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RESEARCH

# Single Nucleotide Polymorphisms (SNPs) of *RAD51*-G172T and *XRCC2*-41657C/T Homologous Recombination Repair Genes and the Risk of Triple- Negative Breast Cancer in Polish Women

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**Abstract** Double strand DNA breaks are the most dangerous DNA damage which, if non-repaired or misrepaired, may result in genomic instability, cancer transformation or cell death. *RAD51* and *XRCC2* encode proteins that are important for the repair of double-strand DNA breaks by homologous recombination. Therefore, genetic variability in these genes may contribute to the occurrence and progression of triple-negative breast cancer. The polymorphisms of the *XRCC2* gene -41657C/T (rs718282) and of the *RAD51* gene, −172G/T (rs1801321), were investigated by PCR-RFLP in 70 patients with triple-negative breast cancer and 70 age- and sex matched non-cancer controls. The obtained results demonstrated a significant positive association between the *RAD51* T/T genotype and TNBC, with an adjusted odds ratio (OR) of 4.94 ($p$=0.001). The homozygous T/T genotype was found in 60 % of TNBC cases and in 14 % of the used controls. Variant 172 T allele of *RAD51* increased cancer risk (OR=2.81 (1.72–4.58), $p$<.0001). No significant associations were observed between -41657C/T genotype of *XRCC2* and the incidence of TNBC. There were no significant differences between the distribution of *XRCC2* -41657C/T genotypes in the subgroups assigned to histological grades. The obtained results indicate that the polymorphism of *RAD51,* but not of *XRCC2* gene, may be positively associated with the incidence of triple-negative breast carcinoma in the population of Polish women.

**Keywords** *RAD51* · *XRCC2* · Triple negative breast cancer · Gene polymorphism

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## Introduction

Triple-negative breast cancer (TNBC) is a subtype of breast cancer defined by the lack of expression of estrogen, progesterone and HER-2 (human epidermal receptor-2) receptors. TNBC refers to about 15–20 % of all breast cancer cases. It is characterised by worse clinical outcome, poor prognosis and absence of prognostic indicators [1–5].

Mutations in DNA of double-strand breaks (DSB) repair genes are involved in the pathogenesis of tumours, however, it is still unclear whether any defects in this pathway may play any role in the aetiology of triple-negative breast cancer.

DSB in DNA may be rectified either by homologous recombination (HR) or non-homologous end joining (NHEJ) [6, 7].

RAD51 is involved in the homologous recombination and repair of double-strand breaks in DNA and DNA cross-links and is responsible for the maintenance of chromosome stability [8].

*RAD51* gene has been mapped to chromosome 15q14-15 and is polymorphic in nature. The involvement of *RAD51* in the DNA repair determines its potential role in maintaining genetic stability, which is disturbed in cancer. Therefore the

problem of genetic variability of the *RAD51* gene in cancer is worthy studying. A substitution G/T at position 172 in 5′ untranslated region of the *RAD51* gene (the 172G/T 5′UTR polymorphism) has been reported as a possible factor to affect the *RAD51* mRNA stability [8, 9]. 172G/T polymorphism of *RAD51* is located in the regulatory element of the *RAD51* promoter and is suggested to be associated with messenger RNA expression [8, 9].

In literature, many of researches suggest that 5′UTR polymorphism of *RAD51* gene may contribute to mammary carcinogenesis. However, the reported results have rather been inconsistent [10–16].

*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 [17].

It is known that polymorphisms in *XRCC2* may modify individual susceptibility to breast cancers [13, 14, 18–20]. Common variants within *XRCC2*, particularly a coding single nucleotide polymorphism (SNP) in exon 3 (Arg188His, R188H, rs3218536), have in recent studies been identified may be associated with a significantly increased risk of breast cancer [13, 14, 18–20].

Unfortunately, it is difficult to find in the literature reports directly binding -41657C/T SNP in DNA repair gene *XRCC2* with breast cancer occurrence.

Because little is known on the association between *RAD51*-172G/T and *XRCC2*-41657C/T polymorphisms and TNBC, it was studied whether the polymorphisms in the two genes, being involved in the homologous recombination of double-strand breaks, could have been linked with the risk for triple-negative breast cancer in that Polish population.

## Materials and Methods

### Patients with Triple- Negative Breast Cancer

A total of 70 patients with histologically-proven diagnosis of TNBC were included in the reported study. The distributions of sociodemographic characteristics, lifestyle risk factors and clinical characteristics of the patients are shown in Tables 1 and 2, respectively. Paraffin embedded tumour tissue specimens were obtained from women with triple-negative breast carcinoma, treated at the Department of Oncology, Institute of Polish Mothers Memorial Hospital, between 2000–2013. The age of the patients ranged in from 36 to 68 years (the mean age 46.2± 10.12). The median follow-up of patients at the time of analysis was 38 months (the range: 2–70 months). The average tumor size was 20 mm (the range 17–32 mm). All the diagnosed tumours were graded by criteria of the Scarf-Bloom-Richardson. DNA from non-cancerous breast tissue ($n$=70) served as control (mean age 45.41±

**Table 1** Characteristics of breast cancer patients[a] with questionnaire data

| Characteristics | Number of cases (%) |
|---|---|
| Age (years) | |
| <45 | 27 (39) |
| 45–54 | 15 (21) |
| 55–64 | 18 (26) |
| >64 | 10 (14) |
| Family history of breast cancer[b] | |
| Yes | 25 (36) |
| No | 45 (64) |
| BMI (body mass index) (kg/m$^2$) | |
| <24.9 | 25 (36) |
| 25–29.9 | 20 (28) |
| >30 | 25 (36) |
| Smoking status[c] | |
| Never | 23 (33) |
| Ever | 27 (39) |
| Moderate | 10 (14) |
| Heavy | 10 (14) |
| Alcohol intake[d] | |
| Never/rare | 22 (31) |
| Light | 18 (26) |
| Moderate | 10 (14) |
| Heavy | 9 (13) |
| Ex–drinker | 11 (16) |
| Menarche (years) | |
| 10 | 5 (7) |
| 11 | 18 (26) |
| 12 | 19 (27) |
| 13 | 13 (19) |
| 14 | 10 (14) |
| ≥15 | 5 (7) |
| Parity | |
| Nulliparous | 25 (36) |
| 1 | 15 (21) |
| 2 | 16 (23) |
| 3 | |
| ≥4 | 9 (13) |
| 5 (7) | |
| Menopause status | |
| Premenopausal | 30 (43) |
| Postmenopausal | 40 (57) |
| Use of menopausal hormones[e] | |
| Never | 37 (53) |
| Estrogen | 33 (57) |

[a] $n$=70

[b] Family history defined as self-reporting of at least one first-degree relative with known breast cancer

[c] Non-smoking patients (never), patients smoking 10 cigarettes per day for 10 years (ever), patients smoking 20 cigarettes per day for 20 years (moderate) and patients smoking 20 cigarettes per day for thirty years (heavy)

[d] Never/rare,<1 U/week; light, 1–8.9 U/week; moderate, 9–17.9 U/week; heavy, ≥18 U/week; where 1 U=22 g ethanol

**Table 2** Characteristic features of triple-negative breast cancer patients[a]

| Triple-negative breast cancer | Patients ($n$=70) | |
|---|---|---|
| | n | % |
| Scarf-Bloom-Richardson stage | | |
| I | 20 | 29 |
| II | 45 | 64 |
| III | 5 | 7 |
| Tumor size grade | | |
| T1 | 8 | 11 |
| T2 | 40 | 57 |
| T3 | 18 | 26 |
| T4 | 4 | 6 |
| Lymph node status | | |
| N0 | 32 | 46 |
| N1 | 12 | 17 |
| N2 | 14 | 20 |
| N3 | 7 | 10 |
| N4 | 5 | 7 |

[a] $n$=70

18.21). The Local Ethical Committee approved the study and each patient gave a written consent for participation in the study.

Breast tissue samples (cancerous and non-cancerous) were routinely fixed in phormaldehyde, embedded in paraffin, cut into thin slices and stained with haematoxylin/eozin for pathological examination. DNA for analysis was obtained from archival pathological paraffin-embedded tumour specimens and from samples of non-cancerous breast tissue, which were deparaffinised in xylene and rehydratated in ethanol and distilled water. In order to ensure that the chosen histological material was representative for cancerous and non-cancerous tissue, each tissue sample, qualified for DNA extraction, was initially checked by a pathologist. DNA was extracted 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 and -172G/T polymorphisms as described previously [21–23].

### Statistical Analysis

For each polymorphism, departure of the genotype distribution from that expected from Hardy-Weinberg equilibrium was assessed using the standard $\chi^2$-test. Genotype frequencies in the study cases and the controls were compared by $\chi^2$-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 STAT ISTICA 6.0 software (Statsoft, Tulsa, Oklahoma, USA).

## Results

Table 3 shows genotype distribution of *RAD51* polymorphism, illustrating the difference between the patients with TNBC and the controls. The Table clearly indicates significant differences ($p$<0.05) between the two investigated groups. A weak association was observed between the occurrence of triple-negative breast carcinoma and the presence of G/T and T/T genotypes. A stronger association was observed for T/T homozygotes than for G/T heterozygotes. Variant 172 T allele of *RAD51* increased cancer risk. The frequencies of G/G, G/T and T/T genotypes, observed in the study patients, differed significantly ($p$<0.05) from the distribution values, as expected from the Hardy-Weinberg equilibrium.

**Table 3** Distribution of *RAD51* genotype and allele frequencies in patients with triple- negative breast cancer and in control groups

| | Patients with TNBC $n$=70 | | Controls $n$=70 | | | |
|---|---|---|---|---|---|---|
| 172G/T | Number | (%) | Number | (%) | OR (95 % CI)[a] | $p$[b] |
| G/G | 17 | 24 | 20 | 29 | 1.00 Ref | |
| G/T | 11 | 16 | 40 | 57 | **0.32 (0.13–0.82)** | **0.028** |
| T/T | 42 | 60 | 10 | 14 | **4.94 (1.91–12.71)** | **0.001** |
| G | 45 | 32 | 80 | 57 | 1.00 Ref | |
| T | 95 | 68 | 60 | 43 | **2.81 (1.72–4.58)** | **<.0001** |

Data in bold font are statistically significant

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

[b] Chi square

No statistically significant differences were observed between the control group and the patients with triple-negative breast cancer, regarding either allele or genotype frequencies of *XRCC2* -41657C/T gene polymorphism (see Table 4).

Scarf-Bloom-Richardson grading was related to *RAD51* and *XRCC2* polymorphisms. Histological grade was evaluated in all the cases ($n$=70), where 20 cases were of grade I, 45 of grade II and 5 of grade III. Grade II and III were grouped together for the purposes of statistical analysis (see Table 5). No differences were observed in those groups between *RAD51* and *XRCC2* genotype distributions, while a lack of correlation was demonstrated between genotypes of the identified polymorphisms and TNBC invasiveness.

We did not find any association of the *XRCC2* and *RAD51* polymorphisms in patients group with cancer progression assessed by breast cancer with (N+) and without (N-) lymph node metastases ($p$>0.05). Our data did not demonstrate any statistically significant correlation between *RAD51* and *XRCC2* polymorphisms and the risk factors for breast cancer, such as BMI (body mass index), smoking status, alcohol consumption, menarche, menopause status, reproductive histories, exogenous hormone use and medical history (data not shown).

**Table 5** Dependence of *RAD51* and *XRCC2* gene polymorphism genotypes and allele frequency on tumour grade in patients with triple–negative breast cancer[a]

| grade[b] *RAD51* 172G/T | I ($n$=20) Number (%) | II+III ($n$=50) Number (%) | OR (95 % CI)[c] | $p$[d] |
|---|---|---|---|---|
| G/G | 4 (20 %) | 13 (26 %) | 1.00 Ref | |
| G/C | 2 (10 %) | 9 (18 %) | 0.72 (0.10–4.82) | 0.560 |
| C/C | 14 (70 %) | 28 (56 %) | 1.62 (0.44–5.91) | 0.671 |
| G | 10 (25 %) | 35 (35 %) | 1.00 Ref | |
| C | 30 (75 %) | 65 (65 %) | 1.61 (0.70–3.68) | 0.345 |
| *XRCC2* 41657C/T | | | | |
| C/C | 4 (20 %) | 14 (28 %) | 1.00 Ref | |
| C/T | 14 (70 %) | 21 (42 %) | 1.19 (0.33–4.23) | 0.526 |
| T/T | 2 (10 %) | 15 (30 %) | 0.47 (0.07–2.95) | 0.357 |
| C | 22 (55 %) | 49 (49 %) | 1.00 Ref | |
| T | 18 (45 %) | 51 (51 %) | 0.79 (0.37–1.64) | 0.647 |

[a] $n$=70

[b] according to Scarf-Bloom-Richardson criteria

[c] Crude odds ratio (OR), 95 % *CI* confidence interval at 95 %

[d] Chi square

## Discussion

Breast cancer classification is in constant evolution, as advances in molecular pathology as well as immunohistochemical staining allow researchers to define the molecular heterogenity of different disease subtypes and to guide the selection of appropriate treatment. The triple negative phenotype, defined as the lack of estrogen receptor, progesterone receptor and HER-2 expression, represents approximately 15-20 % of breast cancer cases and has a worse clinical outcome and prognosis than other breast cancer subtypes [1–5].

As it has already been mentioned above, little is known on the association between the homologous recombination repair *RAD51* and *XRCC2* SNPs and triple-negative breast cancer. Therefore, it was attempted to investigate the role of genetic variation in homologous recombination repair genes and the risk of TNBC.

As mentioned in Introduction mutations in DNA double-strand breaks repair genes are involved in the pathogenesis of tumours. Defects in this pathway may play a role in development and progression of breast cancer [24, 25].

In the literature, many reports confirm the significance *RAD51* gene polymorphisms in the 5′UTR, regarding the risk of breast carcinoma [16, 26–28]. However, the reported results have rather been inconsistent [10–16].

No significant associations were observed between the 172G/T and breast cancer in Korean women. The genotype distributions of *RAD51* SNP did not differ significantly from Hardy-Weinberg equilibrium ($P$>0.05) and the frequencies of minor alleles were 0.13 for *RAD51* 135C and 0.05 for *RAD51* 172 T. When the two loci in the same gene were evaluated for

**Table 4** Distribution of *XRCC2* genotype and allele frequencies in patients with triple- negative breast cancer and in control groups

| | Patients with TNBC $n$=70 | | Controls $n$=70 | | | |
|---|---|---|---|---|---|---|
| −41657C/T | Number | (%) | Number | (%) | OR (95 % CI)[c] | $p$[b] |
| C/C | 18 | 26 | 17 | 24 | 1.00 Ref | |
| C/T | 35 | 50 | 37 | 53 | 0.89 (0.39–2.00) | 1.000 |
| T/T | 17 | 24 | 16 | 23 | 1.00 (0.38–2.59) | 0.806 |
| C | 71 | 51 | 71 | 51 | 1.00 Ref | |
| T | 69 | 49 | 69 | 49 | 1.00 (0.62–1.59) | 0.920 |

[a] Crude odds ratio (OR), 95 % *CI* confidence interval at 95 %

[b] Chi square

linkage disequilibrium, two loci in *RAD51* gene (135G/C and 171G/T) were in negative linkage disequilibrium [15].

Shin et al. examined the role of SNPs in *RAD51* repair genes and the risk of breast cancer. In the reported study, the 135G/C but not 172G/T polymorphism, of *RAD51* gene, was associated with breast carcinoma occurrence [16].

Other experimental study confirms the significance *RAD51* gene G135C polymorphism, regarding the risk of breast carcinoma [10–14].

The role of -41657C/T variation of *XRCC2* in breast cancer is still unknown. Some reports documented 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 [22, 29].

It appears from literature review that *RAD51* and *XRCC2* polymorphisms have been investigated in various types of malignancy. A large number of studies confirm a significant role of the influence of specific genetic variants on repair phenotype and cancer risk [29–34].

Unfortunately, it is difficult to find reports in the available literature, which would directly bind *RAD51* and *XRCC2* SNP in DNA repair gene by HR with clinical-pathological features of breast tumour. Only in single studies the researchers suggest that the homologous recombination repair gene polymorphism may play some role in the development of breast carcinoma [13].

Two single nucleotide polymorphisms of *XRCC2*-41657C/T, and *RAD51*-172G/T were investigated in the reported study, as well as their association with human triple- negative breast cancer.

In literature, neither *XRCC2*-41657C/T nor *RAD51*-172G/T polymorphism is correlated with risk of breast cancer [15, 16]. What are important, recent reports introduce the role of *RAD51* 135G/C polymorphism in the development of triple-negative breast cancer [27].

In the recent studies, 135G/C polymorphism of *RAD51* may be associated with an elevated tumour risk in the Polish populations, regarding TNBC [28], while there are still no data, which would be illustrating the significance of *RAD51* polymorphism for triple-negative breast cancer development in other populations.

The obtained results confirm the important role of *RAD51* G172T polymorphism for TNBC occurrence in Poland. In the reported study, *RAD51* T/T genotype increased the risk of breast cancer in the Polish population. There was a 4.94-fold increased risk of breast carcinoma for *RAD51*-T/T genotype carriers, compared with subjects with *RAD51*-G/G, G/T genotype. The 172 T allele increased the risk of TNBC. *RAD51* G172T polymorphism was not related to cancer grade. It is possible that the presence of the 172 T allele is in some disequilibrium with another, so far unknown, mutation, located outside the coding region in *RAD51* gene, which may be of importance for RAD51 concentration in plasma.

No significant associations were observed between -41657C/T genotype of *XRCC2* and the incidence of TNBC in the Polish women.

In conclusion, the obtained data confirm the important role of *RAD51* 172G/T - but not of -41657C/T of *XRCC2* gene polymorphism in triple-negative breast cancer aetiology.

Finally, we suggest that *RAD51* 172G/T may be used as a prognosing factor of precancerous lesions, predicting TNBC in the Polish population. Further studies are required, regarding the role of these genes in the aetiology of triple-negative breast cancer.

**Conflict of Interests** The authors declare that there are no conflicts of interests.



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