Saudi Pharmaceutical Journal 28 (2020) 215–219

Contents lists available at ScienceDirect

Saudi Pharmaceutical Journal

journal homepage: www.sciencedirect.com

Original article

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

Kara Pala Zeliha [a], Ozturk Dilek [b], Oztas Ezgi [c], Kara Halil [d], Uras Cihan [d], Ozhan Gul [c,*]

[a] Department of Pharmacology, Faculty of Pharmacy, Istanbul University, Istanbul, Turkey
[b] Department of Pharmacology, Faculty of Pharmacy, Bezmialem Vakif University, Istanbul, Turkey
[c] Department of Pharmaceutical Toxicology, Faculty of Pharmacy, Istanbul University, Istanbul, Turkey
[d] Department of General Surgery, Faculty of Medicine, Acibadem University, Istanbul, Turkey

ARTICLE INFO

Article history:
Received 8 April 2019
Accepted 29 November 2019
Available online 7 December 2019

Keywords:
MDR1
BCRP
COX-2
Breast cancer
Genetic susceptibility
Genotype analysis

ABSTRACT

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

* Corresponding author: Department of Pharmaceutical Toxicology, Faculty of Pharmacy, Istanbul University, 34116 Beyazit, Istanbul, Turkey.
E-mail address: gulozhan@istanbul.edu.tr (O. Gul).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.jsps.2019.11.024
1319-0164/

(He et al., 2013), acute lymphoblastic leukemia (Yaya et al., 2014), glioma (Miller et al., 2005) and renal epithelial tumors (Haenisch 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). BRCP 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; Ghafouri 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 (Ristimäki et al., 1997) and breast (Liu and Rose, 1996). In recent studies, *COX-2 T8473C* (rs5275), *G899C* (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 in-patients with various diagnoses (e.g., eye diseases, pulmonary diseases, cardiovascular diseases and neurological disorders) at the Hospital of Istanbul University (Istanbul, Turkey). All participants provided informed consent, and the study was approved by the ethics committees of Istanbul and Acibadem Universities (2011/87-555; 2012/291). Demographic and anthropometric factors were assessed using a short questionnaire. The pathological types of the patients were categorized as invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC) or ductal carcinoma in situ (DCIS). We also evaluated the association between patient genotypes and the status of ERα, PgR and HER2.

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 $MgCl_2$, 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 (χ^2) test. For the analysis of genotype frequencies, the wild-type category (chosen either as the most common wild-type frequency or

Table 1
Reference sequences of custom-designed LightSNiP assay probes.

LightSNiP	Reference Sequence	Melting temperature
ABCG2 *C421A* (rs2231142)	GCACTCTgACggTgAgAgAAAACTTA [A/C] AgTTCTCAgCAgCTCTTCggCTTgC	57.74 °C for allele [C] 61.92 °C for allele [A]
ABCB1 *C3435T* (rs1045642)	AgCCgggTggTgTCACAggAAgAgAT [C/T] gTgAgggCAgCAAAggAggCCAACA	55.76 °C for allele [C] 63.05 °C for allele [T]
COX-2 *G306C* (rs5277)	TTCgAAATgCAATTATgAgTTATgT [C/G] TTgACATgTAAgTACAAgTgTCTTT	53.64 °C for allele [G] 62.30 °C for allele [C]
COX-2 *T8473C* (rs5275)	TTTgAAATTTTAAAgTACTTTTggT [C/T] ATTTTTCTgTCATCAAACAAAAACA	52.94 °C for allele [T] 61.12 °C for allele [C]

rs: reference SNP number; alleles in the square brackets indicates the polymorphisms.

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
			60	Single	10
			72	None	15
Melting Curve	1	Melting Curve	95	None	30
			40	None	120
			75	Continuous	–
Cooling	1	None	40	None	30

arbitrarily if the two alleles exhibited similar frequencies) was used as the reference group. Data comparisons were done by using Fisher's exact test. To evaluate the association between the genotype frequencies and breast cancer, odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. All of the statistical analyses were performed using Statistical Package for Social Sciences (SPSS) software (Version 17; SPSS Inc, Chicago, IL, USA). A two-sided *p* value less than 0.05 was considered to be statistically significant.

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/cm^2) between the breast cancer and control groups, respectively, suggesting that the matching based on these two variables was adequate. Secondly, the genotype distributions did not significantly deviate from the HWE in either the case or control groups for any of the examined SNPs ($p > 0.05$). After determining a lack of bias among the study populations, the differences between cases and controls in the distributions of *ABCG2 C421A*, *ABCB1 C3435T*, *COX-2 T8473C* and *COX-2 G306C* genotypes were analyzed (Table 3).

The *ABCG2 C421A* variant has been shown to be associated with a reduction of BCRP protein expression, and therefore decreased carrying capacity (Hira and Terada, 2018). The protein expression in subjects with the *C421A* mutant variant is reduced compared with that of 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). Ghafouri 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 Ghafouri 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*

Table 3
Genotype distributions and features of the studied SNPs.

				Frequencies			
SNPs	Amino acid change	Variant allele	Genotypes	Cases (n = 104, %)	Controls (n = 90, %)	OR (95% CI)	*p value*
ABCG2 C421A (rs2231142)			*CC*	90 (86.5)	61 (67.7)	*CC* vs. any *A* 3.06 (1.49–6.25)	0.002*
	Q141K	*C*	*CA*	14 (13.5)	25 (27.7)		
			AA	0 (0.0)	4 (4.4)		
MAF				**0.072**	**0.183**		
ABCB1 C3435T (rs1045642)			*CC*	25 (24.2)	16 (18.1)	*CC* vs. any *T* 1.24 (0.61–2.53)	0.361
	I1145I	*C*	*CT*	37 (35.9)	40 (45.4)		
			TT	41 (39.8)	32 (36.3)		
MAF				**0.422**	**0.418**		
COX-2 G306C (rs5277)			*GG*	46 (44.6)	39 (43.3)	*GG* vs. any *C* 1.06 (0.59–1.86)	0.853
	V102V	*G*	,*GC*	47 (45.6)	36 (40.0)		
			CC	10 (9.7)	15 (16.7)		
MAF				**0.325**	**0.366**		
COX-2 T8473C (rs5275)			*TT*	72 (69.2)	58 (64.4)	*TT* vs. any *C* 1.24 (0.68–2.26)	0.479
	–	*T*	*TC*	28 (26.9)	28 (31.1)		
			CC	4 (3.8)	4 (4.4)		
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.

genotype interestingly had a higher risk of disease compared with the patients carrying any *A* allele (OR = 3.06; 95% CI = 1.49–6.25) (Table 3). We indicate the results should be confirmed with the larger group because the frequency of the patients carrying *AA* genotype was ≤ 4.4%. The other variants, *CA* and *AA* genotypes, might be not associated with breast cancer ($p \geq 0.632$) (Table 3).

Many epidemiological studies have examined the relationship between *ABCB1* polymorphisms and breast cancer. Wang et al. (2013), in a meta-analysis, evaluated 10 case-control studies that encompassed 5282 breast cancer patients and 7703 healthy controls. It was suggested that *ABCB1 C3435T* polymorphism might contribute to individual susceptibility to breast cancer. The recent studies have demonstrated a significant difference in the distribution of *C* and *T* alleles between breast cancer patients and healthy controls (Abuhaliema et al., 2016; Gutierrez-Rubio et al., 2015; Macías-Gómez et al., 2014). However, some studies failed to find a significant relationship (Li et al., 2017; Ghafouri et al., 2016). Turgut et al. (2007) assessed the relationship between breast cancer risk and the *ABCB1 C3435T* variant in 50 healthy volunteers and 57 breast cancer patients in Turkish population. They found the polymorphism was associated with a 1.5-fold increase in breast cancer risk. However, we found no relationship between the *ABCB1 C3435T* variant and breast cancer development (OR = 1.242, 95% CI: 0.61–2.53; $p = 0.36$) (Table 3).

COX-2 T8473C is a common polymorphism associated with several cancers in different ethnic populations (Jiang et al., 2014). Thus far, more than 20 *COX-2* genetic variations have been investigated for the risk of breast cancer (Dai et al., 2014). However, Li et al., 2015 have been assessed the results as conflicting. In a recent meta-analysis, Jiang et al. (2014) found that the *COX-2 T8473C* gene polymorphism might not be a risk factor for breast cancer among Caucasians. Three studies focused on *COX-2 G306C* and the risk of breast cancer, however, failed to find any significant relationship between polymorphism and breast cancer risk (Dossus, et al. 2010; Abraham et al., 2009). Similarly, we did not find any significant differences in *COX-2* gene variants between breast cancer patients and the control group (Table 3).

As it is well known, ERα plays an important role in the progression of breast cancer. Patients with high ERα or PgR expression have a better prognosis. It has been shown that E2-mediated downregulation of P-gp expression occurs in ERα-positive human breast cancer cells and possibly also in normal breast tissues (Hua et al., 2018). In addition, estrogenic activity has been shown to downregulate P-gp expression via post-transcriptional processes in ERα-positive cell lines, leading to increased cellular uptake of P-gp substrates (Mutoh et al., 2006).

Some studies have been reported that no statistically significant association between *ABCB1 C3435T* and *ABCG2 C421A* polymorphisms and tissue expression of ERα, PgR, HER2/neu, and Ki67 (Ghafouri et al., 2016; Li et al., 2017). Comparing the pathological parameters with the variants, we found that the *ABCB1 C3435T C* allele was less frequent in breast cancer patients with ERα-positive (OR = 2.25; 95% CI: 0.75–6.76; $p = 0.041$) and PgR (OR = 3.67; 95% CI: 1.34–10.03; $p = 0.008$) status. No significant differences in HER2 status, triple negative status (none of ERα-, PgR and HER2 expressed) or pathological type were found with the variants (Table 4).

Based on the results reported by Ghafouri et al. (2016), the *A* allele of the *ABCG2 C421A* variant was associated with IDC ($p < 0.05$). Wu et al. (2015) found that an association between this polymorphism and ER and PgR status in breast cancer patients. However, we not find any relationship between the clinicopathological status of breast cancer patients and the *ABCG2 C421A* polymorphism (Table 4). Similarly, Li et al. (2017) did not find a significant difference in the distribution of the *ABCG2 C421A* variant between breast cancer patients and healthy controls; there was also no difference based on the clinical status of the patients ($p > 0.05$).

Like other studies (Leo et al., 2006; Ranger et al., 2004), we did not find a significant correlation between *COX-2* SNPs and the clinical status of breast cancer patients (Table 4).

4. Conclusion

We observed that *ABCG2 C421A* was significantly associated with an increased risk of breast cancer ($p = 0.0019$). No studies have demonstrated the prevalence of the *ABCG2 C421A* polymorphism in Turkish society and its relationship to breast cancer; our results are the first data. *ABCB1 C3435T* did not exhibit any relationship with breast cancer development. However, we found significant differences between *ABCB1 C3435T* variant and ERα and PgR status with

Table 4
Relations between polymorphisms and clinicopathological characteristics.

Variables	No. of patients (%)	*ABCG2 C421A* (rs2231142)			*p* value	*ABCB1 C3435T* (rs1045642)			*p* value	*COX-2 G306C* (rs5277)			*p* value	*COX-2 T8473C* (rs5275)			*p* value
		CC	*CA*	*AA*		*CC*	*CT*	*TT*		*GG*	*GC*	*CC*		*TT*	*TC*	*CC*	
Pathological type					0.657				0.975				0.056				0.080
IDC	61 (58.7)	53	8	0		16	22	23		45	14	2		25	32	4	
ILC	8 (7.7)	7	1	0		2	3	3		7	1	0		3	2	3	
DCIS	8 (7.7)	6	2	0		1	3	3		6	0	2		2	5	1	
unknown	27 (25.9)																
ERα status					0.367				0.041*				0.062				0.896
positive	57 (54.8)	49	8	0		12	26	19		40	3	14		23	29	5	
negative	17 (16.3)	16	1	0		6	2	9		15	2	0		6	9	2	
unknown	30 (28.9)																
PgR status					0.904				0.008*				0.449				0.896
positive	42 (40.4)	42	6	0		11	24	13		35	9	3		29	23	4	
negative	31 (29.8)	23	3	0		7	4	15		19	5	0		9	15	2	
unknown	31 (29.8)																
HER2 status					0.108				0.878				0.927				0.399
positive	16 (15.4)	12	4	0		4	5	7		12	3	1		4	10	2	
negative	56 (53.8)	51	5	0		14	21	21		40	13	3		24	25	7	
unknown	32 (30.8)																
Triple negative					0.987				0.317				0.596				0.675
yes	8 (7.7)	7	1	0		3	1	4		7	1	0		2	5	1	
no	63 (60.5)	55	8	0		15	25	23		45	15	3		26	31	6	
unknown	33 (31.7)																

IDC, Invasive ductal carcinoma; ILC, Invasive Lobular Carcinoma; DCIS, Ductal carcinoma in situ; ERα, estrogen receptor-α; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2. *$p < 0.05$ indicates statistical significance.

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.

Acknowledgements

This work was supported by the Research Fund of Istanbul University. Project Number: 25158.

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.

References

Abraham, J.E., Harrington, P., Driver, K.E., et al., 2009. Common polymorphisms in the prostaglandin pathway genes and their association with breast cancer susceptibility and survival. Clin. Cancer Res. 15 (6), 2181–2191.
Abuhaliema, A.M., Yousef, A.M., Elmadany, N.N., et al., 2016. Influence of Genotype and Haplotype of MDR1 (C3435T, G2677A/T, C1236T) on the Incidence of Breast Cancer–a Case-Control Study in Jordan. Asian Pac. J. Cancer Prev. 17 (1), 261–266.
Andersen, V., Svenningsen, K., Knudsen, L.A., et al., 2015. Novel understanding of ABC transporters ABCB1/MDR/P-glycoprotein, ABCC2/MRP2, and ABCG2/BCRP in colorectal pathophysiology. World J. Gastroenterol. 21 (41), 11862–11876.
Brasky, T.M., Bonner, M.R., Moysich, K.B., et al., 2011. Genetic variants in COX-2, nonsteroidal anti-inflammatory drugs, and breast cancer risk: the Western New York Exposures and Breast Cancer (WEB) Study. Breast Cancer Res. Treat. 126, 157–165.
Campa, D., Butterbach, K., Slager, S.L., et al., 2012. A comprehensive study of polymorphisms in the ABCB1, ABCC2, ABCG2, NR1I2 genes and lymphoma risk. Int. J. Cancer 131 (4), 803–812.
Dai, Z.J., Shao, Y.P., Ma, X.B., et al., 2014. Association of the three common SNPs of cyclooxygenase-2 gene (rs20417, rs689466, and rs5275) with the susceptibility of breast cancer: an updated meta-analysis involving 34,590 subjects. Dis. Markers 2014, 484729.
DeGorter, M.K., Xia, C.Q., Yang, J.J., et al., 2012. Drug transporters in drug efficacy and toxicity. Annu. Rev. Pharmacol. Toxicol. 52, 249–273.
Dossus, L., Kaaks, R., Canzian, F., et al., 2010. PTGS2 and IL6 genetic variation and risk of breast and prostate cancer: results from the Breast and Prostate Cancer Cohort Consortium (BPC3). Carcinogenesis 31 (3), 455–461.
Eberhart, C.E., Coffey, R.J., Radhika, A., et al., 1994. Up-regulation of cyclooxygenase 2 gene expression in human colorectal adenomas and adenocarcinomas. Gastroenterology 107 (4), 1183–1188.
Fletcher, J.I., Williams, R.T., Henderson, M.J., et al., 2016. ABC transporters as mediators of drug resistance and contributors to cancer cell biology. Drug Resist. Updat. 26, 1–9.
George, J., Dharanipragada, K., Krishnamachari, S., et al., 2009. A single-nucleotide polymorphism in the MDR1 gene as a predictor of response to neoadjuvant chemotherapy in breast cancer. Breast Cancer 9 (3), 161–165.
Ghafouri, H., Ghaderi, B., Amini, S., et al., 2016. Association of ABCB1 and ABCG2 single nucleotide polymorphisms with clinical findings and response to chemotherapy treatments in Kurdish patients with breast cancer. Tumour Biol. 37 (6), 7901–7906.
Gutierrez-Rubio, S.A., Quintero-Ramos, A., Durán-Cárdenas, A., et al., 2015. 1236 C/T and 3435 C/T polymorphisms of the ABCB1 gene in Mexican breast cancer patients. Genet. Mol. Res. 14 (1), 1250–1259.
Haenisch, S., Zimmermann, U., Dazert, E., et al., 2007. Influence of polymorphisms of ABCB1 and ABCC2 on mRNA and protein expression in normal and cancerous kidney cortex. Pharmacogenomics J. 7 (1), 56–65.
Hahn, N.M., Marsh, S., Fisher, W., et al., 2006. Hoosier Oncology Group randomized phase II study of docetaxel, vinorelbine, and estramustine in combination in hormone-refractory prostate cancer with pharmacogenetic survival analysis. Clin. Cancer Res. 12 (20 Pt 1), 6094–6099.
He, T., Mo, A., Zhang, K., Liu, L., 2013. ABCB1/MDR1 gene polymorphism and colorectal cancer risk: a meta-analysis of case-control studies. Colorectal Dis. 15 (1), 12–18.
Hira, D., Terada, T., 2018. BCRP/ABCG2 and high-alert medications: Biochemical, pharmacokinetic, pharmacogenetic, and clinical implications. Biochem. Pharmacol. 147, 201–210.
Hoffmeyer, S., Burk, O., von Richter, O., et al., 2000. Functional polymorphisms of the human multidrug-resistance gene: multiple sequence variations and correlation of one allele with P-glycoprotein expression and activity in vivo. Proc. Natl. Acad. Sci. 97 (7), 3473–3478.
Hua, H., Zhang, H., Kong, Q., et al., 2018. Mechanisms for estrogen receptor expression in human cancer. Exp. Hematol. Oncol. 7, 24.
Ishikawa, T., Shimizu, D., Yamada, A., et al., 2012. Impacts and predictors of cytotoxic anticancer agents in different breast cancer subtypes. Oncol. Res. 20 (2–3), 71–79.
Jiang, J., Quan, X.F., Zhang, L., et al., 2014. Lack of association between COX-2 8473T>C polymorphism and breast cancer risk: a meta-analysis. Contemp. Oncol. (Pozn) 18 (3), 177–181.
Klaassen, C.D., Aleksunes, L.M., 2010. Xenobiotic, bile acid, and cholesterol transporters: function and regulation. Pharmacol. Rev. 62 (1), 1–96.
Kim, K.A., Joo, H.J., Park, J.Y., 2010. ABCG2 polymorphisms, 34G>A and 421C>A in a Korean population: analysis and a comprehensive comparison with other populations. J. Clin. Pharm. Ther. 35, 705–712.
Korenaga, Y., Naito, K., Okayama, N., et al., 2005. Association of the BCRP C421A polymorphism with nonpapillary renal cell carcinoma. Int. J. Cancer 117 (3), 431–434.
Lala, P.K., Nandi, P., Majumder, M., 2018. Roles of prostaglandins in tumor-associated lymphangiogenesis with special reference to breast cancer. Cancer Metastasis. Rev. 37 (2–3), 369–384.
Leo, C., Faber, S., Hentschel, B., et al., 2006. The status of cyclooxygenase-2 expression in ductal carcinoma in situ lesions and invasive breast cancer correlates to cyclooxygenase-2 expression in normal breast tissue. Ann. Diagn. Pathol. 10 (6), 327–332.
Li, F., Ren, G.S., Li, H.Y., et al., 2009. A novel single nucleotide polymorphism of the cyclooxygenase-2 gene associated with breast cancer. Clin. Oncol. 21, 302–305.
Li, Q., Liu, L., Liu, Y., et al., 2015. Five COX-2 gene polymorphisms and risk of breast cancer: an updated meta-analysis based on 19 case-control studies. Med. Oncol. 32 (1), 397.
Li, W., Zhang, D., Du, F., et al., 2017. ABCB1 3435TT and ABCG2 421CC genotypes were significantly associated with longer progression-free survival in Chinese breast cancer patients. Oncotarget 8 (67), 111041–111052.
Liu, X.H., Rose, D.P., 1996. Differential expression and regulation of cyclooxygenase-1 and -2 in two human breast cancer cell lines. Cancer Res. 56 (22), 5125–5127.
Macías-Gómez, N.M., Gutiérrez-Angulo, M., Leal-Ugarte, E., et al., 2014. MDR1 C3435T polymorphism in Mexican patients with breast cancer. Genet. Mol. Res. 13 (3), 5018–5024.
Miller, K.L., Kelsey, K.T., Wiencke, J.K., et al., 2005. The C3435T polymorphism of MDR1 and susceptibility to adult glioma. Neuroepidemiology 25 (2), 85–90.
Mizuarai, S., Aozasa, N., Kotani, H., 2004. Single nucleotide polymorphisms result in impaired membrane localization and reduced atpase activity in multidrug transporter ABCG2. Int. J. 109 (2), 238–246.
Mutoh, K., Tsukahara, S., Mitsuhashi, J., et al., 2006. Estrogen-mediated post transcriptional down-regulation of P-glycoprotein in MDR1-transduced human breast cancer cells. Cancer Sci. 97 (11), 1198–1204.
Ranger, G.S., Jewell, A., Thomas, V., et al., 2004. Elevated expression of cyclooxygenase-2 in breast cancer and ductal carcinoma in situ has no correlation with established prognostic markers. J. Surg. Oncol. 88 (2), 100–103.
Ristimäki, A., Honkanen, N., Jänkälä, H., et al., 1997. Expression of cyclooxygenase-2 in human gastric carcinoma. Cancer Res. 57 (7), 1276–1280.
Robey, R.W., To, K.K., Polgar, O., et al., 2009. ABCG2: a perspective. Adv. Drug Deliv. Rev. 61 (1), 3–13.
Siegel, R.L., Miller, K.D., Jemal, A., 2019. Cancer statistics, 2019. CA A Cancer J. Clin. 69, 7–34.
Torre, L.A., Islami, F., Siegel, R.L., et al., 2017. Global cancer in women: Burden and trends. Cancer Epidemiol. Biomark. Prev. 26, 444–457.
Turgut, S., Yaren, A., Kursunluoglu, R., et al., 2007. MDR1 C3435T polymorphism in patients with breast cancer. Arch. Med. Res. 38 (5), 539–544.
Turkey Ministry of Health, Public Health Association. (2017) Cancer statistics of Turkey. https://hsgm.saglik.gov.tr/depo/birimler/kanser-db/istatistik/2014 RAPOR._uzuuun.pdf [accessed: 20.03.2019].
Ucan, B., Özbek, M., Şahin, M., et al., 2017. Cyclooxygenase-2 (COX-2) gene polymorphism in patients with differentiated thyroid carcinomas in the Turkish population. Turk. J. Med. Sci. 47 (6), 1848–1853.
van Herwaarden, A.E., Schinkel, A.H., 2006. The function of breast cancer resistance protein in epithelial barriers, stem cells and milk secretion of drugs and xenotoxins. Trends Pharmacol. Sci. 27 (1), 10–16.
Wang, Z., Wang, T., Bian, J., 2013. Association between MDR1 C3435T polymorphism and risk of breast cancer. Gene 532 (1), 949–959.
Wang, J., Wang, B., Bi, J., et al., 2012. MDR1 gene C3435T polymorphism and cancer risk: a meta-analysis of 34 case–control studies. J. Cancer Res. Clin. Oncol. 138, 979–989.
Wu, H., Liu, Y., Kang, H., et al., 2015. Genetic variations in ABCG2 gene predict breast carcinoma susceptibility and clinical outcomes after treatment with anthracycline-based chemotherapy. Biomed Res. Int. 2015, 279109.
Yaya, K., Hind, D., Meryem, Q., et al., 2014. Single nucleotide polymorphisms of multidrug resistance gene 1 (MDR1) and risk of chronic myeloid leukemia. Tumour Biol. 35 (11), 10969–10975.
Yu, K.D., Chen, A.X., Yang, C., et al., 2010. Current evidence on the relationship between polymorphisms in the COX-2 gene and breast cancer risk: a meta-analysis. Breast Cancer Res. Treat. 122, 251–257.