XRCC2 and XRCC3 Polymorphisms and Breast Cancer – A Case-Control Study from West India

Kinjal D. Patel, Shruti R. Patel*, Kinjal R. Patel*, Bhoomi V. Tarapara*, Jayendra B. Patel*, Franky D. Shah**, Prabhudas S. Patel***

Abstract :

Background: The double strand break repair pathway, comprising XRCC2 and XRCC3 has crucial role in maintenance of genomic stability and prevention of tumor initiation and progression. Therefore, sequence variants of such DNA repair genes may compromise individual's DNA repair capacity and can influence risk of developing breast cancer. **Method and Results:** To estimate the impending effect of XRCC2 (Arg188His) and XRCC3 (Thr241Met) polymorphisms on breast cancer, 133 breast cancer patients and 154 healthy controls were evaluated by PCR-RFLP method. In the present study, it was noted that there was no significant correlation between these polymorphisms and breast cancer risk. However, within patient group, significant association of XRCC2 variants with PR negative breast cancer was detected. Further, patients with XRCC2 variant genotypes were also at high risk of developing TNBC and Her2 enriched subtypes as compared to luminal A subtype. Significant relation was also obtained between XRCC3 variants and large sized and infiltrative breast tumors. **Conclusion:** These noteworthy observations demonstrate potential involvement of XRCC2 and XRCC3 polymorphisms in pathophysiology of breast cancer.

Key words : XRCC2, XRCC3, Polymorphism, Breast Cancer

Introduction :

Breast cancer is one of the major consequences for women's health, emotional and psychological well-being. Despite of recent advances in cancer diagnosis and management, this malignancy has shown serious implication to the world's health care system during past 4 years; Incidence and mortality rates of breast cancer were increased by 20% and 14% respectively, in 2012 than 2008 estimates. [1, 2] The statistics directed a need of in-depth understanding of breast pathogenesis.

There are several lines of evidences that have confirmed the central role of DNA repair in cancer initiation and progression. It was demonstrated that double strand breaks (DSBs) can cause massive loss of genetic information, chromosomal abbreviations or cell death. [3] There are two major DSBs repair mechanisms: homologous recombination (HR) and non-homologues end joining, that differ in the fidelity and template requirements. HR repair is more error immune and play prominent role in replication associated DSBs repair.[4] XRCC2 and XRCC3 proteins are members of RAD51 protein family and act as auxiliary proteins which directly interact with RAD51. These two proteins are necessary in HR repair as they required for RAD51 focus formation.[5] It was also proven that XRCC2 and XRCC3 deficient hamster cell lines showed higher frequency of aneuploidy, multiple centrosomes and abnormal spindle formation and lower spontaneous frequency of sister chromatid exchange than wild type cells. [6,7] In XRCC2 gene, there is a G to A substitution in exon 3 (codon 188), resulting into replacement of arginine (Arg) by histidine (His) amino acid. His allele showed reduced DNA repair capacity than Arg allele for mitomycin C induced DNA damage. [5] In XRCC3 gene, there is a C to T substitution in exon 7 (codon 241), resulting into substitution of threonine (Thr) to methionine (Met) amino acid. Functional studies proved that individuals carrying Met allele showed reduced DNA repair proficiency. [8-10]

These two polymorphisms have been widely studied to find their influence on breast cancer risk.[11, 12] However, role of XRCC2 and XRCC3 polymorphisms in breast

* Molecular Oncology Laboratory, Gujarat Cancer and Research Institute, Ahmedabad, Gujarat, India
** Stem Cell Biology Laboratory, Gujarat Cancer and Research Institute, Ahmedabad, Gujarat, India
*** Professor and Head, Department of Cancer Biology, Gujarat Cancer and Research Institute, Ahmedabad, Gujarat, India
Corresponding Author : Dr. Prabhudas S. Patel
E-mail : prabhudas_p@hotmail.com

cancer have not been explored in Indian population. Therefore, we aimed to study contribution of XRCC2 Arg188His (rs3218536) and XRCC3 Thr241Met (rs861539) polymorphisms in breast cancer development and pathogenesis.

Methods:

Sample Collection

In the study, eligible breast cancer cases (n=133, untreated) were recruited from the out patient's department of The Gujarat Cancer and Research Institute (Gujarat, India). Ethnically matched controls (n=154) were included from health check-up programme from community oncology center of the Institute. Exclusion criteria for subjects were included genetically related, ethnically unmatched, previous history of cancer/benign conditions and HIV/HBsAg positive status. The study was approved by the institutional review board. Blood samples (4ml) were collected from each subject with written consent. Demographic data and clinical data were collected using a standard questionnaire and hospital records.

XRCC2 (rs3218536) and XRCC3 (rs861539) Genotyping

White blood cells were isolated from blood samples and stored at -80^{0}C. The genomic DNA was extracted using DNA blood mini kit (Qiagen, USA) as per the manufacturer's instructions and stored at -20^{0}C until analysis. The DNA region flanking polymorphic sites were amplified using following primers: XRCC2, 5'-GGTGTACTGACGTAGTAGCACCCACTTAC-3' (F) and 5'-CACATCACACAGTCGTCGAGAGGC-3' (R); XRCC3, 5'-GGTCGAGTGACAGTCCAAAC-3' (F) and TGCAACGGCTGAGGGTCTT (R). The PCR reactions were carried out in 25µl mixture, containing 100ng DNA, 0.2^M of each forward and reverse primers and 12.5µl PCR mastermix (Fermentas, USA) on Proflex PCR system (Applied Biosystems, USA) under following PCR cycle conditions: 94^{0}C for 5 mins (initial denaturation); 94^{0}C for 1 min, specific annealing temperature (56.5^{0}C for XRCC2 and 52.6^{0}C for XRCC3) for 1 min and 72^{0}C for 1 min, repeated in 35 cycles; 720C for 7 mins (final extension). The amplification was checked on 1.5% agarose gel using gel documentation system (Alpha Innotech, USA).

XRCC2 PCR products (307bp) were digested with SexAI (NEB, USA) at 37^{0}C for 60 mins. The digested products yielded single band of 307bp for wild type (Arg/Arg), two bands of 214 and 93bp for homozygous mutant (His/His) and all three sized fragments for heterozygous mutant (Arg/His). Further, XRCC3 PCR products (455bp) were digested with NlaIII (NEB, USA) at 37^{0}C for 15 mins which produced two bands of 315 and 140bp for wild type (Thr/Thr), three bands of 210, 140 and 105bp for homozygous mutant (Met/Met) and all four sized fragments for heterozygous mutant (Thr/Met).

Statistical Analysis

$\chi 2$ tests were used to analyze the obtained data: goodness of-fit $\chi 2$ test [to check genotype frequencies for Hardy–Weinberg equilibrium (HWE)], Pearson's $\chi 2$ test (to test genotype distribution in cases and controls) and $\chi 2$ test for linear trend (to assess dose dependent effect of risk alleles). The association of individual genotypes with breast cancer risk and specific pathological features was estimated by calculating odds ratios (ORs) and 95% confidence interval (CI). All the tests were two tailed and p value $\leqslant 0.05$ was considered to be statistically significant.

Results:

Genotype Frequencies and Risk Estimation

In the study, the observed genotype frequencies of XRCC2 and XRCC3 polymorphisms did not deviate from HWE ($p>0.05$) (Table 1). The genotype frequencies of XRCC2 (Arg188His) were 82%, 16.5% and 1.5% in cases and 79.9%, 19.5% and 0.6% in controls for Arg/Arg, Arg/His and His/His, respectively. For XRCC3 (Thr241Met), the genotype frequencies were 62.4%, 32.3% and 5.3% in cases and 61%, 33.8% and 5.2% in controls for Thr/Thr, Thr/Met and Met/Met, respectively. In case of both the polymorphisms, they did not differ significantly between cases and controls and therefore not associated with breast cancer risk (Table 1).

Table 1: Distribution of XRCC2 and XRCC3 genotypes in cases and controls

Polymorphism	Cases (n=133)		Controls (n=154)		χ2 Value 'p' value	cOR* (95% CI) 'p' value	aOR‡ (95% CI) 'p' value
	N	(%)	N	(%)			
XRCC2 Arg188His (rs3218536)							
Arg/Arg	109	82.0	123	79.9	#χ2 HWE=0.32 p= 0.56; Pearson's χ2=0.87 p=0.64	1.0 (Ref)	1.0 (Ref)
Arg/His	22	16.5	30	19.5		0.82 (0.45-1.51) p=0.54	0.91 (0.44-1.90) p=0.82
His/His	2	1.5	1	0.6		2.25 (0.20-25.23) p=0.50	1.54 (0.08-26.92) p=0.76
Arg/His+His/His	24	18.0	31	20.2		0.87 (0.48-1.57) p=0.65	0.94 (0.46-1.92) p=0.94
MAF_{Con}=0.10; ¥Ptrend=0.80							
XRCC3 Thr241Met (rs861539)							
Thr/Thr	83	62.4	94	61.0	#χ2 HWE=0.05 p= 0.81; Pearson's χ2=0.67 p=0.96	1.0 (Ref)	1.0 (Ref)
Thr/Met	43	32.3	52	33.8		0.93 (0.56-1.54) p=0.79	0.73 (0.39-1.36) p=0.33
Met/Met	7	5.3	8	5.2		0.99 (0.34-2.85) p=0.98	1.05 (0.28-3.93) p=0.93
Thr/Met+Met/Met	50	37.6	60	39.0		0.94 (0.58-1.52) p=0.81	0.80 (0.45-1.42) p=0.44
MAF_{Con}=0.22; ¥Ptrend=0.85							

HWE Hardy-Weinberg equilibrium, *OR* odds ratio, *CI* confidence interval, *MAFcon* minor allele frequency in control population

¥p value of χ2 test for linear trend (Canchran-armitage test)

#χ2 goodness of fit test for Hardy-Weinberg Equilibrium in controls

*Crude odds ratio

‡Adjusted odds ratio: odds ratio were adjusted for age, menopausal status, family history, age at menarche, age at menopause, age at first time full pregnancy, numbers of child, numbers of abortions and breast feeding.

Association of XRCC2 and XRCC3 Variants with Breast Cancer Phenotype

The genotype frequencies were also compared with distinct breast cancer phenotypes (Table 2-3) and the data revealed high prevalence of Arg/His genotype of XRCC2 in PR negative tumors (χ2=4.85, p=0.08; Ptrend=0.07) (Table 2-3). An OR analysis revealed significant association of XRCC2 variants with PR negative tumor (Arg/Arg vs Arg/His, OR=3.2, 95% CI=1.09-9.36, p=0.03; Arg/Arg vs Arg/His+His/His, OR=2.83, 95% CI=1.03-7.74, p=0.04) (Table 3). Further, an increasing trend was observed in number of Arg/His genotype from luminal

Table 2: Association of XRCC2 and XRCC3 genotypes with different pathological features of breast cancer

Characteristic		N	XRCC2 Arg188His (rs3218536)		XRCC3 Thr241Met (rs861539)	
			χ2*; 'p' value	¥Ptrend	χ2*; 'p' value ¥	¥P trend
Age of Disease Onset (years)	< 45	54	4.66; **0.09**	0.82	1.46; 0.48	0.96
	>45	79				
Stage	Early	68	2.53; 0.28	0.96	1.57; 0.45	0.85
	Advanced	64				
T stage	T1aT2	86	0.22; 0.89	0.86	5.22; **0.07**	**0.04**
	T3aT4	44				
Lymphnode Metastasis	Negative	44	0.24; 0.88	0.79	1.96; 0.37	0.56
	Positive	87				
Histologic Grade	I + II	58	2.83; 0.24	0.24	0.54; 0.76	0.75
	III	43				
Invasion	No	62	1.30; 0.52	0.38	1.14; 0.50	0.49
	Yes	52				
Infiltration	No	98	1.45; 0.48	0.57	7.40; **0.02**	0.12
	Yes	16				
Organ Metastasis	No	127	0.11; 0.94	0.98	0.77; 0.67	0.37
	Yes	5				
Estrogen Receptor	Positive	70	1.34; 0.50	0.29	0.46; 0.79	0.68
	Negative	59				
Progesterone Receptor	Positive	59	4.85; **0.08**	**0.07**	2.70; 0.25	0.17
	Negative	70				
Her2 Receptor	Positive	72	0.25; 0.88	0.87	0.54; 0.76	0.69
	Negative	46				
Molecular Subtypes	Luminal A	24	7.57; 0.27	0.75	2.99; 0.80	0.19
	Luminal B	45				
	Her2 enriched	27				
	TNBC	22				

Her2 human epidermal growth factor receptor 2

*Pearson 2 test; ¥p value of χ2 test for linear trend (Canchran-armitage test)

A (4.2%) to luminal B (15.6%) to Her 2 enriched (22.2%) to TNBC (27.3%) subtypes (data not shown). Thus, carriers with Arg/His genotype were at elevated risk of developing Her2 enriched and TNBC subtype as compared to luminal A subtype (Luminal A vs Her2, OR=6.6, 95% CI=0.72-59.68, p=0.09; Luminal A vs TNBC, OR=8.25, 95% CI=0.90-75.41, p=0.06) (Table 3).

The distribution of XRCC3 variant genotypes was significantly associated with Tumor size (χ2=5.22, p=0.07; Ptrend=0.04) and infiltration (χ2=7.40, p=0.02, Ptrend=0.12) (Table 2). Accordingly, OR analysis presented significant association of Met/Met genotype with large tumor size (OR=5.93, 95% CI=1.07-32.75, p=0.04). Moreover, patients with XRCC3 variants genotype were more prone to have infiltrating tumors (Thr/Thr vs Thr/Met, OR=3.86, 95% CI=1.28-11.68, p=0.01; Thr/Thr vs Thr/Met+Met/Met, OR=3.28, 95% CI=1.09-9.81, p=0.03) (Table 3).

Discussion:

Unrepaired DSBs could be lethal to a cell or produce tremendous genomic instability in a cell. This triggers initiation and development of malignancy.[3,4]

Table 3: Distribution of XRCC2 and XRCC3 genotypes according to distinct disease phenotype

Polymorphism	Distinct Disease Phenotype N (%)		cOR* (95% CI) 'p' value	aOR‡ (95% CI) 'p' value
XRCC2Arg188His (rs3218536)	**PR Positive**	**PR Negative**		
Arg/Arg	53 (89.8)	53 (75.7)	1.0 (Ref)	
Arg/His	5 (8.5)	16 (22.9)	3.20 (1.09-9.36)	0.03
His/His	1 (1.7)	1 (1.4)	1.0 (0.06-16.40)	1.00
Arg/His+His/His	6 (10.2)	17 (24.3)	2.83 (1.03-7.74)	0.04
XRCC2Arg188His (rs3218536)	**Luminal A Subtype**	**Her2 enriched Subtype**		
Arg/Arg	22 (91.7)	20 (74.1)	1.0 (Ref)	
Arg/His	1 (4.2)	6 (22.2)	6.60 (0.72-59.68)	0.09
His/His	1 (4.2)	1 (3.7)	1.10 (0.06-18.77)	0.94
Arg/His+His/His	2 (8.4)	7 (25.9)	3.85 (0.71-20.74)	0.11
XRCC2Arg188His (rs3218536)	**Luminal ASubtype**	**TNB CSubtype**		
Arg/Arg	22 (91.7)	16 (72.7)	1.0 (Ref)	
Arg/His	1 (4.2)	6 (27.3)	8.25 (0.90-75.41)	0.06
His/His	1 (4.2)	0 (0)	NA	-
Arg/His+His/His	2 (8.4)	6 (27.3)	4.12 (0.73-23.15)	0.10
XRCC3Thr241Met (rs861539)	**T1-T2**	**T3-T4**		
Thr/Thr	57 (66.3)	24 (53.3)	1.0 (Ref)	
Thr/Met	27 (31.4)	16 (35.6)	1.40 (0.64-3.07)	0.39
Met/Met	2 (2.3)	5 (11.1)	5.93 (1.07-32.75)	0.04
Thr/Met+Met/Met	29 (33.7)	21 (46.7)	1.71 (0.82-3.59)	0.14
XRCC3Thr241Met (rs861539)	**Non-infiltrative**	**Infiltrative**		
Thr/Thr	65 (66.3)	6 (37.5)	1.0 (Ref)	
Thr/Met	28 (28.6)	10 (62.5)	3.86 (1.28-11.68)	0.01
Met/Met	5 (5.1)	0 (0)	NA	-
Thr/Met+Met/Met	33 (33.7)	10 (62.5)	3.28 (1.09-9.81)	0.03

OR odds ratio, CI confidence interval, NA not applicable, PR progesterone receptor, Her2 human epidermal growth factor receptor 2, TNBC triple negative breast cancer

Functional polymorphisms in genes that are involved for repair of DSBs, such as XRCC2 and XRCC3, are thought to be potential risk factor for breast cancer development. Until now, several studies have investigated the association between these polymorphisms and breast cancer, yet results were inconclusive. [11, 12] Additionally, as far as our knowledge, there is no such report available on Indian population and this is the first Indian study. In the present investigation, distinct association of these polymorphisms with specific breast cancer phenotype was observed.

Globally, the frequency of His allele is 0.05 (dbSNP database), which is lower in comparison to our population, while the frequency of Met allele is 0.21 (dbSNP database) which is accordance with our observation. In the present study, the breast cancer risk was not found to be associated with any specific genotype. Consistent with our findings, in 2015, two meta-analysis have demonstrated lack of association between XRCC2 and XRCC3 polymorphisms and overall breast cancer risk. [11, 12]

The possible reason for insignificant effect of studied polymorphisms on breast cancer risk is might be due to little functional consequences or indirect involvement of these polymorphisms. Rafii et al.[5] demonstrated reduced repair efficiency of XRCC2 His allele than Arg allele for mitomycin C induced DNA damage, yet the effect was little. It was also suggested that XRCC2 Arg188His polymorphism may not directly involved in breast cancer risk. [5, 3] In XRCC3 polymorphism, neutral thronine is replaced by hydrophobic methionine, which may results into important changes in protein structure and function. [14] However, Araujo et al. [8] reported possible association of XRCC3 polymorphism with slight but non-significant reduced DNA repair capacity. Further, functional studies demonstrated higher frequency of X-ray induced chromosome deletions [9] and bulky adducts [10] in carriers of Met allele, but showed no effect on repair of UV-induced DNA damage. [15] Moreover, presence of other interactive regions in the proteins that defeat the effect of the polymorphism might be another reason for the insignificant association of XRCC2 polymorphism. Rafii et al. [5] have recognized other regions of XRCC2 gene that do not overlap with codon 188 position and interact with other RAD51-like protein, RAD51L3. This interrelationship can overcome the influence of XRCC2 polymorphism. Besides, limited studies in different population might results into contradictory or insignificant findings. In recent meta-analysis, Chai et al. [12] suggested likely association of XRCC3 polymorphism with breast cancer in Asian population. On the contrary, in another meta-analysis, it was showed that Met allele was not correlated with breast cancer risk in Chinese women. [16] These findings, together, indicate need of more such studies in diverse population with same ethnicity.

The relationship between studied polymorphisms and distinct breast cancer phenotype were also evaluated. The variant genotypes (Arg/His and/or His/His) of XRCC2 were found to be significantly associated with PR negative tumors. Similar to our observations, Pooley et al. [17] demonstrated that patients carrying common Arg allele would be at a significantly higher risk of developing PR positive breast tumors. On the contrary, Lee et al. [18] and Romanowicz-Makowska et al. [19] did not find any association between XRCC2 gene polymorphism and hormone receptor status (ER and PR) in breast tumors. Arg/His of XRCC2 polymorphism was found to be associated with higher risk of developing TNBC and HER2 enriched tumor. Smolarz et al. [20] have suggested XRCC2 polymorphism as a risk modifier for TNBC subtype. In our study, XRCC3 polymorphism was also significantly linked with large tumor size and infiltrative tumors. However, in the studies regarding the association of XRCC3 polymorphism with breast cancer phenotypes remains contradictory. Few studies did not find correlation of XRCC3 polymorphism with tumor size, cancer type and hormone receptor status [21, 22] while other studies have observed its association with local metastasis and histological grading. [22, 23]

Overall, XRCC2 and XRCC3 variants are not associated with breast cancer risk in our population. Further, positive association of these polymorphisms with large tumor size, infiltration, PR negative tumors and molecular subtype suggests that these polymorphisms might be playing important role in breast cancer pathology.

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Conflict of Interest

The authors declare no conflict of interests.

References:

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM (2010) Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 127: 2893-2917. doi: 10.1002/ijc.25516
2. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136: E359-386. doi: 10.1002/ijc.29210
3. Lengauer C, Kinzler KW, Vogelstein B (1998) Genetic instabilities in human cancers. Nature 396: 643-649. doi: 10.1038/25292
4. Ralhan R, Kaur J, Kreienberg R, Wiesmüller L (2007) Links between DNA double strand break repair and breast cancer: accumulating evidence from both familial and nonfamilial cases. Cancer Lett. 248:1-17 Doi: 10.1016/j.canlet. 2006.06.004
5. Rafii S, O'Regan P, Xinarianos G, Azmy I, Stephenson T, Reed M, Meuth M, Thacker J, Cox A (2002) A potential role for the XRCC2 R188H polymorphic site in DNA-damage repair and breast cancer. Hum Mol Genet 11: 1433-1438.
6. Griffin CS (2002) Aneuploidy, centrosome activity and chromosome instability in cells deficient in homologous recombination repair. Mutat Res 504: 149-155.
7. Nagasawa H, Wilson PF, Chen DJ, Thompson LH, Bedford JS, Little JB (2008) Low doses of alpha particles do not induce sister chromatid exchanges in bystander Chinese hamster cells defective in homologous recombination. DNA Repair (Amst) 7: 515-522. doi: 10.1016/j.dnarep.2007.11.014.
8. Araujo FD, Pierce AJ, Stark JM, Jasin M (2002) Variant XRCC3 implicated in cancer is functional in homology-directed repair of double-strand breaks. Oncogene 21: 4176-4180.
9. Matullo G, Guarrera S, Carturan S, Peluso M, Malaveille C, Davico L, Piazza A, Vineis P (2001). DNA repair gene polymorphisms, bulky DNA adducts in white blood cells and bladder cancer in a case–control study. Int J Cancer 92: 562-567.
10. Au WW, Salama SA, Sierra-Torres CH (2003) Functional characterization of polymorphisms in DNA repair genes using cytogenetic challenge assays. Environ Health Perspect. 111: 1843-1850.
11. Kong B, Lv, ZD, Chen L, Shen RW, Jin LY, Yang ZC (2015) Lack of an association between XRCC2 R188H polymorphisms and breast cancer: an update meta-analysis involving 35,422 subjects. Int J Clin Exp Med 8: 15808-15814.
12. Chai F, Liang Y, Chen L, Zhang F, Jiang J (2015) Association between XRCC3 Thr241Met Polymorphism and Risk of Breast Cancer: Meta-Analysis of 23 Case-Control Studies. Med Sci Monit 21: 3231-3240.
13. Yu KD, Chen AX, Qiu LX, Fan L, Yang C, Shao ZM (2010) XRCC2 Arg188His polymorphism is not directly associated with breast cancer risk: evidence from 37,369 subjects. Breast Cancer Res Treat 123: 219-225 doi: 10.1007/s10549-010-0753-y.
14. Kuschel B, Auranen A, McBride S, Novik KL, Antoniou A, Lipscombe JM, Day NE, Easton DF, Ponder BA, Pharoah PD, Dunning A (2002) Variants in DNA double-strand break repair genes and breast cancer susceptibility. Hum Mol Genet 11: 1399-1407.
15. Matullo G, Palli D, Peluso M, Guarrera S, Carturan S, Celentano E, Krogh V, Munnia A, Tumino R, Polidoro S, Piazza A, Vineis P (2001) XRCC1, XRCC3, XPD gene polymorphisms, smoking and (32)P-DNA adducts in a sample of healthy subjects. Carcinogenesis 22: 1437-1445.
16. Economopoulos KP, Sergentanis TN (2010) XRCC3 Thr241Met polymorphism and breast cancer risk: a meta-analysis. Breast Cancer Res Treat 121: 439-443. doi: 10.1007/s10549-009-0562-3
17. Pooley KA, Baynes C, Driver KE, Tyrer J, Azzato EM, Pharoah PD, Easton DF, Ponder BA, Dunning AM (2008) Common single-nucleotide polymorphisms in DNA double-strand break repair genes and breast cancer risk. Cancer Epidemiol Biomarkers Prev 17: 3482-3489. doi: 10.1158/1055-9965
18. Lee KM, Choi JY, Kang C, Kang CP, Park SK, Cho H, Cho DY, Yoo KY, Noh DY, Ahn SH, Park CG, Wei Q, Kang D (2005) Genetic polymorphisms of selected DNA repair genes, estrogen and progesterone receptor status, and breast cancer risk. Clin Cancer Res 11: 4620-4626. doi: 10.1158/1078-0432.CCR-04-2534
19. Romanowicz-Makowska H, Smolarz B, Zadrozny M, Westfa B, Baszczyski J, Kokoaszwili G, Burzyfiski M, Poa I, Sporny S (2012) The association between polymorphisms of the RAD51-G135C, XRCC2-Arg188His and XRCC3-Thr241Met genes and clinico-pathologic features in breast cancer in Poland. Eur J Gynaecol Oncol 33: 145-150.
20. Smolarz B, Makowska M, Samulak D, Michalska MM, Mojs E, Wilczak M, Romanowicz H (2015) Association between single nucleotide polymorphisms (SNPs) of XRCC2 and XRCC3 homologous recombination repair genes and triple-negative breast cancer in Polish women. Clin Exp Med 15: 151-157. doi: 10.1007/s10238-014-0284-7
21. Sobczuk A, Romanowicz-Makowska H, Fiks T, Baszczyski J, Smolarz B (2009) XRCC1 and XRCC3 DNA repair gene polymorphisms in breast cancer women from the Lodz region of Poland. Pol J Pathol 60: 76-80.
22. Krupa R, Synowiec E, Pawlowska E, Morawiec Z, Sobczuk A, Zadrozny M, Wozniak K, Blasiak J (2009) Polymorphism of the homologous recombination repair genes RAD51 and XRCC3 in breast cancer. Exp Mol Pathol 87: 32-35. doi: 10.1016/j.yexmp.2009.04.005
23. Romanowicz-Makowska H, Smolarz B, Zadrozny M, Westfal B, Baszczynski J, Polac I, Sporny S (2011) Single nucleotide polymorphisms in the homologous recombination repair genes and breast cancer risk in Polish women. Tohoku J Exp Med 224: 201-208. doi.org/10.1620/tjem.224.201