study could enrich the scarce literature about the polymorphisms in breast cancer susceptibility.

### 2. Materials and methods

#### 2.1. Subjects

We evaluated the influence of ABCG2, ABCB1 and COX-2 gene polymorphisms on susceptibility to breast cancer in 104 Turkish female patients and 90 ethnic- and age-matched healthy controls between 2012 and 2015. These 104 patients had a mean age of 52 ± 12 years were operated upon at the Acibadem Maslak Hospital Breast Health Centre (Istanbul, Turkey) or admitted for follow-up after breast cancer surgery. Healthy control volunteers with a mean age of 49 ± 14 years who never had any type of cancer were selected.

#### 2.2. Genotyping

Genomic DNA was extracted from whole blood using standard phenol chloroform extraction protocol and further purification was done by using High Pure PCR Product Purification Kit (Roche, Mannheim, Germany). SNP analysis was performed using a LightCycler FastStart DNA Master HybProbe (Roche, Mannheim, Germany) and custom-designed LightSNiP assay probes (Roche, Mannheim, Germany) according to the manufacturer’s instructions. ABCG2 C421A, ABCB1 C3435T, COX-2 T8473C and COX-2 G306C were genotyped using a Roche Light Cycler 480 (Roche, Mannheim, Germany) real-time PCR platform and melting curve analyses were performed by the carousel-based system PCR program. In a final volume of 20 ml reaction mix per sample, the following mixtures were added: 1X FastStart DNA Master Mix, 2 mM MgCl₂, 0.2 mM LightSNP HybProbe, appropriate amount of PCR grade water and 500 ng DNA sample. The plates were sealed and centrifuged at 3000 rpm for a minute. Details of custom-designed LightSNiP assay probes were summarized in Table 1 and carousel-based system PCR program setup was given in Table 2.

Genotyping was performed by scientists blinded to the patients’ case control status. A 10% random sample was genotyped twice for quality assurance. Also, to confirm the genotyping results of the variants, the selected PCR amplified DNA samples (n = 2, for each genotype in the cases and controls) were examined with DNA sequencing. The results were 100% concordant.

#### 2.3. Statistical analysis

The sample size was calculated by an online sample size estimator (http://osse.bii.a-star.edu.sg). Hardy-Weinberg equilibrium (HWE) analysis was performed using the Chi-square ($\chi^2$) test. For the analysis of genotype frequencies, the wild-type category (chosen either as the most common wild-type frequency or

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#### Table 1

Reference sequences of custom-designed LightSNiP assay probes.

| LightSNP | Reference Sequence | Melting temperature |
|----------|--------------------|---------------------|
| ABCG2 C421A (rs2231142) | GCAACTCGAGGTTAGAGAAACTTA [A/C] AgTTCTCAGACCTCTTGGCTGC | 57.74 °C for allele [C] 61.92 °C for allele [A] |
| ABCB1 C3435T (rs1045642) | AGCAAGACTGGTCTAGAAGAT [C/T] TGTAGAAGGTAAGTTGAAACA | 55.76 °C for allele [C] 63.05 °C for allele [T] |
| COX-2 G306C (rs5277) | TCGAATTTAGTCTAGTTATG [C/T] TTGACATGATACTCAGCTGT | 53.64 °C for allele [C] 62.30 °C for allele [T] |
| COX-2 T8473C (rs5275) | ATTGATTCTATTACCTCTGG [T/C] ATTTTCTACCATACCAAAACAAA | 52.94 °C for allele [T] 61.12 °C for allele [C] |

rs: reference SNP number; alleles in the square brackets indicates the polymorphisms.
Genotype distributions and features of the studied SNPs.

Table 2
Carousel-based system PCR program setup.

| Program Name    | Cycles | Analysis Mode | Target (°C) | Acquisition Mode | Hold (sec) |
|-----------------|--------|---------------|-------------|-----------------|------------|
| Pre-Incubation  | 1      | None          | 95          | None            | 600        |
| Amplification   | 45     | Quantification| 95          | None            | 10         |
| Melting Curve   | 1      | Melting Curve | 95          | None            | 30         |
| Cooling         | 1      | None          | 40          | None            | 30         |

Genotypes

| SNPs               | Amino acid change | Variant allele | Genotypes | Frequencies | OR (95% CI) | p value |
|--------------------|-------------------|----------------|-----------|-------------|-------------|---------|
| ABCG2 C421A (rs2231142) | Q141K             | C              | CC        | 90 (86.5)   | CC vs. any A | 0.002*  |
|                    |                   | CA             | AA        | 14 (13.5)   | 3.06 (1.49–6.25) |
| MAF     |                   |                |           | 0.072       | 0.183       |
| ABCB1 C3435T (rs10455642) | I1145I         | C              | CC        | 25 (24.2)   | CC vs. any T | 0.361   |
|                    |                   | CT             | TT        | 37 (35.9)   | 1.24 (0.61–2.53) |
| MAF     |                   |                |           | 0.422       | 0.418       |
| COX-2 G306C (rs5277) | V102V             | G              | GG        | 46 (44.6)   | GG vs. any C | 0.853   |
|                    |                   | GC             | CC        | 47 (45.6)   | 1.06 (0.59–1.86) |
| MAF     |                   |                |           | 0.325       | 0.366       |
| COX-2 T8473C (rs5275) |                 | T              | TT        | 72 (69.2)   | TT vs. any C | 0.479   |
|                    |                   | TC             | CC        | 28 (26.9)   | 1.24 (0.68–2.26) |
| MAF     |                   |                |           | 0.173       | 0.200       |

Snps, single nucleotide polymorphisms; rs, reference SNP number; MAF, minor allele frequency; OR, odds ratio; 95% CI, 95% confidence intervals. *p < 0.05 indicates statistical significance.

3. Results and discussion

Although the correlation between the SNPs of the ABCG2, ABCB1 and COX-2 genes with breast cancer risk has been reported in some studies, no meaningful relationship has been demonstrated thus far. The substrate specificities of ABCG2 and ABCB1 are quite similar, and ABCG2 and ABCB1 are involved in the transport of COX-2 mediated inflammatory agents (Klaassen and Aleksunes, 2010; Yu et al., 2010). Therefore, we evaluated the association between functional and common variants (ABCG2 C421A, ABCB1 C3435T, COX-2 T8473C and COX-2 G306C), and susceptibility to breast cancer in a cohort of Turkish women.

Firstly, we determined that no significant differences in age (52.4 ± 12.5 vs. 49.4 ± 14.2 years) or BMI (27.9 ± 5.3 vs. 24.5 ± 4.5 kg/cm²) between the breast cancer and control groups, respectively. However, the patients carrying the AA genotype of COX-2 G306C variant have been shown to have significantly higher BMI than patients carrying the wild-type variant (Mizuarai et al., 2004). While the incidence of the ABCG2 C421A polymorphism is 30% in Far Easterners, it has been reported to be approximately 10% and 13% in Caucasians and Middle Easterners, respectively (Kim et al., 2010). Ghafari et al. (2016) found that the most frequent genotype in patient groups was the AA genotype; its frequency was significantly different from that of the control subjects (p = 0.04). In the present study, CC genotype was the most frequent genotype in both our case and control groups, unlike to Kurdish populations in Sanadaj-Iran in comparison with Ghafari et al., 2016. Wu et al. (2015) investigated the correlation between the ABCG2 C421A polymorphism and breast cancer susceptibility in 1169 patients with breast cancer and 1244 healthy controls. The authors showed that the ABCG2 C421A AA genotype was significantly associated with an increased risk for developing breast carcinoma (p = 0.033). According to our results, ABCG2 C421A was significantly associated with an increased risk of breast cancer (p = 0.0019). However, the patients carrying the CC
Relations between polymorphisms and clinicopathological characteristics.

- **ER**: Estrogen receptor; **PgR**: Progesterone receptor; **HER2**: Human epidermal growth factor receptor 2.

**Table 3**

| Polymorphism | No. of patients (%) | p value | p value | p value | p value |
|--------------|---------------------|---------|---------|---------|---------|
|             | IDC                 |         |         |         |         |
|             | ILD                 |         |         |         |         |
|             | DCIS                |         |         |         |         |
|             | unknown             |         |         |         |         |
|             | ER status           |         |         |         |         |
|             | positive            |         |         |         |         |
|             | negative            |         |         |         |         |
|             | unknown             |         |         |         |         |
|             | PgR status          |         |         |         |         |
|             | positive            |         |         |         |         |
|             | negative            |         |         |         |         |
|             | unknown             |         |         |         |         |
|             | HER2 status         |         |         |         |         |
|             | positive            |         |         |         |         |
|             | negative            |         |         |         |         |
|             | unknown             |         |         |         |         |
|             | Triple negative     |         |         |         |         |

**Table 4**

| Variables       | No. of patients (%) | ABC2 C421A (rs2231142) | p value | ABC2 C4345T (rs1045642) | p value | COX-2 C306C (rs2231142) | p value | COX-2 T8473C (rs5277) | p value |
|-----------------|---------------------|-------------------------|---------|-------------------------|---------|-------------------------|---------|----------------------|---------|
| Pathological type| IDC                 |                         |         |                         |         |                         |         |                      |         |
|                 | ILD                 |                         |         |                         |         |                         |         |                      |         |
|                 | DCIS                |                         |         |                         |         |                         |         |                      |         |
|                 | unknown             |                         |         |                         |         |                         |         |                      |         |
|                 | ER status           |                         |         |                         |         |                         |         |                      |         |
|                 | positive            |                         |         |                         |         |                         |         |                      |         |
|                 | negative            |                         |         |                         |         |                         |         |                      |         |
|                 | unknown             |                         |         |                         |         |                         |         |                      |         |
|                 | PgR status          |                         |         |                         |         |                         |         |                      |         |
|                 | positive            |                         |         |                         |         |                         |         |                      |         |
|                 | negative            |                         |         |                         |         |                         |         |                      |         |
|                 | unknown             |                         |         |                         |         |                         |         |                      |         |
|                 | HER2 status         |                         |         |                         |         |                         |         |                      |         |
|                 | positive            |                         |         |                         |         |                         |         |                      |         |
|                 | negative            |                         |         |                         |         |                         |         |                      |         |
|                 | unknown             |                         |         |                         |         |                         |         |                      |         |
|                 | Triple negative     |                         |         |                         |         |                         |         |                      |         |
|                 | yes                 |                         |         |                         |         |                         |         |                      |         |
|                 | no                  |                         |         |                         |         |                         |         |                      |         |

**Table 4**

| Variables       | No. of patients (%) | ABC2 C421A (rs2231142) | p value | ABC2 C4345T (rs1045642) | p value | COX-2 C306C (rs2231142) | p value | COX-2 T8473C (rs5277) | p value |
|-----------------|---------------------|-------------------------|---------|-------------------------|---------|-------------------------|---------|----------------------|---------|
| Pathological type| IDC                 |                         |         |                         |         |                         |         |                      |         |
|                 | ILD                 |                         |         |                         |         |                         |         |                      |         |
|                 | DCIS                |                         |         |                         |         |                         |         |                      |         |
|                 | unknown             |                         |         |                         |         |                         |         |                      |         |
|                 | ER status           |                         |         |                         |         |                         |         |                      |         |
|                 | positive            |                         |         |                         |         |                         |         |                      |         |
|                 | negative            |                         |         |                         |         |                         |         |                      |         |
|                 | unknown             |                         |         |                         |         |                         |         |                      |         |
|                 | PgR status          |                         |         |                         |         |                         |         |                      |         |
|                 | positive            |                         |         |                         |         |                         |         |                      |         |
|                 | negative            |                         |         |                         |         |                         |         |                      |         |
|                 | unknown             |                         |         |                         |         |                         |         |                      |         |
|                 | HER2 status         |                         |         |                         |         |                         |         |                      |         |
|                 | positive            |                         |         |                         |         |                         |         |                      |         |
|                 | negative            |                         |         |                         |         |                         |         |                      |         |
|                 | unknown             |                         |         |                         |         |                         |         |                      |         |
|                 | Triple negative     |                         |         |                         |         |                         |         |                      |         |
|                 | yes                 |                         |         |                         |         |                         |         |                      |         |
|                 | no                  |                         |         |                         |         |                         |         |                      |         |
breast cancer in our population of Turkish women. ABCB1 C3435T might be associated with a potential risk for breast cancer in Turkish women. These data might be useful for identifying individuals at risk of developing breast cancer. However, our results were obtained with a limited sample size; we were accordingly only able to draw preliminary conclusions at this time. Future studies based on larger, stratified case-control populations are still necessary to clarify the different effects of the ABCB1, ABCG2 and COX-2 polymorphisms on cancer risk. Larger sample sizes and functional assays will be required to confirm our findings.

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Author Disclosure Statement

The authors declare that there are no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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