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ORIGINAL ARTICLE

Genetic Variations of DNA Repair Genes in Breast Cancer

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Abstract Genetic variations in DNA repair genes may affect DNA repair capacity therefore increase risk for cancer. In our study, we evaluted the relation between DNA repair gene polymorphisms XRCC1 rs1799782, rs25487, rs25489; XPC rs2228000, rs2228001; XPD rs1799793, rs13181; XRCC3 rs861539; RAD51B rs10483813, rs1314913 and breast cancer risk for 202 Turkish cases in total, in which 102 patients with breast cancer and 100 controls. Genotyping of the DNA samples was carried out by multiplex PCR and matrix-assisted laser desorption/ionization mass spectrometry with time of flight measurement (MALDI-TOF) using Sequenom MassARRAY 4 analyzer. Genotype and allele distributions were calculated between the groups. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported. rs25487 AA genotype and A allele was found to be increased in the control group (respectively, OR 0.16 95% CI 0.02–1.06, $p = 0.058$; OR 1.55, 95% CI 1.01–2.36, $p = 0.043$) and rs861539 T allele was found to be decreased in the patient group (OR 1.53, 95% CI 1.01–2.30, $p = 0.049$). No association with breast cancer was found for the remaining SNPs. Our findings suggest that XRCC1 rs25487 AA genotype and A allele, XRCC3 rs861539 T allele may have protective effects in breast cancer for Turkish population.

Keywords Breast cancer · DNA damage · DNA repair · Polymorphism

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Introduction

Breast cancer (BC) is one of the most common malignancies observed among women [1]. It is a multifactorial disease and many factors including genetic, environmental, reproductive and lifestyle related factors effect forming of the disease [2]. Even though the mechanism underlying breast carcinogenesis is not fully understood, various risk factors are defined for the disease, such as induction of DNA damage by endogenous and exogenous agents [3].

Failure in repairing a damage in the chemical structure of DNA plays an important role in cancer progression [4]. Detection and repair of DNA damage by DNA repair mechanisms, plays an important role in preventing carcinogenesis, maintaining genome integrity and protecting against mutations [3]. More than 150 DNA repair genes have been so far identified [5] and the role of DNA repair in cancer is still investigated commonly. Scientific studies have suggested that an impaired DNA damage response may increase the risk of breast cancer. Single nucleotide polymorphisms (SNPs) in DNA repair genes may alter the effects of DNA repair and protein function, and additionally may affect the development of various cancers including breast cancer [2].

Studies from different populations investigating SNPs in DNA repair genes and breast cancer risk were reported conflicting results. Ethnic and geographic diversity were shown to be the reason for this. In the current study conducted in a Turkish population, we aimed to contribute to the literature about DNA repair genes and breast cancer risk association.

Therefore in this study, we evaluated the interaction between prognostic markers and risk factors, and the DNA repair gene polymorphisms in breast cancer, such as X-Ray Repair Cross-Complementing Protein 1 (XRCC1) gene rs1799782, rs25487, rs25489 SNPs of base excision repair (BER) pathway; Xeroderma Pigmentosum Group C-Complementing Protein (XPC) gene rs2228000, rs2228001 and Xeroderma Pigmentosum Group D-Complementing Protein (XPD) gene rs1799793, rs13181 SNPs of nucleotide excision repair (NER) pathway; X-Ray Repair Cross-Complementing Protein 3 (XRCC3) gene rs861539 SNP and RAD51 Homolog B (RAD51B) gene rs10483813, rs1314913, rs999737 SNPs of double strand break (DSBR) pathway.

Materials and Methods

Patients

The study protocol was in accordance with the Declaration of Helsinki, and approved by the Acıbadem University Medical Research Assessment Committee (Decision dated 14 May 2013, numbered 2013–495).

In the current study, 102 post-menopausal patients with breast cancer admitted to Acıbadem Bursa Hospital, Department of Medical Oncology (mean age: 62.0 ± 7.8 years) and 100 post-menopausal healthy controls without breast cancer neither in them nor in their family (mean age: 52.6 ± 3.7 years) were included. From all the cases participated in the study, a signed informed consent form was obtained. Breast cancer diagnosis was verified by an expert pathologist histologically and pathologically.

For every of the patients, information such as, medical history, demographic properties, age of menarche, age of first delivery, number of children, age of menopause, hormone replacement therapy, smoking and alcohol consumption history, family history were obtained. For breast cancer patients additional information such as, age of diagnosis, tumor grade, tumor histology, tumor metastasis, tumor size, lymph node metastasis, estrogen receptor status, progesterone receptor status, and Her2Neu status were also collected.

DNA Extraction and Genotyping

Extraction of genomic DNA of all the cases was performed using a High Pure PCR Template Preparation Kit (Roche, Diagnostics GmbH, Mannheim, Germany), according to the instructions of the manufacturer.

Genotyping of the DNA samples was carried out by multiplex PCR and matrix-assisted laser desorption/ionization mass spectrometry with time of flight measurement (MALDI-TOF) using Sequenom MassARRAY 4 analyzer. Multiplex PCR was performed on a plate with 384 wells and 2 wells are used for all cases. Prepared PCR mix was distributed 4 μl and 1 μl (10 ng) DNA sample was also added for each well. PCR conditions were 15 min at 95 °C; 44 cycles of 94 °C for 20 s, 56 °C for 30 s, and 72 °C for 60 s; 3 min at 72 °C; 5 min at 4 °C and hold at 15 °C. Later, shrimp alkaline phosphatase (SAP) reaction, iPLEX reaction were carried out; transferring of the samples to the spectro chip, ionization of the samples were done on Sequenom MassARRAY 4 analyzer and mass spectra analysing was performed by MassARRAY TYPER 4.0 software (Agena Bioscience, San Diego, USA) as described before [6].

Statistical Analysis

Genotype distribution within the groups of the cases and controls was compared with values predicted by Hardy-Weinberg equilibrium (HWE) using the chi-square test. Continuous variables are expressed as mean ± SD (Standard Deviation), and the significance level was defined as $p < 0.05$. Demographic and clinical data were compared with Student T test and Mann–Whitney U test. The differences of allelic and genotypic frequencies between the case and control groups were estimated by the Pearson's chi-square test and Fisher's exact test. The odds ratios (ORs) and 95% CI for all potential risk factors were calculated by multivariate logistic regression analyses. SPSS 18.0 software (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.) was used to evaluate all statistical analyses.

Results

Clinical Characteristics of the Study Subjects

Some factors such as age, body mass index (BMI), smoking, alcohol consumption, age of menarche, age of first delivery, number of children, family history, receiving hormone replacement therapy (HRT) were included in the demographic profile (Table 1) of the cases. Whereas no statistically significant difference were detected in BMI, number of children, receiving HRT, alcohol consumption history; difference was significant in age, smoking, age of menarche, age of first delivery, family history between the two groups (respectively, $p = 0.000$ $p = 0.041$, $p = 0.017$, p = 0.000, p = 0.000).

Table 1 Demographic and clinical characteristics of the BC patient and control subjects

Characteristics	Cases (%) $N = 102$	Controls (%) $N = 100$	p value*
Age, years (mean ± SD)	62.0 ± 7.8	52.6 ± 3.7	0.000*
BMI (mean ± SD)	29.5 ± 5.2	30 ± 5.1	0.482
Smoking			0.041*
Yes	18 (17.6)	8 (8)	
No	84 (82.4)	92 (92)	
Alcohol consumption			0.323
Yes	3 (2.9)	1 (1)	
No	99 (97.1)	99 (99)	
Age at menarche			0.017*
≤ 14	77(76.2)	89 (89)	
> 14	24 (23.8)	11 (11)	
Age of first birth, years (mean ± SD)	21.6 ± 4.1	24.3 ± 4.9	0.000*
Number of childbirth, n (%)			0.721
0	4 (3.9)	3 (3)	
≥ 1	98 (96.1)	97 (97)	
Family history of cancer in first-degree relatives, n (%)	46 (45.1)	71 (71)	0.000*
No Family history of breast cancer	20 (19.6)	9 (9)	
Family history of other cancers	36 (35.3)	20(20)	
HRT			0.499
No	88 (86.3)	89 (89)	
1–6 months	5 (4.9)	7 (7)	
> 6 months	9 (8.8)	4(4)	

BMI Body Mass Index, *HRT* Hormone replacement therapy

*Indicates that p values less than 0.05

Genotype and Allele Distribution of SNPs

The genotype and allele frequency distributions of the XRCC1, XPC, XPD, XRCC3 and RAD51B genes' SNPs in two groups, namely cases and controls, were given in Table 2. Genotype frequency distributions in the SNPs between two groups were not found to be statistically different from each other. Whereas there was no difference in allele frequencies of the SNPs rs1799782, rs25489, rs2228000, rs2228001, rs1799793, rs13181, rs10483813, rs1314913; a statistically significant difference was observed in rs25487 (p = 0.039) and rs861539 (p = 0.040). All polymorphisms were in Hardy-Weinberg equilibrium in breast cancer cases and controls.

In order to evaluate the effects of age, BMI, receiving HRT, smoking, alcohol consumption, age of first delivery, number of delivery, age at menarche, family history of cancer together with the polymorphisms over BC development risk, binary logistic regression model was carried out. rs25487 AA genotype and A risk allele was found to be significantly increased in the control group (respectively, OR 0.16 95% CI 0.02–1.06, $p = 0.058$; OR 1.55, 95% CI 1.01–2.36, $p = 0.043$). The minor allele frequencies of rs25487 in the patient and control group was 0.275 and 0.370, respectively. rs861539 T risk allele was found to be significantly decreased in the patient group (OR 1.53, 95% CI 1.01–2.30, p = 0.049). The minor allele frequencies of rs861539 in the patient and control group were 0.363 and 0.430, respectively.

SNPs and Histopathological Characteristics of Breast Tumors

Histopathologic properties of the breast tumors were given in Table 3. Most of the tumors were invasive ductal carcinoma (83.3%) and all of the tumors were Estrogen-receptor positive (ER+) positive. The frequencies of the other properties were as follows; Progesterone-receptor-(PR) positivity 81.4%, Human epidermal growth factor receptor 2 (Her2Neu) positivity 24.5%, lymph node positivity 52%, Grade 1–2 tumors 60.8%, and metastasis 11.7%. No relation was detected between tumor grade, metastasis status, tumor size, lymph node positivity and the SNPs. PR positivity was significantly associated with rs1314913 (p = 0.044), Her2Neu negativity was significantly associated with rs25489 and rs861539 (respectively $p = 0.047$, $p = 0.042$) and invasive ductal carcinoma was significantly associated with rs13181 and rs1314913 (respectively, p = 0.025, p = 0.042).

Table 2 Genotype and Allele distributions of SNPs

Genotypes	Cases (n = 102)	Controls (n = 100)	X^2 p-value	OR (95% CI) Adjusted	p-value
rs1799782 (XRCC1)			0.889		
CC	83(81.4)	81(81)		1[a]	
CT	16(15.7)	17(17)		0.40(0.10–1.64)	0.207
TT	3(2.9)	2(2)		0.27(0.00–14.18)	0.258
CC/CT + TT	19(18.6)	19(18.6)	0.544	1.02(0.50–2.07)	1.000
Alleles					
C	182(89.2)	179(89.5)	0.926	1[a]	
T	22(10.8)	21(10.5)		0.97(0.51–1.82)	1.000
	HWE:0.06	*HWE:0.339*			
rs25487 (XRCC1)			0.085		
GG	51(50)	38(38)		1[a]	
AG	46(45.1)	50(50)		0.48(0.14–1.56)	0.226
AA	5(4.9)	12(12)		0.16(0.02–1.06)	0.058
GG/AG + AA	51(50)	62(62)	0.057	1.63(0.93–2.85)	0.091
Alleles					
G	148(72.5)	126(63)	0.039*	1[a]	
A	56(27.5)	74(37)		1.55(1.01–2.36)	0.043*
	HWE:0.181	*HWE:0.468*			
rs25489 (XRCC1)			0.221		
GG	92(90.2)	82(82)		1[a]	
GA	9(8.8)	17(17)		0.24(0.04–1.22)	0.087
AA	1(1)	1(1)		17.2(0.24–1226.4)	0.192
GG/GA + AA	10(9.8)	18(18)	0.069	2.02(0.88–4.62)	0.106
Alleles					
G	193(94.6)	181(90.5)	0.115	1[a]	
A	11(5.4)	19(9.5)		1.84(0.85–3.97)	0.131
	HWE:0.172	*HWE:0.909*			
rs861539 (XRCC3)			0.234		
CC	42(41.2)	37(37)		1[a]	
TC	46(45.1)	40(40)		1.65(0.54–5.06)	0.374
TT	14(13.7)	23(23)		0.35(0.07–1.66)	0.187
CC/TC + TT	60(58.8)	63(63)	0.321	1.19(0.67–2.09)	0.567
Alleles					
C	130(63.7)	114(57)	0.040*	1[a]	
T	64(36.3)	86(43)		1.53(1.01–2.30)	0.049*
	HWE:0.804	*HWE:0.06*			
rs2228000 (XPC)			0.219		
CC	57(55.9)	67(67)		1[a]	
TC	38(37.3)	26(26)		1.20(0.34–4.19)	0.765
TT	7(6.9)	7(7)		0.63(0.06–5.94)	0.693
CC/TC + TT	45(44.1)	33(33)	0.070	0.62(0.35–1.11)	0.114
Alleles					
C	152(74.5)	160(80)	0.188	1[a]	
T	52(25.5)	40(20)		0.73(0.45–1.16)	0.194
	HWE:0.846	*HWE:0.06*			
rs2228001 (XPC)			0.424		
AA	28(27.5)	31(31)		1[a]	
CA	55(53.9)	45(45)		2.93(0.78–10.97)	0.110

Table 2 (continued)

Genotypes	Cases (n = 102)	Controls (n = 100)	X^2 p-value	OR (95% CI) Adjusted	p-value
CC	19(18.6)	24(24)		3.59(0.58–22.11)	0.167
AA/CA + CC	74(72.5)	69(69)	0.345	0.84(0.45–1.54)	0.643
Alleles					
A	111(54.4)	107(53.5)	0.854	1[a]	
C	93(45.6)	93(46.5)		1.03(0.70–1.53)	0.921
	HWE:0.380	*HWE:0.339*			
rs1799793 (XPD)			0.174		
GG	30(29.4)	42(42)		1[a]	
GA	54(52.9)	44(44)		2.10(0.50–8.83)	0.310
AA	18(17.6)	14(14)		2.53(0.27–23.11)	0.408
GG/GA + AA	72(70.6)	58(58)	0.043*	0.57(0.32–1.03)	0.078
Alleles					
G	114(55.8)	128(64)	0.096	1[a]	
A	90(44.2)	72(36)		0.71(0.47–1.06)	0.105
	HWE:0.456	*HWE:0.651*			
rs13181 (XPD)			0.768		
TT	35(36.4)	37(37)		1[a]	
GT	52(49.5)	46(46)		0.49(0.11–2.10)	0.339
GG	15(16.2)	17(17)		0.13(0.12–1.60)	0.114
TT/GT + GG	67(65.7)	63(63)	0.401	0.88(1.50–1.58)	0.769
Alleles					
T	122(59.8)	120(60)	0.967	1[a]	
G	82(40.2)	80(40)		0.99(0.66–1.47)	1.000
	HWE:0.542	*HWE:0.676*			
rs10483813 (RAD51B)			0.485		
TT	66(64.7)	71(71)		1[a]	
AT	30(29.4)	26(26)		2.19(0.66–7.23)	0.198
AA	6(5.9)	3(3)		8.81(0.56–136,78))	0.120
TT/AT + AA	36(35.3)	29(29)	0.210	0.74(0.41–1.35)	0.368
Alleles					
T	162(79.4)	168(84)	0.233	1[a]	
A	42(20.6)	32(16)		0.73(0.44–1.22)	0.249
	HWE:0.309	*HWE:0.743*			
rs1314913 (RAD51B)			0.463		
CC	67(69.7)	71(71)		1[a]	
CT	30(28.8)	27(27)		0.50(0.13–1.87)	0.306
TT	5(3.5)	2(2)		4.52(0.15–134,92)	0.383
CC/CT + TT	35(34.3)	29(29)	0.255	0.78(0.43–1.41)	0.452
Alleles					
C	164(80.4)	169(84.5)	0.278	1[a]	
T	40(19.4)	31(15.5)		0.75(0.44–1.26)	0.298
	HWE:0.498	*HWE:0.758*			

Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) adjusted for age, BMI, HT use, smoking, alcohol consumption, age of first birth, number of childbirth, age at menarche, family history of cancer. *HWE* Hardy-Weinberg equilibrium

*Indicates that p values less than 0.05

[a] Reference genotype/allele

Table 3 Histopathological parameters of the breast tumors of the cases

Characteristics	Cases (%) $N = 102$
ER status, n (%)	
Positive	102 (100)
Negative	0
PR status, n (%)	
Positive	83 (81.4)
Negative	19 (18.6)
Her2/Neu status, n (%)	
Positive	25 (24.5)
Negative	77 (75.5)
Tumor size, n (%)	
≤ 2 cm	36 (35.3)
2–5 cm	53 (52)
> 5 cm	9 (8.8)
Unknown	4 (3.9)
Clinical stage at diagnosis, n (%)	62 (60.8)
Grade 1–2	27 (26.5)
Grade 3–4	13 (12.7)
Missing data	
Lymph node metastasis, n (%)	53 (52)
Positive	46 (45.1)
Negative	3 (2.9)
Missing data	
Distant metastasis	
Positive	12 (11.7)
Negative	89 (87.3)
Missing data	1 (1)
Histological type	
Invasive ductal carcinoma	85 (83.3)
Invasive lobular carcinoma	7 (6.9)
Others/unknown	10 (9.8)

ER estrogen receptor, *PR* progesterone receptor, *HER2/neu* human epidermal growth factor receptor 2

Discussion

Polymorphisms in DNA repair genes may change protein function of these genes by triggering DNA damage and accumulation of mutations [7]. Decreased DNA repair capacity may lead to genomic instability and carcinogenesis [8].

BER pathway is responsible for DNA single strand breaks and oxidative DNA damage repair [9]. XRCC1 gene has a central role in BER pathway [8]. In some molecular epidemiologic studies relationship between breast cancer risk and XRCC1 gene rs1799782 (Arg194Trp), rs25487 (Arg399Gln), rs25489 (Arg280His) polymorphisms was previously investigated.

Whereas Al Mutairi et al., Przybylowska-Sygut et al. reported an association between BC and rs1799782 frequency; Smith et al. suggested a weak relation and Moullan et al. reported no associations [9–12].

In the previous studies, rs25487 had a ressesive effect on BC risk in Iranian women, and rs25487 variant alleles were correlated with an increased BC risk in Korean women [13, 14]. rs25487 was not associated with any of the phenotypic parameters and BC susceptibility in the studied Saudi population [9]. In Iowa Women and Greek Cypriot women, rs25487 was not associated with BC risk [15, 16].

In our study, we did not detect any relations in genotype and allele frequencies of rs1799782, rs25489 variants between the patient and the control group. rs25489 GG genotype frequency was found to be significantly higher in Her2Neu negative tumors compared to the positive ones ($p = 0.047$). Whereas rs25487 was on the border of significance in genotype distribution ($p = 0.085$); rs25487 AA genotype had a p value near to the border ($p = 0.058$) and A allele frequency was found to be significantly increased in the control group compared to the patients ($p = 0.039$).

In NER pathway, XPC protein complex has function in recognizing the damage and XPD protein complex has function in unwinding of DNA [7]. Some of the polymorphisms in XPD gene regions were found to be related to BC susceptibility [17]. Brewster et al. could not find a significant relation between rs13181 genotypes and BC risk [18].

Smolarz et al. reported a significant association between rs13181 GG genotype and triple negative BC risk. Whereas rs13181 genotype, allele distributions and histologic staging, lymph node metastasis were not found to be related, increase of G allele correlated with tumor size [19].

The role of rs13181 in BC development risk is still unclear. In our study, we couldn't detect any relation between rs13181 and BC risk. When we evaluated tumor histopathology, we observed rs13181 polymorphism to be more frequent in invasive ductal carcinoma. XPD gene rs1799793 and XPC gene rs2228000, rs2228001 genotype and allele distributions were not found to be related with histopathologic characteristics and BC risk.

In a comprehensive study evaluating 100 SNPs from DNA repair genes in 4470 cases and 4560 controls, rs861539 polymorphism of DSBR gene XRCC3 did not show any association with breast cancer risk; many other studies also did not report an association including a meta-analysis [20, 21]. In contrast, some studies and meta-analyses showed an association between this SNP and cancer risk, even some suggested it to be protective in cancer [22]. Whereas rs861539 showed an increased risk in breast cancer in some populations such as British, Taiwanese populations [23, 24], it failed to show association with breast cancer risk including Saudi, Polish, Belgian and Jordanian populations [22, 25–27].

In a study consisting 19 studies from 10 different countries made with 16,895 Caucasians; rs10483813 polymorphism of DSBR gene RAD51L1 showed association with mammographic density in breast cancer [28]. In another study conducted in 859 cases and 1083 controls from Radiologic

Technologists from USA, no association was found between radiation-related breast cancer risk and RAD51L1 rs10483813 as previosly had hypothesized [29].

In our study, we found rs861539 T allele to be significantly low in the patient group ($p = 0.049$). Genotype and allele frequencies of RAD51B gene polymorphisms didn't differ between the groups. rs1314913 polymorphism were found to be more frequent in PR+ BC patients and invasive ductal carcinoma (respectively; $p = 0.044$, $p = 0.042$). Rs861539 significantly correlated with Her2Neu negative BC patients ($p = 0.042$).

Personalized cancer treatment seems to be a very important and effective way for individual therapy, in order to perform this, genetic alterations and DNA repair capacity of a person are needed to be known. Genetic polymorphisms of cancer patients, including DNA repair gene polymorphisms may affect their response to the therapy [30]. Different studies conducted for different types of cancers such as Non-Small Cell Lung Carcinoma, Squamous Cell Carcinoma of the Head and Neck, Primary Small Cell Carcinoma of the Esophagus; polymorphisms in DNA repair genes ERCC1, XRCC1; XPD, XRCC1 and minimum three certain DNA repair genes are reported to help estimating the prognosis and deciding individual therapies according to the genomic changes [31–33]. Therefore as we did so, genotyping of certain DNA repair gene polymorphisms in cancers, might be a useful tool for evaluating cancer prognosis and treatment.

In conclusion, in the current study, we didn't find a significant difference between DNA repair genes genotype distributions and BC risk. In the literature XRCC1 rs25487 A allele and BC risk was reported to be related; but in contrast to this, we found AA genotype ve A allele frequencies to be higher in the control group. Again in contrast to the literature, XRCC3 gene rs861539 T allele was significantly low in our patient group ($p = 0.040$).

Although our study is a comprehensive one, it has limitations such as to have relatively small sample size and low control group age. Due to these reasons, our results should be verified by studies with larger case numbers and well matched control groups including many candidate genes and polymorphisms.

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Compliance with Ethical Standards Human Blood samples used in the study were obtained using protocols approved by the Acıbadem University Medical Research Assessment Committee. The written informed consent was taken from all the cases participated in the study.

Conflict of Interest The authors declare that they have no conflict of interest.

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