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THE SINGLE NUCLEOTIDE POLYMORPHISM ARG399GLN RS25487 IN *XRCC1* GENE IS A BREAST CANCER RISK FACTOR, BUT IS NOT RELATED TO *TP53* MUTATION STATUS

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Genetic changes in DNA repair genes, such as X-ray cross-complementing group1 *(XRCC1)*, can cause modifications in the capacity of damaged DNA repair and affect the risk of cancer. Several mutations in *TP53*, which is a tumor suppressor gene, have been associated with breast cancer. In this study, it is aimed to evaluate the association of genetic variation in *XRCC1*rs25487 single nucleotide polymorphism (SNP) with *TP53* mutation and breast cancer risk. In this research, 200 breast cancer women and 200 controls from the Iranian-Azeri population, Iran, were enrolled. Genomic DNA was extracted from the whole blood of controls patients. PCR-RFLP was carried out to genotype all participants for *XRCC1*rs25487SNP. Determination of possible mutations of *TP53* in exons 5,6,7, and 8 were performed on 30 cancerous breast tissues through sequencing the amplified fragments. Our results of the case-control study indicated that the GA genotype of *XRCC1* gene in rs25487polymorphism has a significantly risk effect on the breast cancer in the dominant genetic model (OR: 1.580, 95% CI: (1.025-2.436); *p*-value =0.049) and also GA genotype of *XRCC1* gene in rs25487polymorphism has a protective effect on breast cancer in overdominant genetic model (OR: 0.591, 95% CI (0.395-0.886), *p*-value = 0.014). Furthermore, genotypes of

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this SNP did not associate with the clinical specifications of the patients and *P53* mutation status. Sequencing results showed the mutational spectrum of *P53* in the studied cases. According to the results of this study, in some of the genetic models, *XRCC1*SNP appears to be a modulator of breast cancer risk in Iranian East-Azerbaijan women. However, there was no correlation between *XRCC1*SNP and *TP53* mutation status of the tumor.

Keywords: Breast cancer, mutation, polymorphism, *TP53*, *XRCC1*

INTRODUCTION

Breast carcinoma has been recognized as the major cause of tumor-related mortality and the most common tumor in women worldwide (JEMAL *et al*., 2008). Currently, the incidence of breast carcinoma is growing, which has more prevalence in developing regions of Africa, South-East Asia, and South America (AGARWAL *et al*., 2009). The etiopathology of breast carcinoma is multi-factorial and has not been obviously defined; however, it has been suggested that breast carcinoma is the result of the interactions between genetic, environmental, and lifestyle-correlated risk factors (GUERRERO *et al*., 2017). Some alterations in *BRCA1*, *BRCA2*, *TP53*, and DNA repair-correlated genes have been recognized to be associated with the risk of breast carcinoma (LONG *et al*., 2012). Additionally, genome-wide association studies (GWAS) emphasis on the direct genetic correlation of SNPs with breast carcinoma development (CAVALLARO *et al*., 2012). However, almost all breast carcinoma-associated SNPs have failed to certainly explain the function of genetic factor in breast carcinoma development (EICHLER *et al*., 2010). As a result, investigations about novel potential SNPs, relating to breast carcinoma risk, probably seem to be a valuable approach to explain the genetic functionality in breast cancer progression. *XRCC1* is involved in DNA repairing processes, which has been revealed to carry genetic polymorphisms that may result in alterations in the DNA repairing capability and, therefore, impress susceptibility to some pathology alterations *(GULBAY et al., 2017; PATRONO et al*., 2014). *XRCC1* has a vital role in the base excision repair procedure. This gene has been proved to harbor two common SNPs in codons 194 (Arg194Trp, rs.1799782) and 399(Arg399Gln, rs25487), which influence the amino acid sequence. Codon 399 change occurs in the C-terminal area of breast cancer susceptibility protein 1 (BRCT1). It has been indicated that non-conservative amino acid substitutions in this domain, which binds to poly (ADP-ribose) polymerase (PARP), show weakened DNA repair capacity in an in vivo status (SHEN *et al*., 1998). P53 is known as a tumor suppressor factor, which is produced by *TP53* gene and plays a vital role in protecting genome stability through preventing alterations, controlling cellular proliferation and apoptosis (MOLCHADSKY *et al*., 2017). *TP53* gene has been associated with breast carcinoma risk; moreover, it is recognized as a common mutated gene in several human tumors (DE MOURA GALLO *et al*., 2005). Herein, it was attempted to assess the possible association between the *XRCC1* gene rs25487 SNP and mutations in *TP53* gene in exons 5, 6, 7, and 8 with the risk of breast cancer in Iranian-Azeri women. Furthermore, the relationship between the genetic background of breast carcinoma patients with regard to *XRCC1* genotypes and the clinical manifestations like tumor stage and size, lymph-node metastases, and the pathological stage of the breast cancer was assessed.

MATERIALS AND METHODS

Study subjects

In this case-control study, 200 women with breast cancer and 200 healthy women were recruited. Patients had been histologically confirmed for breast carcinoma and referred to Noor-Nejat Hospital, Tabriz, Iran, for mastectomy. In the current study, in order to increase the validation of results and to decrease the possible biases, standard confirmed safeguards were used. All breast cancer and healthy women of the studied population were chosen from cases native of the same geographic region (East-Azerbaijan). Patients had no history of other cancers and radiotherapy. Based on clinicopathological features, 188 patients represent invasive ductal carcinoma (IDC), 8 patients with ductal carcinoma in situ (DCIS), and 4 had invasive lobular carcinoma (ILC). The healthy control group encompassed women with no history of any cancer either in themselves and their family members. In addition, healthy individuals with a history of radiotherapy were excluded from the studied population. Patients and healthy controls were matched for age and race to get real results. We considered 129 DNA samples for statistical analysis, which, 30 of them sequenced in current study, and 99 were sequenced in our previous investigations (KHANI *et al.*, 2012; POULADI *et al.*, 2016). The Ethical Committee of Tabriz University of Medical Sciences approved the study protocol, and written informed consent was obtained from all subjects. About 5 ml of venous blood was taken from each patient and control through EDTA-anticoagulated venoject tubes. We collected 129 tumorous breast tissues for DNA sequencing. Genomic DNA was extracted from peripheral blood and tissues using the salting-out method (WANG *et al.*, 2014) and analyzed for both quality and quantity using the NanoDrop spectrophotometer at 260/280 nm (NanoDrop ND-2000C Spectrophotometer, Thermo Fisher Scientific, USA).

XRCC1 gene rs25487 SNP genotyping

The allele and genotype frequencies of *XRCC1* gene rs25487 SNP were evaluated by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. The primers were designed using Primer3Plus (http://www.bioinformatics.nl/cgi-bin/primer3plus/primer3plus.cgi) and were blasted in NCBI website: http://www.ncbi.nlm.nih.gov/tools/primer-blast/. The primers for the amplification of 615 bp target fragment were the forward primer of 5'- TTGTGCTTTCTCTGTGTCCA-3' and the reverse one of 5'-CCTCCAGCCTTTTCTGATA-3'.

PCR-RFLP on *XRCC1* rs25487 SNP was carried out with 1 µl (50-100 ng) of the genomic DNA in 25 µl reaction volume with 2.5µl Buffer PCR, 1 µl of 10 pmol/ml forward primer, 1 µl of 10 pmol/ml reverse primer, 0.5 µl of dNTPs, 0.15 µl of Taq DNA polymerase, 1 µl of $Mgcl_2$, and 17.85 µl of deionized water. PCR was done under the following situations: initial denaturation at 94°C for 5 min followed by 35 cycles of denaturation at 94°C for 30 s, annealing at 63°C for 30 s and extension at 72°C for 30 s. A final extension at 72°C for 10 min was done. The 615-bp PCR product was digested with 0.2 µl of BsisI restriction enzyme (Fermentas Inc., Burlington, ON, Canada) at 37°C overnight and was evaluated on a 2% agarose gel (Figure 1). The sizes of specifically digested fragments were considered as follows: 615 bp product digested to 239 and 376 bp, if the product was digested, the allele was identified as G; if not, it was identified as A (Figure 1).

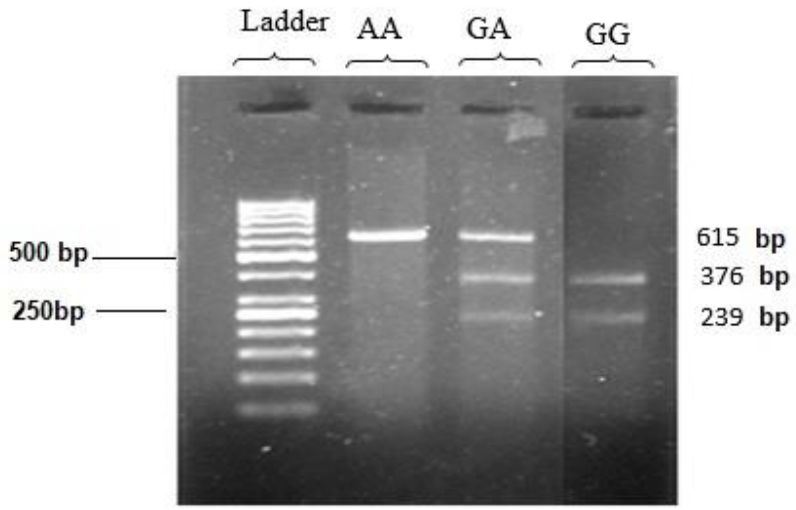

Figure 1. Gel electrophoresis pattern of *XRCC1* rs25487 SNP. The amplified fragments of *XRCC1* rs25487 SNP were digested with BsisI; the PCR product was 615 bp. If the product was digested, creating two fragments of 376 and 293 bp, the allele was identified as G; if there were no digestion, it would be identified as A.

Table 1. Primers used for detection of mutations in exons 5, 6, 7, and 8 on TP53 gene

Primer	Sequence	Amplicon size (bp)
P5AF (Forward)	5´-TTATCTGTTCACTTGTGGCCC-3´*	472
P6R (Reverse)	5´-TTAACCCCTCCTCCCAGAGA-3´	
Int6F (Forward)	5´-GCCTCCCCTGCTTGCTTGCC-3´*	682
P8R (Reverse)	5´-TCCACCGCTTCTTGTCCTGC-3´	

*Oligonucleotide primers used for sequence analysis

Detection of TP53 gene mutation

The screening of *TP53* gene in exons 5, 6, 7, and 8 (listed in Table 4) was done through PCR amplification and sequencing in 30 breast cancer patients. We have previously performed the screening of 99 breast cancer patients in terms of *TP53* mutations through PCR and sequencing methods (KHANI *et al*., 2012; POULADI *et al*., 2016). The mixture tube content was amplified in a final volume of 25µl containing 1 µl of DNA, 2.5 µl of PCR buffer, 0.75 µl $Mgcl_2$, 0.75 µl of forward and reverse primers, 0.5 µl of dNTPs, and 0.2 µl of Taq DNA polymerase. Briefly, the amplification conditions were: initial denaturation at 94°C for 2 min, primer annealing at 60°C for 40 s, and then an extension of 35 cycles at 72°C for 45 seconds. Final

extension was done at 72°C for 5 min. For quality assessment, PCR products were electrophoresed prior to sequencing analysis on 2% agarose gel. Afterward, the amplified DNA samples were sequenced (Macrogen, Seoul, Korea) for identifying the possible mutations. Analysis of the sequenced amplicons was carried out using Chromas software (Figure 2).

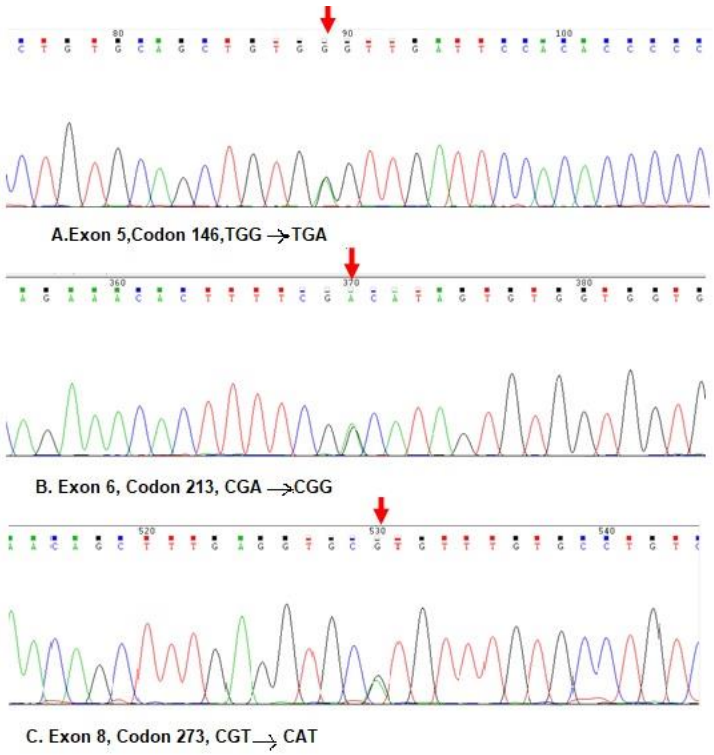

Figure 2. The sequencing diagram of the identified mutations in *TP53*. The diagrams A, B, and C show a mutation in exon 5, 6, and 8, respectively. The red arrows indicate the detected mutations.

Statistical analysis

Statistical evaluation was performed using the SPSS (version 22.0, IBM SPSS Inc., USA). Allele and genotype distribution of *XRCC1* rs25487 SNP between patient and control groups were calculated by the Chi-Square test. Pearson's $\chi 2$-tests were applied in order to determine the association between genotype/allele frequencies and risk of breast carcinoma and also to identify the correlation between *TP53* mutations and *XRCC1* genotypes. The odds ratio (OR) and 95% confidence interval (95% CI) were calculated. A *p*-value of less than 0.05 was regarded as the significant level of the tests. The genotype distributions were examined in terms of deviation from Hardy-Weinberg equilibrium in controls, using an online program, HWE calculator, accessible at http://www.oege.org/software/hwe-mr-calc.shtml.

RESULTS

Multiple logistic regression models (codominant, dominant, recessive, overdominant) were used to estimate odds ratios (ORs), 95% confidence intervals (CIs), and p-values. In the dominant model, a single copy of allele was enough to modify the risk with heterozygous and homozygous genotypes having the same risk. In the recessive model, two copies of allele were necessary to change the risk. In the overdominant model, heterozygotes were compared to both allele homozygotes. The logistic regression analysis in this study, demonstrated a significant association of the GA genotype of *XRCC1* gene in rs25487polymorphism with patients according to the dominant genetic model (OR: 1.580, 95% CI: (1.025-2.436); *p*-value =0.049), but the GA genotype in the overdominant model proposed to has a protective effect (OR: 0.591, 95% CI: (0.395-0.886) *p*-value =0.014. The other genotypes do not induce any protective or risk effects.

Table 2. Genotype and allele frequencies of XRCC1 rs25487 SNP

dbSNP	Genetic models	Genotypes/Allele	Case (n=200)	Control (n=200)	OR (95%CI)	*P* value
XRCC1 rs25487	Codominant	GG	69 (34.5%)	50 (25%)	Reference	
		GA	108 (54%)	133 (66.5%)	1.699 (1.090-2.649)	0.025
		AA	23 (11.5%)	17 (8.5%)	1.020 (0.494-2.106)	1
	Dominant	AA+GA	131 (65.5%)	150 (75%)	1.580 (1.025-2.436)	0.049
	Recessive	AA	23 (11.5%)	17 (8.5%)	1.399 (0.723-2.707)	0.405
		GG+GA	177 (88.5%)	183 (91.5%)	Reference	
	Overdominant	GA	108 (54%)	133 (66.5%)	0.591 (0.395-0.886)	0.014
		GG+AA	92 (46%)	67 (33.5%)	Reference	
		G	246 (61.5%)	233 (58.25%)	reference	
		A	154 (38.5%)	167 (41.75%)	1.145 (0.863-1.519)	0.387

This study demonstrated that *XRCC1* gene rs25487 SNP was associated with increased breast cancer risk according to the dominant genetic models (dominant model OR: 1.580, 95% CI: (1.025-2.436); *p*-value =0.049) and the G,A allele frequency of *XRCC1* rs25487 SNP was not significant for susceptibility for breast cancer (OR: 1.145; 95% CI (0.863-1.519) *p*-value=0.387. Our results demonstrated that the GA genotype on the dominant model was represented as the most frequent genotype, which was seen in 65.5% of the patients and 75% of the controls (*p*-value =0.049, OR=1.580, 95% CI: (1.025-2.436). The G and A alleles of *XRCC1* rs25487 SNP were seen in 61.5% and 38.5% of the breast carcinoma patients, respectively, which were almost equal to frequencies observed in the control group (58.25 and 41.75,

respectively). Therefore, no significantly different allelic distribution was identified between the patient and control groups (*p*-value =0.387). In addition, there was no significant difference for distribution of AA between the patient and control groups (11.5% *vs.* 8.5%, respectively; *p*-value=0.405, OR=1.39, 95% CI: 0.723-2.707, Table 2).

Evaluation of relations between the genotypes of *XRCC1* rs25487 SNP and clinical manifestations of breast carcinoma cases, including tumor stage and size, lymph-node metastases, and the pathology, concluded in no statistically significant differences among patients (Table 3). Investigation of *TP53* mutations in 30 breast carcinoma patients demonstrated that there were 4 mutations, which all were transition alterations (Figure 2). Of these substitutions, 2 cases occurred in exon 8, including CGT→ CAT at codon 273 with Arg→His Amino acid substitution. Each of exon 5 (TGG→ TGA at codon 146, with Trp→Stop, amino acid substitution) and 6 (CGA→ CGG at codon 213 with Arg→Arg), where identified as a conservative replacement. Table 4 shows the mutations in breast cancer patients with more details. With regard to pathological classification, all the patients with mutations in *TP53* were detected to be IDC, and histopathological stage III were detected. We have previously evaluated 99 breast carcinoma samples in terms of *TP53* mutational status. Out of them, 18 have been exhibited with *TP53* mutations (Table 4), and 81 had no mutations in *TP53* (KHANI *et al*., 2012; POULADI *et al*., 2016) Mixed analysis of *XRCC1* rs25487 SNP and *TP53* mutational status in 129 breast carcinoma patients resulted in no significant differences (*P* =0.234, Table 5).

Table 3. Relationship between XRCC1 rs25487 genotypes and clinical properties of breast cancer patients.

Clinical Properties	*XRCC1* Genotypes				
	GG	GA	AA	*P* value	OR (95% CI)
Tumor stage					
Stage 0	3 (33.3%)	6 (66.7%)	0 (0%)	0.426	0.415 (0.331-0.5)
Early (I&II)	35 (40.2%)	40 (46%)	12 (13.8%)		
Late (III&)	30 (31.2%)	55 (57.3%)	11 (11.5%)		
Tumor size (cm)					
<2cm	21 (46.7%)	18 (40 %)	6 (13. 3)	0.072	0.085 (0.037-0.132)
≤2cm≤5cm	35 (38.5%)	45 (49.5%)	11 (12.1)		
>5cm	12 (21.8%)	37 (67.3%)	6 (10.9%)		
Lymph-node					
Positive	45 (34.4%)	70 (53.4%)	16 (12.2%)	0.92	0.962 (0.928-0.995)
Negative	24 (35.8%)	36 (53.7%)	7 (10.4%)		
Pathology					
DCIS	5 (62.5%)	3 (37.5%)	0 (0%)	0.24	0.215 (0.145-0.286)
IDC	64 (34%)	102 (54.3%)	22 (11.7%)		
ILC	0 (0%)	3 (75%)	1 (25 %)		

Table 4. Identified mutations in TP53 gene in breast cancer patients

Sample	codon	age	stage	Histopathological type	Exon/ Intron	Nucleotide change	Amino acid change	Transition/ Transvertion	XRCC1	Ref
99	160	53	III	IDC	Ex5	ATG→ AAG	Met→Lys	Tv		19
100	163	40	II	IDC	Ex5	TAC→ TGC	Tyr→Cys	Ts	GA	19
344	146	42	III	IDC	Ex5	TGG→TGA	Trp→Stop	Ts	GG	present study
40	193	35	III	IDC	Ex6	CAT→ AAT	His→Asn	Tv	GG	19
76	195	61	II	IDC	Ex6	ATC→ TTC	Ile→Phe	Tv	AA	19
125	195	39	I	IDC	Ex6	ATC→ ACC	Ile→Tyr	Ts	GA	19
42	198	45	II	IDC	Ex6	GAA→ TAA	Glu→Stop	Tv	AA	19
120	213	30	II	IDC	Ex6	CGA→ CTA	Arg→Leu	Tv	GA	19
110	214	49	III	IDC	Ex6	CAT→ CGT	His→Arg	Ts	GA	19
39	214	64	III	IDC	Ex6	CAT→ CGT	His→Arg	Ts	GA	19
70	220	49	I	IDC	Ex6	TAT→TGT	Tyr→Cys	Ts	GG	19
109	220	35	III	IDC	Ex6	TAT→TGT	Tyr→Cys	Ts	GA	19
449	213	40	III	IDC	Ex6	CGA→ CGG	Arg→Arg	Ts	GA	present study
142	248	37	III	IDC	Ex7	CGG→ CAG	Arg→Gln	Ts	GA	20
58	248	55	II	IDC	Ex7	CGG→ CAG	Arg→Gln	Ts	GA	20
173	257	51	III	IDC	Ex7	CTG→ CCG	Leu→Pro	Ts	GA	20
170	Intronic	46	III	IDC	Int7	G → T	-	Tv	GA	20
166	272	34	III	IDC	Ex8	GTG→ ATG	Val→Met	Ts	GA	20
128	262	46	II	ILC	Ex8	(GGT) 3 bp Deletion	Gly→ -	Deletion	GA	20
111	278	49	I	IDC	Ex8	CCT-TCT	Pro→Ser	Ts	GA	20
338	273	36	III	IDC	Ex8	CGT→ CAT	Arg→His	Ts	GG	present study
405	273	37	III	IDC	Ex8	CGT→ CAT	Arg→His	Ts	GA	present study

DISCUSSION

In human cancer, *TP53* is among the five most frequently mutated genes. The frequency of *TP53* mutations is highly variable between different cancer types. The *TP53* alteration data can be accessed from the IARC *TP53* Database (BOUAOUN *et al*., 2016). The effects of TP53 mutations were statistically significant in nine cancers (lung adenocarcinoma, hepatocellular carcinoma, head and neck squamous cell carcinoma, acute myeloid leukemia, clear cell renal cell carcinoma (RCC), papillary RCC, chromophobe RCC, uterine endometrial carcinoma, and thymoma) for survival time and in five cancers (pancreatic adenocarcinoma, hepatocellular carcinoma, chromophobe RCC, acute myeloid leukemia, and thymoma) for disease-free survival time (LI *et al*., 2019).

Alterations, such as mutations in the *TP53* tumor suppressor gene and in genes involved in the control of damaged DNA repairing system, have been related to the initiation and development of diseases. It appears that molecular changes in the *TP53* gene are the most common genetic variations in numerous human cancers (LI *et al*., 2019; POPOVIĆ *et al*., 2010) and these changes are estimated to occur in approximately 20-40% of breast carcinoma cases (OLIVIER *et al*., 2010; WALERYCH *et al*., 2012).

Genetic variations in *TP53* gene like PIN3 Ins16bp and Arg72Pro (FRANCISCO *et al*., 2011) as well as the *XRCC1* gene polymorphisms such as Arg194Trp and Arg399Gln are the frequently studied variants in breast malignancy (HUANG *et al*., 2009; SAADAT, 2010). However, these studies have been based on the case-control analysis in different populations with different methodologies. Hence the results do not clearly indicate the actual association of the polymorphic variants. Also, the extraordinary variety of *P53* mutational patterns among cohorts has been revealed in numerous geographical and ethnically different cancerous populations (ARCAND *et al*., 2015; SOUSSI, 2011).

We had previously conducted the analysis of *TP53* gene variations in exons 5-8 using East Azerbaijan breast cancer samples. There were 18 gene variations in the mentioned area, which comprised of 17 single nucleotide alterations and 1 deletion (POULADI *et al*., 2016).

Exon 6 was revealed as the mutation hotspot of *TP53* (9 out of 18 mutations). Most of the detected mutations were missense, located on DNA-binding domain of p53 protein. In the current investigation, we identified that there were *TP53* gene mutations in 4 cases of breast cancer patients, and all were transitions. Among the observed mutations, 2 cases occurred in exon 8 (CGT→ CAT at codon 273), one patient had a mutation in exon 5 (TGG→ TGA at codon 146), and one case demonstrated one mutation in exon 6 (CGA→ CGG at codon 213). In sum of our previous and present studies, 22 mutations were seen in *TP53* of breast cancer cases, which are shown in table 4. Compared to the information showed in the IARC (SAADAT, 2010), our *TP53* alteration data show several differences, such as the observed higher frequency of mutations in exon 6, the distinct pattern of the *TP53* alterations and the dissimilarities in hotspot frequency distribution, which may reveal geographical and ethnical disparity in our investigation. Mounting evidence has indicated that XRCC1 plays a crucial role during the efficient base excision repair process and, therefore, some genetic variations may change the circumstances of its biological activity, leading to cancer development (SEEDHOUSE *et al*., 2002) A meta-analysis performed on 37 studies demonstrated that *XRCC1* gene rs25487 SNP was associated with increased breast cancer risk (HUANG *et al*., 2009). Another meta-analysis

conducted on 10 studies assessed *XRCC1* gene Arg194Trp and rs25487 polymorphisms and showed that it is difficult to reach unique conclusion about this association (SAADAT, 2010). Considering these, no certain indication has been taken from such studies. Correlation of SNPs in the genes *XRCC1*, *XRCC3*, *XPD*, and *RAD51* with tumor manifestations in a group of Brazilian women with breast cancer was evaluated by Dufflot *et al.* (2008). The authors did not find polymorphisms to be associated with high tumor grade or estrogen receptor negativity in the studied population. Also, a meta-analysis of 10 case-control investigations studying a sum of 4732 breast carcinoma patients and 5677 healthy controls, demonstrated that *XRCC1* rs25487 alteration might not be a risk factor for breast carcinoma susceptibility in China (CHEN *et al*., 2017). However, BEWICK *et al.* (2006) indicated that *XRCC1* gene rs25487 SNP may be used as a prognostic value for the estimation of the outcome of patients with metastatic breast carcinoma who had a history of DNA damaging chemotherapy. Additionally, in a study of Portuguese breast cancer patients, the possible impression of polymorphisms in DNA repair-related genes on breast cancer clinic-pathological characteristics was investigated. The study established a plausible correlation between the Gln/Gln genotype status of *XRCC1* Arg399Gln SNP and less aggressive tumor (COSTA *et al*., 2008).

As we studied, there are a few reports about the correlation between *XRCC1* or other DNA repair genes polymorphisms and *P53* mutations. In one of these studies in Taiwanese oral squamous cell cancer (OSCC) patients, the codon 399 Gln/Gln status showed a significantly more frequency of *P53* gene mutation compared to those with an Arg/Gln and or Arg/Arg (OR (95%CI) 4.50 (1.52-13.36) (HSIEH *et al*., 2003). A study on lung tumors from USA was performed for *P53* mutations and genotypes of *XPD* as well as *XRCC1* (DNA repair genes). In the mentioned study, *P53* mutations are correlated with neither *XPD* Lys751Gln nor *XRCC1* Arg399Gln alterations. Also, their findings suggest that persons who have the *XPD* codon 312 Asp/Asp status may be at a higher risk of *P53* alterations, particularly if combined with other SNPs that may lead to unsuccessful DNA repair (MECHANIC *et al*., 2005). In the ongoing investigation, we detected that neither alleles nor genotypes of *XRCC1* rs25487 polymorphism were associated with breast carcinoma risk. Clinical characteristics of breast carcinoma patients did not associate with the genotypes of this position. Regardless of statistically insignificant results, GG genotype had less frequency in DCIS patients rather than GA status. But, GA showed more frequency in IDC cases compared to GG genotype. This may be a possible determinant of breast pathological status. Also, we did not find any significant differences in mixed analysis of *XRCC1* rs25487 SNP in relation to *TP53* mutational status in breast carcinoma patients. However, further data should be assessed to confirm this finding, and it can increase the information about the association between *P53* mutations and *XRCC1* codon 399 genotypes in breast cancer patients.

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POLIMORFIZAM POJEDINAČNIH NUKLEOTIDA *ARG399GLN RS25487* U *KSRCC1* GENU JE FAKTOR RIZIKA RAKA DOJKE, ALI NIJE U VEZI SA STATUSOM MUTACIJE TP53

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Izvod

Genetske promene u genima za obnavljanje DNK, kao što je rentgenska unakrsna komplementarna grupa1 (XRCC1), mogu prouzrokovati promene u kapacitetu za popravku oštećene DNK i uticati na povećanje rizika od raka. Nekoliko mutacija kod *TP53*, gena za supresiju tumora, povezano je sa rakom dojke. U ovom radu cilj je da se proceni povezanost genetskih varijacija u *XRCC1rs25487* polimorfizmu pojedinačnih nukleotida (SNP) sa *TP53* mutacijom i rizikom od raka dojke. U ovo istraživanje uključeno je 200 žena sa rakom dojke i 200 kontrolnih pacijentkinjaiz iransko-azerbejdžanske populacije Irana. Genomska DNK je ekstrahovana iz krvi kontrolnih pacijenata. PCR-RFLP je primenjen za SNP genotipizaciju svih učesnika za *XRCC1rs25487*. Određivanje mogućih mutacija *TP53* u eksonima 5,6,7 i 8 izvršeno je na 30 kanceroznih tkiva dojke sekvenciranjem amplifikovanih fragmenata. Naši rezultati studije kontrolisanog "slučaja" pokazali su da GA genotip gena *XRCC1* u polimorfizmu rs25487 ima značajan uticaj na rak dojke u dominantnom genetskom modelu (OR: 1.580, 95% CI: (1.025-2.436); p-vrednost = 0,049), a takođe i GA genotip gena *XRCC1* u polimorfizmu rs25487 ima zaštitni efekat od raka dojke u superdominantnom genetskom modelu (OR: 0,591, 95% CI (0,395-0,886), p-vrednost = 0,014). Dalje, genotipovi ovog SNP-a nisu povezani sa kliničkim specifikacijama pacijenata i statusom mutacije P53. Rezultati sekvenciranja pokazali su mutacijski spektar *P53* u ispitivanim slučajevima. Prema rezultatima ove studije, u nekim od genetskih modela, čini se da *XRCC1* SNP predstavlja modulator rizika od raka dojke kod iranskih istočno-azerbejdžanskih žena. Međutim, nije bilo korelacije između *XRCC1* SNP i statusa mutacije *TP53* tumora.

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