Pathol. Oncol. Res. (2017) 23:117–123
DOI 10.1007/s12253-016-0110-5

ORIGINAL ARTICLE

Analysis of DNA Repair Genes Polymorphisms in Breast Cancer

Hanna Romanowicz[1] · **Łukasz Pyziak**[1] · **Filip Jabłoński**[1] · **Magdalena Bryś**[2] · **Ewa Forma**[2] · **Beata Smolarz**[1]

Received: 29 December 2015 / Accepted: 24 August 2016 / Published online: 29 August 2016

Abstract Genetic polymorphisms in the DNA repair genes may be associated with increased cancer risk. The purpose of this study was to evaluate the association of the DNA repair genes polymorphisms with the risk of breast cancer development. The study included 200 breast cancer patients and 200 healthy controls. The following polymorphisms were studied: C/G (Ser326Cys, rs1052133) of the *hOGG1*, A/C (IVS5 + 33, rs3212961) of the *ERCC1*, A/C (Lys939Gln, rs2228001) of the *XPC*, C/T (Thr241Met, rs861539) of the *XRCC3*, G/T (Leu787Leu, rs1800392) of the *WRN* and G/T (Ser307Ser, rs1056503) of the *XRCC4* gene. Presented study showed statistically significant increase in the breast cancer development risk of the G/G *hOGG1* genotype (OR 8.13; 95 % CI, 4.37–15.14; $p < 0.001$) and for the G *hOGG1* allele (OR 5.11; 95 % CI, 3.69–7.06; $p < 0.001$), as well as for the C/C *ERCC1* genotype (OR 10.61; 95 % CI, 5.72–19.69; $p < 0.001$) and the C *ERCC1* allele (OR 4.66; 95 % CI, 3.43–6.34; $p < 0.001$) in patients with breast cancer in comparison with healthy control group. We also observed positive association of the C/C *XPC* genotype (OR 3.80; 95 % CI, 2.27–6.38; $p < 0.001$) as well as the C *XPC* allele occurrence with an increased breast cancer development risk (OR 2.65; 95 % CI, 1.98–3.55; $p < 0.001$). Furthermore, we found an association of the G/T *WRN* gene polymorphism with increased risk of carcinoma. The *hOGG1*, *ERCC1*, *XPC* and *WRN* genes polymorphisms may be related to development of breast cancer.

Keywords Breast cancer · DNA repair · Genes · Polymorphism

✉ Hanna Romanowicz
hanna-romanowicz@wp.pl

[1] Laboratory of Cancer Genetics, Department of Pathology, Institute of Polish Mother's Memorial Hospital, Rzgowska 281/289, 93-338, Lodz, Poland

[2] Department of Cytobiochemistry, Faculty of Biology and Environmental Protection, University of Lodz, Pomorska 141/143, 90-237, Lodz, Poland

Introduction

Breast cancer is still the most frequent entity among malignant neoplasms encountered in women with worryingly increasing number of new cases [1]. In spite of a noticeable improvement in diagnostic approach and treatment which reduced cancer-related mortality, more efficient methods of diagnosis and therapy are undoubtedly needed. Presumably, the current progress in molecular biology will have a significant impact on that field. One of the promising research areas is the variability of genetic background of DNA repair mechanisms in population [2, 3] and its assumable relation to breast cancer development. The repair process strictly depends on the nature of DNA impairment. A single-strand damage, which allows to use the intact DNA strand as a template for reconstruction of the damaged one, may be corrected by one of three amendment systems: base excision repair (BER), nucleotide excision repair (NER) or mismatch repair (MMR) [4, 5]. More complicated process of repairing, which is connected with a double-strand damage, includes two pathways: non-homologous end joining (NHEJ) and homologous recombination (HRR) [6, 7].

A group of specific proteins is involved in the mechanisms of DNA repair and the variability of the genes encoding such proteins is responsible for possible modulations of this process.

It is suggested in the literature that the differences in response to DNA damage based on genetic polymorphism may

be significantly related to the risk of carcinogenesis [8, 9] thus it is reasonable to investigate that subject in the context of determining potential risk group among patients. BER is the most important reaction to the oxidative damage of the DNA [10]. The protein which plays the essential role in that pathway is the human 8-oxoguanine DNA N-glycosylase 1 (hOGG1) [11]. The group of proteins valid for NER, a mechanism connected mainly with repairing damage of the DNA induced by ultraviolet light, include ERCC1 (excision repair cross-complementing 1) and XP (xeroderma pigmentosum groups A, C, F, G) [12, 13]. Another important protein group, which is involved in HHR process, referring to precise repair of severe DNA impairment with the sister chromatid or homologous chromosome used as a template, encompasses XRCC3 [14] and WNR [15]. Finally, the significant component of NHEJ pathway is XRCC4 [16], a cofactor in DNA ligase complex which participates in joining two DNA ends. The essential source of genetic variability in DNA-repair systems are single nucleotide polymorphisms (SNPs).

In the present study we analyzed an association between breast cancer occurrence and the SNPs encountered in one BER-related, two NER-related, two HRR-related and one NHEJ-related gene: *hOGG1-C/G* (Ser326Cys, rs1052133), *ERCC1-A/C* (IVS5 + 33, rs3212961), *XPC-C/T* (Lys939Gln, rs2228001), *XRCC3-G/T* (Thr241Met, rs861539), *WRN-G/T* (Leu787Leu, rs1800392) and *XRCC4-G/T* (Ser307Ser, rs1056503), respectively.

Materials and Methods

Patients

The study included 400 patients: 200 with breast cancer (aged 42–82 years) and 200 gender- and age-matched healthy controls. All patients and healthy subjects were Caucasian. We enrolled only women born and living in central Poland (Lodz region). Analysed patients were hospitalized in Department of Oncology, Institute of Polish Mother's Memorial Hospital, Lodz, Poland between 2005 and 2010. The study protocol was approved by the ethical committee of the Institute of Polish Mother's Memorial Hospital, Lodz, Poland. The samples, previously collected for diagnostic purposes and anonymized, were used for molecular analysis. Only patients with confirmed pathology diagnosis of ductal breast carcinoma were included into the study. All the tumors were graded by a method, based on the criteria of Scarf-Bloom-Richardson. Tumour grade was classified into Grade 1 (well differentiated), Grade 2 (moderately differentiated) and Grade 3 (poorly differentiated). The distributions of clinical characteristics of the patients are shown in Table 1.

Table 1 The characteristic of breast cancer patients and controls

Characteristics	Patients (n = 200)	Controls (n = 200)
Age (years)		
< 45	57 (28.5 %)	59 (29.5 %)
45–54	50 (25 %)	48 (24 %)
55–64	53 (26.5 %)	46 (23 %)
> 64	40 (20 %)	47 (23.5 %)
Family history of breast cancer[a]		
Yes	90 (45 %)	82 (41 %)
No	110 (55 %)	118 (59 %)
Menarche (years)		
10	30 (15 %)	23 (11.5 %)
11	38 (19 %)	46 (23 %)
12	39 (19.5 %)	41 (20.5 %)
13	38 (19 %)	35 (17.5 %)
14	30 (15 %)	32 (16 %)
≥ 15	25 (12.5 %)	23 (11.5 %)
Parity		
Nulliparous	51 (25.5 %)	46 (23 %)
1	41 (20.5 %)	46 (23 %)
2	42 (21 %)	38 (19 %)
3	35 (17.5 %)	39 (19.5 %)
≥ 4	31 (15.5 %)	31 (15.5 %)
Menopause status		
Premenopausal	95 (47.5 %)	89 (44.5 %)
Postmenopausal	105 (52.5 %)	111 (55.5 %)
Use of menopausal hormones		
Never	102 (51 %)	95 (47.5 %)
Estrogen	98 (49 %)	105 (52.5 %)
Bloom-Richardson grading		
1	65 (32.5 %)	
2	95 (47.5 %)	
3	40 (20 %)	
Tumor size grade		
T1	57 (28.5 %)	
T2	85 (42.5 %)	
T3	58 (29 %)	
Lymph node status		
N0	64 (32 %)	
N1	48 (24 %)	
N2	46 (23 %)	
N3	42 (21 %)	

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

High Resolution Melting Analyses

Peripheral venous blood samples were obtained from all analysed patients at the time of hospital admission. Genomic DNA was prepared using DNeasy Blood & Tissue Kit

(Qiagen GmbH, Hilden, Germany) according to the manufacturer instruction. PCR products for the analysed variants were analysed by High-Resolution Melter (HRM) analysis. Primers for HRM analysis of all examined SNPs are summarized in Table 2. Analysis of the SNPs was performed by help of Light Cycler® 480 High Resolution Melting Master Kit (Roche, Mannheim, Germany) according to recommendations of producer. The non-template control contained water instead of genomic DNA as a negative control. Additionally, positive controls (DNA samples with known genotype) were employed in each HRM analysis run. PCR amplification was performed in LightCycler® 96 (Roche, Mannheim, Germany) Thermocycler. Collected data were analyzed using LightCycler® 96 software version SW 1.1 (Roche, Mannheim, Germany).

Statistics

To determine differences between groups, standard $\chi 2$ test or Fisher's exact test were used. Clinical significance of analyzed polymorphisms was determined using logistic regression analysis and presented in tables as odds ratios (OR) with their 95 % confidence intervals. The deviations from Hardy-Weinberg equilibrium were analyzed using the $\chi 2$ test. All the results were determined to be statistically significant when they reached the significance level of $p \leq 0.050$.

Results

The genotype distributions of analyzed the *hOGG1*-C/G (Ser326Cys, rs1052133), *ERCC1*-A/C (IVS5 + 33, rs3212961), *XPC*-A/C (Lys939Gln, rs2228001), *XRCC3*-C/T (Thr241Met, rs861539), *WRN*-G/T (Leu787Leu, rs1800392) and *XRCC4*-G/T (Ser307Ser, rs1056503). Genes polymorphisms are summarized in Table 3.

In the studies on a series of 200 DNA samples from patients with breast cancer, originating from an ethnically homogenous population, we found a relationship of the studied polymorphisms *hOGG1*-C/G, *ERCC1*-A/C, *XPC*-A/C and *WRN*-G/T with breast cancer occurrence.

In the present work we succeeded to demonstrate that G/G genotype of C/G polymorphism of *hOGG1* gene was associated with an increased risk of breast cancer in studied population, almost eight (OR 8.13; 95 % CI 4.37–15.14) times higher than in case of the other genotypes. We observed that G allele of C/G polymorphism of *hOGG1* gene was strongly associated with breast cancer (OR 5.11; 95 % CI 3.69–7.06, $p < .0001$).

Table 3 shows genotype distribution values of A/C, IVS5 + 33 polymorphisms of *ERCC1* in breast cancer patients and controls. We found a relationship of the studied A/C, IVS5 + 33 polymorphism with breast cancer occurrence. We have demonstrated in the presented report that the C/C variant may increase the risk of studied tumour development (OR 10.61; 95 % CI 5.72–19.69, $p < .0001$). Variant C allele of *ERCC1* increased cancer risk (OR 4.66; 95 % CI 3.43–6.34, $p < .0001$).

We presented that C/C genotype of A/C polymorphism of *XPC* gene (OR 3.80; 95 % CI 2.27–6.38, $p < .0001$) and for the C *XPC* allele (OR 2.65; 95 % CI 1.98–3.55, $p < .0001$), as well as for T/T genotype of G/T polymorphism of *WRN* gene (OR 1.94; 95 % CI 1.12–3.37, $p = 0.024$) and the T *WRN* allele (OR 1.45; 95 % CI 1.09–1.92, $p = 0.011$) were strongly associated with the incidence of the tumour.

We also simultaneously showed that neither C/T polymorphism of *XRCC3* gene nor G/T polymorphism of *XRCC4* gene was in any way related to an increased risk of breast cancer ($p > 0.05$).

The potential relationship between *hOGG1*, *ERCC1*, *XPC*, *WRN*, *XRCC3* and *XRCC4* genotype distribution and clinical data of breast cancer patients was investigated. However the current study failed to show the correlation between analysed genes polymorphisms and tumor size, grade or lymph node status. DNA repair genes polymorphisms were also unrelated to the patients age, menarche, parity, menopause status and family history of cancer ($p > 0.05$).

Table 2 Primer sequences for real-time PCR and the following HRM analysis of the examined DNA repair genes SNPs

	Polymorphism	Primers
hOGG1	Ser326Cys (rs1052133)	5′-CCCTCCTACAGGTGCTGTTC-3′
		5′-TGGGGAATTTCTTTGTCCAG-3′
ERCC1	IVS5 + 33 (rs3212961)	5′-TTGTCCAGGTGGATGTGGTA-3’
		5′-CCTCGCTGAGGTTTTAGCTG-3’
XPC	Lys939Gln (rs2228001)	5′-CCTCAAAACCGAGAAGATGAAG-3’
		5′-CAGGTGTGGGGCCTGTAGT-3’
XRCC3	Thr241Met (rs861539)	5′-CCATTCCGCTGTGAATTTG-3’
		5′-GAAGGCACTGCTCAGCTCAC-3’
WRN	Leu787Leu (rs1800392)	5′-TGGGAATTTGAAGGTCCAAC-3’
		5′-GCATGGTATGTTCCACAGGA-3’
XRCC4	Ser307Ser (rs1056503)	5′-AGGCCTGATTCTTCACTACCTG-3’
		5′-GGCTGCTGTTTCTCAGAGTTTC-3’

Table 3 Distribution of *hOGG1, ERCC1, XPC, XRCC3, WRN* and *XRCC4* genotypes estimated by HRM analysis in DNA samples of breast carcinoma patients

	Patients (n = 200)		Controls (n = 200)			
hOGG1	Number	(%)	Number	(%)	OR (95 % CI)[a]	p^b
C/C	23	11.5	44	22	1.00 Ref	
C/G	24	12	120	60	0.38 (0.20–0.75)	0.007
G/G	153	76.5	36	18	8.13 (4.37–15.14)	<.0001
C	70	18	208	52	1.00 Ref	
G	330	82	192	48	5.11 (3.69–7.06)	<.0001
ERCC1	Number	(%)	Number	(%)	OR (95 % CI)	*p*
A/A	28	14	56	28	1.00 Ref	
A/C	34	17	118	59	0.58 (0.325–1.04)	0.093
C/C	138	69	26	13	10.61 (5.72–19.69)	<.0001
A	90	22.5	230	57.5	1.00 Ref	
C	310	77.5	170	42.5	4.66 (3.43–6.34)	<.0001
XPC	Number	(%)	Number	(%)	OR (95 % CI)[a]	*p*
A/A	36	18	64	32	1.00 Ref	
A/C	44	22	80	40	0.98 (0.56–1.69)	1.000
C/C	120	60	56	28	3.80 (2.27–6.38)	<.0001
A	116	29	208	52	1.00 Ref	
C	284	71	192	48	2.65 (1.98–3.55)	<.0001
XRCC3	Number	(%)	Number	(%)	OR (95 % CI)[a]	*p*
C/C	48	24	52	26	1.00 Ref	
C/T	72	36	72	36	1.08 (0.67–1.81)	0.862
T/T	80	40	76	38	1.14 (0.69–1.88)	0.698
C	168	42	176	44	1.00 Ref	
T	232	58	224	56	1.08 (0.82–1.43)	0.617
WRN	Number	(%)	Number	(%)	OR (95 % CI)[a]	*p*
G/G	39	19.5	50	25	1.00 Ref	
G/T	85	42.5	100	50	1.09 (0.65–1.81)	0.841
T/T	76	38	50	25	1.94 (1.12–3.37)	0.024
G	163	40.8	200	50	1.00 Ref	
T	237	59.2	200	40	1.45 (1.09–1.92)	0.011
XRCC4	Number	(%)	Number	(%)	OR (95 % CI)[a]	*p*
G/G	52	26	57	28.5	1.00 Ref	
G/T	92	46	82	41	1.23 (0.76–1.98)	0.471
T/T	56	28	61	30.5	1.01 (0.59–1.69)	0.920
G	196	49	196	49	1.00 Ref	
T	204	51	204	51	1.00 (0.75–1.31)	0.920

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

[b] Chi square

Discussion

The results of our study showed statistically significant correlation between the investigated SNPs of *hOGG1*, *ERCC1*, *XPC* and *WRN* genes and the breast cancer development in women. However, this correlation was not observed in the case of the examined SNPs of *XRCC3* and *XRCC4* genes.

The relation between *hOGG1* gene and the development of different malignant neoplasms, including breast cancer, has been intensively studied recently [17–52]. A significant correlation between the *hOGG1* Ser326Cys polymorphism and general cancer risk is suggested in the literature, however, according to further meta-analysis, limited to Asian population with no explicit evidence of such strong association in Caucasians [53]. Moreover, the studies of the *hOGG1* Ser326Cys polymorphism in relation to breast cancer risk lead to contradictory conclusions [54]. Our present study revealed an 8-fold increased risk of breast malignancy within the population of Polish women with G/G genotype of *hOGG1* Ser326Cys polymorphism in comparison to the group with

other genotype variants. Furthermore, among the patients with the C/C genotype of the *ERCC1* polymorphism the risk of the breast carcinoma morbidity is 10.61-fold increased compared to the control group. The results confirm the positive correlation between SNP of *ERCC1* and significantly higher risk of breast malignant entities in Caucasian population, which is indicated in the literature [55].

Another conclusion drawn from our research is the significant association between the homozygous C/C variant of *XPC* Lys939Gln polymorphism and the breast carcinoma occurrence which is contrary to the studies reporting the lack of association between polymorphic xeroderma pigmentosum genes and the breast cancer in the Caucasians [56]. In addition, the T/T genotype of *WRN* Leu787Leu polymorphism revealed a strong association with the development of breast malignant tumors in Polish women. This finding generally confirms the connection between the polymorphic *WRN* genes and the increase of breast cancer risk, although the reports indicate this association in Asian population [57].

Although researchers report the significant correlation between the *XRCC3* Thr241Met and polymorphism [58], our study performed on population of Polish women provided opposite results.

Similarly, our analysis of the *XRCC4* Ser307Ser polymorphism did not reveal a considerable association between this SNPs and the breast malignancy in the population of Polish women. However, the results of our research may contribute the current perception of the complex role of *XRCC4* polymorphisms in breast cancer development which are poorly recognized yet [59].

Our research are affected certain limitations. The sample for the present study comprised of 200 patients with cancer. This sample is only a very small proportion of the entire population of breast cancer women in the country. Therefore the obtained results can not be considered as definitive and require further, more extensive evaluations, performed on bigger groups of patients.

To conclude, the SNPs within the analysed genes of DNA repair systems comprise the new potentially important group of risk factors of breast cancer development in the Polish women. The SNPs analysis may be used in the near future as a convenient method of selecting patients with high risk of morbidity. However, considering the equivocal results of the studies presented in the literature, further research in this field on larger groups of patients is recommended.

Conclusions

1. A significant correlation was found between single nucleotide polymorphisms (SNPs) of the *hOGG1* gene of DNA repair by base excision repair (BER) and the formation of breast cancer in women.
2. A significant relationship was demonstrated between SNPs of *ERCC1* and *XPC* genes, participating in DNA repair by excision of nucleotides (NER – nucleotide excision repair) and the occurrence of breast cancer.
3. A significant correlation was found between single nucleotide polymorphism (SNP) of the *WRN* gene of DNA double fracture repair by homologous recombination (HRR) and the formation of breast cancer in women.
4. No correlations were found between SNPs of *XRCC3* and *XRCC4* genes, participating in DNA repair by HRR and non-homologous end joining (NHEJ) and the occurrence of breast cancer.
5. The polymorphisms of single nucleotides within the studied genes of the DNA repair system constitute a group of new risk factors of breast cancer for women.
6. The analysis of the polymorphisms of the studied DNA repair genes may be used in the qualification of patients to high-risk groups.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interests.

References

1. Yeo B, Turner N, Jones A (2014) An update on the medical management of breast cancer. BMJ 348:g3608
2. Helleday T, Petermann E, Lundin C, Hodgson B, Sharma R (2008) DNA repair pathways as targets for cancer therapy. Nat Rev Cancer 8:193–204
3. Matta J, Echenique M, Negron E, Morales L, Vargas W, Gaetan FS, Lizardi ER, Torres A, Rosado JO, Bolaños G, Cruz JG, Laboy J, Barnes R, Medina SS, Romero A, Martinez R, Dutil J, Suarez E, Alvarez-Garriga C, Bayona M (2012) The association of DNA repair with breast cancer risk in women. A comparative observational study. BMC Cancer 12:490
4. Melis JP, van Steeg H, Luijten M (2013) Oxidative DNA damage and nucleotide excision repair. Antioxid Redox Signal 18:2409–2419
5. Larrea AA, Lujan SA, Kunkel TA (2010) DNA mismatch repair. Cell 141:730
6. Brandsma I, Gent DC (2012) Pathway choice in DNA double strand break repair: observations of a balancing act. Genome Integr 3:9
7. Truong LN, Li Y, Shi LZ, Hwang PY, He J, Wang H, Razavian N, Berns MW, Wu X (2013) Microhomology-mediated end joining and homologous recombination share the initial end resection step to repair DNA double-strand breaks in mammalian cells. Proc Natl Acad Sci U S A 110:7720–7725
8. Huang C-S, Chen J-J, Yang S-Y, Cheng C-W, Chern H-D, Chang K-J, Wu P-E, Shen C-Y (2004) Breast Cancer Risk Associated with Genotypic Polymorphism of Oxidative DNA Damage Repair Genes - A Multigenic Study of Base Excision Repair and Transcription-Coupled Repair in Cancer Susceptibility. Journal of Genetics and Molecular Biology 15:116–136
9. Butkiewicz D, Rusin M, Enewold L, Shields PG, Chorazy M, Harris CC (2001) Genetic polymorphisms in DNA repair genes and risk of lung cancer. Carcinogenesis 22:593–597

10. Lu AL, Li X, Gu Y, Wright PM, Chang DY (2001) Repair of oxidative DNA damage: mechanisms and functions. Cell Biochem Biophys 35:141–170
11. Park J, Chen L, Tockman MS, Elahi A, Lazarus P (2004) The human 8-oxoguanine DNA N-glycosylase 1 (hOGG1) DNA repair enzyme and its association with lung cancer risk. Pharmacogenetics 14:103–109
12. Sinha RP, Häder DP (2002) UV-induced DNA damage and repair: a review. Photochem Photobiol Sci 1:225–236
13. Yang J, Liu X, Niu P, Zou Y, Gong Z, Yuan J, Wu T (2007) Dynamic changes of XPA, XPC, XPF, XPG and ERCC1 protein expression and their correlations with levels of DNA damage in human bronchial epithelia cells exposed to benzo[a]pyrene. Toxicol Lett 174:10–17
14. Pierce AJ, Johnson RD, Thompson LH, Jasin M (1999) XRCC3 promotes homology-directed repair of DNA damage in mammalian cells. Genes Dev 13:2633–2638
15. Brosh RM Jr (2013) DNA helicases involved in DNA repair and their roles in cancer. Nat Rev Cancer 13:542–558
16. Junop MS, Modesti M, Guarné A, Ghirlando R, Gellert M, Yang W (2000) Crystal structure of the Xrcc4 DNA repair protein and implications for end joining. EMBO J 19:5962–5970
17. Sterpone S, Mastellone V, Padua L, Novelli F, Patrono C, Cornetta T, Giammarino D, Donato V, Testa A, Cozzi R (2010) Single-nucleotide polymorphisms in BER and HRR genes, XRCC1 haplotypes and breast cancer risk in Caucasian women. J Cancer Res Clin Oncol 136:631–636
18. Romanowicz-Makowska H, Smolarz B, Makowski M, Polac I, Pertynski T (2008) Ser326Cys polymorphism in DNA repair genes hOGG1 in breast cancer women. Pol J Pathol 59:201–204
19. Synowiec E, Stefanska J, Morawiec Z, Blasiak J, Wozniak K (2008) Association between DNA damage, DNA repair genes variability and clinical characteristics in breast cancer patients. Mutat Res 648:65–72
20. Sangrajrang S, Schmezer P, Burkholder I, Waas P, Boffetta P, Brennan P, Bartsch H, Wiangnon S, Popanda O (2008) Polymorphisms in three base excision repair genes and breast cancer risk in Thai women. Breast Cancer Res Treat 111:279–288
21. Cai Q, Shu XO, Wen W, Courtney R, Dai Q, Gao YT, Zheng W (2006) Functional Ser326Cys polymorphism in the hOGG1 gene is not associated with breast cancer risk. Cancer Epidemiol Biomark Prev 15:403–404
22. Zhang Y, Newcomb PA, Egan KM, Titus-Ernstoff L, Chanock S, Welch R, Brinton LA, Lissowska J, Bardin-Mikolajczak A, Peplonska B, Szeszenia-Dabrowska N, Zatonski W, Garcia-Closas M (2006) Genetic polymorphisms in base-excision repair pathway genes and risk of breast cancer. Cancer Epidemiol Biomark Prev 15:353–358
23. Loizidou MA, Michael T, Neuhausen SL, Newbold RF, Marcou Y, Kakouri E, Daniel M, Papadopoulos P, Malas S, Hadjisavvas A, Kyriacou K (2009) DNA-repair genetic polymorphisms and risk of breast cancer in Cyprus. Breast Cancer Res Treat 115:623–627
24. Roberts MR, Shields PG, Ambrosone CB, Nie J, Marian C, Krishnan SS, Goerlitz DS, Modali R, Seddon M, Lehman T, Amend KL, Trevisan M, Edge SB, Freudenheim JL (2011) Single-nucleotide polymorphisms in DNA repair genes and association with breast cancer risk in the web study. Carcinogenesis 32:1223–1230
25. Dhillon VS, Yeoh E, Fenech M (2011) DNA repair gene polymorphisms and prostate cancer risk in South Australia-results of a pilot study. Urol Oncol 29:641–646
26. Agalliu I, Kwon EM, Salinas CA, Koopmeiners JS, Ostrander EA, Stanford JL (2010) Genetic variation in DNA repair genes and prostate cancer risk: results from a population-based study. Cancer Causes Control 21:289–300
27. Chen L, Elahi A, Pow-Sang J, Lazarus P, Park J (2003) Association between polymorphism of human oxoguanine glycosylase 1 and risk of prostate cancer. J Urol 170:2471–2474
28. Xu J, Zheng SL, Turner A, Isaacs SD, Wiley KE, Hawkins GA, Chang BL, Bleecker ER, Walsh PC, Meyers DA, Isaacs WB (2002) Associations between hOGG1 sequence variants and prostate cancer susceptibility. Cancer Res 62:2253–2257
29. Li D, Suzuki H, Liu B, Morris J, Liu J, Okazaki T, Li Y, Chang P, Abbruzzese JL (2009) DNA repair gene polymorphisms and risk of pancreatic cancer. Clin Cancer Res 15:740–746
30. McWilliams RR, Bamlet WR, Cunningham JM, Goode EL, de Andrade M, Boardman LA, Petersen GM (2008) Polymorphisms in DNA repair genes, smoking, and pancreatic adenocarcinoma risk. Cancer Res 68:4928–4935
31. Gangwar R, Ahirwar D, Mandhani A, Mittal RD (2009) Do DNA repair genes OGG1, XRCC3 and XRCC7 have an impact on susceptibility to bladder cancer in the north Indian population? Mutat Res 680:56–63
32. Arizono K, Osada Y, Kuroda Y (2008) DNA repair gene hOGG1 codon 326 and XRCC1 codon 399 polymorphisms and bladder cancer risk in a Japanese population. Jpn J Clin Oncol 38:186–191
33. Karahalil B, Kocabas NA, Ozcelik T (2006) DNA repair gene polymorphisms and bladder cancer susceptibility in a Turkish population. Anticancer Res 26:4955–4958
34. Srivastava A, Srivastava K, Pandey SN, Choudhuri G, Mittal B (2009) Single-nucleotide polymorphisms of DNA repair genes OGG1 and XRCC1: association with gallbladder cancer in north Indian population. Ann Surg Oncol 16:1695–1703
35. Engin AB, Karahalil B, Engin A, Karakaya AE (2011) DNA repair enzyme polymorphisms and oxidative stress in a Turkish population with gastric carcinoma. Mol Biol Rep 38:5379–5386
36. Palli D, Polidoro S, D'Errico M, Saieva C, Guarrera S, Calcagnile AS, Sera F, Allione A, Gemma S, Zanna I, Filomena A, Testai E, Caini S, Moretti R, Gomez-Miguel MJ, Nesi G, Luzzi I, Ottini L, Masala G, Matullo G, Dogliotti E (2010) Polymorphic DNA repair and metabolic genes: a multigenic study on gastric cancer. Mutagenesis 25:569–575
37. Poplawski T, Arabski M, Kozirowska D, Blasinska-Morawiec M, Morawiec Z, Morawiec-Bajda A, Klupińska G, Jeziorski A, Chojnacki J, Blasiak J (2006) DNA damage and repair in gastric cancer–a correlation with the hOGG1 and RAD51 genes polymorphisms. Mutat Res 601:83–91
38. Brevik A, Joshi AD, Corral R, Onland-Moret NC, Siegmund KD, Le Marchand L, Baron JA, Martinez ME, Haile RW, Ahnen DJ, Sandler RS, Lance P, Stern MC (2010) Polymorphisms in base excision repair genes as colorectal cancer risk factors and modifiers of the effect of diets high in red meat. Cancer Epidemiol Biomark Prev 19:3167–3173
39. Stern MC, Conti DV, Siegmund KD, Corral R, Yuan JM, Koh WP, Yu MC (2007) DNA repair single-nucleotide polymorphisms in colorectal cancer and their role as modifiers of the effect of cigarette smoking and alcohol in the Singapore Chinese health study. Cancer Epidemiol Biomark Prev 16:2363–2372
40. Upadhyay R, Malik MA, Zargar SA, Mittal B (2010) OGG1 Ser326Cys polymorphism and susceptibility to esophageal cancer in low and high at-risk populations of northern India. J Gastrointest Cancer 41:110–115
41. Xing DY, Tan W, Song N, Lin DX (2001) Ser326Cys polymorphism in hOGG1 gene and risk of esophageal cancer in a Chinese population. Int J Cancer 95:140–143
42. Lan Q, Mumford JL, Shen M, Demarini DM, Bonner MR, He X, Yeager M, Welch R, Chanock S, Tian L, Chapman RS, Zheng T, Keohavong P, Caporaso N, Rothman N (2004) Oxidative damage-related genes AKR1C3 and OGG1 modulate risks for lung cancer due to exposure to PAH-rich coal combustion emissions. Carcinogenesis 25:2177–2181

43. Qian B, Zhang H, Zhang L, Zhou X, Yu H, Chen K (2011) Association of genetic polymorphisms in DNA repair pathway genes with non-small cell lung cancer risk. Lung Cancer 73:138–146
44. De Ruyck K, Szaumkessel M, De Rudder I, Dehoorne A, Vral A, Claes K, Velghe A, Van Meerbeeck J, Thierens H (2007) Polymorphisms in base-excision repair and nucleotide-excision repair genes in relation to lung cancer risk. Mutat Res 631:101–110
45. Cho EY, Hildesheim A, Chen CJ, Hsu MM, Chen IH, Mittl BF, Levine PH, Liu MY, Chen JY, Brinton LA, Cheng YJ, Yang CS (2003) Nasopharyngeal carcinoma and genetic polymorphisms of DNA repair enzymes XRCC1 and hOGG1. Cancer Epidemiol Biomark Prev 12:1100–1104
46. Elahi A, Zheng Z, Park J, Eyring K, McCaffrey T, Lazarus P (2002) The human OGG1 DNA repair enzyme and its association with orolaryngeal cancer risk. Carcinogenesis 23:1229–1234
47. Krupa R, Sobczuk A, Poplawski T, Wozniak K, Blasiak J (2011) DNA damage and repair in endometrial cancer in correlation with the hOGG1 and RAD51 genes polymorphism. Mol Biol Rep 38: 1163–1170
48. Zhao H, Qin C, Yan F, Wu B, Cao Q, Wang M, Zhang Z, Yin C (2011) hOGG1 Ser326Cys polymorphism and renal cell carcinoma risk in a Chinese population. DNA Cell Biol 30:317–321
49. Li Q, Huang L, Rong L, Xue Y, Lu Q, Rui Y, Li J, Tong N, Wang M, Zhang Z, Fang Y (2011) hOGG1 Ser326Cys polymorphism and risk of childhood acute lymphoblastic leukemia in a Chinese population. Cancer Sci 102:1123–1127
50. Stanczyk M, Sliwinski T, Cuchra M, Zubowska M, Bielecka-Kowalska A, Kowalski M, Szemraj J, Mlynarski W, Majsterek I (2011) The association of polymorphisms in DNA base excision repair genes XRCC1, OGG1 and MUTYH with the risk of childhood acute lymphoblastic leukemia. Mol Biol Rep 38:445–451
51. Sakamoto T, Higaki Y, Hara M, Ichiba M, Horita M, Mizuta T, Eguchi Y, Yasutake T, Ozaki I, Yamamoto K, Onohara S, Kawazoe S, Shigematsu H, Koizumi S, Tanaka K (2006) hOGG1 Ser326Cys polymorphism and risk of hepatocellular carcinoma among Japanese. J Epidemiol 16:233–239
52. Dianzani I, Gibello L, Biava A, Giordano M, Bertolotti M, Betti M, Ferrante D, Guarrera S, Betta GP, Mirabelli D, Matullo G, Magnani C (2006) Polymorphisms in DNA repair genes as risk factors for asbestos-related malignant mesothelioma in a general population study. Mutat Res 599:124–134
53. Wei B, Zhou Y, Xu Z, Xi B, Cheng H, Ruan J, Zhu M, Hu Q, Wang Q, Wang Z, Yan Z, Jin K, Zhou D, Xuan F, Huang X, Shao J, Lu P (2011) The effect of hOGG1 Ser326Cys polymorphism on cancer risk: evidence from a meta-analysis. PLoS One 6:e27545
54. Gu D, Wang M, Zhang Z, Chen J (2010) Lack of association between the hOGG1 Ser326Cys polymorphism and breast cancer risk: evidence from 11 case–control studies. Breast Cancer Res Treat 2010; 527–531.
55. Guo XG, Wang Q2, Xia Y3, Zheng L (2015) The C8092A polymorphism in the ERCC1 gene and breast carcinoma risk: A meta-analysis of case-control studies. Int J Clin Exp Med 8: 3691–3699.
56. Jorgensen TJ, Visvanathan K, Ruczinski I, Thuita L, Hoffman S, Helzlsouer KJ (2007) Breast cancer risk is not associated with polymorphic forms of xeroderma pigmentosum genes in a cohort of women from Washington County, Maryland. Breast Cancer Res Treat 101:65–71
57. Wang Z, Xu Y, Tang J, Ma H, Qin J, Lu C, Wang X, Hu Z, Wang X, Shen H (2009) A polymorphism in Werner syndrome gene is associated with breast cancer susceptibility in Chinese women. Breast Cancer Res Treat 118:169–175
58. Sangrajrang S, Schmezer P, Burkholder I, Boffetta P, Brennan P, Woelfelschneider A, Bartsch H, Wiangnon S, Cheisilpa A, Popanda O (2007) The XRCC3 Thr241Met polymorphism and breast cancer risk: a case-control study in a Thai population. Biomarkers 12:523–532
59. Chiu CF, Wang HC, Wang CH, Wang CL, Lin CC, Shen CY, Chiang SY, Bau DT (2008) A new single nucleotide polymorphism in XRCC4 gene is associated with breast cancer susceptibility in Taiwanese patients. Anticancer Res 28:267–270