Studies of Correlations Between Single Nucleotide Polymorphisms of DNA Repair Genes and Endometrial Cancer in Polish Women

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Abstract. *Aim: The goals of this study included an analysis of the incidence of single nucleotide polymorphisms (SNPs) genotypes and alleles in DNA repair genes and evaluation of the effects by which this genetic variability may influence the risk for endometrial cancer. Materials and Methods: The study group included 610 women with endometrial cancer and was compared with a quantitatively matched control group of 610 women without any diagnosed malignancy. The following polymorphisms were analyzed: X-Ray repair cross complementing 1 (XRCC1)-Arg399Gln (rs25487); XRCC2-Arg188His (rs3218536); XRCC3-Thr241Met (rs861539); ERCC excision repair 2, TFIIH core complex helicase subunit (ERCC2)-Lys751Gln (rs13181); and 8-oxoguanine DNA glycosylase (OGG1)-Ser326Cys (rs13181). Results: Allele XRCC2-188His [odds ratio (OR)=5.24, 95% confidence interval (CI)=4.36-6.29; $p<0.0001$], hOGG1-326Cys (OR=1.60, 95% CI=1.36-1.88; $p<0.0001$) and ERCC2-751Gln (OR=1.67, 95% CI=1.42-1.96; $p<0.0001$) strongly correlated with neoplastic disease. Conclusion: The evaluated SNPs may be approached as a group of new risk factors for the development of this cancer type.*

The incidence of cancer in Poland has more than doubled during the past three decades. The most frequent cancer types, diagnosed in women, include breast (20% of all cancer cases), colonic (10%), lung (9%), endometrial (7%), ovarian (5%), uterine cervix, kidney, gastric and thyroid (1).

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Endometrial cancer is responsible for 3% of neoplastic mortality in women. The recognized risk factors of endometrial cancer include obesity at the age of 50-59 years, endo-and exogenous hyperestrogenism, early menarche and late last menstruation, the occurrence of anovulatory cycles, polycystic ovary syndrome, diabetes mellitus and hypertension (2, 3). Unfortunately, however, there are no diagnostic methods, enabling an early diagnosis of endometrial cancer. Thus far, it has not been possible to design and develop an effective screening test for this cancer type (2).

Because of the current lack of unequivocal molecular markers of endometrial cancer in its early stages, the primary objective of our study became the evaluation of the possibility to enrich a range of molecular markers, allowing for a more effective prognosis of endometrial cancer.

Personal predisposition to malignancy, including endometrial cancer, may be of polygenic character, involving a relatively high number of low-penetration genes (4).

DNA repair protects cells from cancer-forming mutations. Cancer is driven by a compromised DNA repair (5, 6). Therefore, a set of alleles of genes for repairing protein encoding may largely define individual capacity for DNA-damage repair, as well as the susceptibility to tumor development. Single nucleotide polymorphisms (SNPs) of DNA-damage repair genes may alter the risk of cancer. SNPs may then be regarded as potential markers of susceptibility to carcinogenesis (7).

The studies, therefore, focused on evaluation of the role of SNPs of DNA-repair genes in the pathogenesis of endometrial cancer and in the prognosis of its further course. One of the objectives of the study was the evaluation of genotype distribution and the frequency of alleles of selected DNA repair gene polymorphisms in patients with endometrial cancer. Constitutive polymorphisms of functional significance were selected for this study, which,

in the majority, have not yet been studied in patients with endometrial cancer, namely: X-Ray repair cross complementing 1 (*XRCC1*)-Arg399Gln (rs25487); *XRCC2*-Arg188His (rs3218536); *XRCC3*-Thr241Met (rs861539); ERCC excision repair 2, TFIIF core complex helicase subunit (*ERCC2*)-Lys751Gln (rs13181); and 8-oxoguanine DNA glycosylase (*OGG1*)-Ser326Cys (rs13181).

Materials and Methods

Patients. The study material included tumor specimens collected from female patients (n=610) with endometrial cancer, surgically treated at the Department of Gynaecology, Polish Mother's Memorial Hospital-Research Institute in Lodz during the years 2003-2017. The material for studies was derived from paraffin blocks, made from the collected, postoperative material. Histopathological studies were carried out at the Department of Clinical Pathomorphology, Polish Mother's Memorial Institute. The study protocol was approved by the Bioethical Committee of the Polish Mother's Memorial Institute (Approval No. 33/2015). Histological differentiation was assessed using the International Federation of Gynecology and Obstetrics (FIGO) scale (8). A group of 610 female patients treated in the same period for uterine fibroids constituted a control group. See Table I for a complete specification of the patients.

DNA isolation. Genomic DNA was prepared from the tumor and control specimens using a QIAamp DNA FFPE Tissue Kit (Qiagen GmbH, Hilden, Germany) according to the manufacturer instruction.

Genotyping. The studies of polymorphic variants of selected DNA repair genes employed the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. The reactive mixture, used when copying the fragments of all studied genes, had the same composition except for the primer sequences. The 25- μ l PCR mixture contained about 100 ng of DNA, 12.5 pmol of each primer, 0.2 mmol/l of dNTPs, 2 mmol/l of $MgCl_2$ and 1 U of Taq DNA polymerase (Takara Bio Inc., Otsu, Shiga, Japan). Amplification was carried out in an MJ Research Inc. PTC-100 thermocycler (Waltham, MA, USA) under conditions tailored to each of the selected genes (see Table II). In order to obtain allelic variants of specific genes, the obtained PCR products were submitted to incubation with appropriate restrictive enzymes, revealing target sequences at a polymorphic site within one of the variants. The PCR products, contained in 10 μ l of the reactive mixture, were incubated for 16 hours with 1 U of an appropriate restrictive enzyme (see Table III). All the applied enzymes were products of MBI Fermentas Company (Vilnius, Lithuania). Table III presents fragment lengths for various polymorphic variants of the studied DNA-repair genes.

Statistical analysis. The obtained results were statistically processed by means of STATISTICA 9 software (StatSoft Poland, Krakow, Malopolska, Poland). The effect of polymorphisms on the risk of endometrial cancer formation was evaluated by odds ratio (OR), together with 95% confidence interval (CI), obtained by means of a logistic regression model. In order to verify whether the Hardy-Weinberg principle was met in the studied populations, tests for deviation from Hardy-Weinberg equilibrium and tests for association were applied, being available at the www.ihg.gfs.de

Table I. Characteristics of endometrial cancer patients and controls participating in this study.

Characteristic	Patients (n=610)	Controls (n=610)
Age, years		
Median (range)	61.2 (47-85)	53.2 (48-84)
Age at first menarche, n (%)		
Before 11 years	120 (19.7%)	140 (23.0%)
12-13 years	110 (18.0%)	130 (21.3%)
14-15 years	140 (23.0%)	140 (23.0%)
After 16 years	240 (39.3%)	200 (32.7%)
Body mass index, n (%)		
<24.9 kg/m ²	205 (33.6%)	200 (32.8%)
25-29.9 kg/m ²	210 (34.4%)	220 (36.1%)
>30 kg/m ²	195 (32.0%)	190 (31.1%)
Number of pregnancies, n (%)		
1	340 (55.7%)	360 (59.0%)
2-3	266 (43.6%)	242 (39.7%)
>4	4 (0.7%)	8 (1.3%)
Use of hormone replacement therapy, n (%)		
Yes	450 (73.8%)	540 (88.5%)
No	160 (26.2%)	70 (11.5%)
Uterine bleeding, n (%)		
Yes	320 (52.5%)	360 (59.0%)
No	290 (47.5%)	250 (41.0%)
Endometrial ultrasound-transvaginal, n (%)		
>5 mm	340 (55.8%)	360 (59.0%)
Diabetes mellitus, n (%)		
Yes	340 (55.7%)	310 (50.8%)
No	270 (44.3%)	300 (49.2%)
Hypertension, n (%)		
Yes	220 (36.1%)	198 (32.4%)
No	390 (63.9%)	412 (67.6%)
Family history of cancer, n (%)		
Yes	220 (36.1%)	180 (29.5%)
No	390 (63.9%)	430 (70.5%)
FIGO grade, n (%)		
G1	270 (44.3%)	
G2	300 (49.2%)	
G3	40 (6.5%)	

FIGO: International Federation of Gynecology and Obstetrics.

(Institute of Human Genetics, Technical University Munich and Helmholtz Center Munich).

All the statistical tests were carried at the level of significance $\alpha=0.05$. In order to verify the hypothesis regarding the significance of age, body mass index (BMI), menarche, hormonal replacement therapy, uterine bleeding, endometrial thickness, diabetes mellitus and hypertension in the studied group, chi-squared analysis was used. Associations with *p*-values of less than 0.05 were considered significant.

Results

Arg188His and Thr241Met polymorphisms of *XRCC2* and *XRCC3* genes, respectively were analyzed in patients with

Table II. Primer sequences and thermal conditions for PCR of DNA-repair gene fragments.

Gene polymorphism	Primer			Thermal conditions of amplification
	Gene name	Forward (5'→3')	Reverse (5'→3')	
<i>XRCC1</i> (c.1196A>G, Arg399Gln)	X-Ray repair cross complementing 1	CAAGTACAGCC AGGTCCTAG	CCTTCCCTCAT CTGGAGTAC	1. 95°C for 5 min 2. 95°C for 20 s 3. 58°C for 20 s 4. 72°C for 20 s 5. 2 → 3 → 4×35 cycles 6. 72°C for 3 min
<i>XRCC2</i> (c.563G>A, Arg188His)	X-Ray repair cross complementing 2	TGTAGTCACCC ATCTCTCTGC	AGTTGCTGCC ATGCCTTACA	1. 95°C for 5 min 2. 95°C for 20 s 3. 60°C for 20 s 4. 72°C for 20 s 5. 2 → 3 → 4×35 cycles 6. 72°C for 3 min
<i>XRCC3</i> (c.722C>T, Thr241Met)	X-Ray repair cross complementing 3	ACAGGGCTCTGGAA GGCACTGCTCAGCTC ACGCACC	GCCTGGTGG TCATCGACTC	1. 95°C for 5 min 2. 95°C for 20 s 3. 63°C for 20 s 4. 72°C for 20 s 5. 2 → 3 → 4×35 cycles 6. 72°C for 3 min
<i>ERCC2</i> (c.2251A>C, Lys751Gln)	ERCC excision repair 2, TFIIH core complex helicase subunit	CTGCTCAGCCTGG AGCAGCTAGAATC AGAGGAGACGCTG	AAGACCTTCTA GCACCACCG	1. 95°C for 5 min 2. 95°C for 20 s 3. 68°C for 20 s 4. 72°C for 20 s 5. 2 → 3 → 4×35 cycles 6. 72°C for 3 min
<i>OGG1</i> (c.686G>A, Ser326Cys)	8-Oxoguanine DNA glycosylase	GGAAGGTGCTT GGGGAAT	ACTGTCACTAGT CTCACCAG	1. 95°C for 5 min 2. 95°C for 30 s 3. 57°C for 30 s 4. 72°C for 1 min 5. 2 → 3 → 4×35 cycles 6. 72°C for 7 min

endometrial cancer (Table IV). The frequency of 188His allele was statistically significantly higher in the group of patients with endometrial cancer *vs.* the control group. The presence of 188His/His homozygote was also found to increase the risk of cancer ($p<0.0001$). Correlation of the studied polymorphisms with histological malignancy grading was identified. The frequencies of 241Thr/Met heterozygote and 188His/His homozygote were higher in patients with G2 or G3 *vs.* those with G1 malignancy grade (Table V). The 188His allele significantly increased the risk of cancer progression ($p<0.0001$).

A correlation was found of Lys751Gln *ERCC2* gene polymorphism with endometrial cancer in the examined patients. The 751Gln allele predisposed to endometrial cancer development ($p<0.001$). The 751Gln/Gln genotype also increased the risk of cancer ($p<0.0001$). However, no correlation was found of Lys751Gln polymorphism with histological malignancy grade (Table V).

Table III. Fragment lengths for polymorphic variants of the studied DNA-repair genes.

Gene	Polymorphism	Restriction endonuclease	Lengths of obtained fragments (bp)
<i>XRCC2</i>	Arg188His	<i>HpnI</i>	Arg/Arg: 290 Arg/His: 142, 148, 290 His/His: 142, 148
<i>XRCC3</i>	Thr241Met	<i>NcoI</i>	Thr/Thr: 136 Thr/Met: 39, 97, 136 Met/Met: 39, 97
<i>ERCC2</i>	Lys751Gln	<i>PstI</i>	Lys/lys: 161 Lys/Gln: 41, 120, 161 Gln/Gln: 41, 120
<i>OGG1</i>	Ser326Cys	<i>SatI</i>	Ser/Ser: 200 Ser/Cys: 100, 200 Cys/Cys: 100
<i>XRCC1</i>	Arg399Gln	<i>BclI</i>	Arg/Arg: 89, 159 Arg/Gln: 89, 159, 248 Gln/Gln: 248

Table IV. Distribution of genotypes and of allelic frequency of single nucleotide polymorphisms (SNP) in patients with endometrial cancer and in the control group.

SNP		Patients (n=610)		Controls (n=610)		OR (95% CI)	p-Value ^a
		N	(%)	N	(%)		
<i>XRCC2</i> -Arg188His	188Arg/Arg	90	14.8	150	24.6	1.00 (Ref.)	
	188Arg/His	50	8.2	370	60.7	0.22 (0.15-0.33)	<0.0001
	188His/His	470	77.0	90	14.7	8.70 (6.16-12.29)	<0.0001
	188Arg	230	18.9	670	54.9	1.00 (Ref.)	
	188His	990	81.1	550	45.1	5.24 (4.36-6.29)	<0.0001
<i>XRCC3</i> -Thr241Met	241Thr/Thr	150	24.6	120	19.7	1.00 (Ref.)	
	241Thr/Met	310	50.8	320	52.5	0.77 (0.58-1.03)	0.094
	241Met/Met	150	24.6	170	27.8	0.70 (0.51-0.98)	0.043
	241Thr	610	50.0	560	46.0	1.00 (Ref.)	
	241Met	610	50.0	660	54.0	0.85 (0.72-0.99)	0.047
<i>XRCC1</i> -Arg399Gln	Arg/Arg	180	25	190	31.1	1.00 (Ref.)	
	Arg/Gln	250	50	224	36.8	1.17 (0.89-1.55)	0.267
	Gln/Gln	180	25	196	32.1	0.96 (0.72-1.29)	0.887
	Arg	610	50	604	49.5	1.00 (Ref.)	
	Gln	610	50	616	50.5	0.98 (0.84-1.15)	0.841
<i>OGG1</i> -Ser326Cys	Ser/Ser	160	26.2	196	32.1	1.00 (Ref.)	
	Ser/Cys	160	26.2	230	37.7	0.85 (0.63-1.14)	0.314
	Cys/Cys	290	47.6	184	30.2	1.93 (1.46-2.55)	<0.0001
	Ser	480	39.3	622	51.0	1.00 (Ref.)	
	Cys	740	60.7	598	49.0	1.60 (1.36-1.88)	<0.0001
<i>ERCC2</i> -Lys751Gln	Lys/Lys	152	25.0	186	30.5	1.00 (Ref.)	
	Lys/Gln	154	25.2	240	39.3	0.78 (0.58-1.05)	0.125
	Gln/Gln	304	49.8	184	30.2	2.02 (1.52-2.68)	<0.0001
	Lys	458	37.5	612	50.2	1.00 (Ref.)	
	Gln	762	62.5	608	49.8	1.67 (1.42-1.96)	<0.0001

CI: Confidence interval; OR: crude odds ratio. ^aChi-square test.

The studies successfully demonstrated that 326Cys allele of *OGG1* gene Ser326Cys polymorphism was correlated with an increased risk of endometrial cancer in the studied population ($p<0.001$). Homozygosity for 326Cys/Cys increased the risk of progression of endometrial cancer ($p<0.001$). The 326Cys allele was also more frequently found in patients with G1 malignancy ($p<0.001$).

Regarding the Arg399Gln polymorphism of *XRCC1* gene, the 399Gln allele was more frequent in patients with G2 or G3 disease ($p<0.001$).

The studied polymorphisms of *XRCC2*-Arg188His, *XRCC3*-Thr241Met, *ERCC2*-Lys751Gln, *OGG1*-Ser326Cys and *XRCC1*-Arg399Gln DNA-repair genes were not significantly associated with other risk factors, such as BMI, menarche, hormonal replacement therapy, uterine bleeding, endometrium thickness, diabetes mellitus or hypertension ($p>0.05$).

Discussion

The presented study focused on an evaluation of the role of SNPs of DNA-repair genes in the pathogenesis of endometrial cancer and in the prognosis of its further course. The primary

objective of the study was to identify SNPs associated with the risk of endometrial cancer and targeted selected polymorphisms in protein encoding genes of the main DNA repair systems, such as base excision repair (BER), nucleotide excision repair (NER), or repair *via* recombination.

Our study was based on the commonly accepted concept that the predisposition to cancer, including endometrial carcinoma, may be polygenic in character, involving a relatively high number of low-penetrance genes.

The study groups of patients were ethnically uniform, including females of the Polish origin, inhabitants of the Lodz Region.

The first stage of the study concentrated on an evaluation of *XRCC2* gene Arg188His and *XRCC3* gene Thr241Met polymorphisms. *XRCC2* and *XRCC3* genes belong to the system of DNA repair *via* homologous recombination, which removes a number of serious DNA defects, such as, for example, double-strand breaks (9, 10). A consequence of faulty repair may be the loss of some chromosomes and translocation of genetic material, which may lead to the development of cancer (11-14). Moreover, such defects are strong inducers of programmed cell death. The system of

Table V. Distributions of genotypes and of allelic frequency of single nucleotide polymorphisms (SNP) of DNA-repair genes in patients with endometrial cancer according to histological grading.

SNP		Grade, N (%) ^a		OR (95% CI)	p-Value ^b
		G1 (n=270)	G2 + G3 (n=340)		
<i>XRCC3</i> -Thr241Met	241Thr/Thr	90 (33.4%)	70 (20.6%)	1.00 (Ref.)	
	241Thr/Met	100 (37.0%)	210 (61.8%)	0.37 (0.25-0.54)	<0.0001
	241Met/Met	80 (29.6%)	60 (17.6%)	1.04 (0.65-1.63)	>0.99
	241Thr	280 (51.9%)	350 (51.5%)	1.00 (Ref.)	
	241Met	260 (48.1%)	330 (48.5%)	0.98 (0.78-1.23)	0.920
<i>XRCC2</i> -Arg188His	188Arg/Arg	20 (7.4%)	70 (20.6%)	1.00 (Ref.)	
	188Arg/His	10 (3.7%)	40 (11.8%)	0.88 (0.37-2.05)	0.920
	188His/His	240 (8.9%)	230 (67.6%)	3.65 (2.15-6.19)	<0.0001
	188Arg	50 (9.3%)	180 (26.5%)	1.00 (Ref.)	
	188His	490 (90.7%)	500 (73.5%)	3.52 (2.51-4.94)	<0.0001
<i>XRCC1</i> -Arg399Gln	Arg/Arg	90 (33.3%)	90 (26.5%)	1.00 (Ref.)	
	Arg/Gln	120 (44.5%)	130 (38.2%)	0.92 (0.63-1.35)	0.751
	Gln/Gln	60 (22.2%)	120 (35.3%)	0.50 (0.33-0.77)	0.002
	Arg	300 (55.6%)	310 (45.6%)	1.00 (Ref.)	
	Gln	240 (44.4%)	370 (54.4%)	0.67 (0.53-0.84)	0.001
<i>OGG1</i> -Ser326Cys	Ser/Ser	30 (11%)	130 (38.2%)	1.00 (Ref.)	
	Ser/Cys	70 (26%)	90 (26.5%)	3.37 (2.03-5.58)	<0.0001
	Cys/Cys	170 (63%)	120 (35.3%)	6.14 (3.87-9.73)	<0.0001
	Ser	130 (24%)	350 (51.5%)	1.00 (Ref.)	
	Cys	410 (76%)	330 (48.5%)	3.34 (2.61-4.28)	<0.0001
<i>ERCC2</i> -Lys751Gln	Lys/Lys	70 (25.9%)	82 (24.1%)	1.00 (Ref.)	
	Lys/Gln	54 (20%)	100 (29.4%)	0.63 (0.40-1.00)	0.066
	Gln/Gln	146 (54.1%)	158 (46.5%)	1.08 (0.73-1.60)	0.764
	Lys	194 (35.9%)	264 (38.8%)	1.00 (Ref.)	
	Gln	346 (64.1%)	416 (61.2%)	1.13 (0.90-1.43)	0.327

CI: Confidence interval; OR: crude odds ratio. ^aAccording to International Federation of Gynecology and Obstetrics criteria (8); ^bChi-square test.

repair *via* homologous recombination allows for defect removal, ensuring high reproductive accuracy of the primary sequence of modified DNA. Cells with defective *XRCC2* and *XRCC3* genes are particular sensitive to ionizing radiation, UV and to factors which induce formation of cross bonds (15). *XRCC2* Arg188His and *XRCC3* Thr241Met polymorphisms were selected for their documented participation in the pathogenesis of cancer. Both polymorphisms may increase the risk of occurrence of various neoplasms, including carcinoma of the pancreas, ovary, breast, and head and neck (16-23). Our study demonstrated a significant association of Arg188His and Thr241Met polymorphisms of *XRCC2* and *XRCC3* genes, respectively, with the occurrence of endometrial cancer.

A subsequent stage of the study focused on Lys751Gln polymorphism of *ERCC2* gene, belonging to the nucleotide excision repair (NER) system. The NER system participates in elimination of damage such as large adducts, intra-strand bonds and photoproducts (24-27). Repair includes the identification of a defective nucleotide, followed by its excision with the synthesis of a new DNA strand on the

complementary strand. There are 30 different proteins which are involved in NER and a deficit or lack of which causes hypersensitivity to UV and induces serious diseases, including malignancy. According to literature data, the most frequently studied SNP of *ERCC2* gene is Lys751Gln. It has been demonstrated in a number of reports to play a significant role in the development of neoplastic diseases, including endometrial cancer (28-35). Our study carried out in a population of Polish women confirmed the relationship of the studied *ERCC2* gene polymorphism with the development of endometrial cancer.

The search for markers of endometrial cancer development was carried on in analysis of the polymorphisms of BER genes *OGG1* and *XRCC1*. BER removes DNA defects which are uncomplicated but dangerous in their consequences. The defects include oxidized and *N*-alkylated nitrogen bases, uracil and apurinic/pyrimidine sites (36). According to the latest literature data, *OGG1* Ser326Cys and *XRCC1* Arg399Gln polymorphisms may be associated with many neoplastic diseases (37-44). In our study, *OGG1* Ser326Cys and *XRCC1*

Arg399Gln polymorphisms were associated with an increased risk of endometrial cancer and influenced the histological malignancy grading.

Based on our study results, the following conclusions were drawn: I. A significant relationship was found between SNP rs13181 of *ERCC2* (involved in BER) and an increased risk of endometrial cancer development. II. A significant relationship was also shown between SNPs rs13181 *OGG1* and rs25487 *XRCC1* (involved in NER) and an increased risk of endometrial cancer development. III. Significant correlation was revealed between single nucleotide polymorphisms of rs3218536 *XRCC2* and rs861539 *XRCC3* (DNA double-strand break repair genes *via* homologous recombination) and endometrial cancer development. IV. SNPs of the studied DNA-repair genes may enrich the scope of new risk factors of endometrial cancer in Polish women.

Conclusion

The presented results provide new cognitive data on the role of individual genetic variability in the predisposition to endometrial cancer. The identification of cancer risk markers is a major challenge for contemporary medicine. Our study attempted to search for polymorphisms of DNA-repair genes predisposing to endometrial cancer. The study was based on an analysis of selected constitutive polymorphisms of functional significance most of which not have not been studied in patients with endometrial cancer. The study demonstrated how polymorphisms of DNA-repair genes may be involved in endometrial cancer etiology. The evaluated SNPs may be approached as a group of new risk factors for the development of endometrial cancer, while their analysis may contribute to the stratification of patients into a group with high cancer risk. In addition, these polymorphisms may be useful in the evaluation of individual risk for malignancy in individuals without any symptoms of cancer. The results of the study may find practical application in improving early diagnosis of endometrial cancer and thus extend the survival rates of women suffering from this type of malignancy.

Compliance with Ethical Standards

The study was approved by the Bioethical Committee of the Institute of the Polish Mother's Memorial Hospital in Lodz (Approval number, No 33/2015). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflicts of Interests

All Authors declare they have no conflict of interest in regard to this study.

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