RESEARCH ARTICLE

Correlation between Selected XRCC2, XRCC3 and RAD51 Gene Polymorphisms and Primary Breast Cancer in Women in Pakistan

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Abstract

Genetic polymorphisms in homologous recombination repair genes cause an abnormal development of cancerous cells. In the present study we evaluated the possibility of breast cancer association with single nucleotide polymorphisms of RAD51, XRCC2 and XRCC3 genes. Polymorphisms selected in this study were RAD51 135G/C, XRCC2 Arg188His; and XRCC3 Thr241Met. Each polymorphism was genotyped using Polymerase chain reaction-restriction fragment length polymorphism in study cohort of 306 females (156 breast cancer patients and 150 controls). We observed that heterozygous variant genotype (GC) of RAD51 135 G/C polymorphism was associated with a significantly (OR=2.70; 95%CI (0.63-1.79); p<0.03) increased risk of breast cancer. In case of the XRCC3 gene we observed that frequency of heterozygous (OR=2.88; 95%CI (1.02-8.14); p<0.02) and homozygous (OR=1.46; 95%CI (0.89-2.40); p<0.04) genotype of Thr241Met polymorphism were significantly higher in breast cancer patients. For the Arg188His polymorphism of XRCC2, ~2fold increase in breast cancer risk (OR=1.6, 95%CI = 0.73-3.50) was associated with GA genotype with a p value for trend of 0.03. Our results suggest that the 135G/C polymorphism of the RAD51, Thr241Met polymorphism of XRCC3 and Arg188His polymorphism of XRCC2 can be independent markers of breast cancer risk in Pakistan.

Keywords: XRCC2 - XRCC3 - RAD51 - breast cancer - RFLP.

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Introduction

Genetic polymorphisms in homologous recombination repair (HRR) genes, which can lead to protein haploinsufficiency, have been associated with increased cancer risk (Areeshi, 2013). The RAD51, XRCC2 and XRCC3 proteins are core components of DNA double strand breaks (DSBs) repair by HRR. XRCC2 and XRCC3 genes are structurally and functionally related to RAD51 gene (Suwaki et al., 2011; Fayaz et al., 2013). Cell deficient with any of these genes product are defective in homologous recombination and demonstrate genomic instability (Fayaz et al., 2013). RAD51 is known to play its role in all three stages of HR and catalyses the invasion of broken ends of the DSB into intact sister chromatid (Zhang et al., 2014). Common RAD51 SNPs (single nucleotide polymorphism) 135 G>C (rs1801320) in the 5'UTR have been reported to be associated with altered gene transcription and might be involve in mammary carcinogenesis (Jara et al., 2010; Sliwinski et al., 2010; Romanowicz-Makoeska et al., 2011).

XRCC2 is second important protein of HRR pathway and has been shown to interact with RAD51 and RAD51 like proteins (Andreassi et al., 2009; Tambini et al., 2010). Insufficiency of this protein cause increased errors in chromosome segregation and other chromosomal aberrations (Shin et al., 2008). The most common XRCC2 Arg188His G>A (R188H, rs3218536) polymorphism has been widely studied in association with breast cancer susceptibility and other cancers (Romanowicz-Makowska et al., 2012; Fayaz et al., 2013; He et al., 2014). XRCC3 take part in DSB repair as it causes slowing of DNA synthesis and recruit RAD51 at repair sites (Economopoulos and Sergentanis, 2010; Parine et al., 2012). Studies have accounted for the role of T241M, polymorphisms in causing breast cancer and other cancers (Krupa et al., 2009; Silva et al., 2010; Zhao et al., 2012).

To identify the association of RAD 51 (5'untranslated region 135 G>C), XRCC2 (Arg188His), and XRCC3 (Thr241Met) polymorphisms with the risk of breast cancer, we conducted a population-based nested case-control study including 156 cases and 150 cancer-free controls in a Pakistani population and it is postulated that these SNPs can possibly be used as predictive factors for breast cancer prognosis.

Materials and Methods

Blood sample collection

This study involved pathologically verified female

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breast cancer patients. Analyzed blood samples from females with breast cancer were collected from NORI (Nuclear Medicine, Oncology and Radiotherapy Institute), Islamabad. A total of 156 patients blood samples along with 150, age and sex matched, healthy and disease free individuals without prior history of any disease were used as controls. Blood samples from cancerous patients with a mean age of 44 (±0.8) and healthy persons with a mean age of 41 (±0.7) were collected in 5ml sterile EDTA containing blood vacutainers. These samples were obtained with informed consent of patients according to approved procedures by the concerned hospital and departmental ethical committee. All the samples were stored in the refrigerator at 4˚C for further processing.

Genotype determination

DNA was isolated from the blood for germ-line mutation screening by phenol organic method as described by Baig et al., 2011 with minute alterations and stored at -20˚C for further processing. PCR cycle conditions for RAD51, XRCC2 and XRCC3 were: one cycle at 94˚C for 5min; 35 cycles of 94˚C for 30sec, 55˚C for 30sec and 72˚C for 30sec and a final extension at 72˚C for 10min. Pairs of PCR primer sequences and restriction enzyme for each DNA product are all listed in Table 1.

The 157 bp PCR product of RAD51 was digested overnight with 3U of the restriction enzyme MvaI. The homozygous G/G genotype produced 86 and 71 bp fragments, heterozygous G/C genotype three fragments: 157, 86 and 51 bp and the homozygous C/C genotype produced one 157 bp fragment. The 307 bp PCR product of XRCC2 was digested overnight with 3U of the restriction enzyme SexAI. The homozygous G/G genotype (lack the restriction site for the enzyme) produce single 307bp fragments, heterozygous G/A genotype (contained the restriction site for enzyme) three fragments: 307, 214 and 93 bp and the homozygous A/A genotype produced 214 and 93 bp fragments. In case of XRCC3, 315 bp PCR product was digested overnight with 3U of the restriction enzyme NIaIII. The homozygous C/C genotype produced 22 and 293 bp fragments, heterozygous C/T genotype four fragments: 22, 105, 188 and 293 bp and the homozygous T/T genotype produced three fragment: 22, 105 and 188 bp. 10≥ of digested products was loaded into a 4% agarose gel containing ethidium bromide for electrophoresis and analysis.

Statistical analysis

The chi-square test was used to compare the distribution of categorical variables such as the RAD51, XRCC2 and XRCC3 genotype, age, sex, and so on. Adjusted and stratified odds ratios (OR) and 95% confidence intervals (CI) were estimated by unconditional logistic regression. All the analysis was performed using statistical software GraphPad PRISM version 5.04 and SPSS.

Results

Genotyping was carried out with the help of sequence specific restriction endonucleases i.e. *MvaI*, *SexAI*, and *NlaIII* for RAD51, XRCC2 and XRCC3 genes respectively (Figure 1). This helps in distinguishing the mutant allele from its normal counterpart either by the presence or absence of a restriction site which is either created or abolished as a result of the single base pair change. The frequency distribution of RAD51 (135G/C), XRCC2 (Arg188His) XRCC3 (Thr241Met) genotypes among cases and controls are presented in Table 2. In case of 135G/C polymorphism of RAD51, ~3fold increase in breast cancer risk (OR=2.70, 95%CI=0.63-1.79) was associated with GC genotype and ~2.4fold increase (OR=2.40, 95%CI=0.45-12.5) with CC genotype. The p for trend was significant (p<0.03). For the Arg188His polymorphism of XRCC2, ~2fold increase in breast cancer risk (OR=1.6, 95%CI=0.73-3.50) was associated with GA genotype and ~1.0fold increase (OR=0.7, 95%CI=0.48-1.02) with AA genotype. The p for trend was significant (p<0.03). In case of Thr241Met polymorphism of XRCC3, ~3folds increase in breast risk (OR=2.88, 95%CI=1.02-8.14) was associated with CT and ~2folds increase (OR=1.46, 95%CI=0.89-2.40) with TT genotype. The p for trend was significant (p<0.0002). These risks persisted even when the data were adjusted for chi-square analysis and were statistically significant.

A difference in genotype frequencies between controls and cases diagnosed before the age of 45 or above the age of 45 was observed (Tables 3 and 4). In case of study cohort below age group 45, the odds ratio of the people carrying GA and AA genotypes were 2.21 (95%CI=0.75-6.60) and 1.37 (95%CI=0.54-19.45) respectively

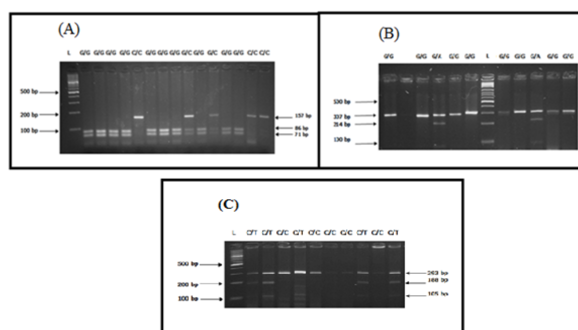

Figure 1. Banding pattern of RAD51 (A), XRCC2 (B) and XRCC3 (C) polymorphisms after enzyme digestion. (G/G, C/C= Wild type, G/C, C/T= Hetrozygous, C/C, T/T= Variant, L= Ladder)

Table 1. RFLP Details for RAD51, XRCC2 and XRCC3 Polymorphism.

Gene (Polymorphism)	Product Size	Primer sequences (5'-3')	Polymorphism: Effect on Restriction site	Restriction patterns after enzyme digestion
RAD51 (135G/C)	157 bp	F-TGGGAACTGCAACTCATCTGG R-GCGCTCCTCTCTCCAGCAG	G>C, Abolish one site for MvaI enzyme	G/G: 86, 71 bp; G/C: 157, 86, 71bp; C/C: 157 bp
XRCC2 (Arg188His)	307bp	F-GGTGTACTGCAGTAGTAGCACCCACTTAC R- CACATCACACAGTCGTCGAGAGGC	G>A, Creates one SexAI site	G/G: 307 bp; G/A: 307, 214, 93 bp A/A: 214, 93 bp
XRCC3 (Thr241Met)	315bp	F-GTACTGCTGTCTCGGGGCATG R-CGATGGTTAGGCACAGGCTGC	C>T, Creates one NlaIII Site	C/C: 22, 293 bp; C/T: 22,105, 188, 293 bp; T/T: 22, 105, 188 bp

compared to those carrying wild type genotype GG of the XRCC2 Arg188His polymorphism. The p for trend was significant (p<0.04). In addition to this, odds ratio of the people carrying CT and TT genotypes were 2.26 (95%CI=1.20-4.24) and 2.20 (95%CI =0.42-11.72) respectively compared to those carrying CC wild type genotype XRCC3 Thr241Met polymorphism. The p for trend was significant (p<0.004). In case of study cohort above age group 45, the odds ratio of people carrying CT and TT genotype were 1.23 (95%CI=0.58-2.60) and 4.18 (95%CI=1.09-15.94) respectively compared to those carrying TT wild type genotype of the XRCC3 Thr241Met polymorphism. The p for trend was significant (p<0.01). Furthermore, we evaluated the association of selected polymorphism (RAD51 135G/C, XRCC2 Arg188His XRCC3 Thr241Met) with age groups and observed that the GC genotype of the RAD51 135G/C polymorphism was more frequent among cancer cases than controls, and this difference was more marked in the age group below 45 compared to age group above 45. Similar trend was observed in case of CT genotype of the XRCC3 Thr241Met polymorphism, and this difference was more marked in the age group below 45 compared to age group above 45.

Table 2. RAD51 (135G/C), XRCC2 (Arg188His) XRCC3 (Thr241Met) Genotypes and Allele Percentage for Patients and Controls

Genotypes	Cases n=156	Controls n=150	OR[a] (95%CI)	P- value[b]
RAD51 135G/C				
G/G	102 (65.4)	104 (69.3)	Ref	
G/C	49 (31.4)	44 (29.3)	2.70 (0.63-1.79)	0.03
C/C	5 (3.2)	2 (1.3)	2.40 (0.45-12.5)	0.2
*P value for trend	0.03			
XRCC2 Arg188His				
G/G, Arg188Arg	131 (84)	137 (91.4)	Ref	
G/A, Arg188His	20 (13)	12 (8.0)	1.60 (0.73-3.50)	0.1
A/A, His188His	5 (3)	1 (0.6)	0.70 (0.48-1.02)	0.3
*P value for trend	0.03			
XRCC3 Thr241Met				
C/C, Thr241Thr	74 (47.4)	101 (67.3)	Ref	
C/T, Thr241Met	67 (42.9)	44 (29.3)	2.88 (1.02-8.14)	0.02
T/T, Met241Met	15 (9.6)	5 (3.3)	1.46 (0.89-2.40)	0.04
*P value for trend	0.0002			

[a]ORs were adjusted by age, age at menarche and age at menopause, [b]p>0.05, by Fisher s exact test, *p>0.05, by chi-square test for trend

Table 3. Association between RAD51 (135G/C), XRCC2 (Arg188His) XRCC3 (Thr241Met) Genotype and Age at Diagnosis

Genotypes	Age at diagnosis ≤45 Cases (%) n=91	Controls (%) n=78	OR (95% CI)[a]	P-value*
RAD51 135G/C				
G/G	48 (53)	51 (65)	Ref	
G/C	42 (46)	26 (33)	1.70 (0.63-1.79)	0.1
C/C	01 (1)	01 (2)	0.85 (0.05-13.5)	
XRCC2 Arg188His				
G/G	77 (85)	73 (94)	Ref	
G/A	12 (13)	5 (6)	2.21(0.75-6.60)	0.04
A/A	2 (2)	0	1.37 (0.54-19.45)	
XRCC3 Thr241Met				
C/C	39 (43)	51 (65)	Ref	
C/T	47 (52)	25 (32)	2.26 (1.20-4.24)	0.004
T/T	5 (5)	2 (3)	2.20 (0.42-11.72)	

[a]ORs were adjusted by age, age at menarche and age at menopause; *p > 0.05, by chi-square test for trend

Table 4. Association between RAD51 (135G/C), XRCC2 (Arg188His) XRCC3 (Thr241Met) Genotype and Age at Diagnosis

Genotypes	Age at diagnosis ≥45 Cases (%) n=65	Controls (%) n=72	OR (95% CI)[a]	P-value*
RAD51 135G/C				
G/G	54 (83)	53 (74)	Ref	
G/C	07 (11)	18 (33)	0.36 (0.14-0.93)	0.5
C/C	4 (6)	1 (2)	4.65 (0.50-42.77)	
XRCC2 Arg188His				
G/G	77 (85)	73 (94)	Ref	
G/A	12 (13)	5 (6)	1.30 (0.44-3.82)	0.2
A/A	2 (2)	0	3.4 (0.34-33.88)	
XRCC3 Thr241Met				
C/C	39 (43)	51 (65)	Ref	
C/T	47 (52)	25 (32)	1.23 (0.58-2.60)	0.01
T/T	5 (5)	2 (3)	4.18 (1.09-15.94)	

[a]ORs were adjusted by age, age at menarche and age at menopause; *p>0.05, by chi-square test for trend

Discussion

RAD51 being a critical protein involved in homologous recombination repair (HRR) pathway interacts with XRCC2, XRCC3 and other different proteins, forming a complex which is important for repairing the double strand breaks and maintaining chromosome stability (Wang et al., 2010). An effort was made in the present study to determine if SNPs in the DNA repair pathway genes (RAD51 135 G/C, XRCC2Arg188His and XRCC3Thr241Met) are linked with breast cancer pathogenesis. For this purpose, PCR-RFLP analysis was used in this study in order to find out the association of potentially functional polymorphisms and genetic markers in the selected genes from a subset of 156 breast cancer patients and 150 control subjects. Polymorphic genes of DNA repair are in great part included to low penetrance genes, which means that single gene product most often slightly affects the disease occurrence risk, but accumulation of changed alleles can have essential significance for its development. The combined effect of investigated XRCC2, XRCC3 and RAD51 polymorphisms on breast cancer occurrence enabled us to investigate several gene-gene interactions in the context of general relationship between a gene and its structural analogues.

Our study found that the heterozygous variant genotype (GC) of RAD51 135 G/C polymorphism was associated with a significantly increased risk of breast cancer. Different meta-analysis and studies on RAD51 have earlier shown an association of this polymorphism with an elevated breast cancer risk (Cole et al., 2011; Falvo et al., 2011; Gao et al., 2011; Hosseini et al., 2012). The RAD51 135G/C polymorphism located in the 5' untranslated region seems to be of functional relevance. There is evidence to suggest that this change enhances the activity of the RAD51 promoter, which may result in increased RAD51 expression (Hasselbach et al., 2005). Altered protein levels may influence the activity of the multiprotein DNA-repair complex of RAD51 (Kuschel

et al., 2002). Thus, the functional consequence of this change on the expression of RAD51 suggests that the RAD51 polymorphism may modify disease risk itself and is not due to any other sequence change in a regulatory region of the gene or in a nearby gene which is in linkage disequilibrium with this polymorphism.

In order to confirm our results that RAD51 polymorphism may modify disease risk itself or in relation to other related genes. We have selected functional polymorphisms of two other genes that are core components of RAD51 in DSBs such as Arg188His polymorphism of XRCC2 and Thr241Met of XRCC3 genes. In current study we observed ~2folds increased risk of breast cancer in patients with GA genotype of Arg188His polymorphism of XRCC2 compared to controls but this increased risk was statistically non-significant. However, this polymorphism was observed statistically significant in breast cancer patients below the age of 45 years. Previous studies on XRCC2 Arg188His polymorphism have shown no association with breast cancer risk (Kuschel et al., 2002; Millikan et al., 2005). However in several other studies the variant allele (188His) has been associated with decreased breast cancer risk (Romanowicz-Makowska et al., 2012; He et al., 2014).

Present study also found that homozygous (TT) and heterozygous (CT) genotypes of Thr241Met polymorphism of XRCC3 were associated with increased risk of breast cancer patients compared to controls. Similar results have earlier been observed in different studies signifying the association of the variant Met allele with breast cancer in both Caucasian and Asian populations (Lee et al., 2007; Economopoulos and Sergentanis, 2010; Romanowicz-Makoeska et al., 2011). The Thr241Met (T241M) amino acid substitution due to a C18067T transition at exon 7 is the most frequent polymorphism in XRCC3, which may affect the coding enzyme's function and/or its interaction with other proteins involved in the DNA repair. The variant allele (241Met) is associated with relatively high DNA adduct levels in lymphocyte DNA, indicating relatively low DNA repair capacity (Alanzi et al., 2014).

Our study lead us to hypothesis that variant genotypes of RAD51, XRCC2 and XRCC3 proteins have decreased repair capacity and thus patients with variant genotypes do not repair double strand DNA breaks efficiently by HRR atleast in Pakistani population. In present study we observed that the 135G/C polymorphism of the RAD51 and Thr241Met in XRCC3 gene can modify the breast cancer risk alone as well as in association with other polymorphisms such as Arg188His in XRCC2 gene. We have also shown that all investigated polymorphisms 135G/C of RAD51, Arg188His of XRCC2 and Thr241Met of XRCC3 should be simultaneously taken into account as a part of polygenic cause of breast cancer occurrence. With limited sample size, our results allow for preliminary conclusions and future larger studies are warranted to further test DNA repair genetic variants in breast cancer susceptibility.

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