RAD51 GENE POLYMORPHISMS AND SPORADIC COLORECTAL CANCER RISK IN POLAND

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Background: DNA repair processes play an important role in protection against carcinogenic factors. Mutations in DNA repair genes, which code proteins engaged in repair processes, may lead to carcinogenesis and among others also to colorectal cancer (CRC) development. The genetic variability in *RAD51* may contribute to the appearance and progression of various cancers including CRC.
The aim of the study was to compare the distribution of genotypes of *RAD51* 135G>C and 172G>T polymorphism between colorectal cancer patients and controls.
Material and methods: Both polymorphisms were evaluated by PCR-RFLP methods in colorectal tissue of 320 colorectal cancer subjects and 320 healthy subjects who served as controls.
Results: In the present work we demonstrated a significant positive association between the *RAD51* C/C genotype and colorectal carcinoma. Variant 135C allele of *RAD51* increased the cancer risk. However, we did not observe any relationship between each polymorphism and colorectal cancer progression assessed by node metastasis, tumour size and Dukes' stage.
Conclusions: Our results suggest that variant genotypes of the 135G>C of *RAD51* polymorphism may be positively associated with colorectal carcinoma in the Polish population. Further studies conducted on a larger group are required to clarify this point.

Key words: RAD51, colorectal cancer, gene polymorphism.

Introduction

Colorectal cancer (CRC) is detected in more than 600 000 cases per year and is the fourth most common form of cancer in the United States and the third leading cause of cancer-related death in the Western world [1].

The risk of colorectal cancer is increased by several factors such as age, polyps of the colon, dietary factors, history of cancer (women who have had cancer of the ovary, uterus, or breast are at a higher risk of developing colorectal cancer), heredity, smoking, alcohol and gene mutations [2-4].

The relationships between risk factors and colorectal carcinoma development are not exactly known. Therefore, the identification of new risk factors for colorectal cancer is urgently needed, and an analysis of some gene polymorphisms could be an interesting option.

Mutations in DNA double-strand breaks (DSB) repair genes are involved in the pathogenesis of tumours.

Defects in this pathway may play a role in development and progression of colorectal cancer. DSB in DNA may be rectified by either homologous recombination (HR) and nonhomologous end joining (NHEJ) [5, 6].

RAD51 is involved in homologous recombination and repair of double-strand breaks in DNA and DNA cross-links and for the maintenance of chromosome stability [7].

RAD51 is associated with BRCA1 and BRCA2 tumour suppressor gene products, suggesting that a defect in recombination leads to tumour development [8, 9].

RAD51 gene is polymorphic. Two common *RAD51* SNPs (single nucleotide polymorphism), 135G>C and 172G>T in the 5'UTR have been reported to be associated with altered gene transcription [10].

This SNP is located in the regulatory element of the *RAD51* promoter and is suggested to be associated with messenger RNA expression.

It is knowledge that *RAD51* gene 135G>C and 172G>T polymorphisms have been studied as a risk factor for various cancers. Data of literature suggest that *RAD51* gene 135G>C polymorphism may contribute to head and neck cancer and mammary carcinogenesis [11-17]. A study of women matched for *BRCA1* mutation revealed that the C allele of this polymorphism is associated with a 2-fold reduction in the breast and ovarian cancer risk as compared with the wild-type G allele [18].

RAD51 172TT homozygous variant genotype was associated with a significantly reduced risk of squamous cell carcinoma of the head and neck (SCCHN) [19].

Moreover, the variant T allele of the *RAD51* 172G>T SNP was shown to be associated with a non-significantly decreased risk of sporadic breast cancer in women [20, 21].

Table I. Characteristics of colorectal cancer patients[a]

CHARACTERISTICS	NUMBER OF CASES (%)
Dukes' stages	
Stage A	91 (30%)
Stage B	179 (66%)
Stage C	28 (3%)
Stage D	22 (1%)
Tumor size	
T1	100 (31%)
T2	70 (22%)
T3	150 (47%)
Lymph node status	
N0	130 (46%)
N1	100 (33%)
N2	40 (8%)
N3	50 (13%)

[a] *n = 320*

The relationships between *RAD51* polymorphisms and colorectal carcinoma development are not exactly known [22, 23]. Therefore, in the present work, the association between *RAD51* 135G>C and 172G>T polymorphisms and colorectal carcinoma in the Polish population was investigated.

Material and methods

Colorectal cancer patients

Tumour tissues were obtained from 320 subjects with colorectal cancer treated at the 2nd Department of Surgery, Military Academy of Medicine in Lodz (Poland) between 2000 and 2006. Clinical data for the patients and histological data were registered (Table I). There were 196 males and 124 females and their mean age was 59 years (range: 37-71 years). All tumours were staged according to Dukes' classification. DNA from normal colorectal tissue (n = 320) served as control (mean age 54.42 ±19.22). The Local Ethic Committee approved the study and each patient gave his written consent.

The colorectal tissue samples (cancerous and non-cancerous) were fixed routinely in formaldehyde, embedded in paraffin, cut into thin slices and stained with hematoxylin/eosin for pathological examination. DNA for analysis was obtained from an archival pathological paraffin-embedded tumour and healthy colorectal samples which were deparaffinized in xylene and rehydrated in ethanol and distilled water. In order to ensure that the chosen histological material is representative for cancerous and non-cancerous tissue, every tissue sample qualified for DNA extraction was initially checked by a pathologist. DNA was extracted from the material using commercially available QIAmp Kit (Qiagen GmbH, Hilden, Germany), a DNA purification kit according to the manufacturer's instruction.

Genotype determination

Single nucleotide polymorphisms 135G>C and 172G>T of *RAD51* gene was determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), using primers 5'-TGG GAA CTG CAA CTC ATC TGG-3' (forward) and 5'-GCT CCG ACT TCA CCC CGC CGG-3' (reverse).

RAD51 135G>C 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 *Mva*I resulting in 86- and 71-bp product. The 135C allele was not digested by the enzyme, resulting in a single 157-bp product.

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, Darmstadt, 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 the three possible genotypes: G/G, G/C or C/C.

PCR for 172G>T SNPs was performed in 25 µl reaction systems containing 5 ng genomic DNA, 0.2 µmol of each appropriate primer (ARK Scientific GmbH Biosystems, Darmstadt, Germany), 2.5 mM $MgCl_2$, 1 mM dNTPs and 1 unit of Taq Polymerase (Qiagen GmbH, Hilden, Germany). The PCR profile consisted of an initial melting step at 95°C for 5 min; 30 cycles of 95°C for 30 s, 65°C for 45 s and 72°C for 50 s and a final extension step of 72°C for 10 min. The product after PCR was digested with *NgoM*IV (New England BioLabs) overnight. The products were separated in 7% polyacrylamide gel. The 172G/G genotype produced two bands (110 and 21 bp), whereas the 172T/T genotype produced only one band (131 bp) and the 172G/T heterozygote displayed all three bands (131, 110 and 21 bp).

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 genotype-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. STATISTICA 6.0 software (Statsoft, Tulsa, OK, USA) was used to perform analyses.

Results

Table II shows genotype distribution of *RAD51* 135G>C polymorphism in cases and controls. Odds ratio analysis showed a statistically significant positive association of colorectal cancer risk for carriers of the 135C allele of the 135G>C polymorphism of the *RAD51* gene. We observed an association between colorectal carcinoma occurrence and the presence of the C/C genotypes. A stronger association was observed for the C/C homozygotes than for the G/C heterozygotes.

No statistically significant differences were observed in the alleles or in the genotype frequencies of the *RAD51* 172G>T gene polymorphisms between the control group and patients with colorectal cancer ($p > 0.05$) (Table III).

The association between the haplotypes analysis of *RAD51* and colorectal cancer is displayed in Table IV. The halophyte/haplotype analysis according to wild-type of G135G-G172G showed a high association with CRC. The findings indicated that a statistically significantly increased risk of colorectal cancer was associated with the combined C/C-G/G genotype and C/C-T/T genotype. The higher risk of CRC occurrence was associated with the combined C135C-G172T genotype but no altered risk was associated with other haplotypes.

Dukes' staging was related to the *RAD51* 135G>C and 172G>T polymorphisms. The histological stage was evaluated in all cases (n = 320). 91 cases were stage A, 179 cases were stage B, 28 cases were stage C and 22 cases – stage D. Stage B, C and D were grouped together for the purposes of statistical analysis (Table V). We did not observe any difference between *RAD51*-135G>C and 172G>T genotype distributions in these groups. There was no correlation between genotypes of the polymorphisms and colorectal cancer invasiveness.

We did not observe any difference in the distribution of genotypes of investigated polymorphisms between patients with lymph node metastasis (N+) and without (N–) lymph node. Additionally, there was no difference in distribution of genotypes and frequency of alleles in a group of patients with different TNMs.

Discussion

Despite advanced diagnostic and therapeutic procedures, colorectal cancer (CRC) is still responsible for

Table II. Distribution of *RAD51* 135G>C genotype frequencies in patients with colorectal cancer and the control group

	Colorectal cancer, n = 320		Controls, n = 320		OR (95% CI)[a]	p[b]
	Number	(%)	Number	(%)		
G/G	51	16	91	29	1.00 Ref	
G/C	56	18	164	51	0.60 (0.38-0.96)	0.050
C/C	213	66	65	20	**5.84 (3.76-9.09)**	**< 0.0001**
G	158	25	346	54	1.00 Ref	
C	482	75	294	46	**3.59 (2.83-4.45)**	**< 0.0001**

Data in boldface are statistically significant

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

Table III. Distribution of 172G>T *RAD51* genotype frequencies in patients with colorectal cancer and the control group

	Colorectal cancer, n = 320		Controls, n = 320		OR (95% CI)[a]	p[b]
	Number	(%)	Number	(%)		
G/G	81	25	84	27	1.00 Ref	
G/T	150	47	142	44	1.09 (0.74-1.60)	0.708
T/T	89	28	94	29	0.98 (0.64-1.49)	0.920
G	312	49	310	48	1.00 Ref	
T	328	51	330	52	0.98 (0.79-1.22)	0.920

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

Table IV. Haplotypes distribution and frequencies of *RAD51* gene polymorphisms in the colorectal cancer patients and controls

Haplotypes RAD51-135–172	Patients (N = 320) N (%)	Controls (N = 320) N (%)	OR (95% CI)[a]	p[b]
G/G-G/G	20 (6%)	37 (12%)	1.00 Ref	
G/G-G/T	21 (7%)	20 (6%)	1.94 (0.85-4.40)	0.164
G/G-T/T	20 (6%)	28 (9%)	1.32 (0.59-2.91)	0.624
G/C-G/G	23 (7%)	37 (12%)	1.15 (0.54-2.44)	0.862
G/C-G/T	21 (7%)	65 (20%)	0.59 (0.28-1.24)	0.233
G/C-T/T	22 (5%)	40 (13%)	1.01 (0.47-2.15)	0.887
C/C-G/G	46 (14%)	28 (9%)	**3.03 (1.48-6.23)**	**0.0037**
C/C-G/T	96 (30%)	37 (12%)	**4.80 (2.47-9.31)**	**< 0.0001**
C/C-T/T	51 (16%)	28 (9%)	**3.36 (1.65-6.87)**	**0.001**

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

Table V. Relation between genotypes and frequencies of the alleles of *RAD51* gene polymorphism, and the tumour stage in patients with colorectal cancer[a]

Stage[b]	A (n = 91)	B + C + D (n = 229)	OR (95% CI)[c]	p[d]
RAD51 135G>C	Number (%)	Number (%)		
G/G	29 (32%)	52 (23%)	1.00 Ref	
G/C	19 (21%)	39 (17%)	0.87 (0.42-1.78)	0.841
C/C	43 (47%)	138 (60%)	0.55 (0.31-0.98)	0.061
G	77 (42%)	143 (31%)	1.00 Ref	
C	105 (58%)	315 (69%)	0.61 (0.43-0.88)	0.077
RAD51 172G>T				
G/G	31 (34%)	60 (26%)	1.00 Ref	
G/T	20 (23%)	39 (17%)	0.99 (0.49-1.68)	0.887
T/T	40 (53%)	130 (57%)	0.59 (0.34-1.04)	0.093
G	82 (45%)	159 (35%)	1.00 Ref	
T	100 (55%)	299 (65%)	0.64 (0.45-0.92)	0.142

[a]*n = 240;* [b]*according to Dukes' criteria;* [c]*Crude odds ratio (OR), 95% CI = confidence interval at 95%,* [d]χ^2

high morbidity and mortality of women. The contribution of polymorphisms of DNA repair genes in developing colorectal carcinoma is controversial. Therefore, we investigated the role of 135G>C and 172G>T genetic variation in homologous recombination repair gene and risk of this cancer.

Engin *et al.* examined the role of SNPs in genes that participate in the base excision repair (BER) pathway (*hOGG1*) which repairs lipid hydroperoxide-induced oxidative DNA base modifications and single-strand breaks and nucleotide excision repair (NER) pathway (*XPD*, *XPC*) which repairs bulky adducts induced by smoking- and lipid hydroperoxide acetaldehyde-induced adducts genes and risk of colorectal cancer. The presence of the *hOGG1*, *XPD* and *XPC* variant allele was not associated with the increased risk of cancer progression [24].

We found in the literature that the studies performed in Chinese and Korean populations did not find any association between variants in DNA mismatch repair genes (MMR) and sporadic CRC [25, 26]. The Asp132His variant was present but not associated with sporadic CRC in the Chinese population [25].

The *MLH1* 415G>C (Asp132His) variant has been shown to be associated with susceptibility to sporadic CRC in the Israeli population, although the CRCs associated with the variant usually are not MSI [27].

The other polymorphism of *hMLH1* gene A655G may play a role in the pathogenesis of colorectal cancer. These results suggest that this polymorphism may be a potential marker to predict the prognosis of colorectal cancer cases [28].

From a review of the literature we learned that polymorphisms in DNA double-strand break repair gene were investigated in CRC.

The researches found the association between *XRCC4* gene C-1622T polymorphism and colorectal cancer [29].

The results of several studies showed that polymorphisms in DNA double-strand break repair gene *XRCC2* may play an important role in colorectal cancer aetiology [30].

Wang *et al.* suggested that the *XRCC3* 241Met allele showed a protective tendency against rectal cancer. Moreover, a combination of the *XRCC1* 399Gln allele with *XRCC3* Thr/Thr genotype and the *XPD* 751Gln allele demonstrated the highest rectal cancer risk [31].

Unfortunately, it is difficult to find in the literature reports directly binding SNPs in DNA repair gene *RAD51* with clinicopathological features of the tumour. Only in single studies, researchers suggest that the homologous recombination repair gene polymorphism 135G>C may play a role in carcinoma of the colorectal occurrence [22, 23].

Few studies have investigated the association between the *RAD51* 172G>T SNP and risk of cancer. In a large European case-control study of patients with breast cancer, the 172T variant genotypes of *RAD51* were found to be associated with a non-significantly reduced risk of breast cancer [20]. Similar results were reported in a Korean case-control study of breast cancer [21].

Conversely, in a recent case-control study of epithelial ovarian cancer, none of the 135G>C and 172G>T variants of *RAD51* were associated with a reduction in risk [32].

Our earlier study suggests that the polymorphism 135G>C of the *RAD51* gene may be positively associated with endometrial carcinoma in the Polish women [33].

In this work we investigated single nucleotide polymorphisms of *RAD51* 135G>C and 172G>T and their association with human colorectal cancer. Single nucleotide polymorphisms have been identified in the 5' untranslated region of the *RAD51* gene and have been shown to influence gene transcription activity. *RAD51* expression is often increased in various malignancies [34].

What is important, recent reports demonstrate the role of *RAD51* 135G>C polymorphism in the development of CRC.

Krupa *et al.* found that C135C genotype decreased the risk of colorectal cancer in the Polish population. However, TNM and Dukes' staging were not related to *RAD51* polymorphism [23].

Other data show that G/C heterozygote of the 135 G/C *RAD51* polymorphism may be associated with the increased risk of colorectal cancer development [23].

In conclusion, in the recent studies, the 135G>C polymorphism of *RAD51* may be associated with an elevated tumour risk in the Polish population in CRC [11]. There are no data about the significance of the *RAD51* 135G>C and 172G>T polymorphisms in CRC in other populations.

Our results confirm the important role of *RAD51* 135G>C polymorphism for colorectal carcinoma occurrence in Poland. In this study, *RAD51* C/C genotype increased the risk of CRC in the Polish population. There was a 5-fold increased risk of colorectal carcinoma for individuals carrying *RAD51*-C/C genotype, compared with subjects carrying *RAD51*-G/G, G/C genotype, respectively. We identified the combined genotype of C135C-G172G, C135C-G172T and C135C-T172T that was associated with CRC risk and may have an impact on identification of a high-risk population. The 135C allele increased the risk of CRC. *RAD51* G135C polymorphism was not related to the cancer stage. The reason can be a relatively small group of A, B and C stage enrolled in our study.

It is possible that the presence of the C allele is in linkage disequilibrium with another, so far unknown, mutation located outside the coding region in the *RAD51* gene, which may be of importance for the RAD51 concentration in plasma. To our knowledge, this is the first study linking the 172G>T polymorphism of the *RAD51* gene with colorectal cancer.

Finally, we suggested that *RAD51* 135G>C might be used as a predictive factor for precancerous lesion for colorectal cancer in the Polish population. Further studies on the role of these genes on CRC is warranted.

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