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ORIGINAL ARTICLE

Data on Single Nucleotide Polymorphism of DNA Repair Genes and Breast Cancer Risk from Poland

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Abstract

Single nucleotide polymorphisms (SNPs) may modify the risk of cancer. They may be then regarded as potential markers of carcinogenesis. The aim of this study was to analyze the frequency of genotypes and alleles of SNPs in DNA repair genes and to investigate the influence this genetic variation exerts on breast cancer in Polish females. The test group comprised 600 females with breast cancer and 600 healthy controls. Genomic DNA was isolated and the SNPs in DNA repair genes were determined by High-Resolution Melter (HRM) technique. Following polymorphisms were analysed: Arg399Gln (rs25487) of the *XRCC1*, Gly322Asp (rs4987188) of the *hMSH2*, Lys751Gln (rs13181) of the *XPD*, Arg188His (rs3218536) of the *XRCC2*, P871L (rs799917) of the *BRCA1* and N372H (rs144848) of the *BRCA2* gene. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each genotype and allele. Statistically significant correlations were identified between 4 single nucleotide polymorphisms and the breast cancer risk: rs25487 rs4987188 rs13181 and rs799917. The alleles *XRCC1*-Gln (OR 5.11; 95% CI 5.68–11.64, $p < .0001$), *hMSH2*-Asp (OR 4.66; 95% CI 3.90–5.56, $p < .0001$), *XPD*-Gln (OR 2.65; 95% CI 2.24–3.14, $p < .0001$) and *BRCA1*-L (OR 1.45; 95% CI 1.24–1.71, $p < .0001$) genes were strongly correlated with this malignancy. No correlation was found between the studied SNPs and tumor grading nor the lymph node status. Further research on larger groups is warranted to determine the influence of above-mentioned genetic variants on breast cancer risk.

Keywords DNA repair · Single nucleotide polymorphism · Breast cancer

Introduction

Breast cancer is the most frequent malignancy in women, both in Poland and worldwide, and accounts for almost 1/4 of overall cancer cases in humans. Moreover, it is one of the most frequent death causes in women suffering from cancer [1, 2]. Annually almost 16,000 Polish women learn of such a diagnosis and the yearly death toll exceeds 5000. Furthermore, according to estimates, annual morbidity in Poland may rise up to 20,000 in 2020 [2]. According to the latest Eurocare-5 data, the breast cancer five-year survival rate in Polish females is 71.6% which is significantly lower than the mean European value: 82% [3]. In addition, the rate of successful 5-year treatment outcomes in Poland is by 10% lower then the EU average [3, 4].

Numerous genetic variations in various genes may be found in breast cancer patients [5]. However, one cannot be always sure whether the abovementioned are the cause or rather the very effect of cancerous transformation. Provided they are considered to be the former, research can easily benefit from investigation on how genetic variations – i.e. genetic polymorphism – influence carcinogenesis or cancer progression.

DNA repair is a vital tool that protects the cell from mutations that may result in its malignant transformation [6, 7]. According to literature, lion share of cancers is triggered by

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the impaired ability of DNA repair. Therefore, a specific set of repair protein genes' alleles may define the individual ability of DNA damage repair, as well as the susceptibility to cancer development. It is then crucial to learn more of the polymorphic variants of DNA repair genes – including SNPs -, as well as of their distribution in population [8].

Although breast cancer displays a significant genetic component, it is also characterized by quite high cure rates provided the diagnosis was early [9, 10]. This may particularly justify the need for a better diagnostic/prophylactic pathway in subjects diagnosed with unfavorable genetic load which may then eventually result in reduced both morbidity and mortality.

The aim of this study was to investigate the association between SNPs in DNA repair genes and the risk of breast cancer in Polish females. Breast cancer patients were tested for polymorphisms in following genes:

– base excision repair (BER) system

XRCC1 gene - Arg399Gln, polymorphism (rs25487),

– nucleotide excision repair (NER) system

XPD gene - Lys751Gln polymorphism (rs13181),

– mismatch repair (MMR) system

hMSH2 gene - Gly322Asp, polymorphism rs4987188),

– repair by homologous recombination

XRCC2 gene - Arg188His polymorphism (rs3218536),
BRCA1 gene - P871L polymorphism (rs799917) and.
BRCA2 gene - N372H polymorphism (rs144848).

Materials and Methods

Patients

Six hundred blood samples were collected from female breast cancer patients treated in the Department of Oncological Surgery and Breast Diseases, Polish Mother's Memorial Hospital, Lodz, Poland. Demographic data and pathological features of the cases are both summarized in Table 1. Breast cancer samples were graded according to Scarf-Bloom-Richardson criteria. 600 age-matched disease-free women were selected as controls (see Table 1). All analyzed subjects were Caucasians and constituted a homogenous population of the same ethnic and geographical origins. Blood samples were derived in EDTA-vacuum tubes and kept frozen in −20 °C until initial processing. All participants gave a written informed consent. A formal consent was also issued by the Bioethical Committee of the Institute of the Polish Mother's Memorial Hospital in Lodz (Approval number: 10/2012).

Table 1 The characteristic of 600 patients with breast cancer and 600 controls

	Patients ($n = 600$)	Controls (n = 600)
Mean ± SD		
Age (years)	61,18 ± 11,76	63,12 ± 10,54
n (%)		
Menopause status		
Premenopausal	275 (46)	210 (35)
Postmenopausal	325 (54)	390 (65)
Menarche (years)		
10	120 (20)	125 (21)
13	140 (23)	148 (25)
14	138 (23)	130 (21)
≥ 15	202 (34)	197 (33)
Parity		
0	150 (25)	138 (23)
1	140 (23)	148 (25)
2	152 (25)	148 (25)
≥ 3	160 (27)	166 (27)
Obesity (BMI ≥ 30 kg/m2)		
Yes	240 (40)	200 (33)
No	360 (60)	400 (67)
Use of menopausal hormones		
Never	242 (40.4)	215 (36)
Estrogen	358 (59.6)	385 (64)
ER and PR status		
ER+	144 (24)	
PR+	158 (26)	
HER2+	222 (37)	
ER + PR + HER2+	38 (6)	
ER-PR-HER2	38 (6)	
Histopathological grading		
G1	180 (30)	
G2	220 (37)	
G3	200 (33)	
Tumor size grade		
T1	150 (25)	
T2	270 (45)	
T3	180 (30)	
Lymph node status		
N0	160 (27)	
N1	150 (25)	
N2	150 (25)	
N3	140 (23)	

Availability of Data and Material Data will not be shared, because it is part of a clinical database.

DNA Isolation

DNA was extracted from blood samples by QIAamp DNA Kit (Qiagen GmbH, Hilden, Germany) according to manufacturer's instruction.

High Resolution Melting Analyses

PCR products for the analyzed variants were tested by High-Resolution Melter (HRM) analysis. The HRM analysis was carried out in a LightCycler® 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 recommendations. All control DNA samples were employed in each run of HRM analysis. The collected data was analyzed, using the LightCycler® 96 software version SW 1.1 (Roche, Mannheim, Germany). SNPs in DNA repair genes were selected using the public domain of the National Center for Biotechnology Information at http://www.ncbi.nlm.nih.gov/snp (Bethesda, MD, USA). Real-time PCR cycling and conditions for HRM analysis of the examined DNA repair SNPs are summarized in Table 2.

Statistical Analysis

Genotype and allele distributions were evaluated and their compatibility with the Hardy-Weinberg distribution (HWE) was assessed by the means of $\chi 2$ test. Differences between distributions in particular groups were evaluated also by $\chi 2$ 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

Table 3 presents the total distribution of genotypes and alleles of SNPs in both breast cancer patients and in controls. Interestingly, statistically significant differences were demonstrated in genotype distribution in the test group and in controls ($p < 0.05$).

We have demonstrated that *XRCC1*-Gln/Gln genotype of Arg399Gln polymorphism was strongly correlated with breast cancer. The Gln/Gln homozygote increased the risk of cancer eight-fold (OR 8.13). The Gln allele in these patients may itself be a risk factor of breast cancer (OR 5.11; 95% CI 4.24–6.16, $p < .0001$).

This study demonstrated that *hMSH2*- Asp/Asp (OR 10.61; 95% CI 7.43–15.16, p < .0001), *XPD*-Gln/Gln (OR 3.81; 95% CI 2.82–5.13, p < .0001) and *BRCA1*-L/L genotypes (OR 1.95; 95% CI 1.42–2.68, p < .0001) were strongly associated with an increased risk of breast cancer. In addition, the alleles of *hMSH2*-Asp (OR 4.66; 95% CI 3.90–5.56, p < .0001), *XPD*-Gln (OR 2.65; 95% CI 2.24–3.14, p < .0001) and *BRCA1*-L genes (OR 1.45; 95% CI 1.24–1.71, p < .0001) are strongly correlated with this malignancy.

No statistically significant differences were observed in genotype frequencies of both *XRCC2* Arg188His polymorphism and *BRCA2* N372H polymorphism between breast cancer patients and healthy controls ($p > 0.05$) (Table 3).

The observed genotype frequency of *XRCC1*-Arg399Gln, *XPD*-Lys751Gln, *hMSH2* - Gly322Asp, *XRCC2*-Arg188His, *BRCA1* - P871L and *BRCA2* - N372H in controls were in agreement with HWE ($p > 0.05$). In case of the 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* L/L genotype in the examined Polish population.

We did not find any correlation between the repair genes polymorphic variants and tumor grade nor the lymph node status (p > 0.05). Nor was there any relationship between the analyzed polymorphisms and the status of the estrogen (ER), progesterone (PR) or HER2 receptors. DNA repair genes

Table 2 The refSNP and conditions for real-time PCR and the following HRM analysis

Gene	*XRCC1*	*hMSH2*	*XPD*	*XRCC2*	*BRCA1*	*BRCA2*
Polymorphism	Arg399Gln	Gly322Asp	Lys751Gln	Arg188His	P871L	N372H
refSNP	rs25487	rs4987188	rs13181	rs3218536	rs799917	rs144848
Thermal conditions	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					

Table 3 Associations between DNA repair genes SNPs and breast carcinoma risk

	Patients (n = 600)		Controls (n = 600)			
XRCC1	Number	(%)	Number	(%)	OR (95% CI)[a]	p^b
Arg/Arg	69	11.5	132	22	1.00 Ref	
Arg/Gln	72	12	360	60	0.38 (0.26–0.56)	<.0001
Gln/Gln	459	76.5	108	18	8.13 (5.68–11.64)	<.0001
Arg	210	17.5	624	52	1.00 Ref	
Gln	990	82.5	576	48	5.11 (4.24–6.16)	<.0001
hMSH2	Number	(%)	Number	(%)	OR (95% CI)	*p*
Gly/Gly	84	14	168	28	1.00 Ref	
Gly/Asp	102	17	354	59	0.58 (0.41–0.81)	0.002
Asp/Asp	414	69	78	13	10.61 (7.43–15.16)	<.0001
Gly	270	22.5	690	57.5	1.00 Ref	
Asp	930	77.5	510	42.5	4.66 (3.90–5.56)	<.0001
XPD	Number	(%)	Number	(%)	OR (95% CI)[a]	*p*
Lys/Lys	108	18	192	32	1.00 Ref	
Lys/Gln	132	22	240	40	0.97 (0.71–1.34)	1.000
Gln/Gln	360	60	168	28	3.81 (2.82–5.13)	<.0001
Lys	348	29	624	52	1.00 Ref	
Gln	852	71	576	48	2.65 (2.24–3.14)	<.0001
XRCC2	Number	(%)	Number	(%)	OR (95% CI)[a]	*p*
Arg/Arg	144	24	156	26	1.00 Ref	
Arg/His	216	36	216	36	1.08 (0.81–1.45)	0.647
His/His	240	40	228	38	1.14 (0.85–1.52)	0.417
Arg	504	42	528	44	1.00 Ref	
His	696	58	672	56	1.09 (0.92–1.27)	0.342
BRCA1	Number	(%)	Number	(%)	OR (95% CI)[a]	*p*
P/P	117	19.5	150	25	1.00 Ref	
P/L	255	42.5	300	50	1.09 (0.81–1.46)	0.617
L/L	228	38	150	25	1.95 (1.42–2.68)	<.0001
P	489	41	600	50	1.00 Ref	
L	711	59	600	50	1.45 (1.24–1.71)	<.0001
BRCA2	Number	(%)	Number	(%)	OR (95% CI)[a]	*p*
N/N	156	26	171	28.5	1.00 Ref	
N/H	276	46	246	41	1.23 (0.93–1.62)	0.163
H/H	168	28	183	30.5	1.01 (0.74–1.36)	1.000
N	588	49	588	49	1.00 Ref	
H	612	51	612	51	1.00 (0.85–1.17)	1.000

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

polymorphisms were also unrelated to the patients' age, hormone replacement therapy (HRT), number of births, the date of menarche, nor menopause status ($p > 0.05$).

Discussion

In this project, we have focused on evaluating the role of single nucleotide polymorphisms of DNA repair genes in the pathogenesis of breast cancer. The primary objective of our study was to identify the SNPs associated with the risk of breast cancer in Polish females and to estimate the cancer risk in SNPs carriers. The results of our research may contribute to a better understanding of the molecular background of the disease development and enable to evaluate the probability of its occurrence in specific subjects in population. Regarding the abovementioned study, we focused on the polymorphisms with an already proven significance in carcinogenesis, but not yet analyzed in breast cancer patients. In our study, the analyzed individuals were ethnically homogenous: Polish females from Lodz Region.

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

Genes involved in MMR include: *hMLH1*, *hMSH2*, *hPMS2* and *hMSH6*. We focused on analyzing of the relationship between Gly322Asp polymorphism of *hMSH2* gene and breast cancer. We selected the 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 malignancy in both colon and stomach, as well as increase the incidence of lymphoma and anemia [11–13].

Our study demonstrated that Gly322Asp polymorphism was strongly associated with an increased risk of breast cancer in Polish women. The Asp allele may as such be a risk factor of breast cancer.

We tested 600 breast cancer females for polymorphisms of both BER system (*XRCC1*) and the NER system (*XPD*) genes. BER is mainly intended to remove uncomplicated but potentially dangerous DNA damages, such as oxidized and N-alkylated nitrogen bases [14]. NER enables the removal of various types of damages, including the more complex ones than those removed by BER, including - among others - the photoproducts, such as pyrimidine dimers, interstrand bonds, large adducts resulting from exposure to aflatoxin, benzo[a]pyrene, psolarens or polycyclic aromatic hydrocarbons [15]. A series of enzymes are involved in BER and NER, including XRCC1 and XPD which harbor polymorphisms associated with the risk of tumors [8, 16, 17].

We have demonstrated that the polymorphic form of *XRCC1* and *XPD* contributes to an increased risk of breast cancer in Polish women: alleles of *XRCC1*-Gln and *XPD* - Gln are strongly correlated with this malignancy.

Literature proves DNA damages to be highly significant in the pathogenesis of breast cancer. This phenomenon is especially found in these damages, where repair by homologous recombination is required [18, 19].

The repair system via homologous recombination repairs DNA double-strand breaks (DSB), which carry the highest cell mortality risk of all known DNA damages. Non-repaired DSBs result in a loss of chromosome fragments and - in consequence – in cell's death. Accumulated DSBs lead to genome destabilization and to its unfavorable rearrangement [20, 21]. Disorders in genomic DNA accumulate with age, causing deregulation of transcription process, which then leads to cancer development [22]. Genes that encode double-strand break repairing proteins are highly polymorphic and - taking into account the significance of the defects in cancer development - it seems crucial to expand the knowledge on the role of genetic polymorphisms in breast cancer [23].

We have demonstrated a possible correlation of rs799917 polymorphism of *BRCA1* repair gene with breast cancer. Yet, it should be emphasized that this is the first paper on Polish breast cancer females that directly addresses this very polymorphism. Earlier reports of various researchers who were dealing with SNPs in *RAD51* gene - with our co-authorship as well – focused mainly on G135C and G172 T polymorphisms at 5′ region, that is not a subject of translation [24–28].

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 [29, 30]. G135C polymorphism can modify the way of mRNA splicing, what - in turn - affects the protein functions or the effectiveness of translation [31]. In spite of the abundance of results, there is still no unequivocal explanation of the role of RAD51 in cancer formation.

Our assumption was that 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 breast cancer development. Our research was then oriented towards less investigated SNPs within *BRCA1* and *BRCA2* genes: P871L (rs799917) and N372H (rs144848).

In this study, significant correlations were identified between breast cancer and the new, not yet reported in literature, SNP-type polymorphism in *BRCA1* (rs799917). No correlation was found between the studied SNP and tumor grade, nor tumor size, nor the lymph node status. Nor was there any relationship demonstrated between the analyzed polymorphism and the status of the estrogen, progesterone or HER2 receptors.

To conclude, this study contributes to a better knowledge of the molecular background of breast cancer. Our results point out the DNA repair genes and their polymorphisms, which can be involved in breast cancer formation in Polish women. They may find practical application in improvement in cancer diagnostics and may eventually result in decrease of morbidity and mortality in breast cancer patients.

Conclusions

1. We demonstrated a significant relationship between the single nucleotide polymorphism of *hMSH2* (rs4987188) gene, participating in DNA repair via mismatch repair (MMR) and an increased risk of breast cancer.
2. We demonstrated a significant relationship between the single nucleotide polymorphism of *XPD* (rs13181) gene, participating in DNA repair via nucleotide excision repair (NER) and an increased risk of breast cancer.

3. We demonstrated a significant relationship between the single nucleotide polymorphism of *XRCC1* (rs25487) gene, participating in DNA repair via nitrogen base excision repair (BER) and an increased risk of breast cancer.
4. We presented a significant correlation between single nucleotide polymorphism of DNA double-strand break repair genes via homologous recombination (HRR) *BRCA1* (rs799917), and breast cancer development.
5. The single nucleotide polymorphisms within the studied DNA repair genes may enrich the scope of new risk factors of breast cancer in Polish women.

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Authors' Contributions Conceived and designed the experiments: MB, BS, HR. Performed the experiments – case group: BS, EF. Case group design and collect: MZ, HR. Performed the experiments – control group: BS, EF. Analysed data: BS, HR, MB. Contributed reagents/materials/analysis tools BS. Contributed to the writing of manuscript: BS, HR, JB. All authors approved the final manuscript.

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Compliance with Ethical Standards Ethics approval and consent to participate.

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Disclosure of Potential Conflicts of Interest Author Beata Smolarz declares that she has no conflict of interest. Author Magdalena Bryś declares that she has no conflict of interest. Author Ewa Forma declares that she has no conflict of interest. Author Marek Zadrożny declares that he has no conflict of interest. Author Jan Bieńkiewicz declares that he has no conflict of interest. Author Hanna Romanowicz declares that she has no conflict of interest.

Informed Consent Informed consent was obtained from all individual participants included in the study.

A formal consent was also issued by the Bioethical Committee of the Institute of the Polish Mother's Memorial Hospital in Lodz (Approval number, 15.12.2010).

Consent for Publication Not applicable, the manuscript doesn't contain any individual person's data.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ (2008) Cancer statistics, 2008. CA Cancer J Clin 58:71–96
2. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, Forman D, Bray F (2013) Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 49:1374–1403
3. Francisci S, Minicozzi P, Pierannunzio D, Ardanaz E, Eberle A, Grimsrud TK, Knijn A, Pastorino U, Salmerón D, Trama A, Sant M; EUROCARE-5 Working Group (2015) Survival patterns in lung and pleural cancer in Europe 1999-2007: Results from the EUROCARE-5 study. Eur J Cancer 51:2242–2253
4. Coleman MP, Gatta G, Verdecchia A, Estève J, Sant M, Storm H, Allemani C, Ciccolallo L, Santaquilani M, Berrino F, EUROCARE Working Group (2003) EUROCARE-3 summary: cancer survival in Europe at the end of the 20th century. Ann Oncol 14:128–149
5. Martin AM, Weber BL (2000) Genetic and hormonal risk factors in breast cancer. J Natl Cancer Inst 92:1126–1135
6. Kelley MR, Logsdon D, Fishel ML (2014) Targeting DNA repair pathways for cancer treatment: what's new? Future Oncol 10:1215–1237
7. Jackson SP, Bartek J (2009) The DNA-damage response in human biology and disease. Nature 461:1071–1078
8. McCullough LE, Santella RM, Cleveland RJ, Millikan RC, Olshan AF, North KE, Bradshaw PT, Eng SM, Terry MB, Shen J, Crew KD, Rossner P Jr, Teitelbaum SL, Neugut AI, Gammon MD (2014) Polymorphisms in DNA repair genes, recreational physical activity and breast cancer risk. Int J Cancer 134: 654–663
9. Pruthi S, Gostout BS, Lindor NM (2010) Identification and Management of Women with BRCA mutations or hereditary predisposition for breast and ovarian cancer. Mayo Clin Proc 85:1111–1120
10. Pal T, Vadaparampil ST (2012) Genetic risk assessments in individuals at high risk for inherited breast cancer in the breast oncology care setting. Cancer Control 19:255–266
11. Dowty JG, Win AK, Buchanan DD, Lindor NM, Macrae FA, Clendenning M, Antill YC, Thibodeau SN, Casey G, Gallinger S, Marchand LL, Newcomb PA, Haile RW, Young GP, James PA, Giles GG, Gunawardena SR, Leggett BA, Gattas M, Boussioutas A, Ahnen DJ, Baron JA, Parry S, Goldblatt J, Young JP, Hopper JL, Jenkins MA (2013) Cancer risks for MLH1 and MSH2 mutation carriers. Hum Mutat 34:490–497
12. Wu S, Chen J, Ji Y, Liu Y, Gao L, Chen G, Shen K, Huang B (2011) Association between the hMSH2 IVS12–6 T>C polymorphism and cancer risk: A meta-analysis. Exp Ther Med 2:1193–1198
13. Bansidhar BJ (2012) Extracolonic manifestations of lynch syndrome. Clin Colon Rectal Surg 25:103–110
14. Maynard S, Schurman SH, Harboe C, de Souza-Pinto NC, Bohr VA (2009) Base excision repair of oxidative DNA damage and association with cancer and aging. Carcinogenesis 30:2–10
15. Huang JC, Hsu DS, Kazantsev A, Sancar A (1994) Substrate spectrum of human excinuclease: repair of abasic sites, methylated bases, mismatches, and bulky adducts. Proc Natl Acad Sci U S A 91: 12213–12217
16. Tse D, Zhai R, Zhou W, Heist RS, Asomaning K, Su L, Lynch TJ, Wain JC, Christiani DC, Liu G (2008) Polymorphisms of the NER pathway genes, ERCC1 and XPD are associated with esophageal adenocarcinoma risk. Cancer Causes Control 19:1077–1083
17. Kumar A, Pant MC, Singh HS, Khandelwal S (2012) Associated risk of XRCC1 and XPD cross talk and life style factors in progression of head and neck cancer in north Indian population. Mutat Res 729:24–34
18. Davis JD, Lin SY (2011) DNA damage and breast cancer. World J Clin Oncol 2:329–338
19. Abramson VG, Lehmann BD, Ballinger TJ, Pietenpol JA Subtyping of triple-negative breast cancer: implications for therapy. Cancer 121:8–16
20. Lieber MR (2010) The mechanism of double-strand DNA break repair by the nonhomologous DNA end-joining pathway. Annu Rev Biochem 79:181–211

21. Li X, Heyer WD (2008) Homologous recombination in DNA repair and DNA damage tolerance. Cell Res 18:99–113
22. Gorbunova V, Seluanov A, Mao Z, Hine C (2007) Changes in DNA repair during aging. Nucleic Acids Res 35:7466–7474
23. Khanna KK, Jackson SP (2001) DNA double-strand breaks: signaling, repair and the cancer connection. Nat Genet 27:247–254
24. Zhao M, Chen P, Dong Y, Zhu X, Zhang X (2014) Relationship between Rad51 G135C and G172T variants and the susceptibility to cancer: a meta-analysis involving 54 case-control studies. PLoS One 9:e87259
25. Al Zoubi MS, Zavaglia K, Mazanti C, Al Hamad M, Al Batayneh K, Aljabali AA, Bevilacqua G (2017) Polymorphisms and mutations in GSTP1, RAD51, XRCC1 and XRCC3 genes in breast cancer patients. Int J Biol Markers. https://doi.org/10.5301/ijbm.5000258
26. Romanowicz-Makowska H, Smolarz B, Zadrozny M, Westfa B, Baszczyński J, Kokołaszwili G, Burzyfiski M, Połać I, Sporny S (2012) The association between polymorphisms of the RAD51-G135C, XRCC2-Arg188His and XRCC3-Thr241Met genes and clinico-pathologic features in breast cancer in Poland. Eur J Gynaecol Oncol 33:145–150
27. Romanowicz-Makowska H, Smolarz B, Zadrozny M, Westfal B, Baszczynski J, Polac I, Sporny S (2011) Single nucleotide polymorphisms in the homologous recombination repair genes and breast cancer risk in Polish women. Tohoku J Exp Med 224:201–208
28. Michalska MM, Samulak D, Romanowicz H, Smolarz B (2015) 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. Pathol Oncol Res 21:935–940
29. Antoniou AC, Sinilnikova OM, Simard J, Léoné M, Dumont M, Neuhausen SL, Struewing JP, Stoppa-Lyonnet D, Barjhoux L, Hughes DJ, Coupier I, Belotti M, Lasset C, Bonadona V, Bignon YJ, Genetic Modifiers of Cancer Risk in BRCA1/2 Mutation Carriers Study (GEMO), Rebbeck TR, Wagner T, Lynch HT, Domchek SM, Nathanson KL, Garber JE, Weitzel J, Narod SA, Tomlinson G, Olopade OI, Godwin A, Isaacs C, Jakubowska A, Lubinski J, Gronwald J, Górski B, Byrski T, Huzarski T, Peock S, Cook M, Baynes C, Murray A, Rogers M, Daly PA, Dorkins H, Epidemiological Study of BRCA1 and BRCA2 Mutation Carriers (EMBRACE), Schmutzler RK, Versmold B, Engel C, Meindl A, Arnold N, Niederacher D, Deissler H, German Consortium for Hereditary Breast and Ovarian Cancer (GCHBOC), Spurdle AB, Chen X, Waddell N, Cloonan N, Kathleen Cuningham Consortium for Research into Familial Breast Cancer (kConFab), Kirchhoff T, Offit K, Friedman E, Kaufmann B, Laitman Y, Galore G, Rennert G, Lejbkowicz F, Raskin L, Andrulis IL, Ilyushik E, Ozcelik H, Devilee P, Vreeswijk MP, Greene MH, Prindiville SA, Osorio A, Benitez J, Zikan M, Szabo CI, Kilpivaara O, Nevanlinna H, Hamann U, Durocher F, Arason A, Couch FJ, Easton DF, Chenevix-Trench G, Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA) (2007) RAD51 135G–>C modifies breast cancer risk among BRCA2 mutation carriers: results from a combined analysis of 19 studies. Am J Hum Genet 81:1186–1200
30. Kadouri L, Kote-Jarai Z, Hubert A, Durocher F, Abeliovich D, Glaser B, Hamburger T, Eeles RA, Peretz T (2004) A single-nucleotide polymorphism in the RAD51 gene modifies breast cancer risk in BRCA2 carriers, but not in BRCA1 carriers or noncarriers. Br J Cancer 90:2002–2005
31. Wang WW, Spurdle AB, Kolachana P, Bove B, Modan B, Ebbers SM, Suthers G, Tucker MA, Kaufman DJ, Doody MM, Tarone RE, Daly M, Levavi H, Pierce H, Chetrit A, kConFab, ABCFS/CFRBCS, AJBCS, NISOC, Yechezkel GH, Chenevix-Trench G, Offit K, Godwin AK, Struewing JP (2001) A single nucleotide polymorphism in the 5′ untranslated region of RAD51 and risk of cancer among BRCA1/2 mutation carriers. Cancer Epidemiol Biomark Prev 10:955–960