RESEARCH ARTICLE

Association of XRCC1 Gene Polymorphisms with Breast Cancer Susceptibility in Saudi Patients

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Abstract

Background: X-ray repair cross-complementing group 1 (XRCC1) plays a key role in the base excision repair pathway, as a scaffold protein that brings together proteins of the DNA repair complex. XRCC1 is reported to be a candidate influence on cancer risk. The aim of our present study was to assess the association of rs1799782 (Arg194Trp) and rs25487 (Arg399Gln) XRCC1 gene polymorphisms with breast cancer in the Saudi population. Materials and Methods: The two SNP's were analyzed in breast cancer patients and healthy control subjects. Genotypes were determined by TaqMan SNP genotype analysis technique and data were analyzed using Chi-square or t test and logistic regression analysis by SPSS16.0 software. Results and Conclusions: Results showed that rs1799782 significantly increased susceptibility to breast cancer with Arg/Trp, Arg/Trp+Trp/Trp genotypes and at Trp allele overall study. It also increased risk of breast cancer in older age patients (above 48) and with the ER positive category. XRCC1rs25487 (Arg399Gln) did not showed any significant association. In conclusion the XRCC1rs1799782 polymorphism may be involved in the etiology of breast cancer in the Saudi population. Confirmation of our findings in larger populations of different ethnicities is warranted.

Keywords: XRCC1 - Saudi population - breast cancer - genetic polymorphism

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Introduction

In most of the cell's DNA is damaged by endogenous and exogenous mutagenic agents. Un-repaired damage can result in apoptosis or may lead to unregulated cell growth and cancer. Among DNA repair mechanisms, the base excision repair (BER) pathway is responsible for repair of single strand breaks and oxidative DNA damage. The X-ray repair cross-complementation group 1 (XRCC1) protein plays a key role in base excision repair (Hung et al., 2005).

XRCC1 interacts with polynucleotide kinase enzyme, DNA pol-β, PARP1 and DNA ligase IIIα (Pramanik et al., 2011). Numerous mutations in XRCC1 have been reported to interrupt the protein function by altering binding sites or catalytic domain of the protein (Caldecott, 2003). The 194Trp codon of XRCC1 is located in a highly conserved hydrophobic linker region between its DNA polymerase β domain and poly (ADP-ribose) polymerase-interacting domains, so the change from arginine to tryptophan could alter theinteraction of XRCC1 with either or both of these DNA repair proteins within the base excision repair complex (Przybylowska-Sygut et al., (2013). The Arg399Gln polymorphism alters Arginine to Glutamine substitution at codon 399 of exon 10 (C>T, rs25487) and is located in the conserved residue of the poly (ADP-ribose) polymerase-binding domain of XRCC1 (Pramanik et al., 2011). The association between the XRCC1 and various types of cancers such as lung cancer (Ratnasinghe et al., 2001), breast cancer (Moullan et al., 2003) and head and neck cancer (Sturgis et al., 1999) has previously been studied.

Previous reports on the association between genetic polymorphisms and risk of different cancer types have provided inconsistent results (Hu et al., 2001; Hung et al., 2005). Data from studies on the association of the XRCC1 polymorphisms with breast cancer risk are also inconsistent (Duell et al., 2001, Kim et al., 2002, Moullan et al., 2003, Figueiredo et al., 2004, Forsti et al., 2004, Chacko et al., 2005). Therefore the association between genetic polymorphism of XRCC1 at codon 194, codon 399 and susceptibility to breast cancer is still an open question (Saadat et al., 2008). The present case-control based study was performed to investigate the effect of two non-synonymous SNPs, rs1799782 (Arg194Trp) and rs25487 (Arg399Gln) polymorphisms in XRCC1 with regard to the risk of developing breast cancer in the Saudi population.

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Materials and Methods

Study population

A total of 200 blood samples were obtained from King Fahad Medical City. These encompassed 100 patients with breast cancer disease and 100 healthy controls. All controls were age-matched and recruited from physical examinations after diagnostic exclusion of cancer and cancer- related diseases. Blood samples of the experimental and control groups were obtained before treatment. Histopathology and medical records were reviewed to confirm diagnosis. Controls were frequency matched to cases on age/race and recruited from the clinic population receiving routine mammography at the breast screening and diagnostic center. Eligibility criteria for controls included normal mammography results and no prior cancer history. Written informed consent was obtained from all participants, and approval was received from the King Fahad Medical City Hospital ethics review committee. Every study participant completed a self-administered baseline questionnaire, which included information on demographics, reproductive history, medical conditions and family history of cancer.

DNA extraction

Approximately 3 ml of blood samples were collected in sterile tubes containing ethylenediaminetetracetic acid (EDTA) from all subjects enrolled in the study. Genomic DNA was isolated from blood samples using QIAmp kit (QIAmp DNA blood Mini Kit, Qiagen, Valencia, CA) following the manufacturer's instructions. After extraction and purification, the DNA was quantitated on a NanoDrop 8000, to determine the concentration and its purity was examined using standard A260/A280 and A260/A230 ratios (NanoDrop 8000) (Sambrook et al., 1989).

Genotyping

Two SNPs (Arg194Trp) and Arg399Gln) in XRCC1 gene were genotyped using TaqMan allelic discrimination assay (Livak, 1999). For each sample, 20 ng DNA per reaction was used with 5.6 μL of 2X Universal Master Mix and 200 nM primers (Applied Biosystems, Foster City, CA, USA). All genotypes were determined by endpoint reading on an ABI 7500 (Applied Biosystems, Foster City, CA, USA). Primers and probe mix were purchased directly through the assays-on-demand service of Applied Biosystems. Five percent of the samples were randomly selected and subjected to repeat analysis as a quality control measure for verification of the genotyping procedures.

Statistical analysis

Genotype and allelic frequencies were computed and were checked for deviation from Hardy—Weinberg equilibrium (http://ihg2.helmholtz-muenchen.de/cgi-bin/hw/hwa1.pl). Case-control and other genetic comparisons were performed using the chi-square test and allelic odds ratios (OR), and 95% confidence intervals (CI) were calculated by Fisher's exact test (two-tailed). Statistic analysis was done using SPSS 16.0 for Windows. We considered p-value of <0.05 as significant.

Results

A total of 100 BR cases and 100 healthy controls were included in this case-control based study. Clinical characteristics of breast cancer cases and healthy controls are given in Table 1. Genotypic distributions of SNP rs1799782 were consistent with that expected in the Hardy–Weinberg model (Table 2). The frequencies of Arg194Trp (rs1799782) genotypes in breast cancer cases were 84 (0.84), 16 (0.16), and 0 respectively, whereas as in healthy controls the frequencies were 96 (0.96), 4 (0.04), and 0 respectively. In SNP Arg194Trp (rs1799782) heterozygous allele (Arg/Trp) and Arg/Trp+Trp/Trp showed significantly higher risk in breast cancer patients when compared with controls (Table 3) (OR=4.571, χ^2=8, p=0.0046 and OR: 4.571, χ^2=8, p=0.0046). The Trp allelic frequency of rs1799782 was higher in the breast cancer patients (0.08) than that in the control group (0.02) (OR=4.261, χ^2=7.58, p=0.00591).

The frequencies of Arg399Gln (rs25487) genotypes in breast cancer cases were 58 (0.58), 32 (0.32), and 10 (0.1) respectively, whereas as in healthy controls the frequencies were 58 (0.58), 34 (0.34), and 8 (0.08) respectively. Frequencies of heterozygous and homozygous carrier in controls didn't deferred significantly when compared with in patients samples (Table 3).

Association of age and ER status with breast cancer risk

In Saudi Arabian patients, the median age of onset of breast cancer is 48 years, substantially lower than 62 years observed in the United States (Alanazi et al., 2013). To evaluate the association of the analyzed SNPs with the young age at diagnosis of breast cancer, we stratified the patients as ≤48 (n=47) or >48 (n=53) years of age and compared with age matched sample of controls. The genotype distributions for the individual SNP along with the statistical analysis are shown in tables 4 and 5.

In older age sample comparison (>48 years), interestingly in above 48 year age breast cancer sample XRCC1 rs1799782 which showed significant risk in overall comparison (Table 3) was associated with significant risk in older age patients (Table 5). XRCC1

Table 1. Clinical Characteristics of Study Subjects.

Variable	Character	No of Samples
Age (Years)	Median age	48
Estrogen receptor	ER+/ER-	55/45
Progesterone receptor	PR+/PR-	56/44
HER Status	HER+/HER-	40/57

Table 2. Distribution of Genotypes and Allele Frequencies on DNA Repair Gene Loci Among Saudi Breast Cancer Patients and Controls

Gene Genotype	Cases	HWE P-value	Controls	HWE P-value
XRCC1	84	0.384538	96	0.83829
rs1799782	16		4	
	0		0	
XRCC1	58	0.092183	58	0.350648
rs25487	32		34	
	10		8	

Table 3. Genotype Frequencies of XRCC1 Gene Polymorphism in Breast Cancer Cases and Controls

Genotype	Cases	Controls	OR	95% CI	X^2	p- value
XRCC1 rs1799782						
Arg/Arg	84 (0.84)	96 (0.96)	Ref			
Arg/Trp	16 (0.16)	4 (0.04)	4.571	1.471-14.210	8.00	**0.00468**
Trp/ Trp	0 (0.00)	0 (0.00)	1.142	0.022-58.182	Nan	1.00000
Arg/Trp+Trp/Trp						
	16 (0.16)	4 (0.04)	4.571	1.471-14.210	8.00	**0.00468**
Arg	184 (0.92)	196 (0.98)	Ref			
Trp	16 (0.08)	4 (0.02)	4.261	1.399-12.980	7.58	**0.00591**
XRCC1 rs25487						
Arg/Arg	58 (0.58)	58 (0.58)	Ref			
Arg/Gln	32 (0.32)	34 (0.34)	0.941	0.514-1.723	0.04	0.84418
Gln/ Gln	10 (0.10)	8 (0.08)	1.25	0.461-3.392	0.19	0.66091
Arg/Gln+ Gln/ Gln						
	42 (0.42)	42 (0.42)	1	0.570-1.753	0.00	1.00000
Arg	148 (0.74)	150 (0.75)	Ref			
Gln	52 (0.26)	50 (0.25)	1.054	0.672-1.653	0.05	0.81853

Table 4. Genotype Frequencies of XRCC1 Gene Polymorphism in Below 48 Age Breast Cancer Cases and Controls

Genotype	Cases	Controls	OR	95% CI	X^2	p- value
XRCC1 rs1799782						
Arg/Arg	40 (0.851)	55 (0.948)	Ref			
Arg/Trp	7 (0.148)	3 (0.051)	3.208	0.781-13.174	2.85	0.09153
Trp/ Trp	0 (0.000)	0 (0.000)	1.370	0.027-70.519	Nan	1.00000
Arg/Trp+ Trp/ Trp						
	7 (0.148)	3(0.051)	3.208	0.781-13.174	2.85	0.09153
Arg	87 (0.925)	113(0.974)	Ref			
Trp	7 (0.074)	3(0.025)	3.031	0.762-12.060	2.70	0.11566
XRCC1 rs25487						
Arg/Arg	24 (0.510)	34 (0.586)	Ref			
Arg/Gln	19 (0.404)	20 (0.344)	1.346	0.595-3.046	0.51	0.47562
Gln/ Gln	4 (0.085)	4 (0.068)	1.417	0.322-6.230	0.21	0.64373
Arg/Gln+ Gln/ Gln						
	23(0.489)	24(0.413)	1.358	0.626-2.946	0.60	0.43873
Arg	67(0.712)	88(0.758)	Ref			
Gln	27(0.287)	28(0.241)	1.267	0.683-2.347	0.56	0.45234

Table 5. Genotype Frequencies of XRCC1 Gene Polymorphism in Above 48 Years Age Breast Cancer Cases and Controls

Genotype	Cases	Controls	OR	95% CI	X^2	p- value
rs1799782						
Arg/Arg	44 (0.830)	41 (0.976)	Ref			
Arg/Trp	9 (0.169)	1 (0.023)	8.386	1.017-69.127	5.30	0.02129
Trp/ Trp	0 (0.000)	0 (0.000)	0.933	0.018-48.081	Nan	1.00000
Arg/Trp+ Trp/ Trp						
	9 (0.169)	1(0.023)	8.386	1.017-69.127	5.30	0.02129
Arg	97 (0.915)	83 (0.988)	Ref			
Trp	9 (0.084)	1 (0.011)	7.701	0.956-62.055	5.01	0.0446
rs25487						
Arg/Arg	34 (0.641)	24 (0.571)	Ref			
Arg/Gln	13 (0.245)	14 (0.333)	0.655	0.262-1.642	0.82	0.36594
Gln/ Gln	6 (0.113)	4 (0.095)	1.059	0.269-4.162	0.01	0.93477
Arg/Gln+ Gln/ Gln						
	19 (0.358)	18 (0.428)	0.745	0.325-1.708	0.48	0.48663
Arg	81 (0.764)	62 (0.738)	Ref			
Gln	25 (0.235)	22 (0.261)	0.870	0.449-1.686	0.17	0.67932

rs1799782 showed higher risk at Arg/Trp, Arg/Trp+ Trp/ Trp (OR=8.386; χ^2=5.3, p=0.0212) and at Trp (OR= 7.701; χ^2=5.01, p=0.044) alleles.

We conducted the association of breast cancer risk with the individual SNPs based on the estrogen receptor (ER) status of the tumors. The genotype distribution in the ER+ (n=55) and ER- (n=45) groups were separately compared with the genotype frequency in the same group of normal healthy women (n=100) (Tables 6 and 7). XRCC1 rs1799782 showed higher risk in both ER+ and ER- breast cancer samples when compared with over all controls at Arg/Trp, Arg/Trp+ Trp/Trp and at Trp alleles. (Tables 6 and 7).

Table 6. Genotype Frequencies of XRCC1 Fene Polymorphism in Breast Cancer Cases with ER Positive

Genotype	Cases	Controls	OR	95% CI	X^2	p- value
XRCC1 rs1799782						
Arg/Arg	45 (0.818)	96 (0.96)	Ref			
Arg/Trp	10 (0.181)	4 (0.04)	5.333	1.587-017.928	8.69	0.00321*
Trp/ Trp	0 (0.000)	0 (0.00)	2.121	0.041-108.580	nan	1
Arg/Trp+ Trp/ Trp						
	10 (0.181)	4 (0.04)	5.333	1.587-017.928	8.69	0.00321*
Arg	100 (0.909)	196 (0.98)	Ref			
Trp	10 (0.090)	4 (0.02)	4.9	1.499-016.015	8.28	0.00775*
XRCC1 rs25487						
Arg/Arg	34 (0.618)	58 (0.58)	Ref			
Arg/Gln	16 (0.290)	34 (0.34)	0.803	0.387-1.665	0.35	0.55476
Gln/ Gln	5 (0.090)	8 (0.08)	1.066	0.323-3.522	0.01	0.91628
Arg/Gln+ Gln/ Gln						
	21(0.381)	42 (0.42)	0.853	0.435-1.673	0.21	0.64332
Arg	84 (0.763)	150 (0.75)	Ref			
Gln	26 (0.236)	50 (0.25)	0.929	0.539-1.600	0.07	0.78944

Table 7. Genotype Frequencies of XRCC1 Gene Polymorphism in Breast Cancer Cases with ER Negative

Genotype	Cases	Controls	OR	95% CI	X^2	p- value
XRCC1 rs1799782						
Arg/Arg	39 (0.866)	96 (0.96)	Ref			
Arg/Trp	6 (0.133)	4 (0.04)	3.692	0.988-013.805	4.21	0.04018
Trp/ Trp	0 (0.000)	0 (0.00)	2.443	0.048-125.288	Nan	1
Arg/Trp+ Trp/ Trp						
	6 (0.133)	4 (0.04)	3.692	0.988-013.805	4.21	0.04018
Arg	84 (0.933)	196 (0.98)	Ref			
Trp	6 (0.066)	4 (0.02)	3.500	0.963-012.724	4.06	0.08007
XRCC1 rs25487						
Arg/Arg	24 (0.533)	58 (0.58)	Ref			
Arg/Gln	16 (0.355)	34 (0.34)	1.137	0.531-2.435	0.11	0.74044
Gln/ Gln	5 (0.111)	8 (0.08)	1.510	0.448-5.087	0.45	0.50368
Arg/Gln+ Gln/ Gln						
	21 (0.466)	42 (0.42)	1.208	0.596-2.452	0.28	0.59995
Arg	64 (0.711)	150 (0.75)	Ref			
Gln	26 (0.288)	50 (0.25)	1.219	0.698-2.127	0.49	0.48599

Discussion

XRCC1 encodes a scaffolding protein that plays a pivotal role in BER by bringing together PARP1, DNA ligase III, and DNA polymerases at the site of DNA damage (Caldecott et al., 1996; Thompson and West, 2000; Zhai et al., 2006). Several molecular epidemiological studies have been conducted to evaluate the association between XRCC1 Arg194Trp and Arg399Gln and breast cancer risk. In this case-control study of breast cancer, we investigated the associations between two non synonymous SNPs in XRCC1 Arg194Trp (rs1799782), Arg399Gln (rs25487), and the risk of breast cancer in a Saudi population. To the best of our knowledge, this is the first molecular epidemiological study on XRCC1 Arg194Trp (rs1799782), Arg399Gln (rs25487), polymorphism and breast cancer risk in Saudi population.

Results showed that rs1799782 had significantly increased susceptibility to breast cancer. rs1799782 showed significant risk at Arg/Trp, Arg/Trp+Trp/Trp genotypes and at Trp allele in over all study. rs1799782 also showed increased risk of breast cancer in older age patients group (above 48) and with ER positive category patients. In conclusion XRCC1 rs1799782 SNP polymorphisms may be involved in the etiology of breast cancer in Saudi populations. XRCC1 rs25487 (Arg399Gln) didn't showed any significant association in overall in breast cancer samples when compared to healthy controls. We have also observed that rs1799782 is associated with the older age and ER receptor status with breast cancer susceptibility (Table 5-7). rs25487 didn't showed any association with breast cancer susceptibility with any phenotypic parameters (Tables 4-7).

Overall, we observed that only 194Trp allele was associated with an increased risk of breast cancer, whereas the 399Gln allele did not show any association with a risk of this cancer (Table 3). A similar observation was also reported in polish population by Przybylowska-Sygut et al. (2013). Moullan et al. (2003) reported that the presence of the Arg194Trp polymorphism in exon 6 of the XRCC1gene might be associated with an increased frequency of breast cancer. Smith et al. (2003) also reported an weak association of the 194 Trp allele with a risk of breast cancer occurrence in white women. Additionally, the 194Trp variant was found to be significantly associated with benign breast disease, which is a risk factor for breast cancer and may have a heritable component (Jorgensen et al., 2009).

In the present study our results with Arg399Gln didn't showed any association with Saudi breast cancer patients. Similar to this even European population didn't show any association with XRCC1 399 polymorphism in lung cancer patients (Lopez-Cima et al., 2007) and in bladder patients (Kelsey et al., 2004). Some studies have also demonstrated a strong association of the Arg399Gln XRCC1 polymorphism with an increased risk of breast cancer (Chacko, 2005; Dufloth et al., 2008; Sterpone et al., 2010). However in 2006, the Breast Cancer Association Consortium, as well as a large meta-analysis, reported no evidence of its association with breast cancer development (Breast Cancer Association Consortium, 2010).

In a recent study by our group, we have observed that XRCC1 Arg399Gln genotype frequencies of central Saudi population showed a significant deviation from Utah residents with Northern and Western European ancestry from the CEPH collection (CEU), Maasai in Kinyawa, Kenya (MKK)and Yoruba in Ibadan, Nigeria (YRI) populations (Alanazi et al., 2013). According to Alanazi et al. (2013) XRCC1 Arg399Gln polymorphism has been reported to be associated with head and neck cancer risk (Alsbeih et al., 2008) in Saudi population in contrary to this Harithy and Ghazzawi, (2011) reported that this loci conferred protection in Saudi colon cancer patients. This is may be due to the SNP association with other SNPs.

Our findings suggest that SNP variants in XRCC1 may play an important role in the development of breast carcinoma. Despite our data supports for a clear association between XRCC1 and breast cancer in Saudi population and XRCC1 gene plays a major role in the susceptibility to the disease. As the sample size of this study is not sufficiently large and is restricted to Saudi population, the present data should be validated in larger samples and in other ethnic groups. Additional functional as well as association studies investigating gene-gene interactions are required to elucidate this issue, and it remains possible that XRCC1 variability may affect disease progression or the susceptibility to develop breast cancer. Confirmation of our findings in larger populations of different ethnicities would provide evidence for the role of XRCC1 gene in breast carcinomas.

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