Genetics polymorphism in DNA repair genes by base excision repair pathway (XRCC1) and homologous recombination (XRCC2 and RAD51) and the risk of breast carcinoma in the Polish population

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Background: Several polymorphisms in the DNA repair gene have been extensively studied in the association with various human cancers such as breast cancer.
Material and methods: We investigated the association of polymorphisms in the DNA repair genes *XRCC1*-Arg399Gln, *XRCC2*-Arg188His and *RAD51*-135G/C with the breast cancer risk. Genotypes were determined by PCR-RFLP assays in 220 patients with breast cancer and 220 age-matched healthy controls.
Results: Our results demonstrated a significant positive association between the *XRCC1* 399Gln/Gln homozygous genotype and breast carcinoma, with an adjusted odds ratio (OR) of 2.08 [1.08-3.98]. The 399Gln allele variant was also associated with type I breast cancer (OR = 1.41 [0.98-2.01], p = 0.034). The distributions of genotypes and alleles of the genes *XRCC2* and *RAD51* polymorphism were not significantly associated with the different stages of breast carcinoma ($p > 0.05$).
Conclusion: These results suggest that 399Gln allele of XRCC1 Arg399Gln may be a risk factor for breast cancer in the Polish population.

Key words: XRCC1, *XRCC2*, RAD51, breast cancer, gene polymorphism.

Introduction

Breast cancer is a genetically heterogeneous disease and kills more women in the world than any cancer [1].

For repair of DNA damage, human cells are supported by five DNA repair systems: direct reversal, mismatch repair, double-strand break repair (homologous recombination [HR] and nonhomologous end joining [NHEJ]), base excision repair (BER), and nucleotide excision repair (NER) [2].

Nearly all oxidatively induced DNA lesions, as well as single-strand breaks, are repaired via the BER pathway in organisms ranging from Escherichia coli to mammals [3, 4].

The human oxoguanine glycosylase 1 (*hOGG1*), APE1 and X-ray repair cross-complementing 1 (*XRCC1*) genes are key genes in the BER pathway [2].

XRCC1 is a multidomain protein that repairs single-strand breaks in DNA [5]. Two major single nucleotide polymorphisms (SNPs) of the *XRCC1* gene have been identified at codon 194 (C → T substitution at position 26304, exon 6, Arg to Trp) and 399 (G → A substitution at position 28152, exon 10, Arg to Gln). There were some reports about the relation between *XRCC1* polymorphisms and risk for several cancers: breast, prostate, laryngeal and bladder cancer [6-14].

RAD51 plays a central role in homologous recombination, through direct interaction with XRCC2, XRCC3, BRCA1, BRCA2, etc., to form a complex essential for the repair of double-strand breaks and DNA cross-links (especially XRCC2 and XRCC3) and for the maintenance of chromosome stability [15]. An SNP, a G to C substitution at position 135 (5'-untranslated region), of the *RAD51* gene has

been found. This SNP is located in the regulatory element of the *RAD51* promoter and is suggested to be associated with messenger RNA expression. A study of women matched for *BRCA1* mutation revealed that the C allele of this SNP is associated with a 2-fold lower breast and ovarian cancer risk than the G allele [16]. However, this finding is inconsistent with the results of several previous studies reporting a significant association of the C allele with an increased risk [17-19].

XRCC2 gene, located on 7q36.1, is an essential part of the homologous recombination repair pathway and a functional candidate for involvement in tumour progression [20]. Common variants within *XRCC2*, particularly a coding single nucleotide polymorphism (SNP) in exon 3 [Arg188His (R188H)], have been identified as potential cancer susceptibility loci in recent studies, although association results are mixed. The *XRCC2* R188H polymorphism has been proposed to be a genetic modifier for smoking-related pancreatic cancer and was associated with an increased risk of pharyngeal cancer and oral cancer risk [21-23]. 188His allele of *XRCC2* may be associated with a significantly increased risk of breast cancer, but not with bladder cancer, colorectal adenoma, and skin cancer [24-27].

In present work the effects of *XRCC1* Arg399Gln, *XRCC2* Arg188His and *RAD51* G135C polymorphism on the breast cancer risk in the Polish population was investigated.

Materials and methods

Patients

Peripheral blood lymphocytes (PBLs) were obtained from 220 postmenopausal women with node-negative (n = 130) and node-positive (n = 90) ductal breast carcinoma aged from 42 to 82 years (median age 58 years) treated at the Department of Oncology, Institute of Polish Mother's Memorial Hospital and 220 cancer-free sex- and age-matched controls. No distant metastases were found in patients at the time of treatment. The average tumour size was 20 mm (range 17-32 mm). All tumours were categorized into groups according to the cancer staging system of the Scarf-Bloom-Richardson criteria. 105 cases were stage I, 110 cases were stage II and 5 cases were stage III. DNA was extracted using commercially available QIAmp Kit (Qiagen GmbH, Hilden, Germany) DNA purification kit according to the manufacturer's instructions.

Determination of the *XRCC1* genotype

Genotypic analyses of the *XRCC1* gene were carried out by multiplex PCR-RFLP, using primers for codons 399 (5'-TTGTGCTTTCTCTGTGTCCA-3' and 5'-TCCTCCAGCCTTTTCTGATA-3') and 194 (5'-GCCCCGTCCCAGGTA-3' and 5'-AGCCC-CAAGACCCTTTCACT-3'), which generate a fragment of 615 and 491 bp. Briefly, PCR was performed in 25 µl reaction buffer containing 12.5 pmol each primer, 0.2 mmol/l of dNTPs, 3 mmol/l of $MgCl_2$, about 100 ng DNA and 1 U of Taq DNA polymerase. The PCR products were digested overnight with 10 U of *Msp*I at 37°C.

The wild-type Arg allele for codon 194 is identified by the presence of a 293 bp band, and the mutant Trp allele by the presence of a 313 bp band (indicative of the absence of the *Msp*I cutting site). For codon 399, the presence of two bands of 375 and 240 bp, respectively, identifies the wild-type Arg allele, while the uncut 615 bp band identifies the mutant Gln allele (indicative of the absence of the *Msp*I cutting site).

Determination of the *RAD51* genotype

RAD51 genotyping was analyzed by PCR amplification of a 175-bp region around nucleotide 135. This region contained a single *Mva*I site that was abolished in the *135C* allele. Wild type alleles were digested by MvaI resulting in 86- and 71-bp product. The *135C* allele was not digested by the enzyme, resulting in a single 157-bp product. The *RAD51* genotype was analysed using the specific primers forward 5' TGG GAA CTG CAA CTC ATC TGG 3' and reverse 5' GCG CTC CTC TCT CCA GCAG 3'.

The PCR was carried out in a GeneAmp PCR system 9700 (Applied Biosystems) thermal cycler. PCR amplification was performed in a final volume of 25 µl. The reaction mixture contained 5 ng genomic DNA, 0.2 µmol of each appropriate primer (ARK Scientific GmbH Biosystems, Darmstad, Germany), 2.5 mM $MgCl_2$, 1 mM dNTPs and 1 unit of Taq Polymerase (Qiagen GmbH, Hilden, Germany). The PCR cycle conditions were 94°C for 60 s, 54°C for 30 s, then 72°C for 40 s, repeated for 35 cycles. After digestion with MvaI for 4 h at 37°C samples were run on 7% polyacrylamide gel and visualised by ethidium bromide staining. Each subject was classified into one of three possible genotypes: G/G, G/C or C/C.

Determination of the *XRCC2* genotype

Polymorphism of the *XRCC2* gene was determined by PCR-RFLP, using primers: forward 5'TGTAGT-CACCCATCTCTCTGC3' and reverse: 5'AGTTGCT-GCCATGCCTTACA3'. The 25 µl PCR mixture contained about 100 ng of DNA, 12.5 pmol of each primer, 0.2 mmol/l of dNTPs, 2 mmol/l of MgCl2 and 1 U of Taq DNA polymerase. The 290 bp amplified

product was digested overnight with 1 U of HpnI at 37°C. The wild-type Arg allele was identified by the presence of two 290 bp bands, while the mutant His allele was represented by 148, and 142 bp bands.

Statistical analysis

For each polymorphism, deviation of the genotype frequencies in the controls from those expected under Hardy-Weinberg equilibrium was assessed using the standard χ^2-test. Genotype frequencies in cases and controls were compared by χ^2-tests. The genotypic-specific risks were estimated as odds ratios (ORs) with associated 95% intervals (CIs) by unconditional logistic regression. P-values < 0.05 were considered to be significant.

Results

XRCC1, *XRCC2* and gene polymorphism in breast carcinoma specimens

220 breast cancer patients and 220 controls were included in this study. Table 1, 2 and 3 summarise the distributions of genotypes and alleles of *XRCC1*, *XRCC2* and *RAD51* genes in patients with breast cancer and controls. The distributions of the genotypes and alleles of the study groups were in Hardy-Weinberg equilibrium. We did not find any significant differences for *XRCC2* and *RAD51* genotype frequencies in patients with cancer and controls (Table I, II). Additionally, there were no differences in the frequencies of alleles between both distributions ($p > 0.05$).

The distribution of *XRCC1* 399Gln/Gln genotype frequencies in patients was significantly different from that of controls ($p < 0.05$). The 399Gln/Gln homozygous genotype was significantly associated with an increased risk of breast carcinoma ($p = 0.025$) with an odds ratio of 2.08 (95% confidence interval 1.08 to 3.98) (Table III).

In order to evaluate whether DNA repair gene polymorphisms were associated with the progression of breast cancer or not, participants were categorized into groups according to the cancer staging system of the Scarf-Bloom-Richardson criteria.

Among the 220 breast carcinoma patients, the histological stage was evaluated in all cases. 105 cases were stage I, 110 cases were stage II and 5 cases were stage III. Stages II and III were grouped together for the purposes of statistical analysis (Table IV).

Only variant 399Gln allele of *XRCC1* increased cancer risk in type I breast cancer. There was a 1.41-fold increased risk of breast carcinoma for individuals carrying *XRCC1*399Gln allele, compared with subjects carrying *XRCC1*399Arg allele, respectively [OR = 1.41; 95% CI (0.98-2.01)].

Table I. Distribution of *XRCC2* genotype frequencies in patients with breast cancer and control groups

	BREAST CANCER PATIENTS N = 220		CONTROLS N = 220			
XRCC2-ARG188HIS	NUMBER	(%)	NUMBER	(%)	OR (95% PU)[A]	P[B]
Arg/Arg	197	89.5	207	94.1	0.95 (0.64-1.40)	0.806
Arg/His	22	8.7	13	5.9	1.69 (0.81-3.53)	0.158
His/His	1	0.4	0	0	–	–
Arg	416	94.5	427	97	0.97 (0.77-1.23)	0.823
His	24	5.5	13	3	1.84 (0.92-3.71)	0.082

[a]Crude odds ratio (OR), 95% CI = confidence interval at 95%, [b]χ^2

Table II. Distribution of *RAD51* genotype frequencies in patients with breast cancer and control groups

	BREAST CANCER PATIENTS N = 220		CONTROLS N = 220			
RAD51-135G/C	NUMBER	(%)	NUMBER	(%)	OR (95% PU)[A]	P[B]
G/G	141	64.1	157	71.3	0.89 (0.59-1.34)	0.603
G/C	69	31.4	58	26.4	1.18 (0.76-1.84)	0.438
C/C	10	4.5	5	2.3	2.00 (0.62-6.35)	0.233
G	351	79.8	372	84.5	0.94 (0.74-1.19)	0.631
C	89	20.2	68	15.5	1.31 (0.91-1.88)	0.150

[a]Crude odds ratio (OR), 95% CI = confidence interval at 95%, [b]χ^2

Table III. Distribution of *XRCC1* genotype frequencies in patients with breast cancer and control groups

	BREAST CANCER PATIENTS N = 220		CONTROLS N = 220			
XRCC1-ARG399GLN	NUMBER	(%)	NUMBER	(%)	OR (95% PU)[A]	P[B]
Arg/Arg	70	31.8	94	42.7	0.84 (0.47-1.87)	0.205
Arg/Gln	100	45.5	102	46.4	0.98 (0.66-1.43)	0.920
Gln/Gln	50	22.7	24	10.9	**2.08 (1.08-3.98)**	**0.025**
Arg	240	54.5	290	65.9	0.82 (0.64-1.06)	0.142
Gln	200	45.5	150	34.1	1.33 (1.01-1.76)	0.050

Data in boldface are statistically significant
[a]Crude odds ratio (OR), 95% CI = confidence interval at 95%, [b]χ^2

Table IV. Dependency of the distribution of *XRCC1*, *XRCC2* and *RAD51* genotype frequencies on the tumour stage in patients with breast cancer

POLYMORPHISM	STAGE I (%) (N =105)	STAGE II + III (%) (N =115)	OR (95% PU)[A]	P[B]
XRCC1-Arg399Gln				
Arg/Arg	24 (22.9)	56 (48.7)	0.48 (0.24-0.94)	0.051
Arg/Gln	55 (52.4)	45 (39.1)	1.34 (0.77-2.3)	0.292
Gln/Gln	26 (24.8)	14 (12.2)	2.04 (0.84-4.90)	0.113
Arg	107 (50.9)	157 (68.2)	0.68 (0.49-0.93)	0.070
Gln	103 (49.1)	73 (31.8)	1.41 (0.98-2.01)	0.034
XRCC2-Arg188His				
Arg/Arg	94 (89.5)	103 (89.6)	1.02 (0.59-1.78)	0.920
Arg/His	10 (9.5)	12 (10.4)	0.95 (0.36-2.29)	0.841
His/His	1 (0.95)	0	–	–
Arg	198 (94.3)	218 (94.8)	0.90 (0.69-1.19)	0.480
His	12 (5.7)	12 (5.2)	1 (0.43-2.27)	1.000
RAD51-135G/C				
G/G	66 (62.8)	75 (65.2)	0.99 (0.55-1.76)	1.000
G/C	33 (31.4)	36 (31.3)	1.01 (0.54-1.84)	1.000
C/C	6 (5.7)	4 (3.5)	1.65 (0.41-6.71)	0.479
G	165 (78.6)	186 (80.9)	0.88 (0.66-1.18)	0.400
C	45 (21.4)	44 (19.1)	1.02 (0.64-1.16)	0.920

Data in boldface are statistically significant
[a]Crude odds ratio (OR), 95% CI = confidence interval at 95%, [a]χ^2

There were no significant differences between distributions of *XRCC2* and *RAD51* genotypes in subgroups assigned to histological stages ($p > 0.05$) (Table IV).

Discussion

Several studies have reported that the genes involved in DNA repair and in the maintenance of genome integrity play a crucial role in protecting against mutations that lead to cancer [28]. SNPs (single nucleotide polymorphisms) have been identified in several DNA repair genes, such as *XRCC1*, *XRCC2* and *RAD51*, but the influence of specific genetic variants on repair phenotype and cancer risk has not yet been clarified.

The polymorphisms chosen for this study have been shown to have functional significance and may be responsible for a low DNA repair capacity phenotype characteristic of cancer patients including breast carcinoma.

In the present study, we determined whether SNPs in the DNA repair pathway (*XRCC1*-Arg399Gln, *XRCC2*-Arg188His, *RAD51*-135G/C) are associated with the risk of breast cancer. In this work Arg399Gln polymorphism of *XRCC1* was

associated with the risk of this cancer. The variant 399Gln/Gln genotype of *XRCC1* increased the risk of breast cancer in the investigated Polish population.

It is known that *XRCC1*-Arg399Gln gene polymorphism has been studied as a risk factor for various cancers. The variant 399Gln allele has been linked to an increased risk of lung cancer [29, 30], head and neck cancer [31] and possibly stomach cancer [32].

On the other hand, this allele was reported to be associated with a reduced risk of bladder cancer [33], esophageal cancer [34] and non-melanoma skin cancer [35]. The amino acid replacement of *XRCC1*-399Arg to Gln might lead to an increased risk of laryngeal carcinoma [13].

In relation to breast cancer, Duell *et al.* [36] reported a positive association between breast cancer and *XRCC1* codon 399 Arg/Gln or Gln/Gln genotypes compared with Arg/Arg among African Americans but not in white American women.

Shu *et al.* showed that the *XRCC1*-Arg399Gln gene polymorphism alone did not appear to play a substantial role in the risk of breast cancer among Chinese women [37].

Smith *et al.* found no association between the *XRCC1*-399 Gln/Gln genotype and breast cancer [38]. However, other studies showed an increased risk of breast cancer with this polymorphism [39-41].

It was also shown that the 399Gln homozygote genotype was significantly associated with increased levels of bulky-DNA adducts in leucocytes of non-smokers [42].

Our study demonstrated the positive association between the Arg399Gln polymorphism of *XRCC1* gene and breast carcinoma. The 399Gln allele increased the risk of breast cancer in the Polish population.

This is in line with the reports indicating that the amino acid replacement of *XRCC1*-399Arg to Gln might lead to an increased risk of breast carcinoma.

In our study we did not find any association between *XRCC2* gene Arg188His and *RAD51* 135G/C polymorphisms and breast carcinoma occurrence.

In the literature many researchers investigated an association of polymorphism and breast carcinoma.

Jakubowska *et al.* suggested that may be a genetic modifier of breast cancer risk in *BRCA1* carriers in the Polish population [43].

Kadouri *et al.* showed that in non-carrier breast cancer cases, bearing *RAD51*-G135C was not associated with breast cancer risk, but they suggested that the risk may be significantly elevated in carriers of BRCA2 mutations who also carry a *RAD51*-135C allele [44].

Błasiak *et al.* suggested that the G/C polymorphism of the *RAD51* gene may not be directly involved in the development and/or progression of breast cancer in the Polish population; therefore, it may not be useful as an independent marker of this disease [45].

Our results confirm the lack of association between *RAD51* G135C SNP and breast cancer risk in Poland.

Additionally, in our study no associations with the risk for breast cancer were found for the other variants of SNPs in *XRCC2* gene of the DNA DSB repair pathways included in this analysis. In the literature database only Raffi *et al.* suggested that *XRCC2 Arg188His* polymorphism was associated with breast cancer [46].

We also express our opinion in discussions on the significance Arg399Gln polymorphism in determination of tumour's aggressive potential in breast cancer. In the literature many researchers confirm the important role *XRCC1*-Arg399Gln in the development of cancer [29-37]. Our results show that the polymorphism Arg399Gln of *XRCC1* gene may be associated with the occurrence of breast cancer in Poland. Further investigations of the combined effects of polymorphisms within these DNA repair genes and other risk factors may help to clarify the influence of genetic variation in the carcinogenic process.

Taken together our findings contribute to a better current understanding of the pathogenesis of breast carcinoma and the function of SNP DNA repair gene polymorphism in this type of neoplasm.

These findings could be helpful for clinicians in the assessment and counselling of patients affected by these cancers or for scientists to consider new potential therapeutic agents for the treatment of these tumours.

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