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ORIGINAL PAPER

An association between the −41657 C/T polymorphism of X-ray repair cross-complementing 2 (*XRCC2*) gene and ovarian cancer

Magdalena M. Michalska · Dariusz Samulak · Beata Smolarz

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Abstract X-ray repair cross-complementing group 2 (*XRCC2*) gene is important for the repair of double-strand DNA breaks (DSB) by homologous recombination (HR). *XRCC2* polymorphisms may be associated with the development of certain types of cancers, but little is known about their association with ovarian carcinoma. *XRCC2* −41657C/T (rs718282) polymorphisms were genotyped by the PCR–RFLP (restriction fragment length polymorphism) method in 608 patients with ovarian cancer and in 400 cancer-free women, who served as controls. In the present work, a relationship was identified between *XRCC2* −41657C/T polymorphism and the incidence of ovarian cancer. An association was observed between ovarian carcinoma occurrence and the presence of T/T genotype [OR = 3.50 (2.46–4.97), $p < 0.0001$]. A tendency for an increased risk of ovarian cancer was detected with the occurrence of T allele of *XRCC2* polymorphism. There were no significant differences between the distribution of *XRCC2* −41657C/T genotypes in the subgroups assigned to histological grades. We suggest that the −41657C/T polymorphism of the *XRCC2* gene may be risk factors for ovarian cancer development.

M. M. Michalska · D. Samulak
Department of Obstetrics and Gynaecology, Regional Hospital in Kalisz, Kalisz, Poland

D. Samulak
Cathedral of Mother's and Child's Health, Poznan University of Medical Sciences, Poznań, Poland

B. Smolarz (✉)
Laboratory of Molecular Genetics, Department of Pathology, Institute of Polish Mother's Memorial Hospital, Rzgowska 281/289, 93-338 Lodz, Poland
e-mail: smolbea@wp.pl

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Introduction

The ovarian cancer is diagnosed in Poland in more than three thousand women a year, out of whom, two-thirds die during five subsequent years [1, 2]. For the time being, there are no reliable diagnostic methods, allowing for an early identification of this neoplasm. The ovarian cancer is diagnosed late, in advanced stages of the disease, as the first, non-characteristic symptoms are ignored by patients. Despite the growing knowledge on the ovarian cancer, no effective screening test has yet been designed. It is then necessary to identify new risk factors.

In the recent years, there has been a considerable progress in the understanding of DNA repair mechanisms. Our knowledge of these processes, their control and various factors which affect their performance and effectiveness may, in future, provide more effective prophylactics against a number of diseases, associated with insufficient or incomplete repair of DNA defects, leading, in consequence, to mutations, genomic instability and neoplastic diseases.

Out of all the DNA damages, double-strand breaks (DSB) are especially dangerous for the cell. Because of the multiplicity of DSB-causing exo- and endogenous factors, the effectiveness of their repair is of key significance for proper cell functionality, preventing DNA fragmentation and the translocation and deletion of chromosomes [3]. The DSB repair system functions via two mechanisms: homologous recombination (HR) and non-homologous DNA end joining (NHEJ) [3, 4].

Mutations in DNA of double-strand breaks repair genes are involved in the pathogenesis of cancers; however, it is

still unclear whether any defects in this pathway may play any role in the aetiology of ovarian cancer.

XRCC2 (X-ray repair cross-complementing group 2) with RAD51 (RecA homolog, *E. coli*; *S. cerevisiae*), XRCC3 (X-ray repair cross-complementing group 3), BRCA1 (breast cancer-1), BRCA2 (breast cancer-2) and other DNA repair proteins are involved in the homologous recombination and repair of double-strand breaks in DNA and DNA cross-links, as well as in the maintenance of chromosome stability [3].

XRCC2 gene, located in 7q36.1, is an essential part of the homologous recombination repair pathway and a functional candidate for involvement in cancer progression [5].

It is known that polymorphisms in *XRCC2* may modify individual susceptibility to various cancer diseases [6–13].

There are also some reports of associated *XRCC2* gene variants, particularly a coding single-nucleotide polymorphism (SNP) in exon 3 (Arg188His, R188H, rs3218536), and the development of ovarian cancer [14–16].

Indeed, recently, several studies have shown that the *XRCC2* −41657C/T genotype was related to increased esophageal squamous cell carcinoma (ESCC), gastric cardia adenocarcinoma (GCA) and in smoking-/drinking-related laryngeal cancer risk [11, 17].

Unfortunately, it is difficult to find in the literature reports directly binding −41657C/T (rs718282) single-nucleotide polymorphism in DNA repair gene *XRCC2* with ovarian cancer occurrence. These data stimulated us to search for an association between ovarian cancer development and the −41657C/T (rs718282) polymorphisms in *XRCC2* gene.

Materials and methods

Patients

Six hundred and eight patients with histologically proven diagnosis of ovarian cancer were included in the reported study (Table 1). Paraffin-embedded tumour tissues were obtained from women with ovarian carcinoma (age range 37–84, mean age 52.23 ± 11.12) treated at Department of Menopausal Diseases, Institute of Polish Mother's Memorial Hospital (Lodz, Poland), between 2000 and 2014. All the diagnosed tumours were graded according to the criteria of the International Federation of Gynaecology and Obstetrics (FIGO) [18]. DNA from normal ovarian tissue obtained from non-cancer women ($n = 400$) served as control. They were non-related women who have never been diagnosed with ovarian tumours, other tumours or chronic disease and were randomly selected and frequency matched to the cases on age (age range 34–83, mean age 51.27 ± 11.18). Informed consent was obtained from patients and controls, and the Ethical Committee approved the study.

Table 1 Characteristic of ovarian cancer patients ($n = 608$)

Characteristics	Number of cases (%)
Histology of tumour	
Serous	206 (34)
Mucinous	18 (3)
Endometrioid	189 (31)
Clear cell	21 (4)
Undifferentiated	159 (26)
Other	15 (2)
Number of pregnancy	
1	240 (39)
2–3	268 (44)
>4	100 (16)
Staging	
I	240 (39)
II	362 (60)
III	6 (1)
Grading	
G1	332 (55)
G2	256 (42)
G3	20 (3)
Ascites	
Present	285 (47)
Absent	323 (53)
Size of tumour	
>5 cm	231 (38)
<5 cm	377 (62)
Menarche	
<12 years old	240 (39)
>12 years old	368 (61)
Tumour wall infiltration/injury	
Present	298 (49)
Absent	310 (51)

The ovarian tissue samples (cancerous and non-cancerous) were fixed routinely in formaldehyde, embedded in paraffin, cut into thin slices and stained with hematoxyline/eosin for pathological examination. DNA for analysis was obtained from archival pathological paraffin-embedded tumour and healthy ovarian samples which were deparaffinised in xylene and rehydratated in ethanol and distilled water. The pathological evaluation report was obtained for each patient (Department of Pathology, Institute of Polish Mother's Memorial Hospital, Lodz, Poland). Genomic DNA was prepared from the material, using a commercially available QIAmp DNA purification kit (Qiagen GmbH, Hilden, Germany), according to the manufacturer's instruction.

Genotype determination

The PCR- restriction fragment length polymorphism method (PCR–RFLP) was used to detect the genotypes of the −41657C/T polymorphism as described previously [17].

Polymorphism −41657C/T of the *XRCC2* gene was determined by PCR–RFLP, using primers (forward 5′-GGAGGCCGCAATGAGCTGAGATG-3′ and reverse 5′-TCGGGAAGCTGAGGTGGGAGGA-3′). The PCR was carried out in a PTC-100 TM (MJ Research, INC, Waltham, MA, USA) thermal cycler. PCR amplification was performed in the final volume of 25 µl of reaction mixture, which contained 100 ng of genomic DNA, 0.2 µmol of each primer (ARK Scientific GmbH Biosystems, Darmstadt, Germany), 2.5 mM of $MgCl_2$, 1 mM of dNTPs and 1 unit of Taq Polymerase (Qiagen GmbH, Hilden, Germany). PCR cycle conditions were the following: 95 °C for 45 s, 72 °C for 45 s and 72 °C for 60 s, repeated in 35 cycles. PCR products were electrophoresed in a 2 % agarose gel and visualised by ethidium bromide staining. The cleavage with *Mva*I (New England BioLabs, Frankfurt am Main, Germany) produced fragments of 315/59/42, 357/315/59/42 and 357/59 bp corresponding to the C/C, C/T and T/T genotypes of the *XRCC2* gene, respectively.

Statistical analysis

For each polymorphism, departure of the genotype distribution from that expected from Hardy–Weinberg equilibrium was assessed using the standard χ^2 test. Genotype frequencies in the study cases and the controls were compared by χ^2 test. Genotype specific risks were estimated as odds ratios (ORs) with associated 95 % intervals (CIs) by unconditional logistic regression. p values <0.05 were considered significant. All the statistical analyses were performed, using the STATISTICA 6.0 software (Statsoft, Tulsa, OK, USA).

Results

All the recruited samples both ovarian cancer ($n = 608$) and control samples ($n = 400$) were successfully genotyped for *XRCC2* polymorphisms. Table 2 shows genotype distribution −41657C/T *XRCC2* polymorphism between endometrial cancer patients and controls. It can be seen from the table that there are significant differences ($p < 0.05$) between the two investigated groups. A weak association was observed between ovarian carcinoma occurrence and the presence of T/T and C/T genotypes. A stronger association was observed for T/T than for C/T heterozygous variant. Variant T allele of *XRCC2* increased cancer risk ($p < 0.05$). The distribution of the genotypes in the patients differed significantly from one expected from the Hardy–Weinberg equilibrium ($p < 0.05$).

Because we were interested in the association between the distribution of genotypes and frequencies of alleles of investigated genetic variability on the tumour grade evaluated according to FIGO criteria, these data were also analyzed.

Histological grading was evaluated in all the cases ($n = 608$): grade 1 (G1)—332 cases, grade 2 (G2)—256 cases and grade 3 (G3)—20 cases. G2 and G3 were accounted together for statistical analysis (see Table 3). We did not find any association of the *XRCC2* polymorphisms in the patients group with cancer progression assessed by ovarian cancer grading ($p > 0.05$).

Clinical FIGO staging was also related to *XRCC2* polymorphisms (Table 4). Staging was evaluated in all the cases ($n = 608$). We did not find any association of the *XRCC2* polymorphisms in the patients group with cancer progression assessed by ovarian cancer staging ($p > 0.05$).

Our data did not demonstrate any statistically significant correlation between *XRCC2* −41657C/T polymorphism and the risk factors for ovarian cancer, such as number of pregnancy, size of tumour, age, menarche, ascites, tumour wall infiltration and women with ovarian cancer, here again erase the remark "(data not shown)".

Discussion

DNA changes, imposed by damaging factors and replication errors, may bring about serious consequences for the cell. Its survival is then determined by the availability of DNA repair systems, eliminating damages and reducing the frequency of DNA mutations. The systems present with high substrate specificity and specialisation. Changes in the encoding genes may lead to an increased general incidence of mutations, development of neoplasms and other serious conditions, including hereditary diseases.

In the process of neoplastic transformation, beside mutations in protooncogenes and suppressor genes, genetic polymorphisms may also play an important role, including the single-nucleotide polymorphisms (SNPs). Our research addressed the role of single-nucleotide polymorphism −41657C/T of DNA repair gene *XRCC2* as a risk factor for ovarian cancer.

Homologous recombination repair plays a critical role in repairing DNA damage [4, 19]. The cellular reaction to DNA damaging agents can modulate the susceptibility towards tumour development [20]. This reaction is mainly determined by the efficacy of DNA repair, which may, in turn, be influenced by the variability of DNA repair genes, expressed by their polymorphisms [21–24].

Table 2 The allele and genotype frequency and odds ratio (OR) of −41657C/T polymorphism of the *XRCC2* gene in ovarian cancer ($n = 608$) and controls ($n = 400$)

XRCC2 -41657C/T	Ovarian cancer patients		Controls		OR (95 % CI)[a]	p[b]
	Number	(%)	Number	(%)		
C/C	96	16	96	24	1.00 Ref.	
C/T	120	20	192	48	**0.62 (0.43-0.89)**	**0.014**
T/T	392	64	112	28	**3.50 (2.46-4.97)**	**<0.0001**
C	312	26	384	48	1.00 Ref.	
T	904	74	416	52	**2.67 (2.21-3.23)**	**<0.0001**

Data in boldface are statistically significant

[a] Crude odds ratio (OR), 95 % CI = confidence interval at 95 %, [b] Chi square

Table 3 Dependence of genotypes and frequencies of *XRCC2* gene polymorphism alleles on tumour grade in ovarian cancer patients[a]

Grade *XRCC2* -41657C/T	G1 ($n = 332$) Number (%)	G2 + G3 ($n = 276$) Number (%)	OR (95 % CI)[b]	p[c] OR (95 % CI)
C/C	52 (16 %)	44 (29 %)	1.00 Ref.	
C/T	52 (16 %)	68 (26 %)	0.64 (0.37–1.11)	0.148
T/T	228 (68 %)	164 (44 %)	1.17 (0.75–1.84)	0.554
C	156 (23 %)	156 (43 %)	1.00 Ref.	
T	508 (77 %)	396 (57 %)	1.28 (0.99–1.66)	0.067

[a] $n = 608$; [b] Crude odds ratio (OR), 95 % CI = confidence interval at 95 %, [c] Chi square

Table 4 Dependence of genotypes and frequencies of *XRCC2* gene polymorphism alleles on tumour stage in ovarian cancer patients[a]

Stage *XRCC2* -41657C/T	I ($n = 240$) Number (%)	II + III ($n = 368$) Number (%)	OR (95 % CI)[b]	p[c] OR (95 % CI)
C/C	40 (17 %)	56 (15 %)	1.00 Ref.	
C/T	60 (25 %)	60 (16 %)	1.40 (0.81–2.40)	0.279
T/T	140 (58 %)	252 (68 %)	0.77 (0.49–1.22)	0.334
C	140 (29 %)	172 (23 %)	1.00 Ref.	
T	340 (71 %)	564 (77 %)	1.28 (0.89–1.84)	0.213

[a] $n = 608$; [b] Crude odds ratio (OR), 95 % CI = confidence interval at 95 %, [c] Chi square

Defects of genes, involved in double-strand breaks repair, often lead to better cancer development [20, 25]. *XRCC2* and *XRCC3* gene are structurally and functionally related to *RAD51*, which plays an important role in the homologous recombination, the process being frequently involved in cancer transformation [5]. *RAD51*, *XRCC2* and *XRCC3* gene are highly polymorphic.

A large number of molecular epidemiologic studies have been performed on various neoplasms, such as cancer of breast, bladder, lung, head and neck and skin, to evaluate the role of *RAD51* polymorphisms [26–30].

Our earlier study of *RAD51* G135C polymorphism in Polish population identified a haplotype associated with ovarian cancer [31, 32]. The *RAD51* 135C allele was associated with a significantly increased risk of ovarian cancer in Poland [31, 32].

The *XRCC2* polymorphisms were found to be correlated with various cancer diseases [7, 14, 16, 33, 34], but little data are available on the association or its lack in ovarian cancer [14–16, 31, 32].

As mentioned in Introduction, *XRCC2* −41657C/T genotype has been associated with an increased risk of esophageal squamous cell carcinoma (ESCC), gastric cardia adenocarcinoma (GCA) and in smoking-/drinking-related laryngeal cancer [11, 15].

The role of *XRCC2* −41657C/T polymorphisms and ovarian cancer development is still unknown. To date, none studies have addressed the association between alterations in this region of the *XRCC2* gene and ovarian cancer. Because a proper functioning of the *XRCC2* gene is important for the genomic stability, its alternations may be associated with higher cancer susceptibility.

Therefore, we analysed the role of −41657C/T genetic variations in the homologous recombination repair gene and for the risk of developing ovarian cancer.

We succeeded to demonstrate—a series of 608 samples from patients with ovarian cancer—that T/T genotype of −41657C/T polymorphism of *XRCC2* gene was associated with an increased risk of ovarian cancer in studied population, almost four times (3.50) higher than in case of the other genotypes, while having no effect on the degree of disease progression, tumour size, number of pregnancy, age or menarche.

It is possible that the presence of T allele remains in some linkage disequilibrium with another, so far unknown, mutation, located outside of the coding region in the *XRCC2* gene, which may be of importance for the *XRCC2* concentration in plasma and more severe cancer development.

In conclusion, the reported study is another evidence for the significance of -41657C/T genotypes in ovarian cancer occurrence. Thus, we conclude that our observations may be an important signal, prompting to appreciate the role of *XRCC2* in ovarian cancer development and likely triggering further studies on this interesting subject.

Conflict of interest The authors declare that there are no conflicts of interest.

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