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Original Article

Association between single nucleotide polymorphism of DNA repair genes and endometrial cancer: a case-control study

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Abstract: *Aim*: The aim of this study was to analyse the frequencies of genotypes and alleles of Single Nucleotide Polymorphisms (SNPs) of six DNA repair genes (*XRCC1*-rs25487, *XPD*-rs13181, *hMSH2*-rs4987188, *XRCC2*-rs3218536, *BRCA1*-rs799917 and *BRCA2*-rs144848 SNPs) and attempt to evaluate the effect this DNA marker on endometrial cancer (EC). *Material and methods*: The patients were recruited to the study at the Department of Operative Gynaecology of the Institute of the Polish Mother's Memorial Hospital in Lodz. The study comprised 510 patients treated for EC. 510 disease-free individuals were used as controls. SNPs were analysed by the high resolutionmelting technique (HRM). *Results*: Statistically significant correlations were identified between four SNPs and endometrial cancer risk: rs25487, rs4987188, rs13181 and rs799917. The alleles *XRCC1*-Gln (OR 2.89; 95% CI 2.39-3.49, P<0.0001), *hMSH2*-Asp (OR 1.65; 95% CI 1.38-1.96, P<0.0001), *XPD*-Gln (OR 3.24; 95% CI 2.69-3.91, P<0.0001) and *BRCA1*-L (OR 1.56; 95% CI 1.31-1.85, P<0.0001) genes were strongly correlated with this malignancy. No relationship was found between the studied polymorphisms of *XRCC2* and *BRCA2* and the incidence of endometrial cancer. There was also not any association between polymorphisms of *XRCC1, hMSH2, XPD, XRCC2, BRCA1, BRCA2*, i.e., the polymorphisms of the analysed repair genes, and the cancer stage progression acc. to FIGO, the body mass index, the number of pregnancies in history, replacement therapy, diabetes mellitus and hypertension. *Conclusions*: The results indicate that rs25487, rs4987188, rs13181, and rs799917 SNPs may be associated with the incidence of endometrial cancer.

Keywords: Single nucleotide polymorphism, DNA repair, endometrial cancer

Introduction

The endometrial cancer (EC) is the 7th in the world and the 4th in Poland in the ranking of malignancy incidence rates in women (after breast, colon, and lung cancer) [1, 2]. The observed imperfections of cancer prophylactics result, among others, from:

- The identification of pathology at the stage of morphological, and not molecular changes,
- Possible technical and diagnostic errors,
- The necessity of frequent repetitions of diagnostic procedures,
- Impossibility of pathology progression prognosis.

At the actual level of medical knowledge, we are capable of dealing with almost any type of cancer, provided it is identified early enough. There are many factors which play a significant role in triggering endometrial cancer formation process, with genetic factors being of major significance. Endometrial cancer is characterised by the occurrence of different genetic changes in various genes [3].

Consequently, it is often not possible to give a straightforward answer to the question, whether these changes are more like causes or more like effects of the disease. If they are perceived as causes, it is justified to study if the genetic variability, observed in many populations and defined as genetic polymorphism, may in any way contribute to induction and/or

Table 1. The characteristic of endometrial cancer patients and controls

	Patients (n=510)	Controls (n=510)
	Mean ± SD	
Age (years)	68.12 ± 10.76	65.10 ± 10.14
	n (%)	
Menarche (years)		
10	112 (21.96)	120 (23.53)
13	132 (25.88)	138 (27.06)
14	125 (24.51)	121 (23.73)
≥ 15	141 (27.65)	131 (25.68)
Number of pregnancies		
0	120 (23.53)	118 (23.14)
1	110 (21.57)	128 (25.10)
2	122 (23.92)	110 (21.57)
≥ 3	158 (30.98)	154 (30.19)
Obesity (BMI ≥ 30 kg/m^2)		
Yes	125 (24.51)	154 (30.20)
No	385 (75.49)	356 (69.80)
Use of hormone replacement therapy (HRT)		
No	242 (40.4)	215 (36.00)
Yes	358 (59.6)	385 (64.00)
Hypertension		
Yes	244 (47.84)	228 (44.71)
No	266 (52.16)	282 (55.29)
Diabetes mellitus		
Yes	214 (41.96)	202 (39.61)
No	296 (58.04)	308 (60.39)
Uterine bleeding		
Yes	265 (51.96)	213 (41.76)
No	245 (48.04)	297 (58.24)
FIGO grade		
G1	170 (33.33)	
G2	230 (45.10)	
G3	110 (21.57)	
FIGO stage		
I	165 (32.35)	
II	231 (45.29)	
III	114 (22.36)	

development of malignant changes, including endometrial cancer.

DNA repair forms a barrier, protecting cells from cancer forming mutations. There are six known systems of DNA repair: pathway of direct reversion of damage, base excision repair (BER), nucleotide-excision repair (NER), mismatch repair (MMR), homologous recombination (HR), and non-homologous DNA end joining (NHEJ) [4-6]. Cancer diseases are driven by a compromised ability of DNA repair. Therefore, a set of alleles of repair protein encoding genes may largely define anindividual abilities for DNA damage repair, as well as the susceptibility to tumor development. It is then significant to learn the polymorphic variants of the genes that are associated with DNA repair, as well as with their degradation in the population. Single nucleotide polymorphisms (SNPs) may change the risk of cancer and may thus be regarded as potential markers of carcinogenesis [7, 8].

Endometrial cancer formation may be associated with exposure of endometrium to exo- and endogenous oestrogens [9]. Oestrogens produce DNA bulky adducts and oxidative base damages which are removed in base excision repair and nucleotide excision repair systems [10, 11]. MMR removes mainly the errors, which occur in the course of DNA replication and erroneous base pairs, formed in result of DNA recombination or either spontaneous or induced deamination, oxygenation, or methylation of nitrogen bases. MMR plays an important role in maintaining genome stability, thus its defects lead to serious diseases, e.g., hereditary nonpolyposis colorectal cancer and other cancer types [4]. Microsatellite instability (MSI) caused by MMR is observed in certain types of cancer, including 20 to 30% of cases of endometrial cancer [12, 13]. These results suggest that MMR gene abnormalities occur frequently in endometrial cancer.

Table 2. The refSNPand conditions for HRM analysis of the examined DNA repair refSNP and genes

Gene	Polymorphism	refSNP	Thermal conditions
XRCC1	Arg399Gln	rs25487	PCR cycling (40 cycles)
			Denaturation 30 s for 95°C
			Annealing 30 s for 58°C
			Extension 30 s for 72°C
			HRM 75-90°C
hMSH2	Gly322Asp	rs4987188	PCR cycling (40 cycles)
			Denaturation 30 s for 94°C
			Annealing 30 s for 56°C
			Extension 30 s for 72°C
			HRM 75-90°C
XPD	Lys751Gln	rs13181	PCR cycling (40 cycles)
			Denaturation 30 s for 95°C
			Annealing 30 s for 56°C
			Extension 30 s for 72°C
			HRM 75-90°C
XRCC2	Arg188His	rs3218536	PCR cycling (40 cycles)
			Denaturation 30 s for 95°C
			Annealing 30 s for 58°C
			Extension 30 s for 72°C
			HRM 75-90°C
BRCA1	P871L	rs799917	PCR cycling (40 cycles)
			Denaturation 30 s for 95°C
			Annealing 30 s for 56°C
			Extension 30 s for 72°C
			HRM 75-90°C
BRCA2	N372H	rs144848	PCR cycling (40 cycles)
			Denaturation 30 s for 95°C
			Annealing 30 s for 58°C
			Extension 30 s for 72°C
			HRM 75-90°C

Repair by recombination enables removal of a number of serious DNA damages, first of all, double strand breaks. These breaks may cause a loss of some chromosomes and induce translocation of genetic material between them. Moreover, they are strong inducers of programmed cell death [4]. SNPs in HR-related genes cause susceptibility to breast, ovarian, and endometrial cancer [14, 15]. In addition, polymorphisms of DNA repair genes may also have an effect on cellular response to radiation therapy in patients with carcinoma [16].

In the present work endometrial cancer patients were analysed for polymorphisms in following genes: BER system (*XRCC1* gene-Arg399Gln, rs25487), NER system (*XPD* gene-Lys751Gln, rs13181), MMR system (*hMSH2* gene-Gly322Asp, rs4987188), repair by homologous recombination (*XRCC2* gene-Arg188His, rs3218536, *BRCA1* gene-P871L, rs799917 and *BRCA2* gene-N372H, rs144848). The aim of this study was to investigate the association between SNPs in six DNA repair genes and the risk of endometrial cancer.

Materials and methods

Endometrial cancer patients

Paraffin embedded tumour tissue-samples were obtainedfrom women with endometrial carcinoma (n= 510) between years 2000-2016. All patients were treated at the Department of Operative Gynaecology, Institute of Polish Mothers Memorial Hospital. All diagnosed tumours were graded by criteria of the International Federation of Gynaecology and Obstetrics (FIGO). Demographic data and pathological features of the cases are both summarized in **Table 1**. 510 individuals treated in the parallel period for uterine fibroids constituted the control group. An appropriate ethical approval was obtained from the Ethics Committee of the Institute of Polish Mother's Memorial Hospital, Lodz, Poland.

DNA isolation

DNA was extracted using theDNeasy Blood & Tissue Kit (Qiagen GmbH, Hilden, Germany) according to the manufacturer's instruction.

Genotype determination

Real-time PCR cycling and conditions for HRM analysis of the examined DNA repair SNPs are summarized in **Table 2**. The High-Resolution Melter analysis was carried out in a Light Cycler® 96 (Roche, Mannheim, Germany) Thermocycler. PCR amplification was performed with support of a Light Cycler® 480 High Resolution Melting Master Kit (Roche, Mannheim, Germany), according to the manufacturer's re-

Table 3. Genotype and allele distributions of SNPs of DNA repair genes in endometrial cancer patients and controls

	Patients (n=510)		Controls (n=510)			
XRCC1	Number	(%)	Number	(%)	OR (95% CI)[a]	*p*[b]
Arg/Arg	75	14.71	152	29.80	1.00 Ref	
Arg/Gln	106	20.78	198	38.82	1.06 (0.75-1.56)	0.729
Gln/Gln	329	64.51	160	31.37	4.16 (2.98-5.82)	<0.0001
Arg	256	25.10	502	49.22	1.00 Ref	
Gln	764	74.90	518	50.78	2.89 (2.39-3.49)	<0.0001
hMSH2	Number	(%)	Number	(%)	OR (95% CI)	*p*
Gly/Gly	80	15.69	118	23.14	1.00 Ref	
Gly/Asp	218	42.75	266	52.16	1.21 (0.86-1.69)	0.306
Asp/Asp	212	41.56	126	24.70	2.48 (1.73-3.56)	<0.0001
Gly	378	37.06	502	49.22	1.00 Ref	
Asp	642	62.94	518	50.78	1.65 (1.38-1.96)	<0.0001
XPD	Number	(%)	Number	(%)	OR (95% CI)	*p*
Lys/Lys	78	15.29	162	31.76	1.00 Ref	
Lys/Gln	102	20.00	210	41.18	1.01 (0.70-1.44)	1.000
Gln/Gln	330	64.71	138	27.06	4.97 (3.55-6.94)	<0.0001
Lys	258	25.29	534	52.35	1.00 Ref	
Gln	762	74.71	486	47.65	3.24 (2.69-3.91)	<0.0001
XRCC2	Number	(%)	Number	(%)	OR (95% CI)	*p*
Arg/Arg	114	22.35	126	24.71	1.00 Ref	
Arg/His	186	36.47	186	36.47	1.11 (0.80-1.53)	0.603
His/His	210	41.18	198	38.82	1.17 (0.85-1.61)	0.371
Arg	414	40.59	438	42.94	1.00 Ref	
His	606	59.41	582	57.06	1.10 (0.92-1.31)	0.301
BRCA1	Number	(%)	Number	(%)	OR (95% CI)	*p*
P/P	87	17.06	120	23.53	1.00 Ref	
P/L	225	44.12	270	52.94	1.14 (0.82-1.59)	0.454
L/L	198	38.82	120	23.53	2.28 (1.59-3.25)	<0.0001
P	399	39.12	510	50.00	1.00 Ref	
L	621	60.88	510	50.00	1.56 (1.31-1.85)	<0.0001
BRCA2	Number	(%)	Number	(%)	OR (95% CI)	*p*
N/N	126	24.71	141	27.65	1.00 Ref	
N/H	246	48.23	216	42.35	1.27 (0.94-1.72)	0.134
H/H	138	27.06	153	30.00	1.01 (0.72-1.40)	1.000
N	498	48.82	498	48.82	1.00 Ref	
H	522	51.18	522	51.18	1.00 (0.84-1.19)	1.000

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

commendations. All control DNA samples were employed in each run of HRM analysis. The collected data was analysed, using LightCycler® 96 software version SW 1.1 (Roche, Mannheim, Germany). SNPs in DNA repair genes were selected using the public domain of the National Centre for Biotechnology Information at http://www.ncbi.nlm.nih.gov/snp (Bethesda, MD, USA).

Statistical analysis

Hardy-Weinberg distribution (HWE) was checked using the X^2 test to compare the observed genotype frequencies with the expected frequencies among the case and control subjects. Differences between distributions in particular groups were evaluated also by X^2 test. The general risks were illustrated as odds ratios (ORs) with associated 95% intervals (CIs) by unconditional logistic regression. The wild type of genotype and allele acted as reference. *P*-values < 0.05 were considered significant.

Results

Hardy-Weinberg equilibrium

The observed genotype frequency of *XRCC1*-rs25487, *XPD*-rs13181, *hMSH2*-rs4987188, *XRCC2*-rs3218536, *BRCA1*-rs799917, and *BRCA2*-rs144848 in controls were in agreement with HWE (P>0.05).

In the case of Arg399Gln polymorphism of *XRCC1* gene, Lys751Gln of *XPD* gene, Gly322Asp of *hMSH2* gene, and P871L of *BRCA1* gene, the distribution of the genotypes in the test group differed significantly from one expected from the Hardy-Weinberg equilibrium (P<0.05). It is caused by the very low abundance of the *XRCC1*Arg/Arg genotype, *hMSH2*Gly/Gly genotype, *XPD* Lys/Lys and *BRCA1*P/P genotype in the examined population.

Relationship between genotypes in SNPs and endometrial cancer

In our study, the analysed individuals were ethnically homogenous: Polish females from Lodz Region. Genotypes in *XRCC1*-rs25487, *XPD*-rs13181, *hMSH2*-rs4987188, *XRCC2*-rs3218536, *BRCA1*-rs799917 and *BRCA2*-rs144848 SNPs, were successfully determined for

all DNA samples obtained from patients and controls selected for genetic tests. This study demonstrates that *XRCC1*-Gln/Gln (OR 4.16; 95% CI 2.98-5.82, P<0.0001), *hMSH2*-Asp/Asp (OR 2.48; 95% CI 1.73-3.56, P< 0.0001), *XPD*-Gln/Gln (OR 4.97; 95% CI 3.55 - 6.94, P<0.0001) and *BRCA1*-L/L genotypes (OR 2.28; 95% CI 1.59-3.25, P<0.0001) are strongly associated with an increased risk of endometrial cancer. In addition, the alleles of *hMSH2*-Asp, *XPD*-Gln, *XRCC1*-Gln and *BRCA1*-L genes werestrongly correlated with this malignancy (P<0.0001).

We demonstrate that Arg188His and N372H polymorphisms of *XRCC2* and *BRCA2* gene, respectively donot have any influence on neoplasm development (P>0.05). (**Table 3**). We did not find any correlation between the repair genes polymorphic variants and FIGO grade nor stage (P>0.05). DNA repair genes polymorphisms were also unrelated to the patients' age, the body mass index, hormone replacement therapy, number of births, the date of menarche, uterine bleedings, the endometrium thickness, diabetes, and hypertension (P>0.05).

Discussion

Endometrial carcinoma is the most frequent malignant neoplasm of female genitals. Despite intensive research EC aetiology remains unknown. The primary objective of our work was to identify the SNPs associated with the risk of endometrial carcinoma and to estimate the cancer risk in SNPs carriers.

Our results fit in the general commonly accepted trend in research based on the concept that assumes that an individual susceptibility to cancer - including EC - is a cumulative outcome of multiple risk factors derived from numerous low-penetrating genetic variables.

There are seven major MMR genes in humans: *hMLH1*, *hMLH3*, *hPMS1*, *hPMS2*, *hMSH2*, *hMSH3* and *hMSH6*. We selected *hMSH2* gene for its well-proven role in the pathogenesis of cancer. According to the literature, Gly322Asp polymorphism of *hMSH2* gene may enhance the risk of colorectal and stomach cancer [17-19].

Some reports provide proof that the *hMSH2* Gly322Asp polymorphism was related to increased risk of endometrial cancer [20].

Our study demonstrates that Gly322Asp polymorphism is strongly associated with an increased risk of endometrial cancer. The Asp allele may as such be a risk factor of EC. We tested ECpatients for SNPs of both BER system and the NER system genes. Endometrial cancer is oestrogen-related. The oestrogens may bring about oxidative DNA defects, which are eliminated by the BER and NER mechanism [11, 21]. A series of enzymes are involved in BER and NER, including XRCC1 and XPD which harbor polymorphisms associated with the risk of tumors [22-24]. We have demonstrated that the polymorphic form of *XRCC1* and *XPD* contributes to an increased risk of endometrial cancer: alleles of *XRCC1*-Gln and *XPD*-Gln are strongly correlated with this malignancy.

DNA damages are highly significant in the pathogenesis of endometrial cancer. This phenomenon is especially found in these damages, where repair by homologous recombination is required [25, 26]. Repair by recombination enables removal of a number of serious DNA lesions, including double-stranded breaks. These breaks may bring about a loss of some chromosomes, causing translocation of genetic material. The repair pathway via homologous recombination allows for lesion removal, while ensuring high reproduction faithfulness of the primary sequence of modified DNA. A DNA molecule, characterised by sequential homology (usually, it is the undamaged homolog of the chromosome) is used as an array in the rep air process of damaged chromosome [27].

Genes that encode double-strand break repairing proteins are highly polymorphic, andtaking into account the significance of the defects in cancer development, it seems crucial to expand knowledge on the role of genetic polymorphisms in endometrial cancer [26, 28, 29].

We have demonstrated a possible correlation of rs799917 polymorphism of *BRCA1* repair gene with EC. Yet, it should be emphasized that this is the first paper on Polish endometrial cancer females that directly addresses this polymorphism. Earlier reports of various researchers focused on SNPs in *RAD51* gene. The study of *RAD51* G135C polymorphism in the Polish population identified a haplotype associated with endometrial cancer. The *RAD51* 135C allele was associated with a significantly increased risk of endometrial cancer in Poland [15, 29, 30].

Since RAD51 participates in DNA repair but also interacts with BRCA proteins (mutations of which are often identified in breast cancer), the above-mentioned polymorphisms may be associated with a higher risk of development this malignancy. It has been found, among others, that 135C variant may increase the risk of breast cancer in *BRCA1* and *BRCA2* genes mutations carriers, whereas no effects of 135C variant were observed on the morbidity in women without the mutations [31, 32]. G135C polymorphism can modify mRNA splicing to affectprotein function or the effectiveness of translation [33]. In spite of the abundance of results, there is still no unequivocal explanation of the role of RAD51 in cancer formation. Our assumption has beenthat another genetic variability factor could act either additively or independently of the above-mentioned polymorphisms in 5'UTR region, what may help to explain the role of *RAD51* in EC development. Our research was then oriented towards less investigated SNPs within *BRCA1* and *BRCA2* genes: P871L (rs799917) and N372H (rs14-4848). In this study, significant correlations were identified between breast cancer and the new, not yet reported in the literature, SNP-type polymorphism in *BRCA1* (rs799917). No correlation was found between the studied SNP and FIGO grade/stage.

In summary, the above presented studies contribute to a better knowledge of the molecular background of endometrial cancer. Our results point outDNA repair genes and their polymorphisms which can be involved in EC formation in Polish women.

Conclusions

The polymorphisms within the studied genes of the DNA repair system may become a group of new risk factors for endometrial cancer.

Disclosure of conflict of interest

None.

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